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Morphometric analysis of symptomatic benign prostatic hyperplasia with and without bladder outlet obstruction

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Abstract To investigate the histological features of benign prostatic hyperplasia (BPH) with and without bladder outlet obstruction (BOO), 32 patients with symptomatic BPH, 22 with BOO and ten without BOO, were studied. The area density of smooth muscle, fibrous tissue, glandular epithelium, and glandular lumen in BPH adenoma resected by transurethral surgery was estimated using morphometric analysis. No differences were found in the area density of stromal and glandular components between the two groups. In the glandular component, neither the epithelium nor lumen differed between the two groups. However, the area density of smooth muscle in the obstructed group showed a decrease compared to that in the unobstructed group ($P < 0.01$). We conclude that a decreased proportion of smooth muscle in BPH adenoma may play an important role in BOO.

Key words Prostatic hyperplasia · Morphometry · Bladder outlet obstruction · Smooth muscle

Introduction

Histologically, benign prostatic hyperplasia (BPH) in humans is a mixture of overgrowth in the gland and stroma in various proportions. Morphometric studies have been performed to determine the relative proportions of stroma, glandular epithelium, and lumen in BPH patients. The increased volume of stroma has been associated with BPH [3, 5, 13, 20]. According to Caine [4], bladder outlet obstruction (BOO) in symptomatic BPH is caused not only by mechanical obstruction of enlarged adenomas but also the tone of prostatic smooth muscles. Therefore, the severity of clinical symptoms and the degree of BOO in patients with BPH are not necessarily related to the prostate size [2, 17]. However, little is known about histological differences between BPH with and without BOO. Herein, we compared the histological features of BPH patients with and without BOO, and the urodynamic outcome of transurethral resection of the prostate (TURP) between the two groups.

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Patients and methods

The study comprised 32 patients with symptomatic BPH who underwent TURP. Before surgery, the prostate volume was estimated by transrectal ultrasonography. Free uroflowmetry with the measurement of the post-void residual volume and an international prostate symptom score (IPSS) were completed before and after TURP for all patients. A pressure-flow study was also performed before and after TURP using an Urodyn 5500 system (Dantec, Denmark) and the methods, definitions and units prescribed by the International Continence Society [8]. Obstruction garde (range 0 - no obstruction to 6 – severe obstruction) was estimated from the linear passive urethral resistance relation to the pressure-flow diagram proposed by Schafer [23]. Men with an obstruction grade 0 or 1 were allocated to unobstructed group while those with an obstruction grade of 2 or more to the obstructed group. Abrams-Griffiths (AG) number ($P_{det}Q_{max} - 2Q_{max}$) [18] and group-specific urethral resistance factor (URA) [7] were also calculated from recorded pressure-flow data for the quantification of BOO. Patients with neuropsychiatric disease, cancer, and urethral stricture were excluded from the study. The patients' clinical characteristics and urodymanic findings are summarized in Table 1.

Tissue samples obtained by TURP were pathologically diagnosed as BPH, then stained with Masson-Trichrome and subjected to quantitative morphometry using light microscopic stereological analysis, as reported previously [3, 5, 20, 24]. The area density (%) of the following tissue components was determined: (a) smooth muscle, (b) fibrous tissue, (c) glandular epithelium, (d) glandular lumen, (e) stromal component (smooth muscle + fibrous tissue) and (f) glandular component (epithelium + lumen). The total area of each component was calculated using a computer-assisted image analysis system (EM manual, Rise Corp., Sendai, Japan) and a microcomputer. At least 30 systemic test areas were analyzed on each of the resected specimens.

Statistical analysis was carried out using the Statview 4.5 software (Abacus Concept, Barkeley, Calif.). Mann–Whitney's U test

Table 1 Comparison of clinical parameters in the obstructed and unobstructed groups before and after transurethral resection of the prostate (TURP). (*$P < 0.05$, ***$P < 0.001$, compared with their pre-TURP data according to Wilcoxon's test, *IPSS* international prostate symptom score, Q_{max} the maximum flow rate, $P_{det}.Q_{max}$ the detrusor pressure at the maximum flow rate, $P_{min.void.det}$ the minimum voiding detrusor pressure, *URA* group-specific resistance factor, *l-PURR* linear passive urethral resistance relation)

Clinical parameters	Obstructed ($n = 22$) (Mean ± SE)	Unobstructed ($n = 10$) (Mean ± SE)	*P*-value[a]
Age (years)	71.4 ± 1.4	68.3 ± 2.2	0.15
Prostatic size (g)	46.0 ± 4.9	30.7 ± 2.4	$P < 0.05$
Before TURP			
IPSS (points)	21.1 ± 1.9	20.5 ± 2.8	0.85
Q_{max} (ml/s)	7.9 ± 0.9	12.2 ± 1.2	$P < 0.01$
Voided volume (ml)	157.0 ± 22.7	196.6 ± 18.6	0.13
Post-void residual (ml)	34.8 ± 8.9	29.9 ± 6.8	0.90
$P_{det}.Q_{max}$ (cmH_2O)	107.1 ± 7.4	40.7 ± 1.9	$P < 0.0001$
$P_{min.void.det}.$ (cmH_2O)	81.0 ± 7.6	24.2 ± 2.3	$P < 0.0001$
URA (cmH_2O)	53.1 ± 6.0	19.8 ± 1.0	$P < 0.0001$
AG number	91.3 ± 7.6	16.4 ± 2.0	$P < 0.0001$
l-PURR (grade)	4.4 ± 0.2	1.4 ± 0.2	$P < 0.0001$
After TURP			
IPSS (points)	6.9 ± 1.0***	14.9 ± 2.6*	$P < 0.005$
Q_{max} (ml/s)	15.4 ± 1.8***	13.7 ± 1.2	0.90
Voided volume (ml)	219 ± 20.9*	222.4 ± 25.0	0.72
Post-void residual (ml)	18.0 ± 3.3*	13.6 ± 3.0*	0.60
$P_{det}.Q_{max}$ (cmH_2O)	59.4 ± 7.4***	50.3 ± 8.0	0.45
$P_{min.void.det}.$ (cmH_2O)	27.6 ± 6.6***	24.1 ± 6.5	0.77
URA (cmH_2O)	25.5 ± 4.1***	20.9 ± 2.4	0.68
AG number	29.5 ± 9.2***	22.8 ± 8.6	0.65
l-PURR (grade)	2.1 ± 0.3***	1.6 ± 0.4	0.36

[a] According to Mann–Whitney's *U* test

was used for comparison of the obstructed and unobstructed groups. Changes in the patients' clinical parameters before and after TURP were analyzed using Wilcoxon's signed rank test; $P < 0.05$ was considered statistically significant.

Results

As shown in Table 1, ten patients were classified as the unobstructed group, 12 as the moderately obstructed group and ten as the severely obstructed group. In the obstructed group, Q_{max} was significantly lower and P_{det} at Q_{max}, $P_{min\cdot void\cdot det\cdot}$ URA, AG number, and l-PURR were significantly higher than those in the unobstructed group ($P < 0.01$–0.001) (Table 1). However, the IPSS score did not differ between the two groups.

After transurethral surgery, the IPSS score, Q_{max}, voided volume (VV), post-void residual volume (PVR), P_{det} at Q_{max}, $P_{min.\ void.\ det\cdot}$, URA, AG number, and l-PURR significantly improved in the obstructed group ($P < 0.05$–0.001). In the unobstructed group, however, only IPSS and PVR significantly improved after operation ($P < 0.05$) (Table 1). After TURP, only international prostate symptom score (IPSS) was considerably reduced in the obstructed group as compared to that in the unobstructed group ($P < 0.05$). However, other urodynamic parameters did not differ between the two groups (Table 1).

As shown in Table 1, patients with an obstruction grade 0 or 1 were considered not to have BOO (unobstructed), those with an obstruction grade 2 or 3 had moderate BOO and those with a grade 4 or more had severe BOO. No difference was shown in area densities of stromal and glandular components between the moderate, severely obstructed and unobstructed groups. Regarding the glandular component, neither the epithelium nor the lumen differed between the three groups. In the stromal component, the area density of smooth muscle in the severely obstructed group showed a significantly lower proportion compared to that in the unobstructed and the moderately obstructed groups ($P < 0.001$) (Table 2). However, the area density of smooth muscle was not different between the unobstructed group and the moderately obstructed group.

Discussion

The homogenicity of tissue composition within individual BPH tissue samples has been demonstrated by

Table 2 The area density of each histological component in benign prostatic hyperplasia patients with moderate and severe bladder outlet obstruction and without bladder outlet obstruction. Each value represents mean ± standard error. (***$P < 0.001$ compared to the severe obstructed group)

Area density of tissue component (%)	Moderately obstructed ($n = 7$)	Severely obstructed ($n = 15$)	Unobstructed ($n = 10$)
Stromal component	77.6 ± 2.4	70.1 ± 2.1	73.5 ± 1.6
Smooth muscle	33.9 ± 2.3***	24.6 ± 1.7	33.7 ± 1.4***
Fibrous tissue	43.7 ± 3.8	45.5 ± 1.8	39.8 ± 1.1
Glandular component	15.9 ± 1.9	20.7 ± 2.2	18.5 ± 1.3
Epithelium	8.5 ± 1.0	10.5 ± 1.1	9.7 ± 0.8
Lumen	7.4 ± 1.2	10.2 ± 1.4	8.8 ± 0.9

quantitative analysis of tissue components in different sections of each specimen [5]. However, Price et al. [21] clarified the structural heterogenicity within individual BPH tissue specimens. According to Costa et al. [5], fibrous tissue and the epithelium were accurately estimated, but a lower proportion of glandular lumen and a greater proportion of smooth muscle were found in single biopsy and systemic sextant biopsies of the prostate. Therefore, it is reasonable to suppose that the whole TURP specimens used in the present study provided for a reliable evaluation of the histology of BPH.

Quantitative morphometric studies of the various components of BPH nodules showed a significant increase in stromal tissue compared to normal prostatic tissue [3, 13]. Recently, Shapiro et al. [24] demonstrated that the histological composition of the prostate is related to the development of symptomatic BPH. Prostate adenomas from men with symptomatic BPH contained a significantly higher percentage of stroma compared to those from men with asymptomatic BPH. However, they did not divide the stromal component into smooth muscle and fibrous tissue.

The mechanism of infravesical obstruction in men with symptomatic BPH includes static and dynamic components [14]. The static component of obstruction is related to the anatomical obstruction resulting from the enlarged adenoma enveloping the bladder outlet, whereas the dynamic component is related to the tone of the prostate smooth muscle. Apparently the size of the prostate, the stromal component and the fibrous component of the stroma did not differ between the obstructed and unobstructed groups in the present study. One would expect no differences in the static component of the obstruction but differences in the dynamic component in the obstructed patients. However, the smooth muscle content was not increased but decreased in the obstructed patients. Regional differences in the contractile property of BPH tissue reflect the differences in the proportions of the smooth muscle component within the tissue [16]. Lepor et al. [15] demonstrated a linear relationship between the phenylephrine E_{max} and the area density of the prostate smooth muscle in dogs. The clinical efficacy of α-adrenergic blockers depends on the proportion of smooth muscle within individual BPH tissue. Since the contractile response of the strips from human hyperplastic prostate is directly dependent upon the area density of the smooth muscle [12], the dynamic component of BOO is mediated by the tension of prostatic smooth muscle. However, prostatic area densities of different components are independent of clinical symptoms and uroflowmetry parameters [10, 11]. Urodynamic types of BOO are not related to histological architecture of the prostate in BPH patients [9]. In addition, the series elastic elements in the stromal and epithelial cells and most importantly the extracellular matrix contribute to a passive tissue force that is not regulated by active smooth muscle contraction [25]. In the present study, the smooth muscle content was decreased in the severely obstructed patient group. It appears that the reduction of the smooth muscle content may enhance passive force in prostatic tissue. However, further studies should be performed to clarify the relationship between passive tissue force and BOO in patients with BPH.

TURP is one of the common major surgical interventions performed by urologists worldwide. However, the emergence of alternative treatment modalities for lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction has placed TURP under intense scrutiny. In the present study, we performed TURP in ten BPH patients without BOO because of severe LUTS. However, approximately 30% of patients are dissatisfied with the surgical outcome [6]. In patients undergoing prostatectomy for BPH with LUTS, 86% experience relief of clinical symptoms and obstruction, despite 7% of patients still being urodynamically obstructed [1]. Rollema et al. [22] studied 29 patients who underwent full urodynamic tests before and after TURP. In contrast to the obstructed group, the PVR and urodynamic variables did not change in unobstructed patients.

According to Madersbacher et al. [19], there is no correlation between the degree of obstruction and the IPSS. In the present study, the IPSS, VV, and PVR did not differ between obstructed and unobstructed groups before TURP. The IPSS, PVR, and urodynamic variables in the obstructed group significantly improved after TURP, whereas urodynamic variables did not change in unobstructed patients. Thus, a pressure-flow study may reliably predict the outcome of TURP in BPH patients with LUTS.

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