Research Article

Evaluation of Renal Functions in Cats with Cardiomyomyopathy

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Abstract

This study was carried out to evaluate the effects of heart failure due to cardiomyopathy on renal function in cats. For this purpose, physical examination, haematological and biochemical analyses, radiographic, electrocardiographic and echocardiographic imaging and cases were systematically investigated. The study material consisted of 25 cats in two different groups, the study group consisting of cats with cardiomyopathy (n:15) and the control group consisting of healthy cats (n:10).

N-terminal pro B-type natriuretic peptide (NT-proBNP) levels were significantly increased in cats with cardiomyopathy ($P<0.05$) and this increase was significantly correlated with left atrial diameter (LA), ventricular wall thickness (LVPF) and pulmonary artery flow velocity (PAVmax) determined echocardiographically (ECHO). In the renal parameters, especially SDMA was found to reflect the early renal effects than creatinine and BUN, which are classical renal markers, and an increase in SDMA values was found ($P<0.05$). In addition, SDMA showed significant correlations with some erythrogram and thrombogram parameters, suggesting its effects on haematopoiesis.

In conclusion, in this study, it was observed that cardiomyopathy-induced renal functions were affected early and significantly in cats. The use of biomarkers such as NT-proBNP and SDMA integrated into classical methods is important for early diagnosis and development of appropriate treatment strategies.

Keywords: Cardiomyopathy, Cat, Heart Failure, Kidney Damage, NT-ProBNP, SDMA.

INTRODUCTION

The heart and kidney are two vital organs that play a central role in maintaining the homeostatic balance of the organism. The physiological interaction between these two organs can turn into a bidirectional cycle of deterioration in pathological conditions. An acute or chronic dysfunction in the heart or kidney causes the functions of the other organ to be negatively affected (Bilgiç et al., 2012). In the clinical practice of veterinary medicine, especially in cats, cardiac and renal diseases are frequently observed simultaneously, which necessitates a multidisciplinary approach. Identification of cardiac and renal damage, grading according to the International Renal Interest Society (IRIS) and development of appropriate treatment strategies accordingly are of great importance in terms of both prognosis and success of patient management (IRIS, 2023). With this study, it was aimed to determine renal involvement in cardiac patients, to reveal its place in the

context of veterinary medicine, especially in feline patients, and to provide a comprehensive evaluation based on the literature for the management of cardiac and renal involvement. Therefore, this study provides the basis for an in-depth examination of the anatomy and physiology of the heart and kidney and understanding the pathological interaction between these two systems. In this context, structural and functional classification of the heart, stages of heart failure according to the American College of Veterinary Internal Medicine (ACVIM) system, common cardiomyopathies in cats: Hypertrophic cardiomyopathy (HCM), hypertrophic obstructive cardiomyopathy (HOCM), restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM) and unclassified cardiomyopathy (UCM), and the effects of cardiac failure on the kidneys were systematically analysed. This suggests an overlap between cardiovascular and renal disease. The haemodynamic interactions of heart and kidney failure, the impact on arterosclerotic disease in both organs and neurohormonal activation are some of the few examples of overlap (Bullettin, 2014).

In this study, various biochemical, hormonal and imaging-based diagnostic parameters were used to demonstrate the presence and clinical significance of cardiomyopathy-induced renal involvement in cats. Specific and general biochemistry indicators such as Symmetric Dimethyl Arginine (SDMA), Blood Urea Nitrogen (BUN) and Creatinine (CRE) and sodium-potassium-chlorine (NA-K-CL) were analysed to evaluate renal function. These parameters were used to determine early and late renal dysfunction by reflecting the glomerular filtration rate (GFR). N-terminal pro B-type natriuretic peptide (NT-proBNP) level, which is a diagnostic and prognostic indicator of cardiomyopathy, was preferred to evaluate myocardial tension and fluid overload. Radiologically, vertebral heart score (VHS) was calculated by thoracic radiography, thus the presence of cardiomegaly was objectively determined. In addition, structural abnormalities of the heart (left atrial enlargement, ventricular hypertrophy and systolic function) were evaluated by echocardiographic (ECHO) examinations. This multifaceted diagnostic approach allowed both the description and classification of the clinical picture of cardiomyopathy and renal involvement. In addition, neurohormonal activation, cytokine response, renin angiotensin aldosterone (RAAS) action, oxidative stress and central nervous system (SNS) mediated physiopathological processes were examined in detail.

One of the most prominent reactions in this process is characterised by an increase in sympathetic nervous system (SNS) activity and a marked decrease in parasympathetic (vagal) tone. However, the renin-angiotensin-aldosterone system (RAAS) is activated and antidiuretic hormone (ADH) release increases (Sarıl, 2021). These neurohormonal changes initially show compensatory effects in heart failure states. The aim is to correct acute hypotension and hypovolemia by increasing body fluid volume and vascular tone. Although compensatory mechanisms contribute to restoring circulatory balance in the short term, the situation is reversed when they are activated for a prolonged and sustained period. The load on the heart increases, the vascular system deteriorates and a chronic cycle of decompensation develops. Therefore, neurohormonal responses, which are beneficial at first, become detrimental over time and negatively affect kidney function as well as the cardiovascular system (Sarıl, 2021).

In conditions such as heart failure, volume overload causes an increase in central venous pressure. This increase leads to congestion in the renal veins, an increase in intra-abdominal pressure and consequently a decrease in glomerular filtration rate (GFR). Decreased GFR causes further activation of the RAAS and sympathetic nervous system. However, this increased activity paradoxically further decreases the GFR, leading to impaired renal function. Thus, a reciprocal relationship of structural and functional damage begins between the heart and kidney and this relationship turns into a chronic vicious cycle over time (Jois and Mebazaa, 2012).

Materials and Methods

The material of this study consisted of a total of 25 cats of different breeds, age, sex and body weight. On the basis of cardiological examination, they were classified according to the ACVIM grading system (Keene et al., 2019) and evaluated in two different groups. In this context: Control group (n=10) and test group (n=15). The test group consisted of cats with cardiomyopathy that was detectable and diagnosable at the symptomatic level based on examination results, which were brought to the Internal Medicine Clinic of the Animal Hospital at Kırıkkale University Faculty of Veterinary Medicine by their owners, who assumed responsibility for all diagnostic and treatment costs. The control group consisted of healthy cats.

This study was evaluated by Kırıkkale University Animal Experiments Local Ethics Committee (Number no: E-60821397-605-341747) within the scope of "Clinical applications for diagnosis and treatment purposes" specified in the "k" clause of Article 8 of the Regulation on Working Procedures and Principles of Animal Experiments Ethics

Committees.

The selection of the cases included in the study was based on ACVIM criteria (Keene ., 2019). Classes A and B were asymptomatic and classes C and D were symptomatic patient groups. General examination, blood ProBNP, SDMA and serum biochemical analyses, X-ray, ECG and echocardiographic examinations, hypertrophic cardiomyopathy (HCM, n=10), hypertrophic obstructive cardiomyopathy (HOCM, n=4) and unclassifiable cardiomyopathy (UCM, n=1) cases with renal involvement were included in the study.

The control group consisted of healthy cats without any complaints who were brought to Kırıkkale University Animal Hospital. Cats were examined clinically, radiologically, electrocardiographically and echocardiographically under optimum conditions and the cases which were determined to be healthy based on complete blood count, serum biochemical results and ProBNP levels (K.Ü. Veterinary Faculty Animal Hospital) were included in the study. All vital signs of the cats in the test and control groups were evaluated, standard clinical diagnosis and treatment procedures were applied and the data were recorded Thoracic radiography was performed after clinical examination of the patients, and abnormal auscultation and inspection findings diagnosed from the anamnesis were supported by radiological imaging. Two poses of thorax radiographs, lateral and ventrosorsal, were taken from each patient and the radiographic morphology of the heart, lungs and thoracic vessels were evaluated together with vertebral heart score (VHS) measurements.

ECG examination was performed with bipolar and unipolar limb leads (Carewell 1103G Veterinary ECG device) in the right parasternal recumbent position in a quiet, calm, minimal stress environment without the use of sedative agents using a properly arranged ECG and echocardiography unit in the test group cats. Cardiac rhythm analyses and ECG wave and interval measurements were performed from the second lead with a standard calibration (10 mm/mV, 50 mm/sec, DII) (Wendy, 2011).

Echocardiographic examination was performed without sedation. Cardiac measurements were obtained by transthoracic echocardiography; standard methods (two-dimensional (2-D), M-mode and colour Doppler) and imaging techniques (right parasternal short and long axis, left apical 4-5 cavity windows) were used for this purpose. In accordance with the echocardiographic examination technique, the right parasternal short-axis papillary muscle level was imaged and the LV, papillary muscles, IVS and RV structures were examined by 2-D echocardiography from the right parasternal short-axis papillary muscle level and their geometric and functional measurements were noted. In this image, LV size, IVS and LVFW were measured as cardiac geometry in systole and diastole, while functionally LV volume, %FS and %EF values at end-systole and end-diastole were calculated automatically by the device (Boon, 2011). While in this window, the aortic (Ao) level was obtained by slightly rotating the probe in the right direction and raising the wrist slightly. During this time, care was taken to ensure that the aorta was clearly visible as a central, circular structure with three leaflets (semilunar valves); the left atrium (LA) was visible at the 6-7 o'clock position, and the main pulmonary artery (MPA) was visible at the 3 o'clock position. With this image, the diameters of the Ao, LA, and MPA were measured, and the LA/Ao ratio was calculated. Dimensional and, when necessary, color Doppler measurements were performed.

Following the short axis view in the right parasternal position, the long axis 4-5 cavity view was obtained by rotating the probe clockwise to the left. Diastolic LA and RA diameters and systolic LVOT and Ao root diameters were obtained, respectively. During five-chamber imaging, M-mode measurements were performed by placing the ultrasound cursor at a 90-degree angle to the ventricular septum and tangentially passing through the apex of the mitral valve opening. Before the right parasternal position was changed, colour Doppler measurements of the MPA were performed by returning to the Ao level short axis image and PA maximum velocity and ejection times were obtained by first CW and then PW measurements (Boon, 2011).

Left apical 4-5 cavity images were preferred to evaluate the right and left atria and ventricles in terms of diameter and volume and colour Doppler characteristics of MV, TV and Ao flows were obtained in this window. Serial measurements were performed in CW and PW mode by positioning the ultrasound cursor at the peaks of MV and TV, respectively; MV and TV E/A ratios were automatically calculated by the device after scanning the flows. In the position where the left ventricular aortic outflow became clearly visible, the Ao flow characteristic was obtained with an ultrasound cursor placed parallel to the flow, and the maximum velocity and ejection times were measured from the right triangular formation below the baseline line (Boon, 2011).

These analyses consisted of serum biochemical measurements (ProBNP, Na-K-Cl, BUN, Crea) together with a complete blood count (Nx600

Biochemistry, Fujifilm and Idexx catalyst one). Blood samples (Bc60 Haemogram, Mindray) were collected from the cephalic veins of the cats using the appropriate technique in tubes with anticoagulant (EDTA) for haemogram and without anticoagulant for serum biochemical measurements.

Serum samples were analysed for electrolytes (Na-K-Cl) and markers of renal damage (blood urea nitrogen and creatinine) (Nx600 Biochemistry). SDMA was also analysed in all patients (Idexx catalyst one). Serum cardiac ProBNP was measured (Vcheck V200) and evaluated with the appropriate kit.

In the statistical analyses of the data obtained, descriptive statistics were performed and the data were tabulated as mean and standard deviation. The homogeneity of the data was evaluated using Shapiro- Wilk analysis and their normal distribution was checked. It was determined that the data that did not show normal distribution did not provide normal distribution although the transformation process was used according to Lognbase. In this context, Mann-Whitney U test, which is a non-parametric test, was used for intergroup comparisons. In addition, Pearson correlation was used to evaluate the correlations between the data obtained from echocardiographic measurements and haematological and other biochemical measurements. In all analyses, P values less than 0.05 were considered statistically significant and SPSS 29.0 (IBM, USA) was used in all analyses.

Results

Results; ACVIM heart failure classification (class B2, C and D) was established and renal effects were evaluated with parameters. Cats without a diagnosis of heart failure (class A) formed the control group (n:10) and renal effects were evaluated. A total of 25 cats of different breeds, age and sex were used in this study.

The cats included in the study were reported to have complaints of heart disease for at least 2 months (maximum 2 years). These complaints were primarily noted as exercise intolerance (12/15), lethargy (3/15), respiratory distress (5/15), vomiting (6/15), polyuria-polydipsia (4/15), diarrhoea (1/15), decreased appetite (9/15), systolic murmurs (6/15) and weight loss (7/15). In physical examinations, parameters such as pallor of the mucous membranes and fullness of the jugular vein, which were recognisable on inspection due to cardiac pathologies, were added to the patient records. As a result of the analyses, although body weight averages were found to be similar between both groups, significant differences were observed in the minimum and maximum value ranges. When the mean age data were compared, the mean age of the cats in the test group (4.06 ± 4.01 years) was significantly lower than that of the control group (6.78 ± 4.15 years for the control group and 8.07 years for the maximum value) and this difference was found to be statistically significant ($p<0.05$). Within the scope of physical evaluation, vital signs such as body temperature (T°), heart rate (P), respiratory rate (R) and capillary refill time (CRT) were also recorded in both groups of cats. There was a significant difference between the T values between the groups; P and R measurements in the test group were found to be statistically significantly higher than those in the control group ($p<0.05$) (Table 1). When the vertebral heart score (VHS) was examined radiologically, a significant increase was found in the test group compared to the control group (7.75 ± 0.35 and 9.51 ± 0.70; $p< 0.001$) (Table 2).

Table 1. Signalement and some clinical findings of the control and test groups; mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
W (kg)	Control	5,8 ± 1,60	3,8 - 8,5	0,019
	Test	4,22 ± 0,97	2,3 - 5,3	
Age (year)	Control	6,78 ± 4,15	2,4 - 17	0,031
	Test	4,06 ± 4,01	0,6 - 17	
T (₀C)	Control	38,48 ± 0,36	38 - 39,1	0,016
	Test	37,48 ± 1,56	32,4 - 39	
P (min)	Control	146,40 ± 20,39	126 - 192	<0,001
	Test	207,73 ± 22,06	162 - 234	
R (min)	Control	26,00 ± 3,65	22 - 32	<0,001
	Test	40,93 ± 9,37	26 - 56	
CRT (sec)	Control	1,84 ± 0,25	1,4 - 2,2	0,103
	Test	1,62 ± 0,38	1 - 2,5	

W: Live weight T: Body temperature, P: Pulse, R: Respiration, CRT: Capillary refill time

Table 2. Vertebral heart scores (VHS) of control and test group cases; mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
VHS	Control	7,75 ± 0,35	7,2 - 8,4	<0,001
	Test	9,51 ± 0,70	8,1 - 10,6	

In ECG examination, respiratory sinus arrhythmia was detected in some (3/10) of the control group cats in which rhythm analysis was performed. In the test group, sinus tachyarrhythmia (5/15) and atrial fibrillation (4/15) as well as atrial (3/15) and ventricular premature complexes (3/15) were detected. Along with this rhythm evaluation, morphological evaluations were made and the duration and voltages of ECG waves were examined. Accordingly; left atrial dilatation (P-mitrale, 2/15), right atrial dilatation

(P-pulmonale, 3/15), left ventricular enlargement (5/15), small QRS complex formation (2/15), ST depression (2/15), pointed T wave (4/15) and left or right axis deviation (5/10) were the primary findings. In echocardiographic evaluations performed in patients with a diagnosis of heart failure, it was frequently noted that the left atrium was markedly enlarged, mitral valve prolapse findings were observed, and insufficiency flows were observed in the mitral and tricuspid valves. In addition, structural changes such as narrowing of the left ventricular outflow tract (LVOT), thickening of the interventricular septum (IVS) and left ventricular posterior wall (LVPW), as well as significant increases in the LA/Ao ratio were found. According to these findings, the IVSd value of the test group (0.60 ± 0.07 cm) was significantly increased compared to the mean in the control group (0.48 ± 0.09 cm) and this difference was found to be statistically significant ($p<0.001$). Although there was no statistical difference between the groups in systole and diastole phases of IVS measurements, LVDd and LVDs diameters were significantly higher in the test group, respectively ($p<0.01$ and $p<0.05$). Fractional shortening (FS) rate, which is a functional evaluation parameter, was significantly lower in the test group (46.21% ± 12.46%) compared to the control group (53.90% ± 9.37%) ($p<0.01$) (Table 3).

Table 3. M-mode measurements taken from the right parasternal short axis papillary muscle level in the control and test groups; mean ± standard error (cm), minimum-maximum, and p-value.

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
IVSd	Control	0,48 ± 0,09	0,29 - 0,6	0,001
	Test	0,60 ± 0,07	0,5 - 0,79	
LVDd	Control	1,49 ± 0,24	1,01 - 1,78	0,238
	Test	1,34 ± 0,27	0,96 - 1,74	
LVPWd	Control	0,55 ± 0,09	0,36 - 0,7	0,002
	Test	0,67 ± 0,07	0,52 - 0,83	
IVSs	Control	0,73 ± 0,12	0,54 - 0,94	0,978
	Test	0,74 ± 0,12	0,52 -1,03	
LVDs	Control	0,68 ± 0,14	0,44 - 0,87	0,683
	Test	0,73 ± 0,25	0,31 - 1,2	
LVPWs	Control	0,80 ± 0,12	0,62 - 1,02	0,605
	Test	0,82 ± 0,09	0,67 - 0,99	
FS %	Control	53,90 ± 9,37	34,69 - 64,77	0,091
	Test	46,21 ± 12,46	25 - 67,44	
EF %	Control	86,70 ± 7,73	68,96 - 94,17	0,129
	Test	79,00 ± 11,99	53,45 - 95,72	

RVDd - Right ventricular diastolic diameter; interventricular septum diastolic (IVSd) and systolic diameter (IVSs); left ventricular diastolic (LVDd) and systolic diameter (LVSd); left ventricular free wall diastolic (LVFWd) and systolic diameter (LVFWs); FS – fractional shortening; and EF – ejection fraction

No significant difference was found between the groups in terms of Ao and MPA diameters. However, LA diameter was significantly higher in the test group (1.57 ± 0.32 cm) than in the control group (1.20 ± 0.21 cm). In parallel, LA/Ao ratio was significantly increased in the test group (1.96 ± 0.36) and this difference was statistically significant ($p<0.01$) (Table 4).

Table 4. Right parasternal short-axis aortic diameter measurements in the control and test groups. Ao: Aorta, LA: Left atrium, and MPA: Main pulmonary artery (mean ± standard error), cm – centimeters, minimum-maximum, and p-value.

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
Ao	Control	8,14 ± 23,13	0,71 - 74	0,177
	Test	0,79 ± 0,10	0,61 - 1,04	
LA	Control	1,20 ± 0,21	0,83 - 1,57	0,003
	Test	1,57 ± 0,32	0,99 - 2,29	
MPA	Control	0,88 ± 0,08	0,81 - 1,05	0,129
	Test	0,81 ± 0,10	0,5 - 0,94	
LA/Ao	Control	1,45 ± 0,32	1,09 - 2,22	0,002
	Test	1,96 ± 0,36	1,47 - 2,5	

The maximal blood flow velocities (velocities) in the aorta and pulmonary arteries and flow profiles through the mitral (MV) and tricuspid (TV) valves were examined by colour Doppler echocardiography and the E/A ratios of MV and TV valves did not show a statistically significant difference in both groups. While the TV-E/A ratio was between 1.07 and 1.59 in the control group, this ratio was

between 0.93 and 3.1 in the test group (Table 5).

Table 5. Doppler measurements (mean ± standard error), minimum-maximum, and p-value of pulmonary artery (PA), aorta (Ao), mitral valve (MV), and tricuspid valve (TV) in the control and test groups.

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
PA Vmax, (cm/sn)	Control	78,11 ± 12,73	54,79 – 94,28	0,129
	Test	104,25 ± 45,63	36,34 - 207,64	
Ao Vmax mmHg	Control	96,81 ± 20,81	74,88 – 136,99	0,129
	Test	166,03 ± 100,90	61,72 - 378,37	
MV E/A	Control	1,23 ± 0,23	1,03 - 1,74	0,978
	Test	1,27 ± 0,45	0,79 - 2,77	
TV E/A	Control	1,25 ± 0,18	1,07 – 1,59	0,892
	Test	1,42 ± 0,68	0,93 - 3,1	

According to the leucogram data, no statistically significant difference was found between the test and control groups in terms of total leucocyte (WBC) counts and differential leucocyte distribution (especially neutrophil and lymphocyte ratios) (Table 6).

Table 6. Leukogram values (x103 / L) of control and test group cases; mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
WBC x10^9/ mL	Control	8,58 ± 3,96	4,13 - 16,6	0,196
	Test	9,88 ± 2,44	5,99 - 13,78	
Lymphocyte x10^9/mL	Control	2,60 ± 1,70	0,74 - 6,62	0,461
	Test	2,02 ± 1,31	0,38 - 4,88	
Neutrophil x10^9/mL	Control	5,49 ± 3,14	1,54 - 12,11	0,196
	Test	7,29 ± 3,18	2,30 - 12,75	
Monocyte x10^9/mL	Control	0,12 ± 0,12	0,02 - 0,43	0,338
	Test	0,17 ± 0,13	0,04 - 0,47	
Eosinophil x10^9/mL	Control	0,35 ± 0,23	0 - 0,75	0,723
	Test	0,37 ± 0,38	0 - 1,16	
Basophil x10^9/mL	Control	0,01 ± 1,82	0,01 - 0,01	0,807
	Test	0,01 ± 0,01	0 - 0,06	

However, remarkable elevations were detected in some individual samples of the test group. In particular, WBC and neutrophil counts in the test group reached 13.78/µL and 12.75/µL, respectively, which may indicate possible inflammatory or stress responses in these animals. In the erythrogram values, as in the leucogram, no statistically significant differences were detected in the averages of both groups. The erythrocyte (RBC) count, haemoglobin, haematocrit (Hct) and erythrocyte index values (MCV, MCH, MCHC and RDW) (Table 7) of the control group were within normal limits. Platelet count (PLT) and indices (PCT, MPV and PDW) were recorded as thrombogram values (Table 8). When the mean values were analysed, no statistically significant differences were found in the mean values of both groups as in erythrogram and leucogram.

Table 7. Erythrogram values of control and test group cases; mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
RBC x10 (mL)	Control	9,24 ± 1,50	6,05 - 11,66	0,567
	Test	8,26 ± 2,46	3,69 - 11,35	
HCT (%)	Control	39,38 ± 6,02	27,4 - 48	0,605
	Test	34,97 ± 10,81	17,6 - 47,8	
HGB (gr/ dL)	Control	14,01 ± 2,02	9,9 - 16,7	0,428
	Test	12,44 ± 3,88	5,9 - 17	
MCV (gr/ dL)	Control	42,80 ± 3,29	37,2 - 47,3	0,683
	Test	42,31 ± 2,92	37,6 - 47,8	
MCH (gr/ dL)	Control	15,24 ± 1,13	13,8 - 17,1	0,849
	Test	15,01 ± 1,06	13,1 - 16,7	
MCHC (gr/dL)	Control	356,40 ± 10,88	336 - 372	0,531
	Test	333,90 ± 83,11	35,5 - 372	
RDW (%)	Control	17,57 ± 0,83	16,3 - 19	0,237
	Test	18,42 ± 1,19	16,4 - 20,4	

RBC – red blood cell count; Hgb – hemoglobin; Hct – hematocrit; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; and RDW – red blood cell distribution width (shape and volume)

Table 8. Thrombogram values of control and test group cases; mean ± standard error, minimum-maximum, and P value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
Platelet x10 (mL)	Control	210,40 ± 96,58	62 - 348	0,723
	Test	207,40 ± 89,67	68 - 458	
PCT (%)	Control	2,39 ± 0,88	0,91 - 3,41	0,807
	Test	2,43 ± 1,18	0,28 - 5,54	
MPV fL	Control	12,02 ± 1,95	9,2 - 14,8	0,428
	Test	12,80 ± 1,47	10,1 - 16,4	
PDW (%)	Control	15,22 ± 0,91	13,9 - 17,1	0,397
	Test	14,99 ± 0,66	13,9 - 16,4	

Serum N-terminal pro B-type natriuretic peptide (NT-proBNP) was studied as a cardiac biomarker;

the mean value of the test group (1267.46 ± 310.84 pmol/L; p<0.001) was found to be higher than the control (70.63 ± 16.47 pmol/L) (Table 9).

Table 9. Serum NT-proBNP values of control and test group cases, mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
NT-ProBNP Pmol/L	Control	70,63 ± 16,47	50 - 98	<0,001
	Test	1267,46 ± 310,84	543 - 1500	

In terms of renal function, BUN and CREA values were significantly higher in the test group (138.2 mg/dL and 4.96 mg/dL, respectively) compared to the controls (30.3 mg/dL and 1.5 mg/dL). BUN and CREA values in the test group (63.44 ± 28.77 mg/dL, 2.51 ± 0.98 mg/dL) were significantly higher than the control group (23.68 ± 5.39 mg/dL, 1.22 ± 0.28 mg/dL). BUN and CREA data in the test group were higher (P<0.01) than those found in the control group. Other parameters analysed were electrolyte panel (sodium (NA), potassium (K), chlorine (CL)) (Table 10) and symmetric dimethylarginine (SDMA) (Table 11). Although there was no statistical significance for serum Sodium (NA) and Chlorine (CL) values between the control and test groups, the values were mostly within the reference ranges reported for cats. Potassium (K) and SDMA values in the test group (4.60 ± 0.65 mmol/L, 19.53 ± 60.03 mg/dL) were higher than the control group (4.03 ± 0.49 mmol/L, 11.40 ± 1.50 mg/dL). K and SDMA data were higher (P<0.01) in the test group compared to the control group. Although there was no statistical significance for serum Sodium (NA) and Chlorine (CL) values between the control and test groups, the values were mostly within the reference ranges reported for cats. Potassium (K) and SDMA values in the test group (4.60 ± 0.65 mmol/L, 19.53 ± 60.03 mg/dL) were higher than the control group (4.03 ± 0.49 mmol/L, 11.40 ± 1.50 mg/dL). K and SDMA data were higher (p<0.01) in the test group compared to the control group.

Table 10. Serum biochemical values of control and test group cases, mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
CREA (mg/dL)	Control	1,22 ± 0,28	0,73 - 1,5	<0,001
	Test	2,51 ± 0,98	1,73 - 4,96	
BUN (mg/dL)	Control	23,68 ± 5,39	17 - 30,3	<0,001
	Test	63,44 ± 28,77	33,2 - 138,2	
Na (mEq/L)	Control	147,50 ± 4,74	139 - 154	0,177
	Test	149,73 ± 8,67	132 - 162	
K (mEq/L)	Control	4,03 ± 0,49	3,5 - 5,1	0,016
	Test	4,60 ± 0,65	2,8 - 5,4	
Cl (mEq/L)	Control	111,70 ± 4,19	106 - 118	0,428
	Test	108,07 ± 8,93	81 - 118	

Table 11. Serum SDMA values of control and test group cases, mean ± standard error, minimum-maximum, and p-value

Parameter	Groups	Mean ± Standard Deviation	Min-Max	p
SDMA (mg/dL)	Control	11,40 ± 1,50	9 - 14	<0,001
	Test	19,53 ± 60,03	14 - 38	

Discussion

In this study, renal dysfunction due to cardiomyopathy in cats was investigated. The similarity of the anamnesis and physical examination findings obtained for the test group of this study material to previous studies (Schober et al., 2010) showed once again the importance of the diagnostic process and clinical findings related to heart failure in cats.

A weak negative correlation was found between serum creatinine level and body weight (kg) (r = -0.500, p = 0.058). This finding is within the limit of statistical significance. In cats with chronic renal failure due to cardiomyopathy, weight loss is usually associated with protein calorie malnutrition, muscle wasting and chronic catabolic processes (Ross, 2009). A low level negative correlation was found between BUN and body temperature (T) (r = -0.055, p = 0.846). Although this finding is far from statistical significance, it is important in terms of the tendency towards hypothermia that may be observed in some cases of advanced azotemia. Hypothermia may occur in cases of severe dehydration, hypoperfusion and metabolic dysfunction (DiBartola, 2012). A significant and negative correlation was found between creatinine and RBC (r = -0.568, p = 0.027). This suggests that there may be a tendency for a decrease in respiratory rate as renal function deteriorates. As chronic renal failure progresses, metabolic acidosis may develop, which may initially increase respiration, but in later

stages may suppress respiratory rate with systemic effects such as fatigue, hypoventilation and even uremic encephalopathy (DiBartola, 2012). Although a negative correlation was found between NT-proBNP and pulse rate (PR), it was not statistically significant (r = -0.208, p = 0.456). As renal function decreases, weakness and fatigue, reluctance to walk (Börkü et al., 2000), respiratory distress and dyspnoea are observed in chronic heart failure (Ware, 2011). A weak positive correlation was found between NT-proBNP and VHS (r = 0.091, p = 0.746). This finding was not statistically significant. NT-proBNP levels increase as ventricular wall tension increases, which is usually associated with cardiomegaly (Ware, 2011). A low positive correlation was found between SDMA and VHS (r = 0.252, p = 0.365). This correlation supports that renal dysfunction develops as a result of impaired renal perfusion as cardiac dysfunction progresses (Ronco et al., 2008). During ECG examination of the patients, rhythm analyses were performed; morphologically detected left atrial enlargement (P-mitrale), right atrial enlargement (P-pulmonale) and left ventricular enlargement were found to increase in R amplitude, prolongation in QRS duration and reflection on deep Q waves and became evident in patients with cardiomyopathy. Since the common clinical finding in HCM is diastolic dysfunction and the mitral valve is open in diastole, the pressure present in the LV in diastole is also present in the left atrium (LA). As a result, an increase in LV diastolic pressure causes an increase in LA pressure, and an increase in LA pressure causes LA dilatation (Kittleson and Cote, 2021). In this study, geometric and functional variations were recorded in cardiomyopathies and LA diameter was often measured higher in the test group (1.57 ± 0.32) than in the control group (1.20 ± 0.21). A positive and significant correlation was found between NT-proBNP and left atrial diameter (LA) (r = 0.579, p = 0.024). This finding supports the information described in the literature that NT-proBNP is directly related to left atrial volume and increased intracardiac pressure. A strong positive correlation was also found between NT- proBNP and LVPW (r = 0.832, p = 0.060). This indicates that left ventricular wall hypertrophy, which is characteristic of HCM, increases NT-proBNP levels (Saponaro et al., 2022). In this study, the fact that the majority of LVDd, LVDs and LA/Ao values were higher than control and reference values (Boon, 2011) in cats with cardiomyopathy revealed the geometric remodelling in the left heart. SDMA was positively correlated with left ventricular diameter (LVDd) (r = 0.404, p = 0.404). This correlation suggests the effect of decreased perfusion due to cardiomyopathy on renal function. NT-proBNP was unexpectedly negatively correlated with LA/Ao ratio (r = -0.579, p = 0.024). This result deviates from the positive correlation trend reported in the classical literature and may be explained by various physiological and methodological reasons. This is because NT-proBNP is associated not only with LA size but also with left ventricular hypertrophy, diastolic dysfunction and systemic hypertension (Saponaro et al., 2022). Accordingly, although the LA/Ao ratio is low, NT-proBNP may increase. In our study, %EF value showed variable values in the test group (79.00 ± 11.99) compared to the control group (86.70 ± 7.73) and %FS value in the test group (46.21 ± 12.46) compared to the control group (53.90 ± 9.37). The significant increase in MV-E/A and TV-E/A ratios in the test group compared to the control group was an indicator of diastolic dysfunction in cats (Smith et al., 2016). No significant correlation and significant statistical results were found between AoVmax values and biochemical markers. A significant negative correlation was found between NT-proBNP and PAVmax (r = -0.551, p = 0.033). This finding suggests that right heart volume increases with the progression of heart failure and pulmonary artery flow velocity decreases due to increased pulmonary vascular resistance. Therefore, it suggests that left heart failure may affect the right heart secondarily and this may cause an increase in NT-proBNP levels (Reinero et al., 2020). In the test material of this study, heart failure was not classified according to the etiological causes; HCM, HOCM and UCM cases, which are frequently seen in cats, were mentioned (Kittleson and Cote, 2021). We believe that this study may form an infrastructure for comprehensive studies in which the follow-up and treatment process will be planned as a different group from chronic (congestive) heart failure, which is the common and final stage of the aforementioned diseases, as well as the mentioned cardiomyopathies.

The statistically higher WBC and neutrophil counts in the test group patients compared to the control group patients suggested the presence of stress leukogram and SIRS (systemic inflammatory response syndrome). Stress leukogram is characterised by neutrophilic leukocytosis with lymphopenia, eosinopenia, monocytosis and/or basophilia (Willard, and Tvedten, 2012). A negative correlation was found between ProBNP and WBC value (r = -0.507, p = 0.054), but this finding has statistically limited significance. This may be explained by immunosuppression or chronic inflammation process. A significant positive correlation was found between SDMA and monocyte ratio (r = 0.529, p = 0.043). This finding suggests that the increase in monocytes, especially in early renal dysfunction, is a haematological reflection of systemic inflammation. The negative correlation between NT-proBNP and basophil ratio is quite strong (r = -0.708, p = 0.003), which is in line with the immune modulation

seen in heart and kidney failure reported in the literature (Weiss, 2020; Reinero et al., 2020). HGB (r = - 0.513, p = 0.051) and HCT (r = -0.506, p = 0.054) show a moderate negative correlation. This indicates that haematological structure is suppressed as renal function deteriorates. Similarly, there is a significant negative correlation between SDMA and HGB (r = -0.540, p = 0.038) and HCT (r = -0.534, p = 0.040). These findings suggest that SDMA may be a useful biomarker in the early detection of renal involvement as well as in the evaluation of the effect of renal anaemia. A significant and negative correlation was found between SDMA and MCH (r = - 0.614, p = 0.015) and MCHC (r = -0.521, p = 0.047) as well as between creatinine and MCH (r = -0.542, p = 0.037), but these did not reach statistical significance. A strong negative correlation was found between creatinine and MPV (r = -0.621, p = 0.013) and between BUN and MPV (r = -0.873, p < 0.001), as well as a similarly significant negative correlation between SDMA and MPV (r = -0.733, p = 0.002). These findings suggest that platelets become structurally smaller or undergo functional suppression as renal function deteriorates. A significant positive correlation (r = 0.597, p = 0.019) was found between SDMA and platelet count (PLT). This indicates that PLT count increases as SDMA level increases, but evaluation with platelet function tests and acute phase protein levels is necessary to clarify whether it is reactive thrombocytosis due to inflammation (Reinero et al., 2020). The high correlation between BUN and CREA values (r = 0.738, p = 0.002) is an indication of parallel deterioration in renal function. A strong and significant positive correlation was found between SDMA and creatinine (r = 0.750, p = 0.001). The negative correlation between NT-proBNP and SDMA (r = -0.357, p = 0.191) is in accordance with the model of chronic kidney disease secondary to chronic heart failure described in the literature (Chuasuwan and Kellum, 2012). Negative correlation trends were observed between creatinine and CL (r = -0.206, p = 0.443) and SDMA and CL (r = -0.195, p = 0.486). This suggests that hypochloremia may develop as renal function deteriorates and that this may be particularly associated with metabolic alkalosis or renal tubular dysfunction (DiBartola, 2012). A weak positive correlation was found between creatinine and K (r = 0.173, p = 0.173), suggesting that the tendency for hyperkalaemia may develop in parallel with progressive renal dysfunction. A moderate negative correlation was found between NT- proBNP and K levels (r = -0.499, p = 0.058). Increased aldosterone level as a result of RAAS activation causes sodium and water retention in the kidneys and increases the excretion of potassium from the distal tubule. This increases the risk of hypokalaemia, especially in patients with chronic heart failure (DiBartola, 2012). In this study, it can be said that neurohormonal haemostasis (SNS and RAAS activations) in response to cardiomyopathy in cats (Urso et al., 2015) was effective in keeping serum electrolyte levels in the test group partially within acceptable limits.

Conclusion

The complex physiopathological relationship between heart and kidney is not only limited to primary systemic involvement, but also triggers mutual loss of function with feedback effect between the organs. In this context, early evaluation of renal function, especially in cases of heart failure due to cardiomyopathy, has become critical in terms of recognition and prognosis. In this study; the findings revealed that renal involvement secondary to cardiomyopathy can be identified with multifaceted laboratory and imaging data. Since renal involvement may often be subclinical in cats with cardiac disease, it is recommended that regular screening and check- up protocols be established and disseminated in veterinary practice. In order to monitor cardiac and renal functions together, screening of new generation biomarkers such as NT-proBNP and SDMA as primary sources and their combined use with classical diagnostic tools (haemogram, biochemistry, imaging) should be integrated into standard protocols. Regular monitoring of haematological changes (nonregenerative anaemia, platelet dysfunction) in patients with cardiomyopathy and associated progressive renal failure and chronic heart failure will ensure early recognition of the multisystemic effects of the disease. Haemodynamic findings support the catabolic effects of heart failure on circulation and renal perfusion. In order to elucidate the exact physiopathology of renal involvement in cats, long- term follow-up studies and repeated biomarker analyses at tissue level will be useful.

Supporting the correlations observed in this study with further studies with larger case groups and samples will increase the generalisability of the data obtained.

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Authors' Contributions:

DK and BBY were actively involved in all stages of the study, from the initial conception to the design and implementation. They contributed to data collection, analysis, and interpretation, and played a significant role in drafting and writing the manuscript. All authors have read and approved the final version of the manuscript.

Ethical approval:
This study was approved by the Kırıkkale University Animal Experiments Local Ethics Committee (Approval No: E-60821397-605-341747).

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