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BLADDER CURRENT PERCEPTION THRESHOLDS CONFIRM THE HYPERESTHETIC BLADDER OF PATIENTS WITH IRRITATIVE LOWER URINARY TRACT SYMPTOMS

Hypothesis / aims of study
The afferent neural activity arising from the bladder plays a central role in micturition control and the overall function of the lower urinary tract (LUT). Sensory information from the LUT are transmitted through the pelvic, hypogastric and pudendal nerves from the bladder and urethra to the dorsal root ganglia at S2–4 and T11-L2 of the spinal cord respectively and are implicated in the sensations associated with the normal bladder filling and bladder discomfort. These nerves are composed of myelinated (Aδ and Aβ) and unmyelinated (C) axons. Normally Aδ-fibres are activated by increased tension in the bladder wall, while C fibres are typically “silent” and begin to send a signal under certain pathological circumstances with an increase during bladder distention. The Aβ-fibres are not thought to be present in the bladder. Numerous studies suggested that alterations of afferent signaling is crucial in the pathogenesis of various disorders at the origin of lower urinary tract symptoms (LUTS), including overactive bladder (OAB) and urinary incontinence. Bladder filling sensations during urodynamic investigation can provide valuable information on filling-related sensory function whereas current perception thresholds (CPT) are testing theoretically selectively measures and quantify responses of different size afferent nerves. The neuroselectivity of CPT testing for the three different afferent fibre types has been demonstrated in neuropathies with good agreement compared to nerve conduction studies. Only few studies have assessed bladder afferent sensation in women with various LUTS. Our aim was to measure CPTs of the bladder in patients who underwent urodynamics and to compare our results to normative current perception thresholds (CPTs) at different frequencies.

Study design, materials and methods
Women with LUTS were recruited via the Outpatient Clinic of a tertiary referral hospital and referred for Urodynamic testing of their condition. The participants were asked to complete the King’s Health Questionnaire (KHQ). Prior to cystometry, all volunteers underwent an evaluation using a Neurometer (Neurotron, Inc., Baltimore, MD). It delivers a bipolar, constant current electrical wave stimuli at three different frequencies, 2,000, 250, and 5 Hz which are thought to specifically depolarize the three types of sensory fibers, the large myelinated Aβ, small myelinated Aδ, and small unmyelinated C fibres respectively. A 5-French urethral catheter with bipolar electrodes was connected to the neurometer and test initiated at 5 Hz. The stimulus intensity was gradually increased until the woman first perceived it, and then decreased until it was no longer perceptible. CPT measurements were established semi-automatically using a forced choice paradigm, in which randomly chosen pairs of stimuli were presented as A or B with a brief rest period until a consistent perception threshold was attained. The catheter position was confirmed using transabdominal ultrasound in supine position with a bladder volume of 50–100 ml, ensuring that the electrode at the catheter tip was in contact with the bladder trigone. We compared our results to previously published normative data for bladder CPTs (2000 Hz: 410 µA, 250Hz: 230 µA; 5 Hz: 140 µA). Lower CPTs were considered to be hyperesthetic and higher values hypoesthetic. We performed a one sample t-test to demonstrate a difference between measured CPTs and normative values and subgroup analyses for patients with OAB, urodynamic stress incontinence (USI) and detrusor overactivity (DO).

Results
32 women participated in our study with a mean age of 60 years (SD 11). 31.3% (n=10) had OAB symptoms with inconclusive urodynamic findings, 25% (n=8) had urodynamic stress incontinence (USI) and 43.8% (n=14) had urodynamically proven DO. In the overall cohort, LUTS women had CPTs which were significantly lower than normative values at 5 Hz ($p=0.001$), at 250 Hz ($p\leq0.001$) and at 2000 Hz ($p\leq0.001$). In OAB patients, bladder CPTs were significantly lower than normative values at 5 Hz ($p=0.016$), at 250Hz ($p\leq0.001$) and at 2000 Hz ($p=0.001$). In USI patients differences of bladder CPTs with normative data were not significant. In DO women bladder CPTs were significantly higher than normative values at 5 Hz ($p=0.014$), at 250 Hz ($p=0.005$) and at 2000 Hz ($p\leq0.001$).

Interpretation of results
Overall, our study showed that afferents from the bladder sacral nerve root sensory thresholds of women suffering from LUTS, OAB and DO are hyperesthetic compared to a healthy population. We were able to confirm previous findings about the correlation of a hypersensitive bladder in OAB and DO patients. Our findings did not reveal lower CPTs in USI patients which may indicate that the hyperesthetic bladder state is predominantly correlated with irritative disorders of the LUT and may be absent or negligible in case of mainly mechanical pelvic floor disorder.

Concluding message
This is the largest study evaluating CPTs in a cohort of patients with various LUTS using the Neurometer. Further studies are needed to confirm our findings and to provide a better understanding of the quantitative disorder on such hypersensitivity. This would improve the understanding of pathogenesis in the individual patient, potentially guiding appropriate targeted therapy.

Table : Comparison of Current Perception Thresholds of the bladder between LUTS patients and healthy individuals

	Bladder CPTs **5 Hz** mean (SD)	Bladder CPTs **250 Hz** mean (SD)	Bladder CPTs **2000 Hz** mean (SD)
Overall cohort (n=32)	95.66 (70.45) *p=0.001**	141.52 (98.20) *p≤0.001**	237.68 (116.78) *p≤0.001**
Patients with Overactive Bladder Syndrome (n=10)	84.80 (58.77) *p=0.016**	106.80 (44.77) *p≤0.001**	206.75 (99.33) *p=0.001**
Patients with Stress Urinary Incontinence (n= 8)	135.75 (59.82) *p=0.846**	186.13 (135.21) *p=0.389**	273.67 (147.06) *p=0.072**
Patients with Detrusor Overactivity (n=20)	80.50 (78.75) *p=0.014**	140.84 (98.04) *p=0.005**	239.93 (116.20) *p≤0.001**

**Calculations performed with one-sample t-test*

References

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