

**Original Article****Ice water test in multiple sclerosis: A pilot trial**Tanja Hüsich,<sup>1</sup> André Reitz,<sup>1,2</sup> Kurt Ulm<sup>3</sup> and Axel Haferkamp<sup>1</sup><sup>1</sup>Department of Urology and Pediatric Urology, University Medical Center of Johannes Gutenberg University, Mainz, Germany,<sup>2</sup>KontinenzZentrum Hirslanden, Zurich, Switzerland, and <sup>3</sup>Institute of Medical Informatics, Statistics and Epidemiology, Technical University of Munich, Munich, Germany**Abbreviations & Acronyms**

AUC = area under the curve

DO = detrusor overactivity

IWT = ice water test

MMS = Medical

Measurement Systems

P<sub>detmax</sub> = maximum detrusor pressure

TRPM8 = transient receptor potential subfamily M member 8

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**Objectives:** To investigate the significance of the ice water test in patients with multiple sclerosis and to evaluate a novel ice water test nomogram in a large patient cohort.

**Methods:** A total of 201 ice water tests of patients with multiple sclerosis were retrospectively evaluated. Incontinence episodes in 24 h and sex were correlated with the ice water test. Furthermore, an ice water test nomogram was developed in order to categorize the detrusor overactivity in severity degrees. Descriptive statistics were carried out for population characteristics. Correlations of categorical variables were calculated by the  $\chi^2$ -test. The independent *t*-test was carried out for correlations of continuous variables. Furthermore, the data were evaluated in the novel ice water test nomogram.

**Results:** The patient population consisted of 141 (70.1%) women and 60 (39.9%) men. A clinically positive ice water test (maximum detrusor pressure >15 cmH<sub>2</sub>O) was identified in 75 patients (37.3%). Significantly more men presented a clinically positive ice water test (*P* = 0.006). In 16.5%, the ice water test unmasked an involuntary detrusor contraction, although routine cystometry did not show any detrusor overactivity. The ice water test nomogram could be successfully applied. The incontinence episodes and maximum detrusor pressure correlated positively with a higher categorization in the nomogram. Therapeutic interventions and follow-up controls could be successfully illustrated by the nomogram.

**Conclusions:** The ice water test is a simple tool for unmasking non-identified detrusor overactivity in neurogenic bladder dysfunction. A severity categorization of the detrusor overactivity can be facilitated by the use of the ice water test nomogram. After further validation, the ice water test could be ultimately used in future as objective assessment for bladder dysfunction.

**Key words:** ice water test, multiple sclerosis, neurogenic bladder dysfunction, nomogram, overactive bladder.

**Introduction**

The IWT was first described in 1957 by Bors and Blinn, and targeted to discriminate between an upper and lower motor neuron lesion in bladder dysfunction.<sup>1</sup> It was carried out by rapid instillation of small amounts of ice water into the urinary bladder by a catheter in patients with spinal upper motor neuron lesion. It was considered positive if the fluid was immediately expelled. Raz modified the examination by recording the intravesical pressure simultaneously.<sup>2</sup> He considered every detrusor contraction during the ice water test as positive irrespective of the expelled fluid.

The bladder cooling reflex is the pathophysiological background of the IWT. The reflex is activated by in the bladder urothelium localized cool and menthol receptor 1 or TRPM8, which respond to cold stimuli.<sup>3</sup> The thermosensitive receptor triggers unmyelinated c-fibers, which provokes a segmental spinal reflex causing an involuntary detrusor contraction. The reflex can be provoked in children by the age of 5 years at the latest, and then becomes suppressed by maturation of the nervous system in neurologically normal infants and adults.<sup>4</sup> The recurrence of the reflex indicates a potential lesion of the upper motor neuron. This

established the ice water test as a diagnostic tool to identify suprasacral lesions in the diagnosis of neurological disorders.<sup>5</sup>

The IWT has been studied ever since in various neurological and non-neurological diseases. The test is positive in up to 97% of patients with complete and 91% of those with incomplete upper motor neuron lesions.<sup>6</sup> Apart from the diagnostic use, the IWT can contribute to recovering bladder contractility in terms of a therapeutic purpose in patients with megavesica, psychogenic bladder dysfunction, postablative pelvic surgery or postobstructive bladder hypo- or areflexia.<sup>7,8</sup>

Until this day, the IWT is only interpreted in a dichotomous manner. It is considered positive or negative depending of the occurrence of an involuntary detrusor contraction. So far, no attempt was made to categorize the strength of the bladder contraction. Therefore, in the present study, an IWT nomogram was developed to classify the IWT response into severity grades and hereby facilitating a quantitative interpretation of the IWT. For this purpose, 201 patients with multiple sclerosis were retrospectively analyzed and furthermore evaluated in the IWT nomogram. To our knowledge, we have evaluated the largest amount of IWTs in patients with multiple sclerosis so far.

## Methods

A retrospective cohort study evaluating 201 IWTs from patients with multiple sclerosis was carried out. None of the patients received medications targeting urinary bladder function before the investigation. The signed informed consent for anonymous data analysis of the urodynamic studies was obtained from every patient at the time of the urodynamic examination in the outpatient clinic. There were no underaged (aged <18 years) patients. Only patients with multiple sclerosis without treatment for bladder dysfunction were included. The study protocol was presented at the local ethics committee. Based on the retrospective character of the study and anonymous data collection, no approval was necessary in the absence of any ethical concerns.

Multiple sclerosis was diagnosed by a certified neurologist. Patients with storage or voiding dysfunction in anamnesis, or abnormalities of voiding/storage function during examination were presented for urodynamic examination in a neurourology outpatient clinic between 2010 and 2014. A urine culture was obtained from every patient before the examination to exclude urinary tract infection. Furthermore, a diagnostic medical urine dipstick and interrogation for urinary infection signs was carried out on the eve of the urodynamic investigation. The urodynamic software from MMS (Solar Gold, Enschede, the Netherlands), database software release version 9.1u (20 November 2013), was utilized for the urodynamic examination. A clinically positive IWT was defined as a  $P_{\text{detmax}} > 15 \text{ cmH}_2\text{O}$ .

## Urodynamic setting

The urodynamic examination was monitored by one consultant specialized and experienced in neurourology. An external pressure transducer with air-charged lines was used, and the

pressure recordings were recorded by the urodynamic system from MMS. The urodynamic examination was carried out and standardized corresponding to the “Good Urodynamic Practice” of the International Continence Society.<sup>9</sup> Correct placement and signal quality were tested by repeated coughing. Recording was carried out with a sample rate of 10 Hz.

Cystometry and the ice water test were carried out in a seated position wherever applicable. If not, the patient remained in a reclined position. First, a videocystometry was carried out in all patients. Subsequently, the ice water test was realized using a sterile saline solution with a temperature of 4°C ( $\pm 39.2^\circ\text{F}$ ). The saline solution was filled at a speed of 100 mL/min into the empty urinary bladder. It was interrupted if a total amount of 200 mL was infused into the bladder or if an involuntary detrusor contraction occurred.

## Data collection and statistics

The data of the IWTs were manually selected and anonymously extracted from the MMS Database in February 2014. The recorded data included patients from 2010 to 2014, and sex, age and incontinence episodes in 24 h of the patients were recorded additionally. The files were exported into a comma-separated value file. Consecutively, they were analyzed with Microsoft Excel (Redmond, WA, USA) for Macintosh 2011 version 14.5.2 and IBM SPSS (Armonk, NY, USA) Statistics version 2.0.0.0 64-Bit for Macintosh.

Each dataset was manually screened for interfering factors, such as cough impact or movement of the patients, which could imitate a false positive detrusor contraction. The factors were highlighted in the database during the urodynamic examination. The detrusor pressure was calculated by the formula: “ $p_{\text{det}} = p_{\text{ves}} - p_{\text{abd}}$ .” For characterization of the detrusor contraction in accordance with physical comprehension to the definition of power (power = work / time) the detrusor gradient was calculated by the formula: “detrusor gradient =  $t\Delta p_{\text{det}} / \Delta t_{\text{sec}}$ ” at the time of the  $P_{\text{detmax}}$ , taking into account the reflex volume – the onset of the pressure rise – and the  $P_{\text{detmax}}$ . Consequently, low reflex volumes, as well as high  $P_{\text{detmax}}$ , implied higher categorizations in the nomogram. Furthermore, the AUC was calculated to include the duration and characteristic of the detrusor contraction (phasic vs tonic contraction, overall duration of the contraction). The higher the AUC, the higher the categorization. Hereby, a diagram was developed by referring the detrusor gradient to the  $x$ -axis and the AUC to the  $y$ -axis. The horizontal and vertical scales were connected by straight lines, with points of intersection at the scaling. Accordingly, categories from 1 to  $\geq 8$  were developed.

Descriptive statistics were carried out for population characteristics. Correlations of categorical variables were calculated by the  $\chi^2$ -test. The independent  $t$ -test was carried out for correlations of continuous variables. Correlation of the IWT categories and independent variables was performed by linear regression.

## Results

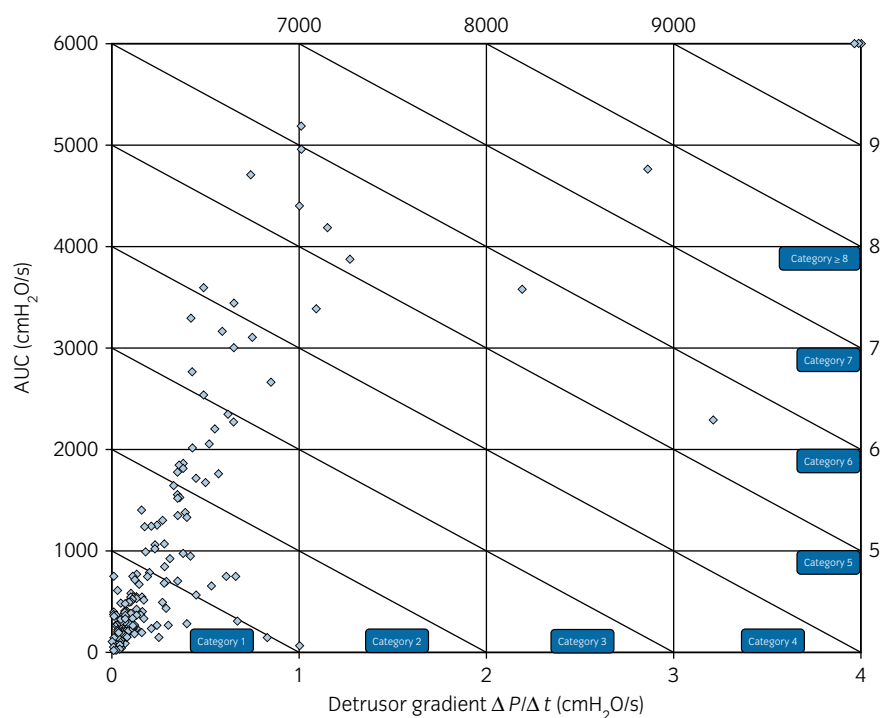
A total of 201 patients with multiple sclerosis and available IWT met the inclusion criteria. There were 141 (70.1%)

women and 60 (29.9%) men with a mean age of  $51.5 \pm 14.3$  years and  $51.2 \pm 12.8$  years, respectively. A clinically positive IWT was identified in 75 patients (37.3%). Significantly more men presented a clinically positive IWT ( $P = 0.006$ , 51.8% vs 30.9%). A positive IWT was correlated with significantly higher  $P_{\text{detmax}}$  ( $P < 0.001$ ), higher AUC ( $P < 0.001$ ) and higher detrusor gradient ( $P < 0.001$ ).

Furthermore, involuntary DOs were evaluated not only during the IWT, but also during cystometry. Considering all identified DO, 69.1% were observed in both, cystometry and the IWT. A positive IWT without DO during cystometry was present in 16.5% patients. Complementary, a DO during cystometry with a negative IWT was observed in 14.4% patients.

## IWT-nomogram

According to the IWT-nomogram, 141 (70.1%) patients appeared in category one. All patients with clinically negative IWTs were localized in category one. The remaining patients spread from degree 2 to  $\geq 8$  (Fig. 1). The corresponding mean values for the detrusor gradient, AUC,  $P_{\text{detmax}}$  and incontinence episodes in 24 h are presented in Table 1, separated by the nomogram, sex and clinically positive/negative IWT. The nomogram categorizations correlated positively with mean  $P_{\text{detmax}}$  ( $P < 0.001$ ), AUC ( $P < 0.001$ ), detrusor gradient ( $P < 0.001$ ) and incontinence episodes ( $P < 0.001$ ). In correlation of the IWT categorization and sex, significantly more men presented with categorizations of  $\geq 2$  ( $P = 0.003$ ; Fig. 2).



**Fig. 1** IWT nomogram of 201 patients with multiple sclerosis.

**Table 1** Corresponding mean  $P_{\text{max}}$ , AUC, detrusor gradient and incontinence episodes in 24 h according to the IWT nomogram, sex and clinically positive IWTs

IWT categorization	Patients, n (%)	Mean $P_{\text{max}}$ , cmH <sub>2</sub> O (range)	Mean AUC, cmH <sub>2</sub> O × s (range)	Mean detrusor gradient, cmH <sub>2</sub> O/s (range)	Mean incontinence episodes/24 h, n (range)
1	140 (70.1)	8.45 (1–36)	294.39 (18.0–787.0)	0.09 (0.00–1.00)	1.24 (0–6)
2	26 (12.9)	35.32 (12–79)	1118.90 (562.5–1644.0)	0.34 (0.16–0.66)	2.73 (0–7)
3	12 (6.0)	55.08 (35–75)	1945.5 (1674.5–2348.5)	0.48 (0.35–0.65)	3.05 (0–6)
4	7 (3.5)	58.43 (45–78)	2933.4 (2536.5–3292.5)	0.60 (0.42–0.85)	2.43 (1–5)
5	3 (1.5)	76.33 (47–110)	3473.83 (3387.5–3592.5)	0.74 (0.49–1.09)	4.00 (3–6)
6	7 (3.5)	87.57 (61–138)	3999.21 (2289.5–4956.5)	1.51 (0.74–3.21)	3.43 (3–5)
7	1 (0.5)	97.00 (–)	5188.00 (–)	1.01 (–)	3
$\geq 8$	4 (2.0)	137.80 (96–162)	6672.40 (4763.5–8097.0)	2.01 (1.01–2.86)	3.60 (3–4)
Clinically negative IWT	126 (62.7)	6.67 (1–15)	269.46 (18.0–787.0)	0.09 (0.00–1.00)	1.12 (0–6)
Clinically positive IWT	75 (37.3)	52.43 (16–162)	2084.67 (193.5–8097.0)	0.60 (0.13–3.21)	2.85 (0–7)
Women	141 (70.1)	17.55 (1–110)	702.64 (18.0–4709.5)	0.21 (0.00–3.21)	1.78 (0–7)
Men	60 (29.9)	38.41 (2–162)	1561.04 (31.0–8097.0)	0.47 (0.01–2.86)	1.70 (0–6)

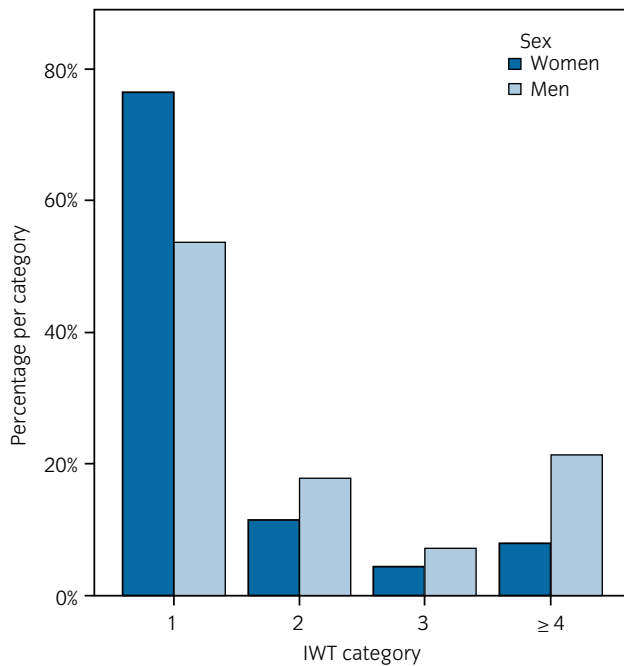


Fig. 2 Correlation of sex and IWT categorization.

The  $P_{detmax}$  ( $P < 0.001$ ), AUC ( $P < 0.001$ ) and detrusor gradient ( $P = 0.001$ ) were significantly higher in men.

The incontinence episodes in 24 h did not differ between the sexes ( $P = 0.616$ ). The incontinence episodes correlated with a higher categorization in the nomogram ( $P < 0.001$ ). In subgroup sex analysis, the incontinence episodes correlated positively with higher categorization in both sexes ( $P < 0.001$ , respectively).

Two exemplary patients were selected for demonstration of therapy and follow-up control, respectively (Fig. 3). An IWT was carried out before and after botulinumtoxin injection into the detrusor due to involuntary DO in one patient. The detrusor contractility could be reduced from category four to category one according to the nomogram. The second patient demonstrates a follow-up control over 3 years. From the year 2013 to 2016, an increase from category 6 to category 8 could be reproduced. In 2014, the category was raised to category 12. According to the medical record, the patient suffered from an acute relapse with clinical progression, which correlated with a significantly higher categorization in this year during the IWT.

### Discussion

The bladder cooling reflex elicited by the IWT is utilized for identification of neurological lesions leading to uninhibited involuntary detrusor contractions. The appearance of a positive IWT after the age of 5 years points to a possible neurological lesion of the central nervous system. The IWT has been investigated in various neurological and non-neurological diseases, but large patient cohorts are still lacking.<sup>10</sup> So far, the IWT has a sensitivity of 65% and a specificity of 85% for the diagnosis of detrusor hyperactivity.<sup>10</sup> Furthermore, no attempt has been made so far to quantify the response of the bladder contraction during the IWT.

In the current study, we investigated, to our knowledge, the largest number of IWTs in a cohort of patients with multiple sclerosis. We identified 37.3% with a clinically positive IWT whereat our definition of a clinically positive IWT was a  $P_{detmax} > 15$  cmH<sub>2</sub>O. There is still no consensus on the

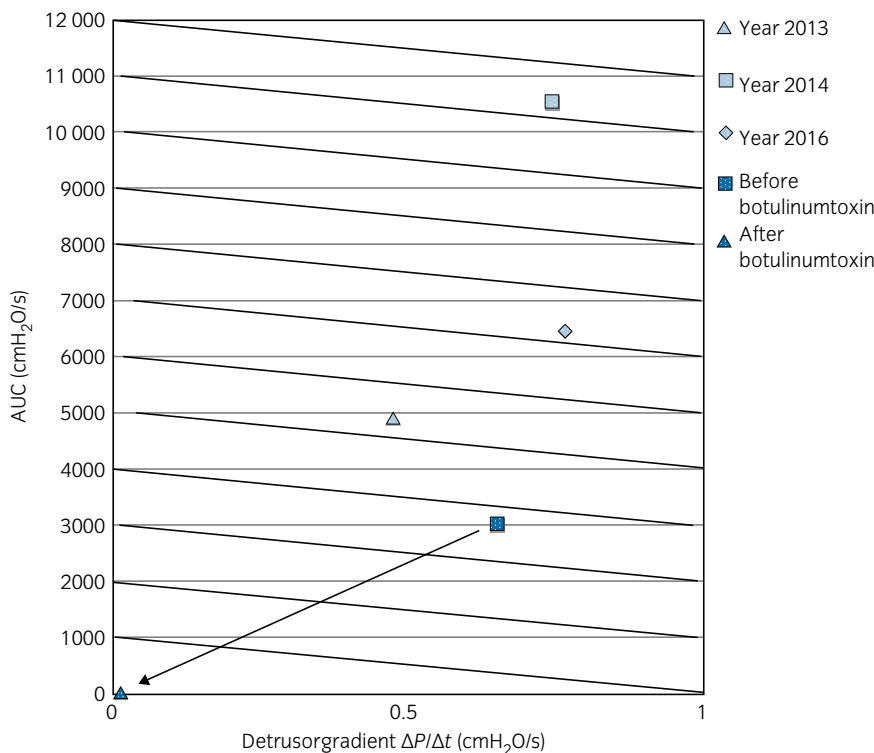


Fig. 3 Exemplary patients and correlation in the nomogram: (i) before and after botulinumtoxin; and (ii) follow-up control over 3 years.

threshold of a positive IWT, and it is described between 3 and 30 cmH<sub>2</sub>O in the literature.<sup>11–13</sup> The results differ significantly depending on the threshold. In our opinion, a threshold of 3 cmH<sub>2</sub>O does not represent clinical practice, as urodynamic study is often not as precise as favored due to interfering factors, such as poor pressure transmissions or pressure drifts.<sup>14</sup> In contrast, a threshold of 30 cmH<sub>2</sub>O is too high in consideration of P<sub>detmax</sub> of 27 cmH<sub>2</sub>O in women during recent pressure flow investigations, implicating lower detrusor contractility in general.<sup>15</sup>

Frequently, the IWT is evaluated in cohorts with patients suffering from overactive bladder syndrome due to different neurological and non-neurological diseases. This could lead to false high rates of positive IWT. Referring to patients with multiple sclerosis, one other study investigated the IWT in 39 patients with multiple sclerosis.<sup>16</sup> The threshold for a positive IWT was set as 15 cmH<sub>2</sub>O, and they could identify just 25.6% positive IWTs after 200 mL. Because of the larger cohort in the present study, we could show that the rate of positive IWTs in patients with multiple sclerosis are even higher than previously assumed.

Furthermore, we investigated the rate of DO separately during cystometry and the IWT. In 16.5% of patients, an involuntary detrusor contraction could be provoked exclusively by the IWT. This emphasizes the importance of the IWT in order to identify neurogenic bladder dysfunction that could not be detected by cystometry. Nevertheless, cystometry was only carried out once, and involuntary DO could be probably shown by a consequent dysfunction. Ambulatory urodynamic studies might be an alternative for revealing undetected DO as well, but time and effort seem to be disproportionally higher in comparison with the IWT.<sup>17,18</sup> Interestingly, in 14.4% of patients, a DO was only present during cystometry and not in the IWT. In these cases, terminal DO was identified. A possible explanation for the negative IWT could be a low motor response with a P<sub>detmax</sub> <15 cmH<sub>2</sub>O, and therefore negative categorized IWT. Another explanation could be the infusion volume during the IWT. Geirsson *et al.* reported almost no dependency of the infused volume for the outcome of the IWT and proposed 100 mL as sufficient capacity for successful provocation of DO.<sup>5,12</sup> He identified a threshold volume of 9–60% (median 32%) of the cystometric bladder capacity for the triggering of the reflex. Therefore, a higher volume in selected cases might be necessary to provoke an existing bladder cooling reflex with DO. This is in line with other studies reporting more positive IWTs depending on the infused volume.<sup>16</sup> Most probably in the present study, the DO during cystometry could be triggered through mechanoreceptors instead of the bladder cooling reflex. In the present findings, the DO in cystometry without positive IWT was always accompanied by a terminal detrusor contraction after reaching the maximal detrusor capacity, initiating a micturition effect rather than a bladder cooling reflex.

Furthermore, we investigated sex differences in the current study. We could first identify significantly lower IWT responses regarding P<sub>detmax</sub>, detrusor gradient and AUC in women. This can be probably referred to lower bladder contractility, as micturition in women is often carried out only by

relaxation of the pelvic floor, allowing low pressures during voiding in women.<sup>19</sup> The higher outlet resistance in men most probably leads to a major detrusor contraction in general. Furthermore, TRPM8 was identified in various genitourinary organs, such as the bladder, urethra or prostate,<sup>20</sup> and it has been recently identified as a crucial initiator for the bladder cooling reflex.<sup>21</sup> TRPM8 antagonists even showed in animal model the inhibition of a formerly positive bladder cooling reflex.<sup>22</sup> In addition, in patients with overactive bladder syndrome, an increase of TRPM8 nerve fibers associated with increased clinical symptoms has been described.<sup>3</sup> Considering the higher incidence of TRPM8 in the prostate in comparison with the bladder, this could additionally possibly influence the higher motor response in men.<sup>23</sup> In clinical practice, men might be more at risk for upper urinary tract damage than women according to frequently higher detrusor pressures.

Independently, the incontinence episodes in 24 h did not depend on sex. We cannot provide a discrimination between stress or urge urinary incontinence, but the positive correlation of the incontinence episodes to higher IWT categorization in men and women implies that probably due to low outlet resistance in women, urinary incontinence episodes seem approximately equal, although detrusor pressures are lower. In conclusion, detrusor pressures in women have to be interpreted more critically, as even low contractions might implicate DO. The aim of a severity categorization for DO during the IWT is the identification of patients at high risk of upper urinary tract impairment. This patient population is characterized by frequent urinary tract infections, hospitalizations and renal failure.<sup>24</sup> The evaluation of these patients depends subjectively of the cystometry interpretation by the medical care provider. Objective categorizations of the DO do not exist, and depend on the assessment of the DO and quality of the cystometry. Furthermore, a nomogram could be utilized for objective follow up in patients with neurogenic bladder overactivity quantifying the detrusor contraction and therefore rating the development over time. Even prognosis of neurogenic diseases and objective treatment evaluation, such as quantifying the effect of oral anticholinergics or intravesical onabotulinumtoxin, could be provided in future by a nomogram.

The IWT nomogram could provide an objective interpretation of DO in neurogenic bladder dysfunction. It includes not only the P<sub>detmax</sub> but also the characterization of the curve by the AUC as well as the reflex volume. Nevertheless, this represents an approximation to the bladder contractility. Other studies targeting the evaluation of bladder contractility are rare, and include an evaluation of the voiding phase (e.g. Watts Factor<sup>25</sup>).

In the current study, we could confirm a positive correlation of categorization and bladder contractility. Furthermore, the incontinence episodes increased according to a higher categorization and the sex differences as previously described could be confirmed in the nomogram as well. Furthermore, in exemplary results, the therapeutic effect of botulinumtoxin into the detrusor could be shown in the nomogram by a significant decrease of the category. Another example demonstrated the clinical correlation of a neurological relapse with a significant increase of the detrusor contractility. This implies

the clinical correlation and significance of the nomogram, which is still pending for further validation of the nomogram.

In future, the implementation of the nomogram could provide objective patient selections with the necessity of frequent medical observation due to the high risk of upper urinary tract impairment. Another application is an objective follow up with categorization of the DO over time, and selecting patients with a progressive disease for a more progressive therapy of DO. Success monitoring of medical interventions, such as sacral neuromodulation or botulinumtoxin, is realizable as well and could influence the treatment strategies of these patients.

The presented IWT nomogram is the first attempt at severity categorization of neurogenic bladder dysfunction. The current study therefore presents a pilot trial to prove the concept and potential of the IWT. Although questions are still pending, in our opinion the nomogram could be utilized in future even for prognosis. A limitation of the nomogram at this point is the interpretation of each categorization. Without further clinical correlation, we cannot exactly define which categories are at specific higher risk for impairment of the upper urinary tract. Further research will address this issue. Larger populations with clinical correlations are future goals for research in order to validate the IWT nomogram.

In conclusion, the application of the IWT after routine cystometry is a simple tool to identify involuntary DOs as a result of neurogenic bladder dysfunction. In the current study, we could identify 16.5% patients with DO that had not been revealed during cystometry. Furthermore, men presented significantly more often with DO during the IWT than women.

Furthermore, the developed IWT nomogram in the current pilot trial was successfully applied in our cohort with the potential for further research. The incontinence episodes correlated positively with the categorization and bladder contractility. We propose the nomogram for objective severity categorization, urodynamic follow-up studies and therapeutic controls after further evaluation of the nomogram, which is the aim of further research.

## Conflict of interest

None declared.

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