Dynamics and modulation of ureteric peristalsis

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CHAPTER 6

INTRALUMINAL PRESSURE CHANGES IN VIVO IN THE MIDDLE AND DISTAL PIG URETER DURING PROPAGATION OF A PERISTALTIC WAVE

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ABSTRACT

Objectives: To establish the characteristics of mechanical activity during ureteric peristalsis and unidirectional bolus transport, pressure changes in the middle and distal (juxtavesical and ureterovesical junction) porcine ureter were quantified in vivo.

Methods: Five female New Yorkshire pigs (50-60 kg) were studied under halothane anesthesia. The endoscopic approach was used to position an 8-channel 6F perfusion catheter under direct vision into the distal ureter via the orifice. Ureteric activity was studied in two separate sessions at a week's interval. Pressure, propagation velocity and length of the peristaltic waves were analyzed.

Results: The average maximum pressure ($P_{\text{max}}$) in a not previously instrumented ureter amounted to $35.7 \pm 1.2 \text{ cm H}_2\text{O}$ in the mid-ureter, and decreased to $19.4 \pm 1.3 \text{ cm H}_2\text{O}$ in the juxtavesical ureter ($P<0.001$) and further to $7.2 \pm 1.0 \text{ cm H}_2\text{O}$ ($P<0.001$) in the submucosal segment. The propagation velocity of the peristaltic wave through the ureter was $2.1 \pm 1.3 \text{ cm/sec}$. The length of the pressure peak was $5.9 \pm 1.6 \text{ cm}$.

Conclusions: A ureteric peristaltic contraction wave travels at approx. 2 cm/sec and is approx. 6 cm long. It is responsible for the unidirectional transport of a urinary bolus and itself acts as an "active" anti-reflux mechanism. $P_{\text{max}}$ in the lumen of the ureter decreases from proximal to distal, but remains sufficiently high at the ureterovesical junction (UVJ) to prevent retrograde urine leakage when the ureter empties its urinary bolus into the bladder and the orifice is open.
INTRODUCTION
Under normal conditions, urine transport in the ureter is unidirectional and as separate urinary boluses. Increase in diuresis leads to increasing bolus sizes until one bolus touches the next and finally it forms an open tube transport system.1

Based on the evidence of our early studies we postulated that contraction of the circular muscle of the juxtavesical ureter functions as the "active" anti-reflux mechanism2-5. Active shortening of the longitudinal muscle layer of the transmural and submucosal ureter segments deposits the bolus into the bladder lumen. To further test the validity of our hypothesis, we studied ureteric peristalsis in the pig model. Electromyographic studies were undertaken to study the excitation of ureteric peristalsis.5 Excitation of ureteric muscle leads first to wall movement, which we studied using endoluminal ultrasonography (ELUS). It also leads to intra-ureteric pressure rise. We measured intraureteric pressures during the passage of peristaltic waves in the mid (10 to 16 cm from the ureteric orifice) and the juxtavesical ureter and the UVJ (0 to 6 cm from the ureteric orifice). We undertook this to establish the characteristics of the intraureteric pressure wave, which is the resultant mechanical force for unidirectional bolus transport.

Our data illustrates the crucial role played by ureteric peristalsis as an active pump to transport urine and simultaneously prevent retrograde leakage into the upper urinary tract (UUT) from the bladder. This can have clinical implications for management of vesico-ureteric reflux (VUR), obstructive uropathy and mega ureters. Our results have encouraged us to undertake further studies on pharmacological modulation of ureteric peristalsis.

MATERIAL AND METHODS
Experimental animals and anaesthetic procedure. Female pigs were studied (n=5, 57±7 kg). The 6F catheter was positioned under endoscopic control so that its tip came to lie at a distance of 7 cm (including 1 cm of tip extension) from the ureteric orifice. Pressure changes in the mid ureter (16 to 10 cm from the ureteric orifice) were also recorded. Urine produced was collected and its quantity measured. Intravenous urograms (IVU) were performed only as a control to confirm the absence of any ureteric dilatation occurring and to prove the existence of bolus transport in the ureter.

As pre-medication 20 mg azaperon, 150 mg ketamine/10 kg body weight and 1 mg atropine were administered intravenously. Anesthesia (1%
halothane, 47.5% N\textsubscript{2}O and 47.5% O\textsubscript{2}) was tailored to maintain optimal muscular activity. For peri-operative antibiotic cover Augmentine (1200 mg) was used. Fynadine\textregistered, a NSAID was administered as postoperative analgesic. Duration of the experiments varied from 3 to 4 hours, as EMG and ELUS recordings were also undertaken. Hydration was maintained by infusing of 6.1±0.1 ml/kg/h physiologic saline. This rate of infusion was required as the animals were fasting for 12 hours and thus were approximately 1250 ml negative in their water homeostasis. During the recordings, approximately 1,400 ml physiologic saline was infused to compensate for negative water homeostasis and insensible fluid loss. Every animal was studied in two sessions at an interval of one week to study the effect of instrumentation on the ureter and bladder. Signals were registered in every pig at every experimental session. During endoscopic inspection of the bladder at the second session, only a minimal edema was observed in the bladder. It did not present a technical problem for recording the pressure curves at the UVJ.

*Eight-channel perfusion equipment.* Figure 1 schematically represents the flexible silicone catheter and its helically positioned side openings at intervals of 0.75 cm, together with the 8-channel perfusion equipment. The catheter was stationary during all measurements. Orientation of the adjacent side holes in the catheter was at 45 degrees to each other. Each channel of the catheter was flushed with physiological saline at body temperature and at a constant perfusion velocity of 0.075 ml/min using a hydro-pneumatic pump. Pressure-transducers, registered the pressure at which perfusion was being performed. The system was initially flushed to evacuate air-bubbles, calibrated and zero balanced at the level of the pig urinary bladder. The base line was undertaken after positioning the catheter inside the ureter and with the perfusion running between two peristaltic waves. Pressure rise per second was 242.8±1.8 cm H\textsubscript{2}O /sec after complete blockage of the side holes. Data was sampled at 100 Hz, digitized and processed in a computer using a program written by our group\textsuperscript{6}. Every positive deviation from the base line in the most proximal channel (channel 1), which was subsequently propagated to the adjacent distal channels (channels 2-8), was defined as a peristaltic wave. Every simultaneous deviation from the base line in more than one channel was considered an artifact and excluded from the study. The software was programmed to recognize each peristaltic curve in each channel when the pressure exceeded 5% of the maximum pressure (P\textsubscript{max}). The end was similarly when pressure declined to under 5% of P\textsubscript{max}. The duration of the pressure curve was measured in seconds.
Figure 1: The equipment used. The distance between side-hole 1 and 8 is 6 cm. Body temperature physiological saline was perfused at 0.6 ml/min (0.075 ml/min per channel). Pressure rise rate when the side hole is completely blocked was 242.8±1.8 cm H₂O/sec. The sample rate was 100 Hz.

The propagation velocity of the peristaltic wave was calculated from the distance between the two adjacent openings (0.75 cm) and divided by the delay in arrival time of $P_{\text{max}}$. Compiled data was imported into a spreadsheet program and used to calculate the average $P_{\text{max}}$ in each channel (cm water), the average length (cm) of the pressure wave-peak as well as the average propagation velocity (cm/sec). All values were expressed as both the mean and standard deviation (Fig. 2, Tab. 1). Probability of significance was calculated using an unpaired, two-tailed student’s t-test.

RESULTS
The pressure generated in the various channels during a peristaltic wave reveals a minimal difference between week one and two, except for channels 7 and 8 which record the submucosal segment of the ureter, suggesting that mucosal edema affects pressure measurements (Fig. 2C). No inter-peristaltic
leakage of urine or ureteric dilatation was observed by IVU. Also, at endoscopy efflux of urine into the bladder could only be observed when active contraction of the intramural ureter and urine bolus deposition were occurring. Urine production was $35 \pm 4$ ml/h in group II.

**Pressure studies in the mid-ureter (week 1).** During the second session, in order to prevent any undue or unnecessary injury to the mildly edematous and very fragile submucosal ureter, all instrumentation had to be limited only to a study of the UVJ. The mid-ureter could thus only be studied by us in the first session.

The $P_{\text{max}}$ was $35.7 \pm 1.2$ cm H$_2$O (n=240) in the not previously instrumented mid-ureter. The $P_{\text{max}}$ values in the various individual channels are presented in fig. 2A. The propagation velocity of the peristaltic wave in the mid ureter was $2.1 \pm 1.0$ cm/sec (n=240). The length of the pressure peak averaged $5.9 \pm 1.3$ cm (n=240).

**Pressure studies in the juxtavesical ureter (week 1 and 2).** Maximum pressure ($P_{\text{max}}$) in the juxtavesical ureter was $19.4 \pm 1.3$ cm H$_2$O during the first (n=258) and the second session (n=63). The propagation velocity of the peristaltic wave through the juxtavesical ureter was $2.1 \pm 1.9$ cm/sec (n=172) in the first session and $2.5 \pm 1.8$ cm/sec (n=42) during the second session. The length of the pressure peak was $4.2 \pm 1.8$ cm in the first week (n=688) and $6.8 \pm 2.1$ in the second week (n=168).
Figure 2: $P_{\text{max}}$ recorded at different locations in the mid-ureter (panel A), and the juxtavesical ureter and the UVJ (panel B). The numbers on the X-axis represent the consecutive channel openings, with channel 1 being the most proximal. Each channel in panel A is located 10 cm more proximally in the ureter than the same channel in panel B. Error bars represent standard error of the mean (SEM) to visualize the significance. $P_{\text{max}}$ decreases from proximal to distal ($P < 0.05$) at the UVJ level. The pressure gradient in the submucosal ureter reveals an increase after manipulation ($P < 0.05$). Panel C represents the propagation velocity (cm/sec) and length of pressure peak (cm) of a peristaltic wave in the ureter and the UVJ ($P > 0.05$ in both). Light grey (panel A): mid-ureter, white (panel B): Juxtavesical and UVJ in week 1, Black (panel B): Juxtavesical and UVJ in week 2.
**Pressure studies in the UVJ (week 1 and 2).** $P_{\text{max}}$ in the submucosal ureteric segment was $6.2 \pm 1.0 \text{ cm H}_2\text{O}$ during the first ($n=172$) and $13.3 \pm 1.2 \text{ cm H}_2\text{O}$ ($n=42$, $P<0.001$) during the second session (fig 2B). This significant rise in $P_{\text{max}}$ in the submucosal segment a week after the previous manipulation is accompanied by a decline in peristaltic frequency (fig 2B and Tab 1). This finding is probably attributable to the resultant mild edema. The significantly higher $P_{\text{max}}$ recorded in the transmural traject may be due to the backing provided by the detrusor to the longitudinally contracting ureteric muscle at this level\(^2\). The propagation velocity of the peristaltic wave through the UVJ was $2.3 \pm 1.9 \text{ cm/sec}$ ($n=172$) in the first session and $2.6 \pm 1.9 \text{ cm/sec}$ ($n=42$, $P=0.58$) in the second session. In the first week ($n=688$) the length of the pressure peak was $5.2 \pm 2.8 \text{ cm}$ and was $7.0 \pm 2.4 \text{ cm}$ in the second week ($n=168$, $P=0.06$, Fig. 2C).

**DISCUSSION**

Ureteric peristalsis is primarily myogenic in origin\(^7\)-\(^8\). The exact role of neuro-humoral mechanisms in ureteric peristalsis is controversial. A plethora of nerve types, including adrenergic, cholinergic, nitrergic, vasoactive intestinal peptide, neuropeptide Y, calcitonin-gene related peptide nerves, have been identified in the ureter and the surrounding ganglion cells, but their exact function still needs to be defined\(^9\)-\(^10\). They are believed to have a modulatory influence on ureteric peristalsis. The influence of these neuro-humoral agents has for the purposes of this study been excluded.

The upper urinary tract in the pig is similar to that of the human. During peristalsis, $P_{\text{max}}$ is 20-30 cm H$_2$O *in vivo* in humans\(^11\) and in the pig. The hydration state of the pigs was maintained as normal as possible to mimic normal ureteric physiology. The flow measured in the ureter (0.30 ml/min) guarantees normal ureteric peristaltic activity\(^1\),\(^12\). Under these circumstances, an approx. 5 cm zone of elevated pressure was recorded passing from the proximal to the distal ureter during peristalsis. This zone of elevated pressure must be responsible for unidirectional transport of urinary bolus through the ureter in a normodiuretic state. $P_{\text{max}}$ decreases gradually from the mid-ureter to the UVJ but remains sufficiently high (ca 20 H$_2$O) at the UVJ for approx. 5 sec during bolus deposition in bladder. This would prevent reflux occurring during the filling phase of the bladder. Previous endoscopic manipulation also results in local edema and $P_{\text{max}}$ rise in the submucosal ureter segment.

The underlying principle of our measurements is that the pressure in a constant perfusion flow system is a measure of obstruction to outflow from
the surrounding tissue. During the passage of a peristaltic wave over a side-hole, the pressure required to perfuse the corresponding channel will thus increase. Perfusion manometry is a reliable method to measure pressure changes, but a valid criticism of our findings could be that it does cause volume load (0.6 ml/min.), which may trigger peristalsis and/or secondary ureteric dilatation\textsuperscript{7,13}. We therefore undertook at regular intervals ultrasound control of the upper tract, and detected no evidence of dilatation. Another criticism could be that the catheter diameter (cross sectional area (CSA): 3 mm\textsuperscript{2}) and its stiffness may act as negative influences. As no reference in the literature exists, we earlier calibrated the internal circumference of ureters of pigs $\geq$50 kg and found it to be ca 20F (CSA: 32 mm\textsuperscript{2}). The relative obstruction caused by our catheter would not be therefore more than 10\%. A stationary catheter would also compensate for the negative effects of stiffness.

We compared the results of perfusion manometry, electromyography, and ultrasonography during ureteric peristalsis and these results are presented in Table 1.

<table>
<thead>
<tr>
<th>Experimental session</th>
<th>EMG</th>
<th>PRESS</th>
<th>ELUS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Velocity cm/sec</td>
<td>Duration Sec</td>
<td>Length of pressure peak cm</td>
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<tr>
<td>Mid-ureter week 1</td>
<td>---</td>
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<td>2.1±1.0</td>
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<td>UVJ, week 1</td>
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<td>4.8±1.8*</td>
<td>9.6±1.2</td>
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<td>UVJ, week 2</td>
<td>2.5±1.9</td>
<td>4.0±1.7*</td>
<td>10.0±1.3</td>
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</table>

Table 1: Comparison of ureteric peristalsis as measured by perfusion manometry, electromyography, and ultrasonography. Asterisks represent a significance of $<$ 0.05 between the excitation, contraction and the pressure data. EMG: electromyography; ELUS: endoluminal ultrasonography. Data from refs. 3, 4 and present study as mean± SD.

The propagation velocity of a peristaltic wave measured by manometry and EMG are similar (2-2.5 cm/sec). Duration of a ureteric peristaltic contraction at any particular location in the mid and distal ureter is approximately 6.5 sec as measured by ELUS, 4.5 sec as measured by EMG and only 2.8 sec as measured by perfusion manometry\textsuperscript{4-5}. These differences are significant (p<$<$0.05), but can be explained as the inherent difference in the physical properties being measured by these different modalities. ELUS time is longest as it also includes the relaxation period of the ureteric muscle. The EMG data in contrast express only the period of ureteric excitation and
can be identified thus as a sharp and easily detectable deviation from the baseline. We included in our measurements pressure curves only after they had risen to and before they had declined to 5% of $P_{\text{max}}$. A further reason for the relatively short pressure signal seen is that the sensitivity of our measurement is further compromised by the intrinsic resting ureteric pressure. Our findings also interestingly reveal that a peristaltic wave in the (juxtavesical) ureter has a duration of approx. 3 sec, during which an approx. 10 cm ureteric segment is electrically active, but only an approx. 5 cm long segment thereof, is sufficiently contracted to enable a pressure rise of approx. 20 cm H$_2$O to be recorded. In our study, peristaltic frequency was approx. 1 wave/min. This low frequency rate, together with the low diuresis (<1 ml/min/ kidney), indicates that the intraluminal flow in the ureter under normodiuretic condition is mainly controlled by ureteric peristalsis.

The maximal number of stable contraction rings in the ureter due to peristalsis is calculated by dividing the length of the ureter (30 cm) by the average length of the pressure peak (5 cm). Thus, maximally 6 contraction rings can be present at any given time. A direct relationship between resistance to flow and peristaltic frequency has been observed in the porcine ureter. An increased number of contracted rings due to peristalsis prevent reflux by increasing resistance of intraluminal flow. A passive anti-reflux mechanism which is established using hydrostatic compression of the diagonal submucosal tract of the ureter cannot theoretically protect the UUT when the ureteric orifice is open to deposit the bolus into the bladder cavity. A contracted ureteric ring just proximal from the orifice at the juxtavesical level is the only relevant anti-reflux mechanism at such a crucial moment of urine transport.

**CONCLUSIONS**

The continued presence of a sufficient pressure gradient from the middle ureter and juxtavesical segments to the ureteric orifice is actively preserved by the contractile function of the ureteric muscle wall. Together they are responsible for unidirectional urinary bolus transport and form also the "active" component of an anti-reflux mechanism.

A ureteric peristaltic wave travels at approx. 2 cm/sec and is approx. 6 cm long. $P_{\text{max}}$ in the lumen of the ureter decreases from proximal to distal ends (mid-ureter: 36 cm H$_2$O, Juxtavesical and transmural: 19 cm H$_2$O and submucosal: 6 cm H$_2$O), but always remains sufficiently high at the ureterovesical junction (UVJ) to prevent retrograde urine leakage from the bladder.
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REFERENCES