

Cardiac biomarkers in clinical practice of dog and cat – a review

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Abstract. A biomarker is an indicator of a normal or pathologic process, or a pharmacologic response to a therapeutic intervention. Nowadays, in veterinary cardiology, the most used biomarkers for assessing the pathological status of the cardio-vascular system, are B-type natriuretic peptide and cardiac troponins. These biomarkers have been very well studied in cardiac pathology in order to assess their diagnostic potential. The aim of the present paper was to discuss the structure, metabolism, function, applicability, reference values and variations in different diseases and to review some practical aspects of the two cardiac biomarkers, used nowadays in small animal cardiology.

Key Words: cardiac, natriuretic peptides, troponin.

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1. Introduction

National Institute of Health Biomarkers defined a biomarker, shortened term from biological marker, as a parameter which can be measured accurately, being an indicator of a normal or pathologic process, or a pharmacologic response to a therapeutic intervention (Strimbu & Tavel 2010; Wells & Sleeper 2008). In the clinical field, a reliable biomarker should respect some criterias: first, it has to be easily measured, with available methods, prompt turnaround time and reasonable cost, second, to bring new and valuable information for the diagnostic or the treatment efficiency, providing a strong and consistent association between the biomarker and the outcome, or disease of interest, and third, to help the clinician in managing the patient offering a superior performance to other diagnostic tests (Morrow & de Lemos 2007). A cardiac biomarker is a parameter that can predict or diagnose a cardiac disease either if it is primary or secondary with as high sensitivity and specificity as possible. The reason of the increasing interest in cardiac biomarkers is easy to understand. They are convenient, low cost, non-invasive, risk free, fast turn-around time, efficient and highly predictive tests (Drobatz 2009).

In the last 30 years many researchers have studied various types of cardiovascular markers, aiming to define better diagnostic aspects of primary and secondary cardiac diseases. In the veterinary field, the most complete studies have been performed in small animals, mainly dogs and cats.

At present, in veterinary clinical practice, the biomarkers with the highest predictability for cardiac diseases are N-terminal pro-brain natriuretic peptide (NT-pro BNP) followed by cardiac troponins I and T (cTnI and cTnT), and less frequent used, atrial natriuretic peptide, endothelin, tumor necrosis factor α (TNF α)

and C-reactin protein, that show lesser specificity (Fonfara et al 2010; Gu et al 2006; Saunders et al 2009; Shaw et al 2004; van Kimmenade & Januzzi 2009). This review will discuss the structure, metabolism, function, applicability, reference values and variations in different diseases of troponin I and N-terminal proBNP in dogs and cats.

2. Cardiac biomarkers in small animal medicine

2.1. Troponin

Troponin (Tn) is a globular protein that binds the actin and miosin, regulating the striated muscle contraction. This protein exists under three different forms, TnI, TnT and TnC. The first two proteins, TnI and TnT are divided in two isoforms, depending on the muscle type they activate (cardiac and skeletal muscle) (O'Brien 2008). Cardiac troponin T (cTnT) and troponin I (cTnI) are myocardial regulatory proteins which are responsible for the control of the calcium binding between actin and myosin. Cardiac TnI has not been identified outside the myocardium while cardiac TnT can be found in small amounts in skeletal muscle, but in irrelevant quantity to crossover the assays (Bodor et al 1995; Ricchiuti et al 1998b; Sharma et al 2004). Cardiac troponins are cardiomyocyte injury specific biomarkers (Liquori et al 2014). Cardiac injury induces myocyte destruction and membrane rupture, then the free cardiac troponin is released in the blood torrent in high concentrations. This process is followed by a slow and continuous release of structurally bound troponins, so explaining the sustained elevated serum concentration (Wells & Sleeper 2008). In dog serum, cTnI is detectable at 4-6 hours and peaked at 10-16 hours after an induced trauma (experimental myocardial infarction), faster

than in humans. Serum cTnI was found elevated for up to 200 hours after an induced trauma (Cummins & Cummins 1987). The increase in level of cTnT is relatively proportional to the degree of myocardial damage, with prognostic implications as well (Tarducci et al 2004).

Normal ranges for cTnI are <0.03 – 0.07 ng/ml in healthy dogs and <0.03 – 0.16 ng/ml in healthy cats, where the lower detectable limit for most of the tests is 0.02 ng/ml, and <0.05 ng/ml for cTnT in healthy dogs (Sleeper et al 2001; Tarducci et al 2004). Also, Oyama (2004) proposed the normal value 0.02±0.02 ng/ml for cTnI in clinically healthy dogs (Oyama & Solter 2004). Troponin levels are determined by using human enzyme-linked immunosorbent-assay (ELISA) tests due to significant homology in the proteins between species (Bodor et al 1992; Wells & Sleeper 2008). There are also two veterinary tests available for the cardiac troponin I (Oyama 2013).

Although elevated cardiac troponin is highly sensitive for myocardial injury, this biomarker do not offer the possibility to distinguish between types of pathology, showing a low specificity (Oyama 2013). As recently implemented in small animal medicine, in human medicine the cTnI assay is considered the gold method to assess the myocardial infarction, reported to have a 97% sensitivity and 95% specificity (Alpert et al 2000; Wong 1996). It was proved that the cTnI has a higher sensitivity in detecting the myocardial injury than cTnT (Linklater et al 2007). In veterinary medicine, several studies had been performed for different pathologies involving myocardial damage, in order to establish the sensitivity and specificity of this biomarker, and the value of the survival prediction (Fonfara et al 2010).

A high concentration of cTnI has been found in dogs with mitral valve disease (MVD) associated to intramyocardial arteriosclerosis and fibrosis (Falk et al 2013). One study on blood concentration of cardiac troponins had been performed in dogs with class IV (according to New York Heart Association classification) of congestive heart failure (CHF) due to MVD. Results showed that 40% of the dogs had detectable cTnI (median of 0.24 ng/ml with a range between 0.12 – 0.31 ng/ml) and only 7% had a detectable cTnT (0.02 ng/ml). Animals with detectable cTnI had a median survival of 67.5 days (range between 1 – 390 days) comparing to non-detectable cTnI dogs with a median survival of 390 days (range between 20-912 days) (Linklater et al 2007). Oyama (2004) found a correlation between the concentration of serum cTnI and the left ventricle and atrial size in dogs with MVD (Oyama & Sisson 2004). Cardiac troponin I can be used as a predictor for fibrosis in natural occurring chronic cardiac disease, produced by various factors including toxic, metabolic, inflammatory or idiopathic origins. In the pathological changes described in heart failure due to mitral valve disease, arteriosclerosis is linked to fibrosis, the latter being almost invariably caused by ischemia (Falk et al 2013).

In dogs with occult dilated cardiomyopathy (DCM), significantly greater plasma concentration (0.21 ± 0.10 ng/ml) comparing to clinically normal group (0.06 ± 0.01 ng/ml) was found (Oyama et al 2007). Regarding Doberman Pinschers with overt DCM, cTnI serum concentrations were found significantly higher than those without clinical signs, and it was demonstrated that the values were relatively higher in subclinic patients which developed DCM within 1.5 years, concluding that cTnI serum concentrations can detect any form of DCM (Wess et al 2010). Furthermore,

cTnI serum levels correlated with left atrium and ventricle size (Oyama & Sisson 2004). Tarducci (2004) showed that cTnT is helpful in discriminating animals with myocardial damage in course from those in which hypokinesis is most likely indicative of a previous injury (Tarducci et al 2004). Finally, a study over Boxers with arrhythmogenic right ventricular cardiomyopathy (ARVC) showed that cTnI serum concentration was increased comparing to clinically healthy group (Baumwart et al 2007). An increase of cardiac troponin plasma levels have been found in dogs with pericardial effusion (PE). Patients with PE secondary to hemangiosarcoma (HAS) had a significantly higher serum concentration of cTnI (median of 2.77 ng/dl with a range between 0.09 – 47.18 ng/dl) than those with idiopathic PE (median of 0.05 ng/dl with a range of 0.03 – 0.09 ng/dl). On the other side, no significant differences were found between serum concentration of cTnT in dogs with HAS and those with idiopathic PE, and no correlation was found between the size of the mass and cardiac troponin concentrations (Shaw et al 2004). Also Linde (2006) observed differences between cTnI serum levels in normal dogs (median of 0.03 ng/ml) and those with PE (0.19 ng/ml), but there were no differences between dogs with non-neoplastic PE and dogs with PE secondary to neoplasia (Linde et al 2006). A potential reason for this finding could have been the involvement of aggressive non-neoplastic lesions such as fungal pericarditis, chronic fibrous pericarditis, lymphocytic-plasmocytic pericarditis and bacterial pericarditis, which can induce high troponin levels, similar to neoplastic disease behaviour.

Serum concentration of cTnI was studied in dogs with varied congenital heart diseases such as patent ductus arteriosus (PDA), subaortic stenosis (SAS), pulmonary stenosis (PS), and ventricular septal defect (VSD). There were no significant differences between groups of healthy and affected dogs (Oyama & Sisson 2004; Spratt et al 2005). A modest correlation was found between cTnI concentration and ventricular wall thickness (Oyama & Sisson 2004). cTnI serum levels have been evaluated before and after cardiac catheterisation in dogs proposed for PDA coil embolisation, balloon valvuloplasty (BV) and pacemaker implantation. Dogs undergoing ovariohysterectomy (OVH) have been used as control group in order to match the potential changes during anesthesia. There was no significant difference between groups before surgery but significant differences were found after 5, 24 and 240 hours. The group with pacemaker implant had the greatest increase in cTnI while the smallest increase was found in PDA group (where the catheter did not touch the myocardium) (Shih et al 2009). Moreover, increased plasma concentration have been found in animals with PS after performing the BV intervention (Saunders et al 2009). Higher concentration of cardiac troponin in most invasive surgical intervention such as pacemaker implantation or BV confirm the direct relation between myocardial damage and blood concentration of troponin.

Implications of parasitic diseases in cardiovascular pathology have also been assessed in several studies. Canine heartworm disease (HWD) caused by *Dirofilaria immitis* produces an increase in cTnI serum concentration due to the right heart myocardial damage (Carreton et al 2012). Furthermore, it have been shown that cTnI serum concentration is increased in complicated stages of canine babesiosis (Lobetti et al 2002).

The prognosis of blunt chest trauma have been studied through cTnI and cTnT serum concentrations. In one study, results showed that cTnT was elevated in 9 of 33 comparing cTnI which was found elevated in 18 of 33 patients, concluding that cTnI is more specific than cTnT in predicting the severity of the injury (Schober et al 1999). Kirbach (2010) showed that cats with blunt thoracic trauma had a significant increase in blood cTnI concentration after 12 to 24 hours post trauma, which then gradually decreased. As in previous study, cTnT was found to be less specific than cTnI (Kirbach et al 2000).

Experimentally induced myocardial infarction in dogs showed a correlation between serum cTn concentration levels and the decrease of cTn in tissue concentration, due to post-lesional loss of cTn, showing the ability to predict the infarct size (Ricchiuti et al 1998a). Exertional heatstroke can produce a severe myocardial damage, increasing cardiac troponins plasma concentration. A case report in a dog stated that cTnI was extremely high (180 ng/ml) and remained as high for over 16 days (Mellor et al 2006). Several studies over cTnI have been performed in order to distinguish between cardiac and non-cardiac respiratory distress, although this test alone is not enough to establish an absolute diagnostic and generally further exams (such as diagnostic imaging) are required mostly because any systemic condition that cause hypoxiemia and myocardial ischemia can provoke elevation of circulating cardiac troponin (Connolly et al 2009a; Oyama 2013). It was demonstrated that cTnI serum concentration can be used in diagnosis of hypertrophic cardiomyopathy (HCM) in cats. Results showed a significantly higher concentration of serum cTnI in patients with HCM (median of 0.95 ng/ml with a range of 0.2-4.1 ng/ml) than in healthy patients (median < 0.2 ng/ml with a range of 0.2 – 0.25 ng/ml) (Connolly et al 2003). Myocardial injury can be induced secondary to chronic exposure to excess of thyroid hormone in cats with hyperthyroidism, increasing cTnI serum concentration (Connolly et al 2005). Also, cardiac troponins have been found in higher concentrations in some pathological conditions and diseases that, through their different pathogenetic mechanisms, might have implications in myocardial damage, such as marked anaemia, lymphoma, neoplasia, respiratory diseases, pancreatitis, Addison's disease, Cushing syndrome, renal failure, and also in geriatric patients and predisposed but cardiac disease free dog breeds (Serra et al 2010). The secondary pathologies and their effect over the cardio-vascular physiology must be always considered when performing the interpretation of the assay, and should be correlated with other exams in order to increase the diagnostic accuracy. Finally, the aged heart, even when there is no proof of the presence of disease, can lose up to 35% of its total myocyte number (Anversa et al 1990). The reason of this finding is unknown, but it may be related to degenerative changes and decrease in tisular perfusion (Ferrari et al 2003; Oxenham & Sharpe 2003).

2.2. Brain natriuretic peptide

Natriuretic peptides represent a class of hormones that control body fluid homeostasis through their natriuretic and diuretic effects, and exert influence over renin – angiotensin – aldosterone mechanism (Liquori et al 2014). Different types of natriuretic peptides are expressed in different tissues and different species, as seen in Table 1.

Table 1. Types of natriuretic peptides and their expression site (from Kimmenade & Januzzi 2009)

Type of natriuretic peptide	Expression
ANP	Mainly atrial myocardium
BNP	Mainly ventricular myocardium
CNP	Brain, endothelium, kidney, chondrocytes, pituitary gland
DNP	Venom gland of <i>Dendroaspis angusticeps</i> (Green Mamba)
VNP	Heart of primitive ray-finned bony fish

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) have been found to be useful in assessing the diagnostic of cardiac diseases, while the C-type natriuretic peptide (CNP) expression is associated with the paracrine function and it also plays a role in the regulation of the vascular tone. *Dendroaspis* natriuretic peptide (DNP) and ventricular natriuretic peptide (VNP) have other utilities or exist in other species, such as VNP which have been found only in primitive ray-finned bony fish (Ciaramella et al 1995; De Luna et al 1992, 1993; van Kimmenade & Januzzi 2009). Atrial natriuretic peptide is found in atrial myocardium, while BNP is found in both atrial and ventricular myocardium, but in higher concentration in the latter (Sudoh et al 1988; van Kimmenade & Januzzi 2009). B-type natriuretic peptide was proved to be more stable than ANP after release into the circulation. N-terminal fragment of the prohormone B-type natriuretic peptide (NT-pro BNP) is an inert molecule similar to active BNP molecule, both cleaved from the pro-BNP molecule (see Figure 1) (van Kimmenade & Januzzi 2009).

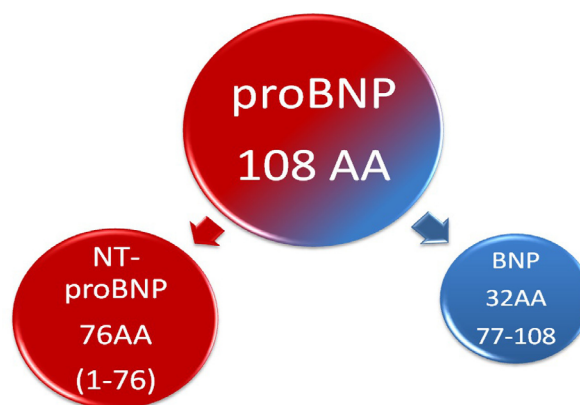


Figure 1. Representation of the cleavage of proBNP (108 amino-acids) into BNP (32 amino-acids) and NT-proBNP (76 amino-acids)

With the same sensitivity and specificity as BNP, NT-pro BNP have the advantage of higher biological half-life (Fox et al 2009). The two fractions, BNP and NT-pro BNP have been used with success to assess the heart failure, acute coronary syndrome or ischemic cardiac disease, and also in guiding the heart failure therapy in human medicine and served as a model for veterinary medicine. (Braunwald 2008; Januzzi et al 2005; Liquori et al 2014; Maisel et al 2002).

In veterinary medicine, sandwich enzyme immunoassay tests (ELISA) are used to assess the NT-proBNP concentrations and normal and pathologic ranges in animals have been proposed: in dogs, a concentration of less than 900 pmol/l of NT-proBNP is not compatible with myocardial increased stretch and stress, but more than 735 pmol/l in Doberman Pinschers indicates an increased risk for DCM, while in cats, a concentration less than 100 pmol/l is not associated with cardiomyopathy, between 100-270 pmol/l clinically significant cardiomyopathy is unlikely but early disease may be present, and more than 270 pmol/l suggests that clinically significant cardiomyopathy is present.

Studies have been performed using NT-proBNP for assessing the cardiac disease and the severity degree in dogs with mitral valve disease and dilated cardiomyopathy compared to healthy dogs, showing that serum concentrations of NT-proBNP were higher in the affected ones. Furthermore, in dogs with cardiac diseases, serum levels of NT-proBNP were correlated with heart rate, respiratory rate, echocardiographic changes and renal function, concluding that NT-proBNP concentrations may be useful in diagnosing cardiac diseases and also in the assessment of the severity grade (Oyama *et al* 2008).

Significant difference was found among dogs in different classes of CHF according to the International Small Animal Cardiac Health Council (ISACHC), that showed a progressive increase of this biomarker according to the worsening of the hemodynamic status. Furthermore a significant correlation was found between NT-proBNP concentration and left atrium/aorta (La/Ao) ratio, suggesting that NT-proBNP is sensitive to intracardiac pressure due to volume overload (Piantedosi *et al* 2009).

NT-proBNP have been studied in dogs with early stages of myxomatous MVD showing that plasma concentrations of natriuretic peptides were higher after reexamination (about 4 years later), correlated as well with the increase of mitral regurgitation jet. This proved that NT-proBNP can predict the progression of mitral valve disease (Tarnow *et al* 2009). Another study showed a significant correlation between NT-proBNP concentration and regurgitation fraction, La/Ao ratio, shortening fraction and end-diastolic left ventricular volume indexed to body surface area (EDVI). Moreover, NT-proBNP concentrations were found higher in dogs that underwent MVD decompensation within 12 months (Chetboul *et al* 2009). Finally, an increase of 100 pmol/l of NT-proBNP plasma concentration would raise the mortality by 7% in dog with MVD (Moonarmart *et al* 2010).

In a study that included 328 dogs with different stages of DCM, the diagnostic value of NT-proBNP have been assessed showing that NT-proBNP concentrations from all affected dogs were significantly higher than healthy dogs. The sensitivity and specificity for all forms of DCM were found to be 81% and 75% using a 400 pmol/l cutoff (Wess *et al* 2011). Twenty-one dogs with occult DCM showed that NT-proBNP concentration greater than 6.21 pg/ml had a sensitivity of 95.2% and a specificity of 61.9%, while the combination of NT-proBNP assay with 24-hours Holter monitoring had a 94.5% sensitivity and 87.8% specificity, but BNP did not correlate with the dog's age (Oyama *et al* 2007; Singletary *et al* 2012). A study regarding the implications in predictability of mortality for dogs with heart failure due to DCM suggested that NT-proBNP concentrations could well correlate with the survival period, concluding that this biomarker could be useful in evaluation of the survival time in dogs

(Noszczyk-Nowak 2011). Also, BNP plasma concentration was found higher in Boxers with arrhythmogenic right ventricular cardiomyopathy (ARVC) than healthy Boxers, but lower than dogs with other cardiac diseases, suggesting that BNP may not be a good indicator in these patients (Baumwart & Meurs 2005).

NT-proBNP have been assessed in ischemic myocardial infarction. Experimentally induced myocardial infarction in dogs have shown to significantly raise the plasma concentration of NT-proBNP early post injury, and gradually decreasing over the next 28 days to baseline. NT-proBNP can be used as a helpful diagnostic indicator in asymptomatic acute and subacute myocardial infarction (Hori *et al* 2012a). Although there is no study in natural occurring cardiac hypertrophy, serum concentrations of NT-proBNP have been assessed in dogs with induced concentric hypertrophic cardiomyopathy by aortic constriction, creating a model of natural aortic stenosis. Results showed that NT-proBNP levels were significantly higher 3 to 6 months post aortic constriction demonstrating the utility of NT-proBNP in identifying early ventricular remodelling due to pressure overload (Hirata *et al* 2001; Hori *et al* 2008). Also, experimentally induced embolic pulmonary hypertension have shown implications in NT-proBNP plasma concentration due to right ventricular myocardial stretch and remodelling. A study showed that NT-proBNP concentration increase significantly in severe chronic pulmonary hypertension, but not in mild pulmonary hypertension, suggesting correlation between NT-proBNP concentration and myocardial remodelling in chronic right ventricular pressure overload (Hori *et al* 2012b).

Many studies have been performed over the potential of BNP in distinguishing between the cardiac and respiratory diseases. One study assessed BNP concentration to distinguish between cardiac and non-cardiac dyspnea. Twenty-two dogs with dyspnea due to congestive heart failure and twenty-six dogs with non-cardiac dyspnea have been subjected to the study showing a higher BNP concentration in dogs with congestive heart failure (mean of 34.97 pg/ml) comparing to non-cardiac dogs (mean 12.8 pg/ml) (Prosek *et al* 2007). A second study used NT-proBNP to distinguish between cardiac and non-cardiac dyspnea, with the same results. Furthermore, it was shown that increased creatinine is associated with NT-proBNP concentration, suggesting that this is a useful marker for diagnosing cardiac diseases, but the interpretation must be made in the light of patient's renal function (Boswood *et al* 2008). In hypertensive cats with chronic kidney diseases the NT-proBNP plasma concentration was found significantly higher. Also, there have been found significant differences between non-hypertensive cats with chronic kidney disease and normal cats, highlighting the effect of renal function alteration over BNP blood concentration (Lalor *et al* 2009). The BNP concentrations in dogs diagnosed with congestive heart failure presenting either cough or dyspnea were found correlated with the disease severity (DeFrancesco *et al* 2007).

Golden Retriever dogs with occult phase of muscular dystrophy cardiomyopathy were found to have higher concentrations of BNP (mean±SD of 117±92 pg/ml) than healthy dogs (mean±SD of 46±22 pg/ml) (Chetboul *et al* 2004). Moreover, NT-proBNP have been assessed in babesiosis with different degrees of severity showing different concentrations among groups, suggesting

Table 2. The use of cardiac troponins and B-type natriuretic peptides in different cardiac and non-cardiac pathologies

Cardiac troponins		B-type natriuretic peptide	
Mitral valve disease	Dog	Mitral valve disease	Dog
Dilated cardiomyopathy	Dog	Dilated cardiomyopathy	Dog
Pericardial effusion (neoplastic and non-neoplastic)	Dog	Arrhythmogenic right ventricular cardiomyopathy in Boxers	Dog
Balloon valvuloplasty in pulmonary stenosis	Dog	Myocardial infarction (induced)	Dog
Cardiac catheterisation and pacemaker implant	Dog	Concentric hypertrophy (induced)	Dog
Distinguish between cardiac and non-cardiac respiratory distress	Cat	Pulmonary hypertension (induced)	Dog
Hypertrophic cardiomyopathy	Cat	Distinguish between cardiac and non-cardiac dyspnea	Dog Cat
Cardiomyopathy due to hyperthyroidism	Cat	Distinguish between cardiac and non-cardiac respiratory diseases	Dog Cat
Heartworm disease	Dog	Congestive heart failure with signs of cough or dyspnea	Dog
Babesiosis	Dog	Occult phase of muscular dystrophy cardiomyopathy in Golden Retriever	Dog
Blunt chest trauma	Dog Cat	Distinguish between cardiac and non-cardiac pleural effusion	Cat
Myocardial infarction (induced)	Dog	Systemic hypertension	Cat
Exertional heatstroke	Dog	Babesiosis	Dog

that NT-proBNP concentration can predict the severity of the disease and the induced cardiac stress (Lobetti *et al* 2012).

Finally, several studies have been performed to assess the clinical implications of BNP in feline cardiac diseases. Plasma concentration of NT-proBNP have been tested in cats with severe hypertrophic cardiomyopathy showing increased concentrations in affected cats comparing to healthy ones. On the contrary, there was no statistical difference between the concentration of NT-proBNP in affected and normal cats, suggesting that this assay has a high sensitivity and specificity in detecting only cats with severe hypertrophic cardiomyopathy (Hsu *et al* 2009). B-type natriuretic peptide concentration differences have also been studied between cardiac and non-cardiac cats with dyspnea. One study of 167 dyspneic cats, 101 cardiac and 66 non-cardiac, showed that NT-proBNP concentration was higher in cats with congestive heart failure (median of 754 pmol/l) than non-cardiac cats (median of 76.5 pmol/l) (Fox *et al* 2009). Also, in a study of 74 cats with respiratory distress, 33 cats with CHF and 41 non-cardiac cats, was shown that those with CHF had higher NT-proBNP serum concentration (median of 523 fmol/ml) than non-cardiac ones (median of 45 fmol/ml) (Connolly *et al* 2009b). A low NT-proBNP concentration is more often associated with a non-cardiac disease, whereas an elevated concentration is more suggestive of CHF (Oyama 2013). Moreover, pleural fluid NT-proBNP concentrations were found strongly correlated with levels of NT-proBNP in both plasma and pleural fluid and were significantly higher in cats with pleural effusion secondary to cardiac disease than those with non-cardiac disease (Humm *et al* 2013).

The implications of cardiac troponin I and B-type natriuretic peptides in cardiac and non-cardiac diseases in small animals are shown in Table 2.

2.3. Other cardiac biomarkers used in domestic carnivores

The first studies on cardiovascular markers date back to 1980s when one of the first described cardiac biomarker was endothelin (ET), a peptide hormone isolated from the aortic porcine cells (Yanagisawa *et al* 1988). There were described three distinct isoforms: endothelin-1, endothelin-2 and endothelin-3 (Inoue *et al* 1989). Its pathophysiological importance is reflected by the plasma level concentration during cardiovascular and renal diseases (Clavell *et al* 1993). The main biological effects of endothelin is the induction of vasoconstriction, mainly in the venous, but also in the arterial sector, with marked action on the pulmonary, renal and mesenteric circulation, and also the inotropic modulation and myocardial hypertrophy development (De Luna *et al* 1994; Ito *et al* 1991; Moravec *et al* 1989). In compare with other hormones, endothelin has a slow and prolonged effect in time over the cardiocirculatory system (De Luna *et al* 1994). This biomarker have been used to assess cardio-circulatory diseases in veterinary medicine, but with lower diagnostic value than other markers. Endothelin and Big endothelin-1, the circulating form of endothelin, were used in diagnosing dogs with dilated cardiomyopathy, congestive heart failure, myocardial ischemia, and in distinguishing between cardiac and non-cardiac diseases (Cavero *et al* 1990; Liu *et al* 1990; Prosek *et al* 2004a; Prosek *et al* 2004b; Prosek *et al* 2007; O'Sullivan *et al* 2007). Piantedosi (2009) used endothelin along with other biomarkers to assess the hemodynamic status and the class of congestive heart failure in dogs with chronic degenerative valvular disease (Piantedosi *et al* 2009).

In 1981, de Bold discovered the effect of atrial natriuretic peptide (ANP), by injecting atrial tissue extracts intravenously and producing diuresis and natriuresis in rats (de Bold *et al* 1981). One of the first studies in veterinary medicine on this biomarker was performed in 1991 by Takemura by assessing its concentration

level in dogs with mitral valve regurgitation (Takemura *et al* 1991b). Atrial natriuretic peptide is a 28 amino acid polypeptide cleaved from proANP precursor, produced in the atrial wall secondary to myocardial tension due to pressure overload. (Ackerman *et al* 1992; Levin *et al* 1998; van Kimmenade & Januzzi 2009). For a long time ANP was used in veterinary medicine to assess cardiac diseases such as mitral valve disease, proving to be discriminating between stages of heart failure, also in dilated cardiomyopathy, heartworm disease, and in distinguishing between cardiac and non-cardiac diseases (Boswood *et al* 2003; Haggstrom *et al* 1994; Prosek *et al* 2007; Takemura *et al* 1991a; Tidholm *et al* 2001; Vollmar *et al* 1991). Creatine kinase (CK) and its fraction CK-MB are also biomarkers used to assess the cardiac function in different types of pathologies or surgery techniques developing myocardial damage, such as ischemia, myocardial necrosis or percutaneous coronary intervention in humans (Apak *et al* 2005; van der Vleuten *et al* 2008). This biomarker is not specific to myocardial tissue, being released also during non-cardiac muscle damage (Norris *et al* 1979). Apak (2005) concluded that cardiac troponin T is a more specific and sensitive marker for myocardial injury than CK-MB.

3. Perspectives and conclusions

The biomarkers represent a new step in both, veterinary and human medicine diagnostic methods, with the major advantages of precision and non-invasiveness. These new tests can help the clinician to formulate a correct diagnosis. One of the most revolutionary discovery in cardiac biomarkers was the BNP capacity to distinguish between dyspnea due to cardiac and non-cardiac pathology. The assay for this purpose was rapidly considered as a gold standard method in human medicine, raising the interest of many researchers also in veterinary medicine. Despite this, the biomarkers are not stand-alone tests and their results should be evaluated in the context of the medical history, physical examination and other diagnostic tests. The biomarkers discussed in this paper are the most used for assessing cardiac condition, with diagnostic potential in most pathologies, but reliability is still lacking and further researches are required. As previously seen, cardiac troponins have implications in myocardial tissue damage, necrosis, fibrosis, ischemia, and cell death with the potential of orientating the gravity of the injury and the elapsed time, although they do not offer any information regarding the mechanism of the injury. Natriuretic peptides are more specific to assess myocardial stress and stretch due to volume overload, but without tissue damage, and furthermore implications in cardio-vascular therapy. These pathophysiological mechanisms, alone or associated, are representative for most of the cardiac pathological conditions, offering the possibility to diagnose the disease through biomarker assay. It was demonstrated in many studies that cTnI is more specific than cTnT, showing higher plasma concentrations in affected patients, but the reason for this finding is unknown. A potential explanation could be a more powerful structural binding of the cTnI with the tropomyosin chain. B-type natriuretic peptide has the ability of diagnosing myocardial stress long before the onset of the clinical signs, making it a very important tool for the occult cardiopathies such as dilated cardiomyopathy. Two of the most important requirements that typify the biomarkers are

sensitivity and specificity. Future researches should improve these aspects to obtain diagnostic tests always more indicative of clinical status of the patients.

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