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URODYNAMIC AND CLINICAL EFFECTS OF TERAZOSIN THERAPY IN SYMPTOMATIC PATIENTS WITH AND WITHOUT BLADDER OUTLET OBSTRUCTION: A STRATIFIED ANALYSIS

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ABSTRACT

Objectives. To evaluate clinical and urodynamic changes in patients with and without bladder outlet obstruction (BOO) and to compare the clinical and urodynamic results of terazosin treatment between patients with and without BOO.

Methods. In a prospective study, 97 patients who completed a full screening program including urodynamic investigation with pressure-flow study analysis started treatment with terazosin. A total of 60 patients completed 6 months of treatment and were re-evaluated with International Prostate Symptom Scores (IPSS), uroflowmetry, and urodynamic investigation with pressure-flow study analysis. Patients were stratified using the linear passive urethral resistance relation (lin-PURR) classification according to Schäfer. Patients with a lin-PURR of 3 or more were classified as patients with BOO and patients with a lin-PURR of 2 or less were classified as patients without BOO. The clinical and urodynamic changes within and between the groups with and without BOO were evaluated.

Results. Terazosin resulted in significant symptomatic relief (9 points on the IPSS scale; $P < 0.01$) and a significant improvement of free urinary flow (3.0 mL/s; $P < 0.01$). In patients with BOO, a statistically significant improvement of all urodynamic obstruction variables ($P < 0.01$) was shown. In patients without BOO, a significant improvement of free urinary flow (4.4 mL/s; $P < 0.01$), a statistically significantly improved bladder capacity (increase of 70 mL; $P = 0.01$), and no statistically significant changes in urodynamic obstruction variables ($P > 0.05$) were shown. Patients with a hypoactive detrusor were more prone to early dropout. When comparing the changes of symptoms ($P = 0.89$), quality of life ($P = 0.85$), and the number of patients with improvements of free uroflow of at least 30% ($P = 0.15$), there appeared to be no significant difference between the groups with and without BOO.

Conclusions. Although there is a statistically significant difference in urodynamic response to terazosin treatment between patients with and without BOO, we cannot recommend the use of pressure-flow studies in the selection of patients for terazosin treatment because the clinical results of treatment appear not to be significantly different between patients with and without BOO. It seems more useful, and certainly less expensive and less invasive, to start alpha$_1$-blocker therapy if, on clinical grounds, the urologist considers the patient to be a candidate for alpha$_1$-blocker therapy, and to continue therapy in those who respond. *Copyright 1997 by Elsevier Science Inc.* UROLOGY **49:** 197–206, 1997.

Lower urinary tract symptoms (LUTS) in elderly men are traditionally labeled as prostatism. The term suggests that the enlarged prostate gland, causing infravesical bladder outlet obstruction (BOO), is exclusively responsible for the LUTS. However, benign prostatic hyperplasia (BPH) is a histologic diagnosis, and LUTS are not necessarily related to urodynamically proven BOO or histologically proven BPH.[1,2] LUTS have been shown to be prevalent in an age-matched female population, indicating that the prostate is not required for the occurrence of these symptoms.[3] It has also been recognized that LUTS are related to detrusor instability or detrusor underactivity in a large per-

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centage of elderly men.[4,5] Obviously, the pathophysiology of LUTS is not always clear without an advanced urodynamic pressure-flow study investigation. Urodynamic pressure-flow study investigation is the reference standard to quantify the grade of BOO in elderly men with LUTS.[6] Precise grading of obstruction is becoming increasingly important in the evaluation and comparison of new therapeutic options in the treatment of patients with LUTS.

Because it is known that alpha$_1$-adrenoreceptors are predominantly present in the bladder neck and prostate smooth muscle, alpha$_1$-blocking agents have successfully been used to relieve symptoms in patients with LUTS.[7–9] Terazosin is a long-acting alpha$_1$-selective blocking agent originally used in the treatment of patients with hypertension. The effects of terazosin on symptom scores and urinary flow rates in large groups of patients with LUTS have been well documented.[8,9] These studies indicate that approximately 60% of patients respond well on treatment with terazosin. So far, it is unknown if it is possible to predict a good response on alpha$_1$-blocker treatment in the individual patient. Consequently, selection of patients who should be treated with an alpha$_1$-blocker or one of the other treatment modalities is still not based on scientific grounds. Earlier studies indicated that inclusion of urodynamic pressure-flow data in the preoperative evaluation may improve the overall clinical results, as does an indication for transurethral resection of the prostate.[5,10,11] Jensen[11] showed that symptomatic patients without BOO have a higher likelihood of subjective postoperative treatment failure when compared with symptomatic patients with BOO. It is unknown if a stratification based on the grade of BOO has any predictive value for patients who are treated with an alpha$_1$-selective blocking agent. In our study, we investigated possible differences in treatment outcome between patients with and patients without BOO who were treated with terazosin.

PATIENTS AND METHODS

In 1992, we started a prospective study to evaluate the outcome of therapy in patients with LUTS treated with terazosin. Between September 1992 and October 1994, all patients were evaluated at baseline by medical history, International Prostate Symptom Score (IPSS), prostate-specific antigen analysis, physical examination including digital rectal examination, ultrasonographic examination of the prostate, and free urinary flowmetry with subsequent ultrasonographic measurement of residual urinary volume. Prostate-specific antigen was determined using the Tandem-E PSA assay (Hybritech, San Diego, Calif). Prostate volume was calculated using the planimetric method with a Kretz Combison 330 ultrasound scanner and a multiplane 3-D rectal transducer (VRW 177AK). For free urinary flowmetry, the Dantec Urodyn 1000 flowmeter was used. For evaluation of the voiding efficiency, the voided percentage (the relative amount of bladder contents that was expelled during micturition), was calculated. All patients were considered neurologically normal, based on history, symptoms, and physical examination (no motor, sensory or reflex deficits). Patients in whom a prostatic carcinoma or other disease beyond the prostate could be expected, which could possibly influence their LUTS (for example, urethral stricture or bladder neck contracture), were evaluated more extensively first (by prostate biopsy or urethrocystoscopy) and excluded if these diseases were confirmed. Excluded were patients previously treated with transurethral (laser) resection of the prostate, transurethral microwave thermotherapy, or 5alpha-reductase inhibitors. Patients treated with alpha-blockers within 4 weeks before the baseline pressure-flow study was performed were also excluded. There were no explicit urodynamic pressure-flow study selection criteria. After the clinical diagnosis was established, patients were informed about the treatment options. When the patient experienced moderate symptoms or the patient was bothered by his symptoms, terazosin treatment was recommended in addition to other minimally invasive therapies. Patients started treatment with an increasing dose, to a maximum of 10 mg/day terazosin at 6 weeks of treatment, administered at bedtime. Every patient's dose was titrated up to 10 mg, but patients not tolerating the 10-mg dose had their dosage decreased to 5 mg. Urodynamic pressure-flow studies before and after 6 months of treatment with terazosin were used to evaluate urodynamic changes. Urinalysis and culture were negative at the time of pressure-flow studies. After 6 months of treatment, patients were reevaluated both clinically and urodynamically.

Urodynamic pressure-flow studies were performed with an 8F transurethral lumen catheter equipped with an intravesical microtip pressure sensor for bladder-pressure recording. Abdominal pressure was recorded intrarectally with an 8F microtip sensor catheter (MTC, Dräger, Best, Netherlands). Before cystometry, the bladder was emptied through the lumen of the transurethral catheter. The bladder was filled with 20°C water at a rate of 50 mL/min, with the patient in supine position. To ensure a reliable micturition diary, free uroflowmetry, and residual urine, care was taken to fill the bladder until the maximum bladder capacity was reached. Filling was stopped when the patient expressed a very strong urge to void. Commercially available equipment (UD 2000, MMS, Enschede, Netherlands) was used to record the pressure and flow data. Digitally stored data were translated to a urodynamic analysis computer program developed at our own department. This program provides a half automatic pressure-flow study analysis with passive urethral resistance relation (PURR) and urethral resistance factor (URA).

To provide an objective and precise grading of obstruction, pressure-flow graphs were fitted with a PURR curve at the lowest pressure part of the graph.[12] The minimal urethral opening pressure during micturition ($Pvoid_{min}$) and theoretical cross-sectional urethral lumen (A_{theo}) were calculated automatically on the basis of these manually adjusted PURR curves.[12] The pressure at maximum flow during the urodynamic investigation ($P_{det}Qmax$) was recorded. Correction for flow artifacts was performed when necessary. URA was determined by fitting the pressure-flow plot at the point of maximum flow (at $P_{det}Qmax$). URA was used to classify patients on a continuous, one-parameter scale of obstruction.[13] We also added a nonparametric analysis of obstruction with clinical classes according to the linear PURR (lin-PURR) pressure-flow nomogram.[14] The lin-PURR was determined by drawing a straight line between the $P_{det}Qmax$ and the $Pvoid_{min}$ points on the pressure-flow curve. The position of this line defined the outlet condition in a simple way and allowed classification of the severity of BOO. The following urodynamic variables were analyzed from free flowmetry: free Qmax; free voided

TABLE I. *Mean baseline characteristics of 97 patients included in the study (standard deviation in parentheses)**

	Whole group (n = 97)	Patients Without BOO (lin-PURR <3) (n = 53)	Patients with BOO (lin-PURR ≥3) (n = 44)	*P* value Between Groups
Age (years)	62 (9)	61 (9)	63 (8)	0.31
Prostate-specific antigen (ng/mL)	3.8 (3.8)	3.4 (3.5)	4.5 (4.1)	0.29
Prostate volume (cc)	38 (18)	34 (16)	42 (20)	0.06
IPSS	19.1 (5.9)	18.9 (5.8)	19.8 (5.8)	0.47
IPSS quality of life score	4.1 (1.2)	4.0 (1.2)	4.2 (1.2)	0.70
Free voided volume (mL)	265 (136)	296 (154)	231 (100)	0.06
Free Qmax (mL/s)	10.5 (5.5)	11.6 (6.5)	9.0 (3.7)	<0.01
Free residual volume (mL)	73 (120)	58 (86)	94 (154)	0.06
Free voided percentage (%)	81 (18)	85 (15)	77 (20)	0.02
Bladder capacity (mL)	424 (134)	437 (144)	400 (118)	0.28
Urod Qmax (mL/s)	7.7 (4.1)	9.4 (4.5)	5.5 (2.0)	<0.01
Urod residual volume (mL)	113 (157)	79 (146)	142 (147)	<0.01
Urod voided percentage (%)	77 (28)	85 (25)	69 (26)	<0.01
$P_{det}Qmax$ (cm H_2O)	57.5 (29.8)	39.8 (16.2)	80.5 (27.6)	<0.01
$Pvoid_{min}$ (cm H_2O)	29.1 (18.1)	18.4 (9.2)	42.8 (17.7)	<0.01
A_{theo} (mm^2)	3.7 (2.7)	4.9 (3.1)	2.1 (0.8)	<0.01
URA (cm H_2O)	35.2 (19.3)	22.5 (7.7)	51.7 (17.3)	<0.01
lin-PURR	2.4 (1.5)	1.3 (0.7)	3.9 (0.9)	<0.01

KEY: A_{theo} = *theoretical cross-sectional urethral lumen; BOO = bladder outlet obstruction; IPSS = International Prostate Symptom Score; lin-PURR = linear passive uretheral resistance relation;* $P_{det}Qmax$ = *detrusor pressure at maximum flow;* $Pvoid_{min}$ = *minimal urethral opening pressure during micturition; Qmax = maximum flow; URA = urethral resistance factor; urod Qmax = maximum flow during urodynamic investigation; urod residual volume = residual volume after urodynamic pressure-flow study; urod voided percentage = voided percentage during pressure-flow study.*

* *P value indicates statistically significant difference (P <0.05) between the baseline characteristics of the groups with and without bladder outlet obstruction*

volume; residual volume after free flowmetry; and free voided percentage. Bladder capacity was analyzed from cystometry. Finally, the following were analyzed from pressure-flow study: maximum flow during urodynamic investigation (urod Qmax), $P_{det}Qmax$, $Pvoid_{min}$, A_{theo}, URA, residual volume after urodynamic pressure-flow study (urod residual volume), and voided percentage during pressure-flow study (urod voided percentage) for the whole group of patients and for subgroups of patients who were categorized as patients with BOO (lin-PURR of 3 or more) and patients categorized as patients without BOO (lin-PURR less than 3).[15]

All statistical tests were two-sided and carried out at the 5% significance level. For numerical variables (such as symptom scores, quality-of-life scores, free flow parameters, and urodynamic parameters), within-treatment changes were assessed using the paired *t* test or the Wilcoxon matched-pairs signed-ranks test; between-treatment group changes were assessed using the *t* test for independent samples or the Mann-Whitney U test. The number of patients with an increase of voided volume of 50 mL or greater and with an improvement of Qmax of 10% or more from baseline in the groups with and without BOO were compared using the chi-square test.

RESULTS

From September 1992 to October 1994, 97 patients started treatment with terazosin. The baseline characteristics of 97 patients—and for subgroups with and without BOO—who were included in the study are indicated in Table I. This table indicates that patients without BOO had, in addition to significantly different urodynamic variables, a significant higher free Qmax and a significantly higher free voided percentage.

Twenty-eight patients (29%) stopped terazosin treatment before the evaluation at 6 months because of side effects (n = 13), no response to therapy (n = 12), or symptoms improving "spontaneously" (n = 3). The most frequent treatment-related side effects were mild headache, dizziness, and asthenia. Usually, these side effects were mild and transient. Of the 13 patients who experienced side effects, 9 stopped treatment because of treatment-related side effects: dizziness (n = 2), asthenia (n = 4), palpitations (n = 1), peripheral edema (n = 1), and paresthesia (n = 1). Dyspnea (n = 2), cardiac arrhythmia (n = 1), and visual disturbances (n = 1) were the reasons why the 4 other patients who experienced side effects stopped treatment; these events were not considered to be treatment related. Nine other patients were not available at 6 months because they were lost to follow-up (n = 4) or they refused their second clinical and urodynamic pressure-flow study evaluation (n = 5). Sixty patients, of whom 30 (50%) were classified as patients with BOO, were evaluated clinically and urodynamically before and after 6 months (median 28 months; range 17 to 45 weeks) of treatment.

The mean variables listed in Table I were compared between the group that continued taking terazosin for 6 months and the group that stopped taking terazosin before 6 months. Patients who stopped terazosin before 6 months were statisti-

cally significantly younger (mean age ± SD 58 ± 9 years) when compared with patients who continued taking terazosin up to 6 months (64 ± 8 years; $P < 0.01$). The mean bladder capacity in those who discontinued terazosin was higher (458 ± 125 mL) when compared with those who continued treatment up to month 6 (403 ± 136 mL; $P = 0.03$). When comparing the mean $Pvoid_{min}$ (23.3 ± 15 versus 32.3 ± 18.8 cm H_2O; $P = 0.01$), the mean URA (29.3 ± 14.1 versus 38.6 ± 21.1 cm H_2O; $P = 0.04$), and the mean lin-PURR category (1.9 ± 1.4 versus 2.7 ± 1.5; $P = 0.02$) between those who stopped terazosin treatment and those who continued it for 6 months, respectively, the mean values of those who stopped were significantly smaller, indicating that patients without BOO had a higher likelihood of stopping terazosin for various reasons before 6 months.

Table II outlines the mean symptom scores and mean urodynamic variables at baseline and after 6 months of treatment of the 60 patients who completed terazosin treatment for 6 months; the patients are divided into two subgroups, those with and without BOO. Also indicated in this table is the comparison of the changes in these variables between the groups with and without BOO. Mean total IPSS improved significantly in both groups: from 19.7 to 10.6 in the group without BOO and from 20.1 to 11.1 in the group with BOO (for both groups, $P < 0.01$). The mean IPSS quality-of-life score improved significantly in both groups: from 4.1 to 2.0 in the group without BOO and from 4.1 to 2.3 in the group with BOO (for both groups, $P < 0.01$). The mean symptom and quality-of-life-related changes between the groups without and with BOO were not significantly different ($P = 0.89$ and $P = 0.85$, respectively). In patients without BOO, mean free Qmax improved significantly by 4.4 mL/s ($P < 0.01$), mean free voided volume increased by 24 mL ($P = 0.52$), and mean free residual volume did not change significantly ($P = 0.24$). In the patients with BOO, mean free Qmax improved significantly by 1.6 mL/s ($P = 0.04$), mean free voided volume decreased by 32 mL ($P = 0.15$), and mean free residual volume decreased significantly from 110 to 59 mL ($P = 0.03$). The mean change of free Qmax was significantly higher in the group without BOO when compared with the group with BOO ($P = 0.01$). This could have been related to an increase of voided volume of 24 mL in the group without BOO and a decrease of voided volume of 32 mL in the group with BOO. The statistically significant difference in the change of free Qmax between the groups with and without BOO was evaluated further. Small improvements in free Qmax (10% or more from baseline) were found significantly more frequently in patients without BOO (77%) than in patients with BOO (48%) ($P = 0.02$). This higher number of patients with a small improvement of free Qmax could be related to an increase in free voided volume in patients without BOO. Forty-seven percent of the patients without BOO had an increase of free voided volume of at least 50 mL, whereas of those in the group with BOO, only 14% had an increase of free voided volume of 50 mL or greater ($P < 0.01$). When comparing the number of patients with larger improvements of free Qmax (30% or 50% or more from baseline), there were no significant differences between the two groups. Sixty percent of the patients without BOO and 41% of the patients with BOO had an increase of free Qmax of 30% or more from baseline ($P = 0.15$), and 43% and 34%, respectively, had an increase of free Qmax of 50% or more from baseline ($P = 0.49$). The mean free voided percentage improved from 85% to 91% in the group without BOO and from 74% to 82% in the group with BOO; changes within and between these groups were not significant.

The evaluation of the pressure-flow study variables urod Qmax, $P_{det}Qmax$, $Pvoid_{min}$, A_{theo}, URA, and lin-PURR in the patients with BOO revealed statistically significant improvements of all mean variables after 6 months of terazosin treatment (Table II). Significant changes of pressure-flow study variables in patients without BOO could not be detected, except for mean urod Qmax which improved significantly with 1.6 mL/s ($P = 0.02$). The mean bladder capacity in patients without BOO improved from 420 to 485 mL, which was statistically significant ($P = 0.01$). When evaluating the mean urodynamic changes between the groups with and without BOO, the changes for the variables urod voided percentage, $P_{det}Qmax$, $Pvoid_{min}$, URA, and lin-PURR were significantly higher in the group with BOO. In Figure 1, the improvements of $P_{det}Qmax$ and total IPSS are plotted for each patient who completed 6 months of treatment. The patients with BOO tended to have a larger urodynamical improvement when compared with patients without BOO. However, the symptomatic improvement is in the same range in both groups.

In Table III, the mean changes in symptoms, quality of life, free uroflow variables, and urodynamic variables are compared between the group of patients who improved urodynamically (that is, the group that had a lin-PURR decrease of 1 point or more on the Schäfer nomogram) and the group who did not. Only the changes in the inter-related urodynamic variables $P_{det}Qmax$, $Pvoid_{min}$, URA, and lin-PURR were significantly higher in the group that improved urodynamically. The mean changes in symptoms, quality of life, and free uroflow variables were not significantly different between those who improved urodynamically and those who did not.

TABLE II. *Mean characteristics, at baseline and after 6 months of terazosin treatment, for the 60 patients who completed the second urodynamic evaluation, divided into subgroups of patients, with and without bladder outlet obstruction (standard deviation in parentheses)**

	Patients Without BOO (lin-PURR <3) (n = 30)	Patients With BOO (lin-PURR ≥3) (n = 30)	*P* Value of the Change Between Groups
Total IPSS	Baseline: 19.7 (6.4)	Baseline: 20.1 (5.8)	
	Month 6: 10.6 (6.7)	Month 6: 11.1 (5.7)	
	Change: 9.5 (7.1)	Change: 9.7 (7.0)	0.89
	P value: <0.01	*P* value: <0.01	
IPSS quality-of-life score	Baseline: 4.1 (1.2)	Baseline: 4.1 (1.1)	
	Month 6: 2.0 (1.3)	Month 6: 2.3 (1.4)	
	Change: 2.0 (1.2)	Change: 1.9 (1.8)	0.85
	P value: <0.01	*P* value: <0.01	
Free voided volume (mL)	Baseline: 286 (163)	Baseline: 219 (99)	
	Month 6: 311 (173)	Month 6: 189 (70)	
	Change: 24 (191)	Change: 32 (111)	0.17
	P value: 0.52	*P* value: 0.15	
Free maximal flow rate (mL/s)	Baseline: 11.4 (8.2)	Baseline: 8.3 (2.7)	
	Month 6: 15.9 (8.2)	Month 6: 9.9 (3.5)	
	Change: 4.4 (4.7)	Change: 1.6 (3.4)	0.01
	P value: <0.01	*P* value: 0.04	
Free residual volume (mL)	Baseline: 59 (99)	Baseline: 110 (177)	
	Month 6: 45 (129)	Month 6: 59 (85)	
	Change: 11 (63)	Change: 53 (176)	0.23
	P value: 0.24	*P* value: 0.03	
Free voided percentage (%)	Baseline: 85 (14)	Baseline: 74 (22)	
	Month 6: 91 (14)	Month 6: 82 (22)	
	Change: 6 (15)	Change: 8 (22)	0.94
	P value: 0.07	*P* value: 0.10	
Bladder capacity (mL)	Baseline: 420 (145)	Baseline: 388 (128)	
	Month 6: 485 (192)	Month 6: 402 (127)	
	Change: 70 (135)	Change: 14 (123)	0.06
	P value: 0.01	*P* value: 0.93	
Urod Qmax (mL/s)	Baseline: 9.7 (5.1)	Baseline: 5.3 (2.2)	
	Month 6: 11.3 (5.6)	Month 6: 7.2 (3.5)	
	Change: 1.6 (4.6)	Change: 1.9 (2.7)	0.73
	P value: 0.02	*P* value: <0.01	
Urod residual volume (mL)	Baseline: 84 (151)	Baseline: 158 (158)	
	Month 6: 72 (134)	Month 6: 95 (114)	
	Change: 12 (161)	Change: 64 (85)	0.12
	P value: 0.62	*P* value: <0.01	
Urod voided percentage (%)	Baseline: 84 (24)	Baseline: 65 (28)	
	Month 6: 88 (22)	Month 6: 79 (22)	
	Change: 4 (26)	Change: 14 (19)	0.01
	P value: 0.35	*P* value: <0.01	
$P_{det}Qmax$ (cm H_2O)	Baseline: 42.5 (16.0)	Baseline: 81.6 (30.3)	
	Month 6: 44.4 (19.4)	Month 6: 62.6 (29.4)	
	Change: 1.9 (24.5)	Change: 19.0 (37.1)	0.01
	P value: 0.70	*P* value: <0.01	
$Pvoid_{min}$ (cm H_2O)	Baseline: 21.1 (9.8)	Baseline: 43.6 (19.1)	
	Month 6: 19.1 (13.6)	Month 6: 29.8 (17.5)	
	Change: 2.0 (15.6)	Change: 13.8 (22.3)	0.02
	P value: 0.51	*P* value: <0.01	
A_{theo} (mm^2)	Baseline: 5.3 (3.7)	Baseline: 2.1 (0.8)	
	Month 6: 5.8 (3.0)	Month 6: 3.3 (2.0)	
	Change: 0.5 (3.3)	Change: 1.2 (1.6)	0.57
	P value: 0.11	*P* value: <0.01	

(continued)

	Patients Without BOO (lin-PURR <3) (n = 30)	Patients With BOO (lin-PURR ≥3) (n = 30)	*P* Value of the Change Between Groups
URA (cm H_2O)	Baseline: 23.7 (8.0)	Baseline: 53.5 (19.6)	
	Month 6: 21.8 (10.6)	Month 6: 37.7 (17.3)	
	Change: 1.9 (9.7)	Change: 15.8 (15.8)	<0.01
	P value: 0.07	*P* value: <0.01	
lin-PURR	Baseline: 1.4 (0.7)	Baseline: 3.9 (1.0)	
	Month 6: 1.2 (1.0)	Month 6: 2.8 (1.6)	
	Change: 0.3 (1.0)	Change: 1.3 (1.2)	<0.01
	P value: 0.30	*P* value: <0.01	

TABLE II. *Continued*

Abbreviations as in Table I.

** P values in the columns regarding patients without and with bladder outlet obstruction indicate the significance of the comparison of baseline versus month 6 within groups. P value between groups indicates the significance level of the comparison of the changes in the variables from baseline to month 6 between the groups with and without bladder outlet obstruction*

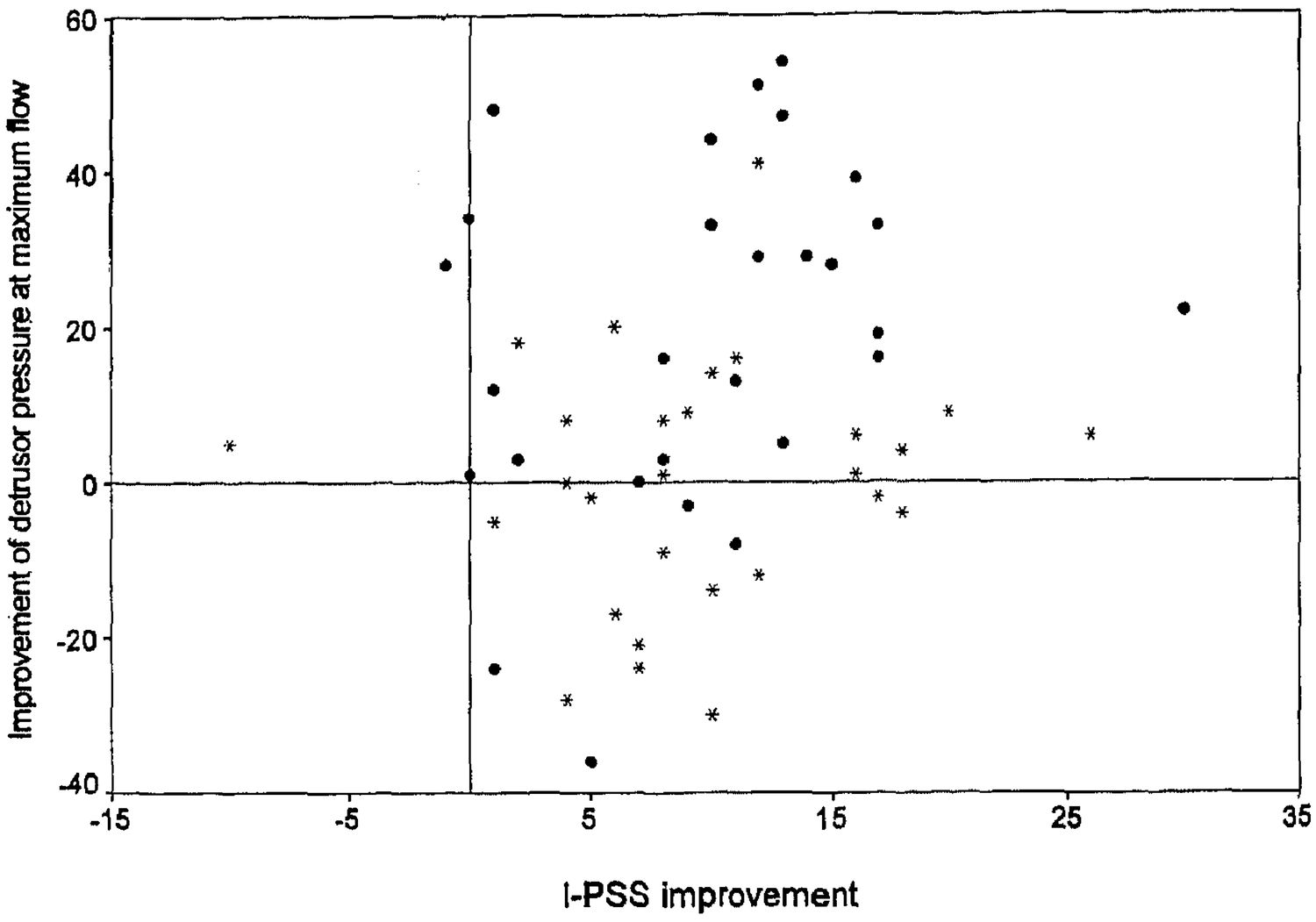

FIGURE 1. *Urodynamic and symptomatic results for each individual patient who completed 6 months of terazosin therapy, labeled according to the bladder outlet obstruction class, with BOO (solid circle) (linear passive urethral resistance relation [lin-PURR] of 3 or more) and without BOO (asterisk) (lin-PURR of less than 3). Improvement of detrusor pressure at maximum flow during urodynamic investigation ($P_{det}Qmax$) in cm H_2O on the y-axis, defined as $P_{det}Qmax$ at baseline minus $P_{det}Qmax$ at month 6, and improvement of total International Prostate Symptom Score (IPSS) on the x-axis, defined as total IPSS at baseline minus total IPSS at month 6.*

After 6 months, 54 of 93 patients (58%) continued terazosin treatment. The others were treated with transurethral microwave thermotherapy (n = 4), transurethral laser ablation of the prostate (n = 9), other medication (n = 7), or unknown procedures or medications (n = 4), or they were followed with the watchful waiting policy (n = 15). treatment; therefore, dropout and overtreatment percentages may decrease considerably.[11,17]

COMMENT

During the World Health Organization international consultation on BPH in 1993, it was advised that, if obstruction is the end point of the study, pressure-flow studies before and after treatment should be used in the evaluation of new therapies.[16] Pressure-flow studies enable us to investigate the relationship between subjective efficacy of treatment and objective voiding parameters. Moreover, the use of pressure-flow studies may help to select patients for a given

With respect to the efficacy of terazosin in the group with BOO, we showed that all mean values of $P_{det}Qmax$, $Pvoid_{min}$, A_{theo}, and URA improved significantly after 6 months of treatment with terazosin. From a theoretical viewpoint, the mechanism of voiding using an $alpha_1$-adrenergic blocker is changed toward better outlet distensibility during voiding; thus, it becomes more efficient. The first effect of a decrease in outlet obstruction is presumably a change in the balance of bladder outlet and contraction toward a lower-pressure micturition with improved efficacy. Theoretically, the increase in Qmax might not be as high as may be expected, which may be partly attributed to a decrease in $P_{det}Qmax$. More efficient voiding can also be shown by lower post-void residual volumes, but this could not be demon-

TABLE III. *Comparison of the changes after terazosin treatment for 6 months between the group that improved urodynamically (lin-PURR decrease of at least 1 point) and the group that did not (standard deviation in parentheses)*

	Patients With a lin-PURR Decrease ≥ 1 (n = 35)	Patients Without a lin-PURR Decrease ≥ 1 (n = 25)	*P* Value Between Groups
Total IPSS	8.7 (5.2)	10.7 (8.7)	0.30
IPSS quality of life score	1.9 (1.5)	2.1 (1.5)	0.70
Free voided volume (mL)	3 (141)	−14 (181)	0.68
Free maximal flow rate (mL/s)	3.1 (5.0)	3.1 (3.3)	0.98
Free residual volume (mL)	48 (164)	12 (71)	0.31
Free voided percentage (%)	9 (21)	4 (15)	0.94
Bladder capacity (mL)	29 (119)	60 (147)	0.33
Urod Qmax (mL/s)	2.4 (3.1)	0.9 (4.3)	0.13
Urod residual volume (mL)	55 (134)	13 (123)	0.21
Urod voided percentage (%)	12 (22)	5 (23)	0.43
$P_{det}Qmax$ (cm H_2O)	24.5 (26.7)	−13.8 (27.5)	<0.01
$Pvoid_{min}$ (cm H_2O)	17.1 (18.9)	−5.0 (13.3)	<0.01
A_{theo} (mm^2)	1.1 (2.6)	0.5 (2.7)	0.48
URA (cm H_2O)	17.2 (11.8)	−2.9 (9.7)	<0.01
lin-PURR	1.6 (0.8)	−0.3 (0.6)	<0.01

Abbreviations as in Table I.

strated by our patients; they had a low mean residual volume of 59 mL with a high standard deviation of 99 mL. A significantly larger A_{theo}, together with a significant decrease in $Pvoid_{min}$, indicates that terazosin has relaxed the bladder outlet so that more efficient voiding can occur.

In the patients without BOO, statistically significant changes of urodynamic variables could not be shown, except for free Qmax, urod Qmax, and bladder capacity. When evaluating the present study, we have to realize that this study is a noncontrolled one, so we have to be careful in drawing far-reaching conclusions with respect to efficacy. Exact quantification of the urodynamic effect of treatment is only possible with a double-blind, placebo-controlled study. This is mainly due to a large placebo effect that exists in patients treated with an $alpha_1$-blocker such as terazosin. In a large randomized, double-blind study, Roehrborn *et al.*[18] showed a 7.6-point improvement in symptom score on the IPSS scale in the terazosin-treated group, whereas in patients treated with a placebo, symptom score improved by only 3.7 points. The improvements in free Qmax were an increase of 2.2 mL/s in the terazosin-treated group and an increase of 0.8 mL/s in the placebo-treated group.[18]

At baseline, patients with BOO had a significantly different voiding mechanism, with lower voided percentages and lower maximum flow rates when compared with the group without BOO (Table I). Because terazosin treatment improves the obstruction classification, some patients will shift from the group with BOO to the group without BOO, and this could result in a favorable improvement of free Qmax.

In the present study, dropout percentages were relatively higher than those reported in the literature. Lepor[8] reported that, of 494 patients enrolled in a 42-month, open-label, multicenter study of terazosin, 213 (43%) withdrew prematurely; 55 (11%) because of lack of effectiveness, 96 (19%) because of adverse events, and 62 (13%) because of administrative reasons. It could be that the 38% dropout rate in the present study (37 of 97 patients dropped out before 6 months) is relatively higher because we offered patients with moderate symptoms or patients who are bothered by their symptoms the choice between an $alpha_1$-blocker or other minimally invasive therapies. With a wide variety of minimally invasive treatment options, patients and urologists may more easily change their original treatment decision, compared with a situation where, after $alpha_1$-blocker treatment, the only options are watchful waiting or prostatectomy.

Patients without BOO were more prone to early dropout for various reasons when compared with patients with BOO. In patients with a lin-PURR of 0 or 1, the poor urinary stream is caused by a hypoactive detrusor muscle. These patients benefit little from transurethral resection of the prostate.[11] It could be that the unobstructed patients are also less likely to benefit from $alpha_1$-blockers. This may be consistent with the assumption that it is unlikely that the detrusor function is improved by these drugs.

Our study design may be criticized for lack of a placebo control group and for potential selection bias. However, the mean changes of peak flow rates and symptom scores observed in this open-

label study were comparable to the data from a randomized study.[19] Earlier studies have indicated that the expected improvement of mean free Qmax after 6 months of treatment with terazosin is between 2.4 and 3.1 mL/s.[8,9,18,19] In our study, the mean improvement of free Qmax in the total group of patients was 3.0 mL/s. One may question the clinical relevance of a 3.0 mL/s improvement of free Qmax. This study indicates that, besides the improved free Qmax, more variables may change after terazosin therapy. In the present study, unobstructed patients had a statistically significantly increased bladder capacity. Patients with BOO had a statistically significantly decreased residual volume. As a result of these changes, another micturition pattern may develop that could result in a significant improvement of the IPSS, especially when taking into account that the questions of the IPSS questionnaire are concerned with bladder emptying, frequency, intermittency, urgency, nocturia, weak stream, and hesitancy. All of these symptoms may improve as a result of improved free Qmax, bladder capacity, or residual volume.

When comparing the changes after 6 months of therapy between the patients with and without BOO, the changes in symptoms and quality of life were not significantly different (Table II). An improvement of free voided volume of 50 mL or more occurred significantly more frequently in the group without BOO. A larger voided volume in the group without BOO could result in a higher number of patients with slight improvements in free Qmax. When comparing the free voided volumes with the free Qmax, using the Liverpool nomograms, it appeared that the values of the first voiding in the group without BOO—a voided volume of 286 mL and a free Qmax of 11.4 mL/s—correspond with the 5th percentile whereas the values of the second voiding—a voided volume of 311 mL and a free Qmax of 15.9 mL/s—correspond with the 17th percentile of the healthy males investigated.[20] For the group with BOO, the values of the flows correspond with the 5th and 10th percentile for the first and the second voiding, respectively. This indicates that, despite the different voided volumes, the free Qmax increases, probably as a result of therapy. When we evaluated the number of patients with greater improvements in free Qmax, there was no significant difference between groups with and without BOO, which demonstrates that, in our patients without BOO, statistically significant improvements in free Qmax were not confirmed by significant improvements of urodynamic variables. Significant changes in urodynamic variables were only shown in the group with BOO. This finding suggests that the way we analyze efficacy in most pharmacotherapy studies for BPH (that is, improvements in symptoms and small improvements of Qmax) does not depend on the urodynamic mechanism of action. Therefore, we cannot recommend the use of pressure-flow studies in the selection of patients for terazosin treatment in daily urologic practice because the changes of symptoms and quality of life between the groups with and without BOO were not significantly different. Moreover, the number of patients with improvements of free uroflow of at least 30% appeared not to be significantly different between groups with and without BOO. Hence, it seems more useful and certainly less expensive and less invasive to start $alpha_1$-blocker therapy if, on clinical grounds, the urologist considers the patient to be a candidate for $alpha_1$-blocker therapy and to continue therapy in those who are satisfied.

However, it is unknown what the long-lasting effect of BOO on the bladder is for patients who are satisfied with their treatment but who remain urodynamically obstructed. Do they have a higher likelihood of developing complications in the long term, such as obstructive nephropathy, urinary retention, infection, bleeding, bladder stones, or other complications that adversely affect their well-being? Is there a difference in the probability of developing complications when compared with patients without BOO? Further follow-up and more prospective, well-controlled investigations are necessary to provide the still-lacking information on the long-lasting effects and complications of pharmacologic treatment.

CONCLUSIONS

We have shown that a stratified analysis, based on the urodynamic classification of BOO, provides insight into the working mechanism of terazosin in patients with and without BOO. Patients with a hypoactive detrusor muscle may be more prone to drop out early when compared with patients who have a normal detrusor function. We also showed that after 6 months of terazosin treatment, the changes of symptoms and quality of life and the number of patients with improvements of free uroflow of 30% or greater appeared not to be significantly different between the groups with and without BOO. Therefore, we cannot recommend the use of pressure-flow studies in daily urologic practice if, on clinical grounds, the urologist considers the patient to be a candidate for $alpha_1$-blocker therapy. It seems more useful, and certainly less expensive and less invasive, to start terazosin therapy for patients and to stop therapy in those who are not satisfied. In the dissatisfied patients, pressure-flow studies could be of help in selecting patients for more invasive treatments. In patients who are satisfied with their treatment, terazosin

could be continued. However, because the long-term complications of pharmacologic treatment in patients with BOO are not well known, we recommend to follow up these patients on a regular basis.

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EDITORIAL COMMENT

The authors have done an extensive urodynamic analysis of a group of men receiving terazosin therapy. A number of interesting points can be gleaned from this report: (1) not surprisingly, men with lower urinary tract symptoms have varying urodynamic findings; (2) the magnitude of response to terazosin cannot be predicted based on pretherapy pressure-flow evaluation; and, most interestingly, (3) the dropouts or discontinuation group tended to be younger, to have higher bladder capacities, and to not have bladder outlet obstruction (BOO).

There are a number of methodologic questions that remain unresolved. Primarily, the population was highly select and not randomized. Although briefly noted by the authors, the primary concern is how many patients were screened. We know that 97 patients were enrolled, but how many were excluded and why? Given the enrollment period of more than 2 years, this relatively low number of patients suggests a potential selection bias.

Second, the magnitude of response in this study is *not* consistent with previously reported studies with terazosin. In patients without BOO, maximum flow (Qmax) increased 4.4 mL/s, more than twice that reported from larger multicenter trials using either terazosin or other alpha-blockers such as doxazosin or tamsulosin. In addition, one would think that patients with BOO would have a greater likelihood of increasing Qmax than those without BOO. In this study, the exact opposite occurred. Although the authors' conjecture that this may be due to higher voided volumes in the group without BOO, the magnitude of response is still extraordinary.

Third, the dropout rate was 29% at 6 months. This also represents a higher rate than other reported clinical studies using alpha blockade. In addition, we reported that more than 70% of patients were on alpha-blockers at 2 years.[1]

Pressure-flow evaluation is an important instrument used in the diagnosis, management, and follow-up of urologic disorders that affect the lower urinary tract. Although the role of routine urodynamic evaluation in lower urinary tract symptoms in men is in question, pressure-flow studies remain the best objective test for BOO. Various investigators have reported an imprecise relationship between subjective parameters such as symptoms and urodynamic findings. In part, this may be secondary to different methods of performing urodynamic studies among investigators, as well as defining the most appropriate parameters of obstruction. In this study, a

linear passive urethral resistance relation of less than 3 was considered urodynamic evidence of no obstruction. Should this parameter be the reference standard? Even urodynamic advocates cannot agree on what should be the parameter used to diagnose obstruction.

For urodynamics to have widespread clinical usefulness, parameters of measurement should (1) ideally correlate with symptoms; (2) delineate which patients are at risk if left untreated; and (3) predict the need for therapy and success of therapeutic options designed to alleviate outlet obstruction. The challenge of those who advocate pressure-flow evaluation prior to instituting therapy is to meet these aforementioned criteria successfully. In this regard, as recommended by the authors, it seems prudent, economical, and clinically reasonable to institute a trial of alpha-blockade in lieu of sophisticated pressure-flow evaluation.

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REPLY BY THE AUTHORS

There is no dispute that there are methodologic questions when comparing the results of noncontrolled studies. A large part of the differences between noncontrolled studies can be explained by selection of patients or by using other techniques of measurement. Our group of patients may be a specifically selected group of patients. In our hospital, when the patient experiences moderate symptoms or is bothered by his symptoms, treatment with an alpha$_1$-blocker is recommended in addition to other minimally invasive therapies, such as transurethral microwave thermotherapy or laser treatment of the prostate. With such a wide variety of treatment options, the group of patients who choose alpha$_1$-blocker treatment may be different when compared with the situation where the only other treatment options are watchful waiting and prostatectomy. Furthermore, patients and urologists may more easily change their original treatment decision and, hence, a larger number of patients will drop out from the study.

In patients without bladder outlet obstruction, the magnitude of improvement of mean free maximum flow (4.4 mL/s) is higher than the previously reported 2.4 to 3.1 mL/s. However, the 95% confidence interval of this improvement indicates that, in this group of patients, the true mean difference lies between 2.7 and 6.2 mL/s, and these values show an overlap with previously reported numbers. Moreover, when the maximum flow during urodynamic investigation was taken into account, the mean improvement of maximum flow was not significantly different between the patients with or without obstruction despite a larger bladder capacity ($P = 0.06$) in patients without bladder outlet obstruction. This indicates that the large improvement in maximum flow in patients without bladder outlet obstruction, as shown in our study, is consistent with previously reported studies.

An imprecise relationship between symptoms and urodynamic findings was recently reported by Ezz el Din *et al.*[1] who, in one center, evaluated the relationship between urodynamic findings and the International Prostate Symptom Score and specific questions in 803 patients. They concluded that these methods measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision of the patient presenting with lower urinary tract symptoms. Witjes *et al.*[2] have recently shown that urodynamics and symptom scores are unable to delineate which patients are at risk when left untreated. Patients with severe obstruction on urodynamics did not worsen in the short term; on the contrary, they were more likely to improve than to deteriorate urodynamically. Symptoms in this specific group of patients did not change significantly, confirming the discrepancy between subjective and objective data.

Because earlier studies have indicated that inclusion of pressure-flow data in the preoperative evaluation and patient selection for interventional therapies such as transurethral resection of the prostate and transurethral microwave thermotherapy may improve the overall clinical results,[3,4] it is our opinion that symptoms alone should not be used as the main indication for deciding on the appropriate minimally invasive or invasive treatment options.

We agree with Dr. Kaplan that, with future analyses of studies such as the ICS-'BPH' study,[5] we may be able to provide vital information on the relative potential of symptoms and urodynamic and other clinical parameters to predict a favorable response to current and innovative treatments.

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