Rational use of cardiac biomarkers in dogs and cats

Cardiac biomarkers, specifically NT-proBNP and cardiac troponin I, are commercially available blood tests that measure cardiac stress and muscle damage. Although they have been available at reference laboratories for around fifteen years, research is still often published which changes how we think about using these tests as part of a rational approach to clinical cases in general practice. Because of this, expert consensus changes rapidly. In this article, we will review the key evidence supporting the use of each biomarker and look at how to integrate theory into clinical practice. Specifically, we will discuss the use of NT-proBNP in screening for occult heart disease, and the prognostic value of cardiac troponin I in cats and dogs.

Key words: NT-proBNP, troponin, prognosis, screening, myocarditis

Introduction

Cardiac biomarker tests measure the serum/plasma concentration of proteins which are released by the heart and rise with increasing severity of heart disease. These tests, therefore, can be used as an indirect assessment of cardiac injury. The two biomarkers which are commercially available and therefore best understood, are N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin I (cTnI).

BNP is released by the atrial and ventricular myocardium in response to stretch and stress. Its plasma concentration increases relatively early in heart disease as a natural braking mechanism on the renin-angiotensin-aldosterone system (RAAS). The assay measures a relatively stable fragment of the molecule’s propeptide, NT-proBNP, which is released in a 1:1 ratio with BNP, and levels can rise with relatively mild heart disease. In contrast, cTnI is a more stable molecule and can be measured on EDTA plasma or serum samples. Various cTnI assays are available but results are not directly comparable; high-sensitivity assays may be best for monitoring change over time, but other assays are probably fair to use when screening for a very high result or near-normal – for example, when investigating possible myocarditis or the suspicion of a myocardial infarction, or when looking for evidence of transient myocardial thickening in cats. Separate canine and feline NT-proBNP assays are required to measure the molecule in these species, and the human assay cannot be used for either. Troponin I is a highly conserved protein which acts as part of a complex that is essential to the contraction of the sarcomere. Owing to this, it is highly conserved and is not released into the circulation in significant concentrations under normal circumstances; measurable levels should be minute. However, in patients with cardiac damage causing cell swelling (and leakiness of the cell surface membrane) or necrosis and rupture of cells, the circulating concentration of cTnI will rise. Logically, cTnI is best used as a marker of more severe heart disease.

Limitations and technical aspects

NT-proBNP can be rather labile and breakdown by plasma proteases is an issue for some older assays. The IDEXX laboratories assay is best reported, and this has shown recovery of over 90% after a sample is left unprocessed, at room temperature for 24 hours (Connolly et al. 2011, Hezzell et al. 2015). This suggests that the measurement obtained from a promptly processed sample (EDTA blood, spun within an hour and plasma transferred to a plain tube), sent via courier or first-class post, should represent an accurate reflection of the circulating NT-proBNP concentration. In comparison, cTnI is a more stable molecule and can be measured on EDTA plasma or serum samples. Various cTnI assays are available but results are not directly comparable; high-sensitivity assays may be best for monitoring change over time, but other assays are probably fair to use when screening for a very high result or near-normal – for example, when investigating possible myocarditis or the suspicion of a myocardial infarction, or when looking for evidence of transient myocardial thickening in cats. Separate canine and feline NT-proBNP assays are required to measure the molecule in these species, and the human assay cannot be used for either. Troponin I is such a highly conserved protein that human assays tend to work well for both dogs and cats, and species specific assays in veterinary laboratories are not required.

Cardiac biomarkers do not provide a firm diagnosis of heart disease, nor do they indicate that a patient is in congestive heart failure. No biomarker result should prompt a clinician to prescribe treatment for heart disease. Non-cardiac diseases may cause increases in cardiac biomarkers that can be mistaken for primary heart disease. In dogs, for example, systemic inflammatory diseases...
and adder envenomation have been shown to increase cTnI. In cats, NT-proBNP is elevated by hyperthyroidism (as is cTnI), systemic hypertension, anaemia and IRIS stage III-IV chronic kidney disease (Borgeat et al. 2015). This should be considered when measuring cardiac biomarkers in patients with significant comorbidities.

Clinical scenarios: when might cardiac biomarkers be useful to measure?

I: Identification of occult heart disease

Canine and feline cardiomyopathy can be present for months or years prior to the onset of clinical signs. Cardiologists often use the term “occult cardiomyopathy” to describe this. These patients are important to diagnose, especially in dogs, where the PROTECT trial proved that occult dilated cardiomyopathy (DCM) benefits from treatment with pimobendan (Summerfield et al. 2012). In cats, early detection of hypertrophic (or other) cardiomyopathy in this pre-clinical stage has the benefit of detecting cats with significant left atrial dilation or poor atrial function who are at risk of arterial thromboembolism, thereby allowing treatment with an anti-platelet drug such as clopidogrel prior to their first event – potentially providing a huge benefit in reducing morbidity and mortality in this, often fatal, disorder. Any diagnosis of occult heart disease also allows us to provide owners with appropriate expectations and advice for monitoring, and to anticipate any future considerations for routine anaesthesia, sedation or fluid therapy for that individual animal.

Thankfully, the most common heart disease diagnosed in general practice, myxomatous mitral valve disease (MVD), has the benefit of always having a left apical, systolic murmur to alert clinicians to its presence. The presence of a grade III/VI or louder left apical systolic murmur should prompt cardiac imaging to stage the disease and decide on the requirement for pre-clinical treatment with pimobendan or not, based on the presence of cardiomegaly (stage B1 vs. stage B2) – not the measurement of a cardiac biomarker.

The utility of cardiac biomarkers in patients with congenital heart disease is not published, and, in the author’s experience, they are unpredictable in dogs with congenital disease (they are often normal in the face of marked echocardiographic changes). As data on this is not published, no definitive recommendation can be made but in the author’s opinion, young patients where congenital disease is suspected should undergo echocardiography by somebody experienced with congenital cases, rather than have blood tests performed.

It is logical that NT-proBNP – released earlier in heart disease – is the better test to use for screening apparently healthy dogs and cats for cardiomyopathy. In cats, a cut-off of approximately 100 pmol/L has been reported by several studies. A point-of-care ELISA test is now available for feline NT-proBNP with a cut-off between 100-150 pmol/L (this varies by batch, but probably not by a clinically significant degree). This has been reported to be a useful test to detect occult cardiomyopathy in cats (Machen et al. 2014). Tests reading “abnormal” (i.e. above the cut-off) are not 100% diagnostic of heart disease, but allow us to select a population of cats where cardiac imaging is required to investigate further (Box 1). The negative predictive value of these tests appears to be high, so a “normal” result (i.e. <100 pmol/L) is likely to represent either a cat with a normal heart, or a cat whose cardiomyopathy is currently clinically insignificant. Repeat screening annually should be performed in the future.