Proceedings of the
World Small Animal Veterinary Association
Sydney, Australia – 2007

Hosted by:

Australian Small Animal Veterinary Association (ASAVA)

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Next WSAVA Congress

33rd Annual
World Small Animal Veterinary Association
14th FECAVA Congress

DUBLIN, IRELAND
20th - 24th August 2008
Laboratory tests for the diagnosis of heart disease and heart failure are a relatively new development in the field of human cardiology. Several assays have now been developed and become available for use in small animals. Before considering the value of individual tests it is worth thinking about the impetus behind the development of new tests.

Why do we need laboratory tests for the diagnosis of heart disease and failure?

There is unlikely to be merit in developing new tests for a disease that we are already able to diagnose cheaply and easily. In order to be of value a new diagnostic test needs to fulfil several criteria. It needs to tell us something clinically relevant that we do not already know. It needs to be at least one, and ideally several, of the following by comparison to the existing diagnostic techniques available:

- more accurate
- more accessible
- cheaper
- more rapid
- more convenient
- less open to interpretative error
- less prone to procedural error
- less risk to the patient

If we think about some of the existing techniques e.g. radiography, echocardiography and electrocardiography, that we have available for the diagnosis of heart disease and failure we can see that there may be value in developing new tests.

Finally to be of genuine value a test needs to tell us more than we already know. Thus if I already know a patient has heart disease and/or heart failure I do not need to carry out a “cardiac” test unless it tells me more than simply that the patient has heart disease and/or failure.

What tests are available for use in the diagnosis of cardiac disease and failure in small animals?

There are essentially two types of test available, those that indicate the death of myocardial cells known as leakage markers, and those that are released from elements of the heart or cardiovascular system when subjected to excessive pathophysiological stresses. These are usually either neurohumoral markers or inflammatory markers.
The leakage markers that have received the greatest amount of interest are the Troponins; T and I. The neurohumoral markers that are currently receiving the greatest interest are the natriuretic peptides.

**Troponins**

The troponin complex is a group of proteins (I, T and C) that regulate the interaction between actin and myosin in the sarcomere. They are intracellular proteins which have distinct myocardial isoforms. Increased concentrations of these proteins are only found in the circulation when a significant number of myocardial cells die simultaneously. In human patients these markers have become the preferred indicators of ischaemia and infarction due to their excellent sensitivity and specificity. They have been evaluated in a number of different circumstances in veterinary patients and their circulating concentrations found to be elevated in association with many cardiac diseases. At first glance this would therefore appear to make them excellent tests but the problem arises when we start to think about their genuine value. The problem with Troponin concentrations lies in their lack of specificity. They increase in response to numerous cardiac diseases and their concentrations do not correlate predictably with the severity of the cardiac disease or failure in dogs. Thus if we already know the patient has heart disease the test simply confirms that the patient has heart disease; it does not tell us more. Although one study suggested that they may have some value in the diagnosis of heart failure in dogs [1] a larger study did not confirm this conclusion [2]. I would regard their greatest clinical value as being in cases where a diagnosis of infarction or myocarditis is suspected; both rare diagnoses in small animal cases. In such cases dramatic elevations of Troponin can be seen – by comparison to the relatively modest elevations seen in most animals with cardiomyopathy or valvular heart disease.

**Natriuretic peptides**

Natriuretic peptides are hormones manufactured in and released from the ventricular and atrial myocardium. Their manufacture is increased in response to myocardial stretch and increased end diastolic wall stress. The heart releases two peptides atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP). Both these peptides are manufactured as larger pro-peptides and the active peptide is cleaved from the C-terminal end of the molecule. This means that equimolar quantities of the N-terminal pro-peptide are also manufactured and released into the circulation. Concentrations of either the peptides themselves or their N-terminal pro-peptides can be measured in the circulation and increase significantly and progressively with advancing cardiac disease.

Assays are available for ANP, NTproANP, BNP and NTproBNP. Their concentrations have all been shown to increase in response to cardiac disease in small animals. A genuine superiority of one assay or one molecule over the others has yet to be demonstrated by there are hypothetical reasons why NTproBNP may be a more stable marker of disease.
We have conducted studies to demonstrate the clinical utility of NTproBNP that have shown it to be superior to NTproANP in dogs. Sensitivity and specificity have been shown to be in the region of 80-85% for the discrimination of dogs with heart disease from dogs with respiratory disease. Other authors have shown similarly promising results for the natriuretic peptides using different assays [3].

Other uses of “cardiac” laboratory tests

As well as being used for the purposes of diagnosis these laboratory tests have other potential uses. Studying how this field has developed in human medicine we might consider the potential use of these markers for the following purposes

- Screening
- Prognostication
- Monitoring and guiding therapy

Screening

One of the original studies demonstrating the value of BNP as a diagnostic test in human patients demonstrated how effectively it could detect individuals with cardiac disease in an apparently normal population [4]. A diagnostic test is likely to perform less well as a screening test since it will be being used in a population that is less severely affected by disease and therefore less likely to have significant perturbations of the marker being assessed. We are currently involved in a study evaluating the utility of NTproBNP as a screening test for dilated cardiomyopathy. Canine studies have been conducted along similar lines and have shown some value in using BNP for this purpose [5, 6]. It is likely that different cut-offs would have to be used for this purpose to optimise the sensitivity or specificity (whichever is of greatest importance) for this particular purpose.

Prognostication

Since markers of cardiac disease and failure tend to increase progressively as the disease worsens it makes intuitive sense to expect that those patients with the more significantly elevated concentrations of markers will have more advanced disease and therefore a worse prognosis. Elevated ANP has been shown to confer a worse prognosis in canine patients with cardiac disease [7]. Patients with dilated cardiomyopathy that have elevated Troponin I concentrations tend to have a worse outcome [2]. Studies in human patients have also suggested that the degree to which one’s BNP concentration falls in response to treatment may be an indicator of prognosis [8].

Monitoring and guiding therapy

Limited studies in human heart failure patients have indicated that if therapy is guided by an effort to reach a target concentration of BNP the outcome may be equal to, or better than, the outcome with conventionally guided therapy.
[9]. A new study is underway to more rigorously test this hypothesis in a larger population of patients [10].

**How will these tests be of greatest value?**

If we come back to consider some of the features that would characterise a useful diagnostic test we can try to anticipate what the value would be of the tests currently available. Laboratory tests may be comparably accurate to some of the test we currently have available for the diagnosis of heart failure. They are certainly widely accessible. It is very likely that they will be cheaper (than say radiographs). Currently the need to send samples off to a laboratory means that results are not obtained quickly. Laboratory tests are often convenient to undertake and they are definitely subject to less operator and interpreter error than radiography and echocardiography. Typically they are also less stressful for patients.

It is often necessary with heart failure patients to have rapid access to diagnostic test results and therefore I believe that these tests would have the greatest clinical utility if they were accessible for semi-quantitative use “in-house”. The place for accurate quantitative measurement of peptide concentrations may be in the longer term monitoring of patients’ therapy. Bedside analysers have been developed for human use in the emergency setting.

One can anticipate that with further development and evaluation these tests have the capacity to radically change the way we diagnose, and potentially treat, heart failure in small animals.

**References**


