# *Association of bladder sensation measures and bladder diary in patients with urinary incontinence*

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***Introduction:*** *Investigation suggests the involvement of afferent actions in the pathophysiology of urinary incontinence. Current diagnostic modalities do not allow for the accurate identification of sensory dysfunction. We previously reported urodynamic derivatives that may be useful in assessing bladder sensation. We sought to further investigate these derivatives by assessing for a relationship with 3-day bladder diary.*

***Materials and methods:*** *Subset analysis was performed in patients without stress urinary incontinence (SUI) attempting to isolate patients with urgency symptoms.*

***Results:*** *No association was demonstrated between bladder diary parameters and urodynamic derivatives (r coefficient range (-0.06 to 0.08)($p > 0.05$)). However, subset analysis demonstrated an association between detrusor overactivity (DO) and bladder urgency velocity (BUV), with a lower BUV identified in patients without DO. Subset analysis of patients with isolated urgency/urge incontinence identified weak associations between voiding frequency and FSR ($r = 0.39$) and between daily incontinence episodes and BUV ($r = 0.35$). However, these associations failed to demonstrate statistical significance.*

***Conclusions:*** *No statistical association was seen between bladder diary and urodynamic derivatives. This is not unexpected, given that bladder diary parameters may reflect numerous pathologies including not only sensory dysfunction but also SUI and DO. However, weak associations were identified in patients without SUI and, further, a statistical relationship between DO and BUV was seen. Additional research is needed to assess the utility of FSR/BUV in characterizing sensory dysfunction, especially in patients without concurrent pathology (e.g. SUI, DO).*

**Key Words:** bladder sensation, hypersensitivity, urodynamics

## Introduction

The pathophysiology of overactive bladder (OAB) and urinary incontinence (UI) is complex and may be associated with numerous and potentially independent abnormalities. Historically, investigation into both the pathophysiology and treatment of OAB has focused on abnormalities of efferent and myogenic actions of the bladder.[1-3] Fundamental to this focus was the early identification of the association of involuntary detrusor contractions with OAB symptomotology.[1] Based on this understanding, anti-muscarinic therapy has remained the focus of pharmacologic intervention for many years.

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In recent years, significant research has focused on characterizing abnormalities of afferent actions associated with OAB/UI. Such research has identified neurochemical, electrophysiological, and organizational changes in afferent bladder pathways to be associated with various lower urinary tract disorders and states of bladder inflammation.[4,5] These changes appear to be part of a complex immunosensory loop, involving unmyelinated and myelinated sensory neurons, neuropeptides, and interactions with supporting cells, including interstitial and inflammatory cell types.

Importantly, such research provides a framework for a large number of diagnostic and therapeutic targets. However, current technologies lack the ability to discriminate afferent dysfunction critical for the development of related diagnostic instruments. While developmental technologies are reported, including the assessment of bladder current thresholds characteristic of afferent neurons, significant advances are necessary to allow for the identification of sensory dysfunction.[6] Further, based on current research, numerous targets have been identified as targets for potential pharmacologic agents and several such agents may be available for use in the near future.[7] Accordingly, it is possible that pharmacologic efficacy may be optimized if methods of better discriminating patients with sensory versus motor dysfunction become available.

We previously reported the identification and analysis of two urodynamic parameters, first sensation ratio (FSR) and bladder urgency velocity (BUV), used in an attempt to capture data regarding bladder sensation.[8] This investigation demonstrated an important correlation between both urodynamic parameters and a validated questionnaire assessing urgency (Urgency Perception Score (UPS)[9]) despite a lack of correlation identified with standard urodynamic parameters of bladder sensation during filling cystometry (e.g. first sensation (FS), first desire). Such data suggested therefore that these urodynamic derivatives may provide an objective method of assessing patients with suspected sensory dysfunction.

### *Investigational objective*

We sought to further investigate these urodynamic derivatives by assessing for a statistical relationship with an additional instrument of OAB assessment, the 3-day bladder diary. Our second investigational objective explored the hypothesis that these markers of bladder sensation may be more useful in cohorts without concurrent pathologies that may contribute to OAB/UI. Accordingly, subset analysis was also performed in OAB/UI patients without detrusor overactivity (DO) or stress urinary incontinence (SUI).

## Materials and methods

We performed a retrospective database review of female patients evaluated for urinary incontinence at the Virginia Urology Center for Incontinence and Pelvic Floor Reconstruction between January 2009 and December 2010. All patients were evaluated with complete history, physical examination, and 3-day bladder diary per Center protocol. Bladder diary variables included daily voiding frequency, nocturia, daily incontinence episodes and daily pad use. Only patients undergoing urodynamic evaluation were included in study analysis. Additional inclusion criteria selected for patients with OAB symptoms of urgency and urge incontinence given the study focus on measures of bladder sensation. Accordingly, patients with pure SUI were excluded. Virginia Urology Center Institutional Review Board approval was obtained for the study protocol.

### *Urodynamic assessment*

Urodynamic study (URD) was performed in accordance with International Continence Society (ICS) recommendations.[10] Intravesical and rectal catheters were placed using sterile technique and zeroed to atmospheric pressure. Self-adhering patch electrodes were placed for EMG measurement. The bladder was filled with room temperature saline at 60 mL/minute. Variables of bladder sensation (first sensation (FS) and maximum cystometric capacity (Cap) were assessed using the ICS definitions.[10] Detrusor overactivity was defined and measured according to ICS standard.[10] Valsalva leak point pressure (VLPP) was assessed at maximum cystometric capacity.

### *Statistical analyses*

Statistical analysis was performed to assess for a relationship between bladder diary parameters (voiding frequency, nocturia, daily incontinence episodes and daily pad use) and urodynamic derivatives (FSR, BUV). The first sensation ratio was defined as FS (mL)/maximum cystometric capacity (mL) and the bladder urgency velocity was defined as maximum cystometric capacity (mL) – FS (mL).

Subset analysis was performed in patients without SUI attempting to isolate patients with urgency symptoms. Analysis was also performed to identify a possible relationship between the presence/absence of DO with these derivatives. Analyses were performed using Pearson's correlation and Mann-Whitney test as appropriate. Quantitative data are expressed as mean value (± SD) as applicable. Each analysis was structured as a two-tailed test at the $\alpha = .05$ level.

## Results

A total of 120 patients were enrolled for study participation. The mean patient age was 64 years (± 13). Of these patients, 49 (41%), 8 (7%), and 2 (2%) had previously undergone hysterectomy, pelvic organ prolapse repair, or anti-incontinence surgery, respectively.

Bladder diary and urodynamic results are detailed in Table 1. Correlation analyses between bladder diary parameters and urodynamic derivatives are detailed in Table 2. No statistical association was demonstrated between bladder diary parameters and urodynamic derivatives (r coefficient range (-0.08 to 0.06)($p > 0.05$, all analyses)).

Subset analysis of bladder diary and urodynamic results demonstrated no differences in comparison of patients with (n = 11) or without (n = 109) DO ($p > 0.05$). However, subset analysis demonstrated an association between the presence of DO and BUV ($p < 0.05$). A lower mean BUV was identified in patients without detrusor overactivity (262 cc versus 249 cc). Further, in the subset analysis of patients with isolated urgency/urge incontinence (no SUI) (n = 20) a weak association was demonstrated between voiding frequency and FSR (r = 0.39) and between daily incontinence episodes and BUV (r = 0.35). However, these associations failed to demonstrate statistical significance.

TABLE 1. **Urodynamic and bladder diary characteristics**

| **Urodynamic variable** | **Variable measurement (mean (± SD))** |
|---|---|
| Filling cystometry | |
| First sensation (mL) | 112 (81) |
| First desire (mL) | 169 (101) |
| Strong desire (mL) | 217 (118) |
| Urge (mL) | 281 (150) |
| Capacity (mL) | 365 (169) |
| DO (present) (n pts) | 11 |
| Urodynamic derivatives | |
| First sensation ratio | 0.34 (0.20) |
| Bladder urgency velocity (mL) | 253 (155) |
| **Urodynamic variable** | **Variable measurement (mean (± SD))** |
| Frequency (episodes/day) | 7.2 (2.7) |
| Nocturia (episodes/night) | 2.5 (1.1) |
| Incontinence episodes (episodes/24h) | 3.1 (3.0) |
| Pad use (n/24h) | 2.3 (2.4) |

DO = detrusor overactivity

TABLE 2. **Correlations between bladder diary and urodynamic derivatives**

| | **Pearson's correlation ($p > 0.05$, all analyses)** | | | |
|---|---|---|---|---|
| | **Frequency** | **Nocturia** | **Incontinence** | **Pad use** |
| FSR | -0.07 | -0.03 | 0.06 | 0.06 |
| BUV | -0.02 | -0.03 | -0.08 | -0.16 |

FSR = first sensation ration; BUV = bladder urgency velocity

## Discussion

Recent study demonstrates a variety of physiological and anatomical changes to afferent pathways that are present in patients with OAB and related animal models, both to peripheral and central functions.[4,5] Such research comprises an evolution to the understanding of OAB/UI, which has historically focused on efferent actions of the bladder. While the use of numerous anti-muscarinic agents has allowed for the more effective treatment of many patients, this pharmacologic class has significant limitations. Indeed, recent metanalysis of anti-muscarinic treatment for OAB, concluded that while significant improvements in OAB symptoms seen, clinical significance is limited given associated side effects.[11] As a result, the singularity of this treatment algorithm has been questioned and related literature highlights the lack of new pharmacologic classes as an important obstacle.[8]

Importantly, the multifactorial pathophysiology of OAB is forwarded as a likely cause for the lack of therapeutic progress.[12] DO is not identified in the majority of patients with OAB/UI, supporting the possibility of alternate mechanisms as contributors to this symptomotology. Indeed, these findings are supported in our data, in which only 11 patients were found to have DO despite the presence of urgency or UI in all patients. Investigation supporting the complex pathophysiology of OAB/UI demonstrates functional differences in comparison of patients with bladder dysfunction as dependent on the presence or absence of DO.[13] Further, the presence of urgency in patients with DO is associated with differing detrusor contraction properties when compared to those patients without urgency.[13]

While more research is needed, this data suggests the possibility that sensory dysfunction may play a significant role in the pathophysiology of OAB/UI. This becomes increasingly important given the

introduction of many pharmacologic agents that target afferent mechanisms that is anticipated in the near future. Accordingly, the TRVP receptor subtypes have been suggested to have a pathophysiologic role in OAB and modulating agents have been shown to produce clinical benefit.[14] Purinergic actions are widely demonstrated to mediate activity of bladder sensory neurons and both anatomic/physiological defects are associated with OAB.[4] Additional afferent targets for OAB pharmacotherapy include receptors of neurokinin, endothelin, nerve growth factor, and cannabinoid families.[15] Finally, several currently available off-label agents (PDE inhibitors, botulinum toxin) modulate afferent pathways and offer the possibility of use in the treatment of OAB/UI. Certainly, the ability to appropriately apply these agents may be optimized if methods of better discriminating patients with sensory dysfunction become available.

Importantly, the development of technologies that allow for the objective assessment of sensory function are needed. Certainly, the limitations of our present ability to discriminate sensory dysfunction are evident in the ICS guidelines, in which vague categories are used to categorize bladder sensation (normal, increased, reduced) while providing no defined methods of doing so. In addition to previously described experimental technologies, additional investigation has focused on variation to URD protocol (continuous sensation recording) in an attempt to capture data regarding bladder sensation.[16] Such investigation is necessary as surrogate instruments are needed until such technologies are realized.

We previously reported the analysis of FSR and BUV, two urodynamic parameters used in an attempt to capture data regarding bladder sensation. Importantly, this investigation demonstrated a correlation between these parameters and a validated urgency questionnaire despite the lack of a correlation observed for standard URD variables including the individual components of these derivatives. Given patients with identical bladder capacity, this finding demonstrates that patients with increased first sensation (FS) actually have worse symptomatology. This is a novel concept, as low FS is often theorized to relate to irritative bladder symptoms. In contrast, a negative correlation between BUV and UPS was identified, showing that patients with a more rapid progression from FS through capacity have more severe symptoms. Such findings suggested that the rate of progression from first sensation through bladder capacity may be more meaningful that the absolute first sensation or bladder capacity.

Our investigation attempted to further investigate the utility of FSR/BUV in the assessment of OAB/UI. Accordingly, several important findings are noted. First, no statistical association was identified between FSR/BUV and bladder diary results. This is not unexpected given that bladder diary parameters may reflect numerous pathologies. Certainly, bladder diary parameters such as incontinence episodes could be affected not only by degree of sensory dysfunction but also the contributions of SUI and DO. Given the inability to discriminate between the contributions of these pathologies in our primary analysis, the lack of an association between urodynamic derivatives and bladder diary results is not surprising.

However, subset analysis demonstrated several additional findings. First, weak associations were seen between urodynamic derivatives and some bladder diary variables in the evaluation of patients without DO or SUI. These findings failed to achieve statistical significance, a finding likely influenced by study power associated with subset analysis. Despite this finding, we believe that such data suggests further research focusing on the utility of these URD derivatives in a focused subset of patients is important. Further, subset analysis demonstrated an association between DO and BUV with a lower mean BUV identified in patients without DO. In analyzing these results, this finding may suggest an expected relationship between the absence of DO and lower BUV. Thus, patients without DO are found to have a more rapid progression from FS through Capacity. Accordingly, such findings may suggest alternate pathologies (DO versus sensory dysfunction) that underlie similar symptomatology.

Several study weakness are present. First, this study was performed in a retrospective fashion. Second, the low patient numbers available for subset analysis may impact outcomes. Finally, as described previously, the variable pathologies that may contribute to bladder diary results complicate the study outcomes assessment. Despite these factors, we believe that the historical inability to demonstrate high predictive value or statistical relationships between a large number of urodynamic parameters and patient symptoms/therapeutic outcomes adds to the strength of our findings.[17,18]

## Conclusion

Significant research suggests that afferent actions may contribute to the pathophysiology of OAB/UI. Current diagnostic modalities do not allow for the accurate identification of sensory dysfunction in these patients. The present study found no statistical association

between bladder diary parameters and urodynamic derivatives. This finding is not unexpected given the contributions that additional pathologies such as DO and SUI may have on bladder diary results. However, weak associations were identified in patients without SUI. Further, a statistical relationship between DO and BUV was seen. These findings suggest that FSR and BUV may have utility in characterizing sensory dysfunction, especially in patients without concurrent pathology (e.g. SUI). Subsequent research is needed to assess whether FSR and BUV may be predictive of therapeutic success given the numerous afferent targets for potential pharmacologic agents that have been identified and are in development. □

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