The Haryana Veterinarian (March, 2023) **62(SI),** 52-55 ISSN 0033-4359 (P) **Research Article**

ASSESSMENT OF CARDIAC FUNCTIONING BY MEASUREMENT OF ECHOCARDIOGRAPHIC INDICES AND CARDIAC BIOMARKERS IN DOGS WITH CHRONIC RENAL FAILURE

SHABNAM SIDHU*, S. K. UPPAL, NEETU SAINI, SUSHMA CHHABRA AND DHEERAJ GUPTA
Department of Veterinary Medicine,
Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana-141004, India

Received: 20.05.2022; Accepted: 06.02.2023

ABSTRACT

Patho-physiological interactions between heart and kidneys have been termed as the cardio-renal syndrome. Cardiac disease secondary to kidney ailments is the leading cause of death in human patients with chronic kidney disease (CKD). The presence of clinical changes in cardiac morphology are not much studied in dogs with severe chronic kidney disease. The present study was undertaken with an objective to evaluate the cardiovascular function with the help of echocardiography and cardiac biomarkers in fourteen dogs with chronic renal failure presented at Teaching Veterinary Hospital, GADVASU, Ludhiana. Fourteen dogs with CKD (n= 1 IRIS stage 3, n= 13 IRIS stage 4), and 17 healthy adult dogs were included for the comparative study between the healthy and CKD patients. All the dogs under went for hemato-biochemical estimation, standard echocardiography and measurement of N-terminal pro-B-type natriuretic peptide (NT-proBNP). In the result, dogs with CKD had decreased hematocrit and significantly increased NT-proBNP values while compared to controls ($P < 0.05$). Majority of the dogs (n-13) were in IRIS stage 4. The most common abnormality upon M-mode echocardiography in CKD was the hypertrophy of the left ventricle (8/14, 57.14%). Similar to humans, LV hypertrophy can be a myocardial change in some dogs with chronic renal failure hence conducting M-mode echocardiography in CKD patients will be helpful in the early detection of any cardiovascular damage. Diagnosis like minor increase in the dimensions of the left ventricular posterior wall at an very early state may be a crucial example for the decision making in regards to prognosis.

Keywords: Biomarker, Chronic kidney disease, Echocardiography, Left ventricular hypertrophy

How to cite: Sidhu, S., Uppal, S.K., Saini, N., Chhabra, S. and Gupta, D. (2023). Assessment of cardiac functioning by measurement of echocardiographic indices and cardiac biomarkers in dogs with chronic renal failure. *The Haryana Veterinarian* **62(SI)**: 52-55.

Chronic renal failure (CRF), including end-stage renal disease (ESRD), is a major concern worldwide and is associated with high morbidity and mortality rates. In addition to CRF, cardiovascular disease is another major cause of mortality in these subjects (Chena *et al.*, 2018). Due to their roles in fluid balance, blood pressure management and tissue perfusion, the physiology of kidney and heart is intertwined (Kingma *et al.*, 2017). Cardiorenal syndrome is defined as disorders of the heart and kidneys in which dysfunction of one organ may induce poor functioning/ disease in the other (Rangaswami *et al.*, 2019). Cardiac dysfunction is associated with a poor prognosis in patients with renal failure and vice versa, an increasing amount of research has focused on the patho-physiological link between a failing heart and the kidneys (Ronco, 2010). Prevention and treatment of cardiovascular disease are major considerations in the management of individuals with chronic kidney disease. Cardiac diseases like left ventricular hypertrophy (LVH) and congestive heart failure (CHF) is common in human patients with chronic kidney disease (CKD). LVH has been found in 47% human patient suffered with CKD who has not considered dialysis as therapeutic management, with a higher prevalence and more severe LVH in those patients with increasingly lower degrees of kidney function (Park, 2012). Canine NT-proBNP appears to be a useful marker of the presence of cardiac disease, although concentrations must be interpreted in the status of the patient's renal function. Increasing creatinine concentration has been found associated with increasing concentration of NT-proBNP (Pelander *et al.*, 2017). It is suggested that in patients with increased serum creatinine concentrations, results of NT-proBNP should be carefully interpreted.

A single pilot study could be traced from the available literature on echocardiographic measurements in dogs with moderate chronic renal failure (Hezell *et al.*, 2020). Keeping in view the close association between renal failure and cardiac functioning and the scarcity of available literature on the topic, the primary aim of this study was to evaluate the echocardiographic changes in dogs suffering from chronic kidney disease which may help in predicting the prognosis of such cases. Secondarily, the study was aimed at evaluating the NTproBNP levels in dogs suffering from chronic kidney disease with altered echocardiographic measurements.

MATERIALS AND METHODS

Thirty one dogs, irrespective of age, breed and sex brought to the Teaching Veterinary Hospital, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, India were selected for this study. Fourteen dogs with signs of vomiting, hypersalivation, melena, oliguria, Polyuria and polydypsia (PU and PD) were hypothesized to be suffering from chronic renal failure. History, signalment and physical examination findings were documented in

*Corresponding author: vetsidhu@gmail.com

clinical case record. Blood was aseptically collected from the cephalic or recurrent tarsal vein after proper restraining of the animal. Two ml of blood was collected in Na2 EDTA vials for haematological examination (ADVIA ® 2120, Hematology system, Siemens Healthcare diagnostics Inc., USA). Five ml of blood was collected for serum extraction and serum biochemical analysis was done with Vitros DT 350 Chemistry system (Ortho Clinical Diagnostics, Johnson & Johnson Company) by using Vitros DT slides. Cardiac biomarker (NTproBNP) was estimated with IMMULITE 1000 Immunoassay System-Siemens Healthineers, which works on the principle of indirect ELISA.

In present study, 2D and M mode echocardiographic examinations of dogs were carried out using GE Logiq P5 Color Doppler machine using a5S sector probe. Dogs were consecutively positioned in right and left lateral recumbency. All echocardiographic measurements were made on conscious dogs inaccordance with the guidelines of the American Society of Echocardiography (Boon 2011). From the right parasternal long-axis M-mode view, the following variables were obtained: interventricular septal thickness (IVS), left ventricular internal diameter (LVID), and left ventricular posterior wall thickness (LVPW) in diastole and systole. The variables were obtained from 2D views i.e. AO and LA from right parasternal short-axis view. The following variables were calculated: left atrial-to-aortic root ratio (LA/Ao), fractional shortening (FS%), left ventricular ejection fraction (EF%), end systolic volume (ESV) and end diastolic volume (EDV). Seventeen healthy dogs without any clinical signs of cardiac disease, irrespective of age, breed and sex were included in the study for comparison with the diseased dogs.

The statistical analysis was done for each response variable with the help of 't' test by using the software SPSS-16.

RESULT AND DISCUSSION

A summary of the physical examination, haematological, routine biochemical testing and cardiac biomarkers is shown in Table 1. Clinical presentation of diseased animals revealed that all the dogs had anorexia (14), followed by vomition (12), melena (6), oliguria (5), polyuria (3) polydypsia (3), occular discharge (2), hypersalivation (2) and facial swelling (1). Increased levels of serum creatinine (2-20.1 mg/dL) and blood urea nitrogen (42-234 mg/dL) were noticed in all the diseased dogs included in this study (Sidhu *et al.*, 2018). Out of 14 diseased dogs in our study, majority of the dogs i.e. n=13 were in the stage 4 of renal failure, with just one dog in stage 2 as per IRIS guidelines. In 12 out of 14 (85.7%) dogs, an increase in hematocrit levels was noticed with values ranging from 19.1% to 41.2%. Most common hematological change in dogs with chronic kidney disease was normochromic and normocytic anemia (11/14) and similar findings were also reported in previous studies by Kralova *et al.*, 2010 and Sidhu *et al.*, 2018.

NTproBNP values of dogs affected with renal failure were significantly higher than the apparently healthy dogs in the present study (Table 1). Schimdt et al. (2009) reported significantly high NTproBNP levels as 617 pmol/L (260-1467 pmol/L) in renal disease as compared to healthy control dogs (261 pmol/L, 225-303 pmol/L) concluding that renal function should be considered when interpreting NTproBNP levels. A weak negative correlation has been found between GFR and NTproBNP levels i.e. decreased GFR is associated with increased plasma NTproBNP concentrations in dogs, similar to that in humans (Miyagawa *et al.*, 2013). Increased NTproBNP in patients with renal failure is probabaly because of decreased excretion by the kidney which appears to be responsible for plasma clearance (Hall 2005). Hezell *et al.* (2020) also reported significantly increased NTproBNP in dogs with moderate CKD at the time of enrollment that could be due to increased production or decreased excretion, both of which stand true in the current scenario.

2-D and M-mode echocardiography was performed in all the cases confirmed with renal failure along with 17 healthy animals. The various M-mode measurements are depicted in Table 2. The values of M-mode echocardiographic parameters in renal failure cases were compared with normal dogs and it was observed that maximum number of dogs (8) had LVPWd and LVPWs were more than the normal range found for apparently healthy mixed breed dogs, followed by LA:Ao (4), LA (3), IVSd & IVSs (3) and LVIDs (2) (Table 2). From these findings it can be construed that the left ventricular posterior wall thickness increases in dogs with chronic renal failure. The Mean ±SEM values of creatinine and phosphorus of the eight dogs with increased LVPW were 10.17±1.11mg/dL and 11.76±1.08 mg/dL i.e. they were in the stage 4 of chronic renal failure as per IRIS guidelines (Boyd *et al.*, 2010). In the present study, the salient echocardiographic finding was concentric hypertrophy of the left ventricle in 8 out of 14 cases of renal failure. Hypertrophic cardiomyopathy (HCM) is characterized by increased cardiac mass with a non- dilated hypertrophied left ventricle along with asymmetrical thickening of interventricular septum (Fox 1999, Philip 2003). Echocardiographic features include greater than 1.3 lateral free wall to septal thickness ratio, higher EF (92%) and FS (86%) (Kumar *et al.*, 2010). Similarly, in human patients with chronic renal insufficiency,

Table 1

Summary of dog characteristics, hematobiochemical parameters and values of cardiac biomarkers

Variable	Reference interval*	Control (n=17)	Renal failure (n=14)
Age (years)	N/A	5.47±0.74[1] (1.5-8)[2]	7.91±0.93 (2.5-14)
Body weight (kg)	N/A	20.13±4.51 (10-41)	25.93±3.69 (7-52)
Heart rate (bpm)	60-180	126.41±5.23 (96-164)	119.78±9.42 (80-202)
Systolic B.P. (mmHg)	110-160	144.76±3.31 (114-165)	146±3.42 (124-164)
Hb (g%)	10-14	15.27±.39 (12.4-17.8)	8.72±0.86** (3.6-13.8)
PCV (%)	41-58	47.73±1.7 (28.7-56)	26.4±2.44** (10.2-41.2)
BUN (mg/dL)	5-30	16.05±1.52 (7-26)	131±18.26** (42-234)
Creatinine (mg/dL)	0.8-1.6	1.22±0.06 (0.7-1.6)	9.72±1.26** (2-20.1)
Phosphorus (mg/dL)	2.8-6.1	3.83±0.18 (2.8-5.2)	11.24±1.10** (6.9-20)
NTproBNP (pmol/lit)	200-400	343.43±6.55 (308.3-394.46)	442.16±13.48** (342.56-508.65)

*Reference: (Hezzell *et al.*, 2020), [1]Mean±SEM, [2]Range, **significant difference between groups

Table 2

Summary of basic echocardiographic parameters compared between control and renal failure patients. Values are reported as Mean±SE and range

Parameter	Control	Renal failure
LVIDd (cm)	2.68±0.16 (1.55-3.65)	2.8±0.64 (0.78-3.98)
LVIDs (cm)	1.68±0.11 (0.97-2.76)	1.91±0.23 (0.39-3.5)
IVSd (cm)	0.70±0.09 (0.23-1.55)	0.54±0.09 (0.12-1.3)
IVSs (cm)	0.74±0.11 (0.16-1.86)	0.42±0.08 (0.08-1.41)
LVPWd (cm)	1.02±0.08 (0.35-1.48)	1.32±0.13 (0.37-2.24)
LWPWs (cm)	0.96±0.09 (0.27-1.44)	1.25±0.45 (0.22-1.38)
FS%	37.02±2.07 (20-83-45.42)	32.98±4.2 (12.7-59.64)
EF%	67.86±2.79 (44.12-78.45)	59.8±5.45 (34.12-88.12)
EDV (ml)	29.35±4.02 (6.59-56.28)	39.5±8.91 (3.47-122.34)
ESV (ml)	9.5±1.67 (1.89-28.45)	15.73±6.12 (2.13-51.24)
EDVI (ml/m^2)	26.3±3.47 (7.84-59.05)	43.92±7.22 (19.2-110.34)
ESVI (ml/m^2)	8.81±1.69 (2.25-29.85)	17.42±5.81 (1.89-54.38
LA (cm)	2.61±0.08 (2.07-3.26)	2.74±0.34 (1.41-3.54)
Ao (cm)	2.12±0.07 (1.4-2.62)	2.01±0.13 (1.2-2.97)
LA:Ao	1.17±0.04 (1.02-1.57)	1.35±0.97 (0.77-1.59)

left ventricular hypertrophy has a prevalence of approximately 40%, and the value that can rise up to approximately 75% by the onset of End Stage Renal Disease (Middleton *et al.*, 2001).The main causes of LVH are increased preload from hypervolemia and increased afterload from increased peripheral resistance, giving rise to a mixture of ecentric and concentric hypertrophy (Amann *et al.*, 1998). Echocardiography is the gold standard for diagnosing LVH (Granata *et al.*, 2005). The findings of our study are similar to the reports in human patients, wherein chronic cardio-renal syndrome in patients with advanced, dialysis-dependent CKD is characterized by left ventricular hypertrophy, myocardial and arterial fibrosis and coronary atherosclerosis leading to diastolic and systolic dysfunction, heart failure or sudden death (Herzog *et al.*, 2011, Tumlin *et al.*, 2013). Unlike present study findings, a recent study documents that echocardiographic measurements were similar between dogs with CKD and control group. It is important to emphasize that the cases included in their study were in stage 2 and stage 3 of CRF, whereas the majority of the dogs in present study were in stage 4 of renal failure as per IRIS guidelines. Further, the authors suggested an association between left ventricle posterior wall measurements and survival in cardiovascular disease/dysfunction that arises secondary to kidney disease (Hezzell *et al.*, 2020).

LVH is an important predictor of mortality in patients with CKD. Patients with coexistent heart failure and chronic kidney disease (CKD) have a poor prognosis, possibly related to the improper use of standard medical therapies angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) (Berge *et al.*, 2007). Hezzell *et al.* (2020) documented that with each 0.1 unit increase in LVPW thickness, the risk of mortality increased by 27% indicating a close association between LVH and survivability in dogs with chronic renal failure. This might suggest that even subtle increases in the left ventricular posterior wall dimensions are an indicator of poor prognosis in dogs with CKD. Tumlin *et al.*, 2013

suggested that in human patients, the primary reason of renocardiac syndrome is pressure overload due to the systemic hypertension. Although there was no systemic hypertension in the present study, still we found some echocardiagraphic alterations in majority of the cases, which was in contrast to the findings reported by Hezell *et al.* (2020), which explained their no change in left heart measurements because of no systemic hypertension in the cases included in their study.

Anaemia and the retention of sodium and water secondary to decreased renal function are responsible for volume overload, determining a hyperdynamic state. Severe anemia increases risk for ventricular hypertrophy, heart failure and reduced quality of life in human CKD patients (Horl, 2013). Some researchers are of the opinion that, the correction of anemia with erythropoietin in CKD patients is advantageous, since it determines LVH reduction. Other risk factors for LVH in CKD patients are documented, as mineral metabolism disorders (hypocalcemia, hyperphosphatemia, low serum vitamin D levels and secondary hyperparath-yroidism), others are non-traditional, such as oxidative stress, hyperhomo-cysteinemia and endothelial dysfunction. This in turn accelerates the process of atherogenesis, triggers the inflammation and pro-thrombotic state of the glomerular and the vascular endothelium and aggravates the process of both CKD and LVH (Taddei *et al.*, 2011).

REFERENCES

Amann, K., Rychlik, I., Miltenberger-Milteny, G. and Ritz, E. (1998). Left ventricular hypertrophy in renal failure. *Kid. Int. Suppl.* **69**: 78-85.

Berge, A.K., Duval, S., Manske, C., Vazquez, G., Barber, C., Miler, L. and Luepker, R.V. (2007). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease. *Am. H. J.* **153(6)**: 1064-73.

Chena, S.C., Huanga, J.C., Sub, H., Chiu, Y.W., Changa, J.M., Hwang, S.J. and Chen, H.C. (2018). Prognostic Cardiovascular Markers in Chronic Kidney Disease. *Kid. Blood Press. Res.* **43**: 1388-1407.

Fox, P.R. (1999). Feline myocardial diseases. In: Fox P.R., Sisson D.D., Moise N.S. (Edts). Textbook of Canine and Feline Cardiology Principles and Practice. (2nd Edn.), pp. 621-678. WB Saunders, Philadelphia.

Granata, A., Clementi, A., Virzi, A. and Hall, C. (2005). NT-proBNP: The mechanism behind the marker. *J. Card. Fail.* **11(Suppl)**: 81-83.

Herzog, R.W., Asinger, A.K., Berger, D.M., Charytan, J., Diez, R.G., Hart, K.U., Eckardt, B.L., Kasiske, P.A., McCullough, R.S., Passman, S.S., DeLoach, P.H. and Pun, E. Ritz. (2011). Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: improving Global Outcomes (KDIGO) *Kid. Inter.* **80**: 572-586.

Hezzell, M.J., Fostera, J.D., Oyamaa, M.A., Buchd, J., Faraced, G., Quinnd, J.J. and Yerramillid, M. (2020). Measurements of echocardiographic indices and biomarkers of kidney injury in dogs with chronic kidney disease. *Vet. J.* **255**: 105420.

Horl, W.H. (2013). Anaemia management and mortality risk in chronic kidney disease. *Nat. Rev. Nephrol.* **9**: 291-301.

Kingma, J.G., Simard, D., Rouleau, J.R., Drolet, B. and Simard, C. (2017). The physiopathology of cardiorenal syndrome: A review of the potential contributions of inflammation. *J. Cardiovascul. Dev. Dis.* **4(4)**: 21.

Kralova, S., Leva, L. and Toman, M. (2010). Changes in lymphocyte function and subsets in dogs with naturally occurring chronic renal failure. *Can. J. Vet. Res.* **74(2)**: 124-129.

Kumar, K.S., Nagaraj, P. and Kumar, V.V.V.A. (2010). Hypertrophic cardiomyopathy in 12 dogs (2004-2008): first report in India. *Vet. Arch.* **80**: 491-498.

Middleton, R.J., Parfrey, P.S. and Foley, R.N. (2001). Left ventricular hypertrophy in the renal patient. *J. Am. Soc. Nephrol.* **12**: 1079-84.

Miyagawa, Y., Tominaga, Y., Toda, N. and Takemura, N. (2013). Relationship between glomerular filtration rate and plasma N-terminal pro B-type natriuretic peptide concentrations in dogs with chronic kidney disease. *Vet. J.* **197**: 445–450.

Park, M., Hsu, C.Y., Li, Y., Mishra, R.K., Keane, M., Rosas, S.E., Dries, D., Xie, D., Chen, J., He, J., Anderson, A., Go, A.G. and Shlipak, M.G. (2012). Chronic renal insufficiency cohort (CRIC) study group. *J. Am. Soc. Nephrol.* **23(10)**: 172.

Pelander, L., Haggstrom, J., Ley, C.J. and Ljungvall, I. (2017). Cardiac Troponin I and Amino-Terminal Pro B-Type Natriuretic Peptide in Dogs with Stable Chronic Kidney Disease. *J. Vet. Int. Med.* **31**: 805–813.

Philip, R.F. (2003). Hypertrophic cardiomyopathy. Clinical and pathological correlates. *J. Vet. Cardiol.* **5(2)**: 39-45.

Rangaswami, J., Bhalla, V., Blair, J.E.A, Chang, T.I., Salvatore Costa, M.S., Lentine, K.L., Lerma, E.V., Mezue, K., Molitch, M., Mullens, W., Ronco, C., Wilson Tang, W.H., McCullough, P.A. (2019). Cardiorenal syndrome: Classification, pathophysiology, diagnosis and treatment strategies: A scientific statement from the American Heart Association. (Ref) **139(16)**: 840-878.

Ronco, C. (2010). Cardiorenal syndromes: Definition and classification. *Contr. Nephrol.* **164**: 33-38.

Schmidt, M.K., Reynolds, C.A., Estrada, A.H., Prosek, R., Sleeper, M.M. and Oyama, M.A. (2009). Effect of azotemia on serum N-terminal proBNP concentration in dogs with normal cardiac function: a pilot study. *J. Vet. Cardiol.* **11**: 81-86.

Sidhu, S., Uppal, S.K., Chhabra, S., Kumar, A. and Bansal, B.K. (2018). Haemato-biochemical aspects in chronic renal failure in dogs. *Ind. J. Can. Pract.* **10(2)**: 101-103.

Taddei, S., Nami, R., Bruno, R.M., Quatrini, I. and Nuti, R. (2011). Hypertension, left ventricular hypertrophy and chronic kidney disease. *Heart Fail. Rev.* **16(6)**: 615-620.

Tumlin, J.A., Costanzo, M.R., Chawla, L.S., Herzog, C.A., Kellum, J.A., McCullough, P.A. and RoncoCardio, C. (2013). Cardio renal syndrome Type 4: Insights on clinical presentation from the elevnth consensus conference of the acute dialysis quality initiative (ADQI) contributions to nephrology. **182**: 158-173.