UNIVERSIDADE ESTADUAL PAULISTA
FACULDADE DE MEDICINA VETERINÁRIA E ZOOTECNIA

DIMETILARGININA SIMÉTRICA (SDMA) EM GATOS COM DOENÇA DO TRATO URINÁRIO INFERIOR OBSTRUTIVA

JESSICA CAVALCANTE DA NÓBREGA

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Dissertação apresentada junto ao Programa de Pós-Graduação em Medicina Veterinária da Faculdade de Medicina Veterinária e Zootecnia da Universidade Estadual Paulista para obtenção do título de Mestre em Medicina Veterinária.

Orientadora: Profa. Ass. Dra. Priscylla Tatiana C. Guimarães Okamoto

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ABREVIAÇÕES

ADMA – Dimetilarginina assimétrica

DRC – Doença renal crônica

DTUIF – Doença do trato urinário inferior de felinos

EPM – Erro padrão médio

FLUT – *Feline lower urinary tract disease*

GC – Grupo controle

GO – Grupo obstruído

LRA – Lesão renal aguda

RPC – Relação proteína e creatinina

sCr – Creatinina sérica

SDMA – Dimetilarginina simétrica

TFG – Taxa de filtração glomerular

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RESUMO

A doença do trato urinário inferior de felinos (DTUIF) corresponde a uma série de afecções que podem acometer a bexiga e a uretra desses animais. A forma obstrutiva é a consequência mais prevalente e mais grave dentre outras DTUIF, podendo levar o animal a azotemia pós-renal, redução da taxa de filtração glomerular (TFG) e a lesão renal aguda (LRA), que caso não seja tratada de forma eficiente, pode evoluir para doença renal crônica (DRC), uma doença frequente na população geriátrica felina. A creatinina sérica (sCr) é o biomarcador de TFG mais utilizado na clínica veterinária, porém apresenta baixa sensibilidade e diversos fatores que podem afetar seus valores. A dimetilarginina simétrica (SDMA) é um biomarcador mais recente na medicina veterinária que vem apresentado maior precocidade na detecção da perda da função renal e menor interferência de fatores extrarrenais, porém poucos são os trabalhos que determinam valores de SDMA em lesão renal de gatos. Este trabalho visou avaliar os valores de SDMA e compará-los com a sCr, ureia, dados hemogasométricos, escore clínico e tempo de obstrução de gatos com DTUIF obstrutiva. Os animais foram alocados em dois grupos experimentais, sendo 17 animais do grupo obstruído (GO) e 13 animais sadios para grupo controle (GC). As amostras foram coletadas antes da desobstrução (M0) e durante o tratamento clínico, nos momentos 12, 24 e 48 horas (M12, M24 e M48). Resultados obtidos demonstraram que no M48 do GO, 50% dos gatos obstruídos apresentavam valores de SDMA acima da normalidade, enquanto para sCr apenas 29,41% dos gatos apresentavam elevados. Quando comparado os diversos momentos de GO com GC, SDMA apresentou mais momentos de diferença estatística do que sCr. O SDMA apresentou correlação forte com sCr, ureia e potássio nos diferentes momentos de GO e forte correlação com tempo de obstrução e escore clínico em M0. A concordância do SDMA com sCr, ureia e potássio foi pobre a leve em M12 e M48, no M24 a concordância foi substantiva. Sugere-se que SDMA é biomarcador mais sensível para avaliar função renal em animais com DTUIF obstrutiva. Além disso, o tempo de obstrução interfere no estado clínico e valores de SDMA.

Palavras-chave: obstrução uretral, gatos, biomarcadores, urologia, nefrologia.

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ABSTRACT

Feline lower urinary tract disease (FLUTD) is a series of conditions that can affect the bladder and urethra of these animals. The obstructive form is the most prevalent and most serious consequence among other FLUTD, which can lead to post-renal azotemia and reduced glomerular filtration rate (GFR) and acute kidney injury (AKI), which if not treated effectively, can progress to chronic kidney disease (CKD), a common disease in the feline geriatric population. Serum creatinine (sCr) is the biomarker of GFR most commonly used in veterinary pratice, but it has low sensitivity and there are several factors that may affect its values. Symmetrical dimethylarginine (SDMA) is a newer biomarker in veterinary medicine that has been shown to be more precocious in detecting loss of renal function and less interference of extrarenal factors, but there are few studies determining SDMA values in feline kidney injury. This work aimed to evaluate SDMA values and to correlate them with sCr, urea, hemogasometric data, clinical score and duration of obstruction of felines with obstructive DTUIF. The animals were allocated into two experimental groups, 17 animals from the obstructed group (GO) and 13 healthy animals for control group (GC). Samples were collected before clearance (M0) and during clinical treatment at 12, 24 and 48 hours (M12, M24 and M48). The results obtained were that in GO M48, 50% of obstructed cats had SDMA values above normal, while for sCr only 29.41% of cats were elevated. When comparing the different moments of GO with CG, SDMA presented more moments of statistical difference than sCr. SDMA showed a strong correlation with sCr, urea and potassium at different times of GO and a strong correlation with obstruction time and clinical score at M0. The concordance of SDMA with sCr, urea and potassium was poor to mild in M12 and M48, in M24 the agreement was substantive. It is suggested that SDMA is the most sensitive biomarker for assessing renal function in animals with obstructive FLUTD. In addition, obstruction time interferes with clinical status and SDMA values.

Key words: urethral obstruction, cats, biomarkers, urology, nephrology.

CAPÍTULO I

REVISÃO DE LITERATURA

1. INTRODUÇÃO

Gatos têm apresentado crescimento de 8,1% no mercado pet brasileiro de 2013 a 2018 (IPB, 2019). Esse índice deve aumentar consequentemente a procura por atendimento veterinário para castração, além de aumentar o número de animais obesos e sedentários, fatores importantes que aumentam a predisposição ao desenvolvimento da doença do trato urinário inferior de felinos (DTUIF), uma doença que corresponde a uma série de afecções que podem acometer bexiga e uretra de gatos, de ambos os sexos, com maior incidência em machos entre 2 a 6 anos de idade (HOSTUTLER; CHEW; DIBARTOLA, 2005; MARTINS et al., 2013; NELSON; COUTO, 2003; RECHE; CAMOZZI, 2015).

Dentre diferentes DTUIFs, a obstrução uretral é a consequência mais prevalente e preocupante, pois pode levar a azotemia pós renal e distúrbios hidroeletrolíticos e/ou metabólicos (BARTGES et al., 1996), com incidência variando de 1 a 10% (CHOW et al., 1975; ELCOCK, 1981; ENGLE, 1977; FOSTER, 1975; LAWLER; SJOLIN; COLLINS, 1985; REIF et al., 1977) e cerca de 9% dos pacientes acometidos podem vir a óbito ou ainda cerca de 23% são eutanasiados (GERBER; EICHENBERGER; REUSCH, 2008).

Acompanhar a função renal de pacientes acometidos com DTUIF obstrutiva após tratamento de desobstrução é importante pois sabe-se que o bloqueio do fluxo urinário desencadeia uma rápida redução na taxa de filtração glomerular (TFG) (NELSON; COUTO, 2015a; RECHE; CAMOZZI, 2015), provocando lesão renal aguda (LRA) e que pode ainda evoluir para uma doença renal crônica (DRC) (WEN et al., 1999), que é uma doença progressiva e irreversível. Portando, o melhor tratamento atualmente ainda é acompanhar a função renal e tratar de forma precoce (POLZIN, 2011).

Observar a função renal na medicina veterinária ainda é um desafio pois o método padrão ouro é pela depuração de inulina após infusão contínua em 24 horas, o que por si só já seria dificultoso para clínica veterinária, mas também kits comerciais e métodos laboratoriais de análise, são de difícil acesso e pouco padronizado em animais (VON HENDY-WILLSON; PRESSLER, 2011). Outro biomarcador estudado para avalição da TFG é iohexol, que depende de infusão única, mas análise rítmica e demorada de

depuração, além de poder apresentar diferença na depuração entre seus isômeros (VAN HOEK et al., 2007, 2008, 2009) e em humanos é nefrotóxico, apesar de em gatos hígidos não demonstrar toxicidade (BAILEY et al., 2009; VAN HOEK et al., 2007, 2008). Hoje na rotina clínica o biomarcador ainda mais utilizado para avaliação de TFG é a creatinina sérica (sCr), porém cerca de 20% da sua excreção é de origem tubular (VAN ACKER et al., 1992) e níveis desse biomarcador podem variar com a idade, sexo, massa muscular magra, metabolismo muscular, estado de hidratação e baixa TFG, além disso a quantidade de secreção tubular de creatinina resulta em uma superestimação da função renal (HALL et al., 2014a). Esse biomarcador é insensível, porque aumentos de sCr são leves e, muitas vezes, permanecem dentro do intervalo de referência, até que aproximadamente 75% de todos os néfrons não estejam mais funcionais (POLZIN, 2011).

Nos últimos anos, a dimetilarginina simétrica (SDMA) tem se mostrado como um novo biomarcador para avaliação da TFG e até presente momento vem demonstrando ser mais sensível do que a sCr e sofrendo menos influência extrarrenal para alteração de seus valores (DAHLEM et al., 2017; HALL et al., 2015, 2016; HOKAMP; NABITY, 2016; NABITY et al., 2015; PEDERSEN et al., 2006).

Nenhum trabalho ainda foi realizado verificando níveis de SDMA em gatos com DUITF obstrutiva, portanto, nosso objetivo é investigar a utilidade deste biomarcador na avaliação da função renal em pacientes felinos machos que apresentem DTUIF obstrutiva.

2. REVISÃO DE LITERATURA

2.1 Doença do Trato Urinário Inferior Obstrutiva

Os termos DTUIF e SUF têm sido usados desde o começo do século XX (KIRK, 1925) para descrever a combinação de sinais clínicos relacionados à micção irritativa, mas não identificam a etiologia subjacente (HOSTUTLER; CHEW; DIBARTOLA, 2005). Recentemente, outra nomenclatura, “síndrome de pandora”, foi atribuída a afecções do trato urinário inferior devido à dificuldade de identificar a etiologia (WESTROPP; BUFFINGTON, 2016).

2.1.1 Epidemiologia

A forma obstrutiva das doenças do trato urinário inferior em felinos é a mais prevalente e também a mais grave, e se não revertida a tempo pode levar o paciente à óbito (WESTROPP; BUFFINGTON; CHEW, 2005). Ademais, taxas de obstrução recorrente após o primeiro episódio são elevadas e variam entre 14,8% e 50% (FULTS; HEROLD, 2012; GERBER; EICHENBERGER; REUSCH, 2008; RECHE; HAGIWARA, 2004; SEGEV et al., 2011).

DTUIF obstrutiva acomete frequentemente gatos machos jovens e adultos, em vista da conformação longa e estreita da uretra (HOUSTON et al., 2003; KRUGER et al., 1991; LEE; DROBATZ, 2003; LEKCHAROENSUK; OSBORNE; LULICH, 2001). Baixo volume urinário e baixa frequência de micção, causados por dietas restritamente secas, pouca atividade física e consequentemente obesidade, podem predispor ao surgimento da forma obstrutiva da DTUIF (SEGEV et al., 2011). A recidiva da obstrução uretral também pode ocorrer quando gatos ficam com restrição ambiental, que vivem apenas em ambientes internos e animais que consomem apenas alimentos secos (SEGEV et al., 2011), embora o tipo de alimento consumido não tenha sido significante em outro estudo (GERBER et al., 2008). Um estudo retrospectivo também mostrou uma associação significativa entre obstrução recorrente e tamanho do cateter ou uso de fármacos antiespasmódicos (EISENBERG et al., 2013).

No Brasil, foi relatado alta prevalência para DTUIF dentre todos os gatos atendidos no Hospital Veterinário da Universidade Federal de Viçosa, sendo 53,7% a forma obstrutiva (BALBINOT et al*.,* 2006). Demais estudos mostram que a DTUIF obstrutiva ocorre entre 18% a 58% (GERBER et al., 2005; GERBER; EICHENBERGER; REUSCH, 2008; KRUGER et al., 1991; LEKCHAROENSUK; OSBORNE; LULICH, 2002). No Hospital Veterinário da Universidade da Pensilvânia, a obstrução uretral representa aproximadamente 9% do percentual anual de casos gatos de emergência (LEE; DROBATZ, 2003).

Outro estudo descreve que 9% dos gatos acometidos pela doença vieram a óbito, 51% apresentaram sinais recorrentes de DTUIF após alta, independentemente da causa, 36% re-obstruíram e 23% foram eutanasiados devido à doença do trato urinário inferior obstrutiva (GERBER, EICHENBERGER E REUSCH, 2008).

2.1.2 Etiologia

Os fatores etiológicos de todas DTUIFs incluem agentes infecciosos, urólitos, cistite idiopática, alterações congênitas, tampão uretral, dieta, neoplasias e traumas (GERBER et al., 2005; OSBORNE; KRUGER; LULICH, 1996). Entre 50 a 65% dos casos a causa da DTUIF não é identificada, sendo designada como idiopática, dificultando o diagnóstico e terapia, já que a etiologia é multifatorial (MARTINS et al., 2013; RECHE; CAMOZZI, 2015; WESTROPP; BUFFINGTON, 2016).

A obstrução do lúmen uretral pode ocorrer de três maneiras: por oclusão mecânica, pela deposição de debris na luz uretral, sendo essa denominada de obstrução intramural; oclusão anatômica, causada por lesão no sítio de obstrução, podendo ser mural ou extramural; e ainda obstrução por oclusão funcional (LAPPIN; BLANCO, 2004).

As principais causas de afecções intramurais compreendem os tampões uretrais (coágulos, mucoproteínas e/ou cristais, debris teciduais, corpo estranho), os urólitos e as neoplasias (BARSANTI et al., 1996). Estudos etiológicos anteriores encontraram evidências de plugue uretral em 60% dos casos, cálculos uretrais em 20%, estenose ou neoplasia em menos de 5%

combinados, e o restante não apresentou evidência clara de obstrução física (OSBORNE; KRUGER; LULICH, 1996). Em estudo posterior, a incidência de obstrução idiopática foi maior em 53%, por urolitíase foi de 29% e apenas 18% de plugues uretrais (GERBER; EICHENBERGER; REUSCH, 2008). No Brasil, um estudo evidenciou que o principal fator causador de DTUIF obstrutiva ocorre por tampões uretrais, afetando 67% dos casos (RECHE et al., 1998). Ainda assim, urólitos ocorrem comumente na uretra de gatos, sendo que o oxalato de cálcio representa 40 a 50% de urocistólitos (BARTGES, 2016).

2.1.3 Fisiopatologia

O bloqueio do fluxo urinário geralmente leva à azotemia pós-renal, prejudicando os néfrons e proporcionando LRA com possível progressão a coma e óbito dentro de 72 horas se não desobstruído, ou de três a seis dias após a desobstrução (FINCO; BARSANTI, 1984). A evolução ocorre devido ao acúmulo de toxinas urêmicas no sangue, acompanhado por desequilíbrios eletrolíticos e ácido-básicos que podem ser analisados por exame hemogasométrico (SEGEV et al., 2011). A obstrução mecânica do fluxo de urina desencadeia uma redução rápida e dramática na TFG, desenvolvimento de inflamação intersticial e edema e, se não for controlada, atrofia tubular, fibrose e morte celular apoptótica (WEN et al., 1999).

A LRA está associada a um aparecimento súbito de dano parenquimatoso renal com comprometimento posterior da função renal. Lesões graves podem levar a falência renal aguda que se caracteriza por altas taxas de morbidade e mortalidade. A alta mortalidade associada à falência renal aguda é causada pela detecção retardada devido a testes diagnósticos insensíveis (COWGILL; LANGSTON, 2011). Ademais, animal que apresente LRA e não tenha boa recuperação, pode apresentar futuramente DRC, que é uma condição comumente diagnosticada na população geriátrica (ALGE; ARTHUR, 2015; ROSS, 2011; SEGEV et al., 2011). A prevalência da DRC aumenta para até 31% em gatos hígidos com mais de 15 anos de idade (LULICH et al., 1992; O'NEILL et al., 2013). As doenças renais são comuns em gatos, e muitas vezes estão associadas a um prognóstico ruim nos estádios avançados da doença (POLZIN, 2011).

2.1.4 Sinais clínicos

Os sinais clínicos da DTUIF obstrutiva dependem da duração da doença e do grau da obstrução. Os primeiros sinais observados são polaquiúria, disúria e/ou estrangúria, hematúria e possível obstrução uretral parcial ou completa (HOSTUTLER; CHEW; DIBARTOLA, 2005; MARKWELL; BUFFINGTON; SMITH, 1998).

Os sinais clínicos típicos da uremia que podem ser observados em pacientes com azotemia pós-renal incluem anorexia, vômitos, letargia, fraqueza e anúria (POLZIN; OSBORNE; BARTGES, 1996). Pacientes com azotemia pós-renal também podem apresentar sinais cardiovasculares resultantes de distúrbios hidroeletrolíticos, além de apresentarem desidratação, hipercalemia e acidose metabólica (POLZIN; OSBORNE; BARTGES, 1996).

2.1.6 Diagnóstico

O diagnóstico é feito pelo histórico clínico e exame físico e laboratoriais, exames radiográficos e ultrassonográficos do paciente (BARSANTI et al., 2004). O exame de ultrassonografia abdominal em gatos com obstrução uretral não fornece dados suficientes para o diagnóstico, já que a uretra não é visível nesta abordagem. Contudo, a radiografia abdominal é recomendada em vista da incidência de 20% de cálculos urinários em gatos com DTUIF obstrutiva, sendo indicada sua realização antes da cistocentese, desde que o animal esteja estável (NELSON; COUTO, 2015b). A radiografia contrastada evidencia cálculos radiotransparentes, ruptura uretral ou vesical, divertículo uracal, neoplasias, estenoses ou obstrução uretral (HOSTUTLER; CHEW; DIBARTOLA, 2005; RECHE; CAMOZZI, 2015).

Urinálise e urocultura devem ser realizadas ao menos uma vez (e em gatos previamente sondados), porém a maioria dos gatos jovens saudáveis não apresenta uma cistite bacteriana verdadeira (NELSON; COUTO, 2015b).

O eletrocardiograma deve ser realizado devido a hipercalemia que pode gerar arritmia, sendo a bradicardia a mais grave (GALVÃO et al., 2010).

2.1.7 Tratamento

A cistocentese é indicada antes do restabelecimento do fluxo de urina pela uretra com o objetivo de facilitar a desobstrução e diminuir os riscos de ruptura da bexiga durante a sondagem. Entretanto, a parede da vesícula urinária pode estar comprometida, podendo ocorrer trauma e ruptura. Pela cistocentese também é possível coletar uma amostra de urina não contaminada para urinálise, cultura e antibiograma (HOSTUTLER; CHEW; DIBARTOLA, 2005).

DTUIF obstrutiva requer tratamento imediato, normalmente acompanhado de hospitalização, que inclui correção de parâmetros eletrolíticos e ácido-básicos. Assim, é de extrema necessidade a realização da hemogasometria, para estabilização clínica do animal, assim que identificado o problema (GERBER; EICHENBERGER; REUSCH, 2008)

A hipercalemia branda ou moderada inferior a 8,0mEq/L, geralmente é tratada com a fluidoterapia inicial (GALVÃO et al., 2010). Estudos mais recentes demonstram que uma solução balanceada, mesmo com potássio, não interfere nos parâmetros eletrolíticos e acido básicos. Ringer com lactato é a solução de escolha para a reposição de gatos com obstrução (RECHE; CAMOZZI, 2015).

Após a estabilização do paciente deve-se promover o reestabelecimento do fluxo urinário pela cateterização em condições anestésicas, após desobstrução a sonda por 48 horas, em alguns casos é necessária a retirada cirúrgica de urólitos e uretrostomia perineal (GERBER; EICHENBERGER; REUSCH, 2008).

A atonia do músculo detrusor é comum em gatos obstruídos associado a um período maior que 24 horas de obstrução devido à distensão excessiva da bexiga. A bexiga deve ser comprimida 4 a 6 vezes ao dia, se não for possível a compressão manual, o cateter permanente é indicado (NELSON; COUTO, 2015b; RECHE; CAMOZZI, 2015).

2.1.8 Prognóstico

O prognóstico é reservado, pois alguns casos podem atingir graus mais avançados como também ocorre recidiva, podendo, ser fatal (GERBER; EICHENBERGER; REUSCH, 2008)

2.1.9 Profilaxia

O tratamento profilático para evitar re-obstrução consiste basicamente em um manejo ambiental, redução de estresse, alterações alimentares e aumento da ingestão hídrica e intervenção medicamentosa (LITTLE, 2012).

2.2 Biomarcadores na clínica veterinária e TFG

Biomarcadores têm por definição serem um indicador físico, funcional ou bioquímico de um processo fisiológico ou de uma doença e que tenha utilidade diagnóstica e/ou prognóstica com a capacidade de ser medido de forma precisa e reprodutível (YERRAMILLI et al., 2016).

Com o investimento em pesquisas médicas foi possível o avanço científico visando obter diagnósticos precoces, antes mesmo que os sinais clínicos das doenças sejam manifestados nos pacientes (YERRAMILLI et al., 2016).

Há uma variedade de biomarcadores já utilizados para o diagnóstico e prognóstico de doenças na pesquisa clínica, mas poucos são usados na rotina ambulatorial e hospitalar (YERRAMILLI et al., 2016). Existem vários requisitos e critérios rigorosos que um biomarcador deve satisfazer para ser adotado na prática clínica (ROLLINS, 2012). Alguns dessas qualidades necessárias estão representadas na Figura 1.

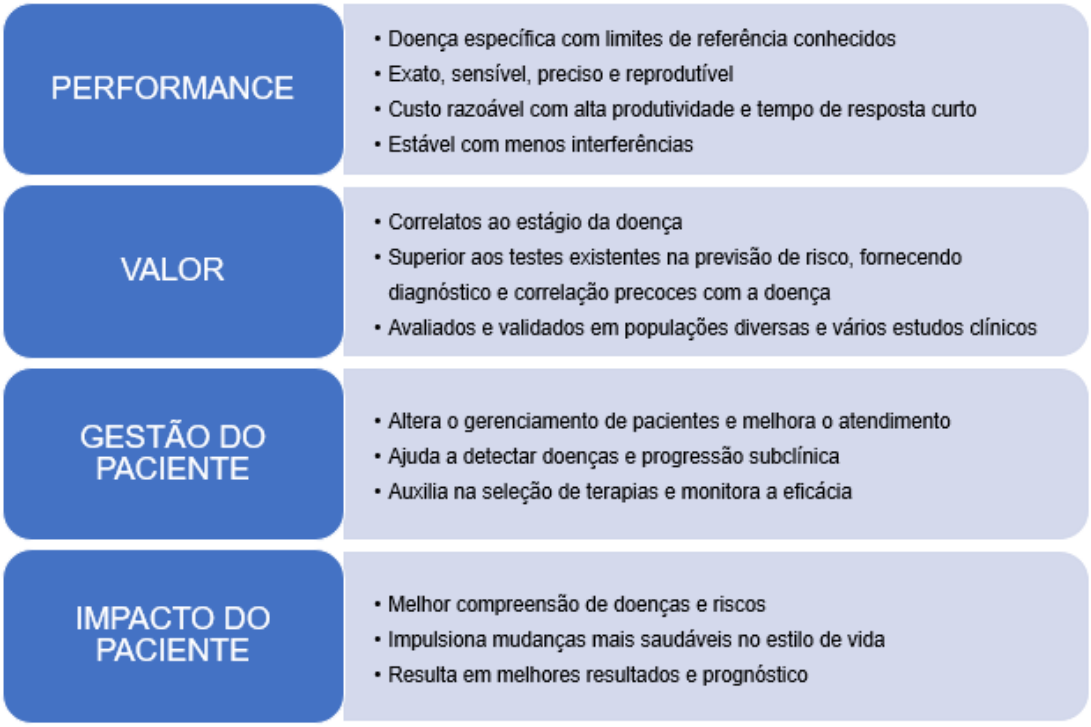

Figura 1. Características de um biomarcador ideal (YERRAMILLI et al., 2016).

Assim como na medicina, a utilização de biomarcadores é necessária em diversas áreas na medicina veterinária, especialmente nas especialidades cardiovasculares, oncológicas, gastroentéricas, endócrinas, reprodutivas e nefro-urológicas (ECKERSALL; BELL, 2010; HENRY, 2010; TARNOW et al., 2007).

Na nefrologia, em que preconiza-se o diagnóstico precoce da lesão renal, os principais biomarcadores utilizados são aqueles que indicam que há uma redução da TFG, bem como a presença de lesões glomerulares, tubulares e em ductos ou que demonstrem a presença de doenças autoimunes antecedentes a lesão renal (VON HENDY-WILLSON; PRESSLER, 2011; YERRAMILLI et al., 2016).

A avaliação da TFG é a mais precisa e mais sensível para a detecção precoce da disfunção renal. No entanto, muitos exames que avaliam a TFG são dispendiosos, demandam tempo e não são adequados para uso generalizado como um teste de triagem (KERL; COOK, 2005). Marcadores apropriados para medição da TFG devem ser filtrados livremente através do glomérulo, não ser ligados às proteínas plasmáticas, pois atrasaria a filtração

e levaria a uma estimativa falsamente diminuída da TFG, e não ser reabsorvidos nem secretados pelos túbulos renais (VON HENDY-WILLSON; PRESSLER, 2011).

A avaliação da TFG foi um desafio impraticável na clínica médica veterinária devido à dificuldade de colheita de sangue, urina ou ambos e mensuração de seus elementos biomarcadores em um tempo específico.

Atualmente, a TFG pode ser realizada pelo *clearance* plasmático de iohexol, inulina e de creatinina (BEXFIELD et al., 2008; BOVEE; JOYCE, 1979; GLEADHILL; MICHELL, 1996; WATSON et al., 2002).

A inulina é um polímero de frutose a qual é considerada padrão ouro para estimação da TFG (FINCO et al., 1991; HALLER et al., 1998; KUKANICH et al., 2007). No entanto, várias limitações minimizaram o uso de depuração renal da inulina em ambientes de pesquisa, pois ensaios disponíveis para medição da inulina são tecnicamente desafiadores e não estão disponíveis facilmente (VON HENDY-WILLSON; PRESSLER, 2011). Além disso, a avaliação da inulina consiste em uma coleta de urina total em 24 horas, desta forma, animais devem ser colocados em gaiolas metabólicas ou serem cateterizados por sonda uretral para a remoção e avaliação da urina colhida em intervalos regulares (KUKANICH et al., 2007; MOE; HEIENE, 1995).

O iohexol é um meio de contraste iodado, solúvel em água, não-iônico, de baixa osmolaridade, que tem se mostrado uma alternativa à inulina e à biomarcadores radioativos para a estimativa da TFG (GOY-THOLLOT et al., 2006) em cães (BEXFIELD et al., 2008; BROWN et al., 1996; FINCO; BRASELTON; COOPER, 2001; GLEADHILL; MICHELL, 1996; GOY-THOLLOT et al., 2006) e em pacientes felinos (BROWN et al., 1996; FINCH et al., 2011; GOY-THOLLOT et al., 2006; MIYAMOTO, 2001a, 2001b, VAN HOEK et al., 2007, 2008, 2009).

O iohexol demonstra endo e exo-isomerismo (FOSTER; SOVAK, 1988) e alguns estudos relataram uma diferença na depuração dos dois isômeros em gatos sugerindo que a medição do iohexol total pode levar a imprecisões para determinar a TFG (VAN HOEK et al., 2007, 2008, 2009). No entanto, estudo não demonstrou diferença na depuração entre os dois isômeros e descobriu que, após a administração, não há conversão significativa de um isômero para o outro (FINCH et al., 2011). Apesar das preocupações em relação às

nefropatias induzidas por contraste em pacientes humanos, não foram relatados efeitos adversos em estudos de depuração plasmática utilizando iohexol em gatos hígidos (BAILEY et al., 2009; VAN HOEK et al., 2007, 2008).

2.2.1 Creatinina sérica

A creatinina é uma proteína que se origina principalmente da biossíntese dos aminoácidos glicina, arginina e metionina (KERL; COOK, 2005) e é produzida constantemente no organismo a partir da quebra do fosfato de creatina nos tecidos musculares (BOVEE; JOYCE, 1979). Essa molécula é minimamente influenciada pela ingestão de proteínas, metabolismo ou atividade física (BOVEE; JOYCE, 1979). É um biomarcador renal pois é eliminado exclusivamente pelos rins no cão e no gato (BRAUN; LEFEBVRE; WATSON, 2003), porém cerca de 20% da sua excreção é de origem tubular (VAN ACKER et al., 1992).

Tradicionalmente, a análise da concentração sCr é utilizada para o diagnóstico da doença renal (FINCH, 2014). No entanto, esse biomarcador é insensível, porque os aumentos em sCr são leves e, muitas vezes, permanecem dentro do intervalo de referência, até que aproximadamente 75% de todos os néfrons não estejam mais funcionais (POLZIN, 2011). Além disso, níveis de sCr podem variar com a idade, sexo, massa muscular magra, metabolismo muscular e estado de hidratação e baixa TFG, ademais a quantidade de secreção tubular de creatinina resulta em uma superestimação da função renal (HALL et al., 2014a). Finalmente, durante alterações agudas na filtração glomerular, a sCr não descreve com precisão a função renal até que o equilíbrio no estado estacionário tenha sido atingido, o que pode exigir vários dias (POLZIN, 2013). Estudos em animais mostraram que, enquanto a LRA pode ser prevenida e/ou tratada por várias manobras, estas devem ser instituídas muito cedo após o insulto, muito antes do aumento da sCr (DEVARAJAN, 2006; HEWITT; DEAR; STAR, 2004).

A sCr também não é marcador apropriado para a sinalização de LRA em estados clínicos graves, principalmente nos quadros de sepse, devido à sua baixa taxa de produção em consequência de distúrbios térmicos, hepáticos e pressóricos (DOI et al., 2009). Ademais, em gatos com diagnóstico de

hipertireoidismo, a elevada TFG associada a baixa quantidade de massa muscular corpórea, leva a concentrações de sCr diminuídas (WILLIAMS et al., 2010).

Complementarmente, animais em tratamento com certas medicações, como cefalosporinas, aminoglicosídeos, trimetropina e fenacemida, podem demonstrar concentrações de sCr aumentadas e a sCr ainda pode apresentar falsos valores laboratoriais nas condições de amostras hemolisadas, lipêmicas e ictéricas (NANJI; POON; HINBERG, 1987; PEAKE; WHITING, 2006).

2.2.2 Dimetilarginina simétrica (SDMA)

SDMA é um biomarcador indireto da TFG e da função renal (DAHLEM et al., 2017; HALL et al., 2016). Esse biomarcador foi identificado pela primeira vez em 1970 (KAKIMOTO; SHIGENORI, 1970) e mais tarde caracterizado como uma molécula que é principalmente eliminada pelos rins (VALLANCE et al., 1992).

A modificação pós-traducional dos grupos da arginina ocorre nas mitocôndrias envolvendo a enzima arginina-metiltransferase, que resulta na formação de 2 isômeros estruturais, SDMA e dimetilarginina assimétrica (ADMA) (TANG et al., 2000), como demonstrado na Figura 2.

Vallance et al. (1992) descreveram o ADMA como um inibidor endógeno da síntese de óxido nítrico, além de ser um competidor da arginina, substrato utilizado pela enzima óxido nítricosintase. Níveis basais de óxido nítrico são necessários para a manutenção do fluxo sanguíneo e perfusão renal, favorecendo a biogênese celular mitocondrial, porém, óxido nítrico em excesso é deletério para organismo, pois também é um radical livre com poder oxidante (DUARTE MOTE et al., 2008), sendo capaz de inibir a cadeia de fosforilação oxidativa e reduzir o consumo de oxigênio levando a apoptose e necrose tecidual (DUARTE MOTE et al., 2008).

Estudos experimentais em ratos indicam que a inibição crônica da síntese de óxido nítrico endotelial resulta em hipertensão sistêmica e glomerular, proteinúria e glomeruloesclerose (ZATZ; BAYLIS, 1998). As concentrações de óxido nítrico também podem estar diminuídas em pacientes humanos com LRA, DRC e falência renal terminal, o que acelera a progressão

da doença (SCHMIDT et al., 1999; SCHMIDT; BAYLIS, 2000; WANNER et al., 2002).

Diferente da ADMA, acreditava-se que a SDMA fosse completamente eliminada pela urina (JEPSON et al., 2008). No entanto, novos dados sugerem que a SDMA também possui, até certo ponto, eliminação enzimática que possa implicar na disfunção endotelial de pacientes com doença renal (JEPSON et al., 2008; SCHWEDHELM; BÖGER, 2011).

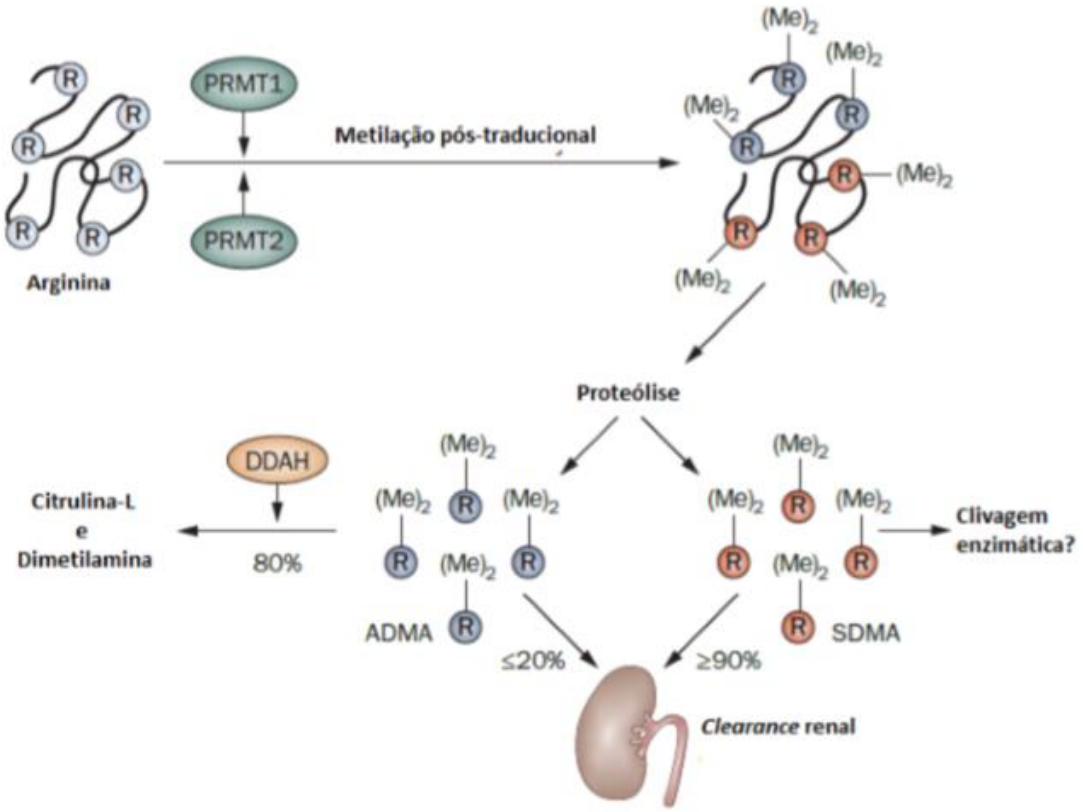

Figura 2. Representação esquemática da metilação da arginina pelas enzimas arginina-metiltransferase por proteólise, formando ADMA e SDMA (SCHWEDHELM; BÖGER, 2011).

Concentrações séricas e urinárias de SDMA apresentaram forte correlação com *clearance* de creatinina em pessoas com DRC em 1997 e SDMA sérico foi sugerido um bom biomarcador de doença renal (MARESCAU et al., 1997). Em 2006, uma metanálise mostrou correlações entre SDMA e testes de função renal significativos em humanos (KIELSTEIN et al., 2006).

O primeiro estudo clínico de SDMA na nefrologia veterinária relatou que SDMA tem forte correlação com a sCr em gatos com DRC e hipertensão

(JEPSON et al., 2008). Braff et al. (2014) demonstraram que níveis séricos de SDMA correlacionaram-se fortemente com a TFG em gatos com presença ou ausência de azotemia. Outros estudos determinaram que o SDMA se correlaciona fortemente com a TFG em gatos com e sem evidência laboratorial e clínica de diminuição da função renal (HALL et al., 2014a, 2014b).

O SDMA apresenta vantagens sobre a sCr, além da detecção precoce da perda da função renal, o biomarcador é menos afetado por fatores extrarrenais como idade, sexo, raça, massa corporal magra e regurgitação mitral (DAHLEM et al., 2017; HALL et al., 2015, 2016; HOKAMP; NABITY, 2016; NABITY et al., 2015; PEDERSEN et al., 2006).

SDMA também não tem papel no comprometimento renal e cardíaco, quando demonstrado que TFG, função cardíaca e pressão arterial se mostraram inalteradas em camundongos que receberam infusões crônicas de SDMA por 28 dias (VELDINK et al., 2013).

Valores de SDMA foram correlacionados em cães com LRA e DRC, porém não há valores que referenciem especificamente LRA com esse biomarcador (DAHLEM et al., 2017). A comunidade científica *International Renal Interest Society* (IRIS) reconheceu o SDMA como um biomarcador diretriz para o diagnóstico precoce da DRC e estadiamento da doença (IRIS, 2019), porém não há um *guideline* para LRA com SDMA (IRIS, 2016). O intervalo de referência para SDMA sérico em gatos adultos e saudáveis foi estabelecido em menos de 14 µg/dL (IDEXX Laboratories, Inc, Westbrook, ME).

Hall et al. (2017) estudaram o SDMA em pacientes felinos com cálculos renais e concluíram que o tempo médio do aumento de SDMA sérico ocorreu em 26,9 meses antes do aumento da sCr. Entretanto, ainda são escassos em literatura veterinária estudos publicados até o presente momento sobre os níveis séricos do SDMA em gatos com LRA e especificamente daqueles em azotemia pós-renal por obstrução urinária.

3. OBJETIVOS

3.1 Objetivo geral

Esse estudo tem como objetivo analisar a concentração sérica de SDMA em gatos machos com doença do trato urinário inferior obstrutiva.

3.2 Objetivos específicos

Avaliar e comparar a depuração de SDMA e creatinina em gatos com DTUIF obstrutiva antes e após tratamento de desobstrução.

Avaliar e correlacionar os resultados de ureia, creatinina, RPC, densidade urinária, glicosúria e dados hemogasométricos com concentração sérica de SDMA em gatos com DTUIF obstrutiva.

Avaliar e correlacionar escores clínicos com a concentração sérica de SDMA em gatos com DTUIF obstrutiva.

CAPÍTULO II

ARTIGO CIENTÍFICO

ARTIGO CIENTÍFICO

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Title: Symmetrical dimethylarginine in cats with obstructive lower urinary tract disease

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ABSTRACT

Objectives This study aimed at evaluating the Symmetrical Dimethylarginine (SDMA) values in cats with obstructive Feline Lower Urinary Tract Disease (FLUTD), in addition to establishing correlations with SCr, urea, blood gas test parameters, clinical score and obstruction time.

Methodology The animals were divided into two experimental groups, with 17 animals in the Obstruction Group (OG) and 13 healthy animals in the Control Group (CG). Samples were collected before the blockage is cleared (M0), as well as during the treatment 12, 24 and 48 hours after the process (M12, M24 and M48).

Results At M48, 50% of the cats in the OG presented increased SDMA values, while only 29.41% presented increased SCr. When comparing the OG with the CG at various moments, the SDMA values presented more instances of statistically significant differences than serum creatinine. These results suggest that SDMA is a sensitive biomarker of renal function in felines with obstructions, unlike serum creatinine. In the OG, SDMA presented a strong correlation with SCr, urea and potassium at various moments, in addition to a strong correlation with obstruction time and clinical score at M0. The correlation with bicarbonate was week. The concordance between SDMA, SCr, urea and potassium was mild at M12 and M48, but substantial at M24.

Conclusions & Relevance These results suggest that SDMA is a sensitive biomarker to evaluate renal function in animals with obstructive FLUTD. In addition, obstruction time interferes with the clinical condition of the animals and with the SDMA values.

Keywords: SDMA, urethral obstruction, biomarkers, urology, nephrology.

INTRODUCTION

The Feline Lower Urinary Tract Disease (FLUTD) corresponds to a series of afflictions that may attack the urinary bladder and the urethra irrespective of sex, although the largest incidence has been observed in males between 2 and 6 years-old due to the long and narrow nature of the urethra, particularly in neutered, obese and sedentary animals. [1–4]

Urethral obstruction is the most concerning complication of the disease, and may lead to postrenal azotemia, electrolytic disorders, metabolic disorders, and, if not treated quickly, may even lead to the death of the animal. [5]

It has been noted that, regardless of therapy or recovery, recurrence happens in about 35 to 50% of the patients, particularly during the six months following the initial episode.[6] Animals that may be predisposed to the recurrence of the urethral obstruction include those with environmental restrictions, living only indoors, and those that are

given only dry feed[7], although the type of food consumed has not been significant in this study.[8]

It is important to monitor the renal function of patients with obstructive FLUTD after the removal of the blockage, because it is known that obstruction in the urinary flow in the species usually leads to postrenal azotemia, which impairs the nephrons and causes acute kidney injury (AKI). This may possibly lead to a coma and death within 72 hours if the obstruction is not cleared, or within three to six days after the obstruction is cleared.[9] The mechanical obstruction of the flow of urine leads to a fast and severe reduction in the glomerular filtration rate (GFR), to the development of interstitial inflammation and edema, and, if uncontrolled, tubular atrophy, fibrosis and apoptosis.[10]

The AKI is associated with the sudden occurrence of parenchymatous damage in the kidneys with later impairment of the renal function. Severe injuries may lead to acute kidney failure, which is characterized by high morbidity and mortality rates. The high mortality rates are associated to the late detection of the condition due to insensitive diagnostic tests.[11] Animals that do not recover well from AKI may later develop Chronic Kidney Disease (CKD), which is a progressive and irreversible condition more commonly diagnosed in the geriatric population. Therefore, the best option available nowadays is to monitor the renal function and institute the treatment early when possible.[7,12-14] Kidney diseases are quite common in cats and are often associated with a bad prognosis during the later stages of the disease.[14]

Monitoring the renal function in the routine of veterinary practice still represents a considerable challenge because the gold standard procedure is inulin clearance following continuous infusion for 24 hours. In addition, the commercially-available kits and laboratory analysis methods are not readily-available and unstandardized in animals.[15] Another biomarker that has been studied to evaluate GFR is iohexol, which depends on a single infusion, but the clearance is slow and the results may differ according to the isomer[16-18]. Iohexol is nephrotoxic in humans, but no toxicity has been observed in healthy cats.[19,16,17] Currently, the most widely used biomarker for the evaluation of the GFR is serum creatinine (SCr). However, about 20% of the excretion of this biomarker is of tubular origin[20] and its levels may vary according to age, sex, lean muscle mass, muscle metabolism and hydration state.[21] Over the last few years, symmetric dimethylarginine (SDMA) has emerged as a new biomarker for the evaluation of the GFR.[22,23] SDMA is an amino acid formed by the methylation of arginine, which is released into the blood flow by the degradation of Type II protein arginine methyltransferase[24] and excreted by the kidneys without any signs of tubular resorption for reuse.[25,26]

SDMA has certain advantages over SCr. In addition to the early detection of the impairment of the renal function, SDMA is less affected by extrarenal factors such as age, sex, breed, lean body mass and mitral regurgitation.[22,23,25,27-29]

It is known that obstructive FLUTD may promote a fast reduction in the GFR and the serum concentration of SDMA in these animals is assumed to be high, similarly to serum creatinine.[4,30] However, the serum concentrations of SDMA in cats with urethral obstruction is yet to be fully studied. Therefore, this study aims at investigating the usefulness of this biomarker in animals with obstructive FLUTD.

METHODS

Animals & Experimental Groups:

Thirty male cats of various ages were recruited for the study irrespective of breed and weight. They were allocated into two distinct groups: the control group (CG), comprised of 13 healthy animals; and the obstruction group (OG), comprised of 17 cats presenting symptoms and clinical profiles compatible with obstructive FLUTD.

A single moment was analyzed for the animals in the CG and four moments were analyzed for the animals in the OG, with the first analysis (M0) before the treatment, and subsequent analyses 12, 24 and 48 hours (M12, M24 and M48, respectively) after the treatment.

Inclusion and Exclusion Criteria

The inclusion criteria for the OG were male cats with the first total urethral obstruction confirmed through the clinical history (with reports of strangury) and a physical examination observing pain upon abdominal palpation and a bloated urinary vesicle due to ischuria. Exclusion criteria were the administration of antimicrobial or anti-inflammatory medication in the 7-14 days before the study, as well as cystocentesis prior to the study. In addition, animals with recurrent or partial obstructions, congenital malformations and neoplasms were excluded from the study.

Clinical Evaluation and Physical Examination

The clinical evaluation was conducted before the start of the cystocentesis and clearance of the lower urinary tract. The clinical score was established by assessing the appetite, emesis, mental state, position of the head and dehydration of the animals according to Table 1. Hydration was evaluated according to Feitosa.[31] The physical examination assessed heart rate (bpm), respiratory rate (mpm), rectal temperature (ºC), systolic arterial blood pressure (mmHg), capillary refill time (CRT), hydration, state of the mucosae and pulse. Systemic arterial pressure (mmHg) was evaluated through a non-invasive method with Doppler ultrasound (Ultrasonic Doppler 404 Flow Detector 811-B; Parks Medical Electronics) as per Brown & Henik.[32]

The time (in hours) for which the animal presented the obstruction before receiving clinical care was also considered according to data provided by the owner. The animals were classified according to obstruction time (12h, 24h, 36h, 48h and 60h).

Hematological Analysis

Blood samples were collected through jugular venipuncture for the following assays: hemogram, determination of serum urea and creatinine, and blood gas assay. A total volume of 3 mL was obtained from the animals and immediately stored in sterile tubes containing anticoagulant EDTA 10% for the hemogram, and in tubes without anticoagulant for the determination of serum urea, creatinine and SDMA. Blood samples were collected for the diagnosis of obstructive FLUTD, before urethral clearance (M0), and then 12 (M12), 24(M24) and 48 (M48) hours after the treatment. The hemogram and platelet counts were performed using commercially-available kits in an automated device (Cobas C111; Roche), with the reference interval as per Kaneko et al.[33] Serum SDMA was assessed and measured using a specific device (Catalyst Dx; IDEXX), considering a reference interval for serum SDMA in healthy felines between 0 - 14 μg/ dL (IDEXX Laboratories, Inc, Westbrook, ME).

Blood Gas Test

A blood sample of 1 mL of venous blood was collected using a sterile 1 mL heparin syringe and a 0.55 x 20 mm sterile needle for a blood gas test in a portable device (i-Stat 1 Handheld; Abbot), with the commercially-available kit Cg8+. The blood gas test was performed at the diagnosis of obstructive FLUTD, M0, M12, M24 and M48 for immediate evaluation of potassium and bicarbonate.

Urinalysis

A sample of urine was obtained through transabdominal puncture (cystocentesis) at the caudal portion of the abdomen, with the animal in dorsal decubitus, using a sterile 10 mL syringe and a 25 x 8 mm sterile needle. The urine was centrifuged at 1200G for 6 minutes before the urinalysis was performed using the reagent strips technique (Combur-Test; Roche) and the urinary protein-to-creatinine ratio (PCR) was determined (UPC method; Sensiprot).

Ultrasound

An ultrasound examination of the abdomen was performed with an ultrasound device (Z6vet; Mindray), equipped with micro-convex (6C2PB at 5 - 8.5 MHz) and linear (7L4P at 5 – 10 MHz) transducers in B Mode. The data analyzed was adapted as per Nevins, Mai & Tomas (Table 2).[34]

Radiographic Examination

A radiographic examination of the abdomen was performed with a radiography device (CRX, model DM 125 with capacity for 300 mA). The projections were taken with the animals in dorsal and lateral decubitus in 18 x 24 cm and 24 x 30 films (T-MAT G/RA, Carestream). The examination assessed the integrity of the urethra and the presence of urolites in the urinary vesicle and urethra.

Treatment of the Animals in the Obstruction Group

Urethral Clearance

For the urethral clearance, the animals were anesthetized with propofol. The penis was exposed and the presence of urethral ‘plugs’ or urolites was evaluated. Massages were performed to promote the ejection of possible plugs. After hair removal and asepsis of the prepuce region, a semiflexible urethral probe (TomCat) was inserted into the urethra with the aid of a syringe (1 mL) for urethral hydropulsion with 0.9% saline solution. The urinary vesicle was then irrigated to remove any plugs and sediments. The urethral probe was then affixed and remained in the animal for 48 hours.

Clinical Treatment

The clinical treatment was instituted simultaneously to the urethral clearance. Electrolytic imbalances were corrected based on the blood gas test results through fluid

therapy with Ringer's Lactate. A pain relief medication (Tramadol Hydrochloride IV) was also administered.

The conventional treatment with antibiotics was performed after obtaining the results of the urinalysis, urine culture and antibiogram tests. The choice of antibiotic and the duration of the treatment were based on the results of the antibiogram.

Statistical Analysis

The normal distribution and homoscedasticity of the data were estimated, respectively, through the Shapiro-Wilk and Barlett tests. Data that did not present normal distribution were log-transformed. The comparison between the variables SDMA, K^+ and HCO_3 between the OG and the CG was conducted through the Analysis of Variance (ANOVA One-Way). The comparison of the variable SDMA in the OG between the various moments was conducted using repeated measures over time (Mauchly's Sphericity Test). The adjustment of the comparisons was conducted through Tukey's test. The results are shown as mean ± standard deviation of the mean. Differences were considered to be statistically significant when $P < 0.05$.

The comparison between the CG and the OG within each moment for the variables SCr, urea, PCR and urinary density (UD) was conducted using the Mann-Whitney test. In addition, the Wilcoxon test was used to compare the various moments within the OG.

The results are shown as medians and limits. Differences were considered statistically significant when $P < 0.05$.

The association of SDMA with SCr, urea, potassium, bicarbonate, obstruction time and clinical score was evaluated using Pearson's or Spearman's correlation. The correlation coefficients were defined as: strong ($r > 0.6$); moderate ($0.6 \leq r \geq 0.4$); or weak ($r < 0.4$). Differences were considered statistically significant when $P < 0.05$.

The Kappa concordance analysis was used to verify the concordance of the results of diagnostic tests within moments M12, M24 and M48. The Kappa coefficients were estimated per point and interval with 95% confidence and were considered statistically significant when the interval did not include the value "zero".

The results for variables clinical score and glucose are shown as frequencies. The statistical analysis was performed using the software GraphPad Prism Version 8 (GraphPad Software Inc, La Jolla, CA, USA) and the SAS statistical suite, version 9.1 (SAS Institute, Inc, Cary NC).

RESULTS

Data obtained from 17 cats with obstructions (OG) and 13 healthy cats (CG) was analyzed. The mean age of the animals was 4.5 years (n = 14, amplitude = 1-12 years).

229 The animals in the OG were evaluated according to the clinical condition score, in which
230 higher scores represent worse clinical conditions (Table 3).
231 The mean, standard deviation and amplitude for variables SDMA, SCr, urea,
232 bicarbonate, potassium, PCR and urinary density of each group are described in Table 4.
233 The percentage of animals above and below the reference interval is also shown. At M48,
234 50% of the cats with obstructions presented SDMA values above the reference values,
235 while for SCr only 29.41% of the cats presented high values at M48.
236 The mean SDMA values were analyzed across each moment for the OG and a
237 progressive decreased was observed in the SDMA values over time, with a statistically
238 significant difference between M0-M24 ($P < 0.0001$) (Figure 1).
239 When comparing the mean SDMA values of the OG with the CG within different
240 moments, no statistically significant differences were observed at M48 ($P > 0.05$), which
241 was the only moment statistically close to the normal SDMA values (14 μg/dL IDEXX
242 Laboratories, Inc, Westbrook, ME) (Figure 2, A). On the other hand, the mean SCr values
243 did not present statistically significant differences in comparison with the CG from M24
244 onwards (M24-GC $P > 0.2$) (Figure 2, B). The mean SDMA and SCr values decreased
245 over time in the OG, but at no point did these values come close to the normal parameters
246 for the species (Figure 2). Some animals presented high values for SDMA and SCr at M0
247 differently from the remaining animals in the OG, and these values remained high until

248 the last moment analyzed, which increased the means and medians for these biomarkers
249 and prevented them from reaching the normality range.

250 When correlating the concentrations of SDMA and SCr, the biomarkers presented
251 a strong positive correlation, as did SDMA with urea and SDMA with potassium. This
252 differs from the values for bicarbonate and SDMA, which presented a weak correlation
253 that was not statistically significant in both groups at all moments. Clinical score and
254 obstruction time also presented a strong correlation with the serum SDMA values at M0.
255 All data presented is shown in Table 5.

256 Regarding concordance, the SDMA values over the normality range were assessed
257 together with the SCr, urea and potassium values (Table 6). SDMA only presented a
258 substantial concordance with SCr and urea at M24. All other Kappa coefficients indicated
259 poor or mild concordance.

260 Animals with glycosuria were detected and the data was organized in Table 7. All
261 animals in the CG presented normal values for glycosuria, as did 7 animals in the OG at
262 M0. Two animals presented traces of glucose in the urine and 8 had a cross for this
263 moment. At the remaining moments, most animals presented traces of glucose in the
264 urine.

265 The data for PCR was compared for all moments between the OG and the CG,
266 with a statistically significant difference at all moments ($P < 0.001$) (Figure 3). UD also

267 presented statistically significant differences at all moments when comparing the OG with
268 the CG ($P < 0.002$) (Figure 4).

269 The ultrasound data was analyzed and organized in a table (Table 8). Urinary
270 sediment was found in all animals with urethral obstruction (mild 47.06%, moderate
271 35.29%, and severe 17.65%). Other abnormalities observed were urethral dilation
272 (76.47%), moderately echogenic urine (64.7%) and renomegaly (52.94%). One animal
273 presented thickening of the vesicle walls and another presented ureteral dilation. No
274 animals presented chronic alterations or alterations in the adrenal glands. All animals in
275 the CG presented no alterations in the ultrasound examination.

276

277 **DISCUSSION**

278 This is the first study evaluating the serum values of SDMA in feline patients with
279 obstructive FLUTD.

280 SDMA is a biomarker of renal function that has proven to be more sensitive than
281 SCr, while also suffering less influence from extrarenal factors.[35,21] In this study, the
282 serum values of SDMA were higher than SCr across all moments. In addition, fifty
283 percent of the animals with obstructive FLUTD presented serum SDMA values over the
284 reference range at M48, while only 29.41% of the animals presented SCr values over the
285 reference range. This suggests that the SDMA values observed in this study remained
286 high over a longer period of time, which corroborates the notion that it is a more sensitive

biomarker of renal function impairment than SCr. However, it is important to consider the molecular weight of SDMA and its distribution in the organism.[36]

Some outliers sought medical care after a longer obstruction time, which may have resulted in a more severe kidney injury and, consequently, in higher values for SDMA and SCr, in addition to more severe clinical alterations. These animals need monitoring for a longer period of time after the urethral clearance to better assess the renal function using the SDMA and SCr biomarkers.

The strong positive correlation observed between SDMA and SCr was already expected because the values of both biomarkers increase when the GFR decreases.[22,23,37,38] The obstruction of the urinary flow leads to intrinsic and extrinsic injuries caused by postrenal azotemia, which may lead to a decrease in the GFR and a impairment of the renal function.[10] Previous studies have observed positive correlations between SDMA and SCr in mice,[39,40] dogs, [23,25,41] and people.[42] It has also been shown that both biomarkers have a strong correlation in cats[21,43-45] and that both are strongly correlated with the GFR,[25,26,39,45] but this study did not perform the gold standard examination to evaluate GFR, which is very important to confirm the impairment of the renal function. Despite the strong correlation, concordance between the biomarkers was mild, particularly at M48, which illustrates the difference in the number of animals with values of SCr and SDMA above the normality range.

306 The strong correlation between SDMA and urea was also expected, considering
307 that Seveg at al. (2011) observed that the most common serum abnormality in animals
308 with obstructive FLUTD was azotemia (85%) due to the impaired renal function caused
309 by the blockage of the postrenal urinary flow.[5]

310 The strong correlation between SDMA and potassium happens because the
311 obstruction of the urinary flow in felines promotes the reduction of the GFR and the
312 inability of the kidneys to excrete potassium.[5,46,47] In addition, hyperkalemia may be also
313 be significant in cases of urethral obstruction due to metabolic acidosis and tissue
314 catabolism.[5] Segev et al.[7] observed hyperkalemia in 48% of the animals with obstructive
315 FLUTD.

316 The variation in the values of bicarbonate did not present any correlation with the
317 serum values of SDMA in cases of obstructive FLUTD, despite the fact that urethral
318 obstruction may lead to metabolic acidemia due to the retention of metabolic acids, the
319 consumption of bicarbonate to stabilize the pH of the plasma, the generation of lactate
320 associated with hypovolemia and hypoxia, and the reduction in the conservation of
321 bicarbonate during post-obstructive period.[5]

322 The strong correlation observed between the clinical signs and the SDMA values
323 was also expected, with healthy animals presenting lower SDMA values and animals with
324 more clinical alterations presenting higher SDMA values. The clinical signs of
325 obstructive FLUTD may vary considerably depending on several factors, such as the

326 degree of obstruction, the duration of the disease and the presence of a secondary bacterial
327 infection, however, larger impairments of the renal function invariably lead to larger
328 metabolic alterations.[5]

329 Dehydration was significant in most cats and is caused by the decrease in oral
330 ingestion of liquid and by the continuous losses by non-renal channels, such as
331 vomiting.[46] Hyperkalemia, azotemia and acidemia are the most common alterations
332 observed in cases of urethral obstruction,[46] as evidenced by this study. In addition, severe
333 hyperkalemia is the alterations that poses the largest risk to the life of the patient.[47,48,49]
334 Hyperkalemic cats also presented high values of SDMA, which, together with the strong
335 correlation with the clinical score, indicates that this biomarker is a relevant tool in the
336 assessment of the severity of the condition of patients with obstructions.

337 The evaluation of the PCR is indicated to determine the magnitude and the
338 significance of proteinuria, which may be associated with kidney injuries. However, cases
339 of bleeding or inflammation in the urinary system may alter the results.[50] In addition, in
340 cats with obstructive FLUTD, there may be kidney injury and cases of inflammation and
341 hematuria are not uncommon,[5] which makes the measurement of proteinuria unreliable.
342 The urinary density should be above 1.035 in cats, with hyposthenuria (< 1.007),
343 isosthenuria (between 1.008 and 1.012) and urinary densities between 1.013 and 1.034
344 indicating inadequacy of the tubular renal function. However, this diagnosis should

include the evaluation of azotemia and dehydration, because low concentrations may also be caused by polydipsia or hyperadrenocorticism.[50]

Hyperglycemia (> 300 mg / dL in cats) exceeds the renal threshold for glucose resorption and may lead to glycosuria. When the blood sugar levels are normal, glycosuria may be considered due to a proximal tubular dysfunction, which has been reported in cats with AKI[13] and obstructive FLUTD, [7] as was the case in this study.

In the ultrasound findings, the presence of urinary sediment, the increase in echogenicity of the urine and renomegaly are also common abnormalities[34]. Urinary sediments are also commonly observed in cases of non-obstructive FLUTD,[51] as is the case of the thickening of the vesicle wall, which is indicative of chronic vesicle inflammation,[52] but this alteration was not common in this study (5.88%). Normally, the ureters are not visible in the ultrasound examination, becoming visible only when dilated by ectopias, bladder neoplasms, ureteritis or obstruction, resulting in hydronephrosis. In this study, dilated ureters were observed in a single animal (5.88%).[53] Feline patients with chronic kidney disease may present altered SDMA values[21], which may impair the analysis of alterations of the GFR caused by urethral obstruction, but no signs of chronicity were observed in the ultrasound examination of the animals.

CONCLUSIONS

These results suggest that the biomarker SDMA has higher sensitivity to evaluate the renal function after clearance treatment in animals with obstructive FLUTD in comparison with creatinine. In addition, it may represent an additional tool to assess the severity of the patient's clinical state.

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CONFLICTING INTERESTS

The authors declare they have no conflicting interests.

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ETHICAL APPROVAL

This study was approved by the Ethics Commission in Animal Use (CEUA, *Comissão de Ética no Uso de Animais*) at FMVZ – UNESP, Botucatu, Brazil, under protocol no. 266/2018.

INFORMED CONSENT

The Free, Prior and Informed Consent (FPIC) Agreement was signed by the persons responsible by the animals treated in the Veterinary Hospital of the *Universidade do Oeste Paulista* – UNOESTE – Presidente Prudente – SP – Brazil, at the Department of Small Animal Medical Practice.

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Tables

Table 1. Score for the evaluation of the clinical state of cats with obstructive FLUTD upon admission in the clinical care.

Variable	Unit
Appetite	0 = normal appetite; 1 = hyporexia; 2 = anorexia
Emesis	0 = absent; 1 = present
Mental State	0 = normal; 1 = lethargic; 2 = depressed; 3 = unconscious or excited
Position of the Head	0 = normal; 1 = ventroflexion
Dehydration	0 = not apparent; 1 = mild; 2 = moderate; 3 = severe; 4 = major
	Maximum score for sick animals: 11

Table 2. Criteria for evaluation of ultrasound alterations in cats with obstructive FLUTD

Bladder and Urethra	
Echogenicity of urine	Anechoic or Mild; Moderate; Severe
Urinary sediment	Absent; Mild; Moderate; Severe
Thickening of vesicle wall (> 2 – 3 mm)	Absent; Present
Peritoneal effusion	Absent; Present
Crystals	Absent; Present
Urethral dilation	Absent; Present
Urolites in the urethra	Absent; Present
Kidneys and Ureters	
Pyelectasis (> 3 – 4 mm)	Absent; Present
Retroperitoneal effusion	Absent; Present
Renomegaly (> 4.3 cm)	Absent; Present
Cortical hyperechogenicity	Absent; Present
Chronic alterations	Absent; Present
Ureteral dilation	Absent; Present

Table 3. Scores of animals in the OG at M0 regarding their clinical state.

Clinical Score OG M0	Appetite	Emesis	Mental State	Position of Head	Dehydration	Total
Animal 01	0	1	0	0	0	1
Animal 02	2	1	2	1	2	7
Animal 03	1	1	1	0	3	6
Animal 04	1	0	0	0	2	3
Animal 05	2	1	3	1	3	10
Animal 06	0	0	0	0	1	1
Animal 07	1	0	0	0	1	2
Animal 08	2	1	1	1	2	7
Animal 09	2	1	1	1	2	7
Animal 10	2	1	2	1	3	9
Animal 11	2	0	1	0	2	5
Animal 12	2	1	2	0	2	7
Animal 13	1	0	2	0	1	3
Animal 14	0	0	1	0	0	1
Animal 15	1	0	1	0	0	2
Animal 16	2	0	2	1	2	7
Animal 17	1	0	0	0	1	2

Table 4. Values for SDMA, SCr, urea, HCO_3, K^+, PCR and UD in healthy cats (CG) and cats with obstructive FLUTD (OG).

Variable	Group	Moment	*n*	Mean & SD	Amplitude	Reference Interval	% of cats below the reference interval	% of cats above the reference interval
SDMA (µg/dL)								
	GO	M0	17	48 ± 7.34	8-100*	0-14	0	82.35
		M12	16	37.94 ± 6.97	6-88	0-14	0	75
		M24	17	29.65 ± 6.09	7-63	0-14	0	58.82
		M48	16	18.31 ± 3.27	7-52	0-14	0	50
	GC		13	8.15 ± 0.46	6-12	0-14	0	0
SCr (mg/dL)								
	GO	M0	16	9.41 ± 1.46	0.7-18.6	0.9-2.1	6.25	81.25
		M12	17	6.02 ± 1.23	0.9-15.5	0.9-2.1	0	70.59
		M24	17	5.27 ± 1.27	0.9-15.5	0.9-2.1	0	58.82
		M48	17	3.22 ± 1.10	0.8-16.6	0.9-2.1	6.25	29.41
	GC		13	1.30 ± 0.07	0.8-1.7	0.9-2.1	7.69	0
Urea (mg/dL)								
	GO	M0	17	284.7 ± 35.43	42.2-467.9	42-64	0	82.35
		M12	17	223.7 ± 31.74	36.1-404.4	42-64	5.88	82.35
		M24	17	219.2 ± 37.79	37.2-489.3	42-64	5.88	76.47
		M48	17	164.2 ± 38.3	35.6-554.2	42-64	5.88	64.7
	GC		13	51.24 ± 1.95	44.7-66.1	42-64	0	7.69
HCO_3 (mmol/L)								
	GO	M0	13	16.77 ± 1.24	9.2-24.7	17-23	61.53	7.69
		M12	15	18.57 ± 0.86	14.2-24.5	17-23	33.33	6.66
		M24	15	18.19 ± 0.83	13-24.7	17-23	33.33	6.66
		M48	15	18.07 ± 0.80	11.7-22.8	17-23	26.66	0
	GC		10	18.52 ± 0.38	16.9-20.1	17-23	10	0

Table 4. Continued.

K^+ (mEq/L)								
	GO	M0	16	7.12 ± 0.57	3.14-11.3	3.7-5.4	12.5	81.25
		M12	16	5.66 ± 0.46	2.96-9.7	3.7-5.4	6.25	43.75
		M24	15	5.18 ± 0.37	3.43-8.17	3.7-5.4	13.33	33.33
		M48	17	5.11 ± 0.35	2.4-8.99	3.7-5.4	5.88	29.41
	GC		11	4.44 ± 0.08	4.01-4.65	3.7-5.4	0	0
PCR								
	GO	M0	14	1.56 ± 0.23	0.3-2.8	0-0.4	0	92.86
		M12	16	1.66 ± 0.29	0.2-4.3	0-0.4	0	81.25
		M24	16	1.55 ± 0.30	0.2-5.3	0-0.4	0	81.25
		M48	17	1.32 ± 0.21	0.2-3.2	0-0.4	0	88.24
	GC		10	0.11 ± 0.01	0.1-0.2	0-0.4	0	0
UD								
	GO	M0	17	1.033 ± 3.59	1.012-1.055*	1.035-1.060	64.71	0
		M12	16	1.032 ± 3.50	1.012-1.055*	1.035-1.060	75	0
		M24	16	1.027 ± 3.10	1.016-1.050	1.035-1.060	68.75	0
		M48	16	1.028 ± 3.05	1.016-1.055*	1.035-1.060	62.5	0
	GC		12	1.055* ± 0	1.055*	1.035-1.060	0	0

*Values over 1.050 are not specified by the urinalysis reagent test, values over this threshold are represented by 1.055

Table 5. Correlations of SDMA with SCr, urea, K+, HCO3, clinical score and TO

	Spearman r	Pearson r	P	Confidence Interval
SDMA vs. sCr	0.8054	-	<0.0001	0.7068 to 0.8733
SDMA vs. UREA	0.856	-	<0.0001	0.7806 to 0.9069
SDMA vs. K+	-	0.7788	<0.0001	0.6684 to 0.8555
SDMA vs. HCO3	-	-0.2402	0.054	-0.4573 to 0.003977
SDMA vs. TO	-	0.7494	0.0005	0.4201 to 0.9043
SDMA vs. SCORE	-	0.7559	0.0004	0.4324 to 0.9070

Table 6. Results of the Kappa concordance analysis between SDMA and SCr, urea and K^+

Moment 12 hours					
Parameter	Condition	SDMA		Kappa	CI 95%
		normal	increased		
SCr	normal	4	0	0.25	0.51 to 1.50
	increased	0	12		
Urea	normal	2	0	0.23	0.15 to 1.05
	increased	2	12		
K^+	normal	3	5	0.33	-0.23 to 0.76
	increased	0	7		
Moment 24 hours					
Parameter	Condition	SDMA		Kappa	CI 95%
		normal	increased		
SCr	normal	6	1	0.76	0.27 to 0.97
	increased	1	9		
Urea	normal	4	0	0.64	0.13 to 0.92
	increased	3	10		
K^+	normal	6	4	0.22	0.06 to 0.93
	increased	0	5		
Moment 48 hours					
Parameter	Condition	SDMA		Kappa	CI 95%
		normal	increased		
SCr	normal	8	4	0.21	0.07 to 0.92
	increased	0	4		
Urea	normal	6	0	0.24	0.27 to 1.22
	increased	2	8		
K^+	normal	8	5	0.19	-0.01 to 0.75
	increased	0	3		

Table 7. Rate of cats with glycosuria in the control and obstruction groups

		5 (normal)	10 (traces)	30 (traces)	50 (+)	100 (++)
GC		12	0	0	0	0
GO	M0	7	1	1	8	0
	M12	0	6	2	7	1
	M24	0	7	0	7	2
	M48	0	13	0	3	1

Table 8. Ultrasound evaluation of structures in the urinary system of cats with obstructive FLUTD before clearance

Bladder and Urethra	OG (*n*=17)	**%**
Urine echogenicity:		
Anechoic or mild (normal)	3	17.65
Moderate	11	64.7
Severe	3	17.65
Urinary sediment:		
Absent	0	0
Mild	8	47.06
Moderate	6	35.29
Severe	3	17.65
Thickening of the bladder wall	1	5.88
Peritoneal effusion	2	11.76
Crystals	8	47.05
Urethral dilation	13	76.47
Urolites in the urethra	2	11.76
Kidneys and Ureters		
Pyelectasis (> 3 – 4 mm)	4	23.53
Retroperitoneal effusion	2	11.76
Renomegaly (> 4.3 cm)	9	52.94
Cortical hyperechogenicity	3	17.65
Chronic alterations	0	0
Ureteral dilation	1	5.88

Figures

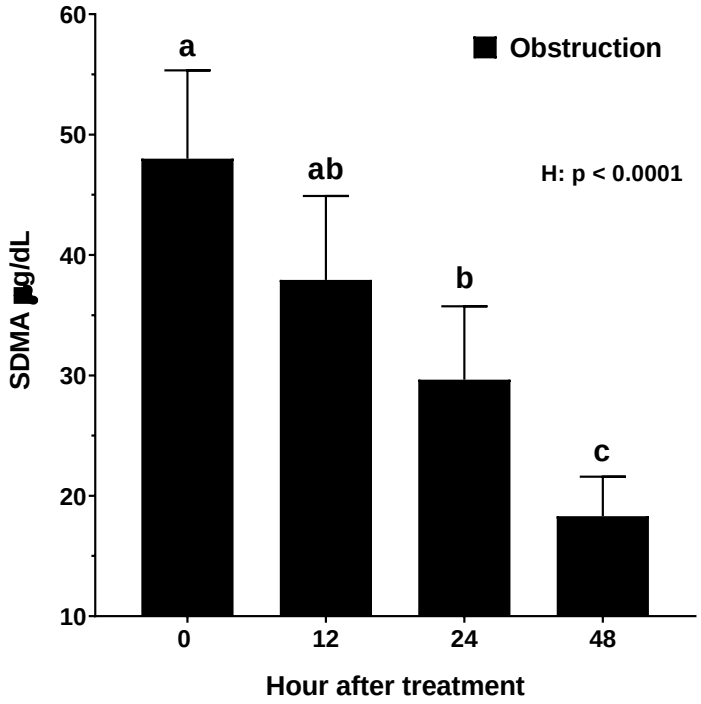
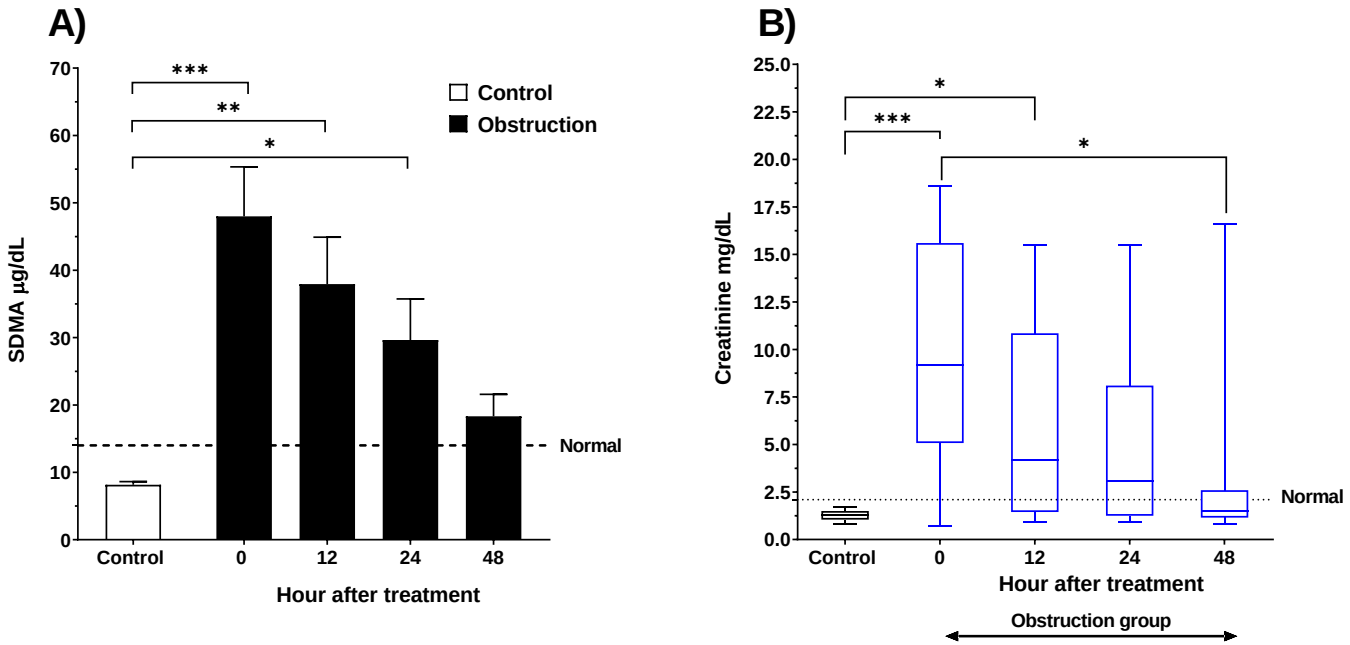


Figure 1. Mean serum values of SDMA in cats with obstructive FLUTD (OG) at moments M0, M12, M24 and M48. Different letters indicate significant differences ($P < 0.0001$).

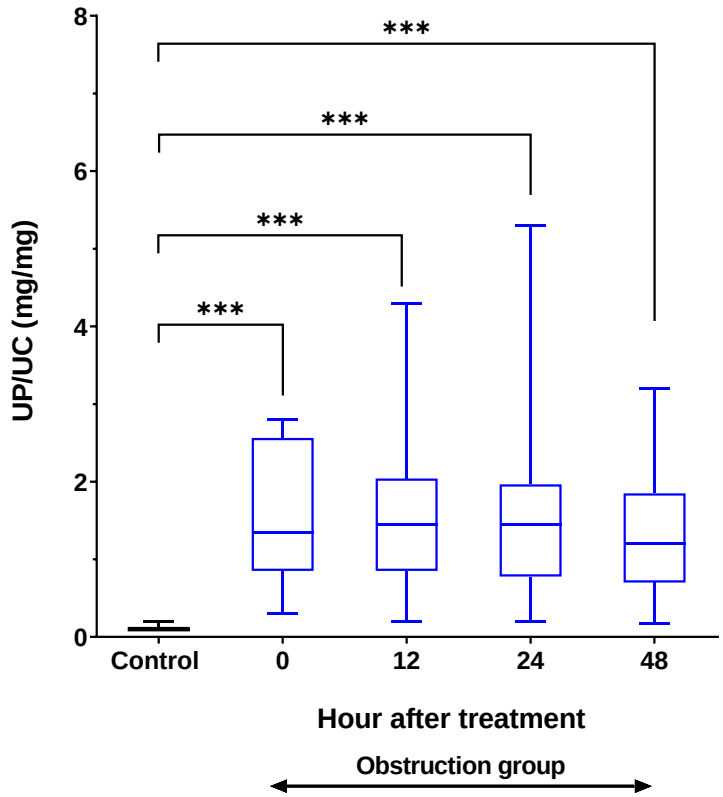


15

16 **Figure 2**. a) Mean (± SD) for SDMA in cats with obstructive FLUTD (OG) at moments M0, M12, M24 and M48

17 and in the control group (CG). b) Box plot of SCr in cats with obstructive FLUTD (OG) at moments M0, M12, M24

18 and M48 and in the control group (CG). (*) $P < 0.04$ (**) $P < 0.002$, (***) $P < 0.0002$



19

20 **Figure 3.** Box plot of PCR in the CG and in the OG across all moments. $P < 0.001$

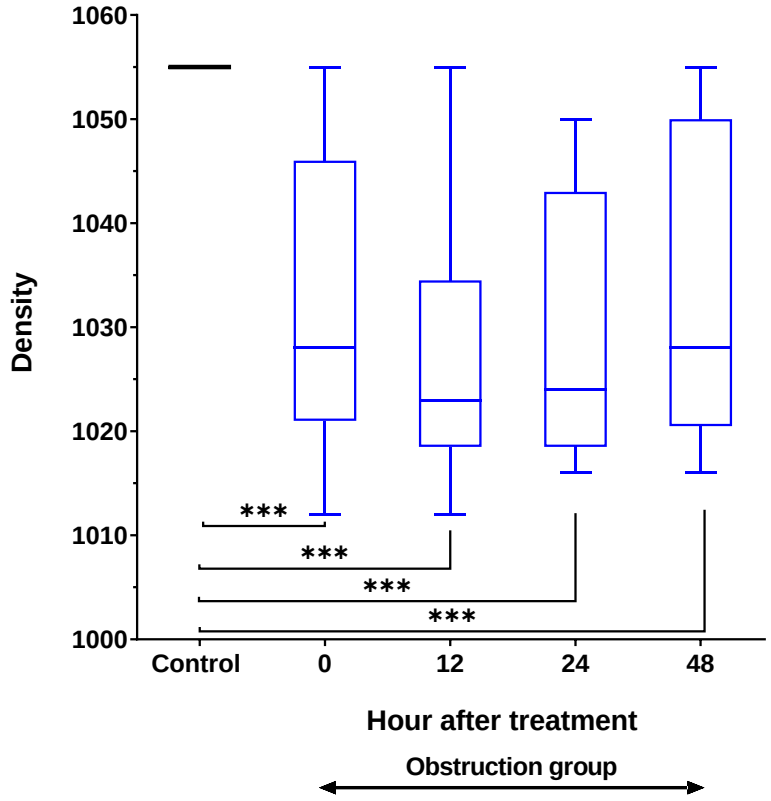


Figure 4. Box plot of UD in the CG and in the OG across all moments. $P < 0.001$

CAPÍTULO III

CONCLUSÕES FINAIS

Sugere que o biomarcador SDMA apresente maior sensibilidade para avaliar a função renal dos gatos com DTUIF obstrutiva quando comparado a creatinina.

Animais com maior tempo de obstrução apresentam valores elevados de SDMA, agravando o estado clínico no atendimento emergencial desses animais.

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