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ORIGINAL PAPER

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Pressure/cross-sectional area relations in the proximal urethra of healthy males: the time dependent pressure response following forced dilation

Part IV: Results in healthy volunteers

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Abstract The significance of the anatomical location and age on the urethral response to a sudden forced dilation was studied in 30 healthy males aged 23–85 years. The pressure decay after dilation was fitted with a double exponential function of the form: $P_t = P_{equ} + P_\alpha e^{-\frac{t}{\tau_\alpha}} + P_\beta e^{-\frac{t}{\tau_\beta}}$ where P_t is pressure at time t, P_{equ} is equilibrium pressure after dilation, P_α and P_β are pressure decay, and τ_α and τ_β are time constants. The pressure response was highly affected by the location of the measurement, with the maximum values of the pressure components in the high pressure zone and significantly lower values in the prostatic part of the urethra. The variation in pressure thus concurs closely with the density of the striated rhabdosphincter. No significant correlation between age and the pressure components could be demonstrated, whereas the velocity of the pressure decay following dilation proved significantly related to age in all urethral segments. The causal background for this correlation is uncertain, but may be discovered in age dependent changes in the periluminal tissue composition, or in changing neuromuscular activity in these structures.

Keywords Male urethra · Stress-relaxation · Pressure · Cross-sectional area

Introduction

The mechanical behaviour of the male urethra is of fundamental importance for its virtually opportunistic functions of preventing leakage during the storage phase, and serving as a compliant conduit during the voiding phase, as well as a combination of these during ejaculation. The normal physiological integrity of the urethra is highly dependent of an intact neuromuscular function which is actively varied according to the functional status [9, 25, 31]. An active dilation of the tube per se has not been reliably demonstrated, and any opening of the tube is presumed to be caused by 'external' effects, which may be physiological by the ingression of urine or semen, or iatrogenic by the insertion of catheters [5, 17, 19, 25]. The course of dilation may follow one of two extremes: 1) a stress-relaxation in which a sudden forced dilation to the final cross-sectional area is obtained by the instant application of a very high stress, or 2) a creep-relaxation in which a slow dilation to the final cross-sectional area is obtained by the application of a constant stress [4, 11, 27]. Physiologically, urethral dilation probably follows neither of these two extremes, but will take a course which may be considered predominantly stress- or creep-dominated, depending on whether the circumstances are a sudden increase in bladder pressure (e.g. a cough) or a normal micturition/ejaculation. Previous analyses of analogous mechanical properties in the female urethra and a number of other hollow organs have indicated that changes in dynamic mechanical characteristics may coincide with pathological function, but no data concerning the male proximal urethra seem to exist [4, 16, 18, 27].

In the first part of this study [6] the urethral reaction to a sudden forced dilation was studied. It demonstrates that the concurring pressure response could be described by a double exponential function of the form:

$$P_t = P_{equ} + P_\alpha e^{-\frac{t}{\tau_\alpha}} + P_\beta e^{-\frac{t}{\tau_\beta}}$$

where P_t is the pressure at time t after dilation, P_{equ}, P_α, and P_β are constants, and τ_α, and τ_β are time constants. The aim of the present study was to evaluate

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the dynamic properties of the proximal male urethra using this mathematical analysis of the pressure response to forced dilation at rest during the reservoir phase, in order to evaluate variations in the dynamic properties related to the location of measurement and age.

Materials and methods

Thirty-four male volunteers aged 23–85 years (median, 42 years) and without past or present urological complaints participated in the study. Urinalysis (dipstick) and blood tests (haemoglobin, sodium, potassium, and creatinine) were normal in all subjects. Informed consent was obtained and the study was approved by the local ethics committee.

The investigation program, which has been described in detail in the first part of this study [6], included:

1. Evaluation of symptoms of benign prostatic hypertrophy (BPH) by filling in a patient weighted symptom score (DAN-PSS).
2. Transrectal ultrasonography (7 MHz rectalscanner, type 8551, Brüel and Kjær, Denmark) with the calculation of prostatic volume using the formula: volume = 0.52*width*height*length.
3. Urodynamic examination including flowmetry, resting urethral pressure profile (UPP), cystometry, and pressure-flow.

The evaluation of intraurethral pressure and cross-sectional area as related to time was performed using a special probe [6]. This was placed into the urethra with the balloon in the bladder, and the examinations were started after the sensing electrodes had been retracted 5 mm from the bladder neck, and were then repeated for every 5 mm throughout the prostatic urethra until the high pressure zone had been passed. At each measurement, the location the balloon was adjusted to a cross-sectional area of approximately 13 mm^2 and then the urethra was dilated approximately 20 mm^2 at a velocity of approximately 235 mm^2/s using a gravitationally operated pump. After inflation, pressure equilibrium, as indicated by a constant balloon pressure, was awaited before the balloon was deflated.

Anal EMG was registered during all examination procedures using surface electrodes, and recorded simultaneously with cross-sectional area, balloon pressure and bladder pressure on a DISA UROsystem 21F16 2100 (Dantec, Denmark) and analog/digitally converted into a computer.

Handling of data

For each dilation, the pressure tracing from the maximum pressure after dilation (P_{max}) until the equilibrium pressure (P_{equ}) was fitted with an equation of the form:

$$P_t = P_{equ} + P_\alpha e^{-\frac{t}{\tau_\alpha}} + P_\beta e^{-\frac{t}{\tau_\beta}}$$

where P_t is the pressure in the balloon at time t, P_{equ}, P_α, and P_β are constants, and τ_α, and τ_β are time-constants. The elastance (φ) (dP/dCA (cm H_2O/mm^2)) was calculated and divided into two dynamic (φ_α, and φ_β (cm H_2O/mm^2)), and one static (φ_γ (cm H_2O/mm^2)) components [6].

Location of measurements

Due to significant variations in the length of the posterior urethra – defined as the distance from the bladder neck to the site of the maximum pressure determined from the UPP – the location of the measurement sites was expressed in percent of the distance from the bladder neck to the site of the maximum pressure determined from the UPP, and the investigated part of the urethra (0–150%) was divided in five segments, each 30 percent of the length, before the analysis of data [10].

Drop outs

Three volunteers aged 30, 32, and 43 years experienced significant bladder contractions during urethral dilation at the bladder neck level, which caused distal dislocation of the measurement probe. Following reinsertion of the probe, the phenomenon was repeated, therefore these examinations were suspended. One volunteer aged 74 years suffered from bronchitis, which made the curve fitting impossible because of frequent muscular activity due to coughing. These four subjects were excluded from the study.

Transrectal ultrasonography was impossible in two subjects because it was not possible to insert the probe, therefore the prostatic size was determined transabdominally. One subject suffered a cerebral stroke before ultrasound scanning had been performed, and one was unable to void during pressure-flow. These four subjects were included in the study.

Statistics

The number of measurement sites varied between subjects, therefore the observations from each subject were subjected to a cubic spline regression procedure using the Box-Cox power transformation, in order to allow for a comparison between individuals [10]. Homogeneity of variation was obtained by logarithmic transformation. The variation along the urethra was studied using Friedman's test. If this test demonstrated a significant difference between segments, the analysis was extended with a multiple test procedure in order to identify the deviating segment(s) [23]. The correlation with age was analyzed with the Spearman-rank test [23]. Significance was taken as $P < 0.05$, and Bonferroni's method was applied when multiple comparisons were performed [2].

Results

Symptoms, prostatic volume, and urodynamic findings are related to age (Tables 1, 2). The length of the posterior urethra ranged from 2.5 to 6 cm (median, 4 cm), and the number of measurement sites in the individual subjects ranged from 9 to 16. A total of 336 dilations were performed, of which the pressure tracings in 288 (86%) could be fitted with a double exponential function, with a median residual standard deviation (s_{res}) of 1.0 cm H_2O (2.5th and 97.5th percentiles: 0.3 and 3.1 cm H_2O). The remaining 48 (14%) dilations could not be

Table 1. Age, symptom score, and prostatic volume in individual age groups of subjects. Figures given are median and range, or number

Age group (No)	Age (Years)	Symptom score			Prostatic volume (cm^3)
		Total	Symptom	Bother	
I (9)	25 (23–28)	0 (0–1)	1 (1–4)	0 (0–1)	15.3 (11.3–20.6)
II (6)	32 (30–37)	0 (0–2)	1 (0–5)	0 (0–1)	22.5 (13.7–32.6)
III (7)	44 (42–57)	0 (0–5)	4 (0–5)	0 (0–4)	21.2 (13.2–23.9)
IV (8)	71 (64–85)	3 (0–9)	6 (3–9)	3 (0–7)	39.6 (31.9–67.3)

Table 2. Urodynamic findings in individual age groups of subjects. Figures given are median and range, or number

Age group	Uroflow (ml s^{-1})	Voided vol (ml)	Bladder capacity (ml)	Obstructed[a] (No)	Unstable[b] (No)
I	26 (20–37)	307 (155–471)	420 (300–538)	0	0
II	21 (18–30)	290 (198–486)	350 (230–480)	0	0
III	16 (15–25)	190 (160–500)	316 (246–560)	1	0
IV	13 (11–25)	185 (154–360)	292 (185–360)	4	2

[a]According to the criteria given by Abrams and Griffiths [29]
[b]Detrusor contractions exceeding 15 cm H_2O during cystometry

analysed because of the muscular activity of the pelvic floor, or were fitted with simpler mathematical functions.

The elastance components (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) and the time constants (τ_α and τ_β (s)) are related to the location of measurement (Figs 1, 2, 3, 4, 5). All three elastance components demonstrated a significant variation along the urethra ($P < 0.00001$), with the maximum values in the high pressure zone (Table 3). The time constants, on the other hand, showed no significant variation between urethral segments ($P > 0.25$).

The variation in the elastance components (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) and the time constants (τ_α and τ_β (s)) as related to age were separately evaluated for each of the urethral segments. No significant correlation with age could be discovered for φ_α, φ_β, φ_γ or τ_α in any of the urethral segments, however τ_β proved significantly negatively correlated with age in all segments (Table 4).

Discussion

The biomechanical characteristics dealt with in this study were evaluated from integrated time dependent pressure responses generated from the periluminal tissues as a reaction to forced urethral dilation. The measurements were performed under standardized conditions at rest during the reservoir phase using uniform stimuli. The variation along the urethra, therefore,

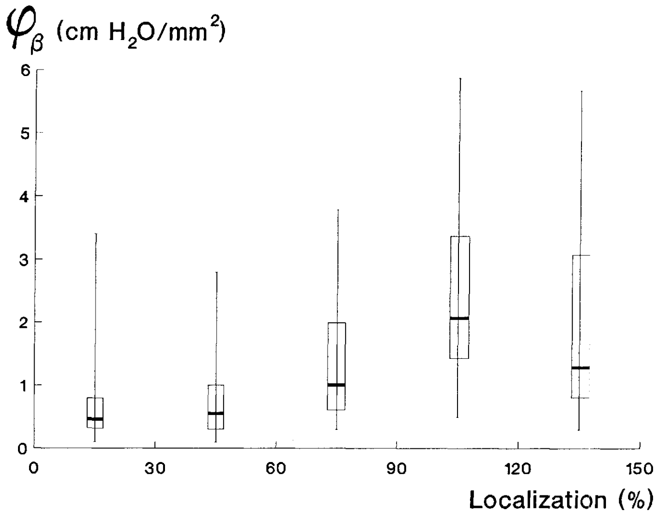

Fig. 2. Elastance component φ_β (cm H_2O/mm^2) related to localization of measurement. Values are determined from the Box-Cox power transformation for each of the five urethral segments. Median, range and quartiles are given

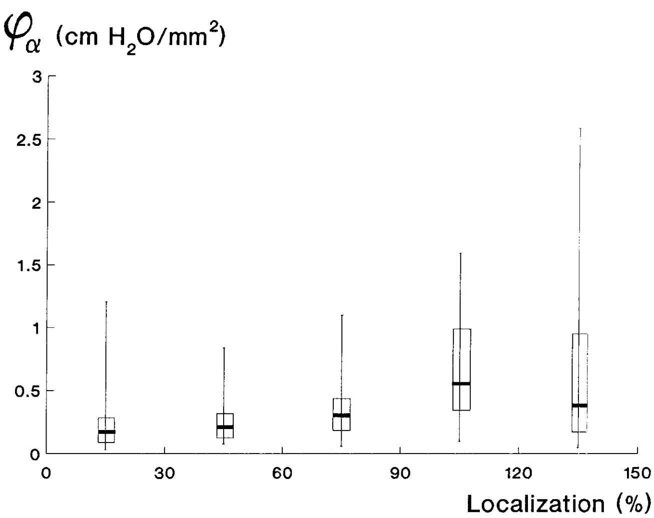

Fig. 1. Elastance component φ_α (cm H_2O/mm^2) related to localization of measurement. Values are determined from the Box-Cox power transformation for each of the five urethral segments. Median, range and quartiles are given

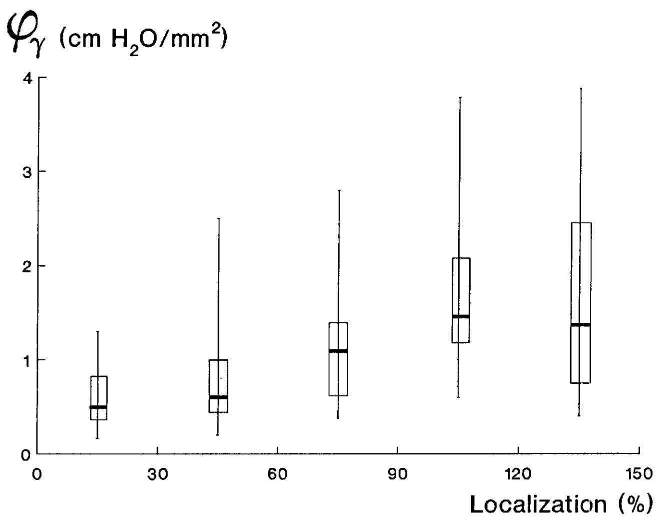

Fig. 3. Elastance component φ_γ (cm H_2O/mm^2) related to localization of measurement. Values are determined from the Box-Cox power transformation for each of the five urethral segments. Median, range and quartiles are given

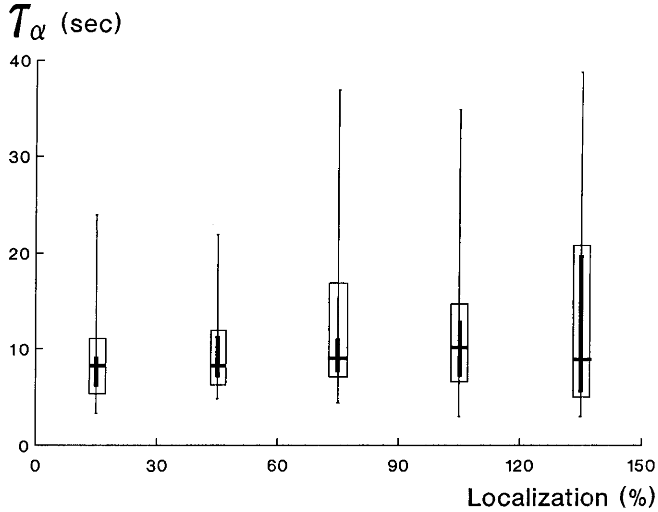

Fig. 4. Time constant τ_α (s) related to localization of measurement. Values are determined from the Box-Cox power transformation for each of the five urethral segments. Median, range and quartiles, as well as 95% confidence limits of the median (*vertical bar*) are given

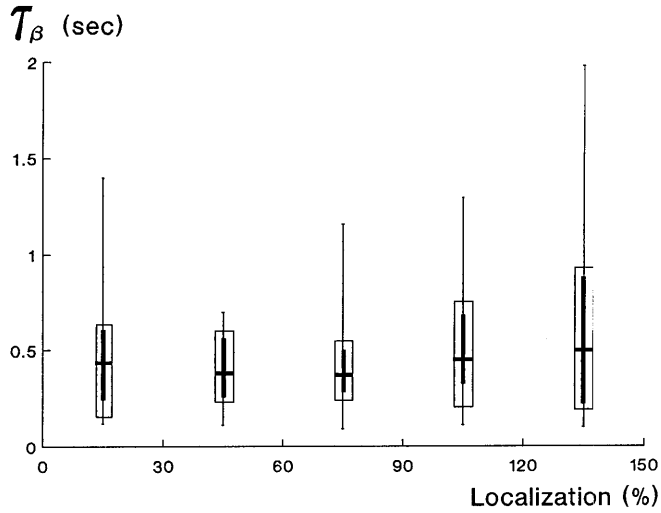

Fig. 5. Time constant τ_β (s) related to localization of measurement. Values are determined from the Box-Cox power transformation for each of the five urethral segments. Median, range and quartiles, as well as 95% confidence limits of the median (*vertical bar*) are given

seems to reflect differences in the periluminal structures. Anatomically, the part of the urethra studied extends from the bladder to beyond the external sphincter region. During this short course the tube per se is surrounded mainly by detrusor muscle, prostatic tissue and the muscular complex of the pelvic floor before it enters the spongiform tissues of the penis distally [13, 20, 25, 26]. Furthermore, the urethra itself shows a certain heterogeneity with a muscular component dominated by smooth muscle fibers proximally, and striated muscle fibers at the level of the rhabdosphincter [12, 13, 20]. The changing but not sharply separable predominance of the various periluminal structures thus seems to corroborate well with the characteristic and parallel variation in the elastance components. All three elastance components proved significantly higher in the high pressure zone, as compared to proximally. This presumably reflects the high density of striated muscle fibers in this region.

The time constants, on the other hand, showed no significant variation along the urethra, and when the confidence intervals of the median for each individual urethral segment were examined (Figs. 4, 5), it appeared that even though a certain variation in width of the confidence intervals was obvious, none of the intervals seemed to diverge from the others. Consequently, no major systematic variation in time constants seems to exist between the individual urethral segments studied. Major differences have been demonstrated in the course of relaxation for various tissue components, yet the uniform character of the pressure response may very well indicate that the same tissue structure dominates the response in the urethral segment studied, and the time course as well as the significant relaxation after dilation are consistent with the findings for striated muscle [1, 3, 4, 14, 16]. Other periluminal structures undoubtedly take part in the response as well, however the applied technique evaluates an integrated tissue response, and does not

Table 3. Elastance components (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) compared between individual urethral segments according to the multiple test procedure. (*P*: level of significance; *n.s.*: not significant)

	P for φ_α (cm H_2O/mm^2)	*P* for φ_β (cm H_2O/mm^2)	*P* for φ_γ (cm H_2O/mm^2)
Urethral segment I (0–30%) vs			
Urethral segment II (31–60%)	n.s.	n.s.	n.s.
Urethral segment III (61–90%)	n.s.	<0.05	<0.01
Urethral segment IV (91–120%)	<0.01	<0.01	<0.01
Urethral segment V (121–150%)	<0.01	<0.01	<0.01
Urethral segment II (31–60%) vs			
Urethral segment III (61–90%)	n.s.	n.s.	n.s.
Urethral segment IV (91–120%)	<0.01	<0.01	<0.01
Urethral segment V (121–150%)	<0.05	<0.05	<0.01
Urethral segment III (61–90%) vs			
Urethral segment IV (91–120%)	n.s.	n.s.	n.s.
Urethral segment V (121–150%)	n.s.	n.s.	n.s.
Urethral segment IV (91–120%) vs			
Urethral segment V (121–150%)	n.s.	n.s.	n.s.

Table 4. Correlation between age and elastance components (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) and time constants (τ_α, and τ_β (s)), respectively, in individual urethral segments. The figures given are for the Spearman-rankcorrelation coefficient (ρ), level of significance (P) following the Bonferroni correction, and 95% confidence limits of the correlation coefficient.(*n.s.*: not significant)

Segment	φ_α (cm H_2O/mm^2)		φ_β (cm H_2O/mm^2)		φ_γ (cm H_2O/mm^2)		τ_α (s)		τ_β (s)	
	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
0–30%	0.22 (−0.16–0.54)	n.s.	0.22 (−0.16–0.54)	n.s.	0.06 (−0.31–0.42)	n.s.	−0.10 (−0.45–0.28)	n.s.	−0.56 (−0.77–0.24)	<0.05
31–60%	0.17 (−0.21–0.51)	n.s.	0.26 (−0.12–0.57)	n.s.	0.17 (−0.21–0.51)	n.s.	−0.19 (−0.52–0.19)	n.s.	−0.72 (−0.86–0.48)	<0.01
61–90%	−0.10 (−0.45–0.28)	n.s.	0.07 (−0.30–0.43)	n.s.	0.18 (−0.20–0.51)	n.s.	−0.05 (−0.41–0.32)	n.s.	−0.57 (−0.77–0.26)	<0.05
91–120%	−0.22 (−0.54–0.16)	n.s.	−0.23 (−0.55–0.15)	n.s.	0.22 (−0.16–0.54)	n.s.	−0.19 (−0.51–0.20)	n.s.	−0.59 (−0.79–0.29)	<0.05
121–150%	−0.05 (−0.42–0.34)	n.s.	−0.36 (−0.65–0.02)	n.s.	−0.06 (−0.43–0.32)	n.s.	−0.39 (−0.67–0.01)	n.s.	−0.51 (−0.75–0.16)	<0.05

allow for the discrimination of components with similar responses, nor for structures which participate only insignificantly. The pressure response demonstrated no differences between those urethral segments surrounded by the prostate, and those which were not. As the reaction of the prostatic tissues is unknown at present, this fact, therefore, may equally well indicate that the prostatic tissues have pressure responses which are inseparable from the dominant tissues, or, alternatively, that they contribute only insignificantly to the pressure response.

When the influence of age was evaluated, no significant correlation between age and the size of the pressure response (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) could be demonstrated in any of the urethral segments studied. The velocity of the pressure decay following dilation, on the other hand, proved significantly related to age, as τ_β, but not τ_α, demonstrated a significant negative correlation with age in all five urethral segments. The causal background for this correlation is uncertain, but it may be indicative of an age determined change in the periluminal tissues or neuromuscular activity.

Age related changes of the periurethral tissue composition have been demonstrated by Shapiro et al. [22], who demonstrated age related changes in prostate glands obtained at autopsy from boys and men up to the age of 40 years morphometrically . This group has also demonstrated significant differences in the tissue composition in men with symptomatic as compared to asymptomatic benign prostatic hyperplasia (BPH). Furthermore, studies of the urethral and periurethral structures in women as well as in animals have shown changes in the density of individual tissue components with age, with an increasing fraction of type I muscle fibres and an increase in connective tissue [8, 15, 30]. Studies on men, however, are very sparse although Tokunaka et al. [29] found no age related variation in the fraction of type I vs type II muscle fibres in the rhabdosphincter between the fifth and eighth decade. Thus, whether the periluminal muscles undergo age related changes similar to those seen in other muscular structures in the male is at present unknown [21]. Alternatively, it is known that the biomechanical properties of muscles is highly influenced by their state of activity, thus changes in the spontaneous activity or tone in the muscles involved might cause the observed variation in the pressure response [11, 14]. Again, the data from men is insufficient, but recent electromyographic studies in women have indicated that a partial denervation of the levator muscles takes place with age as well as parity [24]. It is at present unknown whether similar age related changes in the urethral stress-relaxation also occur in women without voiding symptoms, and even though the pressure decay after urethral dilation has proved significantly faster in stress-incontinent women as compared to continent women [18, 28], this does not necessarily indicate a causal connection between these factors. Furthermore, the course of stress-relaxation is not identical in men and women [7, 18, 27], and parallels between the sexes should therefore be drawn with care.

In conclusion, the present study has demonstrated a significant variation in the stress-relaxation after forced dilation throughout the proximal part of the male urethra. The pressure response proved maximal in the high pressure zone, whereas the time-response was unaffected by location. These results are in accordance with the presumption that the striated muscles are the dominant influence on the pressure response. In relation to age, only the time-response varied, as the time constant τ_β proved negatively correlated with age in all urethral segments studied. The reason for this correlation, however, remains unclear.

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