UNIVERSIDADE FEDERAL DO PARANÁ

ELOISA MUEHLBAUER

TÓPICOS AVANÇADOS NO DIAGNÓSTICO E EPIDEMIOLOGIA DE UROABDOME EM PEQUENOS ANIMAIS

Curitiba

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

Orientador: Profª. Drª. Tilde Rodrigues Froes

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação CIÊNCIAS VETERINÁRIAS da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **ELOISA MUEHLBAUER** intitulada: **Tópicos avançados no diagnóstico e na epidemiologia de uroabdome em pequenos animais**, 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.

A outorga do título de doutora está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

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TILDE RODRIGUES FROES
Presidente da Banca Examinadora

Assinatura Eletrônica
22/05/2023 16:01:57.0
ANELISE CARVALHO NEPOMUCENO
Avaliador Externo (UNIVERSIDADE FEDERAL DE MINAS GERAIS)

Assinatura Eletrônica
25/05/2023 09:24:32.0
PATRÍCIA ERDMANN MOSKO
Avaliador Externo (AUTÔNOMO)

Assinatura Eletrônica
30/05/2023 10:01:49.0
SABRINA MARIN RODIGHERI
Avaliador Externo (UNIVERSIDADE POSITIVO)

Assinatura Eletrônica
22/05/2023 14:15:08.0
JUAN CARLOS DUQUE MORENO
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DEDICATÓRIA

Dedico este trabalho ao meu sobrinho e maior amor, Pedro. Vou sentir saudades para sempre.

“Cada um de nós é um universo, Pedro
Onde você vai eu também vou
Pedro, onde cê vai eu também vou
Mas tudo acaba onde começou”

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Meu mundo é composto por personagens comuns, mas, que são reais, feitos de carne e osso, cheios de amor e que são minha principal motivação para tudo. Diante da responsabilidade que é esse “Muito obrigado” corro o risco de não dar conta de expô-lo como é merecido e, por isso, livro-me da mera formalidade de um agradecimento e passo a tratar esse texto como uma teia de solidariedade e parceria que se criou não só nos últimos quatro anos, mas, em toda minha trajetória acadêmica.

Miria Muehlbauer foi professora durante toda a sua vida. Dedicou a sua história a ensinar língua portuguesa a jovens e adultos. Foi diretora, coordenadora, voluntária, catequista. Miria é minha avó e eu queria que pelo menos uma vez ela se enxergasse pelos meus olhos: amável, decente, infalivelmente generosa. Tenho orgulho de ser sua neta.

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“Era preciso vencer o medo; e o grande medo, meu maior medo na viagem, eu venci ali, naquele mesmo instante, em meio à desordem dos elementos e à bagunça daquela situação. Era o medo de nunca partir. Sem dúvida, este foi o maior risco que corri: não partir. Não estava obstinado de maneira cega pela ideia da travessia, como poderia parecer — estava simplesmente encantado. Trabalhei nela com os pés no chão, e, se em algum momento, por razões de segurança, tivesse que voltar atrás e recomeçar, não teria a menor hesitação. Confiava por completo no meu projeto e não estava disposto a me lançar em cegas aventuras. [...] Pelo simples fato de estar ali onde estava, debatendo-me entre os remos, xingando as ondas e maldizendo a sorte, me sentia profundamente aliviado. Feliz por ter partido.”

Amyr Klink. Cem dias entre céu e mar. 1995.

RESUMO

O uroabdome acontece em resultado ao extravasamento de urina, de alguma porção do trato urinário, para a cavidade peritoneal. Esse quadro, leva a peritonite urêmica e progressivamente ao desequilíbrio hídrico e eletrolítico, descompensação hemodinâmica e, se não corrigido, ao óbito dos pacientes. A vesícula urinária é a porção do sistema urinário mais envolvida nos casos de uroabdome em pequenos animais e, dessa forma, tornou-se foco principal neste estudo. Para tanto, este trabalho foi divido em três capítulos. Em dois deles, nós objetivamos determinar a eficácia da utilização da solução salina agitada, como contraste de microbolhas, durante a cistosonografia para o diagnóstico de ruptura de vesícula urinária em cães e gatos. Este estudo foi dividido em um estudo cadavérico e em um estudo observacional prospectivo em animais vivos. A terceira parte deste trabalho, objetivou relacionar as intercorrências ocorridas com o temperamento e o tipo de contenção realizada em cães e gatos submetidos a coleta de urina por cistocentese guiada por ultrassonografia. Os três estudos agrupam informações importantes quanto ao diagnóstico e epidemiologia do uroabdome em pequenos animais, demostra a utilização do contraste de microbolhas como eficiente para o diagnóstico de ruptura de vesícula urinária em animais de companhia e determinam, tanto o perfil de intercorrências relacionadas a cistocentese guiada por ultrassonografia, quanto o perfil do paciente com maior chance de sofrer algum tipo de intercorrência durante este procedimento.

Palavras-chave: Ultrassom; uroabdome; cistocentese; complicações; pequenos animais.

ABSTRACT

Uroabdomen occurs as a result of urine extravasation from some portion of the urinary tract into the peritoneal cavity. This condition leads to uremic peritonitis and progressively to electrolyte and fluid imbalance, hemodynamic decompensation, and, if not corrected, patient death. The urinary bladder is the portion of the urinary system most involved in cases of uroabdomen in small animals and, therefore, became the main focus of this study. For this purpose, this work was divided into three chapters. In two of the three, we aimed to determine the efficacy of using agitated saline solution as a microbubble contrast during cystosonography for the diagnosis of bladder rupture in dogs and cats. This study was divided into a cadaveric study and a prospective observational study in live animals. The third part of this work aimed to correlate the occurrences during and after with the temperament and type of restraint used in dogs and cats undergoing ultrasound-guided urine collection by cystocentesis. These three chapters compile important information regarding the diagnosis and epidemiology of uroabdomen in small animals, demonstrate the use of microbubble contrast as an efficient diagnostic tool for urinary bladder rupture in companion animals, and determine both the profile of complications related to ultrasound-guided cystocentesis, as well as the patient profile with the highest chance of experiencing some type of complication during this procedure.

Key words: Ultrasound; uroabdomen; cystocentesis; complications; small animals.

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1 INTRODUÇÃO GERAL

O uroabdome é definido como a presença de urina livre na cavidade abdominal fora do trato urinário. A origem do extravasamento inclui rins, ureteres, vesícula urinária e uretra, sendo a vesicula urinária, o local de extravasamento mais comumente encontrado em cães e gatos, seguido de rupturas uretrais (SELCER, 1982; STAFFORD E BARTGES,2013). Rupturas renais ou ureterais são raramente encontradas (STAFFORD E BARTGES,2013).

Em pequenos animais, o uroabdome, é mais comumente associado a traumas abdominais ou pélvicos (ANDERSON et al, 2006; STAFFORD E BARTGES,2013; HOFFBERG et al, 2016). As lesões do trato urinário associadas a uroabdome foram encontradas em 3,6% dos cães com fraturas pélvicas (HOFFBERG et al, 2016). A ruptura uretral iatrogênica, durante a sondagem, é a segunda causa mais comum de uroabdome em animais de companhia (AUMANN et al, 1998; ANDERSON et al, 2006; STAFFORD E BARTGES,2013). O uroabdome pode ocorrer após procedimentos cirúrgicos no trato urinário e foi identificado em 16% dos gatos submetidos a cirurgias ureterais (KYLES et al, 2005). As causas não traumáticas incluem hiperdistensão secundária a obstrução uretral, por urólitos ou neoplasia, compressão vesical e cistocentese (ANDERSON et al, 2006; STAFFORD E BARTGES,2013; MANFREDI et al, 2018).

Ruptura de vesícula urinária secundária a cistocentese, embora incomum, foi previamente descrita em cães e gatos e tais episódios foram associadas a peritonite química e séptica (SPECHT et al, 2015; MANFREDI et al, 2018; MATO et al, 2018). Outras intercorrências também foram descritas como possíveis após a cistocentese em pequenos animais, como a laceração de aorta e cava abdominal (BUCKLEY et al, 2009), lesões na parede abdominal, convulsão e sincope (ODUNAYO et al, 2015; MANFREDI et al, 2018). No entanto, mesmo com graves complicações relacionadas à técnica, há uma escassez de estudos relacionados ao tema.

O diagnóstico de uroabdome é tipicamente confirmado por meio da análise bioquímica da efusão peritoneal. Este teste tem 86% de sensibilidade e 100% especificidade quando o valor de creatinina na efusão é pelo menos duas vezes o valor da creatinina sérica. Ao associar a avaliação do potássio, a sensibilidade do teste aumenta para 100%, quando a relação do potássio da efusão for superior a 1,4 vezes o valor encontrado no sangue venoso (SCHMIEDT et al, 2001). Contudo, para a localização exata do extravasamento o uso de diagnóstico por imagem se faz obrigatório (AUMANN et al, 1998; ANDERSON et al, 2006; STAFFORD E BARTGES,2013).

O padrão ouro para o diagnóstico de uroabdome é a urografia excretora para lesões do trato urinário superior e a uretrocistografia retrógrada com contraste positivo para lesões do trato urinário inferior (AUMANN et al, 1998; ESSMAN, 2005; ANDERSON et al, 2006; STAFFORD E BARTGES,2013). Apesar de ser padrão-ouro para localizar e diagnosticar uroabdome, o uso de imagens contrastadas apresenta algumas limitações, uma vez que o contraste pode causar dor e irritação da mucosa e peritônio (WEISSE et al, 2002; RIESER, 2005; STAFFORD E BARTGES,2013).

Assim, há a necessidade de técnicas mais rápidas para diagnosticar uroabdome em situações de emergência, especialmente com o uso de avaliação ecográfica abdominal focada em trauma (AFAST) e exames de ultrassom à beira do leito (POCUS).A ultrassonografia abdominal é uma excelente ferramenta diagnóstica para a identificação de líquido livre, possíveis fontes de extravasamento dentro do abdômen e pode fornecer boas informações diagnósticas quando combinado com análise de fluidos. Todavia não determina com exatidão origem ou causa da efusão, sendo necessário a associação de técnicas ou abordagens invasivas (FORD et al, 2009; LISCIANDRO, 2011; LAL et al, 2019).

Em pacientes politraumatizados, o AFAST é o método diagnóstico empregado e o principal objetivo da técnica é a detecção de líquido livre na cavidade peritoneal. Esta técnica também permite a aspiração e coleta do fluido presente para análise laboratorial (LISCIANDRO, 2011). Contudo, a ausência de líquido livre ou a não identificação correta da parede da bexiga não excluem a presença de ruptura do trato urinário, o que dificulta e atrasa o diagnóstico (SRINIVASA et al, 2008; STAFFORD E BARTGES,2013; LISCIANDRO, 2011).

A literatura tem relatado a ultrassonografia de contraste com microbolhas incorporadas em solução salina como um método diagnóstico para doenças cardiovasculares há anos (ARNDT e OYAMA, 2008). Essa técnica é facilmente realizada, indolor e não requer contraste químico. No entanto, como há apenas um relato com dois casos clínicos e um estudo cadavérico discutindo a viabilidade do método no diagnóstico de ruptura da bexiga (CÔTÉ et al, 2002; MUEHLBAUER et al, 2023) a validade clínica da cistosonografia de contraste ainda é desconhecida.

O tratamento de uroabdome depende da localização do extravasamento. Muitos animais que sofreram traumas graves apresentam evidência de hipovolemia e são considerados emergências na abordagem inicial. Além disso, o desequilíbrio hidroeletrolítico associado à hipercalemia, situação potencialmente fatal, é comum nesses pacientes dada a incapacidade de excreção adequada. A fluidoterapia e a terapia para o controle da hipercalemia e da azotemia são necessários para estabilização antes de qualquer correção cirúrgica (RIESER, 2005).

Dada a complexidade do diagnóstico e da resolução dos quadros de uroabdome, objetivou-se neste trabalho compilar informações quanto à etiologia e ao diagnóstico de uroabdome em pequenos animais, demonstrando novas alternativas diagnósticas principalmente se correlacionarmos ao uso do FAST. Dessa forma, evidenciando a utilidade clínica do uso do contraste de microbolhas para o diagnóstico de ruptura de vesícula urinária e dos riscos inerentes a prática de cistocentese em cães e gatos.

2 CHAPTER 1 - The use of agitated saline as contrast agent in a contrast-enhanced cystosonography for detection of urinary bladder rupture – an animal cadaveric study[1]

2.1 Abstract

Objective: To determine the value of microbubble contrast cystosonography in the diagnosis of bladder rupture in animals.

Design: Prospective, method comparison study from November 2019 to October 2020.

Setting: University teaching hospital.

Animals: 34 ethically sourced cadavers of dogs, rats and rabbits.

Interventions: In a prospective and blinded study, the cadavers were divided into two randomized groups: with bladder rupture (CR), and without bladder rupture (SR). Urinary catheterization was performed in all cadavers. Through the urethral catheter, bladders in CR group were ruptured using a rigid stainless steel guide wire. Microbubble contrast was infused into the bladder through the urethral catheter, whilst a single, blinded observer sonographically assessed the bladder. The time to diagnosis, and the number of attempts needed for diagnosis were recorded.

Measurements and Main Results: The study included cadavers of: 16 female Wistar rats, 6 female dogs, 11 male dogs and 1 male rabbit. Time to diagnosis in dogs (2.25 ± 0.91 min) was statistically higher when compared to rats (1.15 ± 0.75 min; $p = 0.03$). Of the 34 cases, incorrect diagnosis of bladder rupture was made in only two dogs (6%), indicating a diagnostic sensitivity of 88.88%, specificity of 100% and an accuracy of 94%. The positive predictive value was 1 and the negative predictive value was 0.9.

Conclusions: Our study showed that the described method is accurate, sensitive, and specific for the detection of bladder rupture in animal cadavers of different species, size and sex.Key-words: ruptured bladder, microbubble contrast, animals, ultrasoun

[1]Chapter published in Journal of veterinary emergency and critical care (ANEXO I).

2.2 Introduction

Uroabdomen is a consequence of the rupture of any portion of the urinary tract and is characterized by the presence of urine in the peritoneal cavity, retroperitoneal space or both.[1] The presence of uroabdomen in companion animals is usually the result of abdominal or pelvic trauma, or urethral or ureteral rupture and is associated with electrolyte and metabolic imbalances.[2] Such changes have adverse effects on renal and cardiovascular function and cause hemodynamic changes that, if not promptly corrected, can irreversibly compromise the animal's quality of life, especially with kidney or urinary tract injuries and may lead to death.[1-3]

In dogs and cats, the bladder is the most common site of rupture of the urinary tract and bladder rupture is therefore the most common cause of uroabdomen.[1,4] In a study performed on cats with uroabdomen,[5] it was reported that 85% of animals had uroabdomen secondary to bladder rupture. In addition to bladder damage, urethral and ureteral ruptures may be present in dogs and cats following trauma.[1,3,4]

Early diagnosis and treatment of the patient with uroabdomen, including surgical correction of bladder rupture, improves prognosis and reduces mortality in people and animals.[6] In human, the gold standard for diagnosis of bladder rupture is computed tomography contrast-enhanced retrograde cystourethrography.[6] The requirement for sedation, high cost of the examination, and the need to transport the patient to a diagnostic center currently makes it unfeasible to use computed tomography for this purpose in veterinary clinical practice.[3,7]

Thus, the diagnosis of uroabdomen in small animals usually follows from the patient history, physical examination, laboratory findings, free abdominal fluid analysis, simple abdominal radiography, contrast-enhanced excretory urography and contrast-enhanced retrograde urethrocystography.[1,3,8-10] Despite being the gold standard for diagnosing and locating the rupture in the urinary tract; the use of contrast imaging has some limitations, as the contrast can cause pain and irritation of the mucosa and peritoneum.[1,3,9] Thus, there is a need for more rapid techniques for diagnosing uroabdomen in an emergency setting, especially with the use of abdominal focused assessment with sonography for trauma (AFAST) and point of care ultrasound (POCUS) exams. Abdominal ultrasound is an excellent diagnostic tool for identification of free fluid and possible sources of extravasation within the abdomen and can provide good diagnostic information when combined with fluid analysis.[11-13]

Currently, the diagnostic method used in polytraumatized patients is AFAST. The main purpose of this is the detection of free fluid in the peritoneal cavity. Ultrasound examination also allows needle aspiration and collection of the fluid for laboratory analysis.[12] However, the absence of free fluid does not exclude urinary tract rupture[1,12,14] and during AFAST it may not be possible to identify the bladder or define the bladder wall accurately, which can make diagnosis of bladder rupture challenging.

Literature have reported contrast cystosonography with microbubbles incorporated into saline solution as a diagnostic method for cardiovascular diseases for years. [15] This technique is easily performed, painless and does not require chemical contrast. However, as there is only one report with two clinical cases discussing the feasibility of the method in diagnosing bladder rupture,[16] the clinical validity of contrast cystosonography remains unknown.

The aim of this study was to determine the clinical applicability of microbubble contrast cystosonography (produced with agitated saline) compared to contrast retrograde urethrocystography in animal cadavers.

2.3 Methods

2.3.1 Animals

This study was approved by the ethics committee on the use of animals of this institution under protocol 067/2018. In this prospective, method comparison, thirty-four ethically sourced cadavers of dogs (*Canis familiaris* - 17), rats (*Rattus norvergicus* - 16) and rabbits (*Oryctolagus cuniculus* - 1) were included. The majority of the cadavers were fresh, although there was mild decomposition in two of the dog cadavers. No animals were euthanized for inclusion in this study and the causes of death were unrelated to this study and were not defined.

2.3.2 Experimental design

Cadavers were randomized[a] into two groups, CR and SR. A urethral catheter was placed in each cadaver and, through the urethral catheter, bladders in the CR group were ruptured using a rigid stainless steel guide wire. This procedure was performed by an author other than the blinded observer. The rats were catheterized with 24-gauge intravenous cannulas[b] following the technique previously described.[17] The dogs and the rabbit were catheterized using a urinary catheter[c] of the appropriate size for the animal's weight. Male dogs underwent urethrostomy in the perineal region distal to the penis. It was necessary to perform urethrostomy in males to avoid the urethral curvature when inserting the guide wire to perform bladder rupture in cadavers in the CR group. The bladder was left intact in the cadavers from the SR group.

Cystosonography was performed using a standard ultrasound machine[d], whilst the bladder was being filled with a predetermined volume of the agitated saline solution containing 20% air by volume (microbubble contrast), 1.5mL per rat and 1mL/kg for dogs and rabbit. The bladder was filled slowly, over 10 to 15 seconds and a real-time exam of the bladder and bladder region was performed. Based on the modified technique of Côté[16] described previously.

Transducers were selected to obtain the best, and most detailed images based on the size of the animal. Dogs and rabbits were assessed with a linear frequency transducer of 5-12 MHz; whilst a high frequency linear transducer of 8-18 MHz was used for the rats.

Bladder ultrasound was performed simultaneously with the injection of the microbubble contrast for cystosonography. A single blinded observer, not experienced with cystosonography, evaluated the agitated saline microbubble contrast cystosonography and determined which animals had a ruptured bladder. The region adjacent to the bladder was also assessed. The agitated saline microbubble contrast movement pattern into the bladder, and its presence outside the bladder were assessed to aid diagnosis. The positive contrast cystosonography was used to better differentiate between administered fluid, and the free abdominal fluid adjacent to the cystocolic window. Bladder rupture was confirmed if leakage of bladder content was identified, the presence of hyperechoic microbubble reverberation outside the bladder after injection (Figure 1). The integrity of the urinary bladder was confirmed if the hyperechoic microbubbles remained within the bladder. The technique was repeated up to three times as required to confirm the diagnosis. The time taken for each attempt, the number of attempts, and total time needed to make a final diagnosis were recorded. The timer started counting at the same time we started the infusion of microbubbles through the catheter and the timer ended as soon as the observer verbalized the diagnosis or requested a new attempt.

After the ultrasound examination, the diagnosis of bladder rupture was confirmed by a positive retrograde cystography technique, considered the gold standard for the diagnosis of bladder rupture. A ventrodorsal projection radiograph[e] was taken immediately prior to administration of the non-ionic iodinated contrast[f], after which a second ventrodorsal projection was made. The radiographic images were obtained using a computed radiography system[g], and appropriated settings for the abdomen region. The radiographic contrast medium was diluted 1:1 in saline solution. For each of the rats, 2 mL of the diluted contrast solution was used and for the dogs and the rabbit, 2.5 mL/kg was injected. A urethral probe was used for retrograde injection of contrast and the radiographs were taken in the final moments of the injection of the contrast (Figure 1).

2.3.3 Statistical analysis

The Shapiro-Wilk test was used to verify the parametric distribution of data. Data with parametric distribution were presented as mean ± standard deviation. Data with non-parametric distribution were presented as median (minimum – maximum). Results with normal distribution were submitted to one-way ANOVA for repeated measurements, followed by Tukey's test. Results with non-parametric distribution were submitted to the Kruskal-Wallis test, followed by the Tukey test.

Descriptive statistical analysis was performed calculating the percentages and indices of sensitivity [true positives/(true positives + false negatives)], specificity [true negatives/(true negatives + false positives)], PPV [true positives/(true positives + false positives)], NPV [true negatives/(true negatives + false negatives)] and accuracy [(true positives + true negatives)/sample total] for detection or not of bladder rupture by the contrast-enhanced cystosonography technique. All these data were obtained for rats, dogs and the total group of animals evaluated (TG).

A significance level of 5% ($p < 0.05$) was considered in this study. All tests were performed using the Sigma Plot[h].

2.4 Results

Cadavers of 16 rats, 17 dogs and one rabbit with an average weight of 0.27 ± 0.01 kg, 13.05 ± 4.69 kg and 2.70 kg, respectively, were included in the study. The sample set consisted of: 16 Wistar female rats, 6 female dogs, 11 male dogs and 1 male rabbit; the dogs and the rabbit had no defined breed. The mean time for diagnosis of the bladder condition for rats, dogs and rabbits was 1.15 ± 0.75, 2.25 ± 0.91 and 3.25 minutes, respectively. Times required for diagnosis in dogs were statistically longer compared to rats ($p = 0.03$).

In 29.47% (5) of the rat cadavers two attempts were required and in one rat cadaver a third attempt was needed for a definitive diagnosis. In dogs, diagnosis were made on the 1st attempt in

18.75% (3) cadavers, on 2^{nd} attempt in 18.75% (3) and in 62.5% (10) three attempts were required to obtain a final diagnosis. Three attempts were needed in the rabbit cadaver to obtain a diagnosis.

Of the 34 animals included in the study, a diagnostic error was made in only two dog cadavers (6%). These two dogs were females and had an intact bladder confirmed on contrast radiograph, misdiagnosed as ruptured on ultrasonographic examination. In all rat cadavers and the rabbit cadaver (100%) the ultrasound diagnosis was confirmed by positive retrograde cystography.

Sensitivity of 100%, 75% and 88.88% and accuracy of 100%, 88% and 94% were obtained for the diagnosis of bladder rupture after cystosonography with microbubble contrast in rats, dogs and TG. NPV was 1, 0.8 and 0.9 for rats, dogs and TG. The PPV was 1 and the specificity was 100% for all groups.

2.5 Discussion

This study is the first to determine the accuracy, sensitivity and specificity of agitated saline for contrast-enhanced cystosonography in detecting bladder rupture in in cadaveric models of different species of animals. A previous study reported the feasibility of the technique *in vitro*, and in two clinical cases, but did not determine the clinical applicability of the method.[16]

When any liquid, including saline solution, is stirred air, bubbles of various sizes form. These microbubbles can be detected ultrasonographically when infused into anaerobic and closed structures, such as blood vessels and the urinary bladder. The use of agitated microbubble contrast infusion has been described in several medical and veterinary diagnostic modalities and has been determined to be safe and effective.[15] Agitated microbubbles cystosonography could be easily incorporated into the AFAST exam scenario, specifically in patients with pelvic trauma. The identification of turbulent movement of hyperechoic microbubbles confined to the bladder lumen was used for diagnosis of an intact bladder.

Positive contrast cystography is the most widely used diagnostic method for the detection of rupture of the urinary bladder in veterinary medicine.[3,10,18] However, this examination results in radiation emission and there is the possibility of chemical irritation of the peritoneum if non-ionic iodinated contrast leaks from the bladder. Furthermore, the need to move an unstable patient to the radiographic examination room or the need to move the x-ray equipment to the emergency room may delay confirmation of bladder rupture in polytrauma patients.[10,18,19] By contrast, ultrasound is innocuous, portable, painless and presents no additional risks to the patient.[11-13]

This study was performed to determine the sensitivity, specificity, and accuracy of the technique and confirm the findings of other authors[16] Microbubble cystosonography was performed in three different species of varying sizes and weights, in a controlled, randomized and blinded study. The same authors previously described the evaluation of extensive bladder lacerations which are straightforward to diagnose, even without the use of contrast. A sensitivity of 88.88%, a specificity of 100% and an accuracy of 94% was obtained. Diagnostic errors were reported in two female dogs and with an intact bladder.

It is important to mention that although this was a cadaveric study, most of the cadavers were fresh and obtained from a clinical setting, making the results relevant to the clinical veterinary medicine.

False positive diagnosis for bladder rupture occurred in only two dogs. These dog cadavers were in a more advanced stage of autolysis despite being theoretically fresh. The presence of peritoneal gas, as a result of tissue deterioration, made accurate definition of the interface between the bladder wall and the contrast more difficult. The presence of reverberation artifacts, associated with intestinal free gas or loss of integrity of the abdominal wall, are reported as limiting factors for the focused abdominal sonography for trauma assessment technique (AFAST).[12,20] The same limiting factors are likely with microbubble contrast cystosonography. Other possibilities for the false positive diagnosis were the size of the dog, or the degree of bladder filling.

Cystosonographic diagnosis of bladder rupture was easier in smaller animals, such as the rats, as the high frequency transducers produce a single, wide, and detailed visual field which allowed more accurate bladder assessment. In larger animals,[21] such as dogs, more manipulation of the transducer was necessary to ensure that the entire bladder has been assessed during contrast medium administration, which may explain the need for repeated administrations of the contrast. These factors could also explain the longer time for diagnosis in larger animals.

Although evaluations in dogs and the rabbit took longer than in the smaller animals (rats), the diagnostic times were still sufficiently short to add to the diagnostic accuracy of AFAST without the need for a second exam, the use of chemical contrasts nor ionizing radiation.

Further studies are required in live animals and those with suspected bladder rupture to determine the clinical applicability of this technique. In addition, no cats were included in the study and this species represents a large percentage of animals with bladder changes that would benefit from the examination in clinical practice.

In this study, cystosonography with agitated saline microbubbles contrast was found to be an accurate, sensitive and specific diagnostic method for the detection of bladder rupture in cadavers from animals of different species. The technique is probably painless, and is an innocuous, rapid and affordable technique which could be used cage-side alongside the AFAST evaluation.

2.6 Abbreviations

AFAST Abdominal ultrasound for trauma

CR With bladder rupture

FAST Focused abdominal sonography for trauma assessment technique

NPV Negative predictive value

POCUS Point of care ultrasound

PPV Positive predictive value

SR Without bladder rupture

TG Total group of animals

2.7 Footnotes

a. Random.org, Randomness and Integrity Services Ltd, Dublin, Leinster.
b. Nipro Medical Corporation, São Paulo, SP.
c. Embramed Industry and Commerce of Hospital Products Ltda, São Paulo, SP.
d. Ultrasound System Logic F6, GE Healthcare, São Paulo, SP.
e. X-Ray CDK XD51 20/40 500ma/125Kv, CDK, Diadema, São Paulo.
f. Omnipaque, GE Healthcare, São Paulo, SP.
g. Radiographic system CR 30-xm, AGFA, Mortsel, Antwerp.
h. Program for Windows 12.0, Systat Software Inc, San Jose, CA.

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2.9 Figure Legends

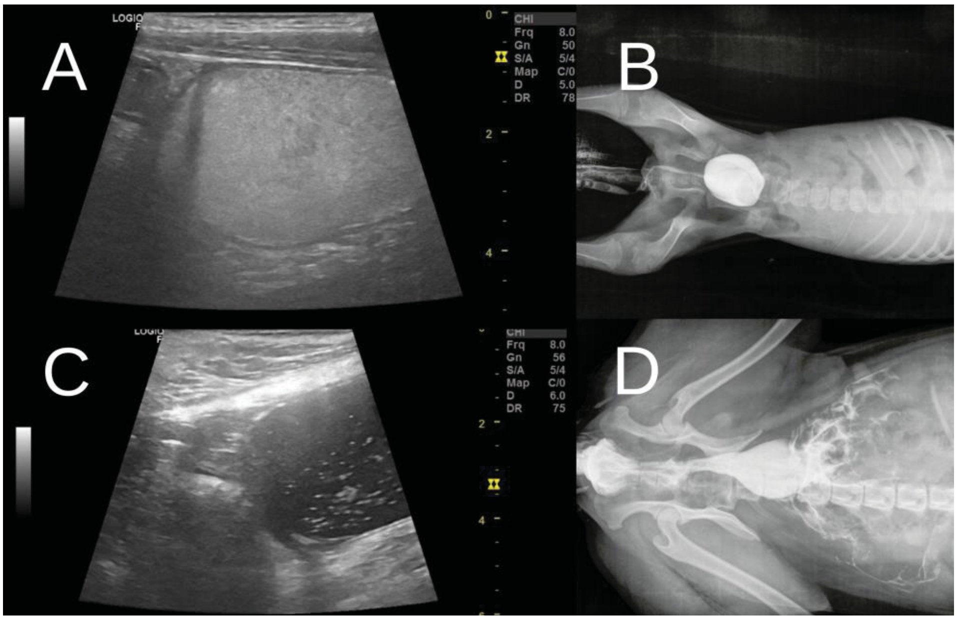

Figure 1 – A – Ultrasonography of the intact bladder after distension with microbubble contrast in dog. B – Ventrodorsal x-ray view of positive retrograde cystography in the same dog without bladder rupture. C – Ultrasonography showing a partial distended bladder with scaping hyperechoic shadowing of microbubble contrast agent in a dog with bladder rupture. D – Ventrodorsal x-ray view of positive retrograde cystography in the same dog with bladder rupture.

3 CHAPTER 2 – The use of agitated saline as a contrast agent in cystosonography for detection of urinary bladder rupture in small animals[2]

3.1 Abstract

Objective: To describe the use of agitated saline ultrasonographic contrast as a diagnostic aid in detection of bladder rupture in dogs and cats.

Design: Prospective observational study.

Setting: University teaching hospital.

Animals: Eleven animals with suspected uroabdomen secondary to bladder rupture.

Interventions: In this study, we demonstrated the use of cystosonography with agitated saline ultrasonographic contrast for confirmation of urinary bladder rupture in animals with a variety of causes of uroabdomen. Urethral catheterization was performed in all animals included in this study. Using the urethral catheter, 1 ml/kg of 0.9% saline solution, agitated and with 20% air incorporated into this volume, was instilled into the bladder. The movement of produces microbubbles was observed in real-time cystosonography by an experienced radiologist in the technique. Bladder rupture confirmed when the movement of contrast hyperechoic microbubbles was visualized outside the urinary bladder. All animals underwent a confirmatory diagnostic technique to verify the findings.

Measurements and Main Results: Eleven animals were included, 10 dogs and one cat. Eight animals had a history of abdominal or pelvic trauma, one had a history of cystotomy, one had urolithiasis, and one had a history of decompressive cystocentesis. Seven animals were diagnosed with urinary bladder rupture, while four animals had intact bladders. All animals included in this study were correctly diagnosed using the agitated saline microbubbles cystosonography.

Conclusions: Agitated saline microbubble contrast was effective in detecting urinary bladder rupture without the necessity for other complementary diagnostic techniques.

Key-words: ruptured bladder, microbubble contrast, cat, dog, ultrasound.

[2]This chapter is formatted to be submitted to the Journal of Veterinary Emergency and Critical Care.

3.2 Introduction

Uroabdomen refers to the rupture of the urinary tract, characterized by the presence of free urine within the abdominal cavity, retroperitoneal space, or both. In companion animals, uroabdomen usually results from abdominal or pelvic trauma, urethral or ureteral obstructions, and is closely associated with electrolyte and metabolic imbalances. Such alterations can have deleterious effects on renal function and cause cardiovascular and hemodynamic changes, which, if not promptly corrected, can result in irreversible morbidity and/or mortality. [1-3] In dogs and cats, the most common site of urinary tract rupture is the urinary bladder.[1, 4]

The diagnosis of uroabdomen in small animals has historically been based on history, physical examination, laboratory findings, plain abdominal radiography, contrast excretory urography, and retrograde urethrocystography with contrast.[1, 3, 5-7] However, despite being the gold standard for diagnosing and locating urine extravasation, the use of contrast can cause pain and irritation of the mucous membranes and peritoneum.[1, 3, 6] Less invasive means for the diagnosis of uroabdomen have been sought, and abdominal ultrasonography has been determined to be an excellent method for detecting free abdominal fluid and possible sources of extravasation.[8-10]

Currently, the diagnostic method used in polytraumatized patients is the Abdominal Focused Assessment with Sonography for Trauma (AFAST), which is designed to detect free fluid in the abdominal cavity with the possibility of subsequent abdocentesis and collection of this fluid for laboratory analysis.[9] Failure to visualize the urinary bladder during AFAST, or the absence of free fluid, does not exclude the possibility of urinary tract rupture.[1, 9, 11]

There are literature reports of cystosonography with agitated saline as a microbubble contrast solution as an alternative method for identifying urinary bladder rupture in dogs. This method is simple to perform, painless, and does not require radiographic chemical contrast media. However, there are only two studies demonstrating the feasibility of this method in confirming bladder rupture[12-13] therefore, further clinical validation of contrast-enhanced cystosonography is needed. The objective of this study was to determine the clinical applicability of microbubble contrast-enhanced cystosonography in dogs and cats with suspected uroabdomen.

3.3 Methods

3.3.1 Animals

This prospective and observational study was approved by the Institutional Animal Ethics Committee under protocol 067/2018. All the animals included in this study were presented to the imaging diagnostic department with a history of abdominal trauma, pelvic trauma, or another complaint that could result in a rupture of the urinary bladder and uroabdomen. The urethra was catheterized in all animals. The exclusion criteria were animals in which urethral catheterization was not performed before the AFAST exam, or animals without confirmatory diagnosis. Confirmation of presence or absent of urinary rupture was made by retrograde cystography with positive contrast, exploratory laparotomy or necropsy.

3.3.2 Experimental Design

The size of the urethral catheter was chosen according to patient size. After catheterization, each animal was positioned in dorsal recumbency on a foam wedge, and underwent AFAST, following the analysis protocol described previously.[9] When free fluid was evident it was collected for laboratory analysis if this was possible.

After the AFAST evaluation, the animals underwent cystosonography with agitated saline contrast. With the aid of two syringes and a three-way stopcock, a solution of 1ml/kg of 0,9% saline solution with 20% incorporated air was prepared, following the technique described previously.[13]

The bladder was filled slowly, over 10 to 15 seconds and a real-time exam of the bladder and bladder region was performed.

The contrast was administered through the urethral catheter, and the movement of microbubbles was observed in real-time using cystosonography. The bladder wall, parenchyma, and adjacent region were carefully examined. The pattern of contrast movement and any signs of extravasation into the peritoneal cavity were observed. When extravasation of contrast material was identified, urinary bladder rupture was diagnosed. The images observed during cystosonography are shown in figure 1. Hyperechoic reverberation movements and air-bubbles outside the bladder wall, in the adjacent abdominal cavity can be seen in cases of bladder rupture. When, the bladder is intact, the hyperechoic reverberation movements and air-bubbles are restricted within the bladder wall. Movements persist for about 1-2 minutes. With the aim of reducing intravesical pressure, after the examination, the urine with the contrast medium was drained through the urethral catheter.

The technique requires the presence of at least two operators. One agitates the saline and performs the infusion and the other individual carefully evaluates the abdominal using ultrasound. The process can be repeated a number of times, if there is any doubt as to the diagnosis.

In addition to positive retrograde cystography, exploratory laparotomy, analysis of peritoneal fluid, and necropsy were used as methods to confirm the diagnosis of uroabdomen and its origin. The ultrasound examinations were performed by trained radiologists proficient in the proposed techniques and with at least two year of experience in diagnostic imaging, three coauthors (TA, EG, TF radiologists, with 2, 8 and 26 years of experience in performing ultrasonographic exam). These co-authors were also responsible for determining the animals included in the study and clinical management.

3.3.3 Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of data distribution. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are presented as median (minimum - maximum). One-way analysis of variance (ANOVA) followed by Tukey's test was used to compare the group of animals with bladder rupture (BR positive) and without bladder rupture (BR negative) for normally distributed data. Kruskal-Wallis test followed by Tukey's test was used for non-normally distributed data to compare between groups. Significance level was set at 5% ($p < 0.05$). All statistical analyses were performed using Sigma Plot for Windows 12.0 software (Systat, CA, USA).

3.4 Results

A total of 11 animals, including ten dogs and one cat, were included in this study. The mean weight and mean age of the included animals were 11.64 ± 7.99 kg and 6.54 ± 3.83 years, respectively. Seven animals had confirmed urinary bladder rupture (BR positive), and four had confirmation of urinary bladder integrity (BR negative). There were no significant differences in weight ($p = 0.188$) or age ($p = 0.788$) between animals in BR positive and BR negative groups. The history of the animals as well as the number of animals are shown in Table 1.

All diagnoses, in animals with or without urinary bladder rupture, were correctly made by cystosonography with agitated saline contrast and confirmed using a confirmatory technique. Agitated saline contrast extravasation, indicative of uroabdomen due to bladder rupture, was observed in seven out of eleven animals. The data regarding the diagnostic confirmation tests used in each evaluation group are shown in table 2.

Of the 11 animals included in the study, retrograde cystography was performed in seven cases, of which four were positive for bladder rupture and three had an intact urinary bladder. Two animals were euthanized, and the diagnosis was confirmed during necropsy, with one of these animals showing bladder rupture and one an intact urinary bladder. The animal with the ruptured bladder was immediately referred for laparotomy and surgical repair of the bladder defect following sonography.

The cat included in this study had a history of urethral obstruction, and therapeutic cystocentesis to relieve pressure had been performed about 12 hours prior to the suspicion of uroabdomen. AFAST revealed a large amount of free peritoneal fluid, and after laboratory analysis, uroabdomen was confirmed. The creatinine level in the peritoneal fluid was 15.3mg/dL, which was about 3 times the value of serum creatinine measured at the same time (4.4mg/dL). Cystosonography with agitated saline solution was performed successfully to determine the location of the urine extravasation. After cystosonography, the animal was referred immediately for laparotomy and bladder repair.

3.5 Discussion

A correct diagnosis of presence or absence of bladder rupture was achieved in all animals evaluated by cystosonography with agitated saline positive contrast. This suggests that cystosonography with agitated saline contrast could be used in an emergency setting during an AFAST exam. The results, in combination with the laboratory analysis of free-fluid abdominal when present, might avoid the need for radiographic retrograde cystography. This alternative may be particularly useful when we consider that x-ray machines are not available in all emergency or intensive care rooms.

Classical ultrasound contrast solutions, such as second-generation UCA consist of phospholipid-stabilized microbubbles filled with sulfur hexafluoride and first became available for use in clinical at the end of 2001, and are expensive.(14) When agitated, liquids such as sterile saline solution contain air bubbles of various sizes, including microbubbles. These microbubbles are readily detected with ultrasound when the solution is infused into an anechoic environment such as the urinary bladder. Agitated saline, has been proven to be safe and is routinely used in human and veterinary ultrasonography.[12, 15] A previous case report in two dogs demonstrated the use of this contrast medium *in vitro* and animal cadaver studies have demonstrated the effectiveness in evaluating the integrity of the urinary bladder wall.[12-13].

Microbubble contrast is as effective as the gold standard technique of retrograde cystography with positive contrast for identification of the cause of uroabdomen[1,3, 5-7] Furthermore, saline solution poses no risk of peritonitis or irritation to the peritoneum, as can occur with the use of chemical contrast agents,[5,7] and avoids the needs for sedation as is frequently required for retrograde cystography with positive contrast,[7] thus providing major advantages for its use in cystosonography for the diagnosis of urinary bladder rupture. The agitated saline microbubble technique is less invasive, inexpensive, and a practical alternative for diagnosis of urinary bladder rupture, without the use of chemical contrast agents or ionizing radiation.

One disadvantage of the microbubble cystosonography is that the infusion of the agitated saline contrast may have to be repeated multiple times, to establish whether the hyperechoic microbubbles are inside or outside the bladder wall. Usually, it is easier to confirm the diagnosis of an intact bladder than bladder with rupture. Ruptures occurring more distally in the urinary tract, for example in the urethra, could be more challenging to diagnose, but were outside the scope of this study.

In a previously published study, it was shown that the diagnosis of uroabdomen can be made with 100% specificity and sensitivity if the peritoneal fluid creatinine concentration is at least twice that of serum creatinine,[3,18]. The cat in this study had peritoneal fluid analysis compatible with the diagnosis of uroabdomen. However, the location of the urine extravasation was only determined after agitated saline microbubbles cystosonography. The combination of these two techniques allowed rapid referral of the animal for surgical correction without the need for more invasive techniques, such as the use of ionizing radiation, chemical contrast agents, and anesthesia.

Although our main goal was not to determine the most common causes of bladder rupture, our study showed that of eleven animals, eight (72%) had a history of abdominal or pelvic trauma And four of them had their urinary bladders ruptured. Other studies also demonstrate the incidence of uroabdomen in animals suffering from trauma and emphasize the importance of investigation and diagnosis in these cases.(1, 4, 19) A study of cats with abdominal or pelvic trauma reported that in 85% of the animals that presented with uroabdomen, the origin of urine was bladder rupture.(19) This underscores the importance of incorporating the use of less invasive, painless, easy, and cheap techniques in the assessment of urinary bladder integrity as part of the emergency approach in polytraumatized animals.

Cystotomy, or the presence of bladder stones obstructing the urine drainage., may reduce the luminal volume of the bladder, increasing the risk of intravesical hypertension and predisposing to suture dehiscence or a bladder wall rupture.(18) Two of the animals included in this study had uroabdomen secondary to cystotomy and urolithiasis, respectively. Uroabdomen after cystotomy or urolithiasis is considered a rare, but possible, complication in dogs and cats. It is likely that these two animals suffered bladder distension, leading to a rupture in the bladder wall. This result highlights the importance of monitoring urinary output and providing appropriate pain management after cystocentesis, as well as monitoring the integrity of the urinary bladder using non-invasive and benign methods such as cystosonography with agitated saline microbubble contrast.

The cat in this study had uroabdomen secondary to cystocentesis. The extravasation occurred at a small and single point in the cranio-dorsal portion of the urinary bladder. The rupture of the urinary bladder after cystocentesis is described as a rare, but possible complication, regardless of the degree of bladder distention of the patient, and therefore monitoring of the animal after the procedure is essential.[19-22] This rupture, although small, was easily visualized in the cystosonography, similar to findings previously demonstrated in cadavers of dogs.[13]

This study has a number of limitations, the time taken to perform the examination the procedure, as well as the exact number of attempts needed to obtain a definitive diagnosis in each dog or cat, were not recorded. However, we know that it was necessary to perform the procedure more than once in all patients to confirm whether or not a rupture was present. Information on procedure time will be important for selection of diagnostic technique in clinical practice, and therefore, we recommend that further studies be conducted with the aim of capturing these data. As previously mentioned, more caudal ruptures, such as urethral ruptures, were not evaluated. We believe that the more caudal or pelvic the rupture, the more challenging the evaluation may be, and therefore further studies are needed to determine whether the position of the lesion influences the results. Additionally, we recommend further studies to demonstrate the sensitivity and specificity profile of the technique in larger populations.

With this study, we confirm that cystosonography with agitated saline contrast is effective for diagnosing urinary bladder rupture in small animals, even with very small defects in the bladder wall, without the need for confirmation by other diagnostic methods and without the use of ionizing radiation, chemical contrast agents or anesthesia. We recommend the use of this technique in conjunction with AFAST in unstable animals or in emergency situations, replacing the need for other diagnostic techniques for bladder rupture.

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3.7 Tables and figure legends

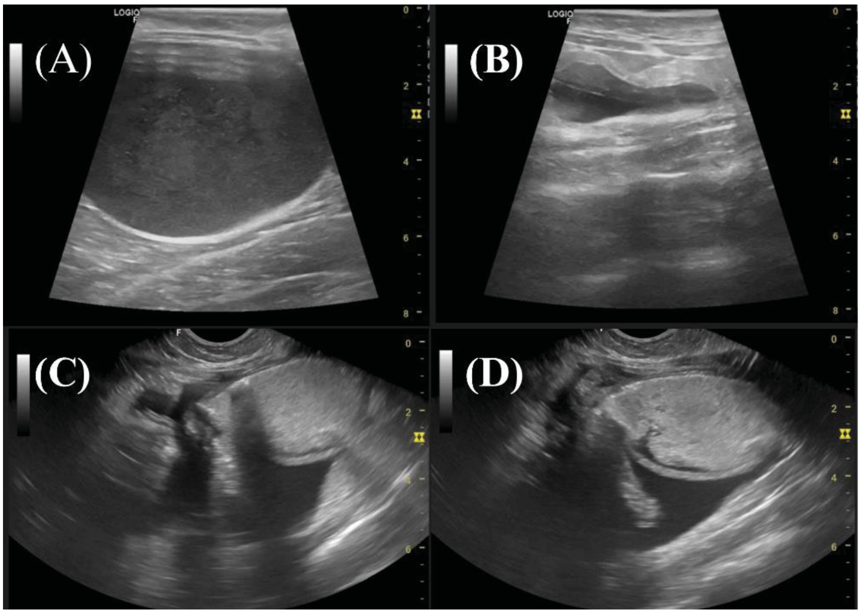

Figure 1. A: Urinary bladder filled with anechoic content and a large amount of suspended hyperechoic sediment. B: Empty urinary bladder before the insertion of agitated saline contrast. C and D: The agitated saline contrast seen at cystosonography. The hyperechoic content of the microbubbles extravasates from the urinary bladder to the peritoneum through a hole in the cranial region of the bladder. Free fluid can also be seen dorsally and around the bladder in these images.

Table 1. Number of animals with a history of abdominal/pelvic trauma, history of urethral obstruction and cystocentesis, recent history of cystotomy, and history of urolithiasis in the group of animals with urinary bladder rupture (RB positive) and without urinary bladder rupture (RB negative).

	RB positive	RB negative	Total
History of abdominal/pelvic trauma	4	4	8
History of urethral obstruction and cystocentesis	1	0	1
History of recent cystotomy	1	0	1
History of urolithiasis	1	0	1

Table 2. Number of animals that underwent different confirmatory techniques for the diagnostic confirmation of urinary bladder rupture in dogs and cats.

	RB positive	RB negative
Positive retrograde cystography	4	3
Exploratory laparotomy	2	0
Necropsy	1	1
Total	7	4

RB positive: group of animals with urinary bladder rupture; RB negative: without urinary bladder rupture.

4 CHAPTER 3 - Risk factors and complications associated with ultrasound-guided cystocentesis in dogs and cats - Epidemiological Study[3]

4.1 Abstract

Cystocentesis in dogs and cats is considered a simple and routine procedure in clinical practice. However, it is an invasive procedure with potential risk of complications. This study describes the main risk factors associated with complications of ultrasound-guided cystocentesis in dogs and cats. A total of 410 animals, 267 dogs and 143 cats, were included in this prospective study. Of these, 31 animals (8%) experienced complications after ultrasound-guided urine collection. Compared to agitated animals, there was an 86% reduction in the likelihood of complications in animals classified as calm and easy to handle. Repeated urine collection attempts increased the chance of complications by 110%, even in calm individuals, and each additional millimeter of needle length used for puncture increased the possibility of complications by 30%. Agitated animals restrained by their owner had a 71% chance of complications compared to 7% when they were restrained by the technical staff. The risks associated with complications of cystocentesis may be potentially fatal. Therefore, although complications are rare appropriate restraint is essential, especially in agitated or uncooperative animals.

Keywords: Cystocentesis, ultrasound, canine, feline, complication.

4.2 Introduction

Cystocentesis is defined as the percutaneous aspiration of urine directly from the urinary bladder[1,2]. This technique is used for obtaining uncontaminated urine samples or for bladder decompression in patients unable to urinate or with urethral obstruction. [3].

Cystocentesis, both in dogs and cats, is a routine procedure in veterinary medicine for laboratory evaluation of urine in urinary tract disease and for bladder decompression [3-8]. However, although it is generally considered a simple procedure that causes little pain and/or discomfort, it is an invasive

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procedure with potential risks of complications[3-6, 9, 10]. Cystocentesis is specifically contraindicated in animals that are difficult to restrain, or when there is an empty urinary bladder, history of abdominal trauma, recent surgery, pyometra, coagulopathy, or ongoing use of anticoagulants[3-6, 11]. In addition, patients with urinary bladder cancer or non-delimited abdominal cancer are not candidates for the procedure, and other means of urine collection or bladder decompression are preferred in these cases [2, 9].

Complications related to cystocentesis, although uncommon, have been described in dogs and cats. These include bladder rupture, with consequent abdominal contamination and peritonitis[4, 9], aortic and vena caval laceration[11], abdominal wall injuries, seizures, and syncope[5]. However, despite severe complications related to the technique, epidemiological studies assessing risk factors[9] and associated complications[8] are scarce. Therefore, this study aimed to correlate risk factors with the main complications of ultrasound-guided cystocentesis in dogs and cats.

4.3 Methods

4.3.1 Animals

The study was submitted to, and approved by, the Animal Ethics Committee of the Agricultural Sciences sector of the Federal University of Paraná – CEUA/AG-UFPR (009/2021). It was a prospective and multicentric study, enrolling routine hospital patients, of four imaging diagnostic centers in the country, from July 2021 to July 2022. All animals in the study had clinical indications for ultrasound-guided cystocentesis for urine collection or bladder emptying.

4.3.2 Experimental design

The animals were admitted to the diagnostic imaging service for ultrasound-guided cystocentesis. The cystocentesis procedure was carried out by veterinarians experienced in imaging and trained in cystocentesis, using ultrasonographic phantoms for at least six months before the beginning of the study. All animals were positioned in dorsal recumbency, on a foam positioning cushion for ultrasonography, and restrained by the pelvic and thoracic limbs with the help of two individuals. Individuals involved in the restraint could be owners and technical staff, only technical staff, or only owners. The imaging specialist who performed the procedure subjectively classified each animal's temperament as either: calm/docile or agitated/difficult to restrain, according to the ease of restraint and positioning of the animal at the time of collection.

Data regarding species, breed, weight, age, sex, needle length, number of attempts, volume of urine collected, and presence of bladder abnormalities seen on ultrasound examination were collected. Needles with lengths of 20, 25, and 30mm were included in this study. In addition to information on the collection procedure, the sonographic findings were recorded along with their respective differential diagnoses. The findings were classified according to Sutherland-Smith and Penninck[12] as: 1) cystitis, when "the bladder wall was diffusely thickened, with mild to moderate thickening, or with focal cranioventral thickening, and the mucosa slightly irregular and the wall hypoechoic"; 2) presence of uroliths, "one or more hyperechoic structures producing acoustic shadowing, intraluminal and mobile, of different sizes were identified"; 3) intraluminal clots, when "the presence of linear or rounded structures, with variable echogenicity were observed"; or 4) obstruction or bladder distention, when "accumulation of large amounts of anechoic content within the urinary bladder was observed". All abnormalities were correlated with the patient's clinical and laboratory findings for final classification.

Data regarding accidental venous or arterial punctures, enteric punctures, punctures of cysts or lymph nodes, skin or muscle lesions, the presence of syncope or convulsions during collection, were recorded. Details of who restrained the animal were recorded. Moreover, the clinical repercussions of the complications listed and the need for surgical or conservative intervention were recorded. At the end of each procedure, data were recorded in a single questionnaire, delivered in print or remotely through the google forms platform, according to the preference of the investigator. After data collection, the animals were divided into two groups; with complications (GCI) and without complications (GSI).

4.3.3 Statistical analysis

The Shapiro-Wilk test was used to verify the normality of the numerical data distribution. Parameters with normal distribution are presented as mean ± standard deviation of the mean. Parameters with non-normal distribution are presented as median (minimum–maximum). Results with normal distribution were submitted to Student's t test for comparison within the different groups. Results with non-normal distribution were submitted to the Mann-Whitney Rank Sum test for comparison between the different groups.

The predictor variables were submitted to logistic regression analysis to determine the chance of these variables causing an intercurrence. For this analysis, the Stepwise technique was used for an additional selection of the predictor variables with the best results. At this point, the predictor variables were removed and added one by one using the t-test. Additionally, a decision tree was built to determine the probability of the collected data influencing the presence of intercurrences during the procedure.

McFadden's pseudo R2 value greater than 0.4 was used to assess the quality of the model, in addition to accuracy, sensitivity, and specificity. Significance level was set at 5% ($p<0.05$). All tests were performed using the R program for Windows 12.0 (*RStudio*, MA, USA).

4.4 Results

Data were collected from 410 animals undergoing ultrasound-guided cystocentesis. This included 267 dogs (174 females and 93 males) and 143 cats (57 females and 86 males).

The average weight of the animals was 9.54 ± 8.82 kg and mean age was 8.61 ± 4.52 years. The average number of attempts and the volume of urine obtained were 1.42 ± 0.74 times and 7.5 ± 4.5mL, respectively. There were no significant differences between the weight of the animals (*p=0.478*) and the amount of urine collected (*p=0.224*) between groups. However, the age in the GSI was significantly higher (*p=0.033*) compared to the GCI, and the number of attempts in the GCI was significantly higher (*p<0.001*) compared to GSI. When comparing dogs and cats, only the weight of the dogs was significantly higher (*p<0.001*).

Data regarding weight, age, sex, number of attempts, and amount of urine collected are shown in Table 1.

Table 1. Data regarding weight, age, number of attempts, and amount of urine collected in patients undergoing ultrasound-guided cystocentesis.

	Weight (kg)	Age (years)	Number of attempts	Amount of urine (mL)	Sex		Temperament	
					Female	Male	Agitated	Calm
Dogs	12.37 ± 9.77*	8.73 ± 4.14	1.41 ± 0.71	7.98 ± 4.11	174	93	80	187
Cats	4.26 ± 1.57	8.44 ± 5.15	1.44 ± 0.79	6.61 ± 5.13	57	86	116	27
GCI	10.67 ± 9.77	6.66 ± 4.82	1.93 ± 0.96#	8.16 ± 10.08	13	18	24	7
GSI	9.44 ± 8.75	8.78 ± 4.46#	1.38 ± 0.7	7.46 ± 3.76	218	161	172	207

GSI: group without complications; GCI: group with complications; *: species with a numerical value significantly higher; #: group with significantly higher numerical value; normal parameters presented as mean ± standard deviation of the mean; non-normal parameters presented as median (maximum-minimum).

Of the animals included in the study, 57 (13.90%) had cystitis, 12 (2.92%) had a combination of cystitis and urolithiasis, and 11 (2.68%) had signs of obstruction with a full urinary bladder. Uroliths were found in 16 (3.90%) animals, one (0.24%) presented with intraluminal clots, and, in 313 (76.34%) animals, no ultrasonographic alterations of the urinary bladder were observed. The distribution and frequency of ultrasound changes in the urinary bladder in both groups are shown in Table 2.

Table 2. Sonographic changes found during the evaluation of the animals included in the study, their distribution, and frequencies within each group of animals.

	cystitis	cystitis + urolithiasis	Obstruction + full urinary bladder	urolithiasis	intraluminal clots	no changes	Total
GSI	46 (12.13%)	10 (2.63%)	9 (2.37%)	16 (2.37%)	1 (0.26)	297 (78.36)	379 (100%)
GCI	11 (35.48%)	2 (6.45%)	2 (6.45%)	0 (0%)	0 (0%)	16 (51.61%)	31 (100%)
Total	57 (13.90%)	12 (2.92%)	11 (2.68%)	16 (2.43%)	1 (0.24%)	313 (76.34%)	410 (100%)

GSI: group without complications; GCI: group with complications; *: group with significantly higher frequency.

Regarding behavior, 196 (47.80%) animals were considered agitated and difficult to restrain, and 214 (52.20%) were considered calm. In 361 (88.04%) animals, the restraint was performed by the technical staff, in 37 individuals (9.02%) by the staff and the owner, and in 12 animals (2.92%) only by the owner.

There were 32 complications in 31 animals (7.56%), of which 22 (70.96%) were dogs, and 9 (29.03%) were cats. The main complications found were: subcutaneous hematoma (46.87% - 15/32), accidental blood vessel punctures (46.87% - 15/32), syncope (3.12% - 1/32) and bladder rupture (3.12% - 1/32). One animal had an aortic puncture followed by syncope.

After the initial evaluation, species, weight, sex, and volume of urine collected were removed from the logistic regression model because they did not show predictive power for the occurrence of any intercurrence. The model showed a McFadden pseudo R2 value of 0.422 ($p<0.001$). In addition, the model had an accuracy of 94.8%, a sensitivity of 98.9%, and a specificity of 45.1%. The model is shown in Table 3, and the effects of sensitivity and specificity in the regression model are graphically shown in Figure 1.

The model suggests that as age increases there is a reduction (14%) in the risk of complications. Moreover, there was a decrease (86%) in complications in calm and easy-to-handle animals compared to agitated and/or difficult-to-restrain animals. If a specialized team handles agitated animals, there is a further reduction in the chances of complications (80%).

Additionally, it was observed that repeated attempts to perform the procedure increased the chance of complication by 110%, even in calm animals. Also, with each extra millimeter of needle length, the possibility of complication increased by 30%.

Table 3. Results of the logistic regression model (Stepwise technique) for complications in dogs and cats submitted to ultrasound-guided cystocentesis, according to age, calm temperament, restraint performed by the technical team, number of attempts, and needle length.

Variable	Estimated	Standard error	OR	Z value	*p*
Intercept	-7.038	2.618	0.001	-2.689	0.007
Weight (kg)*	-0.037	0.027	0.964	-1.358	0.174
Age (years)	-0.153	0.059	0.858	-2.598	0.009
Temperament – Calm/easy restraint	-1.945	0.531	0.143	-3.666	0.000
Restraint - Technical team	-1.591	0.595	0.204	-2.675	0.007
Restraint - Owner*	1.631	0.944	5.108	1.728	0.084
Number of attempts	0.740	0.279	2.096	2.648	0.008
Needle length (mm)	0.263	0.093	1.301	2.836	0.005
Bladder changes on ultrasound *	0.732	0.498	2.080	1.472	0.141

*: Variables without significance were kept in the model, as they interfered with the predictive value of the other variables.

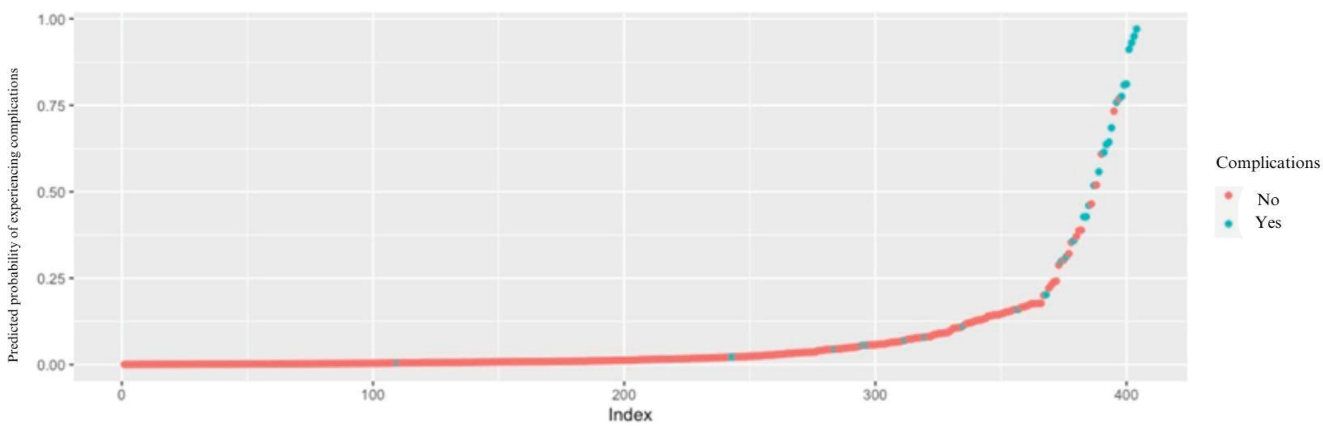

Figure 1. Scatter plot showing the probability of intercurrence estimated by the logistic regression model and the intercurrences that actually occurred in 410 animals evaluated after the ultrasound-guided cystocentesis procedure.

The main predictor variables for the decision tree were patient temperament and the type of restraint used for the procedure. This model had an accuracy of 94.6%, a sensitivity of 98.4%, and a specificity of 48.5%.

In this study there was an 8% probability of complication. The first node of the decision tree shows a reduction of 4% when the technical team carried out the restraint and an increase of 35% when restraint was performed by the owners. Moreover, when restrained exclusively by the owners, calm patients had a 7% probability of complication, while agitated animals had 71%. These results are shown in Figure 2.

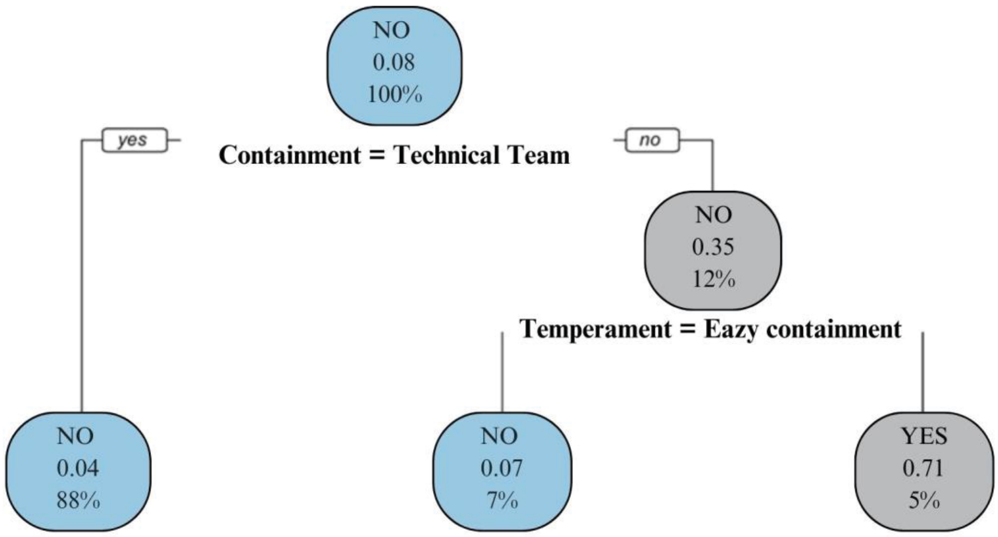

Figure 2. Decision tree constructed with temperament and restraint data from the animals evaluated after the ultrasound-guided cystocentesis procedure.

One of the animals that had aorta or vena cava puncture developed syncope during the procedure. This animal was the only one to suffer hemodynamic repercussions, with an accumulation of free fluid after the procedure, and volume replacement and abdominal packing was required for stabilization and hemostasis. A second animal developed free fluid accumulation after an accidental puncture of an intra-abdominal blood vessel, but without hemodynamic repercussions.

One cat suffered bladder rupture after relief cystocentesis. Laboratory analysis of the free fluid showed a creatinine value of 13g/dL. After diagnosis, the animal was referred for exploratory laparotomy and surgical correction of the laceration. No animal died as a result of cystocentesis.

4.5 Discussion

This study presents a prospective analysis describingthe risk factors associated with complications of ultrasound-guided cystocentesis in dogs and cats. The data show that, although the probability of complications is low (8%), there is the possibility of catastrophic outcomes that can be fatal. It is therefore important to consider all the risk factors for the individual patient when cystocentesis is indicated. The low probability for complications was reflected in the specificity of the logistic regression model and the construction of the decision tree.

In this study, it was found that with each additional year of life in these animals, there was a 14% reduction in the likelihood of experiencing a complication. We believe that as the animals age, they become more accustomed to physical restraint and also become calmer and more disciplined. This factor may have influenced the incidence of complications in this study.

Animals restrained by a specialized team had a significant reduction in the risk of complications, even when agitated and difficult to handle. This has not previously been reported in the literature and highlights the importance of appropriate restraint by a trained team. In addition, repeated attempts to collect urine by cystocentesis significantly increased the risk of complications, as has been described previously(11).

A single study reporting complications related to ultrasound-guided cystocentesis in dogs and cats has been published. The authors retrospectively described the adverse effects of urine collection by cystocentesis in 21 animals and classified them as major or minor according to the severity of the event(8). These animals were screened from a large group of animals (around 26,000), clearly showing that the probability of a complication after cystocentesis is small, but potentially dangerous.

Accidental punctures of large vessels and subcutaneous hematomas were the most frequent complications in this study, with 15 animals in each group. The complication profile described by

Manfredi et al.[8] was similar to that found in our research. In addition to the potential for severe complications, such as iatrogenic laceration of large vessels, septic peritonitis, and acute abdomen; minor complications have also been described, such as fat necrosis, abscesses, intravesical hemorrhage and hematoma, urinary bladder rupture, focal peritonitis, subcutaneous and cutaneous hematomas, urinary sediments and intravesical mucosal edema.

In the present study, accidental puncture of a large vessel occurred in two animals. They both presented with free fluid in the abdomen and the formation of a clot dorsal to the urinary bladder. One of these animals had hemodynamic repercussions associated with hemorrhage, but blood transfusion/ surgery was not required. This animal's condition improved after fluid therapy for volume replacement and packing for hemostasis. Immediate identification of the complication using ultrasound follow-up to visualize blood extravasation and clot formation, and serial follow-up examinations were able to reduce the morbidity and potential mortality risk in these animals.

Accidental punctures of large vessels during cystocentesis has previously been reported on two occasions[8, 11]. In the first report, the dog had active hemorrhage secondary to cystocentesis which resolved after a massive blood transfusion and surgical correction of the laceration. This dog had been physically restrained and classified as agitated. In addition, three attempts at cystocentesis were made before a urine sample was collected, and the procedure was performed without ultrasound guidance[11]. Both our patient with hemodynamic instability, and the patient reported by Buckley et al.[11], were classified as agitated and uncooperative, and the complication was observed after repeated attempts to perform the collection. These results suggest that agitated animals must be adequately restrained, including the use of sedation where necessary, and that repeated collection attempts may significantly increase the risk of complications. A second study reported that two animals suffered focal hemorrhage without hemodynamic repercussions and the need for clinical or surgical interventions[8], similar to the other animals in our study that had accidental punctures of the vena cava or abdominal aorta.

One of the dogs included in this study, in which an accidental puncture of the aorta occurred, suffered syncope shortly after cystocentesis. This event has been previously reported in a cat[5] related to the excessive parasympathetic activity by vasovagal stimulation during the stressful event of abdominal puncture[5, 13, 14]. This type of vagal response has also been described in human patients and is characterized by a combination of bradycardia and arterial vasodilation[13-15].

The vasovagal reflex can develop due to relative or absolute blood loss. However, it can also occur due to intense emotions and mechanical stimulation of the vagal nerve, as seen in vascular punctures or cystocentesis[14]. In mammals, the vagal nerve is responsible for the parasympathetic innervation of all viscera, abdominal and thoracic, including the urinary bladder, making its stimulation an additional risk for the activation of the vasovagal reflex[5, 14, 16]. The syncope seen in our patient could be related to the accidental aortic puncture and subsequent hemorrhage, as well as to the vagal stimulation caused by the puncture of the urinary bladder.

In this study, one cat was diagnosed with uroabdomen due to a urinary bladder rupture after relief cystocentesis. In cats with urethral obstruction, the combination of bladder distention and increased intra-abdominal pressure can lead to severe pain, and electrolyte and hemodynamic decompensation[17-19]. Relief cystocentesis in these animals is currently indicated as emergency therapy until urethral flow is reestablished, accepting the risk of bladder rupture and uroabdomen. Urethral obstruction and electrolyte imbalances offer a greater risk to the patient's life than uroabdomen and its resolution [3, 8, 10, 17-19]. Furthermore, there is a risk of bladder rupture or damage to the urinary bladder wall, leading to uroabdomen after cystocentesis[1, 8, 18]. The animal in this study recovered completely after surgical correction of the bladder rupture and relief of the urethral obstruction, as previously reported in the literature[8, 18-20].

In addition, there was a 30% increase in the likelihood of complications for each additional mm needle length used for the procedure. Longer needles may damage the tissues and puncture vessels in dorsal to the urinary bladder. Ultrasound-guidance is therefore very useful in cystocentesis to monitor needle placement and selection of an appropriate length of needle urine collection will reduce the risk of damage dorsal to the bladder. Although cystocentesis has been described without the use of ultrasound, this technique is not recommended due to the associated risks and difficulty in assessing damage after the procedure[1, 6, 8, 10, 11]. Our results reinforce the need to monitor the patient with ultrasound after the procedure.

In this study, data regarding bladder filling was not included. Therefore, empty or very distended urinary bladders may have influenced the results and/or the difficulty of performing the procedure. Furthermore, behavioral assessment scales were not used to determine levels of agitation or anxiety, and subjective assessment was made which was not standardized.

Ultrasound-guided cystocentesis is invasive and the potential risks must be considered and explained to the owners, although probability of complications is low. In addition, the risk of complications is significantly reduced if the animal is restrained by a trained team, and sedation should be considered in very agitated or uncooperative animals.

4.6 Conclusion

In conclusion, complications were seen in around 8% of ultrasound-guided cystocenteses. Complications of the procedure can be significant, including the puncture of large vessels and the rupture of the urinary bladder. In addition, complications are more common in agitated animals and in animals restrained by owners.

Conflicts of interest: The authors declare no conflicts of interest.

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5 CONSIDERAÇÕES FINAIS

Com este trabalho podemos reunir informações importantes quanto ao diagnóstico e epidemiologia de uroabdome em pequenos animais. Tais informações nos mostram que diante da suspeita de uroabdome o diagnóstico precoce, preciso e, principalmente, inócuo tornam o prognóstico favorável aos pacientes.

O uso do contraste de microbolhas pela cistosonografia mostrou-se eficiente para o diagnóstico de ruptura de vesícula urinária em diferentes espécies animais e, sobretudo, mostrou-se indolor, prático e acessível aos diferentes cenários da medicina veterinária. Chama-se especial atenção a ausência do uso de radiação ionizante, não necessidade de sedação ou tranquilização e risco ausente de peritonite química secundária ao uso de contrastes iodados não iônicos.

Em adicional, este projeto demonstra que a cistocentese, mesmo guiada por ultrassonografia e realizada por operadores experientes em diagnóstico por imagem, apresenta riscos importantes e potencialmente fatias para cães e gatos. Dentro deste contexto, o trabalho nos apresenta a importância de prover a correta contenção para esses animais, principalmente aqueles com a índole agressiva ou agitada. Além disso, o trabalho propõe a necessidade de treinamento da equipe envolvida com o procedimento e da instrução dos tutores quanto ao risco inerente a técnica empregada.

Por fim, a nossa perspectiva é que este trabalho seja continuado e complementado com o estudo clinico em animais de diferentes espécies, mas, que também o uso do contraste de microbolhas seja viabilizado e testado para observação uretral em animais com suspeita de ruptura de uretra.

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7 VITA

Médica veterinária graduada pela Universidade Federal do Paraná (UFPR), setor Palotina no ano de 2014.

Concluiu o Programa de Residência multiprofissional em área da saúde – Anestesiologia veterinária, modalidade de pós-graduação "Lato sensu", nível I e II no hospital veterinário da UFPR do setor de ciências agrárias, no período de fevereiro de 2014 a fevereiro de 2016.

Cursou o Programa de Pós-graduação em Ciências Veterinárias da Universidade Federal do Paraná (UFPR), nível Mestrado, no período de março de 2016 a março de 2018.

Cursou o Programa de Pós-graduação em Ciências Veterinárias da Universidade Federal do Paraná (UFPR), nível Doutorado, no período de março de 2019 a março de 2023.

8 ANEXOS

8.1 ANEXO I – Artigo publicado na revista *Journal of veterinary emergency and critical care.*

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ORIGINAL STUDY

Veterinary Emergency and Critical Care

WILEY

The use of agitated saline as contrast agent in a contrast-enhanced cystosonography for detection of urinary bladder rupture in animal cadavers

Eloisa Muehlbauer MSc | André Saldanha MSc | Elaine M. Gil PhD | Thais L. Alves DMV | Juan C. M. Duque PhD | Tilde R. Froes PhD

Veterinary Sciences Graduate Program, Department of Veterinary Medicine, Federal University of Paraná, Curitiba, Brazil

Correspondence
Eloisa Muehlbauer, Department of Veterinary Medicine, Federal University of Paraná, Rua dos Funcionários 1540, Juvevê, Curitiba – PR, CEP 80035-050, Brazil.
Email: eloisamuehlbauer@hotmail.com

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Abstract

Objective: To determine the value of microbubble contrast cystosonography in the diagnosis of bladder rupture in animals.

Design: Prospective, method comparison study from November 2019 to October 2020.

Setting: University teaching hospital.

Animals: Thirty-four ethically sourced cadavers of dogs, rats, and rabbits.

Interventions: In a prospective and blinded study, the cadavers were divided into 2 randomized groups: with bladder rupture (CR), and without bladder rupture (SR). Urinary catheterization was performed in all cadavers. Through the urethral catheter, bladders in CR group were ruptured using a rigid stainless steel guide wire. Microbubble contrast was infused into the bladder through the urethral catheter, while a single, blinded observer sonographically assessed the bladder. The time to diagnosis and the number of attempts needed for diagnosis were recorded.

Measurements and Main Results: The study included cadavers of 16 female Wistar rats, 6 female dogs, 11 male dogs, and 1 male rabbit. Time to diagnosis in dogs (2.25 ± 0.91 min) was statistically higher when compared to rats (1.15 ± 0.75 min; $P = 0.03$). Of the 34 cases, incorrect diagnosis of bladder rupture was made in only 2 dogs (6%), indicating a diagnostic sensitivity of 88.88%, specificity of 100%, and an accuracy of 94%. The positive predictive value was 1 and the negative predictive value was 0.9.

Conclusions: Our study showed that the described method is accurate, sensitive, and specific for the detection of bladder rupture in animal cadavers of different species, size, and sex.

KEYWORDS
animals, microbubble contrast, ruptured bladder, ultrasound

Abbreviations: AFAST, abdominal-focused assessment with sonography for trauma; TG, total group of animals.