Overactive Bladder in the Male Patient: Bladder, Outlet, or Both?

*Khaled F. Abdel-Aziz, MD and Gary E. Lemack, MD**

Address
*Department of Urology, University of Texas, Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9110, USA.
E-mail: gary.lemack@utsouthwestern.edu

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Generations of urologists have presumed that the cause of lower urinary tract symptoms (LUTS) in men is infravesical (prostatic) obstruction. When symptoms such as urinary urgency and frequency can't easily be explained directly by obstruction, secondary effects of obstruction on the bladder are identified as causative factors. Although to some extent this explanation may still be accurate, emerging concepts in the pathophysiology of LUTS in men may be at odds with these traditional explanations. The idea that primary bladder pathology may explain the symptom complex in at least one subset of men with LUTS has both experimental and clinical support. This review discusses the physiologic and clinical observations used to explain the mechanisms underlying LUTS. Specifically, this review focuses on two data sets: one supporting infravesical obstruction as the causative factor for LUTS, and another positing that a primary bladder abnormality is responsible.

Introduction

Lower urinary tract symptoms (LUTS) are extremely common among aging men. A recent study conservatively estimated that at least 30% of men older than 50 years of age report LUTS, whereas 8% required surgery for relief of bladder outlet obstruction (BOO) due to failure of medical management [1]. Nevertheless, in many cases the cause of these debilitating symptoms remains largely unknown. In the past, LUTS were largely attributed to benign prostatic hyperplasia (BPH), a diagnosis most often made by history and physical examination alone, and treatment (often surgical) was directed at the prostate gland.

It has long been a tenet of urologic teaching that the most common cause of LUTS is BPH, a histologic diagnosis. With the passage of time, BPH may cause benign prostatic enlargement (BPE), which in turn, can lead to BOO. BPH itself is an extremely common condition, found in 50% of men between 51 and 60 years of age; however, not all men with BPH are symptomatic. The development of so-called obstructive symptoms (loss of flow, hesitancy, and postvoid dribbling) associated with BOO may be explained logically by dynamic compression of the urethral luminal capacity by an enlarging BPE-related adenoma. Other outlet obstruction-associated symptoms seen with advancing age, such as urinary urgency, frequency, and nocturia, are not necessarily as easily explained by obstruction alone. Nonetheless, several pieces of evidence do firmly suggest that treatment of obstruction, either by medical or surgical means, can reduce the incidence of all urinary symptoms. Moreover, experimental data derived from animal models have demonstrated why infravesical obstruction may be associated with bladder dysfunction. Still, several pieces of evidence, including the finding that women (who less frequently suffer from obstruction) and men often have very similar symptom complexes, and that urodynamic obstruction has repeatedly failed to show correlation with symptom levels [2], suggest that obstruction alone is not the sole cause of LUTS in men.

Symptoms of overactive bladder (OAB), which include urinary urgency (with or without urge incontinence, usually associated with frequency and nocturia) overlap tremendously with those attributed to BOO secondary to BPE [3]. OAB, by definition, is not associated with any identifiable physiologic or metabolic cause that may explain the development of LUTS, and indeed, all such causes must be definitively excluded before the term OAB can be assigned. OAB currently is thought to be largely due to detrusor overactivity (DO) during periods of bladder filling. The cause of this overactivity is essentially unknown; however, both neurogenic and myogenic explanations have been offered. Current treatment modalities are directed principally at blocking the muscarinic receptor, the presumed site of neurogenically mediated DO. However, because heightened bladder sensation appears to be a contributing factor, intravesical agents such as capsaicin and resiniferatoxin clearly have a role in the treatment of refractory patients. In addition, other central (*ie*, gamma-aminobutyric acid agonists) and peripheral (*ie*, calcium channel blockers) mechanisms have been studied, as has locally applied botulinum toxin. Future treatments will, undoubtedly, focus on some of these alternative mechanisms.

Like BOO, the prevalence of OAB increases dramatically with advancing age, with one study [4•] estimating that 16% of all adults suffer from symptoms of OAB. This translates to

more than 33 million Americans with this disorder [4•]. Although many of these patients are women, it is fairly clear that the prevalence of OAB symptoms in men exceeds that of women, particularly in men older than 60 years of age. Because many men fail to respond to either pharmacologic or surgical treatment of BOO, and a majority of women with very similar symptoms respond to pharmacologic bladder treatments, there is reason to suspect that outlet obstruction is not solely responsible for the development of LUTS in all men. The key is sorting out which patients will respond to which modes of therapy. Also troublesome is the known fact that BOO and DO frequently coexist. It is not always clear that DO is induced by BOO, or if this condition is an independent attribute of the bladder's response to aging, ischemia, or other unknown events [5–7]. This review discusses the pathophysiologic mechanisms underlying the development of LUTS in men, focusing on data supporting a primary obstructive (prostatic) etiology, and a primary bladder pathology.

Pathophysiologic Explanations for Bladder Outlet Obstruction-induced Instability

Through several different animal models urologists have begun to understand the cascade of events leading to the development of detrusor dysfunction after BOO. The apparent central factor contributing to BOO-induced instability is the development of tissue ischemia. Relative tissue hypoxia was originally demonstrated in dogs after mild distension [8], and more recently reduced detrusor blood flow has been documented in hypertrophic bladders during filling [9]. Tissue hypoxemia appears to be a result of increased oxygen demand by hypertrophic tissue and diminished oxygen supply in the presence of elevated intravesical pressures. One group [10] noted a rise in nitric oxide synthase (a vasodilatory substance) shortly after obstruction, implying an induction of mechanisms to restore blood flow to underperfused areas. Several authors [11,12] have speculated that smooth muscle injury occurs after a cycle of relative tissue hypoxia during distension and voiding, followed by reperfusion injury after micturition. Still, the question remains why this injury manifests as DO in many patients.

Changes in extracellular matrix composition (largely affecting collagen), possibly induced by the alteration of locally expressed growth factors after BOO, appear to have an effect on passive bladder properties (compliance). However, it has also been suggested that these changes can affect the way bladder smooth muscle cells communicate with one another. Smooth muscle is also directly affected at the macroscopic (largely hypertrophy) and microscopic levels. In several elegant ultrastructural studies of aging and obstructed human bladder specimens, Elbadawi *et al.* [13] noted altered cell-to-cell junctions (protrusion junctions and ultraclose abutments), and theorized that this change was the anatomic basis for DO in humans with BOO. The authors contend that these microstructural changes permit quick transmission of the depolarization wave synchronously to a large number of smooth muscle cells, creating a greater bladder mechanical capability. This results in both stronger and faster (better synchronized) micturition contractions, and less favorably, the capacity for involuntary (spontaneous or stretch-evoked) activation of detrusor muscle cells. Even if only a few cells are initially affected, this response could rapidly spread and produce detectable DO.

Other changes in smooth muscle properties have also been noted. Some authors [14] have attributed the development of DO to denervation supersensitivity after BOO (cholinergic receptor up-regulation), whereas others [15] have noted alterations in the activity of the sodium-potassium pump membrane after experimental induction of BOO. Altered calcium mobilization has also been noted after BOO, which may affect the ability of an individual smooth muscle to contract in response to pharmacologic or electric stimulation [16]. Still others [16] have noted a change in the expression of contractile proteins (the elements of smooth muscle cells that confer the ability to contract, such as myosin heavy chain) to more typically embryonic isoforms after obstruction, clearly affecting the bladder's ability to empty effectively as a whole.

Obstruction-induced effects on smooth muscle innervation have been described in several animal and human models. Selective axonal degeneration has been noted in patients with obstructed detrusors, and absent in age-matched controls [18], a finding that has been evoked to explain the diminished contractile function of obstructed bladders. This finding also may explain the presence of denervation supersensitivity in response to cholinergic stimulation in isolated muscle strips. Others have noted nerve growth after BOO, and have attributed DO, at least in part, to this finding. In the rat, both afferent and efferent neuronal hypertrophy has been described, possibly in response to the induction of nerve growth factor after BOO [19].

Together these data suggest that BOO induces alterations in bladder innervation and contractile properties, and in this manner affects its functional properties.

Urodynamic Studies: A Clinical Link Between Detrusor Overactivity and Bladder Outlet Obstruction

Several studies have investigated the correlation between LUTS, BOO, and DO. It is clear that uninhibited contractions during filling are more common in aging men, regardless of the finding of BOO [5–7]. Whether this finding is caused by occult neurologic events, alterations in the composition of the bladder wall extracellular matrix, microvascular supply, or smooth muscle function remains a matter of some debate.

The finding that the incidence of DO increases with age does not appear to negate the association between urodynamically proven BOO and DO. Most urodynamic studies (UDS) have confirmed that approximately 50% to 60% of

men diagnosed with BOO during UDS will have DO [20]. Hyman *et al.* [21] recently studied 160 men with LUTS and found 68% to have BOO, of whom 46% also had DO [21]. Except for urge incontinence (which correlated with the finding of DO) no other urinary symptom was correlated with a particular urodynamic finding. BOO was equally likely to be seen in men complaining of urgency and men reporting difficulty voiding. Knutson *et al.* [22•] noted that 45% of men presenting with LUTS who underwent UDS studies had coexisting BOO and DO (criteria for DO not rigidly defined), whereas the remainder had varying degrees of BOO alone. In this study, BOO grade was more severe in patients with the two coexisting conditions. Similarly, a study of 565 men with non-neurogenic LUTS by Eckhardt *et al.* [23••] noted that men with bladder overactivity during filling cystometrogram tended to have greater degrees of obstruction (Schafer grade) than those without (Fig. 1) [23••]. Still, several studies [5,24] have refuted the finding that severity of obstruction predicts the likelihood of diagnosing DP with UDS.

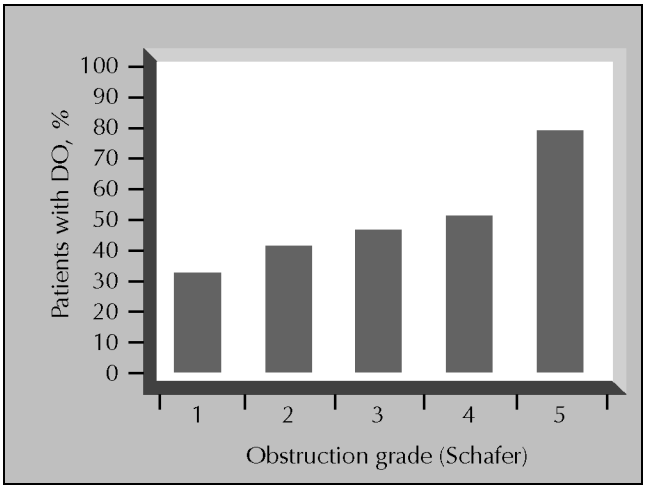

Figure 1. Prevalence of urodynamically confirmed detrusor overactivity (DO) stratified by obstruction grade. Based on Schafer's criteria. (*Adapted from* Eckhardt *et al.* [23••]; with permission.)

It is not clear why some patients with BOO develop DO and others do not. BOO seems to alter the electric coupling between detrusor smooth muscle cells, promoting a more efficient bladder contraction (*ie*, greater strength and shortening velocity), but also appears to lead to aberrant detrusor activity [25]. It would seem, therefore, that the mechanism by which the detrusor attempts to strengthen itself in response to obstruction results in the development of overactivity. In general, animal studies suggest that more severe forms of obstruction lead to progressive detrusor dysfunction typified by overactivity.

These findings underscore the lack of specificity in pinpointing the etiology of LUTS, and the importance of proceeding with urodynamic testing before embarking on any interventional treatment, particularly surgical procedures. When we test men suspected to have BOO-induced overactivity, it is our practice to fill the bladder slowly during UDS in order to cause minimal provocation If a fluctuation in vesical pressure is noted, filling is stopped and the bladder allowed to recover. If no spontaneous leakage results from the observed contraction, the bladder is filled further, with the idea being to obtain an accurate pressure-flow study while the bladder is not in the midst of a spontaneous detrusor contraction. If the patient's pressure-flow study is nonobstructive with minimal residual, the patient is considered to have a diagnosis of OAB, and is treated accordingly.

Surgical Treatment for Bladder Outlet Obstruction

The observation that symptoms characterizing DO (*ie*, frequency and urgency) often respond to treatments aimed at relieving obstruction has often been cited as a reason that LUTS in men typically occur secondary to BOO. This appears to be particularly true in young men, in whom over 60% of patients undergoing transurethral resection of the prostate (TURP) for LUTS can be expected to experience postoperative relief of urodynamically confirmed DO [26]. Symptoms of DO, which were present in 60% of patients preoperatively, were still observed in only 25% of men after TURP. Similarly, symptoms of nocturia and frequency were improved in approximately 60% to 70% of men undergoing the procedure, albeit usually delayed when compared with more typical obstructive symptoms.

Animal models of ligation and deligation have confirmed these findings. Rats subjected to partial urethral obstruction responded with increased voiding frequency, a finding that was reversed in 80% of animals after removal of the obstructive process [27]. This finding suggests DO can be the result of a persistent obstruction (which was ruled out in this study) [27] or the induction of a myogenic or neurogenic abnormality that persisted in the minority of animals after removal of the obstruction.

Elderly men undergoing TURP had a much less favorable outcome than younger men undergoing the same procedure. In a study by Gormley *et al.* [28] only one of 12 men with preoperative DO had resolution of symptoms after TURP, although the majority of patients, particularly those with greater degrees of obstruction, noted improvement in urge incontinence. These findings imply that either the detrusor becomes irreversibly affected with longer periods of obstruction, or that aging alone results in significant detrusor dysfunction. Both processes may have a role. A more recent study involving the long-term evaluation of men undergoing prostatectomy revealed that DO may return well after the relief of obstruction, even among patients without DO before surgery (Fig. 2) [29••].

It may not be safe to assume, however, that men who experience symptomatic improvement after surgical treatment of BOO do so because of relief of obstruction. Sirls *et al.* [30] noted that most men with urodynamically proven BOO responded favorable to transurethral incision

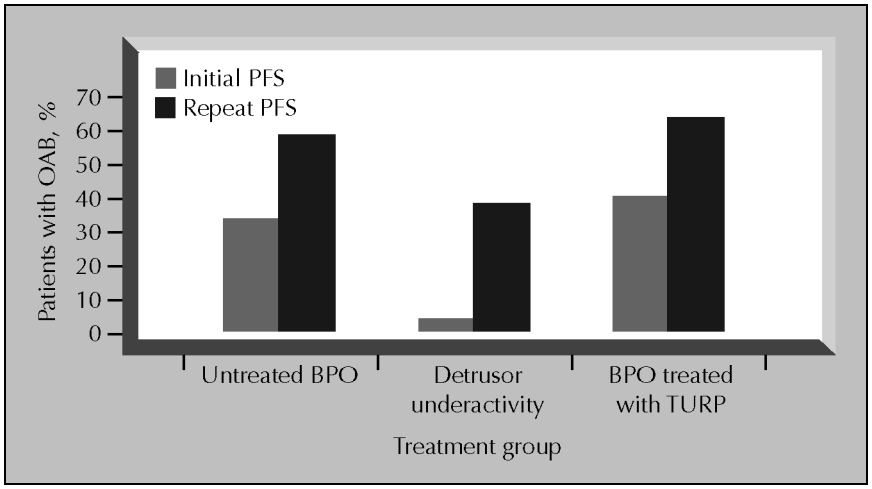

Figure 2. Incidence of overactive bladder (OAB) with long-term urodynamic follow-up (mean > 13 years). BPO—benign prostatic obstruction; PFS—pressure-flow study; TURP—transurethral resection of the prostate. (*Adapted from* Thomas and Abrams [29••]; with permission.)

of the prostate (TUIP), regardless of postoperative resolution of BOO. It has even been postulated that a partial denervation of the bladder neck and/or prostatic urethra due to transmitted energy from electrocauterization at the time of TURP (or perhaps TUIP) may alter bladder sensation and result in symptomatic improvement [31]. For example, it has been suggested that transurethral microwave therapy may result in symptomatic improvement, not only by reducing functional obstruction, but also by reducing urethral instability through the alteration of prostatic innervation [32]. Additionally, De Nunzio *et al.* [33] recently noted a much more significant improvement in preexisting DO among patients undergoing TURP than among those receiving medical therapy, even though significant improvements in pressure-flow parameters were noted in all treatment groups [33].

It is not clear that the presence of coexisting DO detected by preoperative UDS predicts a worse outcome after TURP than the presence of BOO alone. Knutson *et al.* [34] investigated 37 patients referred to their clinic with suspected benign prostatic obstruction, and stratified them on the basis of obstruction grade and presence or absence of overactivity. The patients were observed for an average of more than 4 years, and those with higher grades of obstruction were significantly more likely to require intervention within this time period. However, the presence of DO did not have an impact on rate of intervention, and even more significantly, the presence of DO in conjunction with BOO did not reduce treatment efficacy [34].

Some researchers have subclassified observed types of overactivity in order to attempt to predict which patients will respond favorably to prostatectomy. Kageyama *et al.* [35] studied 19 men with evidence of non-neurogenic DO who had previously undergone TURP for treatment of BPH. Patients in whom a single large unstable contraction occurred during later filling (after 160 cm^3), usually prompting voiding, had complete resolution of their overactivity 6 months after treatment for obstruction. These data seemed to correlate with clinical outcome. In contrast, patients with phasic instability, poor compliance, or those who developed a single unstable contraction during the initial periods of bladder filling (< 160 cm^3) rarely had resolution of their DO after surgery. At this point it still seems implausible to argue that the characteristics of unstable bladder contraction (timing, duration, and amplitude) are specific enough to indicate whether DO is secondary to BOO, and would therefore more likely respond to treatment aimed at BOO.

Medical Treatment for Bladder Outlet Obstruction

α-Blockade therapy: clinical data

The rapid (although less dramatic) improvement in obstructive and irritative symptoms with α-blockade treatment compared with the less speedy results of TURP suggests that the two therapies do not exert their effects by the same means. Smooth muscle relaxation in the prostate and bladder neck clearly impacts voiding dynamics. Urine flow is commonly improved, usually in parallel with symptom score [36]. However, it is abundantly clear that BOO need not be present for most patients to experience symptomatic improvement after treatment with α-blockers. In a study of 50 men treated for LUTS presumed to be due to BPH, a dramatic improvement in symptom score was noted (20.6 to 10.6) after 3 months of treatment with doxazosin [37]. Well over half of the patients continued to be urodynamically obstructed at the conclusion of the trial period. Moreover, the presence of BOO before the institution of therapy had no impact on treatment success. In fact, the UDS of most patients taking α-blockers (prazosin, terazosin, doxazosin, and tamsulosin) have noted modest (often not significant) changes in voiding pressures after therapy [38–40], despite reporting significant symptomatic improvement.

Because it is apparent that α-blockers seem to, at least partially, exert their effects by means other than reducing outlet obstruction, several authors have raised the possibility that α-blockade somehow mitigates DO by either central or peripheral receptor blockade unrelated to prostatic smooth muscle receptors. The observation that

some women derive benefit from α-blockade therapy speaks to this possibility [41]. Furthermore, studies have indicated that a specific α_1-receptor, α_{1d}, predominates in the bladder body and spinal cord, unlike α_{1a}, which predominates in the trigone, urethra, and prostatic smooth muscle. Several investigators believe that α_{1d} has a central role in the development of LUTS in men [42••].

The failure of α_{1a}-receptor blockade to improve LUTS in many men [43] compared with nonselective blockers (terazosin, doxazosin) and partially selective blockers (tamsulosin, α_{1a} and α_{1d}) may be explained by the importance of this different receptor subtype in the evolution of LUTS [44]. The fact that an α_{1a}-receptor- blocker improves flow rate without dramatically improving LUTS further supports this concept [45]. The development of specific α_{1d}-receptor-blockers should help clarify the role of this receptor in LUTS.

α-Blockade therapy: experimental data

Support for the efficacy of α-blockers outside of their effect on BOO has come from the recognition that α-adrenergic receptor (AR) function appears to be enhanced compared with β-mediated activity in certain models of outlet obstruction [46]. Similar findings have been noted in clinical studies of bladder strips obtained from outflow obstruction induced hypertrophic bladders [47], where α-receptor–mediated contractions predominated after norepinephrine administration. In comparison, β-mediated relaxation predominated in nonobstructed tissue. Therefore, in the presence of BOO, α-blockade may be more effective, because of the enhanced role of α-receptors. Conflicting data do exist [48], however, so the effect of changing the balance of adrenoreceptors in the obstructed bladder remains undetermined.

A role for α-blockade in the treatment of LUTS, independent of its effect on BOO, has also been demonstrated in animal models. Hampel *et al.* [49] studied changes in α_1-AR–subtype gene expression in surgically obstructed female rats. Although bladder weight increased sixfold at 6 weeks, α_{1b}-AR density (measured as receptor concentration per gram tissue wet weight) only showed a slight upward trend, a nonsignificant change. However, change in the relative α1-AR–subtype expression was detected in the bladder at the mRNA level; there was 0.6-fold reduction in α_{1a}-AR, and a three- to fivefold increase in α_{1d}-AR mRNA expression compared with control animals [49]. These data suggest that rather acute fluctuations in receptor status may result from BOO and influence the progression of LUTS.

α-Receptors in the spinal cord and peripheral ganglia have also been shown to affect urinary symptoms in animal models. For example, intrathecal administration of doxazosin, a nonspecific α_1-receptor, diminished urinary frequency and micturition pressure in normal and obstructed rats, although the effect was more pronounced in obstructed rats. In this model the beneficial effect may be due in part to the inhibition of spinal reflexes to the bladder, and perhaps reduction in the level of spontaneous bladder contractions induced by partial outlet obstruction [50,51]. In another model (the spontaneously hypertensive rat) a similar diminution of DO was noted after administration of intrathecal doxazosin. It is also possible that blockade of α-receptors in the brainstem may influence bladder function by altering parasympathetic outflow from the lumbosacral spinal cord [52].

Medical Treatment for Overactive Bladder: Antimuscarinic Agents

The fear of pushing patients with BOO and DO into urinary retention clearly has influenced the direction of pharmacologic therapy in men with LUTS. Still, given that urinary symptoms are often present in the absence of BOO, and that the majority of women with similar symptoms will respond to antimuscarinic therapy, there seems to be a rationale for proceeding with medical treatment aimed directly at the bladder, even among aging men.

Abrams *et al.* [53] studied the safety and tolerability of tolterodine, a bladder-selective antimuscarinic agent, in men with BOO and symptomatic OAB. A total of 221 men older than 40 years of age with urodynamically proven DO and BOO (more than half with moderate to severe BOO) were enrolled and randomized (2:1) to receive either tolterodine 2 mg twice a day or placebo. Concurrent treatment for BOO with α-blockade or finasteride was not permitted. Of the 221 men, 193 (87%) completed 12 weeks of treatment, with a slightly greater percentage of men on placebo withdrawing during the study. Changes from baseline in peak flow rate (Q_{max}) and detrusor pressure (P_{det}) Q_{max} in the tolterodine group were statistically equivalent to placebo, whereas tolterodine significantly increased volume at first contraction and maximum cystometric capacity. A small but significant increase in postvoid residual (from 22 to 47 cm^3) was noted in the group treated with tolterodine, whereas no change was noted in the placebo-treated group. Adverse events were nearly identical in the two groups, with one patient in each group developing acute urinary retention. These data suggest that tolterodine is well tolerated in men with BOO and OAB and demonstrates urodynamic efficacy. Proof of clinical improvement in this select group of men with obstruction and urodynamically proven DO has yet to be demonstrated convincingly, although the fairly low dropout rate in this study suggests clinical effectiveness [53].

Conclusions

It is quite difficult, if not impossible, to sort out the precise etiology of LUTS in any one patient. The very fact that the majority of men will have an improvement in urinary frequency and urgency after surgical relief of obstruction is

strongly suggestive that ongoing obstruction clearly is involved in the pathogenesis of LUTS in men. Still, emerging data on the location and activity of α-ARs in the lower urinary tract and spinal cord, and the clinical finding that medical intervention can often very swiftly improve LUTS, even in the absence of BOO, have highlighted the fact that obstruction is not solely responsible. It is hoped that with improvements in diagnostic techniques and understanding of lower urinary tract innervation our therapeutic approaches will become more focused and efficacious.

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One hundred sixty-two men with LUTS were evaluated urodynamically, of whom 55% had BPO alone and 45% had coexisting BOO and DO. Men with DO were more likely to be older, have BOO, and had higher prostate-specific antigen levels. Symptom scores, Q_{max}, flow rate, and residual volume did not differ between the groups.

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Five hundred sixty-five men with LUTS were assessed with UDS, of whom 53% were confirmed to have obstruction and 46% had DO. Increasing grades of obstruction were associated with increasing likelihood of DO. Patients with DO were older than those without, although age was not correlated with BOO in this study.

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