RESEARCH ARTICLE

Diagnosis of Cardiovascular Renal Axis Disorder Subtype Hin Non-azotemic dogs

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Abstract

Two types of cardiac disorders, viz Dilated cardiomyopathy (DCM) and acquired valvular disease, were diagnosed in dogs. Thirty non-azotemic dogs with clinical signs suggestive of cardiovascular dysfunction formed part of this study. Standard treatment regimens as required were administered during the study. Serum inosine, urine specific gravity, and microalbumin were the renal biomarkers evaluated to diagnose these dogs' cardiovascular renal axis disorder subtype H ($CvRD_H$). A decline in serum inosine values on day 45 as compared to day 0 was suggestive of reduced renal functional status. Lowered urine-specific gravity in these non-azotemic dogs indicated renal dysfunction. Urine microalbumin values documented were consistent with microalbuminuria,which proved to be a reliable biomarker of glomerular damage and developing nephropathy. The renal biomarkers aided in the diagnosis of $CvRD_H$ in these dogs.

Keywords: Cardiac diseases, $CvRD_H$, Microalbumin, Renal biomarkers, Serum inosine, Urine specific gravity.

Ind J Vet Sci and Biotech (2022): 10.21887/ijvsbt.18.2.22

Introduction

The cardiovascular and renal systems are a part of an axis called the cardiovascular renal axis. These systems are interlinked so that disease/dysfunction of one of the systems leads to the ongoing detriment of the other. The resultant disorders are termed cardiovascular, renal axis disorders. Cardiovascular renal axis disorder subtype H ($CvRD_H$) is described as renal damage due to primary cardiovascular diseases and their management. It is further sub-grouped into acute and chronic types (Pouchelon *et al*., 2015). Neuro-hormonal systems up-regulation, reactive oxygen species synthesis, and decreased cardiac output leading to decreased kidney perfusion could be the plausible mechanisms involved in the development of $CvRD_H$. Early detection of renal dysfunction due to cardiovascular diseases and their management is a great challenge. There is a need for specific renal biomarkers to detect kidney injury caused by cardiovascular diseases and their management, at the earliest, for better survival outcomes. Serum inosine is a functional renal biomarker and is highly sensitive to renal tubular injury (Yerramilli *et al.,* 2016). Hence, it is currently under investigation of being a potential renal tubular injury marker due to cardiac dysfunction in dogs (Orvalho and Cowgill, 2017). Urine-specific gravity estimation reflects upon the concentrating ability of the kidneys, while urine microalbumin is a marker of glomerular permselectivity. The concept of $CvRD_H$ in veterinary medicine is rather new and lacks extensive studies. The objective of this study was to evaluate the role of renal biomarkers *viz*. serum inosine, urine specific gravity and urine microalbumin in the diagnosis of $CvRD_H$ in dogs.

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How to cite this article: Ghag, R.S., Unny, N.M., Pillai, U.N., Ajithkumar, S, Martin, KD.J., & Shynu, M. (2022). Diagnosis of Cardiovascular Renal Axis Disorder Subtype Hin Non-azotemic dogs. Ind J Vet Sci and Biotech. 18(2), 105-108.

Source of support: Nil

Conflict of interest: None.

Submitted: 20/10/2021 **Accepted:** 31/01/2022 **Published:** 10/04/2022

Materials and Methods

Dogs presented to Teaching Veterinary Clinical Complex, Mannuthy, with clinical signs suggestive of cardiovascular disorders like lethargy, nocturnal cough, syncope and exercise intolerance were screened for cardiovascular disorders, irrespective of age, breed and sex. Thirty non-azotemic (serum creatinine <1.6 mg/dL) dogs with confirmed cardiovascular disorders were included in the study. The cardiac function of the selected dogs was evaluated

using thoracic radiography, electrocardiography, and echocardiography on days 0, 45, and 90. All the patients were subjected to radiographic examination of the right lateral view of thorax using Siemens X-Ray (200 mA) and CarestreamImagesuite Vita CR. An echocardiography was performed using Estate My Lab 30 vet Gold with a multi-frequency cardiac probe. M-mode and 2D echocardiography and Colour Flow Doppler were performed. Non-invasive blood pressure monitoring was carried out using the BP-Accugardoscillometric digital blood pressure apparatus. Blood and urine samples from all dogs were collected on days 0, 45, and 90. Serum biochemical parameters viz. total protein and albumin, blood urea nitrogen, creatinine (SCR), and phosphorous were assessed using standard kits. Serum inosine was estimated using Thermoscientific Dionex UltiMate 3000 ultra-high performance liquid chromatography unit. Urine-specific gravity was estimated using the refractometer having a scale reading from 1.000 to 1.060. Microalbumin-turbilatex quantitative turbidometric test was used for the measurement of microalbumin. In all the dogs with DCM and stage C CVHD, treatment was started from day 0 with enalapril @ 0.25 mg/kg b.wt. PO BID, furosemide @ 2 mg/kg b.wt. PO BID, pimobendan @ 0.2 mg/kg b.wt. PO BID, one hour before food and cardiac supplement, cardiosupport® @ 1tab/10 kg b.wt. and two tablets in divided doses for more than 10 kg. Dogs with stage B2 MVD were treated with enalapril @ 0.25 mg/kg b.wt. PO BID, furosemide @ 2 mg/kg PO BID and cardiac supplement, cardiosupport® @ 1 tab/10 kg b.wt. and two tablets in divided doses for more than 10 kg b.wt. Data recorded from the clinical study was analysed statistically with repeated measures of ANOVA, using SPSS version 24.0.

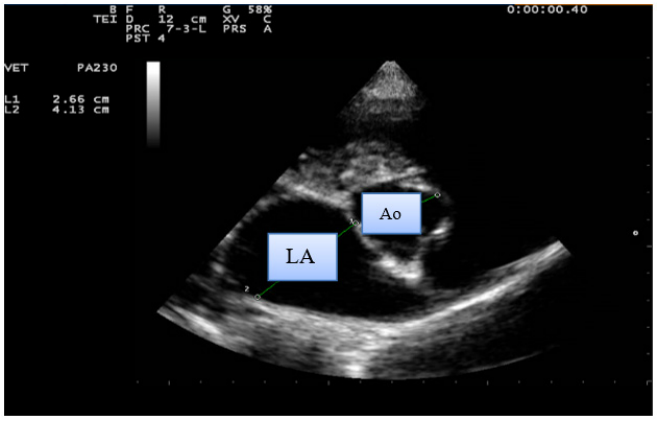

Fig. 1: Increased LA : Ao – Right parasternal short axis view

Results and Discussion

The results revealed that based on clinical signs and findings of electrocardiography, radiography and echocardiography, dilated cardiomyopathy and acquired valvular disease was diagnosed in 36.6% (11/30) and 63.33% (19/30) dogs respectively. Out of the 19 dogs diagnosed with acquired valvular disease, 15 (78.94%) had stage B2 mitral valve disease (MVD) and four dogs (21.05%) had stage C chronic valvular heart disease (CVHD).

The echocardiographic parameters *viz*. left atrium aorta (LA/Ao) ratio, E point to septal separation (EPSS), ejection fraction (EF), and fractional shortening (FS) values of dogs with DCM and valvular disease are presented in Table-1. Gross enlargement of cardiac chambers and an increase in LA/Ao ratio was evident in dogs with DCM (Fig 1). The dogs with DCM in this study had consistent low values of EF and FS characteristic of systolic dysfunction. Thinning of the left ventricular free wall, interventricular septum, and ventricular hypokinesis was also documented in these cases. These findings corroborated well with Oyama (2016), who documented such echocardiographic changes in advanced occult to overt DCM. In dogs with the valvular disease, LA/Ao ratio was elevated throughout the study. The EF values of dogs in this group were within the normal range, while the FS values showed an increment during the study period. The FS values of these dogs observed on day 90 were significantly increased from those observed on day 0 and day 45. Elongation of anterior leaflets of mitral and tricuspid valves was also detected. Chetboul and Tissier (2012) opined that as the chronicity of degenerative MVD increased, cardiac remodeling, increased left ventricular filling pressure, pulmonary hypertension, and myocardial dysfunction set in. In dogs suffering from DCM and valvular disease, mild, moderate, and severe degrees of regurgitation into the atrium across the atrioventricular valves were observed in color Doppler studies.

Throughout the study, radiography revealed elevated vertebral heart score (VHS) values in dogs with DCM. Enlarged, globoid, and obscured cardiac silhouette, straightened left

Table 1: 2-D Echocardiography parameters in dogs with DCM and Valvular disease

	DCM (MEAN ± SE)			*Valvular disease (MEAN ± SE)*		
Parameter	*DAY 0*	*DAY 45*	*DAY 90*	*DAY 0*	*DAY 45*	*DAY 90*
LA: Ao	2.05 ± 0.21	2.06 ± 1.8	2.02 ± 0.91	1.65 ± 0.08	1.74 ± 0.09	1.74 ± 0.08
EPSS (mm)	6.09 ± 0.98	5.09 ± 0.97	6.05 ± 0.98	5.29 ± 0.66	5.31 ± 0.70	5.32 ± 0.73
FS (percent)	23.55 ± 1.40	24.09 ± 1.35	25.27 ± 1.23	30.79 ± 0.81[a]	31.21 ± 1.01[a]	32.74 ± 0.90[b]
EF (percent)	31.55 ± 1.78	31.28 ± 1.98	33.82 ± 2.04	59.0 ± 1.95	59.94 ± 1.78	60.84 ± 1.87

Mean ± S.E. bearing different superscripts differ significantly within the groups.

cardiac border, rounded right cardiac borders, loss of caudal waist, and increased sternal contact were the evident changes documented on thoracic radiography (Fig. 2). At the end of the study period, one dog developed pericardial effusion, which was appreciated as a sharp border of the cardiac silhouette. Johnson *et al.* (2008) stated that a blur of the beating heart is appreciated on the radiograph in healthy conditions. This blur disappeared in this patient due to the fluid-filled pericardium around the heart. A bronchial pattern seen as doughnuts and diffuse interstitial pattern were the prominent patterns documented in DCM dogs' caudal - dorsal lung lobe. Two dogs with pleural effusion showed an alveolar pattern in the cranio-ventral lung lobe and air bronchogram in the caudo-dorsal lung lobe. Dogs with the valvular disease had increased VHS values in the study. Keene *et al.* (2019) advocated using thoracic radiography in dogs with myxomatous mitral valve disease in stages as early as stage B to visualize the haemodynamic changes and the concurrent tracheal bronchial disease. Tracheal elevation at the right atrial level and the right heart border rounding were observed in dogs with stage C CVHD. The lung patterns more pronounced in dogs with valvular disease of this study were bronchial and vascular patterns.

Four animals had mild risk, and five animals had a moderate risk of developing target organ damage (TOD) at the start of the study, as evidenced by systolic blood pressure measurements. Four dogs each had a mild and moderate risk of TOD as indicated by diastolic blood pressure measurements. Except for two cases in which the diastolic values were above the limit, the values were reduced to the minimal criteria for developing TOD in all other cases. Brown *et al.* (2007) gave the classification of blood pressure based on the risk of development of future TOD. Dogs with systolic and diastolic blood pressure < 150 mm Hg and < 95 mm Hg, respectively, were at minimal risk. The criteria for mild risk was a systolic blood pressure of 150–159 mm Hg, diastolic being 95–99 mm Hg. The moderate risk criteria were 160–179 mm Hg systolic and 100 - 119 mm Hg diastolic pressure. While the high-risk criteria were systolic and diastolic blood pressure of ≥ 180 mm Hg and ≥ 120 mm Hg, respectively

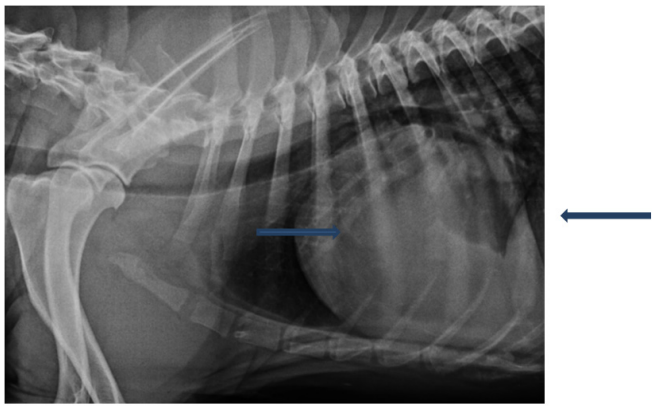

Fig. 2: Rounding of right cardiac border and straightened left cardiac border suggestive of cardiomegaly

The albumin values documented in this study indicated mild hypoalbuminemia. The blood urea nitrogen and sCr values of all dogs were within the normal range on day 0. One dog each diagnosed with MVD and DCM, had an elevation in sCr value on day 45 and day 90, respectively. Hyperphosphatemia recorded in six animals during the course of the study could be attributed to remodeling of major endocrine systems and/or calcification of vasculature. The serum biochemistry parameters are given in Table-2.

The potential renal biomarkers of $CvRD_H$ *viz.* serum inosine, urine specific gravity, and microalbumin values are stated in Table-3. A decline in serum inosine values on day 45 and day 90, from day 0, suggestive of reduced renal functional status. Serum inosine is an absolute origin from renal tubular epithelia and is associated with the energy metabolism pathway. There is active renal tubular injury-causing depletion of inosine in an acute episode of cardiac dysfunction or precipitous worsening of cardiac function. The mean value of inosine increased by day 90 but remained below that of day 0. This indicated that renal function was below pre-treatment levels. The lowest value of serum inosine recorded on day 0 in one dog was 5.71 µg/mL. This dog was suffering from stage C CVHD. However, all the

Table 2: Serum biochemical parameters in dogs on days 0, 45 and 90

Parameters	*Day 0*	*Day 45*	*Day 90*
Total protein (g/dL)	5.78 ± 0.12	5.85 ± 0.09	5.92 ± 0.08
Albumin (g/dL)	2.47 ± 0.07	2.51 ± 0.05	2.54 ± 0.06
Blood urea nitrogen (mg/dL)	19.01 ± 1.40	17.98 ± 1.44	17.46 ± 1.04
Creatinine (mg/dL)	1.11 ± 0.05	1.20 ± 0.06	1.17 ± 0.04
Phosphorous (mg/dL)	4.16 ± 0.21	4.31 ± 0.20	4.34 ± 0.22

Table 3: Renal biomarkers values in dogs on days 0, 45 and 90

Parameters	*Day 0*	*Day 45*	*Day 90*
Inosine (µg/mL)	17.67 ± 1.39	14.78 ± 1.11	16.86 ± 1.30
Urine specific gravity	1.000-1.025	1.000-1.025	1.010-1.025
Unrinemicroalbumin (mg/dL)	12.45 ± 4.76	7.12 ± 3.20	5.32 ± 2.79

values were within the normal limits,>2 µg/mL (Orvalho and Cowgill, 2017).

On day 0 and day 45, the urine specific gravity ranged from 1.000 - 1.025, while on day 90, it was between 1.010 – 1.025. The normal urine-specific gravity in dogs is > 1.020. The lowered urinary specific gravity observed in dogs of this study, which suggests submaximally concentrated urine, is a direct indicator of reduced renal function. Underlying chronic kidney disease could be a possible etiology for lowered urine concentration, leading to reduced specific gravity (Chew *et al.,* 2011).

The mean estimated day 0 value of urine microalbumin was 12.45 ± 4.76 mg/dL. It decreased to 7.12 ± 3.20 mg/dL on day 45 and further decreased to 5.32 ± 2.79 mg/dL on day 90. These values were consistent with microalbuminuria throughout the study. Grauer (2007) concluded that microalbuminuria is a reliable biomarker of glomerular damage and developing nephropathy in dogs. It highlights the hemodynamic and neuroendocrine interaction of renal tubules and glomerulus with cardiac muscles and vessels. Thus, the occurrence of $CvRD_H$ in the dogs of this study is established.

The decreasing trend in urine microalbumin values in the present study is an indication of improvement in renal function as treatment progressed. The control of microalbuminuria achieved in the dogs in this study is attributed to the angiotensin-converting enzyme inhibitor enalapril and aldosterone receptor blocker spironolactone used as a part of the therapeutic protocol for cardiovascular dysfunction. This could also be due to the resolution of the microalbuminuria after the venous congestion was cleared in the dogs on treatment with diuretics (Grauer, 2009).

Conclusion

Cardiovascular dysfunction and its management, through various mechanisms, cause renal dysfunction. Microalbuminuria and lowered urine specific gravity recorded in non-azotemic dogs were indicators of renal dysfunction. An evaluation protocol comprising estimating sCr, albumin, phosphorous, urine specific gravity, urine microalbumin, and systemic blood pressure evaluation could be carried out in animals with cardiac disease to diagnose $CvRD_H$.

Acknowledgments

The authors acknowledge the authorities of Kerala Veterinary and Animal Sciences University for the facilities provided.

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