Urethral function in overactive bladder syndrome

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CHAPTER 8

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

GENERAL DISCUSSION

The aim of thesis was to elucidate the role of urethral function in overactive bladder syndrome (OAB). In the last decade, there has been more awareness that the underlying cause of OAB does not necessarily have to come from the bladder, but could lie within the urethra as well. The knowledge about various influencers on afferent signalling from the bladder has increased, especially by reports on the active role of the urothelium in afferent signalling.

At the annual conference of the EAU in 2019, an expert panel explained that the pipeline for drug therapy for treatment of OAB in the near future is empty and that there especially is a great need to improve efficiency in treating urgency and nocturia. With this assumption that no new treatment modalities will be introduced in the foreseeable future, the existing treatment options will therefore have to be used more efficiently, to achieve better clinical outcome. In other words, if this very heterogeneous group of patients could be further divided by analogy of the underlying cause, proposals for targeted therapy will be easier to define.

With this assumption and the knowledge that Groenendijk et al demonstrated in the past that URI was a better predictor of success for treatment with sacral neuromodulation in patients with OAB[3], we wanted to elucidate the phenomenon of urethral pressure variations (UPV) or urethral instability (URI). If the detrusor muscle can fail to adapt and relax in storage phase, it is plausible that its antagonist, the smooth urinary sphincter and or the striated urethral sphincter may fail to maintain contracted.

One of our assumptions was that if there can be an active role from the urothelium in the bladder, the urothelium and the stratified squamous epithelium in the urethra could have an active role as well. In the past, studies to urethral closure function in female patients concluded that the sympathetic nerve system dominates in regard to maintaining the tonus in the urethra[18, 19]. Nowadays, with a sympathomimetic in the form of a selective β3 receptor (ADRB3) agonist available in drug therapeutic options for patients with OAB, it is important to know what the targets are in the urethra. If ADRB3 is present in the urethra, this could have consequences for the urethral pressure. We demonstrated for the first time expression of ADRB3 in the epithelial layer of the female urethra. The expression of ADBR3 is present in almost the entire length of the urethra, with the highest level in the mid-urethra. No direct connection between

ADRB3 and nerve endings was observed, suggesting the existence of an extra afferent signaling pathway originating in the epithelial layer of the urethra.

By conducting a systematic review, we aimed to define a clear working definition for URI, to use for our clinical studies. Unfortunately, the generalizability of the performed studies was limited because the very heterogeneous and poorly defined patient populations and measurement methods. In the past, opponents have set aside URI as movement artefacts. The closed urethra in storage phase has no lumen, so current techniques applied for intravesical or abdominal pressure measurement are probably imperfect to measure the physics of urethral closure. On the other hand, abdominal pressure measurement is often performed with a vaginal sensor and the vagina has no closed lumen either. In the studies performed with multiple urethral pressure sensors, all sensors registered UPV simultaneously, which argues against an artefact as the cause of these findings.

In the past, Venema and Kramer described results of urodynamics in patients with and without urethral instability[9]. During the urethral pressure measurement in the filling phase, both urethral and anal electromyography (EMG) were performed simultaneously by the use of a thin intramuscular needle sensor. Urethral pressure measurement was performed with three urethral sensors. In this measurements, UPV were seen in all leads. A striking difference was seen in urethral EMG in patients with URI and without URI. In normal cystometry was seen that at the start of voiding phase, both anal and urethral EMG demonstrated relaxation, followed by a gradual relaxation of the urethral pressure and a gradual increase in detrusor pressure until urinary flow initiated (Figure 8.1). In patients with UPV, a sudden stop in the EMG occured during the filling phase, followed by a rapid drop in urethral pressure (Figure 8.2). If a pattern of rapid successive pressure variations was observed, changes in urethral EMG were seen simultaneously (Figure 8.3). This argues against a movement artefact as well.

We then conducted a prospective study to determine if and to what extend the use of a multi-sensor urethral catheter contributes in demonstrating UPV. If measurement with a single urethral sensor catheter is as sensitive as a multi-sensor urethral catheter, the applicability will be greater in daily practice. We demonstrated that despite the use of a relatively high cut-off value for the definition of UPV, the prevalence still was 37% and therefore much more common than the prevalence

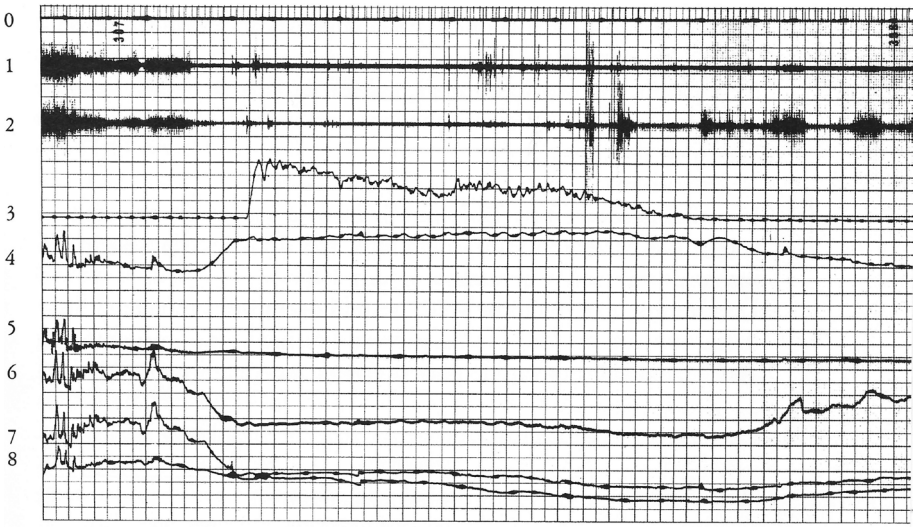

Figure 8.1* Example of normal cystometry 0. Time-scale (seconds) 1. Urethral EMG 2. Anal EMG 3.flowmetry 4. Intravesical pressure 5. Abdominal pressure 6-8 urethral pressure

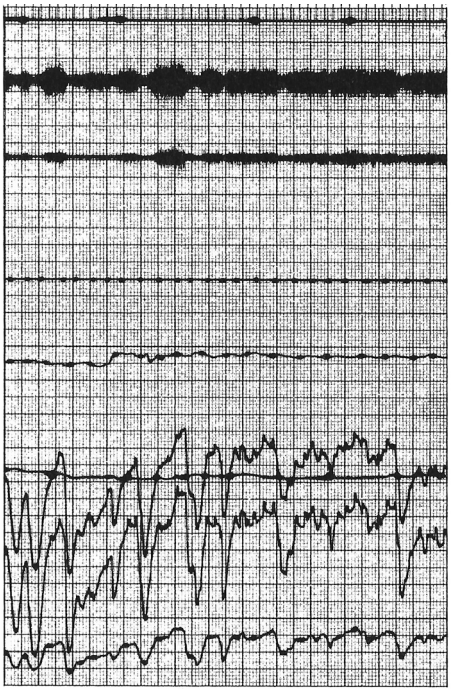

Figure 8.2* Sudden drop in urethral pressure

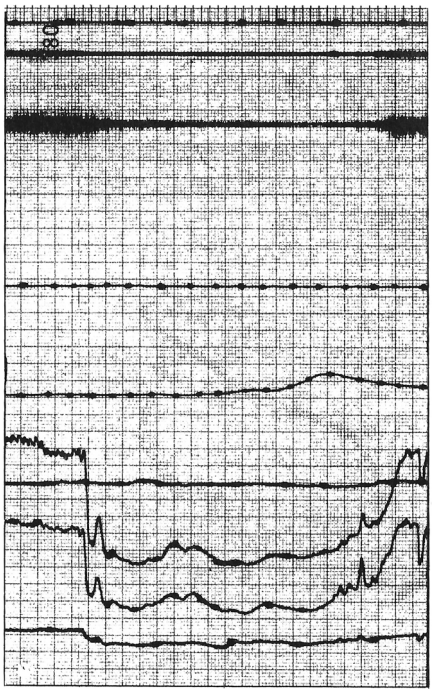

Figure 8.3* Rapid urethral pressure variations

* From P.L. Venema, clinical importance of the unstable urethra in females

of DO. If UPV was demonstrated, it was visible in all urethral sensor derivations. We found that there is additional value in measurement with triple urethral sensor catheter for the demonstration of UPV during filling cystometry. Opponents of UPV in the past have argued that UPV is a physiological phenomenon prior to the voiding reflex in DO or as a result of voluntary holding to suppress the desire to void [8, 12, 13]. If you assume that the rapid decrease in urethral pressure is caused by a sudden inhibition in the sympathetic system, but compensated via the somatic system by contraction of the external sphincter, the opponents are partly right. However, the fact that the sudden pressure drops occur, is not explained by this.

Now that we demonstrated expression of ADRB3 in the urethra, the next question was whether and to what extent urethral pressure is influenced by the ADRB3-agonist mirabegron. To date, Vecchiolo Scaldazza and Morosetti have reported the only study with urodynamic results of treatment with mirabegron in 60 patients with OAB [18]. Urodynamic parameters as first, normal and strong desire and continuous urethral pressure measurement were not mentioned and/or performed in this study. In line with our study to the additional value of using a multi-sensor urethral catheter in demonstrating UPV, we demonstrated that UPV is a more common urodynamic phenomenon than detrusor overactivity with an incidence of one third in female patients at presentation with OAB. In this study, urethral pressure measurements were performed with a single urethral sensor catheter, so the prevalence could be underestimated. An important finding of this study is that patients with UPV have a different response to mirabegron than patients with the same clinical symptoms without UPV. Treatment with mirabegron had a significant effect on all sensation parameters and the difference between maximal and minimal urethral pressure decreased significantly in the UPV-group.

This fits in the above-mentioned hypothesis that urethral pressure drops occur when a sudden inhibition in the sympathetic system (hypogastric nerve) occurs. Because of this inhibition, the contraction of bladder outlet is no longer maintained. If the sympathetic system is subsequently stimulated with the ADRB3 agonist with demonstrated target receptor in the urethra, the urethral pressure can recover.

Finally, a pilot study was performed to determine whether local chemical denervation by subtrigonal botulinum toxin-A injections in patients with UPV, result in a relief of symptoms. If assumed that the feeling of imminent micturition has its origins in the urethra[11], intervening in

afferent sensory input from the urethra could have a positive effect on OAB symptoms of patients. This pilot study was performed in four patients with a long history of refractory idiopathic OAB and in one patient with painful bladder syndrome. After treatment with subtrigonal botulinum toxin-A injections, UPV were still present in post-treatment urodynamic evaluation, but with an decreased amplitude of variations. Treatment was successful in 4 of 5 patients. The largest improvement was in the urodynamic sensation marker first sensation of filling.

CONCLUSIONS AND FUTURE PERSPECTIVE

UPV is a more common urodynamic phenomenon than DO within the described cohort of OAB-patients in this thesis. The demonstration of UPV is best performed by the use of a multi-sensor urethral catheter. UPV appears to be an underlying cause or expression marker of sensory urgency complaints in the studies we performed and it improved significantly in treatment with ADRB3 receptor agonist and in treatment with local (subtrigonal) Botulinum toxin-A injections. Patients with OAB and UPV differ from patients without UPV in their response to same medical treatment. This makes an important contribution to improving targeted therapy in patients with OAB. Future research will have to test these findings in a larger prospective population. Further anatomical research will also have to be carried out to further explore the afferent signalling routes and thus explore further possibilities of targeted local treatment options. The ICS should reintroduce UPV in its terminology to enable standardized research.

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