THE EFFECTS OF FUROSEMIDE ON URETERAL DIAMETER AND ATTENUATION USING COMPUTED TOMOGRAPHIC EXCRETORY UROGRAPHY IN NORMAL HEALTHY DOGS

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The undersigned, appointed by the Dean of the Graduate School, have examined the thesis entitled

THE EFFECTS OF FUROSEMIDE ON URETERAL DIAMETER AND ATTENUATION USING COMPUTED TOMOGRAPHIC EXCRETORY UROGRAPHY IN NORMAL HEALTHY DOGS

Presented by Scott Secrest

A candidate for the degree of
Master of Science

And hereby certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

Although rare, ectopic ureter is one of the most common causes of urinary incontinence in young female dogs.[1] This congenital disorder has also been reported in humans, cats, horses, cattle and llamas. In domestic animals afflicted with ectopic ureters, one or both ureters terminate distal to the urinary bladder trigone, but renal anatomy is usually normal.[2-6] In people however, there is usually ipsilateral renal pelvic duplication or renal dysplasia.[7-9]

Female dogs account for 89-95% of all ectopic ureter cases and are diagnosed at the median age of 10 months.[1] Male dogs however are often diagnosed later in life with a median age of 24 months.[1] The difference in age at which ectopic ureters is diagnosed is thought to be due to urinary incontinence being more readily identified in females as the longer urethra in males is better able to prevent distal flow of urine.[10] In all species the most common clinical sign is intermittent urinary incontinence with periods of more normal urination.[11] Affected dogs may also have a history of reoccurring urinary tract infections.[12] Several breeds have been noted to be at increased risk for ectopic ureters, suggesting a genetic role. These breeds include Siberian husky, Newfoundland, bulldogs,

West Highland white terrier, fox terrier, Labrador retriever, golden retrievers, Skye terriers, miniature and toy poodles.[13]

Embryologically, the normal ureter arises from the ureteral bud of the mesonephric duct.[3] As the mesonephric duct elongates, it joins the metanephric duct distally to form the common nephric duct. The metanephric duct continues to grow proximally, toward the metanephros which will become the kidney. At the same time the urinary bladder absorbs the common nephric duct, leading to separate openings for the mesonephric and metanephric ducts. With continued growth, the mesonephric ducts are displaced caudally, opening on the dorsal urethral wall. The metanephric duct then becomes the ureter while the mesonephric duct becomes the deferent duct in males and is a vestigial structure in females. In dogs with ectopic ureters the metanephric duct is located more proximal on the mesonephric duct and thus fails to have a single opening into the urinary bladder.[3] Instead it is carried caudally, opening into the neck of the urinary bladder or urethra. It is not completely known how ectopic ureters open into the uterus or vagina as these structures originate from the mullerian duct.

A variety of imaging modalities have been used to evaluate the ureters including retrograde vaginourethrography, ultrasonography, computed tomography and excretory urography. With radiographic excretory urography and vaginourethrography, evaluation of the distal ureters and ureterovesicular junction can be difficult due to insufficient contrast resolution and superimposition of the gastrointestinal tract and

osseous structures. Ultrasonography has its own disadvantages including limited spatial resolution, which prohibits identification of the ureters unless abnormally distended. Also gas within the adjacent colon or small intestines may prevent identification of the terminal ureters and ureterovesicular junction because of reverberation artifact.

Different techniques have been suggested to help improve evaluation of the ureterovesicular junction in dogs. These techniques include fluoroscopy, vaginourethrography and pneumoscystography.[12] In previously published reports, a correct anatomical diagnosis of ectopic ureters was made in only 62-77% of patients on excretory urography and retrograde vaginourethrography.[1,5-6] Because evaluation of the distal ureters and ureterovesicular junction can be challenging, a definitive diagnosis of ectopic ureters cannot always be made.

Computed Tomographic Excretory Urography (CTEU) has overcome many of the problems associated with radiographic excretory urography. In recent years it has become the imaging modality of choice in both human and canine patients suspected of having ectopic ureters.[7,8,11] In one canine study, excretory urography correctly identified only 70% of patients with ectopic ureters compared to 94% with CTEU.[11] CTEU has greater contrast resolution as well as improved spatial and temporal resolution. The ability to obtain transverse and multiplanar reformatted images decreases the effects of superimposition of other anatomic structures. It also provides more information about renal anatomy when compared to radiography.[14]

The major disadvantage with CTEU in both human and canine patients is that normal ureteral peristalsis causes intermittent disappearance of the contrast media within the ureter, resulting in inconsistent visualization of the ureter.[11,15-17] This makes it difficult to obtain a single scan where the ureter is seen in its entirety. When normal peristaltic contractions occur in the region of the vesicoureteral junction, multiple scans may have to be performed to completely visualize the entire ureter, resulting in increased scanning and anesthesia time and greater radiation exposure. A number of modifications, such as saline boluses and/or furosemide have been investigated as adjuncts to the CTEU protocol in human patients in an effort to overcome the effects of normal ureteral peristalsis.[17-19] In one study, furosemide improved visualization of the middle and distal ureteral segments specifically.[17] Furosemide increases urinary flow rate and decreases urinary transit time by inhibiting sodium chloride reabsorption in the ascending limb of Henle, resulting in a decrease in fluid reabsorption in the renal medulla.[20-21] Thus, by increasing urine flow rate, furosemide increases the diameter and the percentage of the ureter that is contrast filled, by allowing a greater volume of contrast media within the ureters.[17]

The use of furosemide as an adjunct to CTEU in dogs has not been reported. Based on the encouraging results in human studies, it is suspected that the addition of furosemide to the CTEU protocol will improve visualization of the ureters by increasing both ureteral diameter and percent attenuation. This could lead to improved detection

of ectopic ureters and other ureteral abnormalities with fewer scans necessary and ultimately a shorter anesthetic period and radiation dose.

CHAPTER 2

COMPUTED TOMOGRAPHIC EXCRETORY UROGRAPHY

TECHNIQUE

The canine CTEU technique was developed in the late 1990's.[15] A non-contrast scan of the abdomen is first obtained with dogs in sternal recumbancy to assess the patient for renal or ureteral calculi or masses. Images are acquired using a 3-5 mm slice thickness and index, taking into account patient size, scan time, resolution limits and radiation dose. An iodinated contrast agent is then administered intravenously at a dose of 400-800 mgI/kg. This dose has been recommended as lower doses have been shown to produce poor and inconsistent attenuation of the ureters.[15] After the intravenous administration of the iodinated contrast agent, a scan delay time of 3 minutes has been established prior to obtaining post contrast images. This time delay is associated with the time to peak ureteral attenuation which occurs from the first pass of highly concentrated contrast.[15] After this point, ureteral attenuation decreases and reaches a plateau for up to 60 minutes as the recirculated iodinated contrast media is excreted.[15]

The previously described CTEU technique in dogs differs from that in humans, in which two different techniques have been developed. The first technique is referred to

as a single bolus technique. With this technique a non-contrast scan of the abdomen is first obtained followed by the intravenous administration of 100-150 mls of a non-ionic iodinated contrast agent. While the timing of post contrast image acquisition varies widely, the first post contrast images are usually obtained 100-120 seconds following contrast administration for evaluation of the nephrogram phase or functional renal parenchyma. A second post contrast scan of the abdomen is then performed 3-15 minutes after contrast administration for assessment of the pyelogram phase which includes the collecting system, ureters and urinary bladder. In a recent survey of uroradiologists it was found that actually 3 or 4 post contrast scans were often obtained with the single bolus technique.[22] The major complaint with this technique is the significant increase in patient radiation dose, especially when compared to radiographic excretory urography.[23]

More recently a split bolus technique has been developed to decrease patient radiation dose by acquiring only a single post contrast scan.[24] In this technique a non contrast scan of the abdomen is first obtained. Approximately 40 mls of iodinated contrast is then administered intravenously and there is a time delay before the remainder of the contrast dose, approximately 80 mls, is given as a second bolus. There is another time delay and then the post contrast scan of the abdomen is obtained. By splitting the contrast dose into two separate boluses it gives time for the first bolus of contrast to be filtered by the kidneys and opacify the collecting system, ureters and urinary bladder while the second contrast bolus would represent the nephrogram

phase. It should be noted that variations in the time delays, contrast doses and method of contrast administration (power injector vs. infusion) have been suggested for both the single bolus and split bolus techniques.[23-27] While the split bolus technique does reduce patient dose it also has some disadvantages. Because of the small volume of the initial bolus there can sometimes be inadequate distention of the ureters and collecting systems which limits the ability of detect abnormalities.[28] In addition beam hardening artifact associated with the highly concentrated contrast media in the renal pelvis can obscure the renal parenchyma.[29]

The main limitation with CTEU in both human and canine patient is the inability to identify non-opacified ureteral segments due to normal peristaltic contractions. A number of modifications to the human CTEU techniques have been evaluated in attempts to improve identification of the ureters by increasing their distention and percent attenuation. Several studies have assessed the addition of saline to the CTEU technique to maximize urine excretion and improve opacification.[19,26,30-31] However, because these studies use various saline volumes, analytical methods and different protocols, a direct comparison is not possible. While saline administration is easy and inexpensive, at this point a clear benefit has not been demonstrated.

Abdominal compression is another easy and inexpensive modification that has been investigated in human patients. With this technique an abdominal compression band/belt is placed around the patient's abdomen prior to the injection of contrast. The kidneys and proximal ureters are then imaged, the compression band is removed and

the distal ureters and urinary bladder imaged. This has been recommended by some researchers, but has shown only slight improvement in ureteral distention and attenuation at best.[19,24-25] Abdominal compression belts have been advocated in canine and feline radiographic excretory urography studies to improve dilation of the renal pelvis and diverticuli, but this has not been evaluated on computed tomography.[32]

One study also found that oral hydration provided acceptable attenuation of the urinary tract.[33] With this technique 750-1000 mls of water are consumed by the patient 15-20 minutes prior to the study. Subjectively there was poor attenuation of the ureters in only 5% of studies, with the distal ureter being the most difficult segment to opacify. It was noted that this method should be used with caution in patients with heart disease, otherwise nearly all patients were able to consume the large volume of water. To the authors knowledge this method has not been utilized in dogs, and would likely be impractical and possibly dangerous due to the concurrent addition of general anesthesia.

CHAPTER 3

FUROSEMIDE AS AN ADJUCT TO THE COMPUTED TOMOGRAPHIC EXCRETORY UROGRAPHY TECHNIQUE

Diuretics, namely furosemide have been utilized in both human magnetic resonance[23] and CTEU.[17,34-35] Pharmacologically, furosemide inhibits sodium chloride reabsorption in the ascending limb of Henley, leading to decreased water reabsorption in the medulla. Furosemide has also been shown to cause a transient increase in renal blood flow and glomerular filtration rate.[36] These changes lead to increased attenuation and distention of the ureters by increasing urine flow. In humans a diuretic effect occurs within 5 minutes of an intravenous injection and peaks around 30 minutes.[36] While furosemide is relatively safe and well tolerated, it does increase the complexity of the study as a physician or nurse, and not a computed tomography technician has to administer the drug. It also is not known whether the increase in ureter attenuation and diameter improves conspicuity of lesion detection.

One of the first studies to utilize furosemide as part of the CTEU technique compared low dose furosemide (10 mg) in normal and mildly azotemic patients to a saline bolus.[35] In this prospective clinical study the authors administered furosemide as an intravenous bolus, 3-5 minutes prior to contrast injection. Post contrast images were

acquired within 10 minutes of contrast injection based on verification of an excretory phase on a test image. Using post processing software the images were reconstructed and maximum intensity projection images evaluated in multiple planes. The authors assessed the degree of opacification of the ureters as well as the pelvicaliceal systems. They also evaluated attenuation (Hounsfield units) within the renal pelvis. What they found was that furosemide enhanced multislice CTEU achieved complete or near complete opacification in 94% of the ureters and 100% of the pelvicaliceal systems.[35] They also found that the attenuation of the pelvicalices was 4-5 times higher and were more inhomogeneous when saline was used verses furosemide.[35] In conclusion the authors suggested that diuretic enhanced CTEU provided a complete examination when a single scan was performed within 10 minutes of contrast injection and that there was no need for additional delayed series.[35]

A more recent retrospective study compared the use of furosemide to saline and the combination of furosemide and saline as adjuncts to the CTEU protocol.[17] In this study, 10 mg of furosemide was administered intravenously over a one minute period, 2-3 minutes prior to contrast injection. When saline was administered it was given as a 250 ml intravenous infusion immediately after contrast administration. Post contrast images then were obtained 100 seconds after contrast injection. The authors then compared the percentage of ureteral opacification and maximum ureteral diameter in 3 segments of each ureter, using transverse and curved planar reformatted images. In this study furosemide significantly increased the percent opacification and maximum

ureteral diameter of the middle and distal ureteral segments when compared to intravenous saline. It also found that there was no significant difference in percent ureteral opacification and diameter between intravenous furosemide and a combination of intravenous furosemide and saline bolus.[17] Thus the authors concluded that the addition of furosemide to the CTEU protocol allowed greater visualization of the ureter, in particular the middle and distal ureteral segments when compared to saline and that it was safe to use.[17] They also concluded that there was no benefit to giving a saline bolus in addition to the furosemide.[17]

The effect of patient positioning and antiperistaltic drugs have also been assessed. A prospective clinical study of patients with urinary tract disease compared saline administration in the prone position to saline administration in a supine position, low dose furosemide (10 mg) and the antiperistaltic agent buscopan.[37] The study utilized a split bolus technique with a 10 minute delay after injection of the first dose of contrast and a 100 second scan delay after the second. In those patients that received furosemide, only a 5 minute delay was utilized following the injection of the first dose of contrast. When saline was administered it was given as a 250 ml infusion. Those patients that received buscopan were given 20 mg intravenously and were placed in a prone position. The saline, furosemide and buscopan injections were performed following the first injection of contrast in all patients. Percent renal and ureteral opacification was scored at six locations on transverse images. In this study complete opacification of the ureters was identified in 93% of those patients that received

furosemide, versus 60% with buscopan and 47% with saline in both prone and supine positioning.[37] In addition, furosemide had significantly higher percent opacification scores in all segments of the ureter compared to buscopan and saline. The authors concluded that low dose furosemide provided better delineation of the ureters compared to buscopan or saline in either prone or supine positions and was safe to use.[37]

The only known use of furosemide with CTEU in animals was a study performed in pigs.[38] This study compared percent ureteral attenuation and distention when pigs were administered an intravenous saline bolus, intravenous furosemide and both intravenous furosemide and saline. When furosemide was administered it was given ninety seconds prior to contrast administration with a four minute delay between contrast administration and image acquisition. The results of this study were similar to the previously described retrospective study in humans. In pigs there was a significant increase in percent ureteral attenuation and approximately a 25% increase in ureteral diameter when furosemide was administered compared to intravenous saline. In addition there was no significant difference in percent attenuation and distention between furosemide and both furosemide and saline.

CHAPTER 4

EXPERIMENTAL PURPOSE AND HYPOTHESIS

As stated previously, a number of imaging techniques have been employed to try and diagnose ureteral disease, including ectopic ureters. The majority of these techniques are not ideal due to their limited spatial or contrast resolution and superimposition of structures. CTEU has overcome those disadvantages and has become the imaging modality of choice for evaluating human and canine patients with ectopic ureters. However, this imaging modality is not perfect. A fundamental problem with CTEU is that normal ureteral peristalsis can prevent identification of the ureters by causing intermittent and inconsistent contrast filling. This means multiple image acquisitions may be necessary to identify the ureters in their entirety, leading to prolonged anesthesia time and increased patient radiation dose.

The primary specific aim of this study is to determine if the addition of furosemide to the standard CTEU protocol will improve identification of the ureters by overcoming normal ureteral peristalsis and increasing attenuation and distention of the ureters. If so, this modification to the standard CTEU protocol may improve its sensitivity and specificity in the diagnosis of ureteral diseases such as ectopic ureters. The secondary specific aim is to determine if any adverse effects are associated with this

technique. Our hypothesis is that furosemide will improve visualization of the ureters by increasing ureteral diameter and attenuation in normal healthy dogs on CTEU without any adverse effects associated with furosemide administration.

CHAPTER 5

MATERIALS AND METHODS

Initial Preparation

This animal experiment was in compliance with the regulations of the Animal Use and Care Committee of the University of Missouri. Based on an α=0.05, 14 volunteer dogs of various breeds, ages and weights were used for this study. All volunteered dogs were owned by faculty, students and staff of the University of Missouri, College of Veterinary Medicine. To be included in this study, each dog had no history of urinary tract disease or other systemic disease. In addition there was no evidence of urinary tract or systemic disease based on a physical exam, serum chemistry, complete blood count, urinalysis and abdominal ultrasound (GE Logiq 9, General Electric Company, Milwaukee, Wisconsin).

Each dog underwent two CTEU studies one week apart. One CTEU study was performed using the previously documented standard technique[15] and the other was performed with the addition of furosemide. The study that was performed first was determined by a flip of a coin.

Dogs were fasted for twelve hours before each procedure. An indwelling intravenous catheter was placed in a peripheral vein. Pre-anesthetic sedation using a combination of acepromazine (0.05 mg/kg) and buprenorphine (0.01 mg/kg) was administered intramuscularly to all dogs. Anesthesia was then induced with intravenous propofol (6 mg/kg) and maintained with isoflourane. During each anesthetic period all dogs were monitored by anesthesia department personnel using an ECG, end-tidal CO_2 monitor and non-invasive blood pressure monitor in addition to visually monitoring chest wall excursions and the anesthetic machine rebreathing bag. Maintenance fluids (lactated Ringer's solution at 10 ml/kg/hr) were administered to all dogs from the time of anesthetic induction until each CTEU procedure was completed to help maintain normal blood pressure and renal perfusion. Each dog was then taken directly from anesthesia post-induction to the computed tomography room with no delays or major variation in time between patients.

Each CTEU study was performed using a single slice helical CT unit (Picker 6000, Phillips Medical Systems, North America, Bothell, Washington). All dogs were placed in sternal recumbancy and non-contrast computed tomographic images acquired from cranial to the right kidney and extending caudally to the urethra. In each dog, images were acquired using a 5 mm slice thickness and 5 mm index. Additional scanning parameters were as follows: 130 kV, 150 mA, helical pitch of 1.25, a 512 x 512 matrix and a standard algorithm. Image size was varied according to patient size. A bolus intravenous injection of non-ionic iodinated contrast media (iohexol) was administered

at a dose of 800 mgI/kg. Post contrast image acquisition was initiated 3 minutes following contrast injection. This image delay time was utilized as it has been shown in previous research to provide the best ureteral visualization.[15] A second delayed post-contrast scan was also acquired 10 minutes after the initiation of the contrast injection. Both post contrast scans were obtained using the same imaging parameters as the non-contrast study. During one of the CTEU studies furosemide was administered at a dose of 4 mg/kg intravenously 90 seconds following the initiation of iohexol administration.

The second CTEU study was performed on each dog one week later, following no significant abnormalities being identified on a renal panel (blood urea nitrogen, creatinine, phosphorus, sodium, chloride, potassium and albumin) and urinalysis. The same imaging protocol and parameters were used. Any side effects noted during the CTEU studies will be documented and evaluation of the anesthesia monitoring chart reviewed as indicated. In addition, follow up with the owners will be performed 48 hours after the study to document any post procedural abnormalities.

Image Interpretation

Blinded, randomized and standardized evaluation of the 3 and 10 minute post contrast scans during both CTEU studies was performed by the principal investigator. Both the left and right ureters were evaluated at three different locations. The proximal segment of the right ureter is defined as that which is located at the level of the L_2-L_3 intervertebral disc space. The left proximal segment was assessed at the L_3-L_4

intervertebral disc space. Both left and right middle ureteral segments are defined as those at the level of the mid-body of L_5. The distal ureteral segments were evaluated at the L_7-S_1 intervertebral disc space. Using the transverse computed tomographic images, ureteral diameter was measured at the described locations for each segment of the left and right ureter on the 3 minute and 10 minute post contrast scans (Figure 1). The narrowest ureteral dimension was selected to avoid obtaining an oblique cross section of the ureter and three separate measurements made using post processing software (eFilm, Merge Healthcare, Milwaukee, WI). Those measurements were then averaged to account for any discrepancies in caliper placement and the final ureteral diameter determined.

Attenuation of the ureters was also evaluated by the primary investigator at the same 6 locations in each dog, on all post contrast scans. The attenuation in Hounsfield units (HU) was determined by averaging 3 measurements obtained from the center of the ureter. Hounsfield unit measurements were obtained using post processing software (eFilm, Merge Healthcare, Milwaukee, WI).

Subjective evaluation of the percentage of visible ureteral length was assessed by three blinded readers using 3D volume reconstructed images (Figure 2) generated from post processing software (Osiryx 3.8, Pixmeo, Geneva, Switzerland). These images can be manipulated in 360 degrees and will allow the evaluators to determine the percentage of each ureter that is able to be visualized. Each reader assigned a score for both the left and right ureter in each dog, on all post contrast scans as follows: A score

of 0 indicated that the ureter is not visible; 1, less than 25% of the ureter is visible; 2, 25%-49% of the ureter is visible; a score of 3, 50%-74% of the ureter is visible; 4, 75%-99% of the ureter is visible; 5, the entire ureter is visible.

Data Analysis

With an α=0.05, the diameter (centimeters) and attenuation (Hounsfield units) of all ureteral segments, as well as each individual segment were compared with and without furosemide on the 3 and 10 minute scans using a paired t-test. A p value of less than 0.05 was considered statistically significant. A test of normality was performed on all comparisons. If the data was not normally distributed a Wilcoxon signed rank test was utilized. The percentage of visible ureter length (scan grades) in both the left and right ureters was also compared with and without furosemide on the 3 and 10 minute scans using a paired t-test. The data was tested for normality and if not normally distributed a Wilcoxon signed rank test performed. In addition inter-observer variability was assessed using a one way analysis of variance on ranks. If the data was not normally distributed a Kruskal-Wallis one way analysis of variance on ranks was performed.

CHAPTER 6

RESULTS

Fourteen normal, healthy volunteer dogs were enrolled in this study. The dogs ranged in age from 1-9 years with a mean of 4.3 years. There were nine castrated males and five spayed females. They ranged in weight from 3.2-45.5 kg with a mean of 24.8 kg. There were seven mixed breed dogs and one of each of the following: Bloodhound, Labrador Retriever, Golden Retriever, English Pointer, Chihuahua, Doberman Pinscher and German Shepherd.

On the 3 minute scans, 79/84 (6 segments in 14 dogs) or 94% of ureteral segments were identified on the standard CTEU study. These ureteral segments ranged from 0.1-0.4 cm with a mean of 0.2 cm (Tables 1-6). Eighty three of 84 ureteral segments or 99% were identified on the 3 minute scan with the addition of furosemide. They ranged in size from 0.1-0.5 cm with a mean of 0.22 cm. A Wilcoxon signed rank test identified a statistically significant difference ($P=0.012$) with ureteral diameter being larger when furosemide was administered. When looking at each individual ureteral segment, no statistically significant difference was detected on the 3 minute scans with and without furosemide. The right proximal, right middle, right distal, left proximal, left

middle and left distal ureteral segments had P values of 0.44, 0.84, 0.84, 0.46, 0.14 and 0.14 respectively.

When evaluating attenuation of all ureteral segments on the three minute scans, there was no statistically significant difference between those with and without furosemide (P=0.147). Attenuation ranged from -87 to 1481 HU with a mean of 431 HU on the standard CTEU studies (Tables 7-12). When furosemide was administered, attenuation ranged from -44 to 2119 HU with a mean of 460 HU. In addition, no statistically significant difference was detected within each ureteral segment. Respectively the right proximal, right middle, right distal, left proximal, left middle and left distal ureteral segments had the following P values: 0.84, 0.54, 0.52, 0.74, 0.71 and 0.82.

On the 10 minute scans, 80 of 84 ureteral segments were identified on the standard CTEU studies. The mean size of these ureteral segments was 0.2 cm and ranged from 0.1-0.4 cm (Tables 13-18). On the 10 minute scans with furosemide, 79 of 84 ureteral segments were identified which ranged from 0.1-0.36 cm with a mean of 0.2 cm. No statistically significant difference was detected in ureteral diameter with a P value of 0.86. In addition a statistically significant difference in ureteral size was not detected in any particular ureteral segment; right proximal ureter (P=0.94), right middle (P=0.23), right distal (P=0.66), left proximal (P=0.69), left middle (P=0.56), left distal (P=0.68).

A statistically significant difference (P= <.001) in attenuation was detected when all ureteral segments were evaluated with and without furosemide on the 10 minute scans (Tables 19-24). Attenuation ranged from 11-1223 HU without furosemide, with a mean of 324 HU. Attenuation of the 10 minute scans with furosemide ranged from -3 to 547 HU with a mean of 209. When evaluating the ureteral segments individually, a statistically significant difference was detected in the right middle (P=0.026) and left proximal (P=0.006) segments. A nearly significant difference was noted in the right proximal (P=0.07) and left distal (P=0.058) ureteral segments. No significant difference was detected in the right distal (P=0.18) and left middle (P=0.10) ureteral segments.

The percentage of the left and right ureteral length that could be identified on 3D volume reconstructed images was determined by three readers on both the 3 and 10 minute scans. A statistically significant difference in scan grad was not detected between those with or without furosemide in either the left or right ureter on the 3 minute scans (Tables 25-26). The p-values were 0.723 for the left ureter and 0.645 for the right ureter with a power of 0.05. A statistically significant difference in scan grade was identified in both the left and right ureter on the 10 minute reconstructed images with a p-value of less than 0.001 in each (Tables 27-28). In both the left and right ureter the scan grade was greater on the standard CTEU study. In the left ureter the mean scan grade was 2.738 without furosemide versus 1.857 when furosemide was administered. The mean scan grade was 2.643 without furosemide and 1.667 with furosemide in the

right ureter. No significant difference was noted between the scan grades of the three readers. The p values values for interobserver variability can be found in Table 29.

The only side effects identified during this study were a mild, transient increase in heart rate and systemic hypotension (mean arterial blood pressure of <60 mmHg) at the time of contrast injection. The increase in heart rate and systemic hypotension was identified in three dogs, which occurred during both CTEU studies in all three dogs. No dog required medical treatment for these transient changes. The increase in heart rate ranged from 6-15 beats per minute with a mean of 10 beats per minute. The systemic hypotension ranged from 52-58 mm Hg.

CHAPTER 7

DISCUSSION

A variety of imaging modalities/techniques have been utilized to diagnose ureteral disease. While they all have disadvantages, CTEU has become the imaging technique of choice because of its superior spatial resolution, lack of superimposed structures and ability to generate three dimensional images. The one inherent problem with this technique and all others is that it cannot overcome normal ureteral peristalsis. In dogs normal ureteral peristalsis is initiated by pacemaker cells in the renal collecting system and occurs at a rate of 3-6/minute.[39] This can prohibit identification of a segment of the ureter by preventing contrast filling.

In canine patients with ectopic ureters, peristalsis in the distal ureteral segments may prohibit identification of the site of implantation of the ureter into the bladder or other lower urinary tract segment. This potentially decreases the sensitivity of the technique and requires multiple computed tomography scans be performed to identify the ureteral segment and at the same time increases the patient's radiation dose and anesthetic time. The addition of furosemide to the standard CTEU protocol would allow us to assess if this would improve identification of the ureters by increasing their diameter as well as the percent of ureteral contrast filling.

As stated previously, furosemide produces a diuretic effect, increasing urine volume and flow and decreasing urine transit time. The mechanism of action is by inhibiting sodium chloride reabsorption in the thick ascending limb of Henle, which in turn decreases fluid reabsorption in the renal medulla.[36] Furosemide is also known to transiently increase renal blood flow and glomerular filtration rate.[36] Based on a scintigraphy study in dogs, this diuretic effect occurs 0.2-2.4 minutes following intravenous injection, with a mean of 1.1 minutes.[40] The duration of the diuretic effect ranges from 0.3-2.35 minutes with a mean of 0.8 minutes.[40] This is much shorter when compared to humans were the onset of action is 3-5 minutes post injection, being maximal at 20 minutes.[41]

In this study, more ureteral segments were identified when furosemide was added to the CTEU protocol (83) than the standard CTEU study (79) on the three minute scans. However, a similar number of ureteral segments were identified with (79) and without furosemide (80) on the 10 minute scans. This difference is likely due to diuresis which presents more urine/contrast to the ureters and the time of onset and duration of that diuretic effect. The three minute scans were obtained 90 seconds following the administration of furosemide which coincides with timing of the diuretic effect described on renal scintigraphy. Thus more urine/contrast was likely present in the ureters when furosemide was administered versus the standard CTEU scans. The 10 minute scans were obtained 8.5 minutes following the administration of furosemide. As

noted in the previous scintigraphy study, a diuretic effect would not have been present at this time. Therefore the ureters likely contained similar volumes of urine.

The mean size (0.2 cm) and range (0.1-0.4) of ureteral segments was the same on the 3 and 10 minute CTEU studies when furosemide was not administered. These sizes are consistent with what has been previously reported for normal canine ureteral size on CTEU.[16] While no significant difference in ureteral diameter was identified with and without furosemide on the 10 minute scans, one was found on the 3 minute scans. When considering all ureteral segments at three minutes, the diameter was greater with the addition of furosemide to the CTEU protocol versus the standard protocol. This is likely due to the diuretic effect of furosemide which increases ureteral diameter by increasing the volume of urine/contrast in the ureter and is consistent with prior studies in humans and swine.[17,38] The absence of a significant difference in ureteral diameter at 10 minutes was expected given the relatively short duration of the diuretic effect.

When evaluating all ureteral segments for attenuation, no significant difference was detected on the 3 minute scans. In addition, no significant difference in attenuation was identified when considering each ureteral segment individually on the 3 minute scans. However, a significant difference was found when considering all ureteral segments on the 10 minute scans. Ureteral segments had greater attenuation on the standard CTEU scan compared to when furosemide was added to the protocol. In addition, a significant difference was detected in the left proximal and right middle ureteral segments specifically on the 10 minute scans. In these segments, attenuation

was also greater on the standard CTEU scans. Factors that affect ureteral attenuation include contrast dose, glomerular filtration, contrast concentration and contrast/urine volume.[42] Contrast dose and glomerular filtration did not likely have an effect on attenuation. On both studies the dose of contrast administered was the same (800 mgI/kg). Glomerular filtration rate was presumed to be the same/similar on both scans based on pre-anesthetic biochemistry, urinalysis and blood pressure measurements taken during the procedure. However it should be noted that glomerular filtration rate was not determined. The difference in attenuation identified on the 10 minute scans is likely due to a difference in contrast volume and concentration. Diuresis prior to the 10 minute scans likely caused excretion of a greater amount of contrast when furosemide was administered. Thus less contrast would have been available to fill the ureters at 10 minutes resulting in less attenuation. In addition the contrast would have been less concentrated relative to the standard CTEU study, also causing them to be less attenuating. Decreased attenuation (HU) of the ureters is a common finding in humans[17] given furosemide and has also been documented in porcine CTEU.[38]

No significant difference in attenuation was detected on the 3 minute scans. This may be due to the small sample size (n=14) and power (0.05) of the study. Thus a significant difference may have been present, but was unable to be detected. While furosemide produces a diuretic effect, presenting a larger volume of urine/contrast to the ureters, the iodinated contrast is also more dilute because of the decreased water

reabsorption within the renal tubules. Thus the increase in urine/contrast volume may have been offset by the dilution of contrast.

Negative Hounsfield units were documented in the ureteral segments of one dog on the 10 minute scans. The attenuation of these ureteral segments was consistent with fat/water (-3 to -44). The ureteral segments were small, measuring 0.1-0.13 cm and were surrounded by intra-abdominal fat. Ureteral segments can be identified when not contrast distended, however it is much more difficult unless they are surrounded by fat. The fat/water attenuation of these ureteral segments is likely due to a combination of absence of contrast in a non-distended ureter and slice thickness artifact from the relatively thick slices (5 mm) obtained in this 14 kg dog. Slice thickness artifact, which is also known as partial volume averaging artifact, occurs when multiple structures of differing attenuation are present within the same voxel. The attenuation measurements of those structures are then averaged to represent the attenuation of that pixel on the final image. This averaging can lead to inaccurate Hounsfield unit measurements.

Unfortunately, no significant difference in percent ureteral attenuation (scan grades) of either the left or right ureter was detected on the three minute reconstructed images. This may have been due to the low power of the statistical analysis (0.05). Thus the limited number of dogs (n=14) and limited number of scan grades may have prevented a statistically significant difference from being detected. This is inconsistent with prior studies in humans and porcine which have demonstrated distention of a greater percentage of the ureters with the addition of furosemide to the CTEU

study.[15,33,35] However, a statistically significant difference in percent ureteral attenuation (scan grades) was identified on the 10 minute reconstructed images. Reconstructed images of the standard CTEU protocol had higher scan grades or percent ureteral attenuation than those when furosemide was added. This is consistent with furosemide induced diuresis which caused increased excretion of contrast prior to the 10 minute scan, thus making less contrast available to distend the ureters on the 10 minute scans.

In this study, side effects were self limiting and transient, and included mild hypotension and increased heart rate. This occurred in three dogs (21%) at the time of contrast injection and did not require medical treatment. These changes were consistent with the previously reported side effects of intravenous iodinated contrast media which include: hypotension, hypertension, tachycardia, bradycardia, erythema, periocular edema, gastrointestinal disturbances, contrast induced acute renal failure and rarely anaphylaxis.[43-,44] The exact mechanism of action for the hypotension and increased heart rate is not completely understood, but is thought to be related to the hyperosmolality of the contrast agent. Hyperosmolar contrast is thought to cause rapid expansion of the plasma volume with subsequent vasodilation and peripheral hypotension with a reflex increase in heart rate.[45] While iohexol is classified as a low osmolar contrast agent it is still hyperosmolar when compared to plasma with an osmolality of 670 mosm/kg.[44] In addition to osmolality, other properties of the contrast agent such as its ionicity and chemical toxicity also contribute to the development of

side effects.[42] In a limited study of anesthetized dogs, at least 4% of dogs had alterations in blood pressure and heart rate.[46] Similar side effects have been reported to occur in 3-15% of humans given non-ionic iodinated contrast media.[47] While a similar incidence rate is thought to occur in dogs, no large scale study has been performed to confirm this.

Previously reported side effects of furosemide include ototoxicity, gastrointestinal disturbances, weakness, restlessness, electrolyte and hematologic abnormalities.[36] None of the dogs in this study demonstrated any of the aforementioned side effects during the procedure, nor were they reported by the owners 48 hours after the procedure. However, mild subclinical electrolyte and hematologic abnormalities cannot be completely ruled out as a complete blood count and electrolyte profile were not performed following each CTEU study. Sodium, chloride, potassium and phosphorus levels were re-evaluated immediately prior to the second study and no abnormalities were identified. As with any drug, the risks and benefits of drug administration must be weighed in each patient. However, based on this study, intravenous furosemide at a dose of 4 mg/kg appears to be a safe addition to the standard CTEU protocol.

The major limitation to this study was the power of the statistical analysis. The power of a study is the probability of finding a statistical difference if one truly exists. Power is affected not only by the number of samples, but also by the difference in the sample measurements, with both having a direct relationship to power. The power of all

our quantitative measurements ranged from 0.05-0.38, well below the desired 0.80. This was due to a combination of both a small difference in sample measurements and insufficient sample size. Unfortunately the smallest size the post processing software could measure was 0.1 cm. As previously stated, the normal ureter on CTEU measures 0.1-0.4 cm. That means at least a 25% change in ureteral diameter would be needed before a measurable difference could be detected. The sample size was limited due to the challenge to find volunteers willing to undergo two separate general anesthetic procedures. This could have been partially alleviated by measuring ureter size and attenuation at more sites. Ultimately the limited power of our statistical analysis means that a true difference may in fact exist, just that it could not be detected. This is likely the case with the size of the individual ureteral segments on the 3 minute scans. While an overall difference in ureteral size was detected, a difference in individual ureteral segments was not.

Another limitation to this study was that only a single dose of furosemide and two time points (3 and 10 minutes) were evaluated. Additional studies would be needed to assess different doses of furosemide and the exact timing of contrast and furosemide injection in relation to image acquisition. While we utilized a moderately aggressive dose of furosemide, could lower doses be used and still have the same or better effect? Another question that still needs to be answered is what is the best time for furosemide injection and image acquisition and does altering the acquisition delay time affect the attenuation and diameter of a particular ureteral segment? For example, does

increasing the time between image acquisition and furosemide injection improve distention and attenuation of the distal ureteral segments versus a shorter acquisition delay which may more readily affect the proximal ureteral segments. In humans there is no one accepted protocol for diuretic CTEU. Protocols vary in regards to timing of contrast and furosemide injection, type of contrast agent used, patient positioning and other modifications such as saline boluses and abdominal compression. This makes comparison of studies difficult and thus the reason why there is not a standard recommended protocol.

In conclusion, the addition of furosemide to the CTEU protocol improved visualization of the ureters by increasing the number of ureteral segments that were able to be identified, as well as their diameter when imaging the patient 3 minutes following contrast injection and 90 seconds following furosemide injection in healthy adult dogs. This study also suggests that furosemide is safe to use at the current dose of 4 mg/kg. There is no advantage to imaging dogs 10 minutes following contrast administration as the ureteral segments are less attenuating and a smaller percentage of the ureter could be identified. While further studies are needed to evaluate the optimal dose of furosemide and the timing of contrast and furosemide injection, the study suggests that there is a benefit to administering furosemide which may ultimately improve the diagnostic utility of the technique.

APPENDIX

Table 1: Left proximal ureteral size at 3 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.2	0.13
2	0.23	0.5
3	0.2	0.2
4	0.3	0.23
5	0.1	0.2
6	0.2	0.2
7	0.1	0.2
8	0.2	0.13
9	0.2	0.4
10	0.26	0.2
11	0.3	0.33
12	0.3	0.33
13	0.2	0.2
14	0.33	0.3

Table 2: Left middle ureteral size at 3 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.1	0.2
2	0.3	0.2
3	0.1	0.2
4	0.2	0.3
5	0.13	0.1
6	0.3	0.26
7	0.1	0.1
8	0	0.2
9	0.1	0.2
10	0.2	0.13
11	0.3	0.26
12	0.3	0.3
13	0.2	0.23
14	0.2	0.4

Table 3: Left distal ureteral size at 3 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.2	0.1
2	0.2	0.3
3	0.1	0.2
4	0.2	0.3
5	0.1	0.1
6	0.3	0.26
7	0.1	0.2
8	0	0.1
9	0.13	0.2
10	0.2	0.1
11	0.3	0.2
12	0.2	0.33
13	0.3	0.2
14	0.2	0.4

Table 4: Right proximal ureteral size at 3 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.2	0.2
2	0.3	0.33
3	0.2	0.2
4	0.3	0.3
5	0.1	0
6	0.33	0.33
7	0.1	0.1
8	0.2	0.23
9	0.3	0.16
10	0.26	0.2
11	0.33	0.3
12	0.2	0.2
13	0.2	0.3
14	0.4	0.4

Table 5: Right middle ureteral size at 3 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.13	0.1
2	0.23	0.2
3	0.3	0.2
4	0.2	0.26
5	0.1	0.1
6	0.2	0.2
7	0.1	0.1
8	0.1	0.13
9	0.1	0.2
10	0.16	0.1
11	0.3	0.1
12	0.2	0.36
13	0.3	0.2
14	0.2	0.3

Table 6: Right distal ureteral size at 3 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.1	0.1
2	0.1	0.3
3	0.1	0.2
4	0.2	0.2
5	0.2	0.16
6	0.2	0.26
7	0.1	0.2
8	0.2	0.2
9	0	0.2
10	0	0.1
11	0	0.16
12	0.2	0.26
13	0.3	0.1
14	0.3	0.3

Table 7: Left proximal ureter attenuation at 3 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	371	7
2	731	2119
3	134	566
4	984	614
5	61	289
6	254	276
7	35	423
8	47	82
9	136	914
10	800	284
11	579	555
12	1452	692
13	281	88
14	504	155

Table 8: Left middle ureteral attenuation at 3 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	583	362
2	602	327
3	47	85
4	167	1229
5	496	27
6	972	268
7	40	7
8	not identified	212
9	85	516
10	636	131
11	1044	597
12	1209	967
13	575	448
14	39	818

Table 9: Left distal ureteral attenuation at 3 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	488	not identified
2	880	684
3	54	74
4	637	884
5	117	513
6	not identified	777
7	93	97
8	493	554
9	not identified	232
10	266	52
11	not identified	349
12	46	796
13	397	44
14	1481	423

Table 10: Right proximal ureteral attenuation at 3 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	20	502
2	659	723
3	280	56
4	919	1979
5	58	not identified
6	574	1097
7	27	63
8	415	871
9	609	418
10	942	266
11	1157	682
12	977	76
13	65	399
14	1020	932

Table 11: Right middle ureteral attenuation at 3 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	-29	-44
2	782	431
3	917	484
4	305	1926
5	36	46
6	128	240
7	104	114
8	71	84
9	37	513
10	242	64
11	584	84
12	75	652
13	785	888
14	115	465

Table 12: Right distal ureteral attenuation at 3 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	-87	336
2	46	604
3	159	362
4	214	40
5	369	258
6	34	757
7	64	675
8	666	39
9	not identified	496
10	not identified	46
11	not identified	96
12	275	370
13	606	595
14	1172	517

Table 13: Left proximal ureteral size at 10 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.13	0.1
2	0.2	0.23
3	0.2	0.26
4	0.2	0.33
5	0.2	0.2
6	0.2	0.23
7	0.1	0.1
8	0.1	0.2
9	0.2	0.2
10	0.3	0.2
11	0.4	0.36
12	0.1	0.2
13	0.3	0.2
14	0.3	0.23

Table 14: Left middle ureteral size at 10 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.13	0.1
2	0.33	0.2
3	0.2	0.3
4	0.3	0.2
5	0.1	0.1
6	0.3	0.2
7	0.1	0.1
8	0.2	0.2
9	0.26	0.2
10	0.2	0.2
11	0.3	0.2
12	0.16	0.3
13	0.2	0.26
14	0.26	0.3

Table 15: Left distal ureteral size at 10 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.1	0.2
2	0.3	0.23
3	0.1	0.2
4	0.2	0.2
5	0	0
6	0.3	0.2
7	0.1	0.2
8	0.2	0.2
9	0.2	0.13
10	0.2	0.2
11	0	0.23
12	0.1	0.2
13	0.26	0.13
14	0.4	0.3

Table 16: Right proximal ureteral size at 10 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.1	0.2
2	0.3	0.23
3	0.2	0.23
4	0.3	0.3
5	0.23	0.1
6	0.3	0.2
7	0.1	0.1
8	0.2	0.3
9	0.2	0.2
10	0.3	0.26
11	0.2	0.3
12	0.1	0.2
13	0.3	0.33
14	0.3	0.2

Table 17: Right middle ureteral size at 10 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.13	0.1
2	0.23	0.2
3	0.2	0.2
4	0.2	0.2
5	0.1	0
6	0.2	0.2
7	0.1	0.1
8	0.2	0.26
9	0.2	0.13
10	0.16	0.16
11	0.26	0.2
12	0.1	0.23
13	0.3	0.2
14	0.3	0.2

Table 18: Right distal ureteral size at 10 minutes

Dog #	Without furosemide (cm)	With furosemide (cm)
1	0.2	0.1
2	0.26	0.26
3	0.1	0.2
4	0.2	0
5	0.2	0
6	0.2	0.2
7	0.13	0.1
8	0.1	0.2
9	0	0.16
10	0.2	0.2
11	0	0.2
12	0.1	0
13	0.3	0.16
14	0.2	0.2

Table 19: Left proximal ureteral attenuation at 10 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	216	-2
2	70	295
3	653	132
4	1024	167
5	427	159
6	44	310
7	317	36
8	11	226
9	743	258
10	876	263
11	717	379
12	1598	46
13	1062	73
14	1012	229

Table 20: Left middle ureteral attenuation at 10 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	529	-3
2	542	222
3	329	353
4	261	187
5	15	30
6	162	123
7	29	41
8	108	146
9	594	209
10	285	547
11	427	284
12	76	223
13	502	451
14	946	272

Table 21: Left distal ureteral attenuation at 10 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	314	255
2	897	403
3	106	267
4	89	226
5	not identified	not identified
6	355	143
7	108	240
8	305	171
9	320	172
10	431	117
11	not identified	261
12	228	251
13	528	136
14	889	140

Table 22: Right proximal ureteral attenuation at 10 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	18.6	207
2	402	207
3	92	305
4	1038	266
5	536	48
6	70	273
7	14	44
8	135	405
9	697	168
10	870	462
11	85	256
12	445	295
13	1223	335
14	730	121

Table 23: Right middle ureteral attenuation at 10 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	230	37
2	599	320
3	336	229
4	37	198
5	76	not identified
6	94	85
7	217	89
8	161	329
9	298	79
10	271	152
11	513	279
12	259	211
13	777	77
14	830	185

Table 24: Right distal ureteral attenuation at 10 minutes

Dog #	Without furosemide (HU)	With furosemide (HU)
1	362	105
2	582	420
3	53	256
4	95	not identified
5	407	not identified
6	60	106
7	387	175
8	211	203
9	not identified	118
10	338	99
11	not identified	237
12	126	not identified
13	854	286
14	127	272

Table 25: Scan grades without furosemide at 3 minutes

Dog #	Reviewer 1 Right Ureter	Reviewer 1 Left Ureter	Reviewer 2 Right Ureter	Reviewer 2 Left Ureter	Reviewer 3 Right Ureter	Reviewer 3 Left Ureter
1	3	4	4	4	4	4
2	4	4	3	3	4	3
3	3	3	3	2	3	3
4	3	2	3	2	3	2
5	2	2	2	2	2	2
6	2	2	2	2	2	2
7	1	1	1	1	1	1
8	3	3	3	2	3	3
9	3	3	3	2	3	2
10	3	4	3	4	3	4
11	2	4	2	4	2	4
12	4	3	4	3	4	4
13	4	4	4	4	4	4
14	4	4	4	4	4	4

Table 26: Scan grades with furosemide at 3 minutes

Dog #	Reviewer 1 Right Ureter	Reviewer 1 Left Ureter	Reviewer 2 Right Ureter	Reviewer 2 Left Ureter	Reviewer 3 Right Ureter	Reviewer 3 Left Ureter
1	3	3	3	3	3	3
2	4	4	4	4	4	4
3	3	3	3	3	3	3
4	4	5	3	5	3	4
5	1	2	1	2	1	1
6	3	3	3	3	3	3
7	2	2	2	2	1	2
8	2	2	2	2	2	2
9	3	2	3	3	3	2
10	1	1	1	1	1	1
11	4	4	4	4	4	4
12	3	4	3	4	4	4
13	4	4	4	4	4	4
14	4	4	4	3	4	4

Table 27: Scan grades without furosemide at 10 minutes

Dog #	Reviewer 1 Right Ureter	Reviewer 1 Left Ureter	Reviewer 2 Right Ureter	Reviewer 2 Left Ureter	Reviewer 3 Right Ureter	Reviewer 3 Left Ureter
1	2	2	2	2	1	1
2	4	4	4	4	4	4
3	3	4	3	3	4	4
4	3	3	3	3	3	4
5	1	1	1	1	1	1
6	2	2	2	2	2	2
7	2	2	2	2	2	2
8	2	2	2	2	2	2
9	3	2	3	2	3	3
10	3	4	3	4	4	4
11	3	3	3	3	3	2
12	3	3	2	3	2	3
13	3	3	3	2	3	3
14	3	4	3	4	4	4

Table 28: Scan grades with furosemide at 10 minutes

Dog #	Reviewer 1 Right Ureter	Reviewer 1 Left Ureter	Reviewer 2 Right Ureter	Reviewer 2 Left Ureter	Reviewer 3 Right Ureter	Reviewer 3 Left Ureter
1	1	2	1	1	1	1
2	3	4	3	4	3	3
3	2	2	2	2	1	3
4	2	3	2	3	2	2
5	0	0	0	0	1	0
6	1	2	1	2	1	2
7	0	1	1	1	1	1
8	3	2	3	2	3	1
9	1	1	1	1	1	1
10	2	1	1	1	1	1
11	2	2	2	2	1	1
12	2	2	2	1	2	1
13	2	3	3	3	3	4
14	2	3	2	3	2	3

Table 29. Interobserver Variability P Values

P Value	Scan/Study/Ureter
0.736	3 Minute/Without Furosemide/Left Ureter
0.961	3 Minute/Without Furosemide/Right Ureter
0.965	3 Minute/With Furosemide/Left Ureter
0.970	3 Minute/With Furosemide/Right Ureter
0.893	10 Minute/Without Furosemide/Left Ureter
0.892	10 Minute/Without Furosemide/Right Ureter
0.788	10 Minute/With Furosemide/Left Ureter
0.936	10 Minute/With Furosemide/Right Ureter

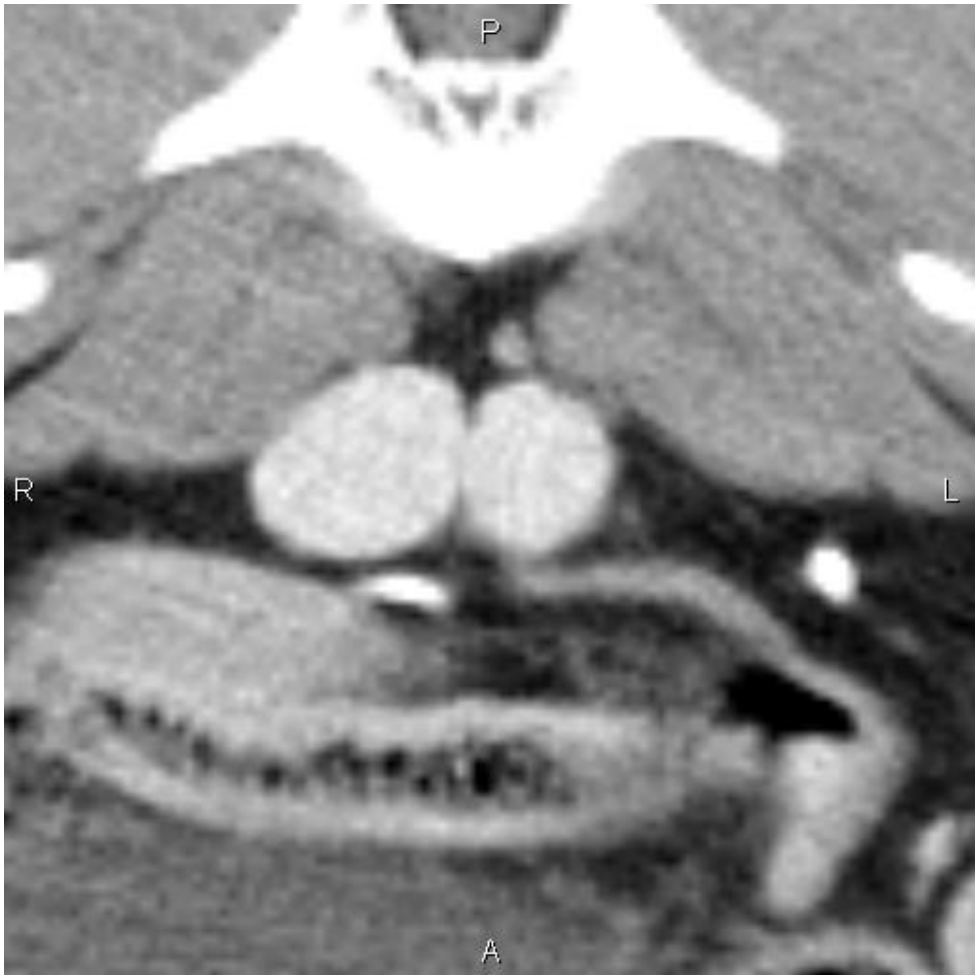

Figure 1: Transverse CT image of the left and right middle ureteral segments where measurements were made for diameter and attenuation.

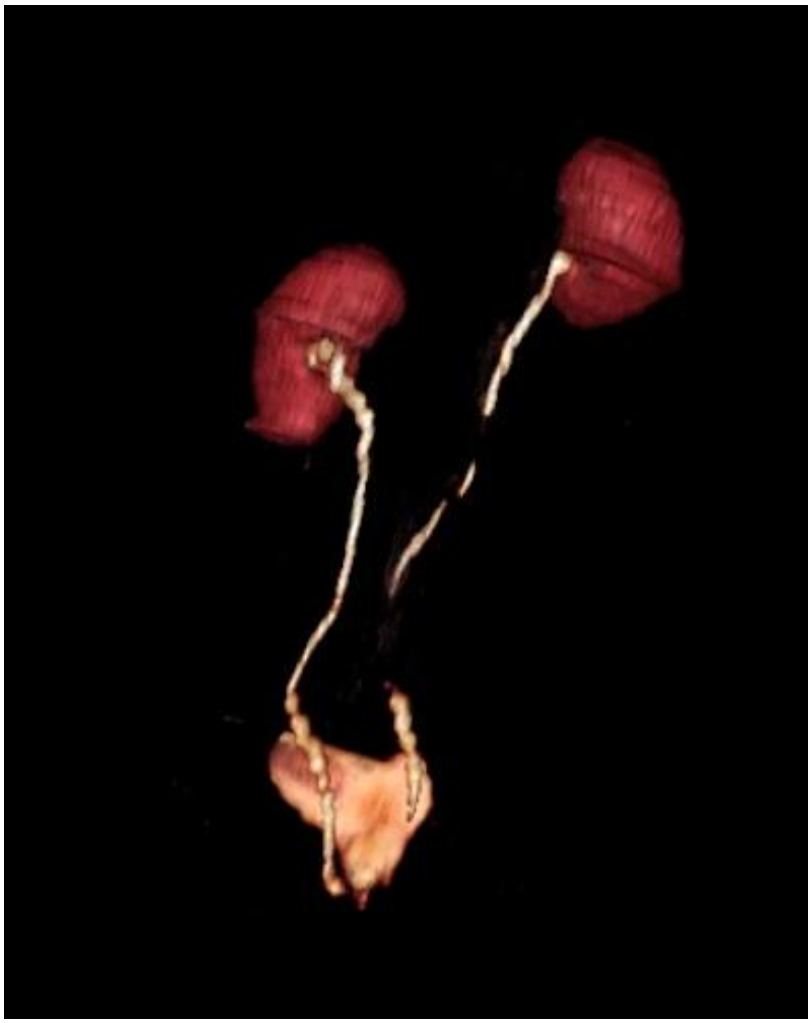

Figure 2: 3D volume reconstructed image which was utilized by readers to determine scan grade or the percent of ureteral filling for both the left and right ureter.

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