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CHAPTER 5

AN IN VIVO ENDOLUMINAL ULTRASONOGRAPHIC STUDY OF PERISTALTIC ACTIVITY IN THE DISTAL PORCINE URETER

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ABSTRACT

**Purpose:** Experiments were performed to quantify the duration and frequency of ureteric peristaltic activity in the laparotomized and non-laparotomized pig in its virgin and post-instrumented states.

**Materials and Methods:** Pigs (n=10) in a steady state of hydration were studied under halothane anesthesia in two groups. The study was undertaken in two separate sessions at a week’s interval. In group I laparotomy and vesicotomy were undertaken to obtain ELUS images. In group II, peristalsis was studied using an ELUS probe introduced through the working channel of a 22F rigid cystoscope. Peristalsis was visualized as a periodic diameter-change of ureter and recorded (for approx. 30 minutes) on videotape after an initial period of adaptation of approx. 30 minutes.

**Results:** The ureter acts like a pump discharging urine into the bladder through peristaltic activity. ELUS imaging of ureteric peristalsis correlated well with “eyeballing” of the passage of peristalsis through a ureter (group I). The shortest peristaltic activity in group I was 6.0±2.0 sec in the non-instrumented- and 5.1±1.4 sec in the instrumented ureter. In group II it was 6.8±1.5 sec in the non-instrumented- and 6.4±1.5 sec in the instrumented ureter. Chronic dilatation of ureter led to decrease in peristalsis frequency. Interestingly, acute dilatation caused an increase in ureteric peristalsis frequency.

**Conclusion:** Ureteric peristalsis acts as a pump discharging urinary boluses (intraluminal fluid load) unidirectionally into the bladder. ELUS provides us an opportunity to quantify and study ureteric peristalsis.
INTRODUCTION

Urine produced in the kidney accumulates only temporarily in the renal pelvis. It is transported by periodic ureteric peristaltic activity towards the bladder. The ureter is a small caliber muscular tube connecting the low-pressure renal pelvis to the bladder cavity where pressures can alter rapidly and over a wide range depending on the micturation cycle. Transportation of urine is essentially unidirectional. Reflux of urine from the bladder into the upper tract (ureter, renal pelvis or collecting system of the kidney) is by definition a pathological entity and can lead to damage of renal function. This may in time lead to chronic renal failure and hypertension. Upper urinary tract infection or bacteriuria in combination with intra-renal reflux is especially harmful to the growing kidney of children.

The ureterovesical junction (UVJ), the distal most portion of the ureter, which traverses the posterior bladder wall to reach its termination at the ureteric orifice in the bladder lumen, has the important function of prevention of vesico-ureteric reflux (VUR). The diagonal passage of the ureter through the bladder wall and especially the length of the submucosal segment are believed to play an important role in this “passive” valvular function of the UVJ. An “active” valvular component has often been considered in the literature, but was never established with certainty.

At first, we studied systematically the functional anatomy of the porcine and subsequently the human UVJ using enzyme-histochemical techniques to visualize the acetylcholinesterase (AChE) and butyryl cholinesterase (BChE, non-specific cholinesterase) activity of its different muscular constituents. We further studied serial EndoLuminal UltraSonographic (ELUS) images obtained from the UVJ of human cadavers to evaluate and establish the correlation between histology and ELUS images at this level of resolution. On the basis of our studies we postulated a dual role for distal ureteric peristalsis. The first function is to assist in depositing the urinary bolus into the bladder lumen. The second and equally important role is to provide the “active” anti-reflux mechanism.

To test the validity of this hypothesis of the dynamic anti-reflux mechanism we studied ureteric excitation, peristaltic contractions and pressure generation in the pig ureter using electromyography (EMG), endoluminal ultrasonography (ELUS) and Segmental ManoProfilometry (SMP) respectively. Since the pig is a suitable animal model for studying UVJ morphology, we anticipate that data obtained from these animal model studies could also be valid in humans. In the current article ureteric contraction, patterns and the effect of ureteric dilatation on peristalsis in the
distal porcine ureter as studied by ELUS are reported and discussed. The regulation and quantification of ureteric motor activity is a less well-known and relatively unexplored area of upper tract pathophysiology.

Several different receptors have been identified in the upper tract$^{3-5}$. They include $\alpha$ and $\beta$ adrenergic, cholinergic (muscarine: M3, M1, M2), and recently NeuroPeptide Y (NPY), Vasoactive Intestinal Peptide (VIP), Nitric Oxide (NO) as well as Tyrosine Hydroxylase (TH), but the exact mode of action of these receptors has still to be identified by further pharmacological modulation studies. The technique of smooth muscle EMG, ELUS and SMP are valuable tools enabling us to obtain insights into disorders of motility in the upper tract. Our current study is concerned with the application of ELUS in studying ureteric peristalsis.

MATERIALS AND METHODS
The animal model used and the anesthetic procedure. Ten female New Yorkshire pigs were studied in two separate groups. In group I ($n=5$, $55\pm3$ kg) sequential VHS recordings of ureteric peristalsis activity by endoluminal ultrasonography were obtained via a lower abdominal laparotomy using an 8F, 20 MHz CVIS® catheter. In group II ($n=5$, $75\pm7$ kg) ELUS recordings were made using the same catheter, via the minimally invasive endoluminal approach. Only a light general anesthetic was administered and maintained with the corneal reflex intact at all times. This was undertaken so that optimal muscular activity during measurements was present. As pre-medication 20 mg Azaperon and 150 mg Ketamine hydrochloride per 10 kg body weight and 1 mg Atropine were administered. General anesthesia was induced using 5% Halothane and a mixture of 50% N2O and 50% O2. Anesthesia was maintained using 1% Halothane (1 MAC: Minimal Alveolar Concentration) and the above mentioned mixture of O2 and N2O. As analgesic 1 mg Sufentanil citrate IV was administered only in group I and at least 2 hours before registration of the recordings was undertaken. Peri- and postoperative antibiotic cover was administered using Augmentine (1200 mg) and Enrofloxacine (25mg/ 10kg body weight/ day), respectively. An NSAID (Fynadine) was sufficient as postoperative analgesic until the next measurement session. The experiments took place in 3.5 to 4 hours. Hydration was maintained in group I by infusing $8.7\pm0.2$ ml/kg/h of physiologic saline solution and $6.1\pm0.1$ ml/kg/h in group II. This infusion rate was required because the animal was fasting for more than 12 hours and they were thus ca. 1250 ml negative in its water homeostasis. Furthermore,
general anesthesia also produces a drop in blood pressure\textsuperscript{20-21}. During the experiments an infusion rate of ca. 1900 ml and ca. 1400 ml of physiologic saline, respectively, was used in group I and II. This infusion regime was adopted to compensate for the negative water homeostasis and the insensible loss during laparotomy and to maintain an optimal circulation. Despite the high infusion rate, urine produced was still macroscopically concentrated. Continuous monitoring of blood pressure, electrocardiographic and pulmonographic parameters was maintained during the whole procedure to ensure optimal metabolic functioning.

Each animal was studied in two separate sessions at a week’s interval. In the first week, the peristaltic activity of the un-instrumented ureter was studied and in the second week, measurements were undertaken to study the effects of prior ureteric instrumentation on ureteric peristalsis.

\textit{ELUS measurements and data analysis}. After 30 minutes of adaptation time for the ureter to the presence of the endoluminal catheter, continuous recording of ureteric activity was started using a super-VHS video recorder. The recording was undertaken for approx. 30 minutes in the juxtavesical ureteric segment at a length of approx. 5 cm from the ureteric orifice. In group I the ELUS catheter was positioned manually under direct vision and in group II endoscopically using a rigid 22F cystoscope. External fixation of the catheter was undertaken to minimize movement artifacts. Flushing of the space between the core and the body of the catheter was undertaken incidentally using warm (37\textdegree{}C) physiological saline solution to stabilize the ELUS imaging. “Pie-slice shaped” artifacts caused by non-uniform rotation of the catheter core, were minimized by minor displacement of the catheter manually until satisfactory imaging was obtained. The duration of peristaltic activity was recorded on tape and the presence and degree of ureteric dilatation were also established. The frequency of peristaltic activity is measured as n/min. Analysis of the data was undertaken using a spreadsheet program (Exel 7.0) run on a 586, IBM compatible PC.

\textbf{RESULTS}
Halothane probably decreases peristaltic activity in the pig\textsuperscript{6}. It would therefore be reasonable to assume that under normal physiological conditions, ureteric peristaltic activity would be more frequent and of longer duration than that recorded by us.
Group I (study of ureteric peristalsis in the laparotomized pig). Retrograde introduction of ELUS catheter was undertaken manually under visual control. An open procedure was undertaken to enable us to first study the ELUS images under direct optical control of peristaltic activity. Peristaltic waves could be observed simultaneously by “eyeballing” the passage of a wave through the ureter by one observer and observing it on the ELUS images as a dynamic change of ureteric diameter by the second. Subsequent discharge of urinary bolus through the ureteric orifice was also visually observed and noted. A total of 54 and 124 individual peristaltic events in the normal non-instrumented and in the post-instrumented ureter were recorded and subsequently analyzed. The duration of peristaltic activity even in the normal non-instrumented ureter varies in range. A frequency distribution analysis of the duration of individual peristaltic activity was performed (Figure 1).
Figure 1: The frequency distribution analysis of peristaltic activity of the ureter in the non-instrumented (solid line, n=54) and instrumented ureter (broken line, n=124) in a laparotomized pig, reveals that the majority of signals take place at ca. 6 sec.

The average duration of the shortest peristaltic activity is 6.0±2.0 (average±SD) in the non-instrumented ureter and 5.1±1.4 sec (average±SD) in the post-instrumented ureter respectively (Figure 2). The frequency of peristalsis in the normal ureters decreases from 1.4±0.6 min⁻¹, (average±SD, range: 0.5-1.8 min⁻¹) to 0.3±0.1 min⁻¹, (average±SD, range: 0.2-0.3 min⁻¹) in the dilated post-instrumented ureters (Figure 3).

Group II (study of ureteric peristalsis in the pig using an endoscopic approach). Through the working channel of a rigid 22F cystoscope, the ELUS catheter is introduced and the other channel is used to empty the bladder continuously. A total number of 147 and 106 individual peristaltic activities were recorded and subsequently analyzed in the non-instrumented and the post-instrumented ureter, respectively. The duration of these activities differed, as is also the case in laparotomized animals. The frequency distribution analysis of the duration of individual peristaltic activity in the non-instrumented and post-instrumented ureter is revealed in figure 4.
Figure 2: The duration of shortest ureteric peristaltic activity did not vary significantly in different studied groups.

The average duration of the shortest peristaltic activity was 6.8±1.5 sec (average±SD) in the non-instrumented ureter and 6.4±1.5 sec (average±SD) in the post-instrumented ureter (Figure 2). The frequency of the peristalsis in the normal non-instrumented and the dilated ureter after instrumentation showed that the peristaltic frequency decreased by a factor 2 from 0.9±0.1 min⁻¹, (average±SD, range: 0.8-1.0 min⁻¹) to 0.5±0.3 min⁻¹, (average±SD, range: 0.2-1.0 min⁻¹) (Figure 3).
Figure 3: The failure of ureteric peristalsis in a chronically dilated ureter manifests itself as hypo-peristalsis compared to normal peristalsis in the same ureter. Reduction of peristaltic activity is less obvious in non-laparotomized animal, possibly due to the absence of co-morbidity of laparotomy.

_Acute dilatation of the ureter and frequency of peristaltic activity._ During our studies in the laparotomized as well as the non-laparotomized pigs, we observed an acute dilatation (n=8, $\varnothing = 6.3\pm2.2$ mm) occurring. Acute dilatation is defined as ureteric dilatation observed in the first experimental session. Chronic dilatation was observed during the second experimental session. The degree of dilatation was not accurately measurable by ELUS. If the ELUS probe is not co-axial with the ureter, it scans different ellipse, which is highly inaccurate. That is why we only looked at the presence or absence of ureteric dilatation. Acute dilatation is an effect of instrumental trauma which is also observed macroscopically only in this group. Interestingly is the finding that the frequency of peristaltic activity in these dilated ureters was higher than that of normal ureters.
Figure 4: Same distribution as visualized in Figure 1 is seen in a non-laparotomized pig. The two curves i.e. post-instrumented (broken line, n=106) and the non-instrumented (solid line, n=147) measurement seems to be identical.

It was $1.0 \pm 0.7 \text{ min}^{-1}$ (average$\pm$SD, range: $0.3-1.7 \text{ min}^{-1}$) and $0.7 \pm 0.5 \text{ min}^{-1}$ (average$\pm$SD, range: $0.3-1.2 \text{ min}^{-1}$) respectively. This finding in our opinion demonstrates that acute dilatation of the ureter results in hyper-peristalsis in an attempt to discharge the same fluid load as before from the ureteric lumen (Figure 5). However, the terminology of hyper- or hypo-peristalsis is difficult to define in absolute terms, as no normal values are available. We use the word hyper-peristalsis thus to mean an increase of peristaltic frequency in the acutely dilated ureter after instrumentation as compared to its normal undilated state. It would seem that increase of peristaltic frequency is related to acute dilatation of the ureter (Figure 6)\textsuperscript{19}.

DISCUSSION
The anatomical substrate of the UVJ as observed by us, suggests the following model of anti-reflux ureteric peristalsis activity in its distal portion. The urine bolus is transported by ureteric peristaltic from the renal pelvis and arrives in the ureteric lumen at the UVJ level. Because of its anatomical structure, the ureter can only shorten its length at this terminal trans-vesical trajectory. Thus, while contracting longitudinally the ureter is simultaneously able to slide freely within its detrusor wall tunnel and actively retracts the ureteric wall over the urinary bolus, thereby discharging it into the bladder.
Chapter 5: ELUS study of peristaltic activity

lumen. At the same time when the ureteric orifice is pulled wide open and no passive anti-reflux mechanism can function, the ureteric constriction initiating the discharge into the bladder lumen still present in the juxtavesical region, preventing thereby retrograde upstream urinary leakage. Further distal immigration of the ureteric “contraction wave” into the superficial trigone, now re-establishes the passive anti-reflux mechanism through an active lengthening of the submucosal ureteric length.

\[ \text{Ureteric peristaltic frequency (min}^{-1}\text{) in normal and the dilated ureter in virgin ureter} \]

![Graph showing ureteric peristaltic frequency](image)

**Figure 5:** Acute dilatation of the ureter causes increased peristalsis. This effect is temporary and should be considered as a compensatory mechanism of the ureter enabling it to discharge an increased urine volume load.

**ELUS and upper urinary tract urodynamics: historical considerations.** Davis (1954) suggested the term “urodynamics” to describe the physiological changes occurring in the urinary tract during urine transport\(^7\). Manometric studies in the urinary tract were undertaken to establish and understand urodynamic principles\(^7\text{-}^{10}\). The intraluminal pressure generated by peristalsis is not only dependent on ureteric contraction but also on compliance of the ureter wall. Thus the visualization of peristalsis as a parameter for the study of bolus volume was necessary. Campbell (1966) used the cinefluorographic technique to investigate ureteric peristalsis in normal individuals\(^11\). He defended the idea that the length of the “ureteric cone” (i.e. the cinefluorographic imaging of the urinary bolus) is dependent on: 1. the state of hydration and 2. the state of diuresis of the individual. The length of ureteric cone in the cinefluorographic studies is comparable to the duration of the urinary bolus in our study. We measured the duration of the
bolus as a function of its volume (the bigger, the longer in time). Our observation in a single pig ureter under a steady state of diuresis reveals however that the duration of passage of the peristaltic waves as observed by endoluminal ultrasound is not constant.

Ultrasonography has been used extensively as an imaging technique to visualize the urinary tract. A disadvantage of this modality as mentioned by Amis and co-workers (1982) is that ultrasonography reveals only morphology and no functional studies could initially be undertaken. Keller and co-workers (1993) have however reported a functional study of ureteric peristalsis in children with ureterectasis. They observed ureteric peristalsis in the proximal ureter during a period of one minute each time, using conventional ultrasonography and concluded that the coexistence of peristalsis in a dilated ureter correlate well with the presence of vesico-ureteric reflux. The disappearance of peristalsis was observed in patients with the severe obstruction or poor renal function. The method used by them was unable to quantify the peristaltic parameters i.e. frequency and duration of passage of the individual urinary bolus.

The first urological application of endoultrasonography was undertaken by Watanabe and co-workers (1968) to evaluate the prostatic tissue using a rigid trans-rectal transducer. In the late eighties, the first miniature flexible ELUS probes were designed for vascular use. These probes enable one to visualize a 360° cross-sectional real time image of a tubular structure. They have the potential to be useful not only for a study of morphological parameters but also for an evaluation of functional parameters. Our earlier experience in the human cadaver and the pig were sufficiently encouraging to use the endoluminal technique to visualize peristaltic contractions of the ureter in order to quantify the duration of contraction and its frequency in the presence or absence of ureteric dilatation.

**ELUS and ureteric urine flow: bio-physical considerations.** Griffiths and Notscheale have reported that ureteric peristalsis transports urine from the renal pelvis in the form of urinary boluses. When diuresis increases, the separate boluses first touch each other to form “kissing boluses” and then merge into adjacent ones to finally form an open tube flow. During these changes from an isolated bolus flow to the open tube one, the ureteric resistance decreases. The ureter in this latter state will be vulnerable to reflux, as well as higher intraluminal pressure and dilatation. They defined the “intrinsic peristalsis carrying capacity” of the ureter as the upper safe
limit of isolated bolus flow rate through the ureter during peristalsis\textsuperscript{16-17}. Our measurements using the ELUS imaging technique were undertaken well below this limit. Ureteric peristalsis can therefore be seen as a dynamic wave of transfer of increased ureteric wall tension from the cranial to caudal end of a ureter segment under observation.

It is known from the literature that ureteric flow velocity is approximately 2 cm/sec, and the Reynolds number is low (<100). The flow is thus laminar in character\textsuperscript{10,16}. This finding implies that below the “intrinsic peristalsis carrying capacity” of the ureter, the ureteric resistance to flow increases with increasing peristaltic frequency resulting to better protection against urinary back-flow. This may well be the underlying reason why the frequency of peristalsis rises during acute dilatation (figure 5). Acute dilatation leads to a stretching of the ureteric smooth muscle, which in turn results in hyper-peristalsis\textsuperscript{18,19}. When a ureter is still able to discharge its “excess” intraluminal fluid volume “normal” peristaltic activity can be restored. However, beyond a certain point of peristaltic frequency, the ureteric pump function fails leading to a chronic state of ureteric volume load. This has been observed by us in some ureters (figure 6).

Another reason, which can be ascribed for this failure of the ureteric pump one week after initial instrumentation, would be edema and bacterial growth (in spite of antibiotic cover) and the resulting negative chrono- and inotropic effects.
Figure 6: Relationship between ureteric peristaltic frequency and ureteric diameter in the acute dilatation group of ureters based on observations by endoluminal ultrasonography. An increase in ureteric peristaltic frequency accompanies ureteric dilatation up to a point only. Further ureteric dilatation affects the ureteric peristalsis negatively.

Disadvantages of ELUS in the study of ureteric motility. The use of ELUS gives us stable real time ultrasonographic images and thus an opportunity to study ureteric motility in a reliable manner. The degree of dilatation can be measured and the presence of edema can be evaluated. But it has, of course, its own limitations and disadvantages. The introduction of the catheter is still an invasive procedure in spite of it being minimal. Analysis of the motility data is time-consuming and an inter-investigator variability might exist. Some of these limitations (inter-investigator variability and time factor) can be solved by standardization of catheters and the software from a urological standpoint. This would require time and co-operation from industry and the bio-engineers.

CONCLUSION
Our results support the idea that the ureteric peristalsis acts as a pump to discharge urinary boluses (intraluminal fluid load) distally into the bladder. The halothane anesthesia used by us has a negative ino- and chronotrope effect and this must be taken into account when interpreting the present results. ELUS offers an opportunity to quantify and study ureteric peristalsis. Future pharmacological modulation in chronically instrumented animals with temporarily implanted measurement registration devices is necessary to further evaluate the findings of our acute study.
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