Neuromodulation and urodynamics in lower urinary tract symptoms

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Aim of this Thesis

The number of patients with Lower Urinary Tract Symptoms (LUTS) will continue to rise. Most important cause for this is the increasing average life span of the population of most developed countries. Furthermore, an increasing knowledge of the general public on this subject, generated by the media, will cause an increase in demand for health care interventions. This implies that workload for clinicians involved with treatment of LUTS will rise. Unfortunately, national health care budgets will not rise in parallel. Therefore, for justification of use of new treatment options, we must not only prove these new, sophisticated treatments to be more effective but also to be more cost-effective compared to existing treatments.

LUTS do highly affect patient's quality of life. Patients with non-neurogenic lower urinary tract dysfunction may present with different complains: besides obstructive complaints in men, urge urinary incontinence, urgency and/or frequency, chronic pelvic pain or non-obstructive urinary retention. Treatments of choice options are firstly conservative and include pharmacotherapy (anticholinergic) and behavioural techniques (pelvic floor muscle exercises, bladder re-education). Unfortunately, only a limited number of patients do respond successful to these conservative options, leaving a group of patients with refractory complaints. In the past, irreversible and aggressive surgical procedures, including urinary diversion and bladder augmentation were performed on these patients.

Monitoring the efficacy of treatment modalities is often disappointing, especially the use of traditional parameters, like urodynamic proven detrusor overactivity, does not lead to a better understanding and patient selection so far. In literature, the value of urethral pressure recording on traditional filling cystometry in relation to clinical treatment outcome is not clear. This is also true for the finding of urethral pressure changes (i.e. urethral instability) during filling cystometry.

With an increasing interest in the "pelvic floor" and multi-disciplinary approach to treat patients, there is a need to look for (urodynamic) parameters, which are valuable for both patient selection and measurement of treatment modalities. Since the 90's, selected patients do respond with good result to new neuromodulation techniques like Sacral Neuromodulation. However, the exact mode of action is still not known as well as the value of urodynamic evaluation in the process of patients' selection and assessment of clinical success. A better understanding of the mechanism of action is definitely needed for good selection of patients with refractory lower urinary tract dysfunctions, favourable for neuromodulation. Furthermore, increasing knowledge on urodynamic parameters and their role in patients selection as well as in evaluating treatment, will led to better clinical results. This thesis gives an outline of different neuromodulation techniques together with urodynamic changes evoked by neuromodulation. Also the predictive value of some urodynamic parameters, especially in relation to urethral pressure variations will be assessed. The role of the urethra and its function seems to be underestimated so far.

Neuromodulation: treatment modalities, indications, clinical efficacy, and mode of action

Neuromodulation, in all its forms, offers a treatment option for patients with refractory lower urinary tract symptoms. Complaints in these patients may vary from voiding disorders, impaired micturition or chronic non-obstructive urinary retention to storing disorders, including complaints of an overactive bladder to chronic pelvic pain. Cause of the lower urinary tract dysfunction in patients without an objective neurogenic laesion is mostly unknown.
Neuromodulation is often used in patients with voiding symptoms who do not respond to conservative therapy. Conservative therapies include physiotherapy, pharmacotherapy and behavioural techniques. In patients with chronic non-obstructive retention, clean intermittent catherization maybe the treatment of choice. From a patient's point of view, this however is a burden with tedious side effects like urinary tract infections. Invasive extensive surgery is irreversible, and in many patients, does not lower the impact of their illness. Therefore, neuromodulation, especially the minor invasive techniques, maybe treatment option of choice for patients with refractory voiding symptoms, who failed all conservative therapeutic options.
Neuromodulation is defined as the physiological process in which the influence of the activity in one neural pathway modulates the pre-existing activity in another through synaptic interaction [1]. Different kind of therapies has been developed for different indications with variable clinical success, illustrating the difficulty to treat lower urinary tract dysfunction [2]. More recent, the use of Sacral Neuromodulation (SNM) and Percutaneous Tibial Nerve Stimulation (PTNS) has been emphasized [3,4]. Both treatment modalities have acceptable clinical success rates although patient selection still is a point of discussion and remains empiric [5]. Further investigation on patient selection is therefore strongly needed. Other 'new' neuromodulation treatment options included Transcutaneous Electrical Nerve Stimulation (TENS) and modulation of the pelvic floor by magnetic stimulation ('magnetic chair'). Unfortunately, clinical success rates of both methods are limited [6].

The use of neuromodulation treatment in daily practice is relatively new. Most research in this field is published during the last three decades. With increasing knowledge concerning neurophysiology, investigators were looking for therapeutic use of stimulation and modulation of the nerve system, both peripheral and central. Most of the work was empiric, but with time, clinical success was fortunately increasing. Better knowledge of involved neurological connections between central and peripheral nerve systems and bladder however did not led to a straightforward explanation of the mode of action and even nowadays there is debate on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction [7]. In recent years, more applications of various types have been developed. This review presents an overview of neuromodulation therapies together with different theories on the mode of action.

Sacral Neuromodulation (SNM)

In SNM therapy, also known as Sacral Nerve Stimulation. the third sacral nerve (S3) is stimulated by a permanent neurostimulator (InterStim®, Medtronic Inc., Minneapolis, Minnesota, USA). An electrode is placed in foramen S3 (sometimes S4)of the sacral bone by a dorsal approach and connected to the stimulator. Stimulation of the nerve occurs with a frequency of 10-20 pulses per second, a pulse width of 210 µsec, and variable amplitude. The procedure is considered as minimally invasive. Unfortunately, reported complication rate in the past was relative high and up to 30% of patients required a new operation. The improved temporary lead design makes the Peripheral Nerve Evaluation more reliable while new techniques, like the tined lead, make the procedure easier. This will hopefully lead to a decrease in re-operations and adverse events ratio over time.

Several groups have studied the efficacy of SNM with the InterStim implantable neurostimulator intensively. Tanagho and Schmidt first reported on this treatment in 1982 after conducting animal studies [3]. In 1988, the three stages of electrode placement were discussed by Schmidt [8]. Reported results vary between 41% and 100%, depending on patient's selection and treatment indication [9]. However, one should kept in mind that the reported success rates are obtained after patient selection based on a positive Percutaneous Nerve Evaluation (PNE) test. Patients are mostly considered for permanent implant after an improvement of more than 50% in their main voiding symptoms, as described by Schmidt, Senn and Tanagho [10]. Approximately 40% of selected candidates do not pass the PNE. Therefore, reported cure rates must be evaluated with some precaution. A prolonged testing with tined lead seems to be more reliable for accurate patient selection with implantation rate increased to 80%. At median follow-up of 22 months 88% of the implanted patients remain successful. No infection was reported during prolonged test period [11]. This new approach for patient selection will lead to more patients positively selected for permanent implant.

Indications for SNM

In 1997, SNM therapy was approved by the FDA for refractory urge urinary incontinence, followed by urgency and frequency symptoms and chronic non-obstructive urinary retention in 1999. Nowadays, patients with complaints of an 'overactive bladder' are considered candidates for SNM when their symptoms are persistent, do affect their quality of life significantly and do not respond to conservative treatment modalities. Contraindications are few. Patients with anatomic variations, like bone abnormalities of the sacrum cannot be treated by SNM due to difficulty to access the sacral foramen. Patients, in which future MRI studies are critical, must also be considered as poor candidates. Furthermore, patients must be able to operate the device and report on comfort of stimulation. This is essential for optimal clinical result. Of course, patients who have failed the PNE test are inappropriate for permanent implant.

SNM success rates for different indications

SNM for urge urinary incontinence (UI) and urgency/frequency (UF)

Reports on SNM outcome on symptoms of an overactive bladder (OAB), i.e. urgency and/or frequency are mostly presented together with patients implanted with a permanent neurostimulator because of refractory UI.

The efficacy of SNM for symptomatic treatment of refractory UI has been published extensively. Hassouna et al reported in 2000 on efficacy and safety for patients treated with sacral neuromodulation. Sacral neuromodulation is safe and shows significant clinical benefit in treated urgency and frequency patients [12]. Long-term effectiveness, with an average follow-up of 30.8 months, showed sustained benefit for urge urinary incontinence patients [13]. In 2006, Latini et al. reported an improvement in symptoms of ≥ 50% in 90% of patients with refractory UI, after one-staged or two-staged InterStim implant [14]. Number of urge incontinence episodes reduced by 74% and number of pads used per day by 83% compared to baseline. Statistically significant improvement in number of UI episodes and quality of life in both younger and older patients is seen [15]. The cure rates in patients with UI are associated with age, with individuals younger than 55 years having a statistically significant better cure rate. Long-term follow-up shows sustained benefit in over 2/3 of patients with refractory complaints of an OAB, implanted with a permanent neurostimulator [16]. Our 5-years follow-up results show a comprehensive outcome with a significant decrease in symptoms in 10 out of 15 UI patients [17]. In an independent investigation of 1827 implants from 34 clinical trials, InterStim therapy was shown to be an effective treatment option for the treatment of UI. In randomized controlled trials 80% of the patients achieved continence or more than 50% improvement in their symptoms, for case series reports this was 67% [18]. SNM may improve sexual frequency and sexual function scores in female patients with UF and UI. Device implant impacted sexual function in a positive way by decreasing urgency and by increasing desire [19]. Recently, the long-term results of 152 patients, enrolled in the worldwide MDT-103 study, were published. At 5-year follow-up, sacral neuromodulation was successful in 68% of patients with urge urinary incontinence, 56% with urgency/frequency and 71% with urinary retention [20].

SNM for chronic non-obstructive urinary retention

Jonas et al reported effectiveness in 83% of patients with urinary retention, 18 months after implantation [21]. Efficacy rates up to 77%, with spontaneous voiding, have been reported on the long term in women with Fowler's syndrome, treated by SNM. Mean post-void residual volume was 75 ml, which is acceptable [22]. Similar good results, defined as complete and lasting disappearance of symptoms or satisfactory symptoms for the patients, were found by van Voskuilen et al. [16]. The presence of Fowler's syndrome, with specific electromyography abnormalities of the external sphincter, is a positive predictive factor for SNM in female urinary retention. Idiopathic urinary retention patients do benefit as well, but the success rate might be less predictable [23].

SNM for constipation and faecal incontinence

Following the use of SNM in patients with voiding disorders, beneficial effects for patients with concomitant bowel dysfunction was seen. SNM in faecal incontinence is not effective for all patients eligible for the procedure. A PNE test period of 2-3 weeks allows selection of those patients who are likely to respond with good result to a permanent implant [24]. Aetiology of faecal incontinence is various and idiopathic, obstetric, surgical and spinal cord pathology causes are mentioned. Complete faecal continence after SNM was reported in 41% to 75% of patients whereas an improvement of more than 50% in number of incontinence episodes was seen in 96% of patients after permanent implant [25,26]. Similar results have been noted in patients with idiopathic constipation [27].

A total of 30000 patients are treated worldwide with InterStim therapy so far. With changing techniques, the procedure can now be performed under local anaesthesia and therefore be considered as minimally invasive.

SNM mode of action

Recently, van der Pal et al. published on the mode of action of all neuromodulation techniques [7]. Once again, it is evident that a straightforward explanation on the mode of action is hard to give. Several hypothesis have been reported in the past. Generally, and adapted by most investigators, it is believed that SNM works via stimulation of afferent rather than efferent nerves [28]. Others however stated that direct stimulation of the nervus pudendus does explain working mechanism of SNM [29]. It is clear that further investigation is needed before this debate will be ended.

By novel neuroimaging techniques (Positron Emission Tomography, PET scan), the existence of abnormal interaction between brainstem and cortical centres in women with urinary retention was seen. The therapeutic effect of SNM is achieved through restoration of activity associated with brainstem auto regulation and attenuation of cingulate activity [30]. Blok et al. performed a PET-scan study on UI patients, previously implanted with a neurostimulator and UI patients, stimulated for the first time in the PET-scan. Group analysis between acute and chronic stimulated patients showed significant differences in the associative sensory cortex, premotor cortex and cerebellum, all three involved in learning behaviour. They concluded that acute SNM modulates brain areas involved in sensorimotor learning. Furthermore, chronic SNM influences, presumably via the spinal cord, brain areas previously involved in detrusor hyperactivy, awareness of bladder filling, the urge to void and timing of micturition. Also SNM affects areas involved in alertness and awareness [31].

Expanding indications for SNM

New frontiers for SNM therapy are patients with interstitial cystitis (IC), chronic pelvic pain syndromes, neurogenic bladder dysfunctions (MS) and erectile dysfunction.

IC symptoms include pelvic pain, dyspareunia, small voided volumes, frequency, nocturia, and urgency. Pharmacological therapy is varied and efficacy is often poor, indicating the difficulty to treat IC. A sustained clinical improvement in symptoms is reported by Comiter in a prospective study, evaluating SNM for refractory IC [32]. A decrease in narcotic requirement for refractory IC patients implanted by a permanent neurostimulator is noted. Patients were overwhelmingly satis-

fied with SNM compared with prior therapies [33]. SNM elevates urinary levels of antiproliferative factor and epidermal growth factors in IC patients. This may explain restoration of normal voiding [34]. SNM improves quality of life and decreases severity and duration of patients with chronic genitourinary pain [35]. Cavernous nerve stimulation achieved full erections in a serie of 15 men with erectile dysfunction [36]. This therapy however is anecdotal at the moment.

Percutaneous Tibial Nerve Stimulation (PTNS)

In PTNS, formerly called Stoller Afferent Nerve Stimulation (SANS), a needle electrode is placed near the tibial nerve, a few centimetres above the ankle. This spot is known by acupuncturists and considered of significance in treatment of urological symptoms [37]. The needle electrode is connected to an external neurostimulator generating 1-10 mA. Working mechanism is unknown. Patients are mostly treated weekly during a 9-week period. After this period, clinical benefit is evaluated and the treatment may be continued with an increasing time interval between treatments. If treatment is terminated this usually results in return of patient's symptoms. PTNS is indicated for refractory symptoms of an OAB, including UF and UI. Treatment is conducted in an outpatient setting and normally, the tibial nerve is stimulated for 30 minutes at an amplitude just below pain threshold. The tibial nerve is sometimes mentioned as posterior tibial nerve, indicating the existence of an anterior tibial nerve. Review of anatomy however shows there is no such nerve. Therefore, it is better to speak of tibial nerve in literature. The tibial nerve originates from spinal roots L4 through S3 and is a mixed sensory-motor nerve. A neuro feedback mechanism via the plexus pelvicus may reduce bladder activity, resulting in a decreased symptom awareness. Modulation of the somatic and autonomic nerve system may influence urinary sphincter and bladder behaviour.

Approximately 50% of all patients do respond positively on PTNS. Treatment however is relatively time consuming and it remains unclear how and/or when treatment can be stopped. Increasing amount of patients may frustrate other activities at the outpatient department. For this reason, some urologists do perform PTNS in day care treatment. Fortunately, only minor side effects, mostly pain at the puncture site, have been reported.

PTNS efficacy is studied by several groups. In 1998, Payne published on a statistically significant improvement in 98 patients with frequency, incontinence and pelvic pain [38]. Van Balken et al. reported a success rate of 60% for urge urinary incontinence, defined as the wish of the patient to continue treatment after an initial 12-week treatment period. A decrease in leaking episodes of 63% was observed, compared to 24% for those patients who did not respond successful. Seven out of 12 patients with non-obstructive retention were considered successful while no significant urodynamic changes could be observed for this group [39].

Transcutaneous Electrical Nerve Stimulation (TENS)

In TENS, carbon-rubber electrodes are placed on the skin and an external stimulator is connected. Intensity, pulse rate and pulse frequency of the stimulation vary in literature. Generally, two methods of TENS are used and published in literature, one providing direct S2 or S3 dermatome stimulation, the other placed suprapubically. First publication on this neuromodulation technique was by Fall et al. in 1980. In this study, suprapubical transcutaneous electrical nerve stimulation was used in interstitial cystitis patients with OAB symptoms and pain. Especially, this method was shown to be effective in relieving pain and decreasing frequency [40]. More recent studies on suprapubical TENS reported an improvement in voiding pattern of 26 to 73% in patients with non-neurogenic voiding dysfunctions [41,42]. By placement of the electrodes over S2 and S3 dermatomes, a better clinical outcome was expected. Reported efficacy however was low and not favourable over anticholinergic drug therapy [43]. Promising results with sacral dermatomes TENS were noted by Walsh et al. Urgency improved in 60% while daytime voiding frequency even improved by 76% [44]. Unfortunately, if stimulation is stopped, symptoms return almost immediately. Although stimulation is given at maximum tolerable intensity, the threshold for proper electrical stimulation of the nerves involved might not be reached by TENS. Unfortunately, this promising non-invasive technique did not show enough clinical outcome for a wide spread use in patients with non-neurogenic voiding dysfunctions. Side events seen in 1/3 of treated patients, are mainly local skin irritation at the site of the carbon-rubber electrodes.

Functional Electro Stimulation (FES)

Different minimally invasive techniques for neuromodulation have been tested, including various direct and indirect percutaneous, vaginal and anal modalities.
Transvaginal stimulation is not well accepted by most patients. Disadvantages include the long period of treatment time and stimulation at high intensity, not easily tolerated by women with normal sensation in the pelvic region. Cure rates vary between 22 and 49% while an improvement in outcome of 81% is reported [45,46].
The use of anal electrical stimulation did not find broad acceptance. Main reason for this is the physical and psychological discomfort, experienced by the patients. With newer more comfortable stimulation techniques, publications on this topic are rare nowadays. Studies published in the 70's and 80's often use both vaginal and anal stimulation. Improvement rates up to 100% are mentioned [47], but the average outcome is an improvement in symptoms of approximately 50% [48].

Functional Magnetic Stimulation (FMS) or Extracorporeal Magnetic Innervation therapy (ExMI)

Announced as a promising non-invasive technique some years ago, the 'magnetic chair' is not widely used in urologic daily practice nowadays. Main reason for this is the poor reported success ratio and relatively high costs of this new technique. Magnetic induction means that a current will flow in response to a changing magnetic field. FMS induces a controlled depolarization of adjacent nerves and subsequent muscle contraction Hypothesis for its mode of action may be 'pelvic floor re-education' by stimulation of the pelvis. By creating a strong magnetic field, nerves and muscles are stimulated, leading to contractions of all pelvic muscles.
Several studies show different clinical outcome. It has to be stated that a wide variety of patients, with various refractory micturition disorders, are treated with this technique. In 74 patients with complaints of urge urinary incontinence, urgency/frequency, stress incontinence, mixed incontinence and defecation problems, no change in pelvic floor function was seen [6]. According to Chandi et al. FMS for the treatment of urinary incontinence in women is a safe, non-invasive and painless treatment, and effective and easy to administer in an outpatient setting. In 58% of the patients an objective (>50%) improvement of incontinence was observed, 71% of the treated patients noticed a subjective improvement. Filling cystometry parameters post treatment did not show statistically significant changes compared to the data recorded prior to treatment [49]. A significant increase in urodynamic parameters maximum intraurethral pressure and maximum urethral closure pressure is seen during and after FMS [50]. A significant reduction in urinary incontinence, measured by median number of pads, detrusor overactivity on cystometry and number of leakages, is reported by Galloway et al. [51]. Groenendijk et al. demonstrated significant urodynamic changes after ExMI; this however could not be correlated with clinical efficacy [52].

Conclusions

Most of these neurostimulating or neuromodulating treatment modalities are tested and evaluated in patients with different lower urinary tract symptoms like urge urinary incontinence, stress incontinence, combined urge- and stress urinary incontinence, symptoms of urgency or frequency and voiding difficulty. However, reported results are mostly not based on single blinded, placebo controlled studies. Therefore, it should be kept in mind that the reported results may be flawed due to patients selection, patients expectations and so on.

References

1. Craggs M, McFarlane J. Neuromodulation of the lower urinary tract. Exp Physiol 1999; 84: 149-160
2. Fandel T, Tanagho EA. Neuromodulation in voiding dysfunction: a historical overview of neurostimulation and its application. Urol Clin N Am 2005; 32: 1-10
3. Tanagho EA, Schmidt RA. Bladder pacemaker: scientific basis and clinical future. Urology 1982; 20: 614-9
4. van Balken MR, Vandoninck V, Messelink EJ, Vergunst H, Heesakkers JPFA, Debruyne FMJ, Bemelmans BLH. Percutaneous tibial nerve stimulation as neuromodulative treatment of chronic pelvic pain. Eur Urol 2003; 43: 158-163
5. Siegel SW. Selecting patients for Sacral Nerve Stimulation. Urol Clin N Am 2005; 32: 19-26
6. Voorham-van der Zalm PJ, Pelger RBM, Stiggelbout AM, Elzevier HW, Lycklama a Nijeholt AAB. Effects of magnetic stimulation in the treatment of pelvic floor dysfunction. BJU Int 2006; 97: 1035-1038
7. van der Pal F, Heesakkers JPFA and Bemelmans BLH. Current opinion on the working mechanisms of neuromodulation in the treatment of lower urinary tract dysfunction. Curr Opin Urol 2006; 16: 261-267
8. Schmidt RA. Application of neurostimulation in urology. Neurourol Urodyn 1988; 7: 585-592
9. Bemelmans BLH, Mundy AR and Craggs MD. Neuromodulation by implant for treating lower urinary tract symptoms and dysfunction. Eur Urol 1999; 36: 81-99
10. Schmidt RA, Senn E, Tanagho EA. Functional evaluation of sacral nerve root integrity, report of a technique. Urology 1990; 35: 388-392
11. Kessler TM, Madersbacher H, Kiss G. Prolonged sacral neuromodulation testing using permanent leads: a more reliable patient selection method? Eur Urol 2005; 47(5): 660-665
12. Hassouna MM, Siegel SW, Lycklama a Nijeholt AAB, et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. J Urol 2000; 163: 1849-1854
13. Janknegt RA, Hassouna MM, Siegel SW, Schmidt RA, van Kerrebroeck PEV, Lycklama a Nijeholt AAB, et al. Long-term effectiveness of Sacral Nerve Stimulation for refractory urge incontinence. Eur Urol 2001; 39: 101-106
14. Latini JM, Alipour M, Kreder KJ. Efficacy of sacral neuromodulation for symptomatic treatment of refractory urinary urge incontinence. Urology 2006; 67: 550-554
15. Amundsen CL Romero AA, Jamison MG, Webster GD. Sacral neuromodulation for intractable urge incontinence: are there factors associated with cure? Urology 2005; 66: 746-750
16. van Voskuilen AC, Oerlemans DJAJ, Weil EHJ, de Bie RA, van Kerrebroeck PEVA. Long term results of neuromodulation by sacral nerve stimulation for lower urinary tract symptoms: a retrospective single center study. Eur Urol 2006; 49(2): 366-372
17. Groenendijk PM, Lycklama a Nijeholt AAB, Ouwerkerk TJ, van den Hombergh U. Five-year follow up after sacral neuromodulation (SNM): single center experience. Neuromodulation 2007: 10(4): 293-298

18. Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for the treatment of urinary urge incontinence: a systematic review. J Urol 2006; 175: 835-841
19. Pauls RN, Marinkovic SP, Silva WA, Rooney CM, Kleeman SD, Karram MM. Effects of sacral neuromodulation on female sexual function. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18(4): 391-395
20. van Kerrebroeck PEV, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol 2007; 178: 2029-2034
21. Jonas U, Fowler CJ, Chancellor MB, et al. Efficacy of sacral nerve stimulation (SNS) for urinary retention: results 18 months after implantation. J Urol 2001; 165: 15-19
22. Dasgupta R, Wiseman OJ, Kitchen N, Fowler CJ. Long-term results of sacral neuromodulation for women with urinary retention. BJU Int 2004; 94: 335-337
23. de Ridder D, Ost D, Bruyninckx F. The presence of Fowler's syndrome predicts successful long-term outcome of sacral nerve stimulation in women with urinary retention. Eur Urol 2007; 51: 229-234
24. Jarrett MED. Neuromodulation for constipation and faecal incontinence. Urol Clin N Am 2005; 32: 79-87
25. Jarrett ME, Varma JS, Dutchie GS, et al. Sacral Nerve stimulation for faecal incontinence in the UK. Br J Surg 2004; 91: 755-761
26. Matzel KE, Bittorf B, Stadelmaier U et al. Sacral nerve stimulation in the treatment of faecal incontinence. Chirurg 2003; 74: 26-32
27. Kenefick NJ, Nicholls JR, Cohen RG, et al. Permanent sacral nerve modulation for the treatment of idiopathic constipation. Br J Surg 2002; 89: 882-888
28. Malaguti S, Spinelli M, Giardiello G, Lazzeri M, van den hombergh U. Neurophysiological evidence may predict the outcome of sacral neuromodulation. J Urol 2003: 170: 2323-2326
29. Bosch JLHR and Groen J. Sacral (S3) segmental nerve stimulation as a treatment for urge incontinence in patients with detrusor instability: results of chronic electrical stimulation using an implantable neural prothesis. J Urol 1995; 154: 504-507
30. Dasgurpta R, Critchley HD, Fowler CJ. Changes in brain activity following sacral neuromodulation for urinary retention. J Urol 2005; 174(6): 2268-2272
31. Blok BFM, Groen J, Bosch JLHR, Veltman DJ, Lammertsma AA. Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulation. BJU Int 2006; 98(6): 1238-1243
32. Comiter CV. Sacral neuromodulation for symptomatic treatment of refractory interstitial cystitis: a prospective study. J Urol 2003; 169: 1369-1373
33. Peters KM, Konstandt D. Sacral neuromodulation decreases narcotic requirements in refractory interstitial cystitis. BJU Int 2004; 93: 777-779
34. Chai TC, Zhang C, Warren JW et al. Percutaneous sacral third nerve root neurostimulation improves symptoms and normalizes urinary HB-EGF levels and antiproliferative activity in patients with interstitial cystitis. Urology 2000; 55: 643-646
35. Siegel S, Paskiewicz E, Kirkpatrick C et al. Sacral nerve stimulation in patients with chronic intractable pelvic pain. J Urol 2001; 166: 1742-1745
36. Sharif A. Extrapelvic cavernous nerve stimulation in erectile dysfunction. Andrologia 1996; 28: 151-156
37. Chang PL. Urodynamic studies in acupuncture for women with frequency, urgency and dysuria. J Urol 1988; 140: 563-566
38. Payne CK. Urinary incontinence: nonsurgical managment. In: Walsh PC, Retik AB, Vaughan ED et al, editors. Campbell's urology, vol 2. Philidelphia: WB Saunders; 2002. p. 1069-91

39. van Balken MR, Vandoninck V, Gisolf KWH, Vergunst H, Kiemeney LALM, Debruyne FMJ, Bemelmans BLH. Posterior tibial nerve stimulation as neurmodulative treatment of lower urinary tract dysfunction. J Urol 2001; 166: 914-918
40. Fall M, Carlsson CA, Erlandson BE. Electrical stimulation in interstitial cystitis. J Urol 1980, 123: 192-195
41. Fall M, Lindstrom S. Transcutaeneous electrical nerve stimulation in classic and nonulcer interstitial cystitis. Urol Clin North Am 1994; 21: 131-139
42. Bower WF, Moore KH, Adams RD. A pilot study of the home application of transcutaneous neuromodulation in children with urgency or urge incontinence. J Urol 2001; 166: 2420-2422
43. Soomro NA, Khadra MH, Robson W et al. A crossover randomized trial of transcutaneous electrical nerve stimulation and oxybutynin in patients with detrusor overactivity. J Urol 2001; 166: 146-149
44. Walsh IK, Johnston RS, Deane PF. Transcutaneous sacral neurostimulation for irritative voiding dysfunction. Eur Urol 1999; 35: 192-196
45. Brubaker L, Benson JT, Bent A et al. Transvaginal electrical stimulation for female urinary incontinence. Am J Obstet Gynecol 1997: 177: 536-540
46. Yaminishi T, Yasuda K, Sakakibara R et al. Randomized, double-blind study on electrical stimulation for urinary incontinence due to detrusor overactivity. Urology 2000; 55: 353-357
47. Ohlsson BL, Fall M, Frankenberg-Sommar S. Effects of external and direct pudendal nerve maximal electronic stimulation in the treatment of the uninhibited overactive bladder. Br J Urol 1989: 64: 374-380
48. Geirsson G, Fall M. Maximum functional electrical stimulation in routine practice. Neurourol Urodyn 1997; 16: 559-565
49. Chandi DD, Groenendijk PM, Venema PL. Functional extracorporeal magnetic stimulation as a treatment for female urinary incontinence: 'the chair'. BJU Int 2004; 93: 539-542
50. Yamanishi T, Yasuda K, Suda S, Ishikawa N. Effect of functional continuous magnetic stimulation on urethral closure in healthy volunteers. Urology 1999; 54: 652-655
51. Galloway NT, El-Galley RE, Sand PK, Appell RA, Russell HW, Carlan SJ. Extracorporal magnetic innervation therapy for stress urinary incontinence. Urology 1999; 53: 1108-1111
52. Groenendijk PM, Halilovic M, Chandi DD, Heesakkers JPFA, Voorham-van der Zalm PJ, Lycklama à Nijeholt AAB. Extracorporeal magnetic innervation therapy: assessment of clinical efficacy in relation to urodynamic parameters. Scand J Urol Nephrol 2008 Apr 2: 1-4

Bladder and urethra anatomy

Improved knowledge of the female lower urinary tract is essential for a better understanding of pathophysiology of this tract. However, several problems still remain. Correlations between urodynamic recordings and clinical observations remain insolvent, as we do not always know how to interpret the recorded findings. Therefore, anatomical understanding is of importance.

Bladder

The bladder consists of an outer adventitial layer of connective tissue, a smooth muscle layer and an inner layer of mucous membrane. A large complex meshwork of bundles of smooth muscle cells forms the muscular coat of the bladder; this structure is mostly known as the detrusor muscle. Longitudinally orientated muscle bundles tend to predominate on the inner and outer aspects of the detrusor muscle coat [1]. Orientation of the smooth muscle detrusor bundles in a random fashion and at all depths of the bladder wall without an arrangement as discrete layers is reported by Elbadawi. Furthermore, there is no evidence for gross anatomic differences in males and females [2]. From a functional point of view, the detrusor comprises a single unit of interlaying smooth muscle fibres. On contraction, this will cause a reduction in all dimensions of the bladder lumen.
The smooth muscle of the trigone consists of two distinct layers, often called deep and superficial trigonal muscles. The deep layer merges into the posteroinferior portion of the detrusor muscle. The superficial trigonal muscle is composed of relatively small diameter muscle bundles that are morphologically distinct from the detrusor muscle. Proximally, this layer is continuous with the urethral wall and distally with the smooth muscle of the proximal urethra [3].

Urethra

The mature female urethra has a length of 3 to 4 centimetre. The female urethra consists of an inner mucosal lining, continuous with the urothelium of the urinary bladder. Two layers of muscle bundles can be identified in the female urethra; an inner layer of smooth muscle fibres, and an outer layer of circularly arranged straited muscle fibres, the rhabdosphincter [3]. A thick inner sheet of longitudinal oriented fibres and a thin outer layer of circular fibres can be distinguished in the urethral smooth muscle layer. A spiral orientation of the inner circular smooth muscle layer was noticed by von Hayek [4]. Proximally, the urethral smooth muscles are continuous with the muscle bundles of the bladder neck. Distally, urethral smooth muscle fibres terminate in the subcutaneous tissue surrounding the external urethral meatus.
Anatomical studies have shown that the female urethra is a much more sophisticated system than was previously thought. In 1979, Huisman published his study on morfology of the female urethra [5]. This study suggests that the longitudinal muscular layer of the detrusor muscle does not extend into the dorsal wall of the urethra. Other studies however concluded that the longitudinal muscular layer of the urethra is formed by extension of the inner detrusor muscle and that the semi-circular musculature of the urethra is an extension of the outer detrusor muscle layer [6,7]. This hypothesis is supported by others on basis of embryological studies [8].
The rhabdosphincter is circularly oriented with its thickest part in the middle third section of the

urethra. It is composed of both fast- and slow-twitch myofibers, with the slow-switch fibres dominating [9]. According to Gosling however, all myofibers of the rhabdosphincter are of the slow-twitch variety [10]. Rhabdosphincter fibres are therefore able to exert tone upon the urethral lumen over a prolonged period. The urethral sphincter fibres (rhabdosphincter) are anatomically separate from the adjacent periurethral straited muscle of the anterior pelvic floor. In the third middle section, the straited muscle fibres do completely surround the urethra [1]. Cranially, rhabdosphincter fibres extend to the level of the bladder neck while caudally; the rhabdosphincter is attached to the lateral vaginal wall [11].

Innervation of urethra and bladder

After years of extensive anatomical studies, even nowadays there is still debate on the innervation of the human pelvic floor. Only few anatomical studies were performed. Even a straightforward approach to determine the origin of a peripheral nerve, leads to a variety of conclusions. Especially, this is true for the pudendal nerve, the pelvic plexus and for the innervation of the external urethral sphincter [12]. All these structures are of major importance for pelvic floor function and control. For optimal control on pelvic floor function and micturition several organs and systems, from 'top' (brain) to 'bottom' (bladder and urethra), have to cooperate in a strict and decent way to ensure normal function of the lower urinary tract, including the autonomic nervous system (sympatic and parasympatic nerves) and somatic nervous system. Striated musculature of the pelvic floor, including the urethra, is innervated by the somatic pudendal nerve.

Brain

Cerebellum, basal ganglia, limbic system, thalamus and hypothalamus are all involved in the control of micturition. The brain stem controls external urethral sphincter and detrusor tone [13]. Stimulation of the M-region in the dorsolateral pons, also called pontine micturition center or Barrington's nucleus [14] produce detrusor contraction while bilateral destruction leads to chronic urinary retention [15]. Located more laterally in the dorsolateral pontine tegmentum is an area called the L-region. This area sends fibres to the nucleus of Onuf in the sacral cord, and is involved in motor innervation of the pelvic floor, including anal and external urethral sphincters. Electrical stimulation of the L-region leads to contraction of pelvic floor and urethral sphincter [14], bilateral lesions produce 'urge' urinary incontinence [15]. The M-region can be considered as micturition control center while the L-region is in control of storage of urine. Afferents in the pelvic nerves send sensory information with regard to bladder filling to sensory neurons in caudal lumbar and sacral spinal cord. This information enters the Peri Aqueductal Gray (PAG) that stimulates the M-region. Micturition starts by inhibition of the urethral sphincter tone and activation of the detrusor muscle by sacral parasympatic neurons [16].

Spinal Center

The spinal center is the connexion between afferent and efferent pathways. In Onuf's nucleus in the anterior horn of S2-S4, somatic efferents are located [17]. Th11-L2 in the spinal cord is the location of the sympatic neurons, parasympatic neurons are located in S2-S4 [18].

Innervation of bladder and urethra

Parasympatic and sympatic afferent nerves of stimuli from the bladder wall proceed towards the spinal cord by the pelvic nerve, consisting of small myelinated A-δ and unmyelinated C-fibres [19]. A-δ fibres detect bladder distension, C-fibres transfer bladder sensations like pain and temperature to the myelum. A-α fibres can be activated by sacral nerve stimulation while the threshold of A-δ and C-fibres is too high to achieve proper stimulating effects. The role of sympatic nerve afferents is still under investigation but they probably pass nociceptive information to the spinal cord.

Sacral nerves mainly consist of neurons originating from the sacral anterior horn. Fine radiculi of myelinated and unmyelinated axons leave the spinal cord both dorsal and ventral to constitute radiculi. The ventral radiculi fuse to form the radi and after passing the sacral foramen S1-S4, the rami enter the pelvic floor. Sympatic branches and efferent parasympatic neurons join these rami. Sacral nerves also contain afferent neurons, connected to the spinal cord by dorsal rami. Information from the pelvic floor, and the bladder including for instance bladder filling, is transferred to the spinal cord by these afferent neurons. Sacral nerves form the sacral plexus, with both afferent and efferent nerve fibres [12]. The inner smooth muscle layer, orientated along the length of the urethra, is parasympatic innervated by the pelvic nerve while the mainly circulary orientated outer smooth muscle layer is innervated by the sympatic hypogastric nerve. The striated muscle layer receives its nerve fibres from the somatic branches of S2 and S3.

Both the autonomic nervous system (parasympatic and sympatic nerves), and the somatic nervous system are involved in controlling the lower urinary tract. Knowledge on these pathways is mainly based on animal studies and so far, consensus has not been established. Innervation and longitudinal orientation of the majority of the muscle fibres suggest that urethral smooth muscle in the female may be active during micturition, serving to shorten and widen the urethral lumen [1].

The external intrinsic urethral sphincter (the straited rhabdosphincter around the membranous urethra) and external extrinsic urethral sphincter, formed by the musculi levator ani and transversus perinei muscles (pelvic floor), receive their innervation through somatic nerve components that emanate from S2 and primarily S3 [20].

Function of the lower urinary tract

Both bladder and urethra form a functional unit. The bladder functions as a reservoir while the urethra is the outlet. There has to be a close relation in working mechanism for proper voiding behaviour. The outmost layer of the urethra, formed by the straited circular muscle is also known as straited sphincter or rhabdosphincter. Most important function of this straited muscle is to achieve increase of urethral pressure during physical stress, thus leading to continence. Almost 70% of the external urethral sphincter pressure derives from neural impulses from the S3 ventral root (m. levator ani en rhabdosphincter), the other 30% is contributed by S2 (pudendal nerve) [20]. Pelvic floor muscles are involved in the closing mechanisme of the female urethra. Training of pelvic floor muscles does diminish genuine stress incontinence.

From a functional point of view, it is necessary for the pressure in the urinary bladder to exceed the closing pressure within the urethral lumen during voiding. Normally, a fall in urethral pressure precedes a rise in pressure in the bladder lumen by active contraction of the smooth muscle detrusor. In case of unvoluntary contraction of the detrusor muscle, the pressure in the lumen of the urinary bladder may exceed that in the lumen of the urethra, thus resulting in undemand loss of urine. This complaint of involuntary leakage may be accompanied by or preceded by urgency and is now defined as urge urinary incontinence [21].
During bladder filling, somatic and sympatic arc reflexes are activated to promote continence [22]. Tension receptors in the bladder wall transport information concerning bladder filling by the afferent sympatic pelvic nerve. The efferent limb of the sympatic reflex travels within the nervus hypogastricus. This results in an increase in urethral smooth muscle tone and relaxation of the bladder wall [23]. The somatic reflex is conveyed in the pudendal nerve and leads to contraction of the external striated muscle urethral sphincter. If there is only small filling of the bladder, one is unconscious of this guarding reflex. If bladder filling increases, the spinal guarding pathway is transferred to a supraspinal mechanism, the pontine micturition centre, leading to a desire to void. If this reflex pathway is blocked, i.e. in patients with a complete spinal cord injury, this may lead to detrusor-sphincter dyssynergie [24]. Activation of this guarding reflexes may well be achieved by sacral neuromodulation, leading to a larger bladder capacity and increased First Sensation of Filling, seen in patients who respond well on the therapy [25]. This mechanism may also influence urethral pressure variations and diminished urethral instability [26].

'Detrusor overactivity'

Well accepted nowadays is the urodynamic observation of unstable detrusor contractions during filling cystometry. According to the International Continence Society committee on standardisation of terminology in 1988, the "unstable detrusor" is "one that is shown objectively to contract, spontaneously or on provocation, during the filling phase while the patient is attempting to inhibit micturition" [27]. In 2002, the ICS changed the definitions of detrusor function during filling cystometry. "Detrusor overactivity" (DO) is now defined as an urodynamic observation characterised by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked. Idiopathic DO replaces "detrusor instability" when there is no defined cause [21]. The urodynamic finding of DO is recorded on filling cystometry. Filling velocity is mostly 50 ml/minute, although several groups prefer 25 ml/minute for a more physiologic recording. Diuresis cystometry is advocated by van Venrooij and may increase the observation of DO [28]. However, cystometric results should be read with caution since involuntary detrusor contractions can be missed or provoked. About 30% of anamnestic urge cannot be confirmed on traditional cystometry [29]. Therefore, some investigators advice natural filling of the bladder during an ambulant urodynamic registration [30]. Although far from standard, ambulant cystometric recordings can help to explain lower urinary tract symptoms in patients where conventional cystometry did not show abnormalities [31]. The diagnosis DO may be twice as high compared to traditional cystometry [32]. However, ambulatory urodynamics has some important drawbacks and recordings should be read with precaution.

The importance of urodynamically observed idiopathic DO is still debated. Most important reason for this is lack of correlation between clinical success of a treatment modality and urodynamic recordings. Furthermore, DO is found in males and females without any micturition complaints. Also, in patients with severe lower urinary tract symptoms, often DO cannot be found on cystometry. A rise in detrusor pressure of 15 cm water is mostly considered as sign of an involuntary detrusor contraction. Other thresholds have been used as well. Several studies tried to correlate urodynamically observed bladder function with lower urinary tract symptoms [33,34]. No evident correlations were found in voiding symptoms of several groups of patients compared to their cystometric recordings. Therefore, the diagnosis of idiopathic DO cannot be made clinically but is a strictly urodynamic one.

An attempt to define urethral instability based on our experiences

At the urology department of the Leiden University Medical Center, Leiden, The Netherlands, filling cytometry in females is performed with the MMS UD-2000 (Medical Measurement Systems, Enschede, the Netherlands) and a Gaeltec CTU/2E/L-4 12F (Gaeltec Ltd, Dunvegan, Isle of Skye, Scotland) catheter with 3 urethral sensors and 1 bladder sensor. Space between each urethral sensor is 7 mm; distance between bladder pressure sensor and mid urethral pressure sensor is 50 mm. The mid urethral pressure sensor is positioned at the maximum urethral pressure. Urethral and detrusor function are monitored, both during filling and voiding. Three urethral sensors are necessary to rule out artefacts due to movements of the catheter in the urethra during filling. Pressure changes caused by movement of the catheter will give a shift in recorded pressures. Only pressure changes that occur on all 3 urethral sensors are considered relevant, because these are caused by pressure changes in the major part of the urethra itself. We define URI when urethral pressure variations of more than 15 cm water are observed in all three urethral recordings. We have the impression that classification into 'minor' urethral pressure changes (16-30 cm water) and 'major' (>31 cm water) may be important for clinical practice. Slow periodical urethral pressure variations with durations of more than 10 seconds and with low amplitude, are considered as normal. The impact of presence or absence of DO for defining URI remains controversial in literature. We do not consider the presence or absence of DO of importance to define URI. Review of the literature did not reveal clear understanding whether sphincter EMG recording is necessary for diagnosing URI. Therefore, we do not take EMG recordings into consideration for the diagnosis of URI. Most studies on urethral pressure variations during filling cystometry use only one urethral sensor. We measure urethral pressure variations with 3 urethral pressure sensors to rule out artefacts. The use of only one urethral pressure sensor may give incorrect recordings and result in a false prevalence for the presence of 'truly' URI. In order to achieve optimal localisation of the pressure sensors in the urethra, at least one sensor has to be positioned at the site of the maximum urethral pressure. In the minority of cases it is impossible, as a result of urethral anatomy, to obtain urethral registration with all 3 sensors.

Figure 1 shows the urodynamic recording of both urethral and detrusor behaviour during filling cystometry. Urethral pressure variations are clearly visible on all three urethral pressure recordings. Concomitant DO is not present in this female patient with symptoms of an OAB.

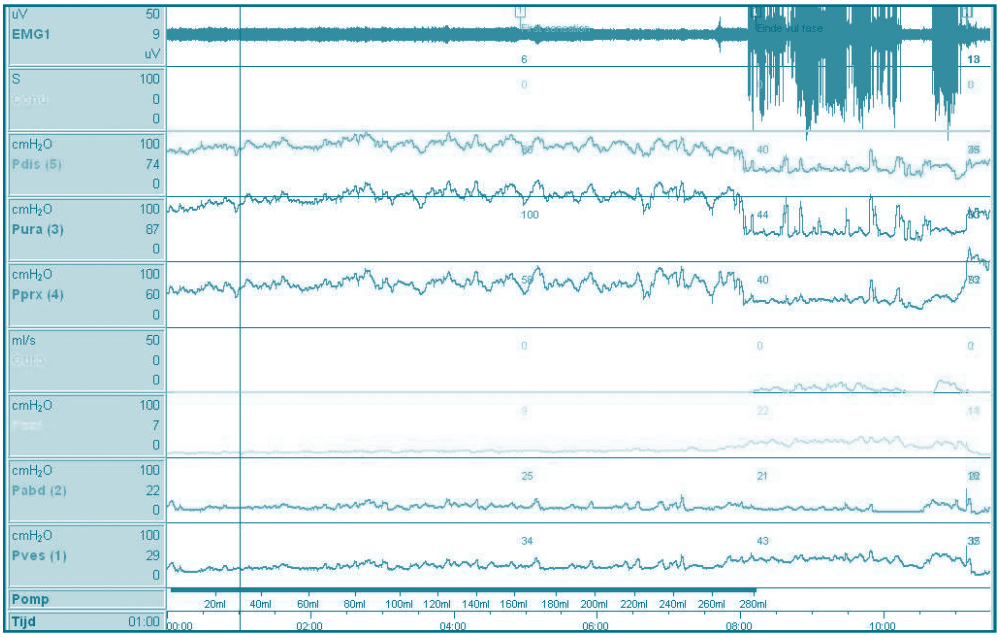

Figure 1: Urethral pressure changes are present in all three urethral pressure measurements. The finding is defined as major URI, exceding an amplitude of more than 30 cm water.

Only when urethral pressure variations are seen on all three urethral pressure recordings, we define the observation as URI. In this patient therefore, with urethral pressure changes only in the proximal and mid urethral sensor, the observation is not defined as URI. If only one urethral pressure sensor would have been used in the same patient, the observation might well be named URI *(figure 2)*.

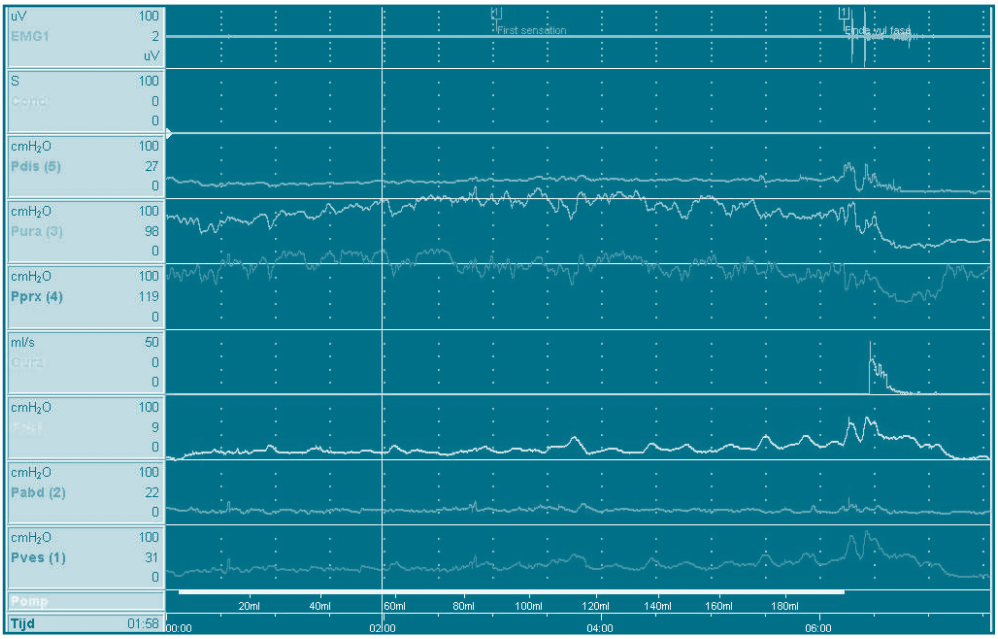

Figure 2: Urethral pressure variations are only seen in 2 urethral recordings. This observation is not defined as URI.

A clear drop in urethral pressure together with a non-physiological early FSF at 60 ml is demonstrated seen in *figure 3*. With continuing filling, following FSF (a sensory parameter indicated by the patient), more pronounced URI is observed. In this patient, DO is also present. Figure 3 illustrates clearly that drops in urethral pressure are synchronic with rises in detrusor pressure. In *figure 4*, the FSF and a drop in urethral pressure is observed, together with an involuntary rise in detrusor pressure, indicating DO. During the filling phase further on, urethral pressure variations are seen without concomitant DO.

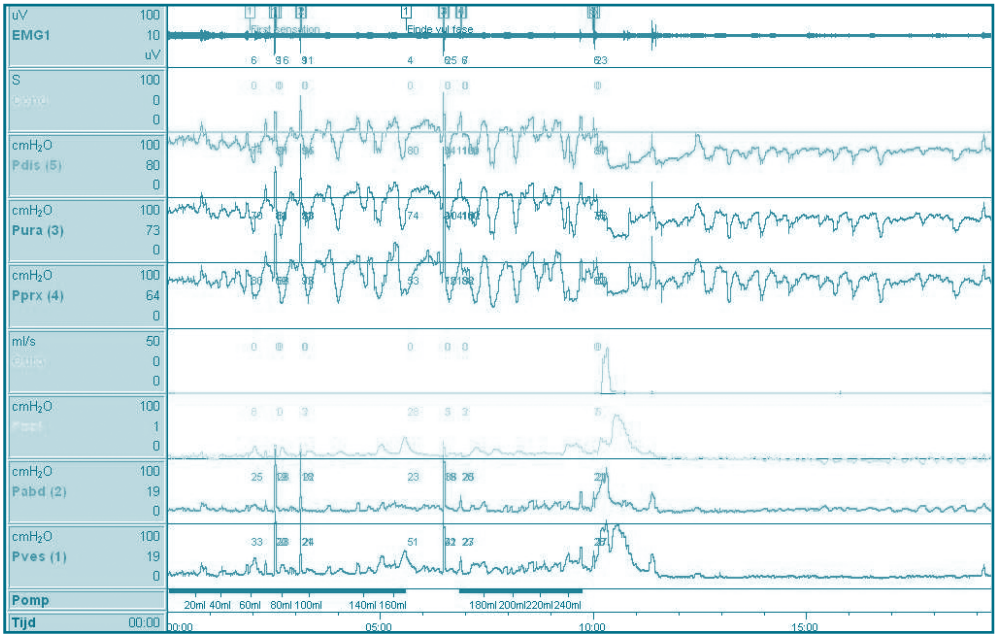

Figure 3: A pathological low First Sensation of Filling is seen at the start of major urethral pressure changes. In this patient detrusor overactivity is also present throughout the filling phase.

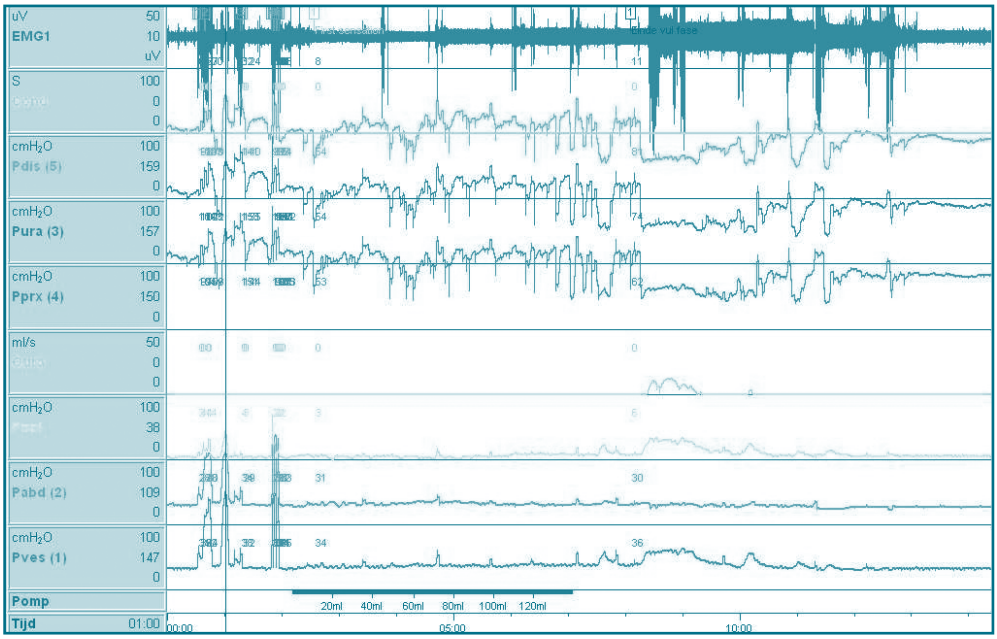

Figure 4: In figure 4, the First Sensation of Filling and a drop in urethral pressure is observed at 15 ml of bladderfilling, together with an involuntary rise in detrusor pressure, indicating detrusor overactivity. During the filling phase urethral pressure changes are seen without concomitant detrusor overactivity.

References

1. Gosling JA. Structure of the lower urinary tract and pelvic floor. Clin Obstet Gyn 1985; 12(2): 285-294
2. Elbadawi A. Neuromuscular mechanisms of micturition. Neurourology and urodynamics. Principles and practice. New York: Macmillan; 1988: 3-36
3. Sullivan MP and Yalla SV. Phyiology of female micturition. Urol Clin N Am 2002; 29: 499-514
4. von Hayek H. Die weibliche Harnrohre. Handbuch der Urologie I: 314-324. Springer Verlag 1969
5. Huisman AB. Morfologie van de vrouwelijke urethra. Thesis, Groningen, The Netherlands, 1979
6. Tanagho EA, Smith DR. The anatomy and function of the bladderneck. Br J Urol 1966; 38: 54-71
7. Tanagho EA, Smith DR. Mechanism of urinary incontinence. Embryologic anatomic and pathologic considerations. J Urol 1968; 100: 640-646
8. Gosling J. Gross anatomy of the urinary tract. Incontinence. United Kingdom: Health Publication Ltd.; 1999, 23-53
9. Elbadawi A, Mathews R, Light JK et al. Immunohistochemical and ultrastructural study of rhabdosphincter component of the prostatic capsule. J Urol 1997; 158: 1819-1828
10. Gosling JA, Dixon JS, Critchley HOD, and Thompson SA. A comparative study of the human external sphincter and periurethral levator ani muscles. Br J Urol 1981; 53: 35-41
11. Elbadawi A. Functional anatomy of the organs of micturition. Urol Clin N Am 1996; 23: 177-210
12. Marani E. The Pelvis, another view. Twente university press 2002
13. Blaivas JG. The neurophysiology of micturition: a clinical study of 550 patients. J Urol 1982; 127(5): 958-963
14. Holstege G, Griffiths D, de Wall H. Dalm E. Anatomical and physiological observations on supraspinal control of the bladder and urethral sphincter muscles in the cat. J Comp Neurol 1986; 250: 449-461
15. Griffiths D, Holstege G, Dalm E, de Wall H. Control and coordination of bladder and urethral function in the brainstem of the cat. Neurourol Urodyn 1990;9:63-82
16. Blok BF, Holstege G. Direct projections from the periaquaductal gray to the pontine micturition center (M-region). An anterograde and retrograde tracing study in the cat. Neuroscience Letter 1994; 166(1): 93-96
17. Holstege G. Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: an HRP and autoradiographic tracing study in the cat. J Comp Neurol 1987; 260: 98-126
18. Schnitzlein H et al. A study of the parasympatic nucleus, J Comp Neurol 163; 120: 477-481
19. Hulsebosch C, Coggeshall R. An analysis of the axon populations in the nerves to the pelvic viscera in the rat. J Comp Neurol 1982; 211(1): 1-10
20. Juenemann K, Lue TF, Schmidt FA and Tanagho EA. Clinical significance of sacral and pudendal nerve anatomy. J Urol 1988; 139: 74-80
21. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al: The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21: 167-178
22. de Groat WC, Steers WD. Autonomic regulations of the urinary bladder and sexual organs. In: Loewy AD, Spyer KM, editors. Central regulations of autonomic functions. Oxford: Oxford University Press; 1990, 310-333
23. Garrett JR, Howard ER, Jones W. The internal anal sphincter in the cat; a study of nervous mechanisms affecting tone and reflux activity. J Physiol 1974; 243(1): 153-166
24. Park JM, Bloom DA, McGuire EJ. The guarding reflex revisited. Br J Urol 1997; 80(6): 940-945
25. Latini JM, Alipour M, Kreder Jr KJ. Efficacy of sacral neuromodulation for symptomatic treatment of refractory urinary urge incontinence. Urology 2006; 67(3): 550-553

26. Groenendijk PM, Heesakkers JPFA, Lycklama à Nijeholt AAB. Urethral instability and Sacral Nerve Stimulation: a better parameter to predict the efficacy? J Urol 2007; 178: 568-572
27. Abrams P, Blavais JG, Stanson SL and Andersen JT. The standardization of terminology of lower urinary tract function. Scan J Urol Nephrol 1988; Suppl 114: 5-19
28. van Venrooij GE, Boon TA. Extensive urodynamic investigation: interaction among diuresis, detrusor instability, urethral relaxation, incontinence and complaints in women with a history of urge incontinence. J Urol 1994; 152: 1535-1538
29. Vereecken RL. A critical view on the value of urodynamics in non-neurogenic incontinence in women. Int Urogynecol J 2000; 11: 188-195
30. Radley SC, Rosario DJ, Chapple CR, Farkas AG. Conventional and ambulatory urodynamic findings in women with symptoms suggestive of bladder overactivity. J Urol 2001; 166(6): 2253-2258
31. Swithinbank LV, James M, Shepherd A, Abrams P. Role of ambulatory urodynamic monitoring in clinical urological practice. Neurol Urodyn 1999; 18: 215-222
32. Porru D, Usai E. Standard and extramural ambulatory urodynamic investigation for the diagnosis of detrusor instability correlated incontinence and micturition disorders. Neurourol Urodyn 1994; 13: 237-242
33. Cardozo LD and Staton SL. Genuine stress incontinence and detrusor instability-a review of 200 patients. Br J Obstet Gynaecol 1980; 87: 184-190
34. Kirschner-Hermanns R, Scherr PA, Branch LG, Wetle T, Resnick NM. Accuracy of survey questions for geriatric urinary incontinence. J Urol 1998; 159: 1903-1908