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First Prize

Pharmacologic Manipulation of the Porcine Ureter: Acute Impact of Topical Drugs on Ureteral Diameter and Peristaltic Activity

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ABSTRACT

***Background and Purpose*: Intraluminal application of pharmacologic agents for acute ureteral dilation may facilitate difficult ureteroscopy. We characterized the *in-vivo* effects of intraluminal application of verapamil and theophylline on ureteral peristalsis and diameter in a porcine model.**

***Materials and Methods*: Twenty-four female domestic pigs (35–40 kg) were incorporated into the study. We deployed a giant magneto resistive (GMR) sensor and electromagnetic (EMG) electrodes laparoscopically onto the ureteral surface for simultaneous measurement of the mechanical and electrical signals of ureteral peristalsis, respectively. The ureteral-luminal diameter was measured at three levels by digital retrograde pyelography and standardized to a 10-mm laparoscope. The results were calculated as change in peristalsis and ureteral diameter from baseline during the first hour after drug injection. We tested two smooth-muscle relaxants, verapamil (2 mg/kg) and theophylline (70 mg/kg), with saline and dimethylsulfoxide (DMSO; solvent) as controls. Six pigs were studied for each of the four groups. Hydration, anesthesia, and intra-abdominal pressure were standardized. The serum concentrations of the drugs were measured to determine systemic absorption.**

***Results*: During the first 10 minutes after intraluminal drug injection, theophylline caused a significant decrease in ureteral peristalsis (6.75 waves/10 minutes) compared with the control group (1.00/10 minutes; $P = 0.02$). This trend persisted for the next hour. However, there were no changes from baseline in ureteral width. Ureteral peristalsis and dilation remained similar after the saline and DMSO injections. Verapamil increased the diameter of the proximal ureter compared with the controls throughout the hour after drug injection. Fifteen minutes after the drug injection, the change in the ureteral diameter with verapamil was 1.38 mm (4.14F), while the control group showed a change of 0.27 mm ($P = 0.03$). At 1 hour, the width of the proximal ureter in the verapamil group had increased by 1.72 mm (5.16F), while the control group had changed by 0.55 mm ($P = 0.03$). There were no statistically significant changes in the widths of the mid or distal ureter. No ureteral dilation was observed in the other groups.**

***Conclusions*: In the porcine model, intraluminal application of pharmacologic agents produced independent effects on ureteral dilation and peristalsis. Theophylline inhibited ureteral peristalsis, and verapamil produced acute proximal-ureteral dilation. The ability to alter ureteral diameter or peristaltic activity acutely may facilitate ureteroscopy.**

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INTRODUCTION

URETEROSCOPY has become a mainstay in the urologist's armamentarium for ureteral and renal collecting-system access for both diagnostic and therapeutic purposes. Occasionally, ureteroscopy can be challenging in a nondilated ureter in which the ureteroscope cannot be passed easily. The inability to pass the ureteroscope may necessitate either acute dilation of the ureter or short-term stenting before ureteroscopy.

Application of an intraluminal drug which, on contact with the ureteral urothelium, causes acute dilation and relaxation of the ureter without appreciable systemic effects may facilitate ureteroscopic procedures and increase safety. In addition, relaxation of the ureter may facilitate the routine use of larger-diameter ureteroscopes, which would have greater deflection and durability and a larger working channel. Acute dilation of the ureter may also engender spontaneous passage of kidney stones. Our primary goal was to evaluate pharmacologic agents to determine if it is feasible to decrease ureteral smooth-muscle tone acutely when such drugs are applied intraluminally within the ureter.

Studies to evaluate ureteral peristalsis have largely used endoluminal methods, employing either a pressure transducer[1–4] or an ultrasound probe[5] to evaluate ureteral physiology. However, these endoluminal devices can themselves alter ureteral peristalsis, and, hence, intraluminal evaluation technologies cannot be applied to measure ureteral peristalsis and the ureter's response to interventions such as stenting accurately.[6] Previously, we reported the design, construction, and implementation of a novel extraluminal system to evaluate ureteral peristalsis.[7] In this study, we utilized this system, which incorporates electromyographic (EMG) and magnetic sensors, for extraluminal evaluation of peristalsis in the porcine ureter. This system is extraluminal and can be deployed using a minimally invasive (laparoscopic) technique to ensure minimal alteration of the ureteral anatomy and physiology.

MATERIALS AND METHODS

Animals and electromyography measurements

Permission for the study was obtained from the Washington University Department of Comparative Medicine and the Washington University Animal Studies Committee. Twenty-four female domestic pigs (35–40 kg) were divided into four groups of six animals each. Animals in group 1 received intraluminal theophylline (70 mg/kg). Animals in group 2 received intraluminal verapamil (2 mg/kg). Groups 3 and 4 represented the control groups, with group 3 receiving 0.9% saline only and group 4 receiving dimethylsulfoxide (DMSO) (solvent) in either 1- (N = 3) or 2-mL (N = 3) doses.

After a 16-hour fast but no fluid restriction, the pigs were anesthetized using xylazine, 0.45 mg/kg, and intubated and ventilated using isoflurane anesthesia at a constant concentration of 2%. Intravenous yohimbine was used to reverse the effects of xylazine soon after the insertion of trocars. Ketamine and atropine were not used because of their known significant effects on ureteral peristalsis. The pig was hydrated with intravenous 5% glucose–0.45% saline at a constant infusion rate of 5 mL/kg of body weight.

The electrical potentials from ureteral peristalsis were measured by two sets of modified bipolar steel wire EMG electrodes (Fig. 1). The bipolar wire electrodes were mounted on a 23-gauge, three-quarter-inch hypodermic needle to facilitate laparoscopic deployment onto the serosal surface of the ureter. The Teflon-coated wires from both electrodes led to two multipin connectors. The EMG signals from the electrodes were amplified and displayed on a multichannel oscilloscope (Gould 1604; Gould Equipment, Ilsford, UK).

The mechanical movement of ureteral peristalsis was measured by the giant magneto resistance (GMR) sensor (Fig. 1). The magnetic sensor technology consists of a 2×0.5-mm disc-shaped neodymium magnet that creates a magnetic field and a GMR sensor (NVE Inc., Eden Prairie, MN), which identifies any change in the magnetic field produced by movement of an object placed within the field. The magnet is positioned, and a small ($4 \times 4 \times 0.75$-mm) sensor plate is placed on the opposite side of the ureter. The GMR sensor was mounted on a custom-made aluminum strip for ease of laparoscopic deployment and for accurate and atraumatic positioning under the ureter. The sensor uses a Wheatstone bridge circuit, and the signals from the sensor were amplified and displayed simultaneously on the same oscilloscope with the EMG signals. This unique sensor and its method of placement were developed in our laboratory and have been described.[7]

Operative technique

The pig was placed in a lateral decubitus position, and, using a three-port laparoscopic technique, the ureter was identified without any dissection. Pneumoperitoneum pressure was maintained between 6 and 8 mm Hg to minimize the physiological effects. The peritoneum overlying the upper and mid ureter was gently reflected medially to expose the surface of the ureter.

After exposure of approximately 1 cm of the proximal ureter, the baseline peristaltic rate was documented by laparoscopic visual observation for 5 to 10 minutes. Next, the EMG electrodes and the magnetic sensor were deployed laparoscopically. The first set of EMG electrodes was placed under the adventitia of the ureter about 3 cm distal to the ureteropelvic junction, with the hooks of the electrode wire facing the muscular surface. Electrode positioning was achieved by inserting the needle through the adventitia and then retracting it back over the wires, leaving the tips of the wire electrodes on the ureteral surface. The second set of EMG electrodes was placed approximately

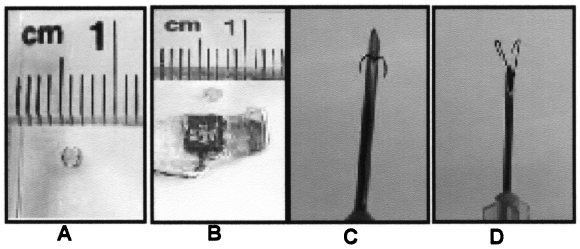

FIG. 1. Experimental equipment. (**A**) Neodymium magnetic disk and (**B**) GMR sensor. (**C**) and (**D**) Bipolar EMG wire electrodes mounted on hyperdermic needle.

6 to 7 cm distal to the first set. A small (<1-cm) window was created under the ureter for placement of the magnet and the magnetic sensor between the two sets of EMG electrodes. Care was taken to preserve the ureteral blood supply to the extent possible and to cause minimal disturbance of the *in-situ* ureter. This arrangement of EMG leads provided good correlation with endoscopically visible propagative peristaltic waves.

To deploy the GMR sensor, the small magnetic disc was mounted on an applicator using K-Y jelly to keep it adherent to the tip. The magnetic surface was coated with a thin layer of fibrin glue and deployed on the anterior surface of the ureter. The sensor was positioned under the posterior surface of the ureter opposite the magnet. As the peristaltic wave propagated along the ureter, the magnet on the ureteral surface moved in relation to the sensor, and this movement produced a change in the magnetic field, which was registered by the GMR sensor.

After the sensors were deployed, the intra-abdominal pressure was reduced to 5 mm Hg to lessen the effect that pneumoperitoneum might have on ureteral physiology. Baseline peristalsis was measured for 1 hour. The GMR and EMG signals correlated with laparoscopically visible peristalsis. Intravenous hydration rate, intra-abdominal pneumoperitoneum pressure, and anesthetic concentration were also documented during the observation period. The rate and frequency of peristaltic waves were recorded.

A standardized retrograde pyelogram was performed by passing a 5F open-ended ureteral catheter 2 cm into the distal ureter under fluoroscopic guidance. The technique for each retrograde evaluation of the ureter was standardized by suspending a 200-mL bag of saline mixed with 60 mL of Conray (Mallinckrodt Inc., Hazelwood, MO) 100 cm above the height of the animal's bladder. Diluted contrast medium was allowed to fill the collecting system by gravity for exactly 60 seconds, at which time, a fluoroscopic plain film was obtained during the animal's end-expiratory phase of ventilation. Precise digital measurements of the ureteral diameter were achieved using OEC software at the proximal, mid, and distal levels to determine the diameter during a nonperistaltic phase (Fig. 2). This method allows accurate measurement, up to 1/100 of a millimeter, with the digital fluoroscopy unit. The proximal-ureteral measurement was made at the level of the lowest portion of the ipsilateral lower-pole calix. The mid-ureteral measurement was acquired at the upper border of the T12 vertebral body, and the distal ureter was measured at the upper border of the S1 vertebral body. A GE-OEC series 9800 digital fluoroscopic unit (GE OEC Medical Systems, Salt Lake City, UT) was utilized for all experiments.

Experimental technique

Animals were then randomized into the four drug groups described previously. A retrograde pyelogram was obtained after 1 hour of baseline peristalsis monitoring. Next, 10 mL of the appropriate pharmacological agent was injected through the 5F ureteral catheter over a period of 1 minute. Animals in group 1 received an average of 2.8 g of theophylline, and those in group 2 received 80 mg of verapamil. These dosages were chosen as they were 10 times the normal systemic dose a human would receive. Each drug was dissolved in injectable saline, and 1 mL of DMSO was added as a solvent, for a total volume of 10 mL.

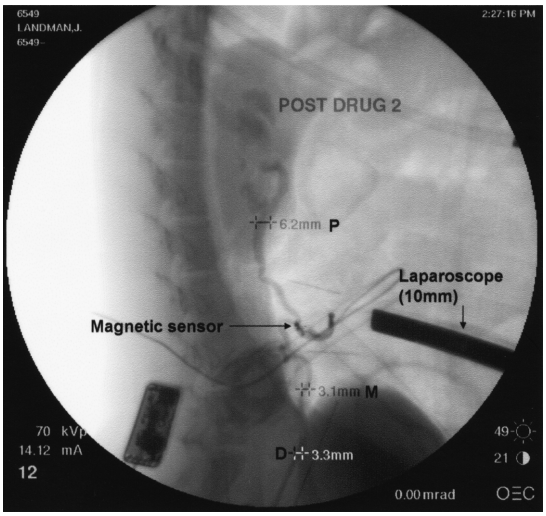

FIG. 2. Standardized retrograde pyelogram with digital measurements of proximal (P), mid (M), and distal (D) ureter.

The cystoscope was immediately placed gently against the ureteral orifice to minimize leakage of the drug out of the orifice; and the catheter, capped by the empty syringe, was held in the distal ureter over the next 15 minutes to keep the drug from leaking out. Ureteral peristaltic activity was recorded for 10 minutes immediately after drug injection using the GMR and EMG configuration described. Immediately after the 10-minute recording, a Bentson wire was placed through the catheter to the level of the distal ureter. The catheter was then removed, allowing drainage of the pharmacologic agent out of the collecting system. Next, the ureteral catheter was replaced into the distal ureter, and a standardized retrograde pyelogram was performed as previously described. The wire was replaced and the catheter removed from the ureteral orifice to reduce the effect the catheter might have on ureteral physiology.

Retrograde studies were procured at baseline and 15, 30, 45, and 60 minutes after drug injection. Ureteral peristalsis was measured at 10-minute intervals at baseline (before drug injection) and then at 0, 15, 30, 45, and 60 minutes postinjection. The bladder remained decompressed with a Foley catheter throughout the experiment. Serum drug concentrations were measured at 15, 30, and 60 minutes after injection of each agent to assess systemic absorption and effects. After the 60-minute recordings, the animal was euthanized.

Statistical analysis

Changes from baseline for both peristalsis and ureteral diameter were compared with the values in the control groups using the least-squares means procedure with Tukey-Kramer adjustment for multiple comparisons. Statistics were calculated using SAS software (V. 9.0; SAS, Cary, NC).

RESULTS

A consistent correlation was found between laparoscopically observed ureteral peristalsis and the peristalsis detected by the

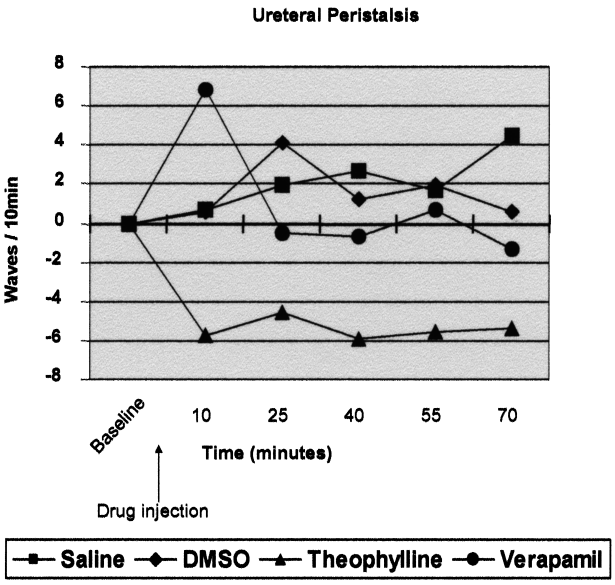

FIG. 3. Ureteral peristalsis after drug injection.

EMG electrodes and the magnetic sensor. The EMG action potentials were characterized by multiphasic bipolar spike potentials with rapid onset and return to the baseline. The signals from the magnetic sensor were characterized as unipolar smooth deflection and bell shaped. The EMG activity preceded the mechanical activity recorded by the magnetic sensor by a few milliseconds. The propagative peristaltic wave seen visually was correlated with the proximal EMG, the GMR sensor, and the distal EMG signals on the oscilloscope. There was no change in the endoscopically visible baseline peristalsis before and after deployment of the EMG electrodes and the magnetic sensor device, indicating that deployment of the devices themselves did not affect peristalsis.

Theophylline

Immediately after intraluminal theophylline injection, peristaltic activity decreased from a baseline of 6.75/10 minutes to 1.00/10 minutes. In contrast, the saline control group manifested no change in the rate of peristaltic activity ($P = 0.02$). The trend to decreased peristalsis continued for the next hour after theophylline injection. This was also statistically significant at 30 minutes, when the number of waves was decreased from 6.75/10 minutes to 0.83/10 minutes. At the 30-minute point, the saline control group demonstrated no significant change in peristaltic rate ($P = 0.05$) (Table 1; Fig. 3). There were no significant changes in ureteral diameter after theophylline injection (Table 2). Serum theophylline concentrations averaged 8, 12, and 20 μg/mL at 15, 30, and 60 minutes, respectively. (Standard human therapeutic values are 10–20 μg/mL) There were no changes in blood pressure or heart rate after theophylline injection.

Verapamil

Immediately after intraluminal ureteral instillation, verapamil resulted in a significant increase in the number of peristaltic waves, from 4.00/10 minutes to 10.83/10 minutes. The saline control group manifested no change in peristaltic rate ($P = 0.03$) (Fig. 3). Intraluminal verapamil administration produced a significantly larger proximal-ureteral diameter at 15 and 60 minutes (Fig. 4). At 15 minutes, the proximal ureter in the verapamil group had changed from a mean diameter of 7.10 mm to 8.48 mm (increase of 1.38 mm or 4.14F) ($P = 0.03$), whereas the saline control group did not manifest a significant change. At 60 minutes, the proximal ureter in the verapamil group had changed from a diameter of 7.10 mm to 8.82 mm (increase of 1.72 mm or 5.16F) ($P = 0.03$). There was no change in the ureteral diameter of the saline control group (Table 2). There were no significant changes in the mid- or distal-ureteral diameters.

Serum verapamil concentrations averaged 30, 35, and 43 ng/mL at 15, 30, and 60 minutes and thus were below standard human therapeutic serum values, which range from 50 to 100 ng/mL. At the 30-minute point, animals in the verapamil group experienced a significant decrease in systolic blood pressure, from 98.17 mm Hg to 75.33 mm Hg ($P = 0.03$). There was no significant change in diastolic blood pressure or heart rate.

DISCUSSION

Several studies have examined the effects of various pharmacologic agents on ureteral motility. Previous studies have suggested that both theophylline and calcium-channel blockers (CCB) such as verapamil may be instrumental in inhibition of ureteral peristalsis.[1,2,8–11]

Theophylline has been found to decrease ureteral contractility when applied systemically in an in-vivo canine model[1,2] and in an *in-vitro* setting when applied to isolated guinea pig ureters in a bath of modified Krebs solution.[8] To our knowledge, ours is the first study to quantitate changes in ureteral diameter in response to pharmacologic manipulation in an *in-vivo* setting.

TABLE 1. CHANGE IN URETERAL PERISTALSIS AFTER INJECTION OF PHARMACOLOGIC AGENT

	10 min	*25 min*	*40 min*	*55 min*	*70 min*
Theophylline	−5.75[a]	−4.58	−5.92	−5.58	−5.42
Verapamil	6.83[a]	−0.50	−0.67	0.67	−1.33
Saline	0.70	1.90	2.70	1.70	4.50
DMSO	0.58	4.08	1.25	1.92	0.58

[a]$P \leq 0.05$ compared with saline-treated control.

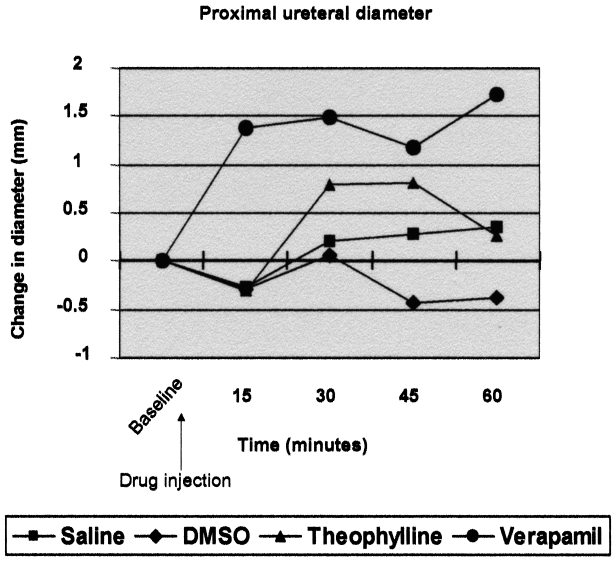

FIG. 4. Proximal ureteral diameter after drug injection.

Several studies have shown the effect of verapamil and other CCB of diminishing peristaltic activity when applied to human and animal ureteral segments *in vitro*.[9–11] Clinically, CCB may facilitate stone passage through the ureter in both nonsurgical[12,13] and post-SWL[14] patients. Stower and colleagues[15] administered intravenous verapamil in a nonanesthetized canine model and found decreased ureteral peristalsis in one of five dogs, but no effect in the remaining four. The current study showed a temporary increase in ureteral peristalsis after verapamil exposure, with a quick return to baseline. The deviation in our results from previous findings may be related to interspecies variability. Alternatively, the most reliable decrease in peristaltic activity has been demonstrated in the *in-vitro* setting, and verapamil may be unreliable in producing ureteral relaxation in the intact, *in-vivo* model. We are uncertain of the reason for the increase in contraction after verapamil administration in our present study. The study of ureteral smooth-muscle pharmacology has been fraught with conflicting findings, possibly because of the many differences in experimental technique and animal models and the lack of sensitive instrumentation.[1]

Many techniques for studying pharmacologic action on ureteral physiology have been described. Investigators have used *in-vivo* models with both unanesthetized[15] and anesthetized[12,13] animals. Also, studies have been done in the unobstructed as well as obstructed ureter.[4] In these studies, the pharmacologic agents were administered systemically[1,2] or applied topically by dripping the agent into the ureteral lumen through a catheter.[12,13] To date, the in-vitro models described have utilized muscle baths to evaluate ureteral physiology.[14,16–18] An interesting approach to the evaluation of ureteral muscle tone has been described by Miyatake and associates,[19] who described a model in which the force required to pull a glass bead through short piece of rabbit ureter was measured before and after application of pharmacologic agents. In this model, less force was required to pull the bead through the ureter after application of isoproterenol compared with a control ureter.

Our model incorporating the extraluminal EMG and GMR technologies has some advantages over previously described techniques for ureteral physiological evaluation. In many contemporary *in-vivo* studies, the authors use an intraluminal pressure transducer to measure ureteral contractions.[12,13] However, the intraluminal transducer itself may result in artefactual results that affect ureteral motility.

A significant issue in the evaluation of pharmacologic manipulation of the ureter is the potential for adverse reactions from systemic absorption. Both Danuser and associates[16] and Hauser and colleagues[17] showed that topical phenylephrine administration within the ureter in an anesthetized pig model produces a local effect on the ureter without the systemic side effects seen when the same drug is given intravenously. These groups used a 6F dual-lumen catheter placed through the renal pelvis and into the ureter. One lumen was used for topical drug administration and the other for recording of ureteral contractions by pressure transducer.

We used topical administration of the pharmacologic agents and saw minimal systemic absorption. One group (verapamil) had a drop in systolic blood pressure 30 minutes after drug administration. In this study, we used dosages approximately 10 times the oral (systemic) dose by intraluminal administration on the basis of our clinical suspicion, as there are no data in the literature to suggest the appropriate dose. Serum drug concentrations were carefully monitored, and although there was some systemic absorption, the serum values remained within human therapeutic limits. Certainly, future clinical trials will have to consider the systemic effects of the pharmacologic agents applied in regard to patient selection, intraoperative monitoring, and postoperative care.

Our study demonstrates a new method of studying ureteral physiology using a unique, laparoscopically deployable extraluminal method. The GMR sensor is sensitive to small changes in the magnetic field and allows accurate measurement of displacements of an object in linear, radial, and rotational systems.

TABLE 2. CHANGE IN URETERAL DIAMETER AFTER INJECTION OF PHARMACOLOGIC AGENT

	15 min			*30 min*			*45 min*			*60 min*		
	Prox	*Mid*	*Distal*	*Prox*	*Mid*	*Distal*	*Prox*	*Mid*	*Distal*	*Prox*	*Mid*	*Distal*
Theophylline	−0.3	0.18	−0.12	0.8	0.53	−0.05	0.82	0.14	0.38	0.27	−0.02	−0.05
Verapamil	1.38[a]	0.57	0.27	1.48	0.28	0.25	1.17	0.43	0.02	1.72[a]	0.55	0.05
Saline	−0.24	0.34	0.10	0.20	0.43	−0.08	0.28	0.50	−0.36	0.35	0.13	−0.72
DMSO	−0.28	0.12	−0.07	0.06	0.20	−0.27	−0.44	0.24	−0.13	−0.38	−0.30	−0.30

[a]$P \leq 0.05$ compared with saline-treated control.

This makes the GMR sensor applicable for measuring peristaltic activity in a tubular structure. The technology is based on the giant magneto-resistive phenomenon that is being used in the automobile and aircraft industries for various purposes (e.g., throttle positioning, wheel-speed sensing). To our knowledge, this is the only such application of GMR sensor technology in a macro biological system and was first described by our laboratory.[7]

Our technique enabled us for the first time to evaluate the acute effects of different smooth-muscle relaxants on ureteral peristalsis. By using this extraluminal approach, we were able to isolate drug effects, without the artifactual changes associated with intraluminal monitoring devices, which are known to alter ureteral peristaltic activity. Additionally, we described the first standardized, digital retrograde urography system to determine changes in ureteral diameter accurately as a function of pharmacologic manipulation of *in-vivo* ureteral physiology.

The use of minimally invasive techniques to study ureteral physiology without placing an intraluminal catheter for measurements may help to reveal differences regarding ureteral smooth-muscle response to pharmacologic agents.

CONCLUSIONS

The pharmacologic agents manifested independent effects on ureteral dilation and peristalsis. Intraluminal ureteral theophylline administration caused acute inhibition in ureteral peristalsis with minor increases in serum concentrations and no significant change in ureteral diameter. Intraluminal ureteral verapamil administration yielded significant acute proximal dilation. The ability to alter ureteral diameter or peristaltic activity or both acutely may have important clinical implications for endoscopic interventions in the upper urinary tract.

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ABBREVIATIONS USED

CCB = calcium channel blockers; EMG = electromyography; GMR = giant magneto resistive.