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The effect of ureteral distension on peristalsis*

Studies on human and sheep ureters

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Summary. Isolated sheep and human ureteral preparations (from patients with bilharzia) were subjected in-vitro to graded elongation and the effect on tension and spontaneous peristaltic frequency was assessed. Sheep specimens were obtained from three locations: the intra- and extrarenal portion of the pelvis and distal ureter. Elongation (stretch) induced an increase in spontaneous frequency only in pelvic ureteric specimens, but not in the distal ureter. Basal tension increased exponentially with stretch and most markedly in the distal sheep ureter and also in human preparations. Active tension (amplitude of phasic contractions) increased with stretch in specimens from all locations and reached a maximum at 110-115% elongation. These data suggest that acute distension of the ureter increases frequency of peristalsic waves only in the intrarenal parts of the ureter. Acute obstruction in renal colic can induce hypermotility in terms of increased frequency and force of contraction.

Key words: Ureteral motility - Renal pelvis - Ureter - Ureteral obstruction - Spastic contractions - Renal calculus

Introduction

The term spasm in connection with ureteral colic is not well defined. Does acute obstruction of urinary flow by a calculus give rise to hypermotility above the block and if so, does this apply to the rate or amplitude of phasic contractions or both? How do different parts of the upper urinary tract respond to distension? The question of stretch-induced contractions obviously has implications for the pathophysiology of impacted ureteral calculi and the treatment of renal colic. Some of these aspects have been investigated by recording in-vivo pressure and diameter changes in dog experiments [11, 12]. Weiss et al. [14] performed length-tension studies on isolated cat ureteral preparations with electrical stimulation, and found that active tension progressively increased with stretch up to a maximum and then declined. This study, however, did not analyse the effect of distension on spontaneous frequency of ureteral contractions.

The present study was undertaken in order to clarify some of the basic changes of ureteral motility that occur with distension in different parts of the upper urinary tract by using model experiments with isolated human and sheep ureteral preparations.

Material and methods

The samples used in this study consisted of human and sheep preparations: eleven rings of ureters removed at surgery from 4 patients with bilharzia (urogenital schistosomiasis). The rings were immediately put into chilled Krebs-Henseleit solution and transferred to the laboratory where they were cut into circumferential strips of a standard length of 10 × 2 mm and mounted in an organ bath for recording isometric tension. Specimens were also obtained from 28 sheep in the local abbatoire immediately after slaughter; the ureters being removed with the kidneys en block and transported to the laboratory in thermos flasks containing chilled Krebs Henseleit solution. The sheep were castrated male Australian Merino weighing 30-37 kg. The ureters were dissected free of connective tissue and fat and 4-mm long rings were cut from the pelvic and distal parts. In addition, 5-mm long strips were obtained from the intrarenal extension, the calyces. Details of the location of the specimens are shown in Fig. 1. The preparations were suspended vertically in 10 ml organ baths filled with Krebs-Henseleit solution, maintained at 37°C and gassed with 95% oxygen and 5% carbon dioxide. The specimens were attached to the bottom of the organ bath and the upper end connected to a Bioscience UF-1 force transducer. Isometric tension was continuously recorded on a Lectromed MX216 two-channel recorder. After suspension the preparation was allowed to hang absolutely slack. At this basal length resting tension is zero. The length of the preparation was obtained by visual estimation of the

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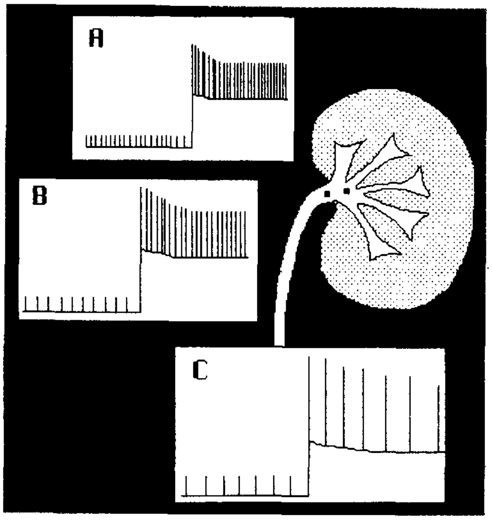

Fig. 1A–C. Origin of ureteral specimens in sheep experiments: **A** intrarenal part of pelvis, **B** pelvis at junction with ureter, **C** distal ureter, 10-15 cm from kidney. Also shown is type of rhythmic peristaltic activity in isolated specimens from the different parts of the upper urinary tract. Model tracing shows spontaneous rhythmic activity before and after stretch. Note difference in starting frequency and change of amplitude and rate of phasic contractions

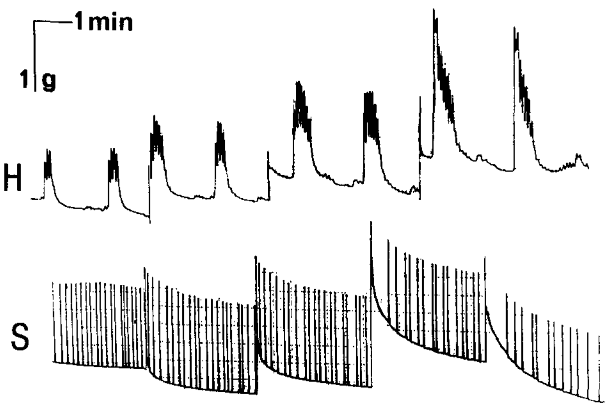

Fig. 2. Tracings of phasic rhythmic contractions of ureteral specimens and the effect of graded elongation. *Upper panel* (H): human specimen from patient with ureteral bilharzia. Note: bursts "primary" (large amplitude) and "secondary" (small amplitude) peristaltic contractions. *Lower panel* (s): sheep specimen. Note: marked stress-relaxation

distance between the ligatures of the strip or ring using a translucent plastic ruler placed at the outside the organ bath, adjacent to the preparation. After an interval of 10–30 min rhythmic contractions started spontaneously in all sheep preparations whereas contractions had to be initiated by addition of 10^{-7} M PGF_2-alpha in the human specimens. This procedure does not seem to influence frequency or force of contraction, but enables transmission of rhythmic pacemaker activity through coordination of persistalsis [13].

At 5 min intervals the preparation was stretched with increments of 0.5 mm at each step. The elongation was obtained using a graduated micrometer screw which moved the isometric gauge with the attached upper string. This stepwise elongation was continued until amplitude and frequency of rhythmic contractions declined. *Basal tension* is the tension measured after stress relaxation for 5 min and at the end of a phasic contraction. *Active tension* is equal to the amplitude of the phasic contractile wave. The cross-sectional area (CSA) of the preparations was calculated by using the equation that the weight (w) of the muscle is equal to the product of its volume and specific gravity, assuming that volume is the product of area (CSA) and length and a specific gravity of unity:

$$CSA = w/l$$

Chemicals and drugs

Drugs were administered with microsyringes and the doses calculated as molar concentrations of the final bath concentration. The Krebs-Henseleit solution contained (mM): NaCl, 115.3; KCl, 4.6; $CaCl_2$, 2.3; $MgS0_4$, 1.2; $NaHC0_3$, 22.1; KH_2PO_4, 1.1; and glucose 7.8 pH was at 7.4. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was supplied by Upjohn Ltd, Crawley, Sussex, UK.

Statistics

Mean value ± SE of all data are shown. Standard statistical methods were used for calculations of unpaired t-tests. Curve-fitting was done on an IBM PCXT using Energraphics.

Results

After each stepwise stretch of the ureteral preparations there was a curvilinear decay in tension both in the human and sheep preparations as shown in Fig. 2. This

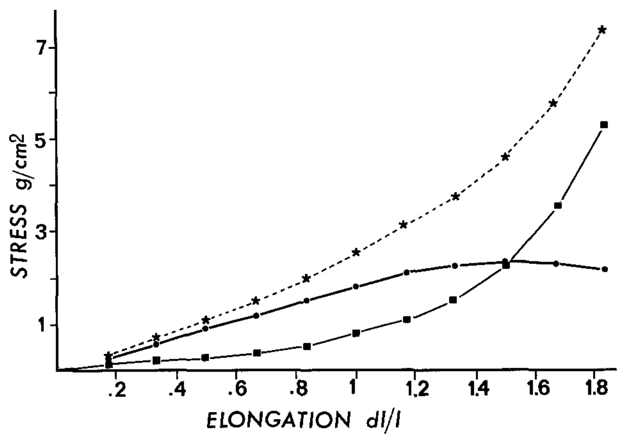

Fig. 3. Strain-stress relationship of spontaneous contractions of the sheep ureter. Diagram shows basal tension, active force of phasic contractile waves and total tension (sum of basal + active tension) in 10 ureteral rings obtained from the extrarenal portion of the pelvis. Strain is expressed as stretch ratio, dl/l. dl is the length of the preparation at any degree of elongation and l is the unloaded in-vitro length

Table 1. Maximum frequency and amplitude of contraction of ureteral motility in relation to per cent elongation for preparations from sheep pelvis, proximal and distal ureter. Human ureteral preparations obtained from patients with bilharzia. Frequency of "primary" waves are included (see Fig. 1). Mean ± SEM

	Frequency (cs/min)	Elongation (%)	Amplitude (g/cm²)	Elongation at 50% stretch (%)	Basal tension g/cm²	N
Pelvis	13.65 ± 0.31	165.00 ± 21.44	10.71 ± 1.57	110.00 ± 7.67	3.42 ± 0.81	10
Proximal ureter	8.62 ± 0.84	95.00 ± 15.53	20.79 ± 3.24	155.00 ± 17.92	2.52[a] ± 0.47	10
Distal ureter	2.50[b] ± 0.27	14.29 ± 3.50	91.21 ± 4.91	122.00 ± 7.02	19.77 ± 3.63	28
Human ureter	1.63 ± 0.32	35.60 ± 4.78	82.12 ± 20.06	52.89 ± 7.94	305.30 ± 53.40	10

[a] Statistical analysis revealed highly significant ($P < 0.001$) differences between parameters of frequency, amplitude and basal tension of sheep data from all locations except between basal tension of pelvis and proximal ureter
[b] No significant change compared to non-stretched preparation

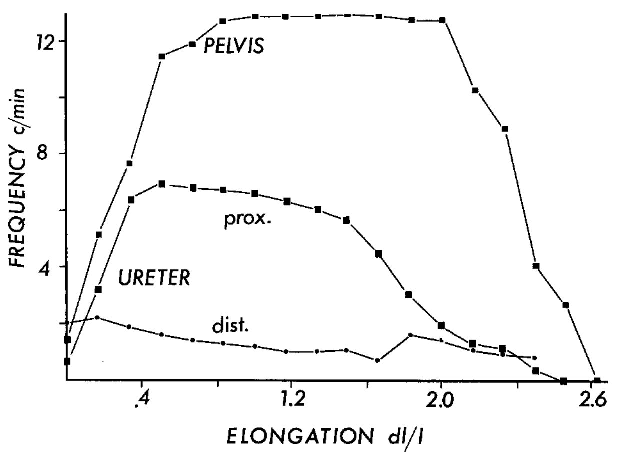

Fig. 4. Strain-frequency relationship of spontaneous contractions of the sheep ureter. Specimens were obtained from the intrarenal (pelvis) and extrarenal portion of the proximal and distal ureter (locations of specimens according to Fig. 1). Note significant increase of peristalsis in the pelvic and proximal ureter, but no significant increase in frequency in the distal specimen

reduction in tension is due to viscoelastic forces of the tissues and known as stress relaxation. In the sheep ureter successive stepwise elongation resulted in a continuous exponential increase in basal tension which was most marked in the distal ureter. Active tension (the amplitude of phasic contractions) increased up to a certain degree of elongation and thereafter declined (cf Fig.3). The maximum amplitude occured at 110–155% of the initial length for sheep preparations from pelvis, proximal and distal ureters as shown in Table 1. The frequency of the rhythmic peristaltic contractions also increased with stepwise elongation up to a maximum plateau and thereafter declined. Only in the distal ureter there was no significant rise of contractile rate (cf. Fig.4).

In the case of the human bilharzial strips the pattern of phasic rhythmic contractions was more complicated than in the sheep preparations. Two types of contractile waves could be distinguished, one of low frequency and high amplitude, here called *primary*, and one of higher frequency and low amplitude superimposed on the primary waves, here designated as *secondary* (cf. Fig. 2). Like in the sheep ureter there was an exponential but much higher increase in basal tension and the amplitude of both types of contraction increased with successive stretch, but without showing a distinctive maximum (cf.Table 1). With further elongation the frequency of the primary and secondary contractile waves showed successive reduction.

Discussion

The present experiments demonstrate that contracting smooth muscle of both sheep and human ureters exhibit features characteristic of other muscles when subjected to stretch. These are commonly known as the Frank-Starling mechanism, originally described to characterise the performance of cardiac [3] and smooth muscle [10]. Essentially it implies that contractile force increases with stretch, reaching a maximum at an optimal length and decreasing beyond this point. In our study active tension during spontaneous contraction progressively increased with stretch up to maximum and decreased with further elongation in much the same way as reported for longitudinal elongation of the electrically stimulated guinea pig or rabbit ureter [7, 8]. In the guinea pig studies maximal active tension was obtained at approximately 100–110% elongation of resting length and the active stress (force/transsectional area) was similar to our sheep data [8].

The mechanism responsible for the inotropic mechanism of stretch seems to be related to intracellular mobilisation of Ca^{++}. This has been shown to occur in cardiac fibers where stretch appears to enhance intracellular Ca^{++}-release [6] and a similar mechanism is operating in smooth muscle cells [9].

The frequency response of the distal ureter to stretch with a declining rate of contractions seems to be typical of an area of the urinary tract which does not display the characteristics of the renal pelvis and the pyeloureteric junction. Normally the intrinsic contractile frequency of the pelvis is higher than that in the upper ureter [13] and there is a relative block at the pyeloureteric junction [1]. It has been suggested that coupling or impulse transmission from the pelvic pacemaker in the pyeloureteric junction is favoured by an increase in urine flow or stretch forces [4]. As shown in the present investigation this distension facilitated transmission does not occur in the more distal ureter. Moreover, at a certain stretch (fixed pretension) the frequency of secondary pacemakers declines along the whole length of the ureter (cf. Fig. 1) [13]. Functionally this makes sense, since otherwise local distension such as with a large bolus of urine in high diuresis might set up secondary and retrograde peristaltic waves.

From the point of view of renal colic our results can be interpreted as follows: ureteral obstruction with secondary distension above the block will induce more forceful contractions and an increase in frequency of peristalsis. The mechanically distended part of the ureter where the stone is impacted will also display increased active tension. From the present data it is, however, impossible to deduce if there is an increased non-rhythmic component of basal tone, a type of contracture that could really qualify to be termed "spasm". In order to elucidate this question further it would be necessary to perform repeated studies with inhibition of all active tone, eg. under the influence . of calcium blockers which are known to eliminate both rhythmic and sustained contractions [7].

The choice of human ureteral preparations with bilharzial wall changes was partially prompted by the fact that this material is more freely available in our hospital but it was also the intention to study the peristaltic dynamics of this disease which is characterised by dilated and hypertrophied ureters but without evidence of obstruction. We have previously shown that the peristaltic pattern of the bilharzial ureter is disturbed and displays irregular phasic contraction with intermittent bursts of activity [1]. The present study shows that a stretch induced increase in both frequency and amplitude may occur. The increased chronotropic response to stretch in the 10 distal ureter must be considered. abnormal response and could be the result of an inflammatory reaction. The very high basal tension can be explained on the basis of increased connective tissue elements which reduce distensibility.

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