UNIVERSIDADE FEDERAL DO PARANÁ

RAFAELLE CRISTINE DEA GEREZ

ESTUDO COMPARATIVO DA ANÁLISE MORFOLÓGICA ULTRASSONOGRÁFICA RENAL E DO DOPPLER RENAL COM OS VALORES SÉRICOS DO BIOMARCADOR SDMA EM GATOS.

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Dissertação apresentada ao curso de Pós-Graduação em Ciências Veterinárias, Setor de Ciências Agrárias, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Mestre em Ciências Agrárias.

Orientador(a): Prof(a). Dr(a). Tilde Rodrigues Froes

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em CIÊNCIAS VETERINÁRIAS da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **RAFAELLE CRISTINE DEA GEREZ** intitulada: **Estudo comparativo da análise morfológica ultrassonográfica renal e do Doppler renal com os valores séricos do biomarcador SDMA em gatos**, sob orientação da Profa. Dra. TILDE RODRIGUES FROES, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

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Dedico este trabalho a Deus, meu esposo Anderson e minha filha, Akemi, que foram o meu suporte no momento mais difícil que passei no meio de tamanha alegria, um misto de emoções.

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“À professora Tilde que foi mais que uma orientadora e me ajudou e impulsionou nos momentos mais difíceis.

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Isaías 45:2,3. (Bíblia Sagrada)

RESUMO

Existe uma grande dificuldade em detectar precocemente a doença renal, a qual atualmente tem atingido gatos cada vez mais jovens. Para o auxílio na detecção precoce da doença renal crônica (DRC), foi desenvolvido um novo método de diagnóstico, a Dimetilarginina Simétrica (SDMA). A ultrassonografia é outra forma de análise do rim, apesar de se avaliar a característica do órgão e não sua função, sinais de alteração podem eventualmente indicar a presença da DRC. Nesta dissertação foi analisado a comparação dos dados obtidos pela ultrassonografia bidimensional e doppler com valores séricos do biomarcador SDMA Idexx® em gatos assintomáticos para DRC. Sendo assim este trabalho foi subdividido em dois capítulos. O primeiro capítulo investigou a correlação entre o escore gerado dos achados ultrassonográficos renais e os valores sérios do biomarcador SDMA. Para isso foram avaliados 101 gatos de diversas raças, pesos e idades. Neste estudo conseguimos pontuar achados ultrassonográficos renais e ureterais específicos que apresentaram uma correlação positiva com valores anormais aumentados séricos de SDMA. Estes achados foram à dilatação pélvica renal, a presença de cálculos ureterais não obstrutivos, a perda de definição corticomedular no rim e a diminuição do tamanho renal. Não conseguimos comprovar pelas análises estatísticas realizadas uma correlação com o escore ultrassonográfico proposto na diferenciação entre os grupos de gatos com aumento ou não do SDMA, todavia, os valores dos resultados do coeficiente de correlação de Spearman apresentaram-se borderline, o que para alguns estatísticos pode ser considerado ainda uma correlação positiva. No segundo capítulo foram recrutados os mesmos 101 gatos, entretanto mantiveram-se na pesquisa 95 deles a fim de correlacionar os valores de índices de resistividades (IR) avaliados pelo Doppler com os valores séricos de SDMA. A ultrassonografia Triplex Doppler e o Doppler pulsado foram realizados a partir da artéria interlobar e medidos os valores de índice de resistividade (IR), creatinina e SDMA. Os gatos foram divididos em dois grupos, gatos assintomáticos com SDMA na faixa normal e com SDMA elevados (> 14µg / dL). O IR médio dos gatos estudados foi de 0,61 ± 0,07 no rim esquerdo e de 0,62 ± 0,07 no rim direito. Não houve diferença significativa entre os RI de rim direito e esquerdo. Notou-se que existe uma correlação significativa entre o IR do rim direito e o aumento da SDMA ($p = 0,001$) e também que a creatinina tem uma correlação positiva nos pacientes com SDMA aumentado ($p = 0,022$). A ultrassonografia parece ser uma ferramenta eficaz na avaliação precoce da DRC em gatos assintomáticos, entretanto para a análise do IR das artérias interlobares em gatos é necessário um paciente cooperativo, sendo necessário mais estudos para descartar outros fatores que possam influenciar os valores de IR e SDMA.

Palavras-chave: Ultrassonografia. DRC. Doppler. IR.

ABSTRACT

There is a difficulty in detecting cronic kidney disease (CKD) in advance, which currently affects young cats. To aid in the early detection of CKD, a new diagnostic method, Symmetric Dimethylarginine (SDMA) was developed. Ultrasonography is another way of analyzing the kidney, although assessing the organ's characteristic and not its function, signs of alteration may eventually indicate the presence of CKD. In this dissertation, the comparison of the data obtained by two-dimensional ultrasonography and doppler with serum values of the SDMA Idexx® biomarker in asymptomatic cats for CKD was analyzed. Thus, this work was subdivided into two chapters. The first chapter investigated the correlation between the score generated from renal ultrasound findings and the SDMA biomarker. For that, 101 cats of different breeds, weights and ages were evaluated. In this study, we were able to score specific renal and ureteral ultrasound findings that showed a positive correlation with increased sSDMA. These findings were renal pelvic dilation, the presence of non-obstructive ureteral stones, loss of corticomedullary differentiation in the kidney and decreased renal size. We were unable to prove by the statistical analyzes a correlation with the ultrasound score proposed in the differentiation between the groups of cats with or without an increase in SDMA, however, the values of the results of the Spearman correlation coefficient were borderline, which for some statisticians it can still be considered a positive correlation. In the second chapter, the same 101 cats were recruited, however 95 of them remained in the research in order to correlate the values of resistivity indexes (RI) evaluated by the Doppler with the serum values of SDMA. Triplex Doppler ultrasonography and pulsed Doppler were performed from the interlobar artery and the levels of RI, creatinine and SDMA were measured. Cats were divided into two groups, asymptomatic cats with SDMA in the normal range and with elevated SDMA (> 14µg / dL). The mean RI of the cats studied was 0.61 ± 0.07 in the left kidney and 0.62 ± 0.07 in the right kidney. There was no significant difference between the right and left kidney IR. It was noted that there is a significant correlation between the right kidney and the increase in SDMA ($p = 0.001$) and also that creatinine has a positive correlation in patients with increased SDMA ($p = 0.022$). Ultrasonography seems to be an effective tool in the early assessment of CKD in asymptomatic cats, however, for the analysis of RI of interlobar arteries in cats, a cooperative patient is needed, and further studies are necessary to rule out other factors that may influence the RI and SDMA.

Keywords: Ultrasound. CKD. Doppler. RI.

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LISTA DE ABREVIATURAS OU SIGLAS

CKD	- chronic kidney disease
SDMA	- Symmetric dimethylarginine
sSDMA	- serum symmetric dimethylarginine
GGT	- gamma glutamyl transpeptidase
RI	- resistive index
GFR	- glomerular filtration rate

LISTA DE SÍMBOLOS

® - marca registrada

SUMÁRIO

CHAPTER 1

TITLE:

Association of renal sonographic findings with elevated serum symmetric dimethylarginine in asymptomatic cats

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ABSTRACT

Objectives: To compare subjective and quantitative renal sonographic findings with serum symmetric dimethylarginine (sSDMA) in asymptomatic cats.

Methods: Qualitative and quantitative renal ultrasound findings from 101 cats were compared with sSDMA and other renal biomarkers in a prospective blind study. Inclusion criteria were cats asymptomatic for chronic kidney disease (CKD). The cats were divided into two groups, those with sSDMA values in the normal range and those with sSDMA values above the normal range (>14µg/dL). Abnormal renal sonographic findings were scored from 1 to 10 for comparative statistical purposes.

Results: Eighty-six cats (85.15%) had normal SDMA, and in fifteen cats (14.85%) sSDMA was increased (>14µg/dL). The sSDMA values were more likely to be above the normal range in cats with reduced corticomedullary differentiation (p=0.029), pelvic dilation (p=0.036), and ureteral calculi (p=0.04). Loss of corticomedullary differentiation was positively correlated with sSDMA, and renal length was negatively correlated. The correlation coefficient between sSDMA and the score was 0.190 (p = 0.057). Sonographic findings were more variable in cats with increased sSDMA than those with normal sSDMA.

Conclusions and relevance: Cats with reduced corticomedullary differentiation, reduced kidney and pelvic dilation on sonographic examination are more likely to have raised sSDMA.

Keywords: CKD, feline, ultrasound, kidney, SDMA.

1. INTRODUCTION

Chronic kidney disease (CKD) is a common disorder in geriatric cats.[1] Although it can occur at any age, the prevalence of CKD in the general feline population is reported to be approximately 0.5 to 1.5%.[2] CKD may be the result incomplete recovery from single or multiple injuries to one or both kidneys[3] which can cause irreversible and progressive structural and functional impairment.[2-4]

Early diagnosis and supportive treatment may slow disease progression[5] but management requires a combination of laboratory and imaging tests. The most useful method of monitoring is measurement of serum urea and creatinine concentrations and urine specific gravity. Urinary tract ultrasound and measurement of symmetric dimethylarginine (SDMA) may provide useful adjuncts. SDMA has emerged as a potential serum biomarker for early detection of CKD and has potential advantages over serum urea nitrogen and creatinine assays. [6]

SDMA is a byproduct of cellular protein metabolism, specifically the intranuclear methylation of L-arginine residues; after proteolysis, these free SDMA residues are released into the circulation. SDMA is not bound to plasma proteins and is eliminated primarily via renal excretion, where it is freely filtered by the glomerulus and not secreted or re-absorbed by the tubules.[7]

There have been previous literature reports of sSDMA as an indicator of compromised renal function in cats with CKD.[6] However, interpretation of results must be made with caution in hyperthyroid cats with a mild elevation of serum SDMA and normal serum creatinine.[8] Cats with thyroid disease (both hyperthyroidism and hypothyroidism), without concurrent renal disease, have been shown to have increased sSDMA concentrations. [9] Moreover, in another study, sSDMA was found to be increased above upper reference limits in 39 of 43 cats with kidney stones.[6]

Ultrasound examination of the urinary tract allows non-invasive assessment of the internal renal architecture, provides information on parenchymal morphology, and excludes some pelvic and obstructive ureteral diseases.[10-11] Nevertheless, there is an overlap between normal and abnormal ultrasound findings in azotemic and non-azotemic cats, with one study reporting that 47% of ultrasound abnormalities were present in kidneys of non-azotemic cats.[12]

This finding can be interpreted in three ways: 1. These cats may have ultrasound abnormalities with subclinical renal disease that does not cause azotemia; 2. the renal lesions may be secondary to other conditions, such as cardiomyopathy or acromegaly; 3. ultrasonography may identify signs of CKD before an increase of serum creatinine.

The aim of this study was to compare the subjective and quantitative renal sonographic findings in cats with serum SDMA values in, and above (>14µg/dl) the normal range, but without clinical signs of kidney disease. Our hypotheses were that abnormalities in kidney size, shape and echogenicity would be associated with an increase in SDMA values and the combination of ultrasonographic findings (by score) would predict elevated sSDMA in cats.

2. MATERIAL AND METHODS

2.1 PATIENT SELECTION

This prospective and cohort study was approved and conducted in accordance with guidelines of the Animal Ethics Committee from Federal University of Parana. Client-owned cats, hospital staff cats, and cats from students were recruited from August 2018 to September 2019.

Inclusion criteria were cats without signs of chronic renal disease. The sample population of cats was divided into two groups: 1. asymptomatic cats with sSDMA values in the normal range and, 2. asymptomatic cats with sSDMA values >14µg/dL. Information collected from medical records included: patient history, breed, sex, age, weight, body condition. All cats were clinically evaluated, blood and urine (collected by cystocentesis) samples were obtained, and B-mode abdominal ultrasound was performed to exclude concomitant

illness. The commonly used renal biomarkers values were reviewed (ie. creatinine, urea, urine specific gravity, urine protein:creatinine ratio, urinary gamma glutamyl transpeptidase - GGT).

Exclusion criteria were: I. had clinical signs of ureteral obstruction or active lower urinary tract infection during the previous year; II. dehydration or clinical signs of kidney disease that may contribute to decreased renal perfusion; III. pelvic dilation > 0.3 cm on ultrasonography; IV. reduced urinary density (urine specific gravity < 1.025) and/or presence of infection/inflammation in the bladder.

2.2 ULTRASONOGRAPHIC EXAMINATION

All cats were fasted for at least 6h before ultrasound examination. For the examination, the cats were gently, manually restrained, with no sedation. Two-dimensional ultrasonographic evaluations were performed using high-resolution ultrasonographic equipment (GE Logic F6 GE Healthcare, Milwaukee, Wisconsin) with a 7.5-12MHz linear multifrequency transducer. All cats were positioned in dorsal recumbency in a sponge trough and were clipped on the ventral abdomen. After examination of the whole abdominal cavity, the kidneys were imaged in transverse and dorsal planes.

A single radiologist (with 5 years of experience) performed all sonographic examinations following a detailed predefined examination protocol that included recording of standard plane images, using video clips, and static images. The sonographic evaluation was blinded, so the radiologist did not have access to the results of the laboratory examinations before performing the ultrasound examination.

2.3 ULTRASONOGRAPHIC SUBJECTIVE EVALUATION

A two-dimensional technique was used to evaluate the kidneys for size (the longitudinal renal length between the poles), shape, outline and echogenicity of cortex and medulla, corticomedullary definition and evaluation of the renal pelvis. Each kidney was imaged in a minimum of two orthogonal planes.

Cortical echogenicity (left kidney) was compared to the splenic parenchyma at the same gain and depth and was usually slightly hypo or isoechoic when compared with the liver parenchyma (right kidney).[10] The echogenicity of the medulla was considered increased when hyperechoic speckles or lines were seen on a normal background echogenicity.

Ultrasound lesions were classified as present or absent and echogenic lesions further characterized as diffuse and/or focal. Focal lesions were

classified as parenchymal or pelvic. Parenchymal (cortical or medullary) lesions include cysts and infarcts (seen as hyperechoic wedge-shaped or triangular lesions) specifically in the cortex.[11]

Renal length was measured by positioning the medical caliper at the level of a line drawn between the medial surfaces of the cranial and caudal poles of the kidney on dorsal plane images. Normal renal length was considered to be 3.0cm to 4.3cm.[11]

Pelvic diameter was measured on transverse planes ensuring that the ureter was excluded from the measurement. The normal renal pelvis width was considered to be 0 to 2mm. However, if the pelvic diameter was > 3mm the cat was excluded from the study. Nephroliths were classified as absent or present (Table 1). Nephroliths were defined as lesions with a curved hyperechoic interface, suggesting a structure that displaced surrounding kidney tissue or projected into the kidney pelvis, and were usually associated with acoustic shadowing artifact.[13]

The retroperitoneal space was carefully examined, searching for alterations in perirenal fat or free fluid. The ureters were examined for dilation and/or ureteral calculi. Finally, bladder ultrasound examined the intraluminal content and bladder wall.

A score from 1 to 10 was given to each kidney based on the sonographic findings. One point was awarded for each of the ten sonographic findings, as shown in Table 1.

TABLE 1 - Score based on renal sonographic findings in all cats included in the study

KIDNEY SONOGRAPHIC FEATURES	NORMAL OR ABNORMAL SONOGRAPHIC SIGNS	SCORE
Echogenicity of the cortex	*Normal*	0
	Increased	1
Echogenicity of the medulla	*Normal*	0
	Increased	1
Renal shape †	*Normal*	0
	Abnormal	1
Renal size +	*Normal range*	0
	Increased or reduced	1
Corticomedullary definition	*Present*	0
	Absent or partially absent	1
Pelvic diameter	*Normal range*	0
	*Dilatation**	1
Calcification in parenchyma	*Absent*	0
	Present	1
Infarcted areas	*Absent*	0
	Present	1
Cystic lesion	*Absent*	0
	Present	1

Pelvic lithiasis	*Absent*	0
	Present	1

†cortical depression, flatted or irregular surface;+ cortical length <3.0cm or >4.3cm. * pelvic diameter >2.0mm

2.4 LABORATORY TESTS

Blood was collected from all cats for measurement of serum creatinine and urea, and abnormalities on blood or urinalysis were used as exclusion criteria. Serum concentrations of SDMA were determined by liquid chromatography-mass spectrometry. Blood samples were centrifuged, and analysis performed using IDEXX laboratory equipment (Sao Paulo, Brazil). Serum SDMA > 14 µg/dL was considered to be raised, and these cats were included in the group with increased sSDMA for further statistical analysis.

Other laboratory analyses, such as urine protein: creatinine ratio, urinary GGT, presence of bacteria in urine, and urinary density, were used as inclusion and exclusion criteria, and to provide better understanding about the composition of groups and to classify the animals according to the IRIS Staging of CKD. These specific laboratory examinations were performed at the Veterinary Clinical Pathology Laboratory at UFPR.

2.5 STATISTICAL ANALYSIS

All statistical analyses were done by one of the authors (R.C.D.G) and a statistician (C.M.M). Two observations were made for each animal, since kidneys were counted individually. Consequently the data were investigated using mixed logistic models. A descriptive data analysis was carried out with an estimation of the mean, median, and standard deviation of the quantitative variables. For qualitative variables, relative and straightforward frequency estimates were made. Data distribution was tested with the Shapiro-Wilk test and all non-normally distributed data was analyzed using a non-parametric approach. To assess the difference in sSDMA between groups (presence and absence of findings and parameters), a Mann-Whitney U test, or non-parametric ANOVA (Kruskall-wallys) with Dunn as post-hoc was used. The Spearman's correlation was used in the correlation of the sSDMA serum values and ultrasonographic kidney score (1-10). The tests were considered significant when $p < 0.05$, and all analysis was performed using SPSS 21.0 (IBM, 2012).

3. RESULTS

A total of 114 cats met inclusion criteria and were recruited for this study. Of these, 101 cats did not meet exclusion criteria and were included in the study. Thirteen cats were excluded from the study: eight due to presence of bacteria in the urine, four had reduced urinary density (below the predetermined

cutoff (<1.025)) and another had significant unilateral hydronephrosis (FIGURE 1). Ultrasonographic imaging was performed for 202 kidneys.

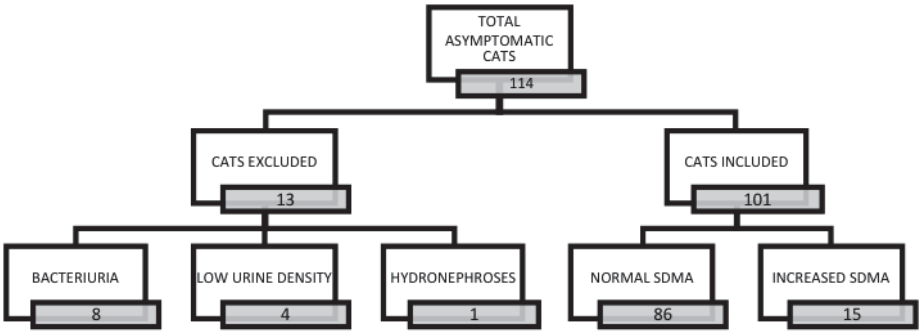

FIGURE 1 - Flow chart of the included and excluded cats, showing grouping and division. Cut off for excluded and included cats were made using urine protein: creatinine ratio > 0.2; urinary GGT> 29.7 UI/L., SDMA > 14ug/dl was considered elevated.

Breeds represented were domestic short hair (87/101, 86.1%), Persian (5/101, 5.0%), Maine Coon (3/101, 3.0%), Siamese (2/101, 2.0%), and one each (1.0%) of Angora, British, Sphynx and Savannah. Forty-four (43.6%) were male and 57 (56.4%) females. Median age was 6.1 years (range <1 year – 18 years). Median weight was 4.7 kg (range 1.98 kg – 11.3kg) with body conditions recorded as obese (8/101, 7.9%), overweight (22/101, 21.8%), normal (61/101, 60.4%) and underweight (10/101, 9.9%). Eleven cats were not IRIS classified. CKD cats consisted of IRIS CKD stage 1 (49/101, 48.51%), IRIS CKD stage 2 (40/101, 39.6%), IRIS CKD stage 3 (1/101, 0.99%) and no cats were IRIS CKD stage 4.

Normal sSDMA values were present in 86 cats (85.15%) and 15 cats (14.85 %) had increased sSDMA (>14µg/dL), six of which had normal creatinine (5.94%); creatinine values were increased (1.6 mg / dL) in 28 (27.7%) ; 65 (85.5%) had increased urinary GGT values.

Subjective sonographic evaluation of kidneys showed 162/200 kidneys to be within normal limits for length (81%), between 3.0cm and 4.3cm. Measurements were not made in two kidneys. In the group with normal sSDMA, 150 kidneys were within normal limits (150/200). At least one abnormal subjective sonographic finding was found in 151/202 of the kidneys, independent of the group (normal or abnormal sSDMA values)

Based on all cats, the right kidney length was 3.46cm (SD ± 0.48). The left kidney was 3.53 cm (SD ± 0.50). Renal length was decreased in 26/200 (13%) and kidney enlargement was present in 12/200 (6%). Renal pelvic diameter was normal in 190/198 (95.95%) of the kidneys (> 0.2cm). Infarcted areas were present in at least 36/202 kidneys. Prevalence of renal lithiasis was 32/202 (15.84%). Areas of renal parenchymal calcification were present in 77/202 (38.11%) kidneys. Corticomedullary definition was lost or decreased in 28/202 (13.86%) kidneys, renal cysts were present in 9/202 (3.96%) (FIGURE 2). Perirenal fluid was present in one cat, 1/202 (0.49%) and no cat had subcapsular

fluid.

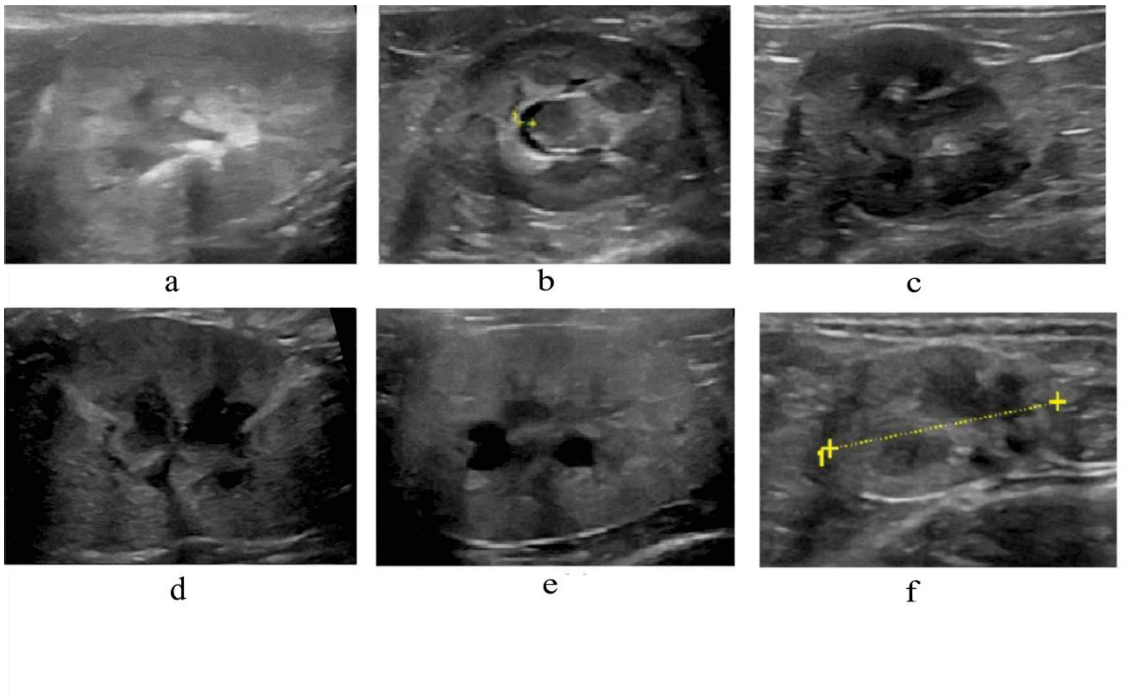

FIGURE 2 - Examples of different ultrasound findings. (a) Renal lithiasis associated with loss of corticomedullary definition; (b) cat with pelvic dilatation and increased medullary echogenicity; (c) infarcted areas in a kidney with an abnormal shape and decreased size; (d) increased echogenicity of the renal cortex in a cat with infarcts; (e) loss of corticomedullary definition with cystic lesions in the renal parenchyma and increased kidney size; (f) loss of corticomedullary definition, decreased kidney size, irregular contour and presence of microcalcification in parenchyma.

Inference statistics were performed to identify which specific sonographic findings had a positive correlation with sSDMA values, showing that cats with pelvic dilation (p=0.036), and cats with kidneys with decreased corticomedullary

differentiation (p=0.029) were more likely to have elevated sSDMA. Cats with ureteral calculi were also more likely (p=0.04) to have elevated sSDMA.

Table 2 shows the relative frequencies of each sonographic finding according to the group, normal or increased sSDMA. The loss of corticomedullary differentiation was positively correlated within higher sSDMA values.

TABLE 2 - Statistical values and summary of association of ultrasound findings with normal and abnormal SMDA values in two groups of cats (101)

Kidney/ureter findings	**Classification**	**Normal SDMA**		**Abnormal SDMA**		**Total**		**p-valor**
		N	**%**	**N**	**%**	**N**	**%**	
Left Kidney length	*Reduced*	12	80.0%	3	20.0%	15	100%	0.816
	Normal size	69	86.2%	11	13.8%	80	100%	
	Increased	5	83.3%	1	16.7%	6	100%	
Right Kidney length	*Reduced*	7	63.6%	4	36.4%	11	100%	0.110
	Normal size	72	87.8%	10	12.2%	82	100%	
	Increased	5	83.3%	1	16.7%	6	100%	
Left pelvic diameter	*Normal size*	80	85.1%	14	14.9%	94	100%	0.568
	Increased size	4	80.0%	1	20.0%	5	100%	
Right pelvic diameter	*Normal size*	83	86.5%	13	13.5%	96	100%	0,059
	Increased size	1	33.3%	2	66.7%	3	100%	
Kidney shape	*Normal*	66	88.0%	9	12.0%	75	100%	0.147
	Abnormal	20	76.9%	6	23.1%	26	100%	
Infarcted areas	*Absent*	66	85.7%	11	14.3%	77	100%	0.500
	Present	20	83.3%	4	16.7%	24	100%	

Hyperechoic cortex	*Normal*	37	86.0%	6	14.0%	43	100%	0.530
	Abnormal	49	84.5%	9	15.5%	58	100%	
Increased medullary echogenicity	*Normal*	69	86.2%	11	13.8%	80	100%	0.715
	Abnormal	16	80.0%	4	20.0%	20	100%	
	Not rated	1	100.0%	0	0%	1	100%	
Parenchyma calcification	*Absent*	53	88.3%	7	11.7%	60	100%	0.474
	Present	32	80.0%	8	20.0%	40	100%	
	Not rated	1	100.0%	0	0%	1	100%	
Corticomedullary differentiation	*Absent*	3	42.9%	4	57.1%	7	100%	0.005
	Decreased	7	87.5%	1	12.5%	8	100%	
	Present	76	88.4%	10	11.6%	86	100%	
Presence of renal cysts	*Absent*	81	85.3%	14	14.7%	95	100%	0.629
	Present	5	83.3%	1	16.7%	6	100%	
Kidney lithiasis	*Multiple and bilateral*	9	75.0%	3	25.0%	12	100%	0.541
	Absent	70	87.5%	10	12.5%	80	100%	
	Only one	5	83.3%	1	16.7%	6	100%	
	One bilateral	2	66.7%	1	33.3%	3	100%	
Ureter lithiasis	*Absent*	86	86.0%	14	14.0%	100	100%	0.149
	Present	0	0.0%	1	100.0%	1	100%	
Cystolithiasis	*Multiple*	1	100.0%	0	0.0%	1	100%	0.837
	Absent	84	84.8%	15	15.2%	99	100%	
	Only one	1	100.0%	0	0.0%	1	100%	

Table 3 shows the statistical results of the correlation coefficient (“r) between SDMA and the proposed sonographic score (1-10) (Table 1).

TABLE 3 - Shows the range, medium, minimal, maximal, interquartile range, standard deviation and P-value of the correlation coefficient for sonographic score (1-10), based on abnormal sonographic findings in cat's kidneys and proximal ureter (202 kidneys)

	Range	**MD**	**Min**	**Max**	**25% Perc.**	**75% Perc.**	**SD**	**"r"**	**P**
Sonographic score*	3	2	0	8	2	3	2	0.190	0.057

* proposed sonographic score correlated with abnormal sonographic findings in kidney and ipsilateral ureter. P was calculated using the spearman's rank correlation coefficient. P<0.05

Table 4 shows the statistical results of the difference between two groups of cats, with or without increased SDMA with the proposed sonographic score (1-10) (Table 1). The Mann-Whitney U test was performed, and there was no statistically significant difference (p=0.784).

TABLE 4 - Shows the range, medium, minimal, maximal, interquartile range, and standard deviation of the sonographic score (1-10) based on abnormal sonographic findings in cat's kidneys and ureter; and compares whether there is a difference in the sonographic score and the SDMA for the two group of cats

	Range	**MD**	**Min**	**Max**	**25% Perc.**	**75% Perc.**	**SD**	**P-value***
Sonographic score								**0.185**
Group SDMA normal values	3	2	0	8	2	3	2	
Group SDMA increase values	3	3	1	7	2	6	2	

SDMA normal values correspond to 86 cats (172 sonographic kidney evaluations). Increased SDMA values correspond to 15 cats (30 sonographic kidney evaluation). P was calculated using the Mann-Whitney U test. P<0.05

Figure 3 shows sample scatterplots of the relations between sSDMA and proposed sonographic score after ultrasound analyses of the kidneys. Figure 4 shows a box plot graph of the sSDMA variable value and the proposed sonographic score (0-10) (Table 1). This box plot graph shows that cats with elevated sSDMA usually have more variable sonographic findings, however this was not statistically significant.

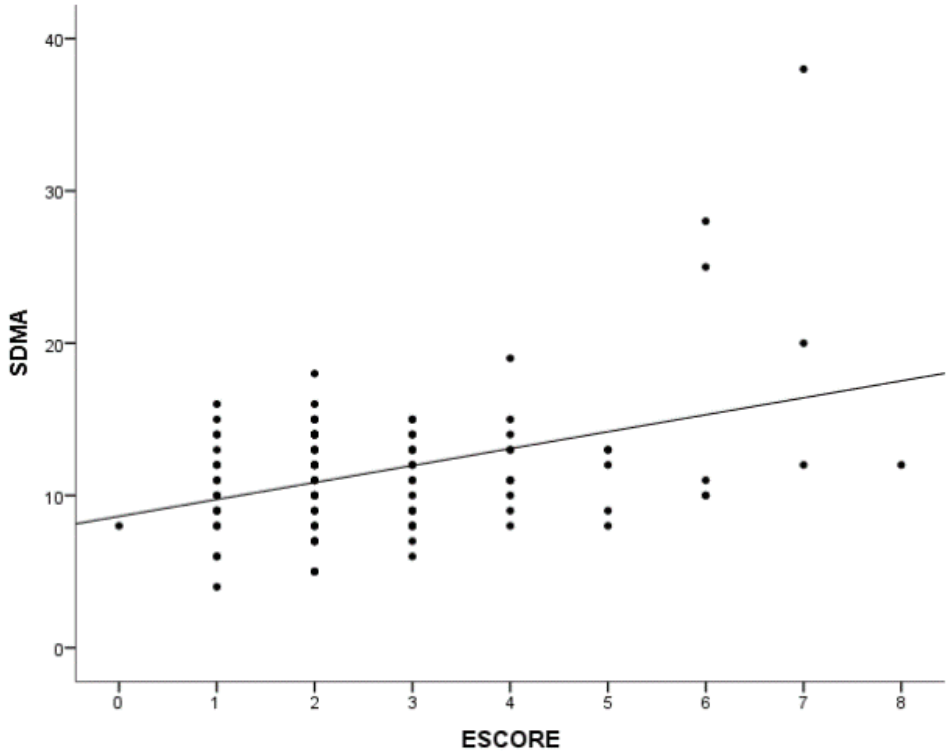

FIGURE 3 - Scatterplots of the relation between serum SDMA values of the 101 cats and proposed kidney and ipsilateral ureter ultrasonographic score.

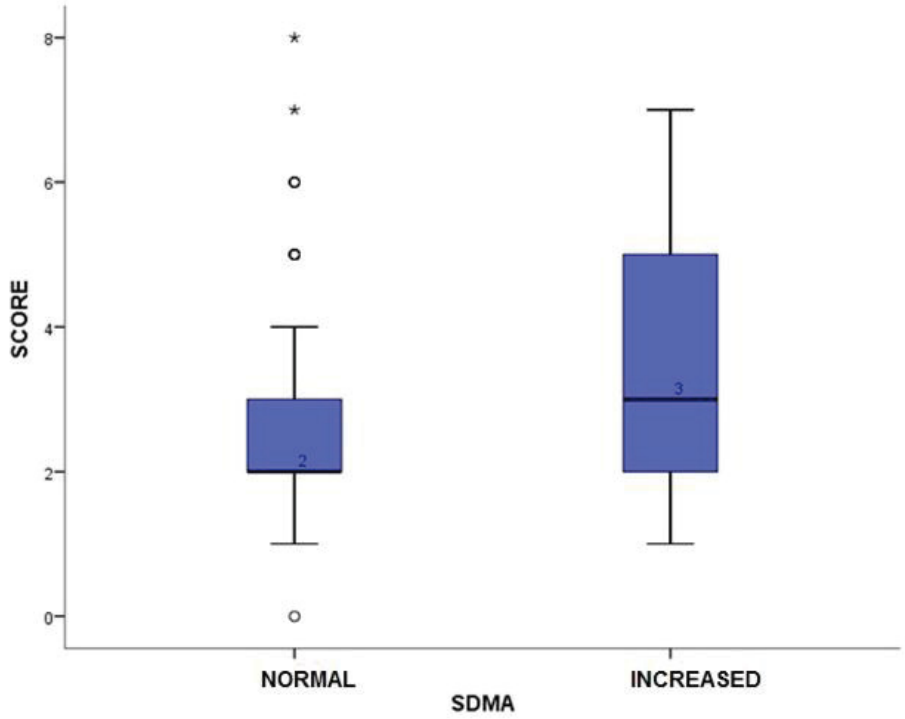

FIGURE 4 - Average sonographic score of kidney and ureter findings in two groups of cats, with normal and increased sSDMA values. There is no statistically significant difference between groups. P<0.05

As previously stated, two sonographic findings were correlated with increased sSDMA; reduced and/or loss of kidney corticomedullary differentiation, and kidney length. Figure 5 shows that when the kidney (left or right) was smaller, there was an increased likelihood of having raised sSDMA values. The correlation coefficient of left renal length with increased sSDMA was – 0.214 with P-value 0.031. The correlation coefficient of right renal length with increased sSDMA was – 0.215 with P-value

0.033

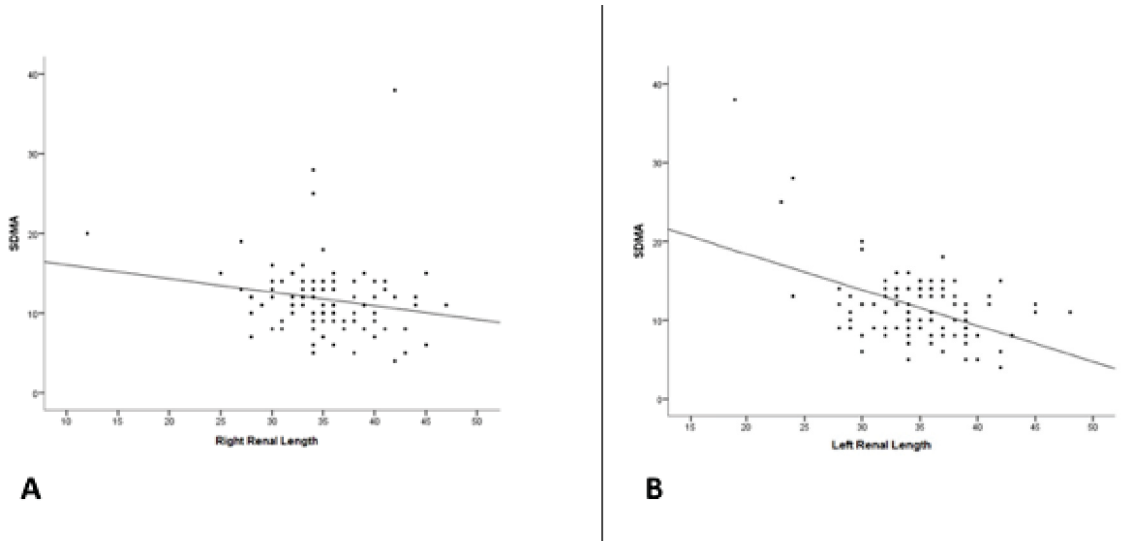

FIGURE 5 - Sample scatterplots showing the linear relationships between right renal length (centimeter) and serum SDMA (ug/dl) (A), and left renal length (centimeter) and serum SDMA (ug/dl) (B)

4. DISCUSSION

Chronic kidney disease has been commonly reported in young cats without clinical signs, thus early diagnosis and monitoring of these animals is important,[5]to increase life expectancy. Early diagnosis is achieved by a combination of laboratory and imaging findings, which are used in IRIS staging of CKD.[14] Parameters studied include sSDMA values and the sonographic imaging of the kidneys. This is the first research that compares the renal ultrasound findings of cats asymptomatic for CKD, with or without increased sSDMA values.

A total of 101 cats were studied. However, 11 cats were considered normal and were not IRIS CKD classified. Cats were classified as IRIS CKD Stage 1 49/101 cats (48.51%), IRIS CKD stage 2 40/101 cats (39.6%) and only one patient IRIS CKD stage 3. The cats represented a wide range of ages, breeds and sex. In total, 202 kidneys were examined sonographically. It is interesting to note that in 89/101 cats (88.11%) there was at least one unilateral or bilateral abnormal ultrasound finding in kidney and/or ureter. The identification of only one ultrasound abnormality in the kidneys might be considered insignificant which makes the correlation between imaging findings and laboratory data difficult.

However, the identification of a single renal ultrasound abnormality is one of the parameters for staging a cat in CKD IRIS stage 1. For some researchers, the signs of renal degeneration are related to renal functional and/or structural loss and a single abnormal ultrasound finding results in classification of cats as IRIS stage 1. [14] Abnormal ultrasound findings, especially single focal changes, such as the presence of a single cyst, slight cortical deformations or increased echogenicity of the renal cortex can be incidental.[11] Increased renal cortical echogenicity in patients with normal sSDMA represented 49/101 (48.51%) animals in this study. Thus, although they may be of no clinical relevance we believe that even mild renal changes indicate the need for further monitoring.

Renal ultrasound is not recommended as a sole investigation in cats with CKD, and some investigators do not even recommend it as a screening technique, since there is a poor correlation between renal ultrasound findings and renal function due to the prevalence of abnormalities in non-azotemic cats.[13]

To determine the relevance of information obtained during renal ultrasound we tried to relate the ultrasound findings with sSDMA. A recent study compared ultrasound findings and glomerular filtration rate in dogs and demonstrated that some ultrasound findings are related to reduced glomerular filtration rate.[15]

Here we identified the specific renal and ureteral ultrasound findings that have a positive correlation with increased serum sSDMA. These findings were pelvic dilatation, ureter calculus, loss of corticomedullary differentiation and reduced renal size (pole to pole length).

Dilation of renal pelvis is a finding common to not only CKD, but also pyelonephritis and partial ureteral obstruction.[16] Additionally, any of these underlying pathologies may occur in isolation or concurrently. We believe that renal pelvic dilation is an indicator of kidney injury, even when only mild dilation (2.0-3.0mm) is present, since small dilations are correlated with increases in sSDMA, and these patients should be followed up.

Another study showed that cats with kidney stones may have early compromised renal function with increased sSDMA and non-azotemia, or more advanced renal dysfunction with azotemia.[6] The authors of that study propose that cats with increased sSDMA should undergo imaging tests to identify kidney stones and we suggest that cats with ureteral stones on imaging examination should undergo SDMA testing.[6]

The other ultrasonographic finding that was positively correlated with increased sSDMA was the reduction in, or loss of, corticomedullary differentiation. This is a classical sonographic abnormality frequently associated with CKD.[10] A previous study of 508 cats identified loss of corticomedullary differentiation in azotemic (26%) and non-azotemic cats (5%) .[12]

We found a negative correlation of renal length with increased SDMA (Figure 5). Cats with reduced kidney length were more likely to have increased sSMDA. Although demonstrating statistical correlation, interpretation of this finding is difficult because there are many other parameters that influence this measurement including body weight, fat accumulation in the kidney, age, sex, or breed. We specifically used strict guidelines for normal length (3.0cm – 4.3cm) that have been standardized for the Brazilian cat population.

There was no specific correlation between diffuse increased parenchymal echogenicity and increased sSDMA. Although this finding had the

highest sensitivity for low IKGFR/PV in dogs and human patients.[15] The histological changes responsible for increased parenchymal echogenicity include glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[17] Intrinsic factors affecting parenchymal echogenicity are normal variation in fat deposition in cat kidneys, wide variability in the normal range of cortical echogenicity and severe dehydration.[18] Extrinsic factors influencing this finding are related to operator experience, variability in image interpretation, and ultrasound system settings. It is difficult to distinguish between normal and pathological kidneys using this finding alone.

At least 24/101 cats (23.8%) in this study had renal infarcts, with 4 having increased sSDMA and 20 normal sSDMA. In cats, chronic renal infarcts result in hyperechoic wedge-shaped tissue sections on sonographic examination, caused by disruption of blood flow to a renal pyramid.[11] There was no statistical correlation between the infarcts and increased sSDMA. This concurs with findings of other studies, which showed no relationship between renal infarcts and kidney disease. However, there is a significant association between renal infarcts and hypertrophic cardiomyopathy and other prothrombotic diseases including hyperthyroidism and neoplasia. [19]

There was no statistical correlation between the proposed ultrasound score and increase in sSDMA (Table 3 and 4; Fig 4). However, the Spearman

correlation coefficient results (Table 3) were borderline significant, which for some statisticians can be considered a positive correlation. It is possible our methodology for score classification was not adequate, since some findings that might be considered incidental were scored with the same value as potentially more important findings.

There was a difference in the sample size of animals recruited for each group. If more asymptomatic cats with high sSDMA had been included perhaps the score classifications would have better sSDMA concentrations. One study in dogs showed a positive correlation between the scoring method and reduced glomerular filtration rate, although a different scoring method was used.[15]

The limitations of this research were related to the small number of cats in the asymptomatic group with elevated sSDMA. A further limitation is that inter-breed differences or sexual differences in the renal length weren't calculated. Nevertheless, only three large cats (Maine-coons) were included in the study, and there was no statistically significant difference between the sexual incidence.[20]

5. CONCLUSION

Ultrasonography appears to be an effective tool in the early assessment of CKD in asymptomatic cats. Our study showed that cats with loss of the

kidney corticomedullary differentiation, small kidneys, and kidneys within pelvic dilation on ultrasound examination are more likely to have increased sSDMA.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article

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CHAPTER 2

TITLE:

Association of renal Doppler resistive index findings with elevated serum symmetric dimethylarginine in asymptomatic cats for early diagnostic in chronic kidney disease.

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ABSTRACT

Objectives: The aim of the present study was to evaluate the effectiveness of measuring the RI in asymptomatic cats and their correlation to serum symmetric dimethylarginine (sSDMA) values.

Methods: A prospective, cohort and blinded study was conduct in 101 non sedated asymptomatic domestic cats for CKD. Triplex Doppler ultrasonography and pulsed Doppler interrogation was performed from the interlobar artery and the RI, creatinine and sSDMA levels were measured. The cats were divided into two groups, asymptomatic cats with sSDMA in the normal range and with sSDMA above (>14µg/dL). We based as increased values for RI, figures equal or higher than 0.59 for the left kidney and 0.54 for the right. Tests were considered significant when $p < 0.05$, and the analysis were performed using SPSS 21.0 (IBM, 2012).

Results: The mean RI in the studied cats was 0.61 ± 0.07 in the left kidney and 0.62 ± 0.07 in the right kidney. No significant difference was present between right and left kidney RI´s. There is a significant correlation between the right kidney and the increase in sSDMA ($p=0.001$). The creatinine has a positive correlation within higher sSDMA ($p=0,022$).

Conclusion and relevance: It is possible to perform the RI of interlobar renal arteries in cats by triplex Doppler ultrasound. There is a significant correlation between the values of the right kidney RI value with increased sSDMA.

Keywords: feline, resistive index, doppler, kidney, SDMA.

7. INTRODUCTION

B-mode ultrasonography is often the modality of choice for imaging the feline kidney because it provides a non-invasive assessment of internal architecture and better information about the renal size and shape [1]Doppler ultrasound can be used to analyze anatomical and functional vascular data, such as blood flow velocity, direction and type.[2] It also permits blood flow measurements to provide indirect information about peripheral vascular resistance [3]Increased vascular resistance reduces diastolic flow to a higher degree than the systolic, resulting in an increase in the RI .[1]

The main flow parameters measured using this technique are the peak systolic velocity (PSV) and end diastolic velocity (EDV). The first parameter, PSV, is formed by the opening of the semilunar valves and the forward ejection of blood. This forth blood flow starts to decelerate when cardiac contraction provides insufficient forward force to overcome the elastic properties of the downstream vascular bed and the viscosity of blood.

Another commonly measured parameter is the resistive index (RI). The resistive index (RI), also known as the Pourcelot ratio, is calculated from blood flow velocities. This index, expressed by (PSV – EDV)/PSV, indicates the downstream resistance in arteries (ranging from 0 to 1, where 0 is no resistance and 1 is maximum resistance)[4] is independent of the angle and position of the

exploratory probe allowing the accurate and reproducible measurement of downstream vascular impedance. [5]

The RI has been proposed as a helpful tool for the diagnosis and prognosis of renal diseases in many species. [6] Chronic kidney disease (CKD) is a silent disease that can remain asymptomatic until an advanced stage, being that unilateral renal abnormalities will not result in azotemia if the contralateral kidney is functioning well. The RI analysis could be an interesting tool to add up more laboratory markers of kidney diseases.

More advanced tests to evaluate kidney function might be considered in cats with suspicious routine blood and urine tests. Measurement of glomerular filtration rate (GFR) would be ideal, however it has critical practical limitations like multiple blood samples, besides not being a routine exam.[7] Symmetric dimethylarginine (SDMA) has been shown to be an earlier marker of kidney dysfunction than creatinine in cats, which is known to increase only after significantly more than 70% of renal function .[8] Ureteral and pelvic dilatation and calculi also influence the serum symmetric dimethylarginine (sSDMA) values. To better define which kidney is more affected, some non-invasive methods for the diagnosis like duplex doppler could be useful.

The kidney RI in arcuate arteries was first described in 1996 in sedated normal cat[9] and further research has shown that doppler ultrasonography can

provide significant information on dogs and cats with renal disease.[2] Normal Doppler measurements of arcuate or interlobar artery blood flow have been reported in normal cats posteriorly[3,5] and in cats with CKD .[10,11] When the kidney is pathological the RI in CKD progressively increases significantly. There are some studies in different breeds, like Persians and Korean domestic short-hair[12,13] and in different species, like horses . [14] The literature shows us RI for healthy and diseased cats, nevertheless there is no correlation in asymptomatic patients for CKD or comparison with an early renal biomarker.

The main of the present study was to evaluate the effectiveness in measuring the RI references in asymptomatic cats and their correlation with increased sSDMA values.

8. MATERIALS AND METHODS

A prospective, cohort and blinded study was conduct in 101 asymptomatic domestic cats with different ages for CKD presented by the staff of the Federal University of Paraná Teaching Animal Hospital. The cats were recruited from August 2018 to September 2019. Triplex Doppler ultrasonography was performed with a GE Logic 5 ultrasound machine (GE Healthcare, Milwaukee, Wisconsin) with a 7.5-12MHz linear multifrequency transducer. For a analyses of a kidney vascular bed, the cats were not

sedated, just manually restrained by their tutors with a calm environment. Hair was clipped and acoustic gel was applied to the skin. The cats were fasted for 6 hours in dorsal recumbency to scan the both kidney at different time, starting by the left kidney. There was no time limitation for the value acquisition.

B-mode ultrasound is done primarily to capture the kidney in the longitudinal section. Subsequent color Doppler was used to visualize the intrarenal vasculature. Pulsed Doppler interrogation from the interlobar artery with better detection from de color Doppler was obtained with a sample width of 1-3mm and a frequency of 7MHz. A single sonographist (with 5 years of experience) performed all exams. The selection of the interlobar artery followed a pattern with no fixed location, but best detectable in the triplex color Doppler and with the best wave quality in pulsed Doppler within a shorter time, so as not to stress the cats. The smallest scale that displayed the flow without aliasing was selected. The mean RI for each kidney was determined by averaging a total of three consecutive Doppler waveforms from the interlobar at three different times.

RI was calculated automatically by a software from the ultrasound machine from GE, after manual delimitation of peak systolic velocity, end diastolic velocity, and time average maximum velocity. The RI values for each individual kidney were averaged from three waves, and the resulting value was

used for correlation analysis (FIGURE 1). Pearson correlation analysis was performed to determine if a statistically significant ($P < 0.05$) correlation existed between RI and concurrent sSDMA.

Creatinine and SDMA levels were measured using a blood sample collected from the jugular vein before the ultrasound exam avoiding stressing changes. Urine collection was performed by cystocentesis after the Doppler exam. sSDMA was determined by liquid chromatography-mass spectrometry. The blood was centrifuged, and the analysis was done by IDEXX laboratory equipment (São Paulo, Brazil). For our classification, sSDMA upper to 14 µg/dL was considered higher, and the cat was joint into the increase SDMA group for further statistical proposal. Inclusion criteria were asymptomatic cats for CKD. We based as increased values for RI, figures equal or higher than 0.59 for the left kidney and 0.54 for the right.[5] The sample population of cats were divided into two groups: 1. asymptomatic cats with sSDMA in the normal range and, 2. asymptomatic cats with sSDMA >14µg/dL. All the statistical analysis were done by one of the authors (R.C.D.G) and a statistician (C.M.M).The tests were considered significant when $p < 0.05$, and the analysis were performed using SPSS 21.0 (IBM, 2012).

This study was approved by Research Ethics on the Use of Animals Committee at CEUA (Comitê de Ética no Uso De Animais), at Federal

University of Paraná. The pet owners signed an 'informed consent' form allowing the use of the collected this research.

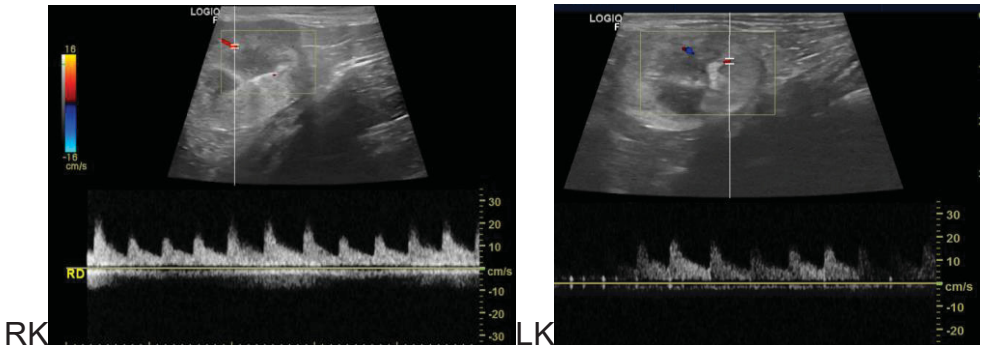

FIGURE 6 - Colour Triplex Doppler ultrasound image and the RI measurement. RI in the right kidney with partial loss of corticomedullary differentiation and the left kidney, with totally loss of corticomedulary differentiation. Note the low general vascularity in the colored Doppler and the difficult in the waveform in the left kidney. The patient above had increase sSDMA

9. RESULTS

The artery interlobar values were obtained from 95 cats, seeing as in six cats it was not possible due to difficulties in optimizing ultrasound images. It was more difficult to obtain good quality recordings from the left kidney than the right one. In some animals, pulsed Doppler registration was more difficult and time consuming due to panting and stress. For that reason, and also to morphological changes in loss of corticomedular differentiation in some kidneys, nine right kidneys were not evaluated and 11 were left kidneys parenchyma.

The mean RI in the studied cats was 0.61 ± 0.07 in the left kidney and 0.62 ± 0.07 in the right kidney. No statistically significant differences were

registered between the mean RI on both kidneys. The lowest RI in all the studied cats was 0.45, which has normal creatinine and sSDMA . The highest RI was 0.83 and has also normal creatinine and sSDMA .

Six patients had an increase of at least 0.1 in RI when compared to their contralateral kidney. Considering all cats, the study revealed increased RI in 46.5% (47/101) of the left kidneys, 36.6% (37/101) RI of the left kidneys obtained normal values. Regarding the right kidney, 73.3.% (74/101) had increased RI values and 11.9% (12/101) normal values. In the blood and urine tests, 86 cats (89.1%) presents normal values of SDMA and 15 cats (14,9%) presents increased of sSDMA (>14µg/dL).

The right RI differed significantly from normal SDMA cats and increased SDMA cats (p=0.001); the right RI in this group were higher in those increased SDMA than the normal SDMA cats (Table 1). This does not apply for values of RI in the left kidney (p=0.246).

TABLE 5 - Inference statistics performed to detect RI and creatinine as a factor or not of increase SDMA in 101cats

Feature	Classification	SDMA			P-value *
		MD	25% Perc.	25% Perc.	
Left Kidney RI*	*Normal*	10	8	13	0.121
	Increased	12	10	14	
Right Kidney RI*	*Normal*	9	8	10	0.001
	Increased	12	10	14	
Creatinine	*Normal*	11	9	13	0.082
	Increased	12	10	15	

* Note that it was possible to measure 84 resistive index (RI) in the left kidney and 86 RI in the right kidney. P was calculated using the Mann-Whitney U test. P<0,05

The table 2 shows the relative frequencies of RI and creatinine according the group, normal or increased SDMA. The creatinine has a positive correlation within higher SDMA values. Analyzing the relative frequencies of each kidney RI, there is no correlation between any group and any kidney.

TABLE 6 - Statistical values of RI and creatinine associated in two group of cats (101), with normal and abnormal SMDA values

Rated Item	**Classification**	**Normal SDMA**		**Abnormal SDMA**		**Total**		**p-valor**
		N	**%**	**N**	**%**	**N**	**%**	
Left	*Not rated*	13	76,50%	4	23,5%	17	100%	0.542
Kidney RI	*Normal*	32	86,5%	5	13,5%	37	100%	
	Increased	41	87,2%	6	12,8%	47	100%	
Right	*Not rated*	12	80,0%	3	20,0%	15	100%	0.144
Kidney RI	*Normal*	12	100%	0	0,0%	2	100%	
	Increased	62	83,8%	12	16,2%	74	100%	
Creatinine	*Normal*	66	90,4%	7	9,6%	73	100%	0.022
	Increased	20	71,4%	8	28,6%	28	100%	

RI: Resistive index. sSDMA increase values correspond to > 14 µg/dL. P was calculated using the Mann-Whitney U test. P<0,05

The correlation coefficient of left renal RI with increase SDMA was – 0.170 with P-value 0.136. The correlation coefficient of right renal RI with increase SDMA was – 0.058 with P-value 0.603.

10. DISCUSSION

A number of papers have shown the value of two dimensional ultrasound analysis of kidney, however, few studies score the diagnostic value of the RI and there are no studies in subclinical patients for CKD in attempt of diagnosis in the early stages. SDMA is a previous biomarker in relation to creatinine,[8] so have we chosen it to make a correlation to RI and, thus, enable us to anticipate CKD.

Doppler is a non-invasive, fast, easy performing and painless diagnostic modality, however, we found out some difficulties in rating some patients, owing to the fact of some kidney numbers have not been quantified. Obesity, bowel meteorism, tachypnoea associated with stress or pain, or poor hemodynamics due to severe renal injury are considered major factors that can limit the performance of the Doppler analysis. [15] Many patients had severe loss of corticomedullary differentiation and other renal morphological changes, what makes difficult the RI assess. Cats in which the renal morphology was preserved, we experienced difficulty assessing RI in agitated or aggressive patients, merely. The selection of an interlobar artery to measure the RI in our study was based on the literature, which points out that the best signals for vascular assessment are always from large segmental arteries and,

consequently, the arcuate arteries from the kidney periphery should be averted). [12,16]

No significant difference was presented between right and left kidney RI´s. In a sample study of RI among a population of healthy and disease cats no statistically significant differences between the mean RI of both kidneys was noticed, either.[11] Oftenly, in case of serious disease already established, evaluating just one kidney may not have much effect on the patient's final RI result. On the other hand, for assessment in advance, changes can start unilateral and might be silent.

Six patients in this study had a difference of, at least 0.10, between the kidneys in the RI. A difference of 0.10 or higher between the kidney indices of the same patient may help to diagnose unilateral illness, even when the RI is within normal limits. [3]

The averages of the RI's presented here still fit within the RI's for healthy patients, [5] even though with values much closer to the RI's of patients with CKD, as the literature suggests an upper value of 0.70 for cats, [3,9] which is the same proposed as a limit for normal mean intrarenal RI in humans.[15]

An increased RI is a non-specific finding and it is seen (although not invariably) in cases of acute obstruction, acute renal disease, acute tubular

necrosis, glomerulopathy, perinephric or subcapsular fluid accumulation and severe hypotension[2].

A ROC curve was performed in order to determine a cutoff to assume a diagnosis of CKD in cats. [11] Based on obtained RI , figures above 0.63 was allowed for CKD. Such numbers demonstrated a sensitivity and specificity of 100%, so as to be very close to our RIs average (0.61 and 0.62), feasibly exposing a likely anticipation of CKD in our population.

Extrarenal factors may influence both the increase in RI and sSDMA, since the cat analyzed with the highest RI value did not have an increase in sSDMA. In human medicine, factors which affect the RI include age, blood pressure, pulse and respiratory rate. [17] This demonstrates the reason of inexistent statistical difference between the groups with normal SDMA and increased SDMA. Certainly, the low number of samples in the increased SDMA group may have interfered this result. The ideal environment would be to have a homogeneous group to perform the test. Recently, researchers have been studying about the SDMA biomarker and the causes of its influence, as in diabetic cats which presents lower values of SDMA than healthy cats. [18]

In our study, a larger population of cats was observed with an increase in the right RI, in spite of there has been a small population with an increase in sSDMA. There was no influence on the results because the study was blind to

the results of SDMA in the doppler evaluation. When comparing the RI to sSDMA, it was possible to peer at a significant correlation between the right kidney and the increase in sSDMA, however a clear reason for this occurrence we cannot explain yet.

In a study by Matos 2017, the indices were evaluated with the biomarker creatinine and, despite not having a correlation, there was a tendency to increase right RI with values of the later renal biomarker. When comparing this late biomarker (creatinine) to the early renal biomarker (SDMA), the creatinine has a positive correlation within higher SDMA.

RI evaluation is not recommended as a screening test for the presence of renal disease, but rather should be considered as an ancillary diagnostic. Evaluation by Doppler ultrasonographic of one kidney is not sufficient to provide an estimate of RI value for both organs in early disease whenever a serious illness is already established; In contrary, the patient's non-cooperation or altered renal morphology can make it difficult to reach this index.

In summary, it is possible to perform the RI of interlobar renal arteries in cats. However, we observed some difficulties in performing the RI analyses on cat exam, especially when they have concomitant the B-mode morphological changes like the loss of corticomedullary differentiation. Moreover, this difficulty also occurs in agitated and impatient and aggressive cats. A significant

correlation between the increased RI values between the increase in sSDMA is obtained, but the precise explanation for that is unclear.

11. CONCLUSION

For analysis of the RI of interlobar renal arteries in cats is necessary a cooperative patient. Our study showed a significant correlation between the values of the RI, specifically in the right kidney, with the increased sSDMA. Further studies are necessary to rule out other things that might influence RI and sSDMA values.

Conflict of interest The authors declared no potential conflicts of interest in regard of this research, authorship, and/or publication of this article.

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ANEXO 1 – FICHA TÉCNICA

Informações do paciente

NOME: **RAÇA:** **PROP:**

- Idade: _____ meses - anos
- Sexo: ⊡ macho ⊡ fêmea
- Peso: _____ kg
- Escore corporal: _____ (classificação 1-5)
- Estado reprodutivo : ⊡ íntegro ⊡ castrado
- Comportamento: ⊡ tranquilo ⊡ estressado ⊡ agressivo
- Sintomas brandos: ⊡ sim ⊡ não , Se sim quais: ⊡ hiporexia ⊡ vômito esporádico (frequência:) ⊡ prostrado ⊡ perda de peso ⊡ outro: _____
- Ingestão hídrica: ⊡ normal ⊡ aumentada ⊡ diminuída
- Histórico anterior? (trauma, obstrução, intoxicações, cirurgia, etc) _____ _____ _____
- Mensuração pressão arterial sistêmica: Comportamento durante mensuração: ⊡ tranquilo ⊡ estressado ⊡ agressivo ⊡ não foi possível

⊡ medida 1 _____ ⊡ medida 2 _____ ⊡ medida 3 _____

- Recebe alguma medicação? Motivo?

Informações do exame ultrassonográfico:

1. Comprimento renal RE: _____ RD: _____
2. Diâmetro pelve (transversal) RE: _____ RD: _____
3. Formato renal ⊡ normal ⊡ irregular ⊡ assimétricos ⊡ arredondado
4. Áreas de infarto ⊡ ausente ⊡ presente Quantas e tamanho: _____
5. Ecogenicidade do córtex ⊡ normal ⊡ aumentado ⊡ heterogêneo
6. Ecogenicidade da medula ⊡ normal ⊡ aumentado ⊡ heterogêneo ⊡ sinal da medular
7. Calcificação de parênquima renal ⊡ presente ⊡ ausente
8. Definição corticomedular ⊡ presente ⊡ parcialmente perdida ⊡ ausente (severamente perdida?)
9. Cisto Renal ⊡ cisto único ⊡ até 3 cistos em um rim ⊡ rins policísticos
10. Líquido livre adjacente ao rim ⊡ não ⊡ leve ⊡ moderado
11. Líquido subcapsular ⊡ não ⊡ presente
12. Cálculo renal ⊡ não ⊡ único ⊡ múltiplo ⊡ bilateralmente

13. Cálculo em ureter ⊡ não ⊡ único ⊡ múltiplo ⊡ bilateralmente
14. Cálculo em bexiga ⊡ não ⊡ único ⊡ múltiplo
15. Gordura perirrenal ⊡ normal ⊡ levemente hiper ⊡ hiperecogênica
16. Alguma alteração relevante em demais órgãos abdominais?
17. IR RE: RD:
18. IP RE: RD:

EXAMES DATA

UNIVERSIDADE FEDERAL DO PARANÁ
SETOR DE CIÊNCIAS AGRÁRIAS
COMISSÃO DE ÉTICA NO USO DE ANIMAIS

ANEXO 2 – CERTIFICADO COMITÊ DE ÉTICA

Certificamos que o protocolo número 043/2019, referente ao projeto **"Análise morfológica ultrassonográfica renal, doppler e elastrografia comparativa a dados clínicos laboratoriais e ao biomarcador SDMA idexx® em gatos assintomáticos e pouco sintomáticos",** sob a responsabilidade **Tilde Rodrigues Froes** – que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de Outubro, de 2008, do Decreto nº 6.899, de 15 de julho de 2009,e com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi aprovado pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA) DO SETOR DE CIÊNCIAS AGRÁRIAS DA UNIVERSIDADE FEDERAL DO

PARANÁ - BRASIL, com grau 2 de invasividade, em reunião de 07/08/2019.

Vigência do projeto	Agosto/2019 até Fevereiro/2020
Espécie/Linhagem	*Felis catus* (felino)
Número de animais	100
Peso/Idade	Variável/Variável
Sexo	Macho e fêmea
Origem	Proprietário/Particular.

CERTIFICATE

We certify that the protocol number 043/2019, regarding the project **"Renal ultrasonographic morphological analysis, doppler and elastrography comparative to laboratory clinical data and the SDMA idexx® biomarcant in asympletic and little symptomic cats"** under **Tilde Rodrigues Froes** supervision – which includes the production, maintenance and/or utilization of animals from Chordata phylum, Vertebrata subphylum (except Humans), for scientific or teaching purposes – is in accordance with the precepts of Law nº 11.794, of 8 October, 2008, of Decree nº 6.899, of 15 July, 2009, and with the edited rules from Conselho Nacional de Controle da Experimentação Animal (CONCEA), and it was approved by the ANIMAL USE ETHICS COMMITTEE OF THE AGRICULTURAL SCIENCES CAMPUS OF THE UNIVERSIDADE FEDERAL DO PARANÁ (Federal University of the State of Paraná, Brazil), with degree 2 of invasiveness, in session of 07/08/2019.

Duration of the project	August/2019 until February/2020
Specie/Line	*Felis catus* (feline)
Number of animals	100
Wheight/Age	Variable/Variable
Sex	Male and emale
Origin	Private.

Curitiba, 07 de agosto de 2019

Chayane da Rocha

Chayane da Rocha

Coordenadora CEUA-SCA

Comissão de Ética no Uso de Animais do Setor de Ciências Agrárias - UFPR

VITA

Médica veterinária graduada pela Universidade Federal do Paraná (UFPR), em 2012. Realizou o Externship em Diagnóstico por Imagem na Michigan State University – MSU nos Estados Unidos. Concluiu o Programa de Residência em Diagnóstico por Imagem modalidade de pós-graduação "Lato sensu", na Clinica Escola de animais de Companhia da Universidade Tuiuti do Paraná (UTP), no período de maio de 2013 a Fevereiro de 2014, totalizando XX horas. Cursou o Aperfeiçoamento em Diagnóstico por Imagem Avançado: Tomografia Computadorizada e Ressonância Magnética pelo CRVimagem no Rio de Janeiro, em 2015. Cursou o Programa de Pós-graduação em Ciências Veterinárias da Universidade Federal do Paraná (UFPR), nível Mestrado, no período de Março de 2018 a Março de 2020.