

## ORIGINAL PAPER

# The Significance of the Influence of Aging and Infravesical Obstruction Caused by Benign Prostatic Enlargement on Detrusor Impairment

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**O**bjective: to analyze the influence of aging and infravesical obstruction on cystometric characteristics of patients with lower urinary tract symptoms (LUTS) and proven benign prostatic enlargement (BPE). **Methodology:** A retrospective analysis was performed of basic characteristics of randomly chosen 213 patients with LUTS caused by BPE and urodynamic findings made in period 2005-2009 at the Urology Department of the Sarajevo University Clinical Center. The patients were divided into groups based on their age (<60 years/46 patients, 60-69 years /95 pat., and >70 years /72 pat.), and the degree of bladder compliance loss (<20 ml/cmH<sub>2</sub>O-76 patients, 20-40 ml/cmH<sub>2</sub>O-57 pat., and >40 ml/cmH<sub>2</sub>O-80 pat.). All patients had International Prostate Symptom Score (IPSS) completed, prostate volume measured transabdominally, free uroflowmetry, as well as complete urodynamic study (UDS) findings – cystometry and pressure/flow studies (PFS). The PFS data were plotted on L-PURR, URA and ICS nomogram, bladder contractility index (BCI) and obstruction coefficient (OCO) were calculated for each patient. **Results:** There was no statistically significant difference of IPSS-S, prostate volume and postvoid residual urine among the age groups. Qmax (ml/sec.) declines significantly with age (mean 11.9 vs. 10.3 vs. 7.9, ANOVA  $p < 0.001$ ), along with statistically significant decrease of cystometric capacity (mean 331ml vs. 293 ml vs. 264 ml,  $p=0.001$ ), bladder compliance (BC-ml/cmH<sub>2</sub>O) (mean 35.3 vs. 31 vs. 26.5,  $p=0.013$ ), with increased incidence of detrusor overactivity (DO) (21.7% vs. 32.6% vs. 45.8%, chi2 test for trend  $p=0.006$ ), followed by a higher incidence of obstruction (URA $\geq$ 29 cmH<sub>2</sub>O) (37% patients vs. 61% patients vs. 72.2% patients Chi2 for trend=13.8;  $p=0.0002$ ), along with noticeable reduction of BCI (117 vs. 121 vs. 106;  $p=0.02$ ). Patients with severe BC damage (<20 ml/cmH<sub>2</sub>O) showed a difference with respect to the degree of obstruction and age, along with decreased cystometric capacity and higher incidence of DO, while the difference in IPP-S was insignificant. OCO with cut-off point of 1 showed significant difference with regard to age (66.3 vs. 66.6 years, T test,  $p=0.015$ ), prostate volume (45 cc vs. 51.8 cc,  $p=0.007$ ) and incidence of DO (26% vs. 43.4%,  $p=0.02$ ). **Conclusion:** the degree of bladder compliance loss and incidence of obstruction increase with age, as reflected in decreased bladder capacity, decreased urine voided volume and increased incidence of DO, along with noticeably impaired detrusor contractility. **Key words:** BPE, UDS, infravesical obstruction, cystometric characteristics.

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## 1. INTRODUCTION

The incidence of benign prostatic enlargement (BPE), as well as the presence of lower urinary tract symptoms (LUTS) increase with age, and these conditions are highly prevalent as early as beyond the fourth decade (1). However, aging increases not only the incidence of clinical BPE, but also the incidence of other factors and illnesses

that may contribute to the symptoms and pathophysiology of voiding dysfunction, causing lower urinary tract symptoms. Biological aging and the changes of bladder detrusor due to aging make the etiopathological mechanism of the benign prostatic enlargement additionally complex due to the occurrence of detrusor underactivity, detrusor overactivity and sensory im-

pairment. Finally, the signs of a combination of these factors can be found in practice, which, along with reduced bladder compliance, reduced functional bladder capacity and high bladder filling pressure may result in a pronounced expression of symptoms, as well as in the damage to upper urinary tract distal type nephropathy (2). Urodynamic measurements (UDS), albeit invasive, are the most accurate studies to assess the actual detrusor condition and behavior during storage phase and emptying phase, revealing bladder comorbidities or bladder outlet obstruction (BOO). However, the clinical value of bladder sensations and detrusor dysfunction still remain poorly understood (3). Since reports in the literature on the relationship between aging and infravesical obstruction due to BPE leading to the change in cystometric characteristics, are rather scarce, a retrospective study was conducted aimed to analyze the impact of the above-mentioned factors on age-related bladder condition and behavior.

## 2. METHODS AND MATERIALS

A retrospective analysis was made of the data on 213 randomly chosen patients from Urology department of the Sarajevo University Clinical Center from the period 2005-2009. All patients had a completed International Prostate Symptom Score, prostate volume measured transabdominally, PSA values, and free uroflowmetry data, as well as a complete finding of urodynamic studies (cystometry and pressure/flow stud-

ies). For each patient, cystometry was carried out in a sitting position with a 25 ml/min infusion rate using the apparatus Dantec UD 5500 and apparatus Andromeda Ellipse 4. Methods, definitions and units conformed to the standards proposed by the ICS (4), except where specifically noted. For each trace, bladder compliance (BC) was manually corrected and defined. The calculation of BC was made by dividing the bladder capacity by the change of pressure corresponding to 25% of capacity and at cystometric capacity before the increase in preicturition pressure, and avoiding a sudden pressure change in case of involuntary detrusor contraction (DO). Therefore, the interference of detrusor overactivity on bladder compliance calculation was reduced. Five methods were used to assess bladder outlet obstruction (BOO). The results from PFS were plotted on Linear passive urethral resistance relation (L-PURR) -Schaefer nomogram (grading BOO); ICS nomogram was used to classify and diagnose BOO, URA nomogram for allocating patients in the clear zone of obstruction. Bladder outlet obstruction index (BOOI) was calculated, according the formula  $P_{det} Q_{max} - 2Q_{max}$ , as well as the obstruction coefficient (OCO), developed by Schaefer, which was used to quantitatively evaluate urethral resistance, following the formula:  $OCO = P_{det} Q_{max} / (40 + 2Q_{max})$  (5). Bladder contractility index (BCI) was also used, which can be derived from formula  $P_{det} Q_{max} + 5Q_{max}$ , where BCI <100 represents weak contractility, BCI 100-150 and BCI >150 represent normal and strong contractility of the detrusor muscle, respectively (6). The patients were then divided as per age groups: <60 years/46 patients (21.6%), 60-69 years /95 patients (44.6%) and ≥70 years /72 patients (33.8%), and as per BC impairment. Severe impairment of BC (<20 ml/cmH<sub>2</sub>O-76 pat./35.7%), mild impairment of BC (20-40 ml/cmH<sub>2</sub>O-57 pat./26.8%) and preserved BC (>40 ml/cmH<sub>2</sub>O-80 pat./37.5%), were presumed. The statistical analysis was conducted by using Medcalc Software for Windows, Version 9, and one-way ANOVA test, T test, linear regression model, stepwise logistic regression model, and correlation coefficient anal-

ysis were used to analyze the relationship among the factors. Statistical significance was defined as a p-value (two tailed) < 0.05.

### 3. RESULTS

The mean age of 213 patients was 65 years (47-87), with an average prostate volume of 48 cc (28-120). The mean value of IPS score was 16.4 (5-32), with average quality of life of 3 (1-6), average PSA level of 2.6 ng/ml (0.8- 5.9), and average Q<sub>max</sub> of 9.9 ml/sec (2.3-36).

Linear regression showed statistically significant correlation of aging and obstruction for the group, defined with BOOI (mean BOOI 46.3±36),  $r = 0.29$  ( $p < 0.0001$ ) (Figure 1).

Kruskal-Wallis test showed a significant difference in the reduction of cystometric capacity by age groups. In the youngest age group, the average cystometric capacity was 331.2 ml, versus 293 ml and 263.7 ml, in older age groups, namely ( $p < 0.001$ ) (Figure 2).

Bladder contractility index showed significant age-related changes, therefore only 5 (6.9%) patients in the oldest group have a strong BCI (≥150), while in the older and the youngest groups 24 (25.3%) patients and 18 (39.1%) patients had a strong BCI, respectively ( $Chi^2 = 0.017$ ). BCI is linked to the obstruction since a statistically significant correlation of BOOI and grade of BCI ( $\rho = 0.23$ ,  $p = 0.0007$ ) was proven.

The patients, as divided into age groups, manifested significant differences (determined by ANOVA test) in cystometric capacity, voided volume, Q<sub>max</sub>, and the incidence of DO, while differences in IPS Score and its subgroups were not shown, nor were shown differences in detrusor contraction duration,  $P_{det} Q_{max}$  or in the amount of postvoid residual urine (PVR). BC (ml/cmH<sub>2</sub>O) significantly decreases with age; from 35.3 to 30.2, to 26.5 ( $p = 0.013$ ), along with concurrent increase in the incidence of DO ( $chi^2$

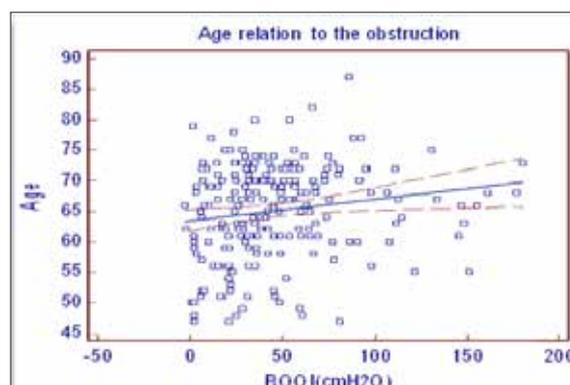


FIGURE 1. Linear regression for aging and obstruction (Regression Equation  $y = 63.466 + 0.0348 x$ )

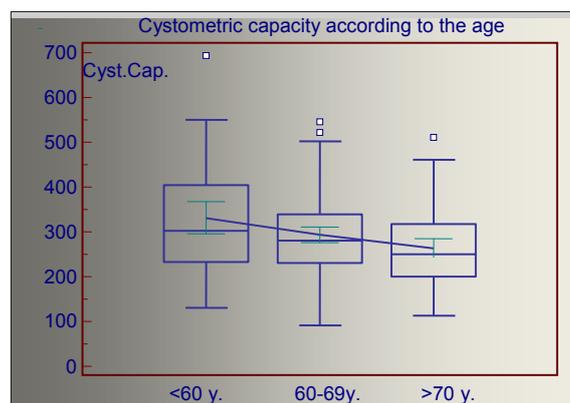


FIGURE 2. Age-related reduction in cystometric capacity

for trend;  $p = 0.006$ ) (Table 1). According to URA, in the youngest age group, 17 (37%) patients fall within the obstruction region, compared to 58 (61%) and 52 (72.2%) patients in the older age groups, respectively, i.e. ( $Chi^2$  for trend=13.8;  $p = 0.0002$ ). Stepwise logistic regression model according to the obstruction (dependent variable  $URA \geq 29$  cmH<sub>2</sub>O) showed that the most significant independent variables are: age (OR 1.06), BCI (OR 1.08) and Q<sub>max</sub> (OR 0.5), with overall model fit significance  $p < 0.0001$ . Variables excluded from the model were DOA, BC and cystometric capacity.

According to various urodynamic determinants of bladder outlet obstruction, statistically significant differences according to age were shown at the level of the obstruction, except for obstruction coefficient (OCO). BCI significantly decreases in the oldest age group. (Table 2).

As no difference was found in obstruction coefficient, according to age groups, the value  $OCO = 1$  was taken as a cut-off point to obstruction. 114 (53.5%)

No pat. 213	AGE<60 y. (46) Mean (SD), Med. ( range)	AGE 60-69 y. (95) Mean (SD), Med. ( range)	AGE ≥70y. (72) Mean (SD), Med. ( range)	Anova (F) p
Age	53.7 (3.8) 54.5(47-59)	64.6 (3) 65 (60-69)	73 (3.2) 72 (70-87)	
IPS Score	16.6 (6.9) 17 (4-29)	16.2 (7) 16 (5-32)	16.6 (6.3) 15.5 (7-29)	0.9 >0.05
Prostate volume(cc)	43.9 (18.1) 40 (24-111)	48.4 (20.1) 45 (26-120)	50.8 (19) 47 (27-120)	1.8 >0.05
Q <sub>max</sub> (ml/sec.)	11.9 (5.4) 11.5 (3.2-27.1)	10.3 (5.9) 8.9 (2.9 -36.2)	7.9 (3.8) 7 (2.6-22.2)	8.9 0.001
PVR (ml)	48.9 (63.4) 23 (0-250)	55.7 (65.5) 34 (90-470)	41.1 (40.4) 30 (0-177)	1.3 >0.05
Voided vol.(ml)	223 (61.2) 218.5 (73-372)	202 (68.8) 192 (85-392)	184.7 (58.2) 173 (75-317)	5.1 0.007
Cyst. Cap. (ml)	331.3 (119.4) 303 (130-694)	293(86) 280 (91-546)	263.8 (87.8) 249 (112-510)	7.1 0.001
BC (ml/cmH2o)	35.3 (15.7) 39.5 (6-58)	30.9 (15.9) 33 (4- 67)	26.5 (15.9) 22.5 (4-56)	4.4 0.013
P <sub>det</sub> Q <sub>max</sub> (cmH2o)	56.6 (26.5) 51 (14-155)	67.9 (34.2) 60 (23-192)	64.1 ( 30.2) 56 (24-196)	2 0.13
DCD (sec.)	101.8 (30.5) 97 (48-222)	107.6 (33) 100 (50-192)	99.4 (38.2) 96 (72-230)	1.3 >0.05
DO	10 (21.7%)	31 (32.6%)	33 (45.8%)	7.5 0.006*

TABLE 1. Main differences in patients divided according to age. DCD-detrusor contraction duration, DO-detrusor overactivity, BC-bladder compliance, PVR-postvoid residual. \* Chi 2 for trend

No pat. 213	AGE<60 y. (No46) Mean (SD), Med. ( range)	AGE 60-69 y. (No 95) Mean (SD), Med. ( range)	AGE ≥70y. (No 72) Mean (SD), Med. ( range)	Anova (F) p
URA	28.2 (18.5) 25 (11-130)	35.7 (18.9) 31 (14-111)	38.6 (19.9) 34 (14-130)	4.2 0.02
LPURR	1.9 (0.9) 2 (0-4)	2.4 (1.2) 3 (0-6)	2.5 (1.2) 3 (0-6)	3.7 0.03
ICS	1.9 (0.8) 2 (1-3)	2.3 (0.8) 3 (1-3)	2.3 (0.8) 3 (1-3)	5.6 0.004
OCO	0.9 (0.5) 0.8 (0.3-3.5)	1.2 (0.7) 0.96 (0.2-3.6)	1.2 (0.6) 1.1 (0.4-3.5)	2.7 >0.05
BOOI	33.9 (31.9) 22.5 (1.2-151.2)	50.6 (39.9) 42 (-2.6-177)	48.5 (31.4) 42.6 (1.6-180)	3.6 0.03
BCI	117.1 (32.8) 118.5 (58-192.5)	121.3 (41.6) 115 (47-247.5)	106.1 (33) 101.3 (53-235.5)	3.5 0.03

TABLE 2. Differences in urodynamic determinants of bladder outlet obstruction according to age groups

patients were outside of the obstruction zone, while 99 of them were inside the obstruction zone. It can be noticed that patients in this obstruction interval tend to be older, with larger prostate volume, lower Q<sub>max</sub>, lower cystometric capacity, lower bladder compliance and smaller voided volume, while the incidence of DOA increases from 26% in patients outside of the obstruction zone to 43.4% in those within the obstruction zone (Table 3).

By trichotomizing the patients into groups according to BC impairment, ANOVA test showed that there is a difference in age, cystometric capacity, DOA incidence, and level of obstruction. In severe bladder compliance impairment the DOA incidence was man-

ifested in 75% of the cases, but it decreased to 23% and 2.5%, respectively. Patients with severe BC impairment have a higher degree of obstruction compared to those with mild impairment or normal bladder compliance. There is no significant difference in IPS Score, prostate volume or residual urine (Table 4).

At the same time, no significant difference in BCI impairment was shown in patients divided into groups ac-

ording to bladder compliance impairment (Chi<sup>2</sup> test; p=0.14). Also, a good group-wise inverse correlation was shown between OCO and BC (r=-0.28; p < 0.0001).

Kruskal-Wallis test showed a significant difference in obstruction increase depending on the lowering of bladder compliance, via group specific factor (URA). Thus, the group with severe BC impairment the mean value of URA was 40.3 cmH<sub>2</sub>O, while the group with mild bladder impairment or the one with preserved compliance had the mean values of URA 36.2 cmH<sub>2</sub>O and 29.2 cmH<sub>2</sub>O, respectively, i.e. (p=0.003) (Figure 3).

#### 4. DISCUSSION

Irreversible physiological characteristics of aging affect the normal functioning of organs; thus, urinary bladder wears out with time, it becomes slower and less able to respond to growing functional demands, notably in the conditions of bladder outlet obstruction caused by prostate enlargement (7). In such conditions, the bladder goes through the primary compensated phase (muscle hypertrophy), when it often irregularly responds to small-volume stimuli by generating insufficient premature contractions. The prostatic obstruction via bladder wall thickening (increase in mass) results in detrusor functional impairment with reduced possibility of effective emptying, as proved by experiments on animals

No patients 213	OCO <1 (No pat. 114) Mean (SD) Median (range)	OCO ≥1 (No pat. 99) Mean (SD) Median (range)	T test P
Age	63.8 (8); 64 (47-80)	66.6 (7.3); 68 (47-87)	1.7 0.008
IPS Score	16.2 (6.9); 17 (5-32)	16.7 (6.4); 15 (6-31)	0.27 >0.05
Prostate volume (cc)	45 (16.2); 43 (20-111)	52.1 (21.9); 47 (21-120)	1.7 0.007
Q <sub>max</sub> (ml/sec.)	11.9 (6.1); 10.9 (3-36.2)	7.6(3); 7.1 (2.9 -17)	6.5 0.0000
PVR (ml)	40.5 (61); 21.5 (0-270)	59.4 (52.5) 39 (0-250)	2.4 0.02
Cyst. Cap. (ml)	302 (104.3); 271.5 (121-512)	279 (87.8); 279 (91-526)	1.7 >0.05
DO	31 (26%)	43 (43.4%)	5.5 0.02*
Voided vol.(ml)	213 (64.7); 218 (85-377)	187 962.8); 174 (73-296)	2.96 0.003
BC (ml/cmH2o)	32.7 (16); 38 (6-58)	27.6 (15.9); 25 (11-67)	2.3 0.02

TABLE 3. Main differences in patients outside or inside the obstruction zone, according to OCO<> 1. \*Chi 2 test

(8). A thickened bladder wall may have lower compliance than a normal wall. This can be explained by early activation of tension receptors with resulting reduced functional capacity, leading to an increase in irritating symptoms, namely the occurrence of frequency, nocturia and urgency. Connective tissue lying between muscle fascicles significantly decreases the bladder elasticity (compliance). The removal of the obstruction in an animal model results in progressive reduction of the bladder mass, compliance increase and a stronger contractile response to all forms of stimulation. When decom-

No pat. 213	BC (<20ml/cmH2O) No 76 Mean (SD), Med. ( range)	BC (20-40 ml/cmH2O) No 57 Mean (SD), Med. ( range)	BC (>40ml/cmH2O) No 80 Mean (SD), Med. ( range)	Anova (F) p
Age	67.1 (7) 68 ( 47-87)	64.5 (8) 64 (48- 80)	63.6 (8) 65 (47-77)	4.3 0.02
IPS Score	16.6 (6.8) 15 (5-32)	17 (5.7) 17 (6-28)	15.9 (7.2) 15 (5-31)	0.5 >0.05
Prost. Vol.(cc)	51.8 (19.8) 48.5 (26-114)	45.9 (17.7) 45 (28-106)	46.5 (19.8) 41 (29-120)	2.1 >0.05
Q <sub>max</sub> (ml/sec.)	9.4 (5.3) 8 (2.3-27.1)	9.5 (4.3) 9 (3-25)	10.6 (6) 9 (3.4-33.2)	1.2 >0.05
PVR (ml)	49.7 (67.4) 30 (0-470)	49.1 (48.2) 34 (0-185)	49 954.9) 30.5 (0-250)	0.03 >0.05
Cyst. Cap. (ml)	245.6 (82.3) 227.5 (91-474)	291 (83.8) 280 (153-522)	3335.2 (100.5) 318 (185- 512)	19.4 <0.001
BOOI	54.6 (43.2) 44.4 (-2.6-180)	53 (33.7) 50 91.6-146)	33.6 (25.1) 29.1 (1.2-146)	8.6 <0.001
DO	59 (74.7%)	13 (22.8%)	2 (2.5%)	96.4 <0.0001*

TABLE 4. Main differences in patients divided according to bladder compliance impairment

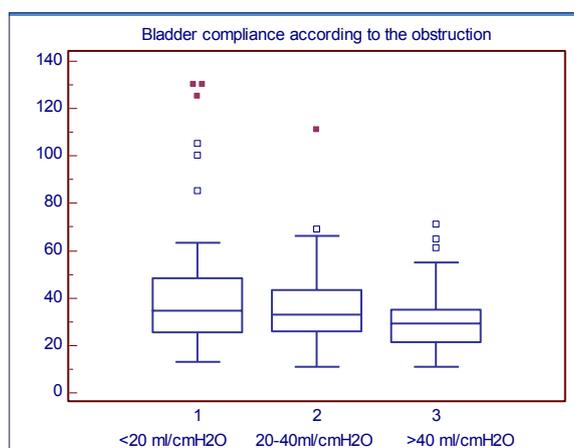


FIGURE 3. URA value corresponding to the BC groups

pensation progresses beyond a certain critical point, the obstruction removal does not result in an improved bladder function; the function deteriorates up to the final stage of decompensation, which is macroscopically represented in an enlarged bladder with a thinned wall and with few muscle components, or as a small thickened fibrous bladder with few muscle elements. This phenomenon is also age-related (9).

Although it is not known when exactly the bladder muscle decompensation occurs, detrusor underactivity and detrusor overactivity are developed consequently, increasing the symptomatology of the lower urinary tract with the symptoms of hard and slow urinary stream, hesitancy, abdominal straining, terminal dribbling, and an increased amount of residual urine.

This study showed the group-wise interdependence between aging and the increase of the obstruction (ex-

pressed by BOOI), with a correlation coefficient of  $r=0.29$  ( $p<0.0001$ ), and concurrent reduction in the bladder contractility, since only 6.9% of the patients in the oldest age group have strong contractility (BCI >150) compared to younger age groups (25.3% and 39.1% of the patients, respectively; or  $\chi^2=0.017$ ), and with a statistically significant correlation between BOOI and grade of BCI ( $\rho=0.23$ ,  $p=0.0007$ ). Schaefer proved that the bladder strength in obstructed condition does not increase, therefore the increased intravesical activity is related to overcoming urethral resistance rather than an increased muscular activity (5).

There is a significant declination of  $Q_{max}$  with aging, followed by smaller voided volumes and lower cystometric capacity. Also, BC significantly declines with age, from 35.3 ml/cmH2O to 31 and 26.5 cmH2O, respectively, i.e. ( $p=0.013$ ), along with increased DO incidence. Uninhibited bladder contractions occur in the youngest age group in 21.7% of the cases, while their percentage in older age groups are 32.6% and 45.8%, respectively ( $\chi^2$ ,  $p=0.006$ ).

The patients, as divided into age groups in this study, could not be differentiated according to clinical variables since, within the observed groups, there is no statistically significant difference in prostate volume, residual urine volume or IPS score ( $p>0.05$ ).

Madersbacher et al (10) did not find correlation between age and IPS-S, but they found a statistically significant decrease in  $Q_{max}$  and voided volume with age, along with an age-related increased incidence of detrusor overactivity from 20% to 47% according to age groups (10). The authors concluded that the proven decrease in  $Q_{max}$  and voided volume in patients with BPE should not necessarily be attributed only to bladder outlet obstruction, but that they depended on aging as well.

The models used for urodynamic evaluation of obstruction revealed a clear difference, namely older patients showed a higher degree of infravesical obstruction. As no clear difference in obstruction coefficient (urethral resistance) was shown, the patients were divided into groups with a cut-off point  $OCO < 1$  (11). A clear difference was shown in prostate volume and residual urine volume (mean 40.5 ml vs 59.4 ml;  $p=0.02$ ), and evidently increased DO incidence of 43.4% was found in obstructive group versus non-obstructive group (26%);  $p=0.02$ . It should be noted that there was no clear cut-off point for PVR volume. In clinical practice, PVR <30 ml can be considered insignificant, while residual urine exceeding 50 ml should be considered as an important indicator (12). Since the residual urine is often found in elderly patients (both women and men) without urethral obstruction or BPE, it is more likely that the urethral obstruction is only a contributing factor rather than the main cause for increased PVR (13).

By dividing the patients according

to BC impairment, it was shown that 35.7% of the patients had severely impaired BC, which was linked with aging as well (mean age 67 vs. 64.5 vs. 63.6,  $p=0.02$ ) and obstruction (mean BOOI 54.6 vs. 53 vs. 33.6;  $p < 0.0001$ ), with the correlation coefficient between OCO and BC of  $r=0.20$ ,  $p < 0.001$ . Liao suggests that the BC gradually reduces with the increased obstructed grade. Liao's correlation analysis shows a weak, but statistically significant inverse correlation between BC and OCO ( $r = -0.132$ ,  $P < 0.01$ ), as well as BC and L-PURR ( $r = -0.135$ ,  $P < 0.01$ ) (11). Having analyzed 170 patients with the lower urinary tract symptoms, Madersbacher (14) found 37% patients with significantly decreased bladder compliance, where the decreased compliance significantly correlated with aging, increased prostate volume and lower Qmax.

This study has shown that decreased compliance is directly linked with aging and obstruction, leading to increased DOA incidence (from 2.5% with preserved compliance to 22.8% and 74.7% with impaired compliance;  $p < 0.0001$ ). Ameda (15), however, found the occurrence of involuntary contractions of up to 41% in symptomatic elderly patients without urodynamic obstruction, resulting in a very low bladder capacity (264 ml).

## 5. CONCLUSION

The degree of bladder compliance impairment and the incidence of obstruction increase with age, which is reflected on decreased bladder capac-

ity, reduced urine voided volume and increased DOA incidence, along with noticeably impaired detrusor contractility and reduced maximum urinary flow rate. There is a group-wise statistically significant correlation between aging, bladder outlet obstruction (expressed as obstruction coefficient) and impaired compliance. Aging and BPE-caused obstruction seem to synergically lead to detrusor impairment, as clearly shown in urodynamic findings.

**Conflicts of interest: the authors have nothing to disclose.**

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