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ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 644–650

www.jcma-online.com

Original Article

Are patients with bladder oversensitivity different from those with urodynamically proven detrusor overactivity in female overactive bladder syndrome?

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Received July 5, 2016; accepted March 15, 2017

Abstract

Background: To determine if there are clinical and urodynamic (UD) differences between female overactive bladder (OAB) patients with bladder oversensitivity (BO) and detrusor overactivity (DO) via a much lower filling rate.
Methods: In total, 205 patients with OAB symptoms were recruited for this study. During filling cystometry, the bladder was filled at a more "physiological" rate of 20 ml/min. All patients underwent a complete urogynecological evaluation including detailed history, physical examination, urinalysis, pad test for quantification of urine leakage, 3-day frequency-volume chart (FVC) documentation, and completion of a UD study.
Results: The overall incidence of BO was 34.2% and that of DO was 65.8%. The first desire to void (FDV) in patients with BO and DO were at filling of 117.47 ± 21.68 ml and 135.23 ± 22.88 ml, respectively ($p < 0.05$). Maximal cystometric capacities (MCC) in patients with BO and DO were recorded at 259.44 ± 33.87 ml and 265.32 ± 44.05 ml ($p > 0.05$). A receiver operating characteristic (ROC) curve was used to find the cut-off values of FDV for sensitivity and specificity in patients diagnosed with DO. Area under the curve (AUC) was 0.702 ($p < 0.005$, 95% confidence interval: 0.626–0.779) if FDV was determined as more than 127 ml. Patients with BO experienced significantly increased daytime urinary frequency and nocturia symptoms (<0.05). Patients with DO had a significantly higher prevalence of urgent urinary incontinence ($p < 0.05$). In this study, a higher FDV and higher body mass index (BMI) were correlating factors for OAB patients with DO after multiple logistic regression analysis.
Conclusion: Patients with BO seemed to be on a different spectrum compared to those with DO and also had different symptom-specific and associative factors. It was also found that FDV could be good predictive indicator for detecting DO at a low filling rate.

Keywords: Bladder oversensitivity; Detrusor overactivity; Filling rate; Overactive bladder; Urgency

1. Introduction

Overactive bladder syndrome (OAB) and lower urinary tract symptoms (LUTS) are highly prevalent in women in both Western and Eastern countries.[1,2] The International Continence Society (ICS) has postulated that overactive bladder syndrome is a type of urinary urgency which may or may not

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2017.03.009

include urgency incontinence and is usually associated with increased daytime frequency and nocturia, if there is no proven infection or obvious pathology.[3] In clinical practice, urodynamic detrusor overactivity (DO) is detected in approximately 50% of women with OAB symptoms.[4,5] Two separate groups of researchers also noted a sex difference in clinical presentations and urodynamic findings for OAB.[6,7] For females in particular, researchers proposed that DO might not be a major underlying pathophysiology for OAB.[8] In the past, the condition of OAB symptoms was once divided into "motor urgency" and "sensory urgency" based on whether urodynamically-detected DO was found, leading to the belief that both conditions were on the same spectrum.[9] Instead, DO is always relegated to a surrogate factor in corresponding OAB animal studies.[10]

Bladder oversensitivity (BO), as is the case with DO, is diagnosed according to reported symptoms and urodynamic investigations including increased perceived bladder sensation during bladder filling, comprising (1) an early first desire to void (FDV), (2) early strong desire to void (SDV), which occurs at low bladder volume, and (3) a low maximum cystometric bladder capacity (MCC).[11,12] BO is also commonly referred to as *increased bladder sensation*[3] and has since replaced the now-obsolete term *sensory urgency*.[9] Some researchers have previously explored whether clinical and urodynamic characteristics differ between OAB women with and without DO (bladder oversensitivity).[5,9,13–16] However, at present, the results are inconclusive. Some researchers have shown that patients with DO have relatively small perception volumes during filling cystometry. These researchers have suggested that OAB with DO may be the late and more severe form of OAB in comparison with those without DO,[9,15] but the precise association between OAB and DO remains unclear.

In a conventional urodynamic study (UDS), the bladder is normally filled at a rate of between 30 and 100 ml/min, which is significantly higher than maximal physiological diuresis. Filling rate is one of crucial factors in detecting DO.[17] Sensitivity of the afferents toward bladder filling is reduced at higher filling rates.[18] One study also demonstrated that a higher filling rate is correlated with a lower incidence of DO.[19] Therefore, the aim of this prospective study was to identify the clinical and urodynamic parameters to predict DO in female OAB patients. We also compared the differences between clinical characteristics and urodynamic perception volume with filling cystometry set at a relatively lower filling rate (20 ml/min).

2. Methods

Initially, 251 consecutive patients with OAB symptoms who were referred to our urodynamic unit were recruited to take part in this study. All patients underwent a complete urogynecological evaluation including detailed history, physical examination, urinalysis, pad test for quantification of urine leakage, 3-day frequency-volume chart (FVC) documentation, and completion of a UDS. Forty-six patients with cerebral vascular disease, previous anti-incontinence, reconstructive pelvic surgery, hysterectomy, or a radical hysterectomy history and polyuria were excluded. In total, 205 patients were recruited for this study. The study protocol was approved by the Institutional Review Board of Chung Shan Medical University Hospital.

These study subjects were interviewed with five validated structural questions to specify their lower urinary tract symptom, including daytime frequency, urgency, nocturia, urge incontinence, and stress urinary incontinence as described previously.[20] Subjects were also informed to avoid diuretic drinks such as coffee and tea 6 h before UDS. We chose 20 ml/min as the filling rate in order to reduce urothelial impact in comparison with a higher filling rate and also to better minimize natural filling volume effect. UDS was performed using a Dantec DUET (Medtronic, Denmark) by a senior technician in an isolated room. Following uroflowmetry and measurement of post void residual urine, each woman was directed to assume a supine position. During filling cystometry, the bladder was filled with sterile normal saline at room temperature at a filling rate of 20 ml/min using a 6-F double-lumen filling catheter in the bladder and a 9-F rectal balloon catheter. Volume at first desire to void (FDV, ml), volume at maximal bladder capacity (MC, ml), pressure changes during filling phase and involuntary detrusor contraction spontaneously or provoked by suprapubic tapping, coughing, the Valsalva maneuver, listening to running water, and postural change from supine to standing were measured.[21] Urodynamic diagnosis was made according to urodynamic parameters formulated by one of the coauthors (GD Chen), who was blinded to patient symptoms and clinical findings. According to An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction in 2010,[12] BO referred to sensory urgency (now-obsolete). We defined BO, previous termed sensory urgency, as OAB with increased perceived bladder sensation during filling, an early first desire to void and low bladder capacity in the absence of recorded urinary tract infection (UTI) or DO. Previously termed motor urgency, DO was defined as occurrence of involuntary detrusor contractions during filling cystometry.

Student's *t*-test was used for continuous variables, and a Chi Squared test was completed for categorical variables to compare the differences between two groups. Pearson's correlation coefficients were estimated to determine associations between DO and variables. We began with univariate regression models to identify baseline variables that were predictive of DO. The baseline variables that showed a significant association in univariate regression models were entered into a multivariate regression model. Receiver operating characteristic (ROC) analysis was performed to identify the optimal cut-off value for detecting DO. All data were analyzed using a qualified statistical software package (SPSS for Windows, Version 16.0, SPSS, Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered to be statistically significant.

3. Results

Two hundred and five patients were included in the analysis. Among patients with OAB symptoms, the overall incidence of BO was 34.2% and that of DO was 65.8%. DO group patients were noted to be significantly older (59.35 ± 14.24 vs. 49.0 ± 11.73; $p = 0.003$) and more likely to experience urgent incontinence (UI) (38.5% of the DO group vs. 14.3% of the BO group, $p < 0.005$). Patients with BO, on the other hand, exhibited significantly increased daytime urinary frequency and nocturia symptoms compared to patients with DO (97.0% vs. 77.7% and 48.6% vs. 29.6%; $p < 0.05$). There was also a significant difference between the first desire to void (FDV) volumes of the two groups (117.47 ± 21.68 ml in the BO group vs. 135.23 ± 22.88 ml in the DO group; $p < 0.05$). However, no significant difference in maximal cystometric capacity (MCC) volumes was found between the two groups (259.44 ± 33.87 ml in the BO group vs. 265.32 ± 44.05 ml in the DO group; $p > 0.05$) (Table 1). Univariate analysis demonstrated that DO was significantly correlated with factors including age, FDV, previous cesarean section, urgent incontinence, nocturia, frequency, and body mass index (BMI). Nevertheless, only FDV and BMI revealed a significant and independent correlation with DO in our multivariate regression models (Table 2). The FDV cut-off value for predicting DO was determined by using a receiver operating characteristic (ROC) curve. Area under the curve (AUC) was 0.702 ($p < 0.005$, 95% CI 0.626–0.779); in addition, an FDV cut-off value of 127 ml (sensitivity 70.6%, specificity 59.1%) was found to be an acceptable predictive value for detecting DO (Fig. 1).

Table 1
Demographic, clinical and urodynamic characteristics of the patients with overactive bladder.

	BO	DO	*p*
Number of patients	70	135	
Age	49.0 ± 11.73	59.35 ± 14.24	0.003*
Parity	2.8 ± 1.76	3.5 ± 1.66	0.883
Presenting symptoms			
F + U	68	105	0.000*
UI + U	10	52	0.000*
F + UI + U	6	20	0.203
SUI	24	58	0.229
Nocturia	34	40	0.007*
Mixed UI	8	20	0.503
Cystocele > Gr II	11	40	0.029*
Myoma	9	13	0.479
FDV	117.47 ± 21.68	135.23 ± 22.88	0.000*
MCC	259.44 ± 33.87	265.32 ± 44.05	0.363
MFR	16.6 ± 7.5	18.9 ± 9.4	0.051
AFR	9.1 ± 4.1	10.2 ± 7.2	0.061
BMI	23.01 ± 3.13	25.44 ± 4.04	0.034*

C = Continuous variables are reported using mean ± standard deviation. Categorical variables are reported in number.
BO = bladder oversensitivity; DO = detrusor overactivity; F = frequency; U = urgency; UI = urge incontinence; SUI = stress urinary incontinence; Gr II = grade II; FDV = first desire to void; MCC = maximal cystometric capacity; MFR = maximal flow rate; AFR = average flow rate; BMI = body mass index.
* Means $p < 0.05$.

Table 2
Univariate and multivariate analysis of relationship between detrusor overactivity (DO) and clinical or urodynamic parameters.

Characteristics	Univariate analysis		Multivariate analysis	
	Pearson C	*p*	OR	*p*
Age	0.323	0.000*	1.028	0.130
Parity	0.205	0.003*	0.968	0.824
MFR	−0.065	0.356		
FDV	0.352	0.000*	1.032	0.003**
MCC	0.064	0.363		
Myoma	0.070	0.319		
Cystocele	0.129	0.066		
Prolapse	0.033	0.637		
CS	−0.234	0.001*	0.217	0.09
SUI	−0.04	0.570		
Nocturia	−0.187	0.007*	1.547	0.322
Urgent incontinence	0.303	0.000*	1.135	0.821
Frequency	−0.253	0.000*	5.285	0.075
BMI	0.250	0.000*	1.182	0.013**

Pearson C = Pearson correlation coefficient; OR = odds ratio; MFR = maximal flow rate FDV = first desire to void; MCC = maximal cystometric capacity; CS = cesarean section; SUI = stress urinary incontinence; BMI = body mass index.
*Means $p < 0.05$ in univariate regression model; **Means $p < 0.05$ in multivariate regression model.

4. Discussion

Our results showed that only about two thirds (65.9%) of OAB patients had urodynamically proven involuntary detrusor contraction in filling cystometry profile at a low filling rate. OAB patients with BO seemed to be on a different spectrum than those patients with DO and also had different clinical symptom-specific and urodynamic characteristics. FDV may

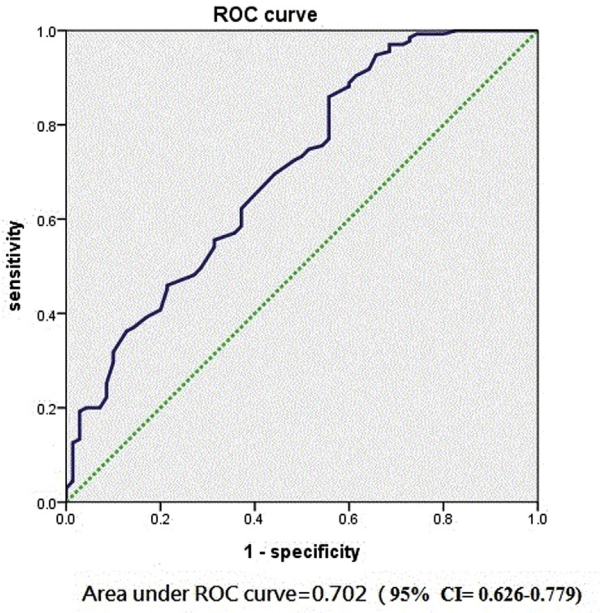

Fig. 1. Receiver operating characteristic (ROC) curve for diagnosing bladder overactivity (DO) by first desire to void (FDV). Area under curve (AUC) was 0.702 ($p < 0.005$, 95% CI 0.626–0.779).

have an acceptable predictive value for detecting DO at a low filling rate.

OAB denotes a syndrome for which the etiology is unknown. Generally speaking, DO is considered to be a major underlying pathophysiology of OAB. However, it is not well elucidated exactly how many OAB patients actually show DO during UDS. Furthermore, the actual association between OAB and DO remains unclear. It is estimated that up to 60% of patients with stable detrusor during conventional UDS have DO during ambulatory monitoring.[22] Another previous study found that about 40% of men and 30% of women without OAB symptoms also present with DO according to the definition used for UDS.[4] Hashim and Abrams stated that urgency, UI, and nocturia significantly increase the possibility of developing DO.[4] Urgency, frequency, and UI were found to be the most sensitive factors for predicting DO (61.0%) in female patients.[23] In addition, UI and nocturia were associated with DO in a study performed by Khan et al.[24] However, among women with DO in our study, only the presence of the subjective symptom of UI during filling cystometry accounted for a significant difference. This finding is consistent with a previous report which found DO to be associated with an increased odds ratio of having UI, even though there was only a moderate association between urodynamic findings and clinically-reported symptoms.[25] In contrast, the BO group demonstrated greater frequency and nocturia symptoms than the DO group in our study. We postulate that, while no statistical significance in multiple logistic regression analyses was found, these findings may also be related to the more hypersensitive nature of BO. In addition, although a previous report questioned the reliability of using the bladder as a witness to predict DO,[4] Abrams found that bladder filling sensation, first sensation, FDV, and SDV were well-correlated with 50%, 75%, and 90% of MCC, respectively.[26]

The aging process results in intrinsic urethral sphincteric deficiency, which increases the prevalence of UI and may potentiate the occurrence of DO and OAB symptoms.[27] Our findings are also consistent with previous reports that patients with DO are more likely to be older[20,28] and have a greater prevalence of incontinence[9] compared to BO patients. Yoshida et al. found that increased urothelial release of acetylcholine and adenosine triphosphate on bladder filling is correlated with aging and suggested to be the pathophysiology of DO.[29] OAB patients with DO present with a greater frequency of UI due to its motor pathology. Thus, it may be misleading to assert that DO is a "later form" of BO based on the fact that a patient in the DO group is older and has a comparatively higher degree or frequency of UI. Another tangential finding is that obesity as measured by BMI is associated with higher prevalence of OAB and LUTS in women.[30] Our study also revealed an association between DO and higher BMI by multivariate regression models. Steward reported that prevalence of OAB with DO in participants with a BMI >30 was 2.2 times higher than the prevalence among those with a BMI <24.[31] The relationship between raised BMI and DO is likely to be mediated through metabolic syndrome, of which obesity is a central component. DO may be the result of metabolic syndrome inducing inflammatory sympathetic overactivity or due to pelvic ischemia resulting from atherosclerosis, or insulin resistance caused by obesity.[32] Moreover, bladder ischemia induced by pelvic atherosclerosis might produce oxidative stress, leading to denervation of the bladder and the expression of tissue-damaging molecules, such as NGF and PG, in the bladder wall and then provoke DO through sensitization of afferent pathways.[33,34] Whether or not intervention for weight loss may contribute to resolution of DO, more trials are needed to further elucidate the mechanisms. Bladder outlet obstruction is one of the causes of DO. Fifty to seventy percent of patients with prostate enlargement to bladder outlet obstruction extent also have OAB with DO.[35] Similarly, OAB is often seen in 40–50% of patients with pelvic organ prolapse (POP) including cystocele, and the prevalence of OAB is approximately six fold greater in POP patients than in patients without POP, which is thought to be because POP causes bladder outlet obstruction as well. Treatment of POP gives an improvement in OAB complaints as well as in the signs of DO, which indicates that the relationship between the two syndromes is likely to be a causal one.[36] However, DO did not show significant association with cystocele in our multivariate analysis. Parity may also play a role in the onset of DO, possibly due to neurologic injury during vaginal delivery. This hypothesis is supported by the finding that cesarean delivery can protect against the development of DO.[37,38] But we did not find significant association with DO in our study.

It is interesting that the results presented here contradict previous findings in perceived bladder volume during filling cytometry in OAB patients with or without DO. Our study results showed that FDV, not MCC, was significantly smaller in the BO group in comparison with the DO group. However, previous reports showed that females with OAB with UDS-proven DO were older and had significantly smaller FDV and MCC.[5,15,16] They suggested bladder function was more severely disturbed when DO existed. We postulated that bladder filling rate may be a key factor in explaining this discrepancy. Traditionally, filling rate is referred to as fast (>100 ml/min), medium, or slow (<10 ml/min). The natural bladder filling rate is, on average, 1–2 ml per minute.[39] ICS now defines the physiological filling rate as a filling rate less than the predicted maximum body weight in kg divided by 4 expressed as ml/min.[40] Research had demonstrated that the mean volume of natural filling and the mean rate of natural bladder filling were 32.8 ml (12.1% of artificial filling) and 1.4 ml/min, respectively, at an artificial filling rate of 50 ml/min.[41] To minimize the natural filling confounding effect, we conducted filling cystometry at optimal 20 ml/min in comparison with Guralnick et al.[5] (30–50 ml/min), Jeong et al.[16] (20–50 ml/min), and Giarenis et al.[15] (100 ml/min). Research has shown that at higher filling rates, the activation pressure threshold is higher and afferent activity at any pressure is significantly lower.[42] Furthermore, a variation in the rate of DO has been found, with slower rates of artificial filling compared with faster rates of filling. Greater inhibition of detrusor function related to a faster filling rate and stretching of detrusor muscle may be contributing factors,[19] suggesting

that sensitivity of the afferents toward bladder filling is decreased at higher filling rates.[18] Klevmark conducted a study with supra-physiological filling rate as used during conventional urodynamics.[39] He suggested that the supra-physiological filling rate might cause mechanical trauma to afferent receptors and associated nerve fibers and then delay stimulation of pelvic afferents, resulting in larger bladder volume. Traumatic urothelium associated with higher filling rate may also be desensitized, which was probably more prevalent in the BO group as a result of its more hypersensitive nature. Furthermore, insufficient afferent activation in the central nervous system of efferent impulses may cause delayed and impaired detrusor contractility.[39] These hypotheses may explain why the lower filling rate (20 ml/min) in our study provoked a smaller FDV in the BO group instead of the DO group. In an assessment of healthy volunteers by means of filling cystometry with filling rate of 50 ml/min and 100 ml/min in comparison with ambulatory monitoring, Robertson et al. found DO in 38% of study subjects on ambulatory monitoring, in 17% on 50 ml/min filling cystometry, but in no patients on 100 ml/min filling cystometry.[19] The sensitivity of afferents to respond to bladder filling is decreased when filling is done at a higher speed. This higher filling rate with a lower incidence of DO findings may explain our relatively high DO identification rate (65.9%) as compared to the 44% rate reported by Hashim et al.[4] and 43% by Giarenis et al.,[15] respectively. Wyndaele discussed the physiology of innervation and concluded that the impulses related to FDV course through the pelvic nerves while impulses for MCC travel through the pudendal nerves.[43] This inference may partially explain the discrepant association of DO occurrence between FDV and MCC.

Previous reports argued that BO and DO appeared to be on same spectrum of bladder dysfunction but the latter had more severe storage disturbance.[6,10,17] Blaivas et al. also reported that two different types of sensations of urgency exist.[44] They proposed that these two types of urgency may have different etiologies and respond differently to treatment. Our results support the points that both types of OAB presentation may fall under different pathophysiological pathways. We suppose that BO is an intensification of the normal urge to a certain threshold, while the other type, DO, is evoked as an on/off switch motor response by increased sensory afferent to some extent. Many studies have also observed the different characteristics between BO and DO in several aspects. Frazer et al. looked at the presence of a significant increase in the number of detrusor mast cells on biopsy only in sensory urgency patients.[45] Using functional magnetic resonance imaging, Griffiths pointed out abnormalities in brain response during bladder filling in OAB patients and identified pattern differences between patients with and without DO.[46,47] Liu et al. also proposed a distinct molecular basis separating BO and DO. Their results demonstrated that BO was associated with an increased expression of vanilloid receptor (TRPV1) mRNA in the trigonal mucosa. In contrast, no upregulation or regional differences of TRPV1 mRNA were seen in DO patients. TRPV1 may play a role in BO and premature first bladder sensation on filling.[48] As regards dysfunction severity, women with BO have been found to have greater psychological impacts, such as low self-esteem and anxiety, compared to women with DO.[49] However, studies have shown that patients with and without DO respond equally well to different antimus carinics.[50,51] Additionally, it has been shown that the clinical effect after sacral neuromodulation is not influenced by the presence of DO before implantation.[52] Nevertheless, combination treatment with antimuscarinic agents and vaginal estrogens has been shown to offer improved efficacy in postmenopausal women with OAB,[53] but not in women with DO.[54] Botulinum toxin A (BoNT-A) injections for OAB are becoming an increasingly popular treatment modality, and a growing body of evidence now shows that BoNT is effective for treating patients with[55] or without[56] DO. However, in a randomized, double-blind, placebo-controlled trial examining the effects of BoNT-A exclusively in patients with BO, Dowson et al.[57] only found a significantly improved parameter in MCC which does not translate to a clinical benefit, and no changes were observed in the symptoms or quality of life for the majority of patients. Based on the evidence above, OAB with BO or DO may comprise two different categories with similar presentations. Dichotomous treatment could be expected with more advanced and delicate diagnostic instruments in the future.

Currently, the diagnosis of OAB with BO is solely reliant on the absence of aberrant detrusor contractions during a filling cystometry; this can, however, be an unreliable means of diagnosis due to lack of reproducibility in addition to the fact that there will undoubtedly be overlap between OAB and DO. From the ROC analysis (Fig. 1), FDV >127 ml with a highest ROC area (0.702, 95% CI 0.626–0.779) may be a good clinical cut-off value with acceptable sensitivity and specificity to screen for DO in a filling cystometry at a 20 ml/min filling rate. FDV at a low filling rate appears to be a useful parameter for differentiating these two distinct entities.

Our study had certain limitations. The enrolled population was entirely Taiwanese, and therefore our results might not be able to be generalized to other populations. Another issue is that the majority of our cohort consisted of women referred to us with persistent OAB who failed to respond to first-line treatments. The prevalence of DO in a community practice would be markedly different. Third, even though this was a prospective study, we performed filling cystometry with only a fixed low filling rate (20 ml/min). Reproducibility of DO during a conventional UDS is another important issue to consider because, upon follow-up UDS, DO in patients with DO during initial UDS is not always demonstrated.[58] The inferred hypothesis — that a high filling rate may reduce the sensitivity of the urothelial afferent impulse — is only supported by previous research; a randomized controlled trial is therefore warranted in order to reach a more reliable conclusion. Finally, the 3-day FVC may have been difficult for patients with a poor compliance record to complete correctly, which could have introduced a slight bias in our findings.

In conclusion, our results show that only two thirds of OAB patients have DO and more than one third of patients have a

stable urodynamic trace without any abnormal increases in detrusor pressure with filling cystometry at a low filling rate. Patients with BO seem to be on a different spectrum compared to those with DO and also have different clinical symptom-specific and urodynamic characteristics. FDV may hold good predictive value for detecting DO at a low filling rate.

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