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New Diagnostics for Male Lower Urinary Tract Symptoms

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Abstract

Purpose of review: Lower urinary tract symptoms (LUTS) is a common constellation of symptoms that affect the aging male population with an astonishing prevalence. New technology and new uses of established technology are being used to help further evaluate LUTS in the male population and help guide treatment options. This review focuses on the developments and future directions in diagnostic modalities for evaluation of male LUTS, focusing on evaluation of both the filling and voiding phases of micturition.

Recent findings: New techniques in evaluating the voiding phase include penile cuff test, external pressure sensing condom catheter, ultrasound measurement of detrusor wall thickness, ultrasound measurement of intravesical prostatic protrusion, doppler ultrasound and NIRS technology. Evaluation of the filling phase is still undergoing much development and requires additional validation studies. The techniques undergoing evaluation include sensation meters during UDS, assessing bladder micromotion and wall rhythm, assessing detrusor wall biomechanics, ultrasound measurement of detrusor wall thickness, pelvic doppler ultrasound, as well as functional brain imaging including fNIRS and fMRI.

Summary: The development of novel, non-invasive, diagnostic tools have the potential for better evaluation of LUTS with earlier and enhanced treatments. This will likely improve the quality of life for men with LUTS.

Keywords

Lower urinary tract symptoms; urodynamics; bladder dysfunction; voiding complaints; diagnosis

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Conflict of Interest
Natalie R. Swavely declares that she has no conflict of interest.
John E. Speich declares that he has no conflict of interest.
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Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Lower urinary tract symptoms (LUTS) are a common chief complaint seen by urologists, with prevalence rates of 50% - 75% in men over 50, and increasing to 80% in men over 70. [1] LUTS is a constellation of symptoms and includes disruption of both the filling and voiding phases of the micturition cycle. These symptoms often increase with age and affect patient quality of life, activities, and even occupation. [1] LUTS has an array of etiologies, and treatment is largely dependent on the etiology for a particular patient. Urinary tract symptoms are often difficult for the patient to describe, and the Urologist may rely heavily on objective measures such as uroflow and urodynamics (UDS) for assistance in diagnosis. [2] Research is being performed on new methods to evaluate the lower urinary tract for etiology of these symptoms, particularly non-invasive measures to improve and expand upon the diagnostic tools already in place. Patients may often be hesitant to undergo UDS given its invasive nature; however, successful treatment often revolves around knowledge of the etiology of patient's symptoms.

The micturition cycle is divided into the filling phase and the voiding phase. Pathology in either phase can lead to LUTS. The current diagnostic adjuncts to UDS include uroflow and post void residual (PVR), but these tools only assess the voiding phase with adjunct evaluation of the filling phase being completed in questionnaires. Unlike other medical specialties where an array of non-invasive, diagnostic tools exist which can be utilized prior to invasive diagnostic testing, evaluation of micturition has little to offer prior to invasive and uncomfortable UDS. Therefore, development of an objective evaluation of male LUTS that is also minimally invasive is critical to continued advancement in diagnosis and treatment. This review will focus on these up-and-coming technologies, divided into separate sections regarding the filling and voiding phases of micturition.

Emerging Technologies and Methods to Evaluate the Voiding Phase

Emerging technology and methods to evaluate the voiding phase are derived from multiple sources. The first is an ongoing randomized trial entitled, "Urodynamics for Prostate Surgery Trial - Randomised Evaluation of Assessment Methods (UPSTREAM)." Other methods include the penile cuff test, a novel pressure sensing external catheter, measurements of detrusor wall thickness, evaluation of intravesical prostatic protrusion, use of pelvic doppler, and bladder Near Infrared Spectroscopy (NIRS) (Table 1). These advancements and their effectiveness will be further discussed in this section.

For men with LUTS, a main cause of voiding phase symptomatology is bladder outlet obstruction (BOO). This commonly treated pathology, benign prostatic enlargement (BPE), often requires surgical management. BOO must be differentiated from an underactive bladder, for which surgical treatment is not employed. The UPSTREAM trial, recently completed with results expected to be published soon, is assessing the use of UDS prior to surgery in men with suspected BOO. [3] Current standard of care does not require UDS prior to operation for BOO and this non-inferiority trial will assess use of UDS prior to surgery. [3,4]

Beyond UDS, a number of additional modalities to establish a diagnosis of BOO have been studied. Malde et al performed a systematic review of non-invasive tests to diagnose BOO. While the heterogeneity of the 42 included studies made conclusions difficult, the study highlights a number of techniques that offer a promise of non-invasive adjuncts. [5] One of these modalities, the penile cuff test, involves place a small, inflatable cuff or pediatric blood pressure cuff around the penile shaft. This is inflated automatically during voiding until urinary flow is stopped. The cuff is rapidly deflated and urine flow is resumed. This cycle is repeated until the end of micturition, and the pressure required to stop urine flow is considered equal to isovolumetric pressure. A nomogram evaluated pressure rise during interruption with pre-interruption flow rate to determine obstructed versus unobstructed patients. [6] Malde et al evaluated 7 studies of penile cuff test compared to pressure flow studies and found 88.9% sensitivity and 75.5% specificity. [5–12] Continued research into penile cuff test has continued to show promising results, with high negative predictive value of 94.9% on a recent prospective study of 146 men. [13]

Similarly, Pel et al used an external condom catheter in comparison to a pressure flow study to evaluate for BOO. [14] The external condom catheter was drained into a uroflow device and a pressure transducer was placed inside the condom catheter to measure pressure during voiding. A constricting pressure cuff was placed around the condom, and a nomogram was again used to evaluate pressure with flow rates to determine obstructed versus unobstructed. Seventy-five percent of their participants were correctly diagnosed using this method compared to pressure flow studies. The majority of the failures were seen in patients who strained during urination. [14]

Increased detrusor wall thickness has also been examined as a potential diagnostic measurement of BOO. Wall thickness can be assessed via non-invasive ultrasound technology. Franco et al measured the wall thickness of men with approximately 200 mL of fluid in the bladder and found that detrusor wall thickness of 6mm was highly correlated with bladder outlet obstruction index (BOOI) and bladder prostatic obstruction (BPO). [15] In a systematic review of 8 studies of detrusor wall thickness compared to pressure flow studies, a range of detrusor wall thicknesses of 2 mm – 6 mm were used as diagnostic criteria BOO. Five of the 8 studies used as a 2 mm cutoff. Pooled analysis found 82.7% sensitivity and 92.6% specificity. [5,15–22]

Using similar ultrasound methodology, intravesical prostatic protrusion has also been examined. Franco et al measured intravesical prostatic protrusion in addition to detrusor wall thickness and found that intravesical prostatic protrusion of 12mm is also highly correlated with BOOI and BPO. They concluded that using detrusor wall thickness with intravesical prostatic protrusion together best predicted BOO, as performing these 2 measurements in succession lead to a diagnostic accuracy of 87%. [15] Systematic review of 10 studies of intravesical prostatic protrusion, with 5 studies using a 10 mm cutoff showed a sensitivity of 67.8% and a specificity of 74.8%. [5,15–17, 23–29]

In addition, non-invasive doppler ultrasound of the detrusor has been compared to UDS for the diagnosis of BOO. Using doppler technology, a resistive index (RI) can be calculated using the formula: (velocity max-velocity minimum)/velocity max. Using the RI as diagnostic test for BOO was found to have accuracy of 86% with a positive predictive value of 95%. [30] This statistically significant increased RI seen in BOO is thought to be secondary to detrusor hypertrophy seen in BOO associated with reduced vascular supply. [30–31] Doppler technology has also been applied to measure the flow of urine to evaluate for BOO. Ozawa et al calculated a velocity ratio (VR) to diagnose BOO. [32] They found a VR greater than 1.6 in men with BOO and a VR less than 1.1 in men that did not have BOO. The VR was calculated during micturition with the maximum velocity of urine in the prostatic urethra compared to the maximum velocity of urine in the membranous urethra. This ratio reduces inter-subject discrepancies due to microbubbles which can affect doppler signaling. The prostatic and membranous urethra were chosen as location points of analysis due to the prostatic urethra being the location of control of flow of urine and the membranous urethra being an area of low resistance. [32] VR was evaluated for reliability and was found to have good intra-rater and inter-rater agreement. [33]

Near-infrared spectroscopy (NIRS) uses near infrared light to quantify changes in tissue oxygenation and has safely been used in human tissue since late 1970s. [34–36] NIRS was first used in urology in the 1990s and has recently been used in evaluation of bladder function. [37–43] Using NIRS in the evaluation of BOO, Stothers et al performed NIRS simultaneously with UDS. A NIRS patch was placed on the abdominal skin 2 cm above the pubis in the midline. A classification and regression tree algorithm (CART) was used to assess patterns in the NIRS data and changes in oxygenation throughout the UDS. A nomogram was created using detrusor pressure at maximum flow versus relative concentration of total hemoglobin at maximum flow to classify patients as either obstructed or unobstructed. They found a sensitivity of 100% and a specificity of 87.5%. [44] Systematic review of 3 studies using NIRS to define BOO found a sensitivity of 85.7% and a specificity of 87.5%. [5,44–46]

Moving forward, a number of these new non-invasive techniques may be combined in an algorithmic manner to provide diagnostic information on BOO without the invasive measures of UDS. [47]

Emerging Technologies and Methods to Evaluate the Filling Phase

New technologies for the assessment of the filling phase of the micturition cycle are still in development and will require additional study and validation prior to widespread application. New metrics to evaluate the filling phase include: sensation metrics, bladder wall micromotion and rhythmic contraction analysis, detrusor biomechanics, pelvic doppler ultrasound, and functional brain imaging using both MRI and NIRS *(*Table 2*)*. The creation and future utility of these techniques will be discussed in this section.

Currently, sensation during UDS is assessed with patient declaration of first sensation, first desire and strong desire. [48] These regimented and subjective terms may not accurately describe what the patient is feeling and may be influenced by investigator prompting as well as the non-physiologic and artificial nature of testing. [49–50] In fact Erdem et al. performed sham UDS studies. [49] In the first sham fill, 83% declared first sensation, 79% had first desire, 64% had normal desire, and 25% had strong desire even in the absence of filling, highlighting the artificial nature of UDS. Nagle et al developed a sensation meter that allows the patient, in real time, to use a touch screen and assess what they are feeling and make changes as their sensations change on a scale of 0 to 100%. [51] This new metric generates a sensation-capacity curve throughout the filling phase which enables comparisons of different pathologies, including overactive bladder (OAB). [51–52] In addition, the technology gives more accurate and detailed description of bladder sensation during filling using the phrases, adopting the terminology established by Heeringa et al., as “tense,” “tingling,” “pressure,” and “painful”. [51–54] Lowenstein et al[55] also developed a similar device to allow for continuous sensation data collection during UDS. These investigators completed a feasibility study with the Urgeometer, a handheld device allowing for reporting of sensation on a continuum from no urge to strongest imaginable urge. The patient was able to move the lever throughout UDS. [55] These sensation meters can be used in standard UDS or during oral hydration studies. [51–55] Oral hydration studies of bladder filling have the patient consume a prescribed volume of fluid and measure their sensation on a continuous sensation meter as well as volume voided. [53–54,56] This technique has demonstrated feasibility in diagnosis of OAB. [51]

During filling, it is known that the bladder displays spontaneous rhythmic contractions (SRC). [57] It has been suggested that SRC may function to maintain bladder tone, which will allow the detrusor to contract and allow for voiding at a range of bladder volumes. [58] Fast Fourier transforms (FFT) have been used to analyze signals and differentiate true signals from background noise to investigate SRC. [59] SRC have been shown to be elevated in a subset of patients with detrusor overactivity (DO) and have additionally been associated with increased micromotion with bladder filling with accompanying increased urgency. [60–61] An FFT algorithm applied to UDS of patients with and without DO showed 100% specificity. [62] This additional analysis of pathology in patients with DO can help individualize treatment strategies.

Ultrasound has also recently been added as an adjunct to UDS in several different methods. Ultrasound shear wave elastography has been shown to be correlated with detrusor pressure throughout the filling phase and was able to be used to determine a non-compliant bladder versus a compliant bladder via a significantly increased shear wave speed seen in the non-compliant bladder, as confirmed on UDS. [63] Ultrasound bladder vibrometry (UBV) has also been studied with concurrent UDS to correlate velocity and elasticity with detrusor pressure, assisting in the evaluation of bladder compliance. [64–65] Both of these new uses of ultrasound technology would allow for bladder compliance to be measured without the need for invasive UDS.

Ultrasound has additionally been utilized during UDS to calculate detrusor wall tension, stress, compliance and elastic modulus. Detrusor wall tension can increase due to filling, with little increase in bladder pressure, and may better correlate with the symptom of urinary urgency. [66–67] Evaluation of OAB symptomatology without DO seen on UDS could possibly be better evaluated with detrusor wall tension. Three dimensional ultrasound has been performed with concurrent UDS to evaluate bladder shape association with LUTS. Alterations in the ultrasound-measured height-to-width ratios of bladders were associated with OAB, identifying a possible shape-associated OAB subtype. [68] Unfortunately, the use of ultrasound to measure bladder wall thickness has not shown to be an effective method for evaluation of DO. [69–70]

In addition to its utility in BOO, doppler ultrasound is currently being evaluated for diagnostic utility of chronic pelvic ischemia leading to DO and potentially detrusor underactivity. Using doppler flow studies, it has been determined that patients with LUTS have significantly decreased pelvic blood flow. [71] Chronic pelvic ischemia, caused by atherosclerosis and imaged by doppler studies is thought to be instrumental in the development of LUTS due to oxidative stress, denervation, and release of tissue damaging molecules. [72] Animal models are currently being used to investigate treatment options for LUTS that could prevent the detrusor damage caused by pelvic ischemia. [73–74] Moving forward, pelvic doppler studies may help clinicians diagnose patients at risk for development of LUTS and prevent the conditions that lead to LUTS.

With much of the evaluation and treatment options for LUTS focused on the urinary tract, there has been little study of diagnostics related to upstream central nervous system control of micturition. Recent research has focused on the role of the brain in the symptomatology of LUTS as a network of cerebral regions has been identified as vital in the micturition cycle, called the brain-bladder control network. [75–79] In order to further investigate this relationship, functional magnetic resonance imaging (fMRI) and brain functional NIRS (fNIRS) have been used.

fMRI has also been used in the evaluation of voiding dysfunction. In one study, patients underwent urodynamic filling while undergoing simultaneous fMRI. Those patients with DO uniformly had increased activation of the supplementary motor area (SMA) which evokes the sensation of urgency as well as contracts the pelvic floor and urethral sphincter. [75] An additional finding in the neural signaling seen in DO is prefrontal deactivation. [78] Moving forward, fMRI is being used to evaluate the differences in signaling in patients with LUTS who respond to treatment, versus nonresponders to develop novel treatment targets for non-responders. [80]

Brain fNIRS has been developed using NIRS technology as a method to evaluate activation of certain regions of the cerebral cortex. The concept behind how the imaging modality works is that active areas of the brain have a large increase in blood flow due to neurovascular coupling, which leads to an excess of oxygenated blood as the amount of oxygenated blood delivered exceeds that of the neuronal oxygen usage. This increase in oxygenated blood is imaged with the NIRS device. [81] fNIRS has the advantage over fMRI of allowing for a more natural testing environment. The patient is free to move around, be positioned as they are comfortable and is not secured, immobile in a large machine. fNIRs has been used to investigate cortical activation during the micturition cycle. [82] During the filling phase of the micturition cycle in normal, healthy adults, fNIRS demonstrated increased blood flow, and thus activation, of the bilateral frontal cortex, an expected finding based on fMRI data. [83] This technology is specific enough to evaluate Brodmann’s areas, which are activated during micturition. [84] This technology is now being used to evaluate the brain’s response to anti-cholinergic medication in the treatment of OAB. [85] Moving forward, fNIRS will help better elucidate the brain's role in the pathology of LUTS, the mechanism of treatments, and the development of new treatments.

Conclusion

There are currently few diagnostic strategies, especially with less invasivity than UDS, available for the evaluation and diagnosis of male LUTS. Emerging technology and methods to evaluate the voiding phase are derived from multiple sources including the penile cuff test, a novel pressure sensing external catheter, measurements of detrusor wall thickness, evaluation of intravesical prostatic protrusion, use of pelvic doppler, and bladder Near Infrared Spectroscopy (NIRS). New metrics to evaluate the filling phase are less well-established but include sensation metrics, bladder wall micromotion and rhythmic contraction analysis, detrusor biomechanics, dynamic elasticity, pelvic doppler ultrasound, and functional brain imaging using both MRI and NIRS. The development of these novel, non-invasive, diagnostic tools have the potential for better evaluation of LUTS with earlier and enhanced treatments. This will likely improve the quality of life for men with LUTS.

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Table 1.

Voiding Phase Diagnostics

Urodynamics	Non-inferiority trial assessing UDS prior to prostate surgery, results pending[3]	UPSTREAM trial[3]
Penile cuff test	Pediatric blood pressure cuff placed around penis and quickly cycle to interrupt flow during micturition. Nomogram of pressure rise during interruption vs pre-interruption flow rate to determine obstructed versus unobstructed patients.[6–13]	Griffiths[6], Bianchi[7], Harding[8], Kazemeyni[9], Matulewicz[10], Salinas[11], Sullivan[12], Ko[13]
External condom catheter	Pressure sensing condom catheter to serve as abdominal pressure and external pressure applied to the condom catheter to interrupt flow. Nomogram of pressure vs flow rate to determine obstructed versus unobstructed patients.[14]	Pel[14]
Detrusor wall thickness	Measured with ultrasound, 2–6 mm diagnostic for BOO[15–22]	Franco[15], Abdel-Aal[16], Aganovic[17], El Saied[18], Kessler[19], Manieri[20], Oelke[21], Oelke[22]
Intravesical prostatic protrusion	Measured with ultrasound, 10–12mm diagnostic for BOO[15–17,23–29]	Franco[15], Abdel-Aal[16], Aganovic[17] Aganovic[23], Chia[24], Dicuio[25], Keqin[26], Lim[27], Pascual[28], Reis[29]
Doppler ultrasound	RI of detrusor muscle significantly increased in BOO[30–31] VR of urine significantly increased, greater than 1.6, in BOO[32–33]	Belenky[30], Kojima[31], Ozawa[32], Ding[33]
NIRS	CART assessed patterns in changes in oxygenation. Nomogram of detrusor pressure at maximum flow versus relative concentration of total hemoglobin at maximum flow to classify patients as either obstructed or unobstructed[44–46]	Stothers[44], Yurt[45], Zhang[46]

UDS=urodynamics, UPSTREAM = Urodynamics for Prostate Surgery Trial; Randomised Evaluation of Assessment Methods, BOO = bladder outlet obstruction, RI = resistive index, VR= velocity ration, NIRS = near–infrared spectroscopy, CART= classification and regression tree algorithm

Table 2.

Filling Phase Diagnositics

Sensation meter	Allows for constant assessment of sensation along a continuum[51–52,55]	Nagle[51], Naimi[52], Lowenstein[55]
Oral hydration studies	Physiologic filling with oral electrolyte consumption with sensation and volume measurements[51,53–54, 56]	Nagle[51], Heeringa[53–54], De Wachter[56]
Bladder micromotion and bladder rhythm	Increased LARC and micromotion in DO[60–62]	Brading[60], Drake[61], Cullingsworth[62]
Detrusor biomechanical properties	Increased ultrasound shear wave elastography in non-compliant bladder.[63] Increased bladder vibrometry in non-compliant bladder.[64–65] Increased detrusor wall tension in OAB.[66–67] Abnormal bladder fill shape in OAB.[68]	Sturm[63], Bayat[64], Nenadic[65], Nagle[66], Habteyes[67], Glass[68]
Ultrasound bladder wall thickness	Bladder wall thickness is not predictive of DO[69–70]	Rachaneni[69], Latthe[70]
Pelvic doppler ultrasound	Doppler ultrasound diagnosing chronic pelvic ischemia, a proposed mechanism of damage leading to LUTS[71–74]	Pinggera[71], Yamaguchi[72], Andersson[73], Andersson[74]
Functional brain imaging	fMRI reveals activation of SMA[75] and prefrontal deactivation in patients with DO[76]. Development of new therapies for patients with DO that do not respond to anti-muscarinic medication.[80] fNIRS is able to demonstrate cerebral region functionality similarly to fMRI in a non-restrictive environment.[81–85]	Tadic[75], Khavari[76], Clarkson[80], Ferrari[81], Matsumoto[82–83], Sakakibara[84,85]

DO = detrusor overactivity, OAB= overactive bladder, LUTS = lower urinary tract symptoms, SMA = supplementary motor area, fNIRS = functional near–infrared spectroscopy, fMRI = functional magnetic resonance imaging