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Role of biomarkers in the diagnosis of myxomatous mitral valve disease in canines

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Abstract
This study focuses on identifying the occult stage of Myxomatous Mitral Valve Degeneration (MMVD) in dogs through the use of cardiac biomarkers. Serum NT-proBNP levels were found to be significantly higher in MMVD than in the healthy control group, suggesting an enlargement of the heart.

Keywords: MMVD, canine, mitral valve, myxomatous disease, diagnosis, biomarkers

Introduction
Heart disease is the second leading cause of premature mortality in dogs. Among geriatric canines, the most prevalent cardiac disorder is chronic mitral valve disease (CMVD), which results from myxomatous degeneration of the mitral valve (MMVD). This condition, recognized for over a century as a major cause of canine congestive heart failure, has historically been described under various terms, including *endocarditis valvularis chronica fibrosa* (*nodosa*), chronic valvular endocarditis, chronic valvular disease, billowing sail distortion of the mitral valve, endocardiosis, chronic mitral valve fibrosis, senile nodular sclerosis, mucoid degeneration, chronic myxomatous valve disease, and degenerative mitral valve disease. The earliest documentation of MMVD in dogs was reported by Delabere Blaine in 1817. According to the Munich MMVD study, valvular lesions were localized to the mitral valve in 27% of cases, while 54% involved both the mitral and tricuspid valves (Borgarelli *et al*., 2012) [3]. Among acquired heart diseases (AHDs), mitral valve disease ranks second only to dilated cardiomyopathy (DCM) in incidence. The disease occurs more frequently in small and toy breeds (Swenson *et al*., 1996) [20], with prevalence increasing with age (Bodegård-Westling *et al*., 2017) [2] and peaking between 8 and 10 years of age.
Clinically, MMVD typically presents with signs such as exercise intolerance, anorexia, coughing, syncope, and lethargy (Erling and Mazzaferro, 2008) [5]. Physical examination may reveal tachycardia, cardiac murmurs (Swenson *et al*., 1996) [20], wheezing, pulse deficits, and other abnormalities (Beardow and Buchanan, 1993) [1].
Early diagnosis and timely management are crucial to improving quality of life and prolonging survival. A variety of diagnostic techniques are currently used, including radiography (Lister and Buchanan, 2000) [12], electrocardiography (Lopez-Alvarez *et al*., 2014) [13], conventional echocardiography (Hezzell *et al*., 2012) [11], colour flow Doppler imaging (Oyama, 2004) [16], tissue Doppler imaging (Chetboul and Tissier, 2012) [4], and biomarker analysis such as NT-proBNP measurement (Wolf *et al*., 2012) [24]. However, systematic studies on rapid, point-of-care diagnostic approaches for early detection of MMVD in Andhra Pradesh remain limited. The present study, therefore, aims to evaluate rapid diagnostic tools for the early identification of mitral valve disease in dogs.

Materials and Methods
In the study period, the number of dogs brought to NTR College of Veterinary Science, Veterinary Clinical Complex and suspected cases referred from Veterinary Super Speciality

Hospital, Vijayawada constituted about 8436. Out of which 40 dogs were with signs of cardiac insufficiency

Groups of clinical study

The study comprises Group I: Apparently healthy dogs (Control group) (N=20), Group II: Mitral Valve Disease (MVD), (N=19). All the selected animals were subjected to routine clinical examination that involves physical examination as suggested by McCurin and Poffenbarger (1991) [14] and detailed cardiovascular assessment as suggested by Tilley *et al.* (1992) [21], Ware (2014) [23] and Ettinger and Feldman (2010) [6]. All enrolled cases were subjected to routine laboratory investigations, carried out in accordance with the standardised clinical protocols outlined by Gunn and Alleman (2005) [8].

Clinical presentation

The clinical examination included documentation of chief complaints, age of onset, management practices, medication history, and chronology of clinical events. Parameters such as appetite, physical activity, dyspnoea, abdominal distension, abnormal pulsations, and other relevant clinical signs were also recorded. Clinical examination further focused on identifying lethargy, weakness, exercise intolerance, syncope, diminished femoral pulse with pulse deficit, tachycardia, and evidence of progressive or refractory congestive heart failure.

Cardiac biomarker: Nt-ProBNP assay

The kits were sourced from BIOCODON, Kansas, USA for Canine Brain Natriuretic Petide ELISA Kit. The analysis was carried out according to the manufacturer's recommended procedure.

Collection of blood samples

Approximately 10 ml of blood was collected from the cephalic or recurrent tarsal vein following standard protocols for haematobiochemical analysis. Of this, 2 ml was transferred into a vial containing 10% EDTA for haematological evaluation, while 5 ml was placed in serum tubes under strict precautions to prevent haemolysis, for subsequent biochemical assays and NT-proBNP estimation.

Animals exhibiting clinical signs suggestive of cardiac disease, particularly dyspnoea and exercise intolerance, were selected for this study. Out of 40 dogs screened, 29 were randomly enrolled, along with 9 healthy controls chosen from a pool of 20. Based on assay outcomes and echocardiographic findings, the animals were categorised into three groups: Control, MMVD (occult phase; N=9), and MMVD with systolic failure (N=9). Echocardiography was performed in all 29 cases to validate the diagnostic utility of the biomarker. The data generated were statistically analysed using SPSS software (IBM Corp., Armonk, NY, USA).

Results

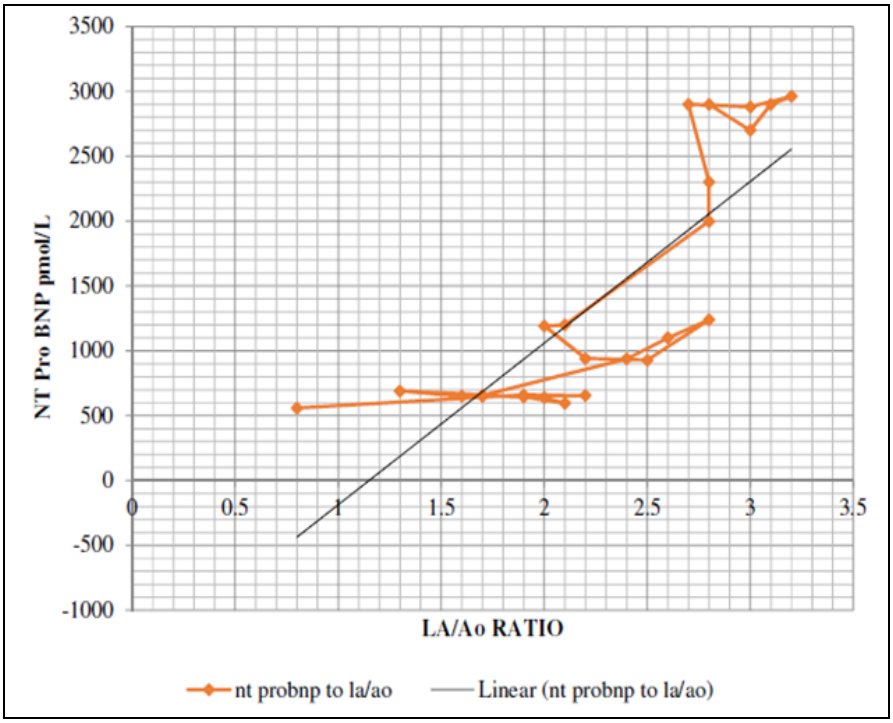
The present study was carried out at the Veterinary Clinical Complex, NTR College of Veterinary Science, Gannavaram and Veterinary Super Speciality Hospital Vijayawada 2016 to 2019.

NT-proBNP Marker Assay

The Mean ± S.D values of NT proBNP assay in control and MMVD dogs are given in Table 1, Plate 1 the Mean ± S.D values of NT proBNP assay in control, MMVD in occult phase, MVD with systolic failure, were found to be 640±36.80 pmol/L, 1192±349.96 pmol/L, 2791.84±231.40 pmol/L, respectively. A highly significant increase were observed between the groups compared with normal control group.

Table 1: NT proBNP Assay Values in Acquired Heart Diseases (MMVD) of Dogs

Marker (Assay pmol/L)	Control (N=9)	MVD dogs with occult phase (N=8)	MVD dogs with systolic failure (N=7)
NT proBNP	640.14±36.80[a]	1192.04±349.96[b]	2791.84±231.40[c]



Means showing different superscripts differ significantly between the groups $p<0.05$.

Plate 1: Correlation Graph Plotted Against LA/AO Ratio (X Axis) and NTPro BNP Values (Y Axis)-1000

Discussion

The Acquired Heart Diseases (AHDs) are the common cardiac diseases in dogs in small, medium and large breed dogs. The common AHDs in dogs were dilated cardiomyopathy, mitral valve disease, and pericardial effusion. In this, DCM is very common in medium and large breed dogs and MVD is common in small and toy breeds as per literature available. In India, more reports available in systolic failure due to myocardial and valvular diseases and very few were available on diastolic failures.

Vanderheyden *et al.* (2004) [22] reported that natriuretic peptides family contains of three major peptides, ANP, BNP, CN.-13, that participate in cardiovascular and cardiorenal homeostasis. Each of these natriuretic peptides binds differentially to specific receptors that signal through different mechanisms. Because of its fast induction and specific expression in cardiac diseases, BNP seems the most promising natriuretic peptide. It were predominantly synthesized in the cardiac ventricles, released as pre-proBNP and then enzymatically cleaved to BNP and the N terminal portion of BNP (NT-proBNP). Blood measurements of BNP and NT-proBNP had shown to identify patients with LV dysfunction. Stretching of ventricular myocardium results in the release of NT-proBNP into the circulation (Oyama *et al*, 2009) [18]. NT-proBNP were used for screening and dogs with left ventricular dysfunction, with or without symptoms. It was found that NT-proBNP was an effective and specific marker in diagnosing and categorising cardiac diseases even in occult form. These findings are in concurrence with Oyama and Singletary, (2010) [17]; Oyama *et al.* (2009) [18]; Serres *et al.* (2009) [19]; Kellihan *et al.,* (2011) [10] and Ettinger *et al.*, (2012) [7]. In this study even though NT-proBNP were found to be effective and specific marker in cardiac disease diagnosis, it has got certain limitations like sample size required, cost of the test involved and controlled lab setting. The Nt ProBNP (pmol/L) values were found to be 640±168.0, 1192.04± 349 and 2791.84±231.40 in group I, group II and group III, respectively. In the present study, in group III three dogs expired after the initiation of treatment and the values of NT ProBNP were found to be 2920 pmol/L (average of three). Though statistical analysis is not possible can be inferred that the elevated levels were often have poor outcomes.

Conclusion

The present study it was found that there exists a positive and linear correlation between NT-ProBNP levels and La/Ao ratio (correlation coefficient being +0.53). This indicates the detection of NT-ProBNP levels in serum is useful in the diagnosis of myxomatous mitral valve disease in canines.

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Conflict of Interest

There is no conflict of interest

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Reference

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