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Analysis of Ureteral Diameter and Peristalsis in Response to Irrigant Fluid Temperature Changes in an In Vivo Porcine Model

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Abstract

Objective: It has been previously reported that warming irrigation fluid higher than body temperature may decrease ureteral spasm and thereby facilitate ureteroscopic access to the proximal ureter. Our objective was to examine the effects on ureteral peristalsis and ureteral diameter if the irrigant was warmed to just under the biological threshold for injury.

Materials and Methods: Two female adult Yorkshire pigs were studied in this pilot study. In the first pig, a dilute mixture of contrast and irrigation fluid at 37°C and then at 43°C was instilled for 30 minutes into each renal pelvis through a ureteral catheter at 40 mm Hg. Retrograde pyelogram images were captured for each trial and the caliber of the ureter was measured using Vitrea® software. In the second pig, a lumbotomy was performed, and a magnetic sensor was placed on the extraluminal surface of the ureter to monitor ureteral peristalsis while repeating the aforedescribed regimen. Thirty minutes after the first regimen, the force exerted during placement of a 16F ureteral access sheath (UAS) was recorded at both temperatures using the University of California, Irvine Ureteral Force Sensor.

Results: There was no statistically significant difference in ureteral caliber along the length of the ureter at 43°C ($p = 0.87, p = 0.32, p = 0.66$ for proximal, middle, and distal ureter, respectively). Indeed, there was an increase in peristalsis from baseline with fluid irrigation at 37°C and at 43°C (59% and 65%, respectively). There was no significant difference in the force exerted for UAS placement at either temperature. On histologic analysis, there were no significant changes in ureteral histology or luminal diameter.

Conclusions: In a porcine model, warming irrigation fluid to just under the biological threshold for injury did not increase ureteral caliber, decrease ureteral peristalsis, or facilitate UAS placement. As such, during ureteroscopy, we continue to warm our irrigation fluid just to body temperature.

Keywords: ureteroscopy, ureter, calculi

Introduction
Ureteroscopy is the most common surgery performed to treat urolithiasis; however, the dimensions of the ureter can limit access to the upper urinary tract. In fact, in ∼8%–10% of patients who have a planned ureteroscopy, the procedure is aborted given the inability of the ureter to accommodate even the smallest flexible ureteroscope. If the ureter could be manipulated to allow for the passage of larger ureteral access sheaths (UASs), then the efficiency of ureteroscopy could theoretically be improved.

To date, many studies have focused on utilizing pharmacotherapies to relax the ureter to facilitate stone passage. Utilizing the same concept, several groups have shown pretreatment with selective alpha-blockers results in a higher likelihood of passage of large UASs and a decrease in the amount of force used to place the UASs. Although initial reports of this treatment modality have shown favorable results, the use of medications in the preoperative period is also associated with the potential for adverse reactions and added cost.

Alternatives to pharmacotherapies include the placement of a ureteral stent at the time of initial attempted ureteroscopy. Studies have shown prestinting creates a state of ureteral aperistalsis, thereby allowing for more effective instrumentation of the upper urinary tract. However, this approach is more costly and more debilitating for the patient, as the stent placement is expensive and commits the patient to an interval of stent-related symptoms before receiving a second anesthetic for the stone removal procedure.

In an effort to create acute ureteral dilation at the initial ureteroscopic procedure, Mohammadzadeh Rezaei and colleagues reported using warmed irrigation fluid to potentially decrease ureteral spasm and thereby facilitate ureteroscopic access to the proximal ureter. The ability to acutely create ureteral relaxation using a nonpharmacologic approach is highly attractive. Given the observational nature of these studies, we sought to study the impact of alterations in the temperature of the irrigant on porcine ureteral physiology and its impact on the force required to pass a UAS as determined by the UCI (University of California, Irvine) Ureteral Access Sheath Force Sensor. This device can be used to detect real-time changes in the force exerted during UAS passage; it is accurate to the 10th of a Newton. We hypothesize that in a porcine model, irrigation of warm saline (43°C) at the highest safely tolerable temperature will induce maximum ureteral dilation, decrease ureteral peristalsis, and lower the force needed to effectively achieve UAS placement.

Materials and Methods

Institutional Animal Care and Use Committee approval was obtained. Two female adult Yorkshire pigs underwent endotracheal intubation with mechanical ventilation and isoflurane anesthesia delivery. An ear vein was cannulated for intravenous fluid administration; temperature, pulse, and blood pressure were continuously recorded throughout the study.

Cystoscopy was performed in the first pig and urine was collected; the baseline temperature of the pig and urine was determined. A guidewire was advanced to the right renal pelvis and placement was confirmed on fluoroscopy. A 12F Foley catheter was placed to drain the bladder throughout the procedure. A 5F ureteral catheter was advanced over the guidewire and positioned within the right renal pelvis. After removing the guidewire, the Thermedx® FluidSmart® Fluid Management System was used to instill a mixture of contrast and saline at 37°C (body temperature) into the right ureteral catheter at 40 mm Hg. Retrograde pyelogram images were captured every 5 minutes for half an hour. The digital images were saved, and the caliber of the proximal, middle, and distal ureter was measured using Vitrea® (v1.51; NIH Administrative and Research and Services Branch, NC) software; this was done independently by two individuals. On retrograde pyelography, the ureteral location was defined as proximal one-third, middle one-third, and distal one-third, given typical landmarks as they relate to the sacrum are not applicable in the pig. At the end of 30 minutes, the ability to pass a UAS into the renal pelvis at this irrigation temperature was determined utilizing the UCI Ureteral Access Sheath Force Sensor (Fig. 1). A 16F UAS was attempted first
and if it did not advance to the renal pelvis at <7 N, then a 14F UAS was used, which if unsuccessful was then followed by attempted pass of an 11F UAS. For the contralateral renal system, the same steps were performed although using 43°C irrigation fluid. At the conclusion of the study, the ureters were harvested for histologic evaluation at the level of the distal, middle, and proximal ureter and caliber of the ureters was measured using a caliper.

In the second pig, the experiment was designed to evaluate changes in ureteral peristalsis secondary to irrigation temperature. The pig was placed under anesthesia and monitored similarly to the first pig. A flexible cystoscope was used to identify the right ureteral orifice, and a guidewire followed by a 5F ureteral catheter was placed into the renal pelvis under fluoroscopic control. A 12F Foley catheter was placed into the bladder to drain the bladder throughout the procedure. A lumbotomy incision was made in the right flank and the right ureter was identified. A neodymium magnet and a giant magnetoresistance (GMR) sensor were affixed to the outer surface of the ureter to measure ureteral peristalsis (Fig. 2). These measurements were based off of the recorded induced voltage change in the GMR sensor caused by movement of the magnet in relation to the sensor during contractions. A baseline ureteral peristalsis rate was then calculated as previously described using a connection to a PowerLab® amplifier running Labchart® ADInstruments® data collection software. A digital band pass filter was performed on the raw data to remove noise and ureteral movements caused by respiration, as well as to correct for a wandering baseline. No calculations were made on the magnitude of the induced voltage as the actual value of the voltage measured was not consistent and varied as a result of arbitrarily small changes in placement of the magnet on the ureter. Once the baseline
ureteral peristalsis rate was calculated, irrigation fluid at 37°C (body temperature) was instilled in the renal pelvis in a similar manner to the first pig followed by a second phase in which the force sensor was used to determine the force exerted during passage of a UAS. At the conclusion of the studies at 37°C, a similar experiment was performed on the contralateral ureter at 43°C. The ureters were then harvested and sent for pathology analysis to assess for any histologic changes in the proximal, middle, or distal ureter.

Two-tailed $t$-tests were performed for statistical analysis. $p \leq 0.05$ was considered significant. Statistical tests were performed with SPSS v21 (IBM, Armonk NY).

Results

There was no statistically significant difference in ureteral caliber along the length of the ureter with irrigation temperatures of 37°C vs 43°C ($p = 0.87, p = 0.32, p = 0.66$ for proximal, middle, and distal ureter, respectively). There was a similar increase in peristalsis from baseline with fluid irrigation at 37°C and 43°C (64% and 65%, respectively). On histologic analysis, all ureteral segments showed no remarkable changes in urothelial epithelium or the subepithelial, mucosal, or serosal layers. There were no differences in the luminal diameter.

_Ureteral caliber measurements at different irrigation temperature_

No clear trend was seen in the change of ureteral caliber in the right and left ureters of Pigs 1 and 2 after irrigation at 37°C and 43°C. The initial measurements of the right ureter of Pig 1 at 37°C were 5.71 mm
proximally, 6.79 mm at the middle position, and 2.36 mm distally. After 30 minutes of irrigation at 37°C, the ureteral caliber measurements were 6.06, 3.95, and 3.81 mm at the proximal, middle, and distal positions, respectively. The left ureter of Pig 1 increased in caliber at all three positions after 30 minutes of irrigation at 43°C, from 3.6 to 6.05 mm proximally, 2.65 to 4.77 mm at the middle ureter, and 2.11 to 3.91 mm distally.

The right ureter of Pig 2 increased in caliber at each position after irrigation. The baseline caliber of the right ureter of Pig 2 was 3.92, 2.99, 3.23 mm compared to 5.69, 3.7, 4.01 mm after 30 minutes of irrigation at 37°C at the proximal, middle, and distal positions, respectively. After 30 minutes of irrigation at 43°C, the left ureteral caliber of Pig 2 changed from 4.75 to 4.93 mm proximally, 5.1 to 5.88 mm in the middle ureter, and 5.02 to 3.97 mm in the distal ureter.

**Force exerted with UAS placement**

Effective placement of a UAS was performed in each of the porcine ureters following irrigation. In the right ureter of Pig 1 after irrigation at 37°C, 16F UAS placement was aborted because of exerting 6.74 N before adequate placement. A 14F UAS was then effectively placed with a maximum force of 4.55 N exerted. A 16F UAS was placed in the left ureter of Pig 1 after irrigation at 43°C, exerting 6.25 N.

In Pig 2, both the right and left ureters underwent effective placement of 16F UAS. In the right ureter with the irrigant at 37°C, a maximum force of 3.22 N was exerted compared with 2.25 N in the left ureter with the irrigant at 43°C.

**Ureteral peristalsis**

Peristalsis was tracked through magnet movement with resulting voltage induction being collected in graph form through the magnetic sensor. Baseline measurement of the rate of peristalsis was conducted for 10 minutes before administration of irrigation at 37°C and demonstrated regular waveforms at an average rate of 2.04 contractions per minute (cpm) (Fig. 3A). After irrigation at 37°C, an increase in rate of contraction was exhibited, reaching average rates of 3.25 cpm, a relative increase of 59%. This was also coupled with a change in the character of ureteral peristalsis from contraction at roughly regular 30 seconds intervals at baseline to periods of high activity and periods with clustered contractions and inactivity after irrigation (Fig. 3B). This variability was exemplified by the change in average period of the peristaltic waves from 31.88 ± 10.76 seconds (standard deviation) at baseline to 27.76 ± 28.82 seconds, shorter time between waves on average with an increase in variability. Similar findings were demonstrated upon irrigation with 43°C saline with a relative increase in contraction rate of 65% from a baseline of 1.53 to 2.52 cpm after addition of 43°C irrigant. The wave patterns both at baseline and after 43°C irrigation had similarly high variability with some clustering in both as evidenced by the waveform and similar variability in the periods at baseline and after 43°C irrigation, 45.48 ± 20.54 seconds and 32.03 ± 17.79 seconds, respectively (Fig. 4). Figures 5 and 6 demonstrate peristaltic waveform at the beginning of irrigation and at the end of irrigation at 37°C and 43°C, respectively. Figure 7 compares the peristaltic waveforms at 37°C and 43°C at the conclusion of the 30 minute time interval.
FIG. 3. (A) Sample ureteral peristalsis waveform for 5 minutes at baseline before irrigation. The peristaltic contractions, as opposed to breathing or noise, are marked with circular markers and counted in analysis. (B) Ureteral peristalsis after 5 minutes of irrigation with 37°C saline. Graph (B) exhibits a more clustered profile of contractions.

FIG. 4. (A) Sample ureteral peristalsis waveform for 5 minutes at baseline before irrigation. The peristaltic contractions, as opposed to breathing or noise, are marked with circular markers and counted in analysis. (B) Ureteral peristalsis after 5 minutes of irrigation with 43°C saline. Graph (B) again exhibits a more clustered profile of contractions.
FIG. 5. (A) Peristaltic waveform for 2 minutes from the beginning of the irrigation cycle at 37°C. (B) Peristaltic waveform for 4 minutes near the end of the 37°C cycle. Similarly note that Graph B also exhibits six complete wavelengths, but this is done with a change in scale of the time axis showing the waveform for 4 minutes as opposed to the 2 minutes of Graph A.

FIG. 6. (A) Peristaltic waveform for ~3 minutes from the beginning of irrigation cycle at 43°C. (B) Peristaltic waveform for 2 minutes near the end of irrigation cycle at 43°C.
Discussion

The ureter is the gatekeeper for performing retrograde upper tract endoscopic surgery. A common hindrance to retrograde access is the unpredictability of the caliber of the ureter. Mechanical manipulation of the ureter with serial or balloon dilation puts the patient at risk for ureteral perforation and the potential for long-term stricture formation. Given that 8%–10% of planned ureteroscopies are aborted because of the inability of the ureter to accommodate even the smallest of endoscopic instruments, the ability to acutely create ureteral dilation is of great interest.

In an effort to manipulate the ureter in real time during ureteroscopy, Mohammadzadeh Rezaei et al. utilized warmed irrigation fluid (40°C) during the procedure and reported that it appeared to facilitate access to the proximal ureter. In that study, 150 patients were randomized to either 20°C–25°C or 40°C saline irrigation. They evaluated access to the proximal ureter, stone retropulsion frequency, and overall stone-free rate. Access in this study was solely with semirigid ureteroscopes. In our study, there was no difference noted in ureteral caliber with irrigation fluid warmed to body temperature or to the extreme physiologic limit of 43°C. Retrograde pyelography images captured after irrigation fluid had been instilled for 30 minutes showed no difference in the caliber of the proximal, middle, and distal ureter (p = 0.87, p = 0.32, p = 0.66, respectively).

Previous studies by Venkatesh et al. demonstrated that placement of 4.8F ureteral stents resulted in an increased frequency of ureteral contraction in the acute to 2 hours period with gradual slowing after this point to an eventual aperistalsis at 1 week, whereas 7F ureteral stents resulted in aperistalsis in as soon as 4 hours. It is unclear whether diminishment in ureteral peristalsis or passive dilation with preplacement of a ureteral stent leads to higher success rates of ureteroscopy. Our study showed that with irrigation there was an increase in peristalsis of the ureter at both 37°C and 43°C compared with baseline; however, the increase was similar (i.e., 59% and 64%, respectively) and may simply be caused by the mere act of running the irrigation fluid into the collecting system regardless of the temperature of the irrigant.

A novel load-sensing device, the UCI Ureteral Access Sheath Force Sensor, was utilized in this study to measure the force applied during UAS placement at the experimental conditions. The hypothesis was that if ureteral dilation or decreased ureteral peristalsis occurred at higher irrigation temperatures, then the force...
required to place a UAS would be lower. A 16F UAS was placed at <6.25 N of force in both ureters at 43°C and in only one of two ureters at 37°C.

There are several limitations to our study. First, this was a pilot study that was conducted in two pigs. The study would have been expanded with appropriate power to limit random error if a difference was found at our experimental temperatures at any of our tested variables (ureteral caliber on fluoroscopy and histology, peristalsis, or force needed to place a UAS). Second, translating our laboratory findings to the clinical scenario is not necessarily reliable; however, within the non-primate animal kingdom, the pig ureter is most similar to the adult human ureter. Third, the experiment was conducted with varying irrigation pressures for only 30 minutes, which may seem impractical in a clinical setting. However, this time duration was chosen for this study as most ureteroscopic procedures are often between 30 and 60 minutes.

The ureter is the least studied and thus most poorly understood organ of the urinary tract. This may well be because of its relative lack of pathology analysis compared with the kidney, renal pelvis, bladder, or prostate and because of its difficult accessibility. The findings of many ureteral studies including those that showed ureteral caliber changes with warmed irrigation fluid are observational in nature as studying the human ureter in vivo is challenging. The ability to acutely create ureteral relaxation using a nonpharmacologic approach is highly attractive and the pursuit for this goal remains elusive. Although we have not been able to document a change in ureteral caliber or a slowing of peristalsis, there is a suggestion that the warmed irrigant may facilitate passage of a UAS at lower force. Plans are underway for a clinical study in this regard.

Conclusion

In a porcine model, warming irrigation fluid to just under the biological threshold for injury (i.e., 43°C) failed to either increase ureteral caliber or decrease ureteral peristalsis; however, there may be other mechanisms at work that resulted in effective passage of a 16F UAS in the two ureters irrigated at 43°C.

Author Disclosure Statement

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References


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**Abbreviations Used**

- cpm = contractions per minute
- GMR = giant magnetoresistance
- UAS = ureteral access sheath
- UCI = University of California, Irvine