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Original Article

Bladder wall micromotion measured by non-invasive ultrasound: initial results in women with and without overactive bladder

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Abstract: Objective: Rhythmic contractions of the bladder wall during filling result from the synchronization of bladder wall micromotion and are often observed in the urodynamic tracings of individuals with urinary overactive bladder (OAB). This study's objective was to develop a novel, non-invasive method to measure bladder wall micromotion and to conduct an initial study to test the hypothesis that elevated micromotion is associated with OAB. Methods: This prospective study enrolled women with OAB and asymptomatic volunteers as measured by the ICIQ-OAB survey. After filling the bladder to 40% cystometric capacity, 85 second cine-loops were obtained using a GE Voluson E8 ultrasound system with an 8 MHz curved, abdominal probe. A custom correlation-based texture tracking MATLAB algorithm was used to measure changes in the bladder wall thickness over time and correlate with changes in vesical pressure. Significant bladder wall micromotion was defined as changes in wall thickness with amplitudes higher than 0.1 mm in the frequency range of 1.75-6 cycles/minute as calculated from Fast Fourier Transform (FFT) analysis. The micromotion algorithm was tested on 30 women including 17 with OAB and 13 asymptomatic volunteers. Results: Micromotion was identified in 41% of subjects with OAB and 0% of asymptomatic volunteers, indicating a significant association of micromotion with OAB (Fisher's exact test, P=0.010). Micromotion was also found to have a significant association with a clinical diagnosis of detrusor overactivity (Fisher's exact test, P=0.031). Frequencies with elevated micromotion correlated with frequencies of vesical pressure fluctuations. Conclusions: The feasibility of a non-invasive method to measure bladder wall micromotion was demonstrated using transabdominal anatomical motion mode (M-mode) ultrasound. Presence of micromotion was significantly associated with OAB and with urodynamic-identified rhythm.

Keywords: Ultrasonography, urodynamics, overactive bladder, fast Fourier transform analysis, detrusor overactivity, lower urinary tract symptoms, diagnostic imaging, image analysis, texture tracking, non-invasive

Introduction

Overactive bladder (OAB) is a condition defined by increased urinary urgency that affects an estimated 36% of adults in the United States [1]. This condition is more common in females than males with 43% of women reporting sometimes having OAB symptoms compared to 27% of men [1]. OAB significantly lowers quality of life [2], but can be challenging to treat effectively due to underdiagnosis, undertreatment, and poor patient compliance [3]. Therefore, a critical research objective is the development of novel bladder diagnostic tools to improve OAB phenotyping while limiting the invasiveness of testing.

The current gold standard tool to assess OAB is multichannel urodynamics. This involves placing catheters with pressure transducers in the bladder and rectum to monitor pressure while the bladder is filled and then voided. One condition that urodynamics is used to diagnose is detrusor overactivity in which non-voluntary,

non-voiding contractions are seen in intravesical pressure (P_{ves}) [4]. Detrusor overactivity was found in 58% of female OAB patients in a study by Hashim et al [5]. While urodynamics is valuable in the assessment of detrusor overactivity and other disorders, the procedure is invasive, can lead to urinary tract infections [6], and many patients find it embarrassing and uncomfortable [7].

There is a growing body of research showing that the rhythmic pressure changes associated with phasic detrusor overactivity during filling are the result of global coordination of bladder wall micromotion in which small contractions of the bladder wall are synchronized together [8, 9]. Several groups have used various techniques to measure these surface contractions and have shown that their rhythmic, frequency characteristics reflect the frequency characteristics seen in P_{ves} [9-12]. These contractions were found to have a rhythm in the frequency range of 1.75-6 cycles/min both in vivo and in ex vivo bladder strip studies [10, 14-18], may be associated with feelings of increased urgency in OAB patients [10, 19], and are likely mediated by tension sensitive afferent nerves [8, 10].

In order to develop a non-invasive tool to quantify bladder wall micromotion, we developed an algorithm utilizing texture correlation to track temporal changes in bladder wall thickness in anatomical motion mode (M-mode) ultrasound cine-loops of the bladder. Texture correlation uses cross-correlation of a small region of interest (ROI) of the tissue between adjacent image frames to determine the ROI's new location in subsequent frames and has been used for numerous applications [20-22]. The objective of this study was to test this novel technique in an initial study involving women with OAB and asymptomatic volunteers to assess its clinical utility. The central hypothesis of this study was that the women with OAB would be more likely to have micromotion as measured by ultrasound imaging.

Materials and methods

Study population

The University's Institutional Review Board approved this prospective ultrasound urodynamic study. Participants were required to be at least 21 years old, female, have no cognitive impairment, and to undergo informed consent before joining the study. Participants were screened using the International Consultation on Incontinence Questionnaire on Overactive Bladder (ICIQ-OAB) [23]. Those who answered 0 or 1 on all questions were enrolled as asymptomatic volunteers. Those who answered 2 ('sometimes'), 3 ('most of the time'), or 4 ('all of the time') on question 5a ('how often do you have to rush to the toilet?') were enrolled as OAB participants. All participants were screened with a standard intake history. In order to be considered an "asymptomatic" volunteer, individuals also had to report no lower urinary tract symptoms, have no medical conditions that could affect bladder function, and be on no medications that could affect bladder function. Other information recorded from participants included age, race, and Body Mass Index (BMI).

Study protocol

Each participant underwent an extended, multichannel urodynamic protocol previously described in Nagle et al [24, 25] and Clark Glass et al [26]. This entailed repeated urodynamic fills using a Laborie Aquarius TT system (Toronto, Canada) with a 7 French urethral catheter at a fill rate of 10% cystometric capacity. Capacity was based on the maximum infused bladder volume of the initial fill plus any post-void residual (determined by direct syringe aspiration). In a subsequent fill, infusion was paused at 40% cystometric capacity to enable acquisition of pressure and ultrasound data with the bladder at rest. During this period, the participant was asked to relax and remain completely still and silent while two consecutive 85 second anatomical M-mode ultrasound cine-loops of the bladder were recorded using a GE Voluson E8 system with an 8 MHz transabdominal transducer (GE Healthcare, Zipf, Austria). The anatomical M-mode cine-loops track a one-dimensional line through the bladder with a resolution of 0.15 mm and frame rate of 44 frames/second allowing the bladder image to be analysed with precision in both time and space (**Figure 1**). P_{ves} was also recorded for comparative analysis. As this study was designed to test the diagnostic utility of ultrasound, no interventions or treatments were performed on participants.

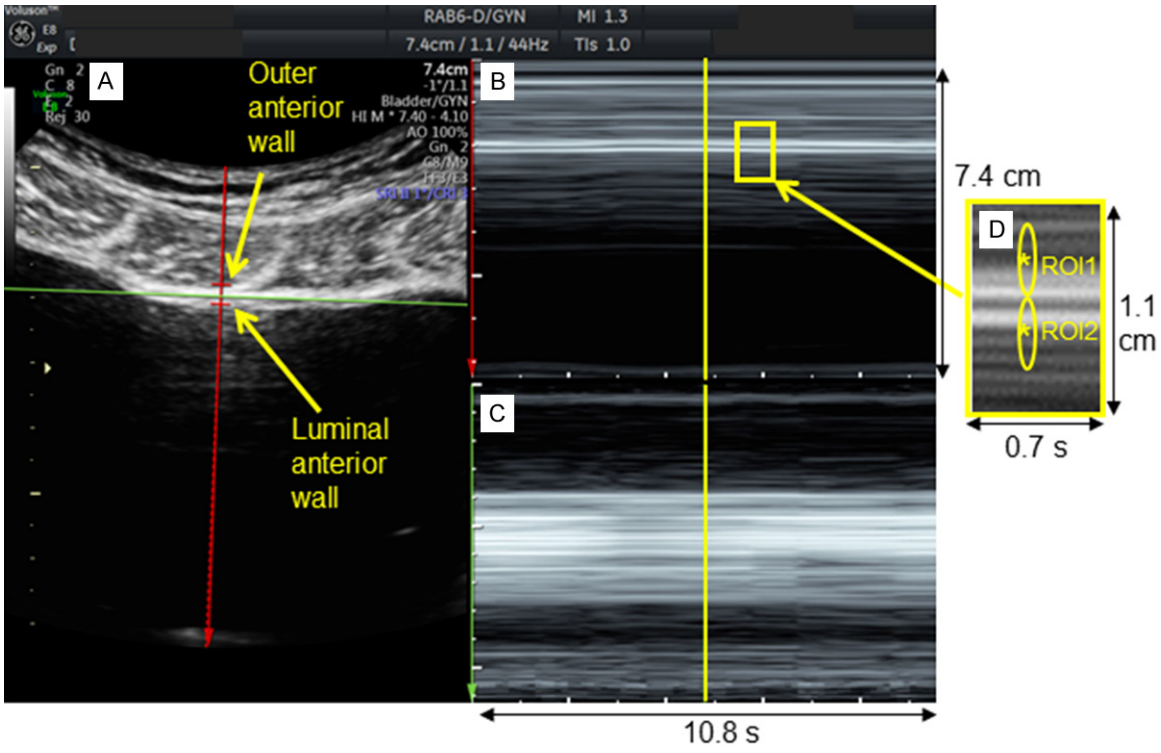

Figure 1. (A) The initial frame of an anatomical M-mode ultrasound cine-loop showing a 2D image of the bladder with red (perpendicular) and green (parallel) 1D lines tracked over time. Labels indicate the outer and luminal anterior bladder walls. (B) Tracking of the 1D red line over time during acquisition of 10.8 s of the 85 s cine loop. (C) Tracking of the 1D green line over time. (D) Zoomed view of the anterior bladder wall from (B) showing the locations of tracked regions of interest (ROI) with center points highlighted with asterisks on the outer (ROI1) and luminal (ROI2) edges of the bladder wall.

Micromotion algorithm

All cine-loops were exported in DICOM format and analysed using MATLAB (MathWorks Inc., Natick, MA). A custom MATLAB program was developed allowing a user to manually identify the outer and luminal edges of the anterior bladder wall at an initial frame of the cine-loop (**Figure 1A**, arrows) and input their locations into a texture correlation algorithm. Identification of these landmarks was determined after training from an ultrasound technologist and a fellowship-trained abdominal radiologist. The program then created 1-3 mm regions of interest (ROI), maximizing ROI length without overlapping previously marked locations (**Figure 1D**, yellow ellipses). The texture (pattern of lightness and darkness) within the ROI was compared to possible ROIs in the subsequent frame. The ROI with the highest level of correlation (most similar texture using Pearson correlation coefficients) was chosen as the new ROI for the next comparison. Thus, the ROI center point (**Figure 1D**, yellow asterisks) was considered the new location of the bladder wall edge. The user input specifying the bladder wall edge had to be near the bladder wall so that the ROI would contain sufficient bladder wall texture to be tracked. The two ROIs were tracked separately and subtracted from each other to compute bladder wall thickness over time (**Figures 2A**, **3A**, black).

The frequency characteristics of wall thickness and urodynamic P_{ves} tracings in the range of interest (1.75-6 cycles/min) were compared over the same 85 second period using the Fast Fourier Transform (FFT) analysis as described in Cullingsworth et al [17] (**Figures 2C**, **2D**, **3C**, **3D** insets). Bladder wall micromotion was considered positive if the peak FFT amplitude of bladder wall thickness was ≥0.1 mm in this range. To aid in visual comparison of MM and P_{ves}, a complex waveform was generated incorporating the top five FFT-identified frequencies. This generated model was then overlaid on top

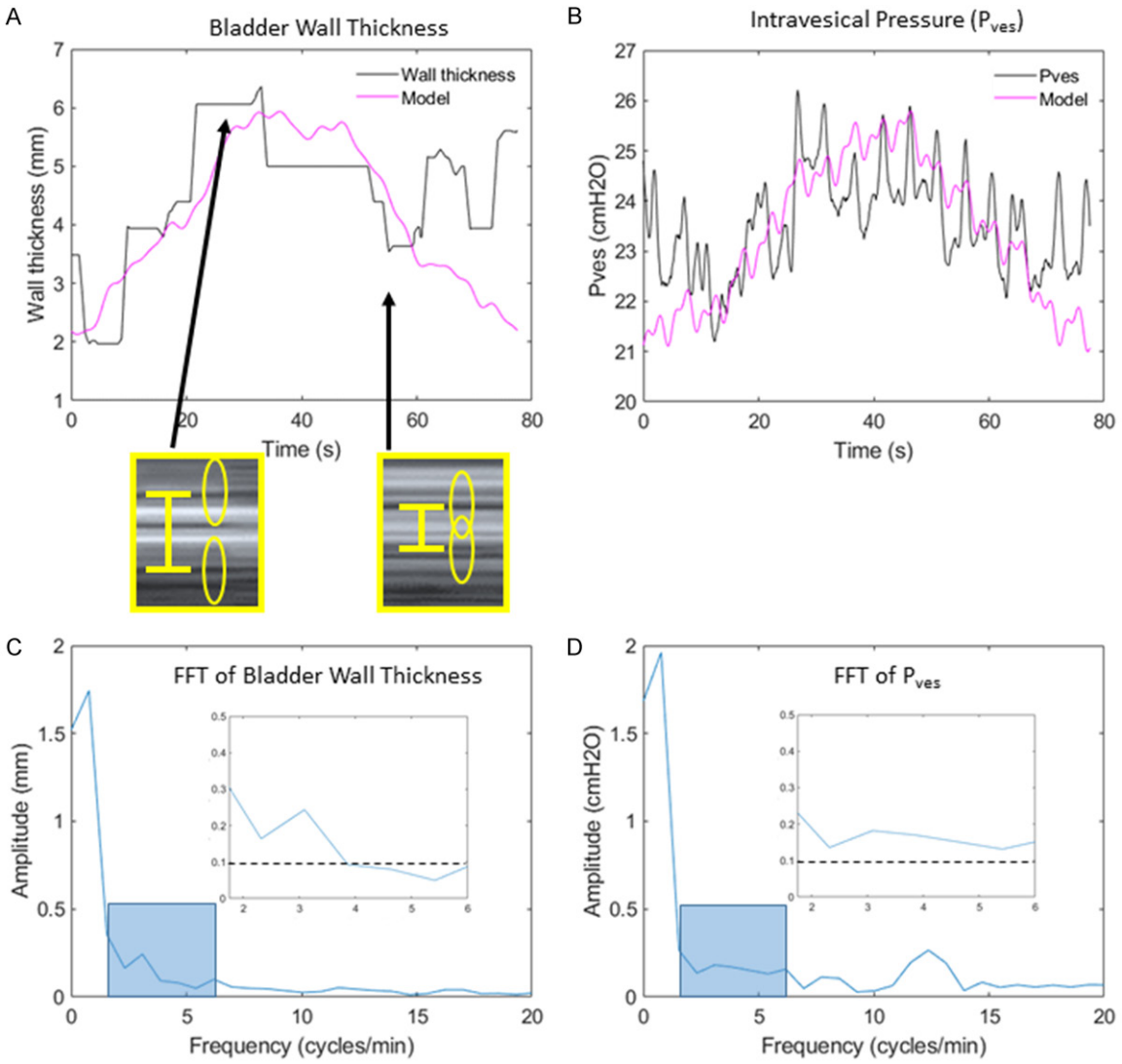

Figure 2. Fast Fourier transform (FFT) analysis shown from a participant with micromotion. (A) The wall thickness as measured by the ultrasound algorithm is shown in black. Zoomed in views of the ultrasound cine loop show the locations of the tracked regions of interest in time ranges with high wall thickness and low wall thickness. The top five peaks from the FFT analysis were transformed back into the time domain to create the waveform model (magenta) which was optimally time-shifted and overlaid on the smoothed data (black). (B) The intravesical pressure (P_{ves}) as measured by urodynamics is shown in black and the model constructed by the FFT is overlaid in magenta. (C) The wall thickness data in the frequency domain calculated by the FFT and (D) P_{ves} data in the frequency domain calculated by the FFT with zoomed insets of the frequency range of interest for micromotion.

of the original data (**Figures 2A**, **2B**, **3A**, **3B**, magenta "model"). In order to further validate this method, a urodynamicist blinded to the data evaluated the time-linked urodynamic tracings to determine the presence of detrusor overactivity.

Statistical analysis

Data are reported as mean ± standard error. For comparisons between the OAB group and the asymptomatic group, unpaired, two-tailed T-tests were performed using Microsoft Excel (version 1808, Microsoft Corporation, Redmond, WA, USA). For the contingency table comparing the association between presence of micromotion and OAB, Chi-square with Yate's correction and Fisher's exact tests were performed using GraphPad Prism (online version 9.0, https://www.graphpad.com/quickcalcs/contingency1.cfm, GraphPad Software, San Diego, CA, USA) to test association between groups and outcomes. Due to the nature of this initial methodologic investigation, a for-

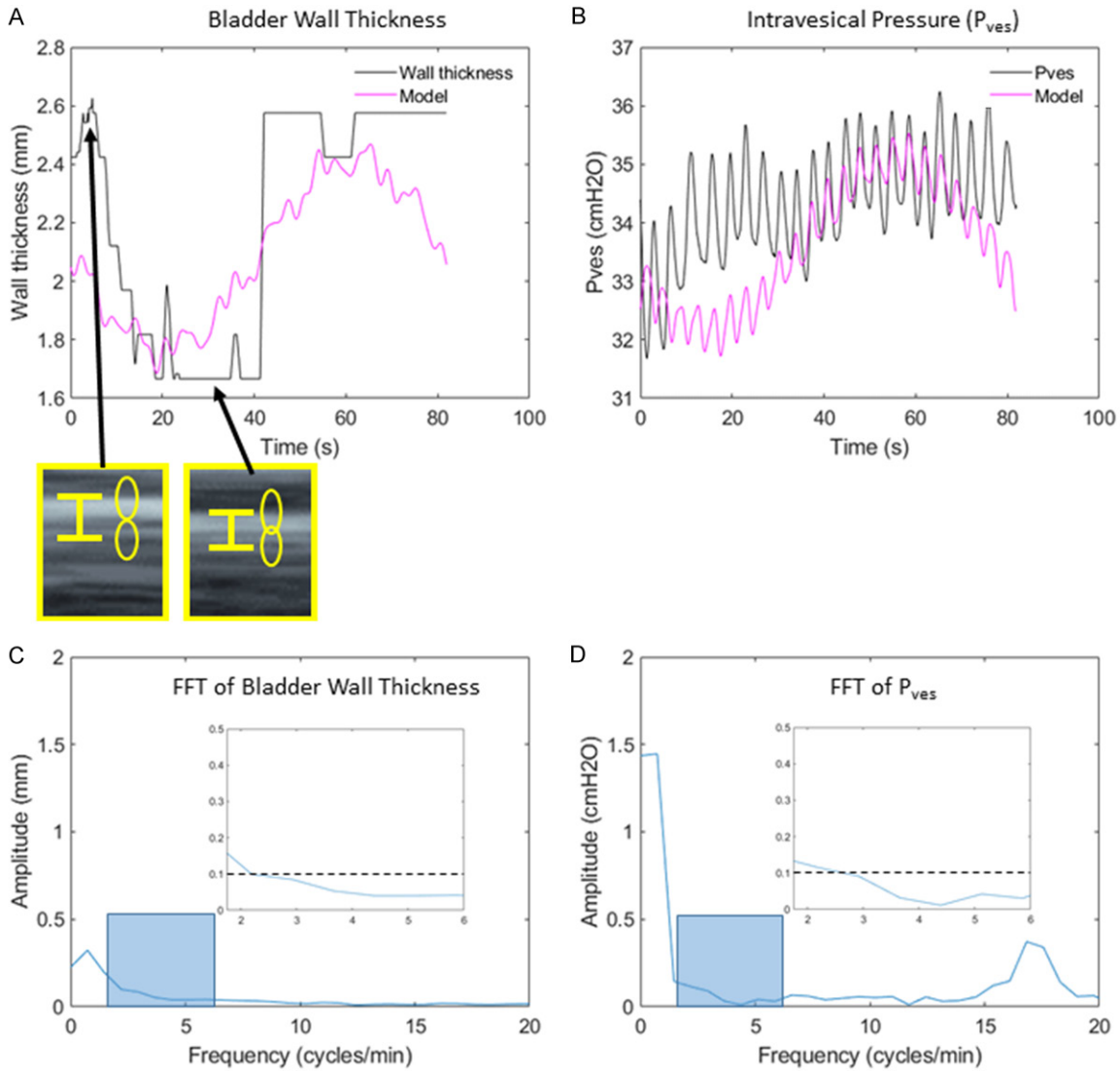

Figure 3. Fast Fourier transform (FFT) analysis shown from a participant without significant micromotion. (A) The wall thickness as measured by the ultrasound algorithm is shown in black. Zoomed in views of the ultrasound cine loop show the locations of the tracked regions of interest in time ranges with high wall thickness and low wall thickness. The top five peaks from the FFT analysis were transformed back into the time domain to create the waveform model (magenta) which was optimally time-shifted and overlaid on the smoothed data (black). (B) The intravesical pressure (P_{ves}) as measured by urodynamics is shown in black and the model constructed by the FFT is overlaid in magenta. (C) The wall thickness data in the frequency domain calculated by the FFT and (D) P_{ves} data in the frequency domain calculated by the FFT with zoomed insets of the frequency range of interest for micromotion.

mal pre-study power analysis could not be performed. However, post-hoc power analysis using SigmaPlot (version 14.0, Systat Software, Inc., San Jose, CA, USA) yielded a statistical power of 0.80. Comparisons were considered significant for $P<0.05$.

Results

Study population

The 30 women that completed this study included 17 with OAB and 13 asymptomatic volunteers. The average ages, BMIs and ICIq-OAB question 5a scores were significantly greater for the OAB participants compared to the asymptomatic volunteers (**Table 1**).

FFT analysis

Example data of participants with (**Figure 2**) and without (**Figure 3**) micromotion are presented to illustrate our step-by-step analytic methods. For the participant with micromotion (**Figure 2C**, **2D**), the FFT identified a large slow

Table 1. Participant characteristics

	Asymptomatic	OAB	*p* Value
n	13	17	
ICIq-OAB Question 5a	0.08±0.27	3.1±0.17	<0.0001
Age (years)	24.7±1.0	50.3±3.9	<0.0001
BMI (kg/m^2)	27.1±2.2	35.8±2.6	0.021

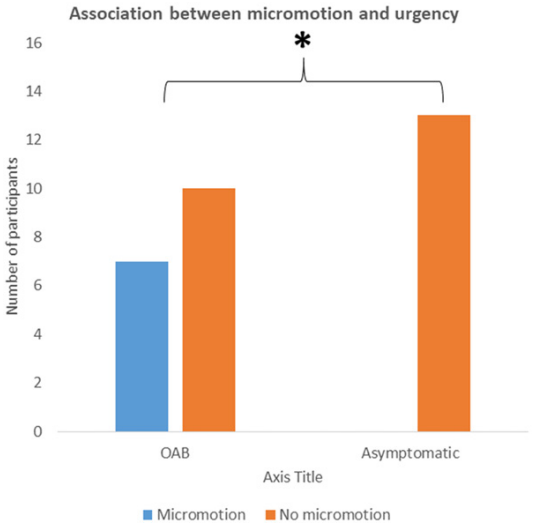

Figure 4. Numbers of overactive bladder (OAB) and asymptomatic participants with and without micromotion. The asterisk indicates that micromotion was significantly associated with OAB (P=0.010).

component (0.8 cycles/min), a faster micromotion component (3.0 cycles/min) in the range of interest (**Figure 2C**, **2D** insets), and a much faster breathing component (12 cycles/min) in both the bladder wall motion and P_{ves}. All of these components had amplitudes above the thresholds of 0.1 mm or 0.1 cmH_2O, and all were included in the reconstructed wall motion and P_{ves} models (**Figure 2A**, **2B**, magenta). For the participant without micromotion (**Figure 3**), the FFT identified similar components, slow (0.7 cycles/min), micromotion (3.7 cycles/min) and breathing (17 cycles/min), but the micromotion components in the frequency range of interest were below the thresholds and therefore not considered significant.

Association of micromotion with OAB

Of the 17 women with OAB, micromotion was identified in 7 (41.2%). However, micromotion was not identified in any of the 13 asymptomatic women (0%) (P=0.010) (**Figure 4**). This demonstrates a significant association between micromotion and OAB.

Association of micromotion with detrusor overactivity

All seven women identified with micromotion had a peak in the frequency domain of P_{ves} within 20% of the peak micromotion frequency (**Table 2**). This implies that the ultrasound-identified micromotion correlates to the rhythmic changes in bladder pressure measured with urodynamics within the frequency range of interest. In terms of the assessment of detrusor overactivity, 8/17 (47.1%) of women with OAB were found to have possible (4/17) or definitive (4/17) detrusor overactivity in the corresponding 85 s urodynamic segment. In contrast, of the 13 asymptomatic women, 3/13 (23%) had possible and 0/13 (0%) had definitive detrusor overactivity in corresponding urodynamic segments. In terms of micromotion, 3/4 (75%) women with definitive detrusor overactivity and 4/7 (57%) women with possible detrusor overactivity had ultrasound-identified micromotion (P=0.031).

Discussion

This study demonstrates the feasibility of a non-invasive method to measure bladder wall micromotion using transabdominal anatomical M-mode ultrasound during urodynamics. In support of our hypothesis, we identified a subgroup (41.2%) of women with OAB that had micromotion detectable with our method which was not identified in asymptomatic volunteers. Furthermore, in all cases, the peak frequency of the ultrasound-identified micromotion was found to be within 20% of the peak P_{ves} frequency using FFT analysis. This suggests that our method may have potential use as a completely non-invasive alternative to urodynamics in the specific diagnosis of phasic detrusor overactivity.

The rhythms observed in bladder wall thickness correlated to the rhythmic changes in bladder pressure measured with urodynamics within the frequency range of interest. Slight discrepancies are expected because of the coarse frequency resolution of these signals of 0.7-0.85 cycles/min. However, the correspondence of micromotion frequency and P_{ves} frequency makes sense considering that rhythmic

Table 2. Comparison of ultrasound micromotion and P_{ves} peak rhythms

Subject	Frequency (cycles/min)		Frequency Difference	Amplitude		Detrusor Overactivity
	MM	P_{ves}		MM (mm)	P_{ves} (cmH_2O)	
1	3.3	3.4	2%	0.28	0.19	No
2	3.6	3.6	0%	0.55	0.86	Yes
3	3.3	4.1	20%	0.34	0.88	Yes
4	5.8	4.8	17%	0.10	0.29	Possible
5	3.2	3.8	15%	0.22	0.31	Possible
6	4.5	4.5	0%	0.39	0.11	No
7	2.3	2.3	0%	0.14	0.32	Yes

MM = micromotion, P_{ves} = intravesical pressure, Frequency Difference = (P_{ves} frequency - MM frequency)/P_{ves} frequency * 100.

detrusor overactivity is thought to be the result of micromotion throughout the bladder wall [8]. Furthermore, **Table 2** shows that the participants with definitive detrusor overactivity were found to have the highest amplitudes in P_{ves} frequency. The identification of a one-to-one correlation with micromotion is consistent with previous studies using ex vivo pig bladders [12, 14]. Alternatively, some studies show that micromotion at a localized point may only represent a fraction of P_{ves} frequency with some individuals showing a one-to-one correlation between micromotion and P_{ves} frequency, but not all [10].

It should be noted that in this investigation, frequency peaks in the range of 12-18 cycles per minute were often detected in both the bladder wall thickness and the P_{ves} frequency plots (**Figures 2** and **3**). These high frequencies are likely due to breathing and demonstrate that the much lower frequencies associated with micromotion and detrusor overactivity would not be corrupted by breathing artifact.

In the current investigation, the majority of individuals with detrusor overactivity were identified as having micromotion. However, two women without detrusor overactivity were also found to have micromotion which may imply this method can identify patients that could be missed with standard urodynamics. The possibility that our technique may be detecting a separate micromotion frequency which cannot be visually identified using current UDS technologies is supported by the evidence that micromotion was only identified in symptomatic women (i.e. those with OAB).

In our study, we chose to apply anatomical M-mode ultrasound during urodynamics in order to determine if observed micromotion correlated with observed changes in P_{ves}, but this technique could potentially be applied in completely non-invasive hydration studies as previously described [27-29]. However, it remains unknown whether micromotion can be identified during the fast fill rates associated with accelerated hydration as this study was performed during a pause in urodynamic filling when only natural filling would be taking place. Rhythmic, non-voiding bladder wall contractions in humans have been characterized from changes in human bladder pressure measured using catheters as early as 1882 [9], but only three teams of investigators have published in vivo micromotion studies that go beyond pressure measurements. Van Os-Bossagh et al [19] and Drake et al [10] used electrodes on a balloon placed in the bladder during urodynamics by measuring their displacements from each other. Both studies found that women with urgency symptoms had significantly higher prevalence of micromotion than in controls [10, 19]. In Drake et al, micromotion was detected in only two of six normal participants where it had a frequency of ~1 cycle/min and did not appear to correlate to any rhythmic frequencies in P_{ves}. Micromotion activity was present in all 9 participants with urinary urgency where it had a frequency of 2-5 cycles/min and corresponded to P_{ves} frequencies in 4 of the women [10]. More recently, Gray et al [13] used transabdominal ultrasound to measure the bladder shape changes resulting from detrusor contractions and showed that women with detrusor overactivity had more ellipsoidal bladders than those without detrusor overactivity.

Limitations of this study include a small sample size and enrolling only women as well as a

younger and less-obese cohort for the control population. However, a post-hoc analysis yielded adequate statistical power to detect an association between micromotion and OAB. Additional studies with greater numbers will be needed to confirm the results of this initial study. The use of women was justified due to the increased prevalence of OAB, and the differences in the age and BMI (**Table 1**) were due to difficulty in the recruitment of age and BMI-matched individuals. Larger scale studies enrolling men and matched groups would be required to address these issues. Other limitations include only examining the anterior bladder wall for micromotion. However, the anterior wall was chosen for analysis because the posterior bladder displayed motion artifact from iliac pulsations and could not be as effectively imaged at high resolution. In addition, identification of micromotion or detrusor overactivity in such a short segment of urodynamic data (85 s) is difficult but was the maximum recordable period using our equipment with the desired depth of 7.4 cm. More advanced recording technologies could potentially provide longer sections for analysis.

This study demonstrates that a non-invasive method using transabdominal anatomical M-mode ultrasound can be used to measure changes in bladder wall thickness during urodynamics. The rhythmic changes observed in bladder wall thickness over time were closely correlated to rhythmic changes observed in P_{ves} during urodynamics. The presence of ultrasound-identified micromotion was significantly associated with OAB. This methodology could potentially be used to identify a novel micromotion-associated OAB phenotype that could be more selectively targeted for overactive bladder treatments.

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Disclosure of conflict of interest

None.

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