Urethral Instability and Sacral Nerve Stimulation (SNS): a better parameter to predict the efficacy?

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Abstract

**Purpose:** Urodynamic parameters that predict the outcome of sacral nerve stimulation (SNS) are difficult to define. We studied the predictive value of urethral instability (URI) and other urodynamic parameters on the efficacy of SNS.

**Materials and Methods:** Patients with refractory voiding disorders were implanted with a neurostimulator after responding with an improvement of more than 50% in their main symptoms after percutaneous nerve evaluation (PNE). Filling cystometry was performed with 3 urethral sensors and 1 bladder sensor, at baseline and at 6 months post implant. Urethral pressure variations > 15 cm H$_2$O were considered as pathological and defined as urethral instability. Clinical efficacy was evaluated by voiding diary data and defined as successful when an improvement of > 50% was observed.

**Results:** Nineteen female patients enrolled the study. At baseline, detrusor overactivity (DO) was observed in 9 of the patients. Eighteen patients showed URI. SNS therapy was successful in 13 patients (68%). The number of pads used per day and the severity of leakages decreased significantly. Twelve of the 13 successfully treated patients showed URI at baseline. DO was present in 4 of the successful treated patients. URI disappeared in 7 of the 13 successful treated patients; DO disappeared in only 1 of these patients.

**Conclusion:** In this study URI appeared to be a valuable urodynamic parameter for predicting the outcome of SNS.
Introduction

Urethral instability (URI), an expression of fluctuation in the urethral pressure during filling, is still regarded as a controversial topic in urodynamics. Even today, the ICS has difficulty in defining this entity. A decrease in urethral pressure, often seen as an initial marker of consecutive urethral instability, is often associated with the first sensation of filling (FSF). This implies a link between sensory factors such as FSF and motor expressions, namely fluctuations in urethral pressure during filling cystometry. Investigators acknowledge more and more the impact of sensory factors on voiding and various publications have discussed URI and the presence of voiding dysfunctions. More recently, McLennan et al., found a close correlation between URI and type II bladder instability, indicating a detrusor contraction preceded by a drop in urethral pressure [1]. They concluded that further studies are needed for patients with lower urinary tract storage symptoms and/or urge incontinence to differentiate between detrusor overactivity and URI for treatment purposes.

Various definitions for URI are used in literature. In 1981 the ICS defined the unstable urethra when there is an involuntary fall in urethral pressure, resulting in urinary leakage, in the absence of detrusor activity [2]. In 1988, however, the ICS was unable to define URI [3]. The standardisation committee of the ICS in 2002 did not mention the term URI, thus demonstrating the complexity and difficulty of this urodynamic feature [4]. According to the standardisation subcommittee of the ICS, the significance of urethral pressure fluctuations lack clarity and therefore, the term “unstable urethra” is not recommended. Instead, if symptoms are seen in association with a decrease in urethral pressure, a full description is recommended.

Over the years, terminology describing an involuntary rise in detrusor pressure during filling cystometry has been changed. It can well be understood that the term ‘detrusor instability’ was abandoned and changed in ‘detrusor overactivity’ (DO). ‘Overactivity’ describes an involuntary increase in detrusor pressure better than ‘instability’. For urethral pressure variations during filling cystometry the discussion is different. Only few investigator groups measure integral urethral pressure during filling cystometry. Reports published by these groups describe the topic as ‘urethral instability’. The term ‘instability’ is selected because both increase and decrease of urethral pressure is observed.

Most studies define URI as urethral pressure variations of at least 15 cm H₂O occurring apart from arterial pulsations and clearly visible during bladder filling [5-8]. Others defined URI as a drop in urethral pressure of at least 20 cm H₂O unrelated to a detrusor contraction, an increase of intra-abdominal pressure, or pulsations of the vascular bed [9]. Wise et al., advocated the definition of URI as a spontaneous fall in maximum urethral pressure of one-third or more, in the absence of detrusor activity, over a 2-minute period [10]. The clinical implications of URI are not always clear and therefore a good treatment strategy remains obscure. However, it is generally accepted that URI is somehow linked to overactive bladder complaints.

Refractory urge incontinence, urgency/frequency and voiding difficulty can be treated effective by sacral nerve stimulation (SNS). Reported cure rates vary between 41 and 100%, with an average of approximately 70% [11]. There is still debate as to its mode of action. Some investigators believe the modulating effect of SNS is related to an enhanced urethral sphincter and pelvic floor
tone, resulting in inhibition of DO [12]. Others, however, believe SNS affects primary the bladder via afferent pudendal and sacral nerve fibres [13]. Clinical studies so far failed to explain the clinical efficacy of SNS by its impact on DO. In our opinion, the significance of the urethral function is underscored in these investigations. We discuss the significance of sensory factors in SNS treatment [14] and perform urodynamics including integral urethral pressure measurement in the filling phase. We analyse the occurrence of urethral pressure variations and the effect of SNS on both clinical and urodynamic data which underscore the effect of SNS treatment on urethral and pelvic floor function.

**Materials and Methods**

Patients with micturition symptoms refractory to physical and medical therapy were implanted with a neurostimulator (Medtronic Inc., Minneapolis, USA) after responding with an improvement of more than 50% in their main symptoms to PNE. Filling cystometry was performed at baseline and 6 months post-implant. A micturition diary was filled out at baseline and 6 months post-implant to document voiding dysfunction and its changes after implant. Cystometry was performed with the MMS UD 2000 and a Gaeltec CTU/2E/L-4 12F catheter, with 3 urethral sensors and 1 bladder sensor. Urodynamic data of patients with urge incontinence and urgency/frequency were evaluated. The following items were scored: URI, DO, first sensation of filling (FSF), relation between URI and both DO and FSF as well as maximum and minimum urethral pressure during filling cystometry. Two investigators assessed the presence of urethral pressure variations. Urethral pressure variations of more than 15 cm H$_2$O seen on all 3 urethral pressure recordings during filling cystometry were considered pathological. Pressure variations of 16-30 cm H$_2$O were classified as minor, and those exceeding 31 cm H$_2$O were considered as major. Pressure variations related to artefacts (mechanical factors, movement of the patient or the catheter, vascular pulsations) were disregarded. Urethral pressure variations were studied separately from possible concurrent bladder pressure fluctuations. All other definitions were according to the guidelines of the ICS [4]. Comparisons between the two groups were done with a two-sample Student’s t-test. Results in the figures are presented as mean ± standard deviation. Statistical results were adjusted according to the equality of variances and for multiple comparisons of the data.
Results

The urodynamic and voiding diary data of 19 female patients who underwent a SNS operation due to refractory overactive bladder complaints were analysed. Fifteen patients suffered from refractory urge incontinence (UI), and 4 from urgency/frequency (U/F). Mean age at study enrolment was 45.6 years (range 31-58, SD 7.7) and mean duration of symptoms was 8.1 years (range 1-36, SD 9.4).

Clinical results
At 6 months post implant, SNS therapy was successful in 13 patients (68%), 4 patients showed an improvement of less than 50% on primary voiding diary parameters. In 2 patients the neurostimulator was removed prior to the 6 months follow-up. The data of all these patients were included in the data analysis. The number of pads used per day, average severity of leakages and number of leaks per day all decreased significantly after implant of the neurostimulator at follow-up (table 1). Six out of the 15 patients with UI were completely dry and 5 demonstrated a more than 50% decrease in leakage episodes.

Table 1. Clinical parameters: Baseline through 6 months (n=19)

<table>
<thead>
<tr>
<th></th>
<th>Mean at baseline</th>
<th>Mean 6 months post implant</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of leaks/24 h</td>
<td>13 ± 10</td>
<td>6 ± 8</td>
<td>0.001</td>
</tr>
<tr>
<td>Average severity of leakages</td>
<td>2.2 ± 0.68</td>
<td>1.5 ± 0.45</td>
<td>0.019</td>
</tr>
<tr>
<td>Number of pads/24 h</td>
<td>8.4 ± 7.0</td>
<td>4.0 ± 6.2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Statistical Comparison: paired t-test
Urodynamic characteristics

Baseline cystometry
Filling cystometry at baseline showed DO in 9 patients (47%). The prevalence of URI was high (95%, table 2). In the 4 patients with urgency/frequency, their complaint was clearly more related to the presence of URI (prevalence 100%) than of DO (prevalence 25%). These correlations were less pronounced in patients with urge incontinence (93% respectively 53%). Furthermore, in all patients with URI, a drop in urethral pressure was noticed at FSF. All 9 patients with DO showed urethral pressure variations exceeding 31 cm H2O.

Table 2. Urethral and detrusor behaviour for all patients at baseline and 6 months post implant

<table>
<thead>
<tr>
<th>Clinical success</th>
<th>URI and DO absent</th>
<th>URI present, DO absent</th>
<th>URI absent, DO present</th>
<th>URI and DO present</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=13</td>
<td>4 (27%)</td>
<td>8 (62%)</td>
<td>0 (0%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>N=17</td>
<td>1</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>N=17</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

URI=Urethral instability; DO=Detrusor overactivity.

Cystometric data at 6 months follow up
Urodynamic data were available for 17 patients. Table 2 shows detrusor and urethral behaviour 6 months post implant, with the stimulator on and off.
A disappearance of URI was seen in 7 out of 13 (54%) successfully treated patients. This effect was seen in 9 (53%) of the 17 urodynamical evaluable patients. In 3 out of 9 (33%) patients with DO at baseline, no DO was observed at 6 months follow-up. Prior to treatment, 16 out of 19 patients had urethral pressure variations of more than 31 cm H2O (84%). However, at 6 months this phenomenon was present in only 5 out 17 patients (29%). When the stimulator is switched off, more pronounced urethral pressure changes (> 31 cm H2O) reappeared instantly in 6 patients and DO reappeared in 1 patient.
The dramatic effect of SNS therapy on urethral pressure variations and DO is illustrated in figures 1 and 2. Figure 1 shows the urodynamic recordings in a patient, suffering from UI, 6 months after successful SNS therapy. In figure 2 the reappearance of both URI and DO in the same patient can be clearly seen when stimulation is switched off.
**Figure 1:** Urethral pressure variations and detrusor overactivity in a patient implanted with a permanent neurostimulator, stimulation switched on showing normalisation of urethral and detrusor behaviour.

**Figure 2:** Urethral pressure variations and detrusor overactivity in a patient implanted with a permanent neurostimulator, stimulation switched off.
Table 3 represents 8 urodynamic test values prior to implant and at 6 months follow-up. A significant increase in FSF was seen as well as a clinical relevant increase in bladder volume prior to void. When the resulting changes in urethral pressure are merely expressed as “peak urethral pressure” or “lowest urethral pressure” instead of the variation in pressure, the changes are not significant.

Table 3. Water Cystometry: Baseline through 6 months

<table>
<thead>
<tr>
<th>Urodynamic Test Variable</th>
<th>Avg. at Baseline</th>
<th>Avg. at six months</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Sensation of Filling (FSF)</td>
<td>98 ± 88</td>
<td>235 ± 159</td>
<td>0.002</td>
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<tr>
<td>Bladder Volume (ml)</td>
<td>284 ± 108</td>
<td>346 ± 166</td>
<td>0.061</td>
</tr>
<tr>
<td>Bladder Volume prior to void (ml)</td>
<td>10 ± 10</td>
<td>7 ± 7.6</td>
<td>0.14</td>
</tr>
<tr>
<td>Peak detrusor pressure (cm H₂O)</td>
<td>42 ± 33</td>
<td>25 ± 14</td>
<td>0.028</td>
</tr>
<tr>
<td>Detrusor pressure at FSF (cm)</td>
<td>24 ± 14</td>
<td>19 ± 12</td>
<td>0.26</td>
</tr>
<tr>
<td>Detrusor pressure at maximum fill or prior to void (cm H₂O)</td>
<td>239 ± 140</td>
<td>317 ± 153</td>
<td>0.041</td>
</tr>
<tr>
<td>Volume at peak bladder pressure (ml)</td>
<td>121 ± 42</td>
<td>113 ± 42</td>
<td>0.15</td>
</tr>
<tr>
<td>Peak urethral pressure during cystometry (cm H₂O)</td>
<td>69 ± 32</td>
<td>86 ± 44</td>
<td>0.86</td>
</tr>
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</table>

* Statistical Comparison: paired t-test
The consistency and reproducibility of URI and its clinical relevance is still a matter of debate. Our study, however, shows the relationship of this urodynamic finding to clinical outcome in patients treated with SNS.

By some investigators, urethral pressure variations during filling cystometry are considered an artefact and therefore of no relevance to explaining patients symptoms [15]. Most studies discussing urethral pressure variations were published decades ago and used only one urethral pressure sensor together with one bladder sensor. The prevalence of urethral pressure variations and their clinical significance is not clear. A URI prevalence of 12% was found in 397 patients with lower urinary tract complains by McLennan [1]. In relation to the clinical significance of URI, Penders et al., reported pure URI in 14 out of 31 (45%) patients with complains of refractory nocturnal enuresis. A prevalence rate of 35% of mixed URI and DO was seen while isolated DO occurred in 3 of the 31 patients. When performing traditional cystometry, 17 of their patients would be considered as ‘normal’. By performing simultaneous urethrocystometry in the same group of patients, only 3 showed no abnormality. Therefore, URI is shown to be a common condition in enuretic patients [6]. In a population of 427 gynaecologic patients with lower urinary tract symptoms, isolated URI was found in 16.4% by Weil et al. [7]. In 27% of all 427 patients, URI was found associated with DO. In their study, DO was more associated with nycturia, urgency, and urge incontinence than URI. In 1985 Vereecken and Das published their data on URI in the Journal of Urology. In 173 patients with a history of incontinence, they showed URI in 25 (14.4%) [8]. Of these 25 patients, 12 also showed DO. They concluded that URI is associated more often with DO and furthermore, only urethral pressure variations of more than 35 cm H$_2$O provoked overactive bladder complaints. This is in line with our observations: in patients with urethral pressure variations of more than 31 cm H$_2$O, DO was always present. URI appears to be close related to urgency/frequency and seems to be a bad prognostic marker that increases the risk of urinary incontinence. In contrast, Wise et al., reported no difference between patients with or without URI in terms of prevalence or severity of urgency/frequency, nycturia or urge incontinence [10]. Both URI and DO was significantly more common in women presenting with stress incontinence. Venema and Kramer already regarded URI as an expression of sensory urge that can give rise to an insufficient sphincter mechanism and may explain incontinence treatment failure [5]. In their study of 71 incontinent female patients with complains of urge, stress or mixed incontinence, URI was seen in 66%. DO occur in 24% of these patients.

In the literature, several definitions of the term URI and associated symptoms are used. To rule out (vascular) artefacts, we perform urethral pressure measurements with 3 urethral sensors. The mid-urethral sensor is placed at the maximum urethral pressure (MUP) and we diagnose URI when pressure variations in all 3 measurements are recorded.

When searching for a correlation between clinical improvement due to SNS treatment and change in urodynamic parameters, the most significant change was seen in FSF. FSF increased from a mean of 98 ml to 235 ml (p=0.002). With regard to DO and URI, disappearance of URI was seen in 7 out of 13 (54%) successfully treated patients, whilst DO disappeared in 1 of the 4 patients.
who responded with good result to the treatment. In the total group, URI disappeared at 6 months in 9 out of 17 patients (53%); in contrast, DO disappeared in 3 out of 9 patients (33%). Analyses of merely peak or lowest value of the continuous urethral pressure measurements did not show significant changes after SNS therapy (table 3). We therefore believe that instead of searching for changes in peak values, the pattern of urethral pressure variations illustrating the differences between peak and lowest value, indicating URI, is of much more importance for evaluation of urodynamic data. An increase in FSF after SNS is reported by Elkelini [16]. Bladder volume at FSF increased by 50% in 18 patients treated with a sacral root implant for urge incontinence. As in our observations, only in one out of four patients who showed DO preoperatively, this urodynamic finding disappeared after implant.

When including urethral measurement during filling in urodynamic evaluation, we often observed that FSF is related to the phenomenon of URI: during filling, more pronounced fluctuations in urethral pressure, indicating URI, often start at FSF. Also, it is often observed that URI is present in patients with sensory urgency, illustrating the sensory impact of URI. Branches of the rami S2, S3 and S4 give rise to the parasympathetic, autonomic plexus pelvis and somatic pudendal nerve. The pudendal nerve innervates among others the urethral sphincter. During neurostimulation, the somatic A-alpha and A-gamma myelinated pudendal nerve fibres are activated at a lower threshold compared to the B and C parasympathetic fibres [12]. This will result in an efferent effect of enhanced urethral sphincter tone and increase of activity of the pelvic floor. Via afferent fibres this will also result in inhibition of the detrusor muscle. If this hypothesis on the working mechanism of neuromodulation were true, one would expect an urodynamic change in urethral function after SNS. This may well explain diminished urethral pressure fluctuations as observed in this study. SNS therapy affects detrusor behaviour via the afferent fibres of the plexus pelvis and pudendal nerve. The plexus pelvis supports both urethral and bladder innervations. Therefore, we believe that SNS may well influence urethral function. Several papers have been published on the mode of action of neuromodulation. All of them fail to give a straightforward explanation for patients with symptoms of an overactive bladder [17]. We therefore believe that in the evaluation of the working mechanisms of SNS, the presence of urethral pressure variations should be considered.

Conclusions

In our study we noticed a marked disappearance of URI after SNS treatment. Such a change was not seen for DO. Successfully treated patients showed an even higher decrease of URI. Our results indicate that the occurrence of FSF and concomitant URI, which are clinically experienced as sensory parameters, do predict the outcome of SNS treatment better than DO.