

## Voiding Dysfunction

# Bladder Wall Thickness is Associated with Responsiveness of Storage Symptoms to Alpha-Blockers in Men with Lower Urinary Tract Symptoms

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**Purpose:** Bladder wall thickness (BWT) is reported to be related to detrusor overactivity and bladder outlet obstruction. We investigated the relationship between BWT and the responsiveness of storage symptoms to alpha-blockers in men with lower urinary tract symptoms (LUTS).

**Materials and Methods:** A total of 74 patients with LUTS were enrolled. International Prostate Symptom Score, uroflowmetry with post-void residual urine volume, and transrectal ultrasonography (TRUS) were investigated. BWT was measured by performing TRUS at the midsagittal plane view, and the average value of BWT at the anterior, dome, and trigone areas was used. After 4 weeks of alpha-blocker medication, patients were reevaluated and divided into two groups. The responder group consisted of patients who reported improvement in the storage symptom subscore of 2 points or more; the non-responder group consisted of patients who reported improvement of less than 2 points. Clinical parameters including BWT were compared between the two groups.

**Results:** A total of 52 patients were followed. BWT was positively correlated with intravesical prostate protrusion (IPP) ( $9.26 \pm 4.99$ , standardized beta=0.393,  $p=0.002$ ) and storage symptom subscore ( $0.35 \pm 0.43$ , standardized beta=0.458,  $p=0.002$ ). Compared with that in the responder group, BWT was thicker in the non-responder group, and improvement in the storage symptom score was correlated with BWT ( $0.58 \pm 0.09$  cm vs.  $0.65 \pm 0.11$  cm,  $p=0.018$ ) and prostate volume ( $27.08 \pm 16.26$  ml vs.  $36.44 \pm 10.1$  ml,  $p=0.018$ ).

**Conclusions:** BWT was correlated with IPP, the storage symptom subscore, and the responsiveness of storage symptoms to alpha-blockers in LUTS/benign prostatic hyperplasia (BPH) patients. As BWT increased, the responsiveness of storage symptoms to alpha-blocker decreased in LUTS/BPH patients.

**Key Words:** Adrenergic alpha-antagonists; Lower urinary tract symptoms; Muscarinic antagonists

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## INTRODUCTION

Bladder outlet obstruction (BOO) is associated with changes in detrusor structure that can account for the resultant voiding dysfunction. Significant detrusor muscle hypertrophy is a well-recognized clinical finding seen in as-

sociation with several obstructive disorders of the lower urinary tract, such as benign prostatic hyperplasia (BPH) [1]. Features of the myohypertrophy can explain the overall weakness of the obstructed detrusor despite hypertrophy of its cells and involuntary contractions of the obstructed detrusor [2].

Observation of a thickened or trabeculated bladder wall is considered to be of great significance in the diagnosis of obstruction. Many studies have been conducted of the clinical usefulness of measurement of bladder wall thickness (BWT). Currently, the clinical usefulness of BWT remains controversial, but interest is increasing in its clinical significance [3-5].

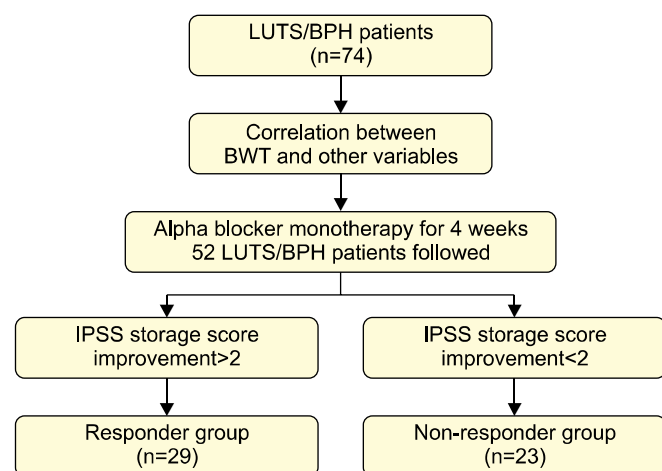
In terms of the guidelines established by the American Urological Association or the European Association of Urology, antimuscarinic agents can be used when lower urinary tract symptoms (LUTS) are predominantly irritative with caution or post-voided residual (PVR) urine volume [6]. The results of studies reported by Abrams et al. [7], Lee et al. [8], and Kaplan et al. [9] support antimuscarinic therapy for treating men with BPH and overactive bladder (OAB) symptoms. They reported that additive antimuscarinic agents to alpha-blocker and/or a 5-alpha-reductase inhibitor for patients with BPH/BOO and OAB are well tolerated and more efficacious in improving storage symptoms. However, debate remains concerning the criteria for use of antimuscarinic agents in treating patients with LUTS and BPH.

Given the above background, we supposed that BWT would be correlated with irritative lower urinary symptoms. We also supposed that alpha-blocker monotherapy would not improve irritative LUTS. To demonstrate these assumptions, we investigated the relationship between BWT and symptoms in patients with LUTS/BPH. We also investigated the relationship between BWT and the responsiveness of the storage symptoms to alpha-blockers in men with LUTS.

## MATERIALS AND METHODS

### 1. Study protocol

From January 2011 to February 2011, 74 men with LUTS who were older than 40 years were reviewed retrospec-



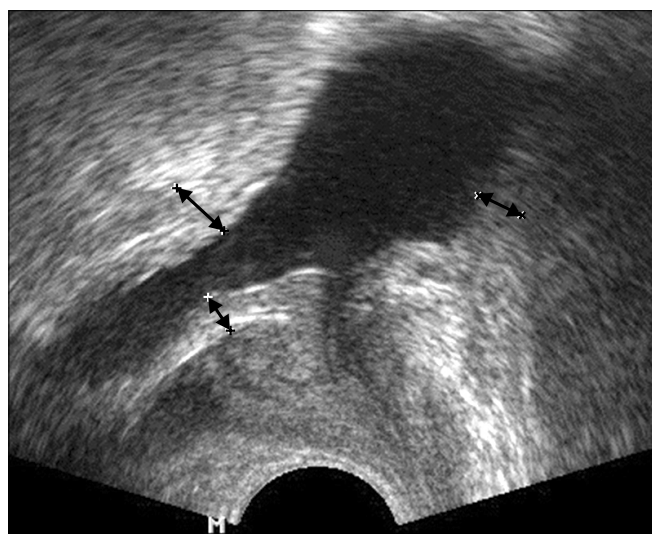
**FIG. 1.** Study design. LUTS/BPH, lower urinary tract symptoms/benign prostatic hyperplasia; BWT, bladder wall thickness; IPSS, International Prostate Symptom Score.

tively. Patients with an International Prostate Symptom Score (IPSS) over 8 and prostate volume over 20 ml were included. Included patients had no previous medical consultation or treatment for LUTS. Exclusion criteria were PVR over 150 ml, diagnosis of prostate cancer, bladder tumor, bladder stone, urethral stricture, urinary tract infection, previous prostate surgery, neurogenic bladder, hypersensitivity to alpha-blockers, and disorders of the liver or kidney. Patients were evaluated by IPSS, uroflowmetry (Medtronic Inc., Minneapolis, MN, USA), and PVR by transabdominal ultrasonography (US) and transrectal US (TRUS).

After the initial evaluations, an alpha-blocker was prescribed to all patients for 4 weeks. Alpha-blockers were tamsulosin 0.2 mg or doxazosin 4 mg or alfuzosin 10 mg. After 4 weeks of medication, the IPSS was reevaluated and the patients were divided into two groups. The responder group included patients who reported improvement of the IPSS storage symptom subscore of 2 points or more; the nonresponder group included patients who improved less than 2 points. We compared the relationship of the clinical parameters and BWT between the two groups (Fig. 1).

### 2. Transrectal ultrasonography (TRUS) measurement

TRUS was performed by one urologist to minimize the sampling bias. TRUS was done with a 6.5 MHz probe (SA-8000, Medison, Seoul, Korea) when bladder volume was approximately 100 ml. BWT was measured by performing TRUS with the 6.5 MHz linear probe in the midsagittal plane view at maximum magnification (Fig. 2). BWT was defined as the length between the outer and inner muscle surface, which was identified by hyperechogenic lines corresponding to subserosal tissue and to bladder mucosa plus submucosal tissue, respectively. It was measured at three different anatomical points: the anterior, the dome, and the



**FIG. 2.** Measurement of bladder wall thickness (black arrow) at 3 different sites by transrectal ultrasonography in the mid-sagittal plane view.

**TABLE 1.** Multiple regression analysis of bladder wall thickness and clinical parameters (n=74)

| Variable              | Beta ( $\beta$ ) | Standardized beta | p-value |
|-----------------------|------------------|-------------------|---------|
| Age (yr)              | 0.001            | 0.037             | 0.734   |
| Voiding symptom score | -0.008           | -0.202            | 0.162   |
| Storage symptom score | 0.017            | 0.458             | 0.002   |
| QoL                   | -0.018           | -0.115            | 0.355   |
| PSA (ng/ml)           | 0.001            | 0.014             | 0.888   |
| Prostate volume (ml)  | -0.003           | -0.274            | 0.401   |
| T-zone volume (ml)    | 0.005            | 0.353             | 0.266   |
| IPP (cm)              | 0.163            | 0.393             | 0.002   |
| Qmax (ml/s)           | -0.005           | -0.231            | 0.032   |
| PVR (ml)              | 0.000            | 0.031             | 0.907   |

QoL, quality of life; PSA, prostate-specific antigen; IPP, intravesical prostate protrusion; Qmax, maximal urine flow rate; PVR, post-voided residual urine volume.

trigone of the bladder, and the average value of measured BWT was used. In performing TRUS, the vertical distance from the tip of the prostate protrusion into the bladder to the bladder circumference at the prostate base in the mid-sagittal plane, which is termed intravesical prostate protrusion (IPP), was also measured.

### 3. Statistical analysis

Statistical analysis was referred to a statistics specialist, and SAS ver. 9.2 (SAS Inc., Cary, NC, USA) was used. The relation of each variable with BWT was examined by multiple linear regression analysis. Comparison between the two groups, before and after alpha-blocker administration, was analyzed by using independent t-tests and paired t-tests. Continuous data were reported as the mean $\pm$ standard deviation. A 5% level of significance was used for all statistical testing.

## RESULTS

At the time the study started, 74 LUTS/BPH patients were enrolled, but 52 patients were followed. The patients' mean age was 61.2 $\pm$ 10.8 years, mean prostate volume was 37.2 $\pm$ 14.7 ml, and mean prostate-specific antigen (PSA) was 2.0 $\pm$ 2.8 ng/ml. BWT was positively correlated with IPP (9.26 $\pm$ 4.99, standardized beta=0.393, p=0.002) and the storage symptom subscore (0.35 $\pm$ 0.43, standardized beta=0.458, p=0.002) (Table 1). BWT had a slightly negative correlation with the maximal urine flow rate (12.73 $\pm$ 8.81, standardized beta=-0.231, p=0.032).

After 4 weeks of alpha-blocker medication, improvement of the IPSS storage symptom subscore of 2 points or more was observed in 29 patients (responder group); the other 23 patients (non-responder group) reported improvement of less than 2 points. There were no significant differences in age, PSA, IPP, maximal urine flow rate, or PVR between the two groups (Table 2). Between the two groups, there was a significant difference in prostate volume and BWT.

**TABLE 2.** Comparison of clinical parameters between the two groups (n=52)

| Variable             | Responder group (n=29) | Nonresponder group (n=23) | p-value |
|----------------------|------------------------|---------------------------|---------|
| Age (yr)             | 60.82 $\pm$ 12.97      | 61.12 $\pm$ 10.90         | 0.928   |
| PSA (ng/ml)          | 2.33 $\pm$ 3.12        | 2.07 $\pm$ 2.32           | 0.737   |
| Prostate volume (ml) | 27.08 $\pm$ 16.26      | 36.44 $\pm$ 10.14         | 0.018   |
| T-zone volume (ml)   | 19.10 $\pm$ 9.23       | 20.73 $\pm$ 7.69          | 0.494   |
| IPP (cm)             | 0.23 $\pm$ 0.28        | 0.42 $\pm$ 0.42           | 0.051   |
| BWT (cm)             | 0.58 $\pm$ 0.09        | 0.65 $\pm$ 0.11           | 0.018   |
| Qmax (ml/s)          | 14.14 $\pm$ 9.05       | 11.62 $\pm$ 8.65          | 0.312   |
| PVR (ml)             | 45.29 $\pm$ 43.82      | 50.79 $\pm$ 53.65         | 0.686   |

PSA, prostate-specific antigen; IPP, intravesical prostate protrusion; BWT, bladder wall thickness; Qmax, maximal urine flow rate; PVR, post-voided residual urine volume.

**TABLE 3.** Logistic regression analysis of prostate volume and bladder wall thickness (BWT) in the nonresponder group

| Variable             | Standardized beta | Odds ratio | p-value |
|----------------------|-------------------|------------|---------|
| Prostate volume (ml) | 0.195             | 1.037      | 0.469   |
| BWT (cm)             | 1.207             | >999.999   | 0.002   |

The non-responder group had a larger prostate volume (27.08 $\pm$ 16.26 ml vs. 36.44 $\pm$ 10.1 ml, p=0.018) and thicker BWT than did the responder group (0.58 $\pm$ 0.09 cm vs. 0.65 $\pm$ 0.11 cm, p=0.018). However, the statistical analysis revealed that prostate volume had no significant influence in either group (Table 3). There was a significant improvement in total IPSS and the voiding symptom subscore in both groups after 4 weeks of alpha-blocker medication (Tables 3, 4).

## DISCUSSION

Urodynamic study is the gold standard clinical test for assessing lower urinary tract function. However, it is time consuming and invasive with associated morbidity [10]. Interest has therefore arisen in the development of non-invasive methods for assessing lower urinary tract function. The diagnostic potential of measurements of BWT, detrusor wall thickness, and US-estimated bladder weight in men with LUTS and various degrees of BOO have been explored [5,11-14].

The changes to the detrusor by BOO are mainly an increase in smooth muscle bulk with or without interstitial collagen deposition. Experimental studies have revealed similar features in animals with BOO [15]. Animal studies have revealed bladder wall hypertrophy and increased bladder weight after partial BOO [16-18]. Histological analysis has shown smooth muscle cell hypertrophy and hyperplasia and increased collagen deposition, ratio of type I to III collagen, and muscarinic cholinergic receptors [17]. Bladder smooth muscle cell hypertrophy shows wide-

**TABLE 4.** Comparison of IPSS total score and subscores in responders and non-responders with alpha blocker

|                       | Total      | Responder group (n=29) | Nonresponder group (n=23) | p-value <sup>a</sup> |
|-----------------------|------------|------------------------|---------------------------|----------------------|
| IPSS total score      |            |                        |                           |                      |
| Baseline              | 17.73±8.25 | 20.45±7.74             | 14.30±7.71                | 0.006                |
| Endpoint              | 10.56±6.52 | 9.69±5.24              | 11.65±7.83                | 0.286                |
| p-value <sup>b</sup>  |            | < 0.001                | 0.001                     |                      |
| Difference            | -7.17±6.38 | -10.76±5.87            | -2.65±3.49                | < 0.001              |
| IPSS storage subscore |            |                        |                           |                      |
| Baseline              | 9.31±5.06  | 11.34±4.43             | 6.74±4.70                 | < 0.001              |
| Endpoint              | 6.65±4.20  | 6.38±3.72              | 7.00±4.81                 | 0.602                |
| p-value <sup>b</sup>  |            | < 0.001                | 0.248                     |                      |
| Difference            | -2.65±3.37 | -4.97±2.71             | 0.26±1.05                 | < 0.001              |
| IPSS voiding subscore |            |                        |                           |                      |
| Baseline              | 8.42±4.11  | 9.10±4.13              | 7.57±3.99                 | 0.182                |
| Endpoint              | 3.90±3.11  | 3.31±2.17              | 4.65±3.93                 | 0.124                |
| p-value <sup>b</sup>  |            | < 0.001                | < 0.001                   |                      |
| Difference            | -4.52±3.80 | -5.79±3.87             | -2.91±3.09                | 0.005                |

IPSS, International Prostate Symptom Score.

<sup>a</sup>:Independent t-test was performed between responder group and non-responder group, <sup>b</sup>:Paired t-test was performed between baseline and endpoint values.

ly separated muscle cells with reduction of intermediate cell junctions and collagen deposition in the markedly widened spaces between individual muscle cells and abundant profiles characteristic of enlarged, hypertrophic muscle cells. BOO is associated with changes in detrusor structure that can account for the resultant voiding dysfunction. Features of the myohypertrophy pattern can explain the overall weakness of the obstructed detrusor despite hypertrophy of its cells. Protrusion junctions and abutments probably mediate electrical coupling of muscle cells, thus leading to involuntary contractions in the overactive obstructed detrusor [2].

Frequent detrusor contractions during the storage phase while the bladder outlet is obstructed are presumed to increase the work load on the muscle with consequent hypertrophy [19,20]. In the largest such study, Hakenberg et al. [5] reported mean transabdominal US measurements of BWT in 172 healthy men and 166 healthy women of 3.33 and 3.04 mm, respectively. Khullar et al. [21] found significant differences in median BWT between female patients with OAB due to detrusor overactivity (DO) and those without DO. A cut-off BWT of 5 mm had 84% sensitivity and 89% specificity for DO. Serati et al. [22] reported significantly thick BWT in patients with urodynamic "pure DO" with 13.33% sensitivity and 97.67% specificity for DO.

The bladder wall consists of bladder adventitia, which gives a hyperechoic (bright) appearance on US, and then the bladder muscle layer, which gives a hypoechoic (dark) appearance on US. The innermost layer is the bladder mucosa, which gives a hyperechoic (bright) appearance on US. BWT is measured by including the inner and outer hyperechoic lines in the measurement [23,24].

Given the above background, we assumed that BWT could be a useful, noninvasive parameter for evaluation of LUTS/BPH patients.

As Khullar et al.[21] founded in female OAB patients, BWT was positively correlated to IPSS storage subscore in male LUTS/BPH patients, as shown in Table 1. BWT was also positively correlated with IPP, which is related to the progression of BOO due to BPH [25]. BWT was correlated with the storage symptom score in LUTS/BPH patients.

Because medical treatment is the first option for LUTS/BPH patients [26], we prescribed selective alpha-blockers to the patients for 4 weeks and divided the patients into two groups according to the degree of improvement in the IPSS storage symptom subscore. We expected that the IPSS storage subscore would not improve in LUTS/BPH patients with larger BWT after alpha-blocker monotherapy. We supposed that the bladder dysfunction induced by bladder wall hypertrophy, such as DO, would not completely improve after the BOO was relieved with alpha-blocker treatment.

The result was, as shown in Table 2, like we expected. Patients in the non-responder group had a larger BWT and larger prostate volume. But as shown in Table 3, larger prostate volume had little influence in the non-responder group. Only BWT had a significant influence in the non-responder group. As shown in Table 4, the IPSS voiding subscore was significantly improved in both groups. However, the IPSS storage subscore was not improved in patients who had larger BWT. According to our results, LUTS/BPH patients with larger BWT have more advanced detrusor changes that cannot be reversed with the relief of BOO. For patients with BPH and DO, alpha-blocker medication with antimuscarinic medication can effectively relieve the symptoms [27]. In cases of LUTS/BPH patients with increased BWT, prescription of antimuscarinic medication with an alpha-blocker would be effective for improving the patient's irritative symptoms.

There are limitations to this study. First, the number of

enrolled and analyzed patients was small. Because of this, the IPSS before medication was significantly different in the two groups. Moreover, we did not perform urodynamic study. The duration of alpha-blocker therapy was not long enough to reverse the detrusor change that is induced by BOO. Also, there was no placebo group for comparison. In order to understand the effect of BWT in LUTS/BPH patients, randomized, large-scale, and controlled studies of longer duration are necessary.

## CONCLUSIONS

BWT was related to IPP and the storage symptom score in LUTS/BPH patients. With BWT increase, the responsiveness of alpha-blockers to irritative symptom was decreased in LUTS/BPH patients. BWT may be a useful parameter for predicting responsiveness of irritative symptoms to alpha-blocker therapy in LUTS/BPH patients.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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