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Review Article

CANINE CARDIAC BIOMARKERS: NATURE, ACTIVITY AND USE

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ABSTRACT: Diagnosis of cardiac diseases and their therapeutic interventions mostly rely on combined clinical examination, radiography, electrocardiography, and echocardiography. However, wide variability among different dog breeds may also mislead the interpretation of ECG, echocardiography, and thoracic radiographs. Thus, the identification and monitoring of blood-based cardiac biomarkers along or in combination with other diagnostic tools could be a promising approach to diagnose cardiac diseases. The most extensively studied cardiac biomarkers in canines are cardiac troponin-I (cTnI) and B-type natriuretic peptide (BNP) concerned with myocardial injury. Recently galectin-3 and interleukin 1 receptor-like 1 protein (ST2) have been reported to be suitable cardiac biomarkers for human patients but, their application is limited in canines due to a lack of research. Genes specific for cytoskeletal protein synthesis in cardio-myocytes such as α-cardiac actin, LIM domain binding factor 3 (LDB3), and myosin heavy polypeptide 7 were reported to be associated with dilated cardiomyopathy (DCM) in dogs. DCM in dogs has been linked to metabolites such as 4-guanidinobutanoate, fructose, N-linolenoyltaurine, uracil, 2-methoxyhydroquinone, and 2-methoxyhydroquinone sulfate. Therefore, the metabolomic and genomic approaches to diagnosing cardiac diseases in dogs could be a promising approach in the future.

Keywords: Biomarker, Cardiac troponin-I (cTnI), B-type natriuretic peptide (BNP), Metabolomics, Genomics.

INTRODUCTION

Detweiler and Patterson's seminal study 57 years ago showed that the prevalence of cardiovascular diseases in dogs in a teaching hospital was 11% [1], and even more recently, the prevalence of cardiac diseases in dogs worldwide was 10%, with chronic valvular heart disease accounting for 75% of all cases [2, 3, 4]. As time passed, the diagnostic modalities of canine cardiac illnesses also gained momentum starting from right heart catheterization and angiocardiography, radiography, electrocardiography, and echocardiography [1, 5, 6] to recently developed cardiac biomarkers and metabolomics [7, 8]. However, wide variability among different dog breeds may also mislead the interpretation of ECG, echocardiography, and thoracic radiograph [9, 10, 11]. Thus, the identification and monitoring of blood-based cardiac biomarkers along with or in combination with other diagnostic tools could be a promising approach to diagnose cardiac diseases [12]. A good biomarker should offer data on diagnosis, prognosis, or therapeutic responses that would not often be obtained through traditional testing like gamma-glutamyl transferase for cholestasis or creatinine for renal diseases [13]. The most extensively studied cardiac biomarkers in canines are cardiac troponin-I (cTnI) and B-type natriuretic peptide (BNP). In recent years cardiac metabolomics has emerged as a promising area for diagnostic and therapeutic interventions. Metabolic pathways and associated genes related to diet-associated cardiac illness [14] and chronic valvular diseases [15] in canines were studied and 105 significant pathways along with seventeen metabolites related to heart diseases were identified [14]. In this present review, some traditional and recently developed canine cardiac biomarkers were discussed along with their merits and demerits.

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CARDIAC BIOMARKERS OF CANINES

Creatine kinase (CK)

It is a dimeric cytosolic enzyme predominantly found in skeletal and cardiac muscles including the brain [16, 17]. The dimer of CK is composed of two monomers namely M (muscle origin) and B (brain origin) [17]. There are three isoenzymes of CK namely CK-MM, CK-BB, and CK-MB. The myocardium-specific CK is CK-MB and its concentration was reported to increase by 35-100% in myocardial ischemia [18] starting from 4-8 hours of myocardial injury to reach a maximum value at 12-24 hours [19]. The reference interval of CK in dogs varied considerably from 10-200 IU/L to 59-895 IU/L studied in two different laboratories for 5 years [20]. The main demerits of CK as a cardiac biomarkers are its short half-life of 2-3 hours, wide variability of reference interval and total CK is more specific for total muscle damage [17].

Lactate dehydrogenase (LDH)

It is a ubiquitous enzyme responsible for the conversion of lactate to pyruvate in the final stem of a glycolytic reaction. LDH has five isoforms namely LDH-1 to LDH-5 but, LDH-5 is most specific to the heart [17]. The LDH level was reported to increase hemodynamic stress in humans [21]. Elevation of serum LDH activity was reported to increase acute myocardial infarction [22], valvular heart diseases, coronary heart diseases, and heart failure in dogs and humans [23, 24]. Sultana *et al.* [25] reported serum LDH activity was increased in cardiomyopathy (151.6±21.39 U/L) and any other cardiac diseases (172.27±3.47 U/L) compared to healthy control (52.83±5.76 U/L) in dogs. In a related study, Bakirel and Gunes reported a significant increase in LDH activity from 187±47.3 U/L to 918±136.4 in cardiac thrill compared to the control [26]. But, on the contrary, Sesh *et al.* [27] reported no variation in the LDH activity in canine dilated cardiomyopathy.

Cardiac troponin I (cTnI)

Cardiac troponin I is a protein attached to actin filaments in the cardiomyocytes involved in cardiac contraction and relaxation [17]. Minor amounts (2%) of cardiac troponin I present in the cytoplasm of cardiomyocytes in dogs and the damage of cardiomyocytes leads to the release of cTnI in the extracellular space [28]. Cardiac troponin I can be detected 2-3 hours after cardiac injury and peak concentration was reported at 18-24 hours post-injury [29, 30]. The half-life of free cTnI in dogs was found 1.85 hours [31]. The concentration of cTnI in healthy and dogs with cardiac diseases has been summarized in Table 1.

The concentration of cTnI can be influenced by several factors. The concentration was higher in Greyhounds and Boxers compared to other breeds of dogs [30, 32] but, there was no significant variation between non-Doberman and Doberman Pinschers [33]. The concentration of cTnI was reported to be increased with age [33]. The dogs fed grain free diet had higher cTnI compared to the dogs fed grain inclusive diet [34].

The cTnI can be measured in both plasma and serum but, the value of cTnI was lower in serum compared to plasma of dogs [35]. The storage condition also affects cTnI concentration. It is stable at – 70°C to – 80°C for a long time [36] whereas, it is not stable at room temperature; it can be stored at 4°C for 24 hours and -20°C for 3 months [37].

Other than myocardial injury, cTnI was reported to increase in babesiosis, sepsis, gastric dilatation, volvulus, brachycephalic airway syndrome, and renal diseases [38, 39, 40].

Natriuretic peptides (NPs)

Natriuretic peptides (NPs) are a family of hormones released from the myocardium in response to myocardial overload [41] and are involved in the inhibition of rennin-angiotensin-aldosterone system (RAAS) together with cardiac remodeling [42]. It is synthesized as pro-hormone namely pro-B-type natriuretic peptide (pro-BNP) and pro-atrial natriuretic peptide (proANP) which are cleaved by serum proteases to form N-terminal fragments like NTproANP or NTproBNP (in active) and C-terminal active fragments like ANP and BNP [41]. BNP and NT-proBNP are reported to increase in various cardiac diseases like mitral valve disease (MVD), DCM, and hypertrophic cardiomyopathy (HCM) hence it is used as diagnostic and prognostic markers of canine cardiac diseases [41, 43]. The level of NT-proBNP in normal and diseased dogs is presented in Table 2.

Anjos *et al.* [44] postulated the prognostic value of NT-proBNP in cardiac illness in dogs. According to his report the concentration of NT-proBNP <800 pmol/L is indicative of a low probability of heart diseases whereas, 800 1800 pmol/L of NT-proBNP indicates a high probability of heart diseases. The concentration of NT-proBNP is >1800 pmol/L in dogs with diagnosed cardiac diseases and >2700 pmol/L in congestive heart failure.

The concentration of NT-proBNP was reported to increase in non-cardiac diseases like visceral leishmaniasis (1346.0 pmol/L) [45] and Parvovirus infection [46]. It is also interesting to note that decreased NT-proBNP concentration was reported in right sided congestive heart failure (6.554 pmol/L) compared to control (510 pmol/L) [47].

Galectin-3

Galectin-3 is a protein of the β-galactoside-binding lectin family mainly associated with fibrosis and inflammation [48]. Galectin-3 stimulates fibroblasts to myofibroblasts together with increased collagen synthesis [49]. It is associated with diseases involving kidneys, liver heart, and cancer [86]. Studies in humans depicted the correlation of galectin-3 with the incidence of congestive heart failure and it can be used as a prognostic marker [49, 50]. Limited studies were conducted on the association between galectin 3 and cardiovascular diseases in dogs. The normal value of circulating plasma Gal-3 concentration in dogs was reported to be 0.64 ± 0.15 ng/mL (n=8) which can be increased up to 1.12 ± 0.83 ng/mL in cardiac diseases (n=26) [51]. A significant increase in the plasma Gal-3 concentration was reported in dogs with degenerative mitral valve disease (DMVD) [52] and patent ductus arteriosus (PDA) [51]. Plasma Gal-3 concentration had a significant positive correlation with NT-proBNP in dogs with myxomatous mitral valve disease but, no such correlation was found in PDA [51]. But, on the contrary, Klein *et al.* reported no alterations in plasma Gal-3 concentration in dogs with DMVD [7].

Interleukin 1 receptor-like 1 protein (ST2)

It is involved in T cell (CD4) activation and production of Th2 cytokines. ST2 was reported to be elevated in cardiac fibrosis in humans [53]. ST2 is a more specific cardiac biomarker than Gal-3 in humans as it is not influenced by age, sex, and other diseases [54, 55]. However, its usefulness as a cardiac biomarker in dogs is yet to be explored due to limited studies and contradictory findings. Increased plasma concentration of ST2 in dogs with DMVD was reported [7] on the contrary; Kim *et al.* reported no such alteration in chronic mitral valve disease and heart warm infestation [56].

Metabolomics

Diet-associated DCM in dogs was reported by the Food and Drug Administration (FDA) [57]. Therefore, the metabolic signature of cardiac diseases in canines could be a promising area for diagnostic and therapeutic interventions. A recent study by Smith *et al.* aimed to analyze metabolomics profiles and associate gene sets in healthy and DCM-affected dogs [14]. The research team identified a total of 63 metabolites associated with DCM in dogs. There was a significantly higher value of creatine, 4-guanidinobutanoate, fructose, N-linolenoyltaurine, and uracil and a lower value of 2-methoxyhydroquinone sulfate in DCM-affected dogs compared to healthy control.

Table 1. The concentration of cTnI in healthy and diseased dogs.

Group	cTnI (ng/mL)	References
Control	<0.05-0.12 (n=54)	[66]
	<0.03-0.07 (n=41)	[67]
	<0.02-0.15 (n=176)	[68]
	<0.006-0.128 (n=24)	[69]
	0.004-0.095 (n=22)	[70]
	<0.006-0.136 (n=30)	[71]
	<0.1-0.17 (n=26)	[72]
	<0.01-0.05 (n=58)	[73]
	0.00-0.11	[74]
Dialated cardio myopathy	0.03-1.88 (n=26)	[33]
Mitral valve disease	0.01-9.53 (n=37)	[33]
Subaortic stenosis	0.01-0.94 (n=30)	[33]
Pulmonic stenosis	0.2-55.4 (n=23)	[75]
Myocarditis	44.65 (n=1)	[76]
Cardiac hemangiosarcoma	10.7 ± 5.78 (n=18)	[77]
Pericardial effusion	0.05-124.97 (n=21)	[78]

Table 2. The concentration of NT-proBNP in healthy and diseased dogs.

Group	NT-proBNP (pmol/L)	References
Control	131-546 (n=12)	[79]
	164-430 (n=82)	[80]
	110-170 (n=13)	[81]
	55-1181 (n=11)	[82]
Heart murmur	121-2614 (n=18)	[79]
Dyspnea of cardiac origin	137-2614 (n=22)	[79]
Dialated cardio myopathy	327-1186 (n=23)	[80]
Mitral valve disease	50-110 (n=39)	[81]
Subaortic stenosis	6912-8976 (n=1)	[83]
Pulmonic stenosis	50-3000 (n=30)	[82]
Pericardial effusion	250-3297 (n=10)	[32]
Persistent truncus arteriosus	895 (n=30)	[84]

Table 3. Different cardiac biomarkers applicable in canines.

Sl. No.	Cardiac biomarker	Main features	Limitations	Possible use	References
1.	Creatine Kinase (CK)	Cytosolic enzyme predominantly found in skeletal and cardiac muscles and released during muscle and cardiac injury.	*More specific for total muscle damage than cardiac injury. *Short half-life *Wide variability of reference interval.	Diagnose and monitoring of muscle and cardiac injury	[16, 17]
2.	Lactate dehydrogenase (LDH)	Enzyme responsible for the conversion of lactate to pyruvate generally increased in hemodynamic stress in human	*Only LDH-5 isoform is most specific to heart *No variation in the LDH activity in canine DCM was reported.	General indicator of acute and chronic diseases. LDH 5 is a diagnostic marker for cardiac metabolism	[17, 21]
3.	Cardiac troponin I (cTnI)	It is a proteins involved in cardiac contraction and relaxation. Damage of cardiaomyocytes leads to release of cTnI in the extracellular space	*Wide variability in breed, age, sex hence variations in the reference range. *The storage condition also affects cTnI concentration *cTnI was reported to increase in other non -cardiac diseases. So additional tools are required to ruled out other clinical conditions.	Diagnosis of cardiac and non cardiac disaeses (babesiosis, sepsis, gastric dilatation and volvulus, brachycephalic airway syndrome and renal diseases)	[17, 33, 38,85]
4.	Natriuretic peptides (NPs)	Hormones involved in inhibition of rennin-angiotensin-aldosterone system. They are released from myocardium in response to myocardial overload.	*Increased in non-cardiac diseases like visceral leishmaniasis and Parvovirus infection	Diagonostic and prognostic markers of canine cardiac diseases	[41, 44, 45]
5.	Galectin-3	It is a protein of β-galactoside-binding lectin family mainly associated with fibrosis and inflammation.	Contradictory reports in dogs. More studies are required to establish reference intervals for different cardiac illness.	Diagnostic marker for diseases of kidneys, liver, heart and cancer	[7,48, 52, 51]
6.	Interleukin-1 receptor-like protein (ST2)	It is acytokine involved in T cell (CD4) activation and production of Th2 cytokines. It isreported to be elevated in cardiac fibrosis in human.	Limited study and contradictory findings in dogs.	It is more specific cardiac biomarker than Gal-3 in human as it is not influenced by age, sex and other diseases	[7, 53, 56]
7.	Metabolites (Creatine, 4-guanidinobutanoate, fructose, N-linolenoyltaurine and uracil, 2-methoxyhydroquinone sulfate)	Involved in diet associated cardiac illness.	Limited study in dogs	Diagnosis and prognosis of diet associated cardiac illness	[57]
8.	Genetic marker (α-cardiac actin, LDB3, myosin heavy polypeptide 7; NCX-1, canine sarcoglycan delta, miR-30b-5p)	They are mainly involved in cytoskeletal protein synthesis.	Studies in dogs revealed striking differences compared to human	Diagnosis and prognosis of congenital heart diseases	[58, 59, 60, 64]

Genetic markers

Several genes were reported to be associated with cardiac diseases in dogs and humans [58, 59, 60]. Some of these genes such as α-cardiac actin, LIMdomain binding factor 3 (LDB3), and myosin heavy polypeptide 7 were concerned with DCM as these genes are involved mainly in cytoskeletal protein synthesis [61]. Whereas, arrhythmic DCM was reported to be associated with genes encoding sodium and potassium channel [62, 63]. The cardiac Sodium-Calcium Exchanger (NCX-1) was reported to increase congenital mitral valve insufficiency in dogs [64]. The studies on the candidate genes associated with DCM in dogs revealed striking differences compared to humans. The mutation of the desmin gene (DES) was associated with DCM in humans but, not in Doberman Pinscher [60]. In a related study canine sarcoglycan delta genes were also not associated with DCM in Dobermann [60]. The circulating micro RNA namely miR-30b-5p was reported to be associated with asymptomatic myxomatous mitral valve disease in Cavalier King Charles Spaniels [65].

Activities of various canine blood cardiac biomarkers are listed in Table 3.

DISCUSSION

Researchers have investigated cardiac biomarkers associated with various heart conditions across different species. Numerous studies aim to comprehend cardiac conditions in various states and animals, seeking correlations between these findings and those in humans. However, some discoveries observed in humans have not been thoroughly examined in canines. Biomarkers like galectin-3 and interleukin 1 receptor-like 1 protein (ST2) are such examples. Cardiac tissue concentration of catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione-s-transferase, acetylcholinesterase, malondialdehyde, total thiols, etc. is measured as antioxidant biomarkers in Wistar rats [87]. However, the present study is confined to the blood biomarkers to understand the cardiac condition of canines. Blood-based cardiac biomarkers in canines emerge as an area of considerable interest together with electrocardiography, echocardiography, and thoracic radiograph. Enzymatic biomarkers such as creatine kinase (CK) and lactate dehydrogenase (LDH) have been used for a long but, but due to their wide variability and lack of specificity, they may not be a good blood-based biomarker for cardiac diseases. The most extensively studied cardiac biomarkers in canines are cardiac troponin-I (cTnI) and B-type natriuretic peptide (BNP). Recently galectin-3, a protein of the β-galactoside-binding lectin family was reported to be associated with cardiac diseases in dogs and it can be used as a prognostic marker. Interleukin 1 receptor-like 1 protein (ST2) is a good cardiac biomarker in humans but, its usefulness in dogs is yet to be explored due to limited study and contradictory findings. Metabolic signature of cardiac diseases in canines could be a promising area for diagnostic and therapeutic interventions. Recently 63 such metabolites were reported to be associated with DCM in dogs. The genetic markers such as α-cardiac actin, LIMdomain binding factor 3 (LDB3), and myosin heavy polypeptide 7 were concerned with dilated cardiomyopathy (DCM) as these genes are involved mainly in cytoskeletal protein synthesis. All these biomarkers have some merits and demerits and their usefulness depends upon collection techniques, storage of samples as well as technical expertise. The variability among breeds is also of great concern and breed-specific suitable reference intervals are worth persuading.

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