CARDIAC BIOMARKERS: WHAT ARE THEY AND HOW CAN I USE THEM IN PRACTICE?
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A blood-based test for heart disease or heart failure in dogs and cats is a compelling concept. Over the last decade significant research has been performed looking into the usefulness of blood-based biomarkers of both myocardial cell injury ("leakage markers") and specific cardiac function proteins ("functional markers") to improve our diagnostic, prognostic, and therapeutic accuracy in patients with heart disease and heart failure. Blood-based cardiac biomarkers should require a small amount of blood; have a quick turn-around time with no special handling or expensive equipment requirements; hopefully have a high sensitivity and specificity for cardiac failure or injury; and should be affordable for the general public. Potential applications include ● an intermediate screening step for asymptomatic or minimally symptomatic heart disease ● distinguishing a cardiac vs. a non-cardiac cause of dyspnea ● identifying myocardial injury associated with myocarditis, gastric dilatation and volvulus, or doxorubicin cardio-toxicity. This talk will focus on the day-to-day clinical utility of troponin and NT-proBNP.

Circulating markers of myocardial injury provide evidence of cell death or loss of membrane integrity, supplying the rationale to use such markers for the diagnosis of a disease process within the heart. Analysis of cardiac leakage markers has progressed from measurement of nonspecific myoglobin, lactate, and creatinine kinase to measurement of cardiac specific structural proteins, including the cardiac troponins. Since the early 1990's, analysis of circulating cardiac troponin I (cTnI) has revolutionized the noninvasive diagnosis of acute myocardial infarction (heart attack) in human beings. The advantage of this biomarker lies in its ability to provide an early, highly cardiac specific diagnosis of considerable cardiac injury with prognostic risk assessment and ability to guide therapy quickly. cTnI is now considered the gold standard test for acute myocardial infarction in humans and despite the lack of important ischemic heart disease in veterinary medicine, studies performed in dogs and cats in a variety of clinical conditions have suggested similar findings indicating superior efficacy of cTnI in the diagnosis of myocardial injury. These investigations have also demonstrated that troponin immunoassays designed for use in humans can be used reliably and specifically in dogs and cats.

The troponin complex is located on the thin filament of the contractile apparatus and regulates the calcium-mediated interaction of myosin and actin. The complex is made up of three structurally and functionally different proteins: Cardiac Troponin I (cTnI), Cardiac Troponin T (cTnT), and Cardiac Troponin C (cTnC). Although there are different isoforms of cTnI and cTnT present in both cardiac and skeletal muscle, these proteins are distinct and encoded by individual genes. cTnT binds the troponin-tropomyosin complex to the actin filament. cTnI is an inhibitory protein that prevents contraction when calcium is not present. cTnC has calcium-binding properties and has limited diagnostic value as the cardiac and skeletal muscle forms are identical.

The diagnostic benefit of assessing myocardial injury in dogs and cats through troponin analysis has been shown in numerous clinical settings, such as congestive heart failure, cardiac contusions, pericardial disease, critically ill patients with cardiac injury (i.e. sepsis or doxorubicin toxicity), gastric dilatation-volvulus, and myocarditis amongst others. In acute disease, an association exists between the severity of myocardial injury and serum troponin concentrations. Unfortunately, this relationship is not as reliable with congenital and acquired chronic heart disease in dogs and cats. For example, minor elevations are the most common finding in dogs with symptomatic dilated cardiomyopathy. Presumably, the continued elevation of circulating troponin reflects ongoing degradation of the contractile apparatus and accompanies the spontaneous progression of heart failure. Serial monitoring of troponin may provide more information and prognostic information for patients with primary chronic cardiac disease. Clinical improvement in signs of congestive heart failure is associated with normalization of troponin levels, which may serve as a biomarker target in the management of primary cardiac diseases, such as dilated cardiomyopathy. Detectable troponin concentrations in dogs with asymptomatic heart disease is variable and therefore screening with troponin analysis does not seem to provide any advantage over the commonly used comprehensive diagnostic methods. However, with further improvement of test sensitivities and large-scale clinical trials in high-risk populations, more promising findings may be anticipated. Studies have shown that cats with moderate to severe

hypertrophic cardiomyopathy have detectably higher troponin than healthy cats, regardless of whether heart failure is present. And cats with clinical congestive heart failure have higher troponin levels than cats with no clinical signs or cats with a history of heart failure. Other promising applications of troponin analysis include detecting myocardial injury in clinically suspected myocarditis in the dog, monitoring for cardiotoxicity in animals undergoing chemotherapy, and utilizing the predictive ability of troponin analysis to identify patients at high risk for fatal outcomes.

Since the discovery of atrial natriuretic peptide (ANP) more than 20 years ago, it has been apparent that the heart is a pump and a true endocrine organ that releases specific hormones in response to defined stimuli. Many functional markers of heart disease have been identified in humans and animals; however the natriuretic peptides have been the most extensively studied. The natriuretic peptides are a family of structurally similar hormones that act as key regulators of salt/water homeostasis and blood pressure control by antagonizing the renin-angiotensin-aldosterone system and the sympathetic nervous system. The natriuretic peptides include Atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP), C-type natriuretic peptide (CNP), Dendroaspis natriuretic peptide (DNP), and urodilatin. ANP is typically produced in the left and right atrium, but can be expressed by the ventricular myocardium with hypertrophy or ischemia. ANP is stored in granules within the myocardium and released in direct proportion to increased atrial stretch, intravascular volume expansion, and heart rate. The plasma concentration of ANP can therefore change rapidly in response to acute alterations in posture, volume loading, or tachycardia. BNP is primarily produced by the ventricles with chronic pressure or volume overloads and is stored to a much lesser extent. Therefore, in contrast to ANP, increased secretion of BNP is preceded by an increase at the transcription level and a longer term stimulus of increased ventricular wall tension, hypertrophy, or myocardial dysfunction is required to increase plasma BNP concentrations. In response to adequate stimulus, proANP or proBNP is cleaved into equal amounts of the active hormone and the N-terminal inactive fragment prior to being released equally into circulation. The half-life of the N-terminal inactive fragment is approximately fifteen times that of the active hormones and therefore these fragments have clinical advantages with respect to plasma concentration, half-life, and stability. The majority of clearance of natriuretic peptides occurs through enzymatic degradation and renal elimination.

In general, the plasma concentrations of natriuretic peptides are increased in disease states characterized by ventricular hypertrophy, tachycardia, hypoxia, expanded fluid volume, or reduced renal clearance of the peptides. As with circulating troponins, ANP and BNP are not specific for a particular cardiac disease, although considering that ANP originates primarily from the atria and BNP from the ventricles, increased circulating levels may reflect different abnormalities. BNP appears to be more sensitive that ANP at detecting chronic left ventricular systolic and diastolic dysfunction with left ventricular hypertrophy of any cause. Both ANP and BNP have been shown to accurately differentiate cardiac vs. non-cardiac dyspnea with good specificity and sensitivity for congestive heart failure in dogs and cats and a veterinary bed-side test for NT-proBNP is currently in production. In humans, BNP may be used as a screening tool, with a value in the normal range virtually excluding left ventricular systolic dysfunction. Veterinary studies have shown similar results with a good sensitivity of BNP to rule out occult heart disease or symptomatic heart failure in dogs and cats. **The value of NT-proBNP lies within increasing our diagnostic accuracy of heart disease and heart failure. NT-proBNP may act as an intermediate diagnostic test for dogs and cats prior to a thorough cardiovascular diagnostic work-up**. **An increase of NT-proBNP should *always* warrant follow-up diagnostic tests, such as echocardiography, to identify underlying cardiac pathology and determine if treatment is warranted.** Specific handling instructions are very important to ensure accurate NT-proBNP levels and interpretation. Additionally systemic hypertension, pulmonary hypertension, and renal disease have been shown to cause increased circulating NT-proBNP. Other upcoming and promising uses of BNP include further data to support prospective screening tests for high-risk populations, predicting disease severity, providing prognostic information, and proving useful as a guide to therapy in chronic congestive heart failure.

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