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ORIGINAL PAPER

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Pressure/cross-sectional area relations in the proximal urethra of healthy males

Part III: The time dependent pressure response following forced dilation: standardization of a technique

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Abstract The urethral response to a sudden forced dilation was studied in ten healthy male volunteers aged from 27 to 71 years. Measurements were performed from the bladder neck and beyond the region of high pressure using a specially designed probe. The pressure response after dilation showed a characteristic course, which 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 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 size and velocity of dilation, as well as the degree of distension before dilation, proved of significance for the magnitude of the pressure response. The characteristics of the pressure response are given by the properties of the periluminal structures strained during dilation, and are thus predominantly determined of elastic, collagen, muscular, and glandular components. However, a high degree of relaxation after straining, and a modest stiffness, indicates that the muscular component dominates the response. The significance of the prostatic tissues remains unclear.

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

Introduction

The distensibility of the urethra has major implications for its normal physiological function, but the urethral resistance against dilation is a complex phenomenon which is highly dependent on the circumstances under which it is evaluated. The urethral response to dilation at rest during the reservoir phase has been extensively studied, but mainly under static conditions as evaluated at steady-state following distension. The time-dependent response has only gained limited attention, and seems not to have been studied in men [11, 13, 24, 27, 28]. The dynamic properties of the urethra may be studied by means of forced dilations, in terms of urethral pressure and cross-sectional area as related to time. This procedure induces an increase in urethral cross-sectional area, and thereby a stretch of the periluminal structures, and a concomitant pressure response characterized by a steep initial pressure increase followed by a slower decay over the next seconds. Similar reactions are well known from other hollow organs, and the character of these responses may reflect alterations associated with disease [6, 15, 22].

The aims of the present study were 1) to evaluate the character of the dynamic pressure response of the prostatic urethra to forced dilation, 2) to evaluate the significance of the size and velocity of the individual dilation, 3) to evaluate the significance of the degree of distension as studied during continued stepwise dilations, and finally 4) to evaluate the reproducibility of the method. All were investigated at rest during the reservoir phase.

Materials and methods

Ten male volunteers aged 27 to 71 years (median, 38 years) without past or present urological complaints participated in the study. Urinalysis (dipstick) and blood tests (haemoglobin, sodium, potassium, and creatinine) were normal in all individuals. Informed consent was obtained and the study was approved by the local ethics committee.

Symptoms of benign prostatic hyperplasia (BPH) were evaluated by filling in a patient weighted symptom score (DAN-PSS) [16], and prostatic volume was determined by transrectal ultrasonography (7 MHz rectalscanner, type 8551, Brüel and Kjær, Denmark) according to the formula: volume $= 0.52 * \text{width} * \text{height} * \text{length}$ [23]. In addition all subjects had an urodynamic examination including flowmetry (standing, filling by diureses), resting urethral

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pressure profile (UPP) (8 F catheter, two sideholes, retraction rate 3 mm s^{-1}, perfusion rate 2 ml min^{-1}), cystometry (supine, saline, transurethral filling, 5 F catheter, filling rate 50 ml min^{-1}), and pressure-flow. Results were recorded on DISA UROsystem 21F16 2100 (Dantec, Denmark) (flowmetry, UPP, cystometry, and pressure-flow) or Urodyn 1000 G22 01 (Dantec, Denmark) (flowmetry). The results of these examinations are given in Table 1.

The relationship between intraurethral pressure and cross-sectional area was determined using a special probe which dilates a short urethral segment and simultaneously registers the urethral pressure and cross-sectional area in this segment. This technique has previously been described in detail [10]. In brief, the probe consists of an outer 14 F PVC catheter and an inner 7 F double-tip transducer (Dantec, Denmark) for pressure measurement. A small PVC balloon is mounted at the end of the outer catheter and covers the urethral pressure-tip, and a short 9 F Polyolefine tube, mounted with four (two generating and two measuring) ring electrodes for cross-sectional area measurement according to the field-gradient principle. The balloon was inflated through a filling channel between the inner and outer catheter. Pressure was measured in the bladder and balloon in the range of 0–250 cm H_2O, and cross-sectional area was measured over a 2 mm segment of the balloon between the measuring electrodes in the range of 11–102 mm^2. The time response for the cross-sectional area and pressure measurement were 0.02 s and 0.007 s, respectively. Measurements in a pressure chamber with covered and uncovered pressure sensors were identical.

The inflation of the balloon was performed using a gravitationally driven pump, which allowed the size of the inflated volume, and thereby the change in cross-sectional area (ΔCA), to be freely adjusted [28]. The velocity of inflation was adjusted by interposing one of three tubes (Q_1, Q_2 and Q_3) between the pump and the infusion line. The corresponding median velocities of dilation were determined to 65 mm^2/s (Q_1), and 135 mm^2/s (Q_2) in the full range of dilation applied (ΔCA 10–40 mm^2), whereas the velocity with the last tube interposed (Q_3) increased slightly from 215 mm^2/s (ΔCA 10 mm^2), to 235 mm^2/s (ΔCA 20 mm^2), and 250 mm^2/s (ΔCA ≥30 mm^2) [8].

The examinations were directed to evaluate the influence of 1) the size and velocity of dilation, and 2) the degree of distension during continuous stepwise dilation, and were performed on two separate days with an interval of at least 1 week. The insertion and localization of the catheter were identical for the two procedures. Investigations were performed with the subject in the supine position with an empty bladder. The catheter was introduced into the urethra, and placed with the balloon in the bladder. The catheter was then mounted in a specially designed retraction device, and the balloon was connected to a pressure reservoir with a pressure of 10–15 cm H_2O above bladder pressure, then slowly retracted until the sensing electrodes entered the urethra as indicated by a fall in cross-sectional area. Measurements were initiated after the catheter was retracted a further 5 mm from the bladder neck, and repeated at every 5 mm until the high-pressure zone was passed. At each site of measurement the balloon was adjusted to a cross-sectional area of approximately 13 mm^2 and one of the following procedures was performed.

1. The significance of the size and velocity of dilation. The balloon was inflated a total of six times, using increments in cross-sectional area of 20 mm^2 and 40 mm^2. Both cross-sectional area changes were performed at three different rates of inflation by changing the interposed tube (Q_1, Q_2 and Q_3). Once inflation was completed, the balloon was only deflated after pressure equilibrium, as indicated by a constant balloon pressure, had occurred. This was also the case before a new inflation was performed.
2. The significance of the degree of distension during continuous stepwise dilation. The balloon was inflated in steps of approximately 10 mm^2 at a maximum rate of inflation (Q_3). After each inflation pressure equilibrium was awaited, and the inflation was continued until a cross-sectional area of 80 mm^2 or a balloon pressure of 150 cm H_2O was reached, before the balloon was deflated.
3. Reproducibility. After approximately 4 weeks, the reproducibility of the technique was evaluated by repeating the examination of the significance of variation in the size and velocity of dilation in five volunteers, aged 27–71 years (median, 44 years).

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.

Table 1. Symptom score, prostatic volume and urodynamic findings. Figures given are median and range, or number

Symptom score	
Total	0 (0–5)
Symptom	3 (1–5)
Bother	0 (0–4)
Prostatic volume (cm^3)	21 (13–33)
Uroflow (ml s^{-1})	24 (13–36)
Voided volume (ml)	191 (155–500)
Bladder capacity (ml)	360 (254–560)
Obstructed[a] (No)	0
Unstable[b] (No)	0

[a] According to the criteria given by Abrams and Griffiths [1]
[b] Detrusor contractions exceeding 15 cm H_2O during cystometry

Localization 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 site of measurement was standardized by dividing the distance from the bladder neck with the length of the posterior urethra and multiplying by 100, thus expressing the measurement location as a percent of the distance from the bladder neck to the site of the maximum pressure. Only measurements performed at a distance of less than 150 percent from the bladder neck were included in the analysis. As major variations in the measurement parameters occurred along the urethra, the investigated part of the urethra (0–150%) was divided into five segments, each of the length of 30 percent (I, 0–30%; II, 31–60%; III, 61–90%; IV, 91–120%; V, 121–150%) before analysis.

Distension parameters

Elastance (φ) is defined as the ratio of pressure (dP) to volume (dV) change, and compliance is the inverse of elastance. For a urethral segment between the measuring electrodes with a distance λ mm, the change in volume is λ*dCA mm^3, where CA is cross-sectional area, provided that the slope of the walls is negligable. If the change in pressure is dP (cm H_2O), then the elastance is dP/(λ*dCA) (cm H_2O/mm^3). It follows that for unity of length ($\lambda = 1$ mm) the elastance is numerically identical with dP/dCA (φ cm H_2O/mm^2).

Statistics

The Wilcoxon test was used to compare paired data from two groups and Friedman's test was applied when more than two paired groups were compared [25]. If Friedman's test demonstrated a significant difference between groups, the analysis was extended with a multiple test procedure in an attempt to identify the deviating group(s) [25]. The mean value was used for analysis when more than one set of data existed per subject per group. Bonferroni's method was applied when multiple comparisons were made and $P < 0.05$ was defined as the level of significance [3]. Reproducibility was evaluated by calculating the median and quartiles of the difference between repeated measurements in the individual subjects.

Results

Curve analysis

The maximum pressure was reached at the end of inflation. The pressure then declined and approximated an equilibrium pressure which was higher than the original pressure (Fig. 1). Following logarithmic transformation and subtraction of the equilibrium pressure, the first part of the residual curve was concave, whereas the second part was straight, indicating an exponential function. By subtracting this exponential function from the residual curve, a second exponential function was demonstrated (Fig. 2a, b). Consequently an equation of the following form appeared to fit the original curve:

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

where P_t is the pressure in the balloon at time t, P_{equ}, P_α, and P_α are constants, and τ_α, and τ_β are time constants. A computer program was therefore developed (The Laboratory of Fotogrammetry and Surveying, University of Aalborg, Denmark), which allowed the pressure tracings, from the maximum pressure after dilation (P_{max}) until the equilibrium pressure (P_{equ}) was reached, to be fitted with the aforementioned double exponential

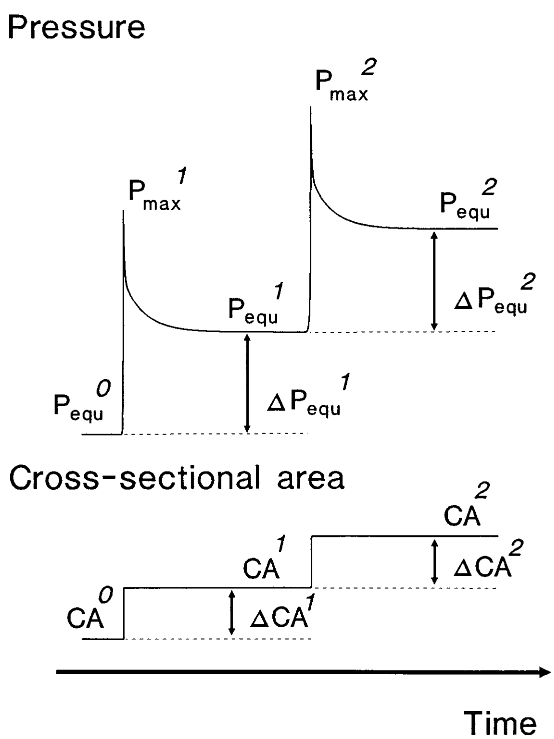

Fig. 1. Stylized drawing of the pressure response to sudden urethral dilations. (P_{max}: maximum pressure after dilation; P_{equ}: equilibrium pressure after dilation; ΔP_{equ}: increase in equilibrium pressure between two consecutive dilations ($\sim P_\gamma$); ΔCA: size of dilation)

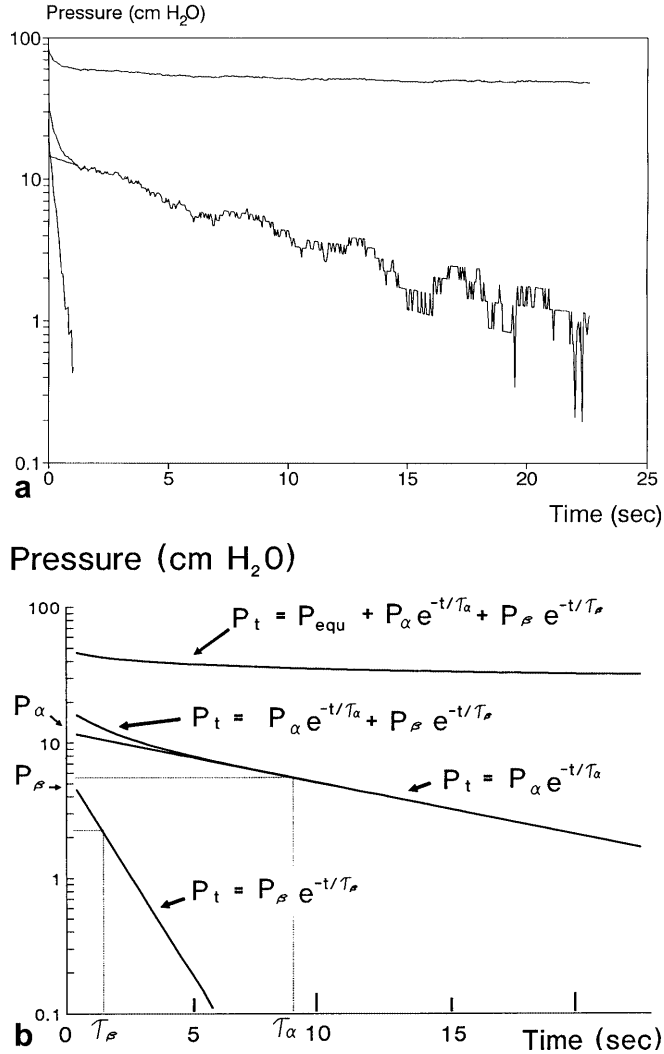

Fig. 2a, b. Pressure response to a sudden change in cross-sectional area. **a** The original pressure response is shown as plotted on a logarithmic scale, together with its components, **b** Stylized drawing of the pressure response as plotted on a logarithmic scale, together with its components

function by means of an iterative procedure. The program determined the constants (P_{equ}, P_α, P_β, τ_α, and τ_β) and calculated the residual standard deviation (s_{res}) from the formula:

$$s_{res} = \sqrt{\sum \left(P_i - P_{fit}\right)^2 / n - 5}$$

The program simultaneously attempted to fit the pressure curve with linear or single exponential functions with a maximum of 150 iterations.

Pressure and elastance parameters

The increase in equilibrium pressure (ΔP_{equ}) between two consecutive dilations was denoted P_γ (Fig. 1). The pressure change at time 0 after a given dilation of the size ΔCA is the sum of P_α, P_β, and P_γ (ΔP_{total}), and as time $\rightarrow \infty$, then $\Delta P_{total} \rightarrow P_\gamma$. It follows that the elastance (φ cm H_2O/mm^2) is highly dependent on the time after dilation at which it is determined, and that φ may be divided into two dynamic components (φ_α, and φ_β), and one static (φ_γ).

The significance of the size and velocity of dilation

A total of 462 dilations were performed, of which the pressure tracings in 394 (85%) could be fitted with a double exponential function, with a median residual standard deviation of 0.9 cm H_2O (2.5th and 97.5th percentiles: 0.4 and 2.1 cm H_2O). The remaining 68 dilations (15%) could not be analyzed because of pelvic floor muscular activity, or were fitted with simpler mathematical functions.

The influence of the size and velocity of dilation as determined from the pooled data from all five urethral segments is shown in Figures 3 and 4. It appears that none of the two elastance components φ_α and φ_γ showed any significant variation with size or velocity of dilation, whereas the elastance component φ_β showed a significant decline with decreasing velocity of dilation, as well as with increasing size of dilation. Neither of the time constants (τ_α, and τ_β) showed any significant variation with the size or velocity of dilation.

An extended analysis of the data directed at the relationship between φ_β and the size of dilation for the

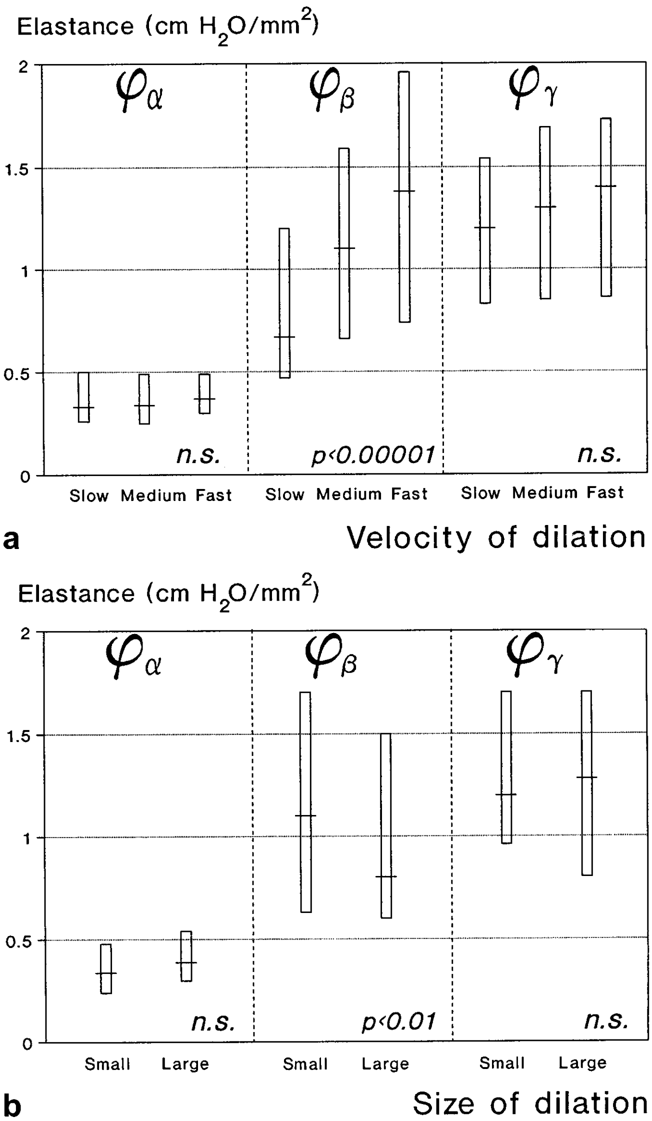

Fig. 3a, b. Elastance components (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) related to: **a** velocity of dilation, and **b** size of dilation. Median, and quartiles are given. Level of significance is given for each parameter (*n.s.*: not significant)

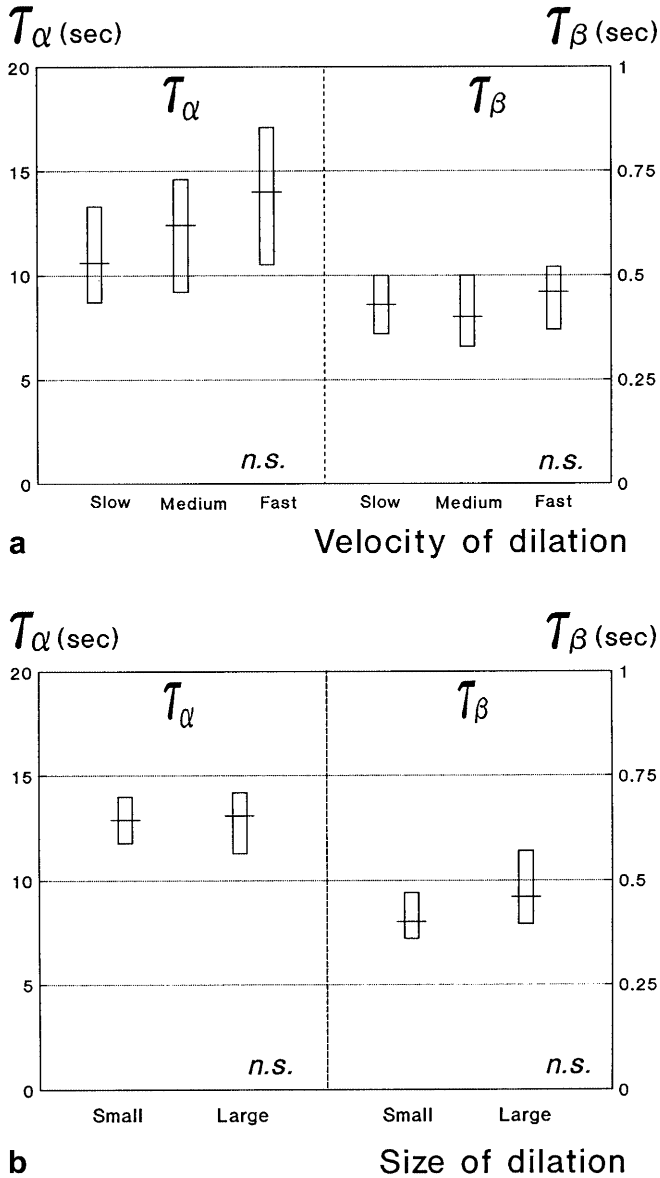

Fig. 4a,b. Time constants (τ_α, and τ_β (s)) related to: **a** velocity of dilation, and **b** size of dilation. Median, and quartiles are given. Level of significance is given for each parameter (*n.s.*: not significant) individual velocities applied showed that φ_β declined significantly with increasing size of dilation when the velocity of dilation was low ($P < 0.001$). When the velocity of dilation was medium or high, however, no significant relationship between φ_β and size of dilation could be found. φ_β proved to be highly related to the velocity of dilation for both sizes of dilation ($P < 0.001$).

The significance of the degree of distension during continuous stepwise dilation

A total of 495 dilations were performed, of which the pressure tracings in 435 (88%) could be fitted with a double exponential function, with a median residual standard deviation of 1.1 cm H_2O (2.5th and 97.5th percentiles: 0.5 and 2.6 cm H_2O). The remaining 60 dilations (12%) could not be analyzed because of pelvic floor muscular activity, or were fitted with simpler mathematical functions.

The significance of the degree of distension was evaluated by division of the measured parameters into four ranked groups according to the cross-sectional area after individual dilation (1: CA ≤ 30 mm^2, 2: CA ≤ 45 mm^2, 3: CA ≤ 60 mm^2, 5: CA > 60 mm^2). Distensions above 60 mm^2 were only infrequently performed in the distal three segments (61–150%) because of high intraurethral pressures exceeding 150 cm H_2O. Only three degrees of distension were therefore studied in these segments, and dilations above 60 mm^2 were excluded. Therefore, the analysis of the pooled data was performed for the two proximal segments (0–60%) and three distal segments (61–150%), separately (Figs. 5, 6). In the two proximal segments, all three elastance components (φ_α, φ_β and φ_γ) proved a significant increase at large distensions (> 60 mm^2), whereas no significant variation was disclosed at smaller distensions. In the three distal segments, φ_α and φ_β raised significantly at distensions above 45 mm^2, whereas φ_γ showed no significant variation at distensions upto 60 mm^2. The time constants (τ_α and τ_β) showed no significant variation with the degree of distension.

Reproducibility

Reproducibility was studied for each of the five urethral segments separately. Results are given in Table 2.

Discussion

The urethral pressure response, as investigated in this study, emerges as an integrated tissue reaction to a strain

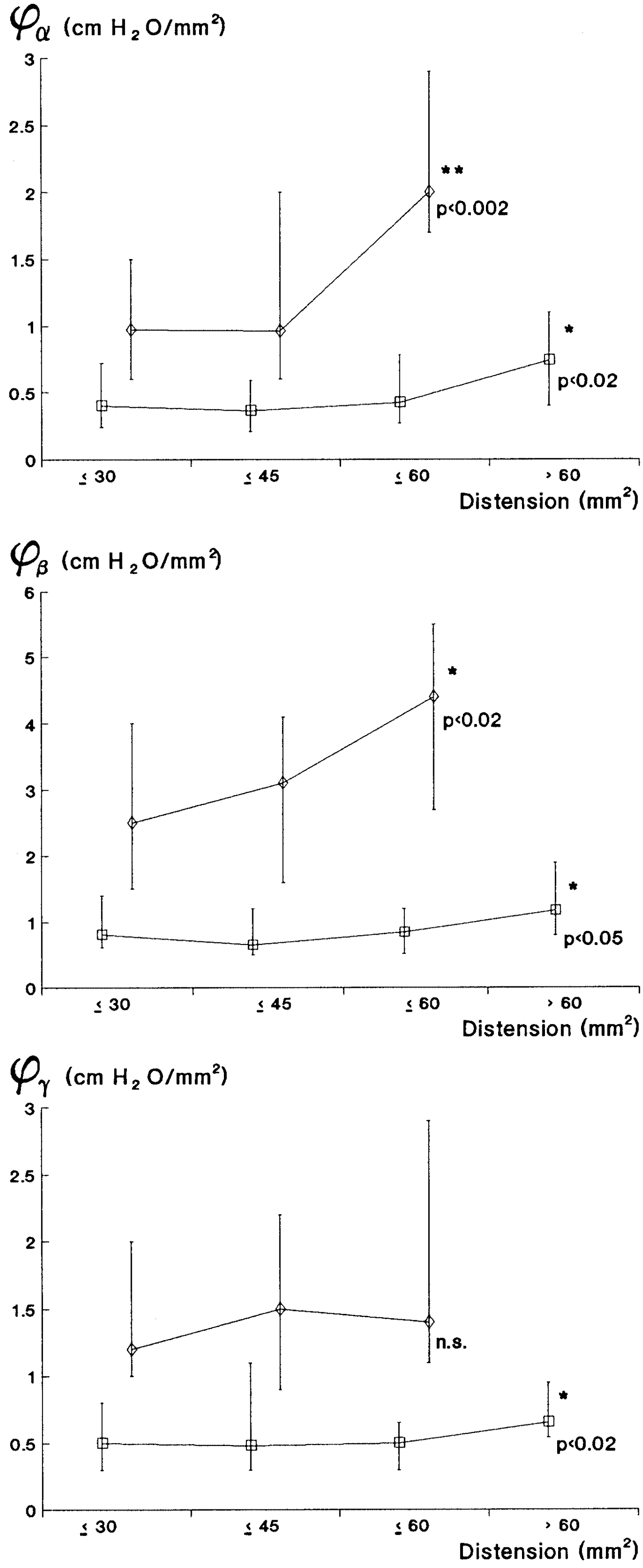

Fig. 5. Elastance components (φ_α, φ_β, and φ_γ (cm H_2O/mm^2)) related to degree of distension during continuous stepwise dilation. Values from the two proximal urethral segments (0–60%) (*open squares*), and three distal segments (61–150%) (*open diamonds*) are shown separately. Median, and quartiles are given. For each parameter the level of significance is given for the proximal (0–60%) and the distal urethral segments (61–150%) separately (*n.s.*: not significant). Statistically significantly deviating groups, according to the multiple tests procedure, are marked (*: $P < 0.05$; **: $P < 0.01$)

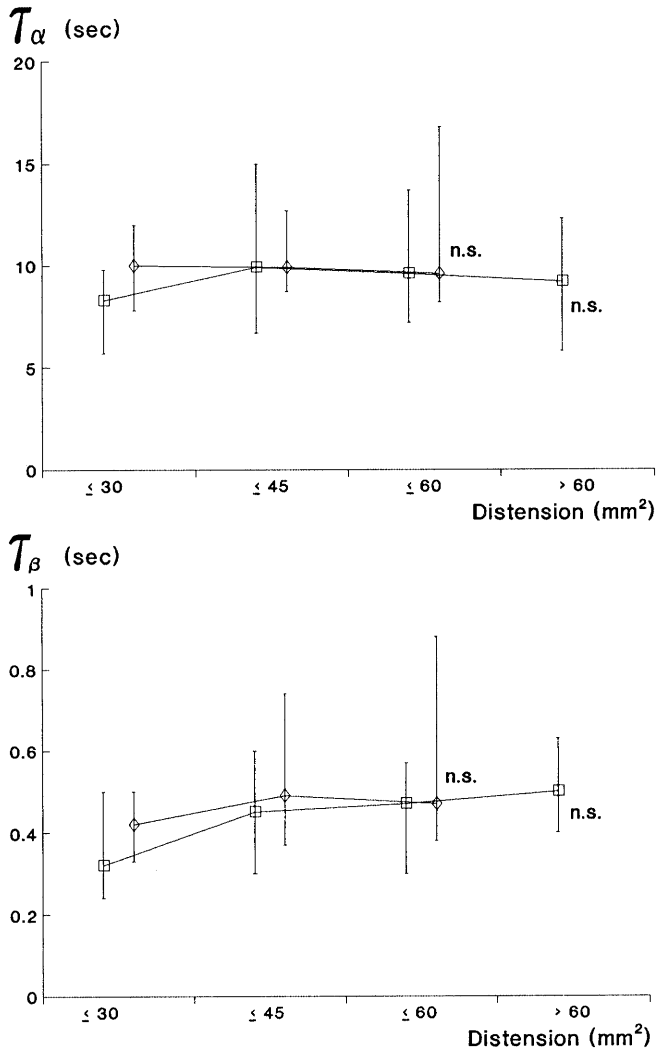

Fig. 6. Time constants (τ_α, and τ_β (s)) related to degree of distension during continuous stepwise dilation. Values from the two proximal urethral segments (0–60%) (*open squares*), and three distal segments (61–150%) (*open diamonds*) are shown separately. Median, and quartiles are given. For each parameter the level of significance is given for the proximal (0–60%) and the distal urethral segments (61–150%) separately (*n.s.*: not significant)

of the periluminal structures. The character of these responses is highly dependent on the composition of the tissues studied, as well as the circumstances under which the experiments are performed [5, 6, 14, 15, 21, 22]. In the present study, investigations were performed in vivo without any medication except for local analgesic jelly, which implies that normal urethral regulation mechanisms were intact. Although recordings with an evident active muscular reaction to dilation were excluded, the results should be interpreted as integrated tissue reactions from the intact organ to standardized stimuli, and not, or only cautiously, as purely passive biomechanical phenomena.

Previous studies have demonstrated that the stress-relaxation following a sudden strain fits a double exponential function well in a large number of intact tissues as well as in vitro preparations. More complicated multi-exponential functions have been applied as well, which, from a theoretical point of view, might offer a better fit [2, 4, 9, 14, 15, 22]. However, with the present technique a median residual standard deviation of approximately 1 cm H_20 was found, which seems acceptable, and only minor improvement can be expected by using multi-exponential functions. Furthermore, it should be emphasized that the present fitting procedure was chosen simply for mathematical reasons, because it appeared to offer an acceptable fit with the pressure tracings, even though it was possibly not strictly correct. The procedure was not adopted in an attempt to define the nature of the tissue components responsible. Besides, the mathematical description of empirical data is not unique, and different multi-exponential functions may frequently describe data equally well [4, 15]. The computer software was therefore programmed to allow a maximum of only two exponential functions, and to handle functions with closely correlated exponents as single exponential functions. Stress-relaxation was followed until pressure equilibrium, as judged visually during examination, was reached, which implied that the relaxation was followed for less than 45 s in most cases, and virtually did not exceed 90 s. It is known, mainly from bench studies, that stress-relaxation may be very protracted [15], yet extended observations were not applied. This was partly because it would prolong the total duration of the examination unacceptably for the subjects, but also because the pressure decay which may be neglected is likely to be so slow that it is of no or minimal physiological significance. Besides, it is uncertain whether extended relaxation takes place in vivo when the normal regulation mechanisms are intact, and extended evaluations of urethral pressure in men as well as in women have shown no signs of a prolonged stress-relaxation, even though significant fluctuations in urethral pressure are evident [20, 26].

No significant variation with the circumstances of dilation could be demonstrated in the elastance components φ_α and φ_γ. This indicates that the pressure increase (P_α and P_γ) following dilation was simply proportional to the change in cross-sectional area. Likewise, the time constants (τ_α and τ_β) seemed unaffected. φ_β, on the other hand, was highly affected by both the size and the velocity of dilation. From the time constant (τ_β) for this function it is clear that this pressure component declines very rapidly after dilation. The evaluation of the pressure response is initiated at maximum pressure after dilation, but it seems reasonable that the relaxation process starts simultaneously with the stretch of tissues, and so the duration of dilation may influence the response. In fact, this was supported by the results because φ_β declined with decreasing velocity of dilation as well as with increasing size of dilation, provided the velocity of dilation was low. When the degree of distension during continued stepwise dilation was analyzed, it was found that none of the parameters studied varied significantly at distensions upto approximately 45 mm^2. Above this, various

Table 2. Reproducibility of the elastance components (φ_α, φ_β, φ_γ (cm H_2O/mm^2)), and time constants (τ_α, τ_β (s)) in individual urethral segments. Median and quartiles of the difference between repeated measurements in the individual subjects are given

	φ_α	φ_β	φ_γ	τ_α	τ_β
Segment					
0–30%	0.01	0.02	−0.19	−0.5	0.0
	(−0.1–0.1)	(−0.2–0.1)	(−0.5–0.1)	(−4.4–3.1)	(−0.1–0.1)
31–60%	0.01	0.02	0.02	−1.5	0.05
	(−0.1–0.1)	(−0.2–0.2)	(−0.2–0.1)	(−7.0–5.6)	(−0.1–0.2)
61–90%	−0.07	0.1	−0.12	0.5	0.03
	(−0.1–0.2)	(−0.1–0.7)	(−0.4–0.2)	(−2.1–6.4)	(−0.1–0.2)
91–120%	0.06	−0.3	−0.15	−0.8	−0.1
	(−0.2–0.3)	(−1.1–0.4)	(−1.0–0.1)	(−4.9–5.1)	(−0.3–0.1)
121–150%	−0.14	−0.4	1.0	3.1	0.08
	(−0.3–0.0)	(−1.0–0.3)	(−1.7–0.7)	(−4.3–6.8)	(0–0.1)

pictures occurred in individual urethral segments, as all three parameters increased significantly at distensions above 60 mm^2 in the proximal segments, whereas φ_α and φ_β only disclosed significant changes in the distal segments, and already at distensions above 45 mm^2. The time constants seemed unaffected by the degree of distension. Thus, at increasing distension, the urethral resistance to further dilation appears to increase.

The characteristics of the pressure response are given by the properties of the periluminal structures strained, i.e. the muscular, elastic, collagen, and glandular components encompassing the proximal urethra. When looking at the individual components' reaction to a sudden strain, relaxed muscle exhibits a modest stiffness and a high degree of relaxation, and furthermore muscle bears high extensions before breakage, in contrast to elastin and collagen [6, 7, 12, 15, 18]. The reactions of the glandular tissues are at present unknown. In addition, the geometrical configuration of the individual tissue fibers is highly important, as the contribution of each fiber to the pressure response will be maximized if circumferentially orientated, and decreased if more or less longitudinally orientated orientated. In fact, both collagen and elastin fibers are predominantly longitudinally orientated in the luminal layers, at least in women, whereas circumferentially orientated collagen fibers are mainly seen in the peripheral layers [17, 19]. The majority of muscular tissue, both smooth and striated, is more or less circumferentially orientated, and thus is probably mainly responsible for the pressure response, a theory which also finds support in the character of the response, with a modest stiffness and a very significant relaxation after straining. Extensive straining of the intact organ may recruit additional tissue components, either of the same or different types, which produce no or only minor tension at small, low distensions, but which do participate at larger distensions. Thus, collagen may be of significance at large distensions. Finally, it should be realised that part of the periluminal structures, e.g. blood and lymphatic vessels, might be compressible, which implies that the dilation is not fully transmitted through the wall.

Repeated measurements showed a certain intra-individual variation, particularly in the distal segments. The variation observed may be caused by methodological as well as biological factors. Technically, cross-sectional area measurement using the present method has proved reliable, even though major inaccuracies may be caused if the wall slope is great or the measuring electrodes are eccentrically displaced. Based on ultrasound examinations in vivo, the error to be expected from these factors has previously been estimated as not exceeding approximately 10 percent [9]. Inaccuracies in probe localization, on the other hand, resulting in slightly different anatomical measurement sites throughout the urethra during repeated measurements, may result in significant variations, particularly in regions with steep changes in the studied parameters, i.e. in the high pressure zone, and may in part account for the variation found. Finally, biological variation is also an influence as it is known that the urethral pressure shows significant spontaneous oscillations which may very well have influenced the present measurements [20, 26].

In conclusion, the present technique enables the evaluation of stress-relaxation in vivo in small segments of the male urethra. Within certain limits, the response seemed to be independent of the degree of distension in the individual urethral segments, whereas the duration of dilation proved of significance. A uniform examination technique must therefore be applied in order to allow for a comparison of the results. Clinically, the method may prove of value in the evaluation of physiologic and pathophysiologic dynamic mechanical properties of the periluminal structures of the male urethra in the phase between micturitions. The technique may thus bring new insight into the obstructive mechanisms related to benign prostatic hyperplasia, as well as into the modes of action of various treatment modalities for this diseased entity.

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