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Detecting Urinary Bladder Contractions: Methods and Devices

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Abstract

In patients suffering from neurogenic detrusor overactivity, continence can be regained by conditional stimulation of the dorsal genital nerve (DGN); that is applying electrical stimulation to the DGN at the onset of an involuntary contraction. For this scheme to work, a sensor capable of reliably detecting the onset of bladder contractions is needed. This article reviews the methods proposed for or associated with detection of bladder contractions, and their applicability to onset detection is assessed. Fourteen methods are described in this review; bladder pressure, urethral sphincter EMG and anal sphincter EMG are the most promising options for onset detection. For all three modalities, however, further research is needed before clinical application becomes viable.

Keywords

Urinary Bladder, Contraction Onset, Chronic Implantable Interface

1. Introduction

The central nervous system plays a vital role in the storage and periodical release of urine. Control of the bladder is complex and distributed, and involves both autonomic and somatic neural circuits located in the brain, pons, spinal cord and peripheral ganglia [1].

Most patients with lesions to the central nervous system, e.g. disorders such as spinal cord injury, multiple sclerosis, Parkinson's disease and similar, develop neurogenic detrusor overactivity (NDO) [2]. Many of these patients also develop detrusor-sphincter-dyssynergia (DSD), which is the concurrent contraction of the detrusor and the urethral sphincters [3]. Despite this antagonistic action, patients with both NDO and DSD may suffer from incontinence episodes. For patients, to whom control of voiding is among their highest priorities [4], incontinence episodes have a severe negative impact on quality of life. However, from a clinical perspective the

high transient pressures are more relevant, as these may cause vesico-ureteral reflux, which ultimately can lead to renal failure [5].

There are both medical (first line treatment) and surgical treatment options available for NDO. However, medical treatment is often insufficient, while surgical treatment has high complication rates, is irreversible, and often used as a last resort. A new and promising treatment option is electrical stimulation of the dorsal genital nerve. Stimulation leads to rapid abolishment of nascent contractions, and this effect is obtained using either continuous or conditional stimulation [6] [7]. Conditional stimulation offers a number of advantages over continuous stimulation. Firstly, it was shown that maximal cystometric capacity was larger when compared to continuous stimulation [8]. In addition, as stimulation is only applied when needed, charge injection is reduced; prolonging electrode life, and the risk of habituation of the reflex loop is reduced as well. For a fully implanted system, battery life is also prolonged. Finally, and perhaps most importantly, a warning signal can be given at the time of the first suppressed contraction, alarming the patient that it is time to empty the bladder when convenient.

In order to realize a neural prosthesis based on conditional stimulation, a sensor capable of detecting the onset of a bladder contraction is needed. Since the application is merely to detect onset of contractions, the requirements to the signal are quite relaxed. Given a pressure sensor as example, it is not necessary to measure exact intravesical pressure. A sensor that has slow baseline drift and that overshoots on contractions may still be able to detect the onset of contractions. However, the bladder undergoes constant filling cycles, and is placed between the pelvic floor muscles and the bowels. Thus, the sensor or method must be tolerant of movement artifacts, and the signal must be separable from the background noise.

This review aims to give an overview of methods proposed in the literature. Advantages and drawbacks of each method are presented, along with current challenges. The methods treated are the following: bladder EMG, anal sphincter EMG, urethral sphincter EMG, sacral root ENG, pelvic nerve ENG, pudendal nerve ENG, pressure based sensors, detrusor blood flow, detrusor oxygen tension, near-infrared spectroscopy, skin potentials, bladder sounds, morphology changes and self-triggered stimulation.

2. Methods for Detecting Bladder Contractions

2.1. Bladder EMG

In striated muscle, contractions occur as a result of membrane depolarization, causing calcium release from the sarcoplasmic reticulum. The resulting EMG can be measured both on the skin surface and intramuscularly using e.g. needle electrodes. Often, the obtained EMG is used to determine the onset of muscle contractions.

If the approach of measuring EMG could be applied to the detrusor muscle, this would be the most obvious method of determining the onset of detrusor contractions. Unfortunately, measuring detrusor EMG is not straight forward. Firstly, the detrusor consists of smooth muscle, yielding a much attenuated signal compared to striated muscle. Secondly, it is now believed that the detrusor cell membranes do not depolarize during contractions in healthy humans.

The first reports of bladder EMG appeared more than half a century ago, and are attributed to Corey *et al.* [9] [10]. It was later shown that signals, similar to those obtained by Corey *et al.*, could be obtained by applying pressure to the electrode, or by small tissue movement [11]. This led to a general accept that the reported bladder EMG was artifact.

Until a study published by Ballaro *et al.* in 2001 [12], there were no generally accepted records of true bladder EMG. Ballaro *et al.* devised a novel technique involving a Pt/PtCl suction electrode applied to the serosal surface of the whole excised bladder of a guinea pig. In this study, intravesical pressure and EMG was recorded; bladder contractions were generated by electrical stimulation applied using a circumferential electrode placed on the base of the bladder. They showed that the signal was 1) completely abolished by tetrodotoxin, 2) sensitive to changes in the extracellular $CaCl_2$ concentration, 3) was abolished by purinergic neuromuscular blockade, and 4) was not abolished by cholinergic blockade.

The line of argumentation for the signals being true detrusor EMG is as follows. 1) This is evidence that the signal is not stimulation artifact. 2) Supports that the signal is of biological origin and not electromechanical artifact. There is (other) evidence that in guinea pigs the membrane depolarization is mediated primarily by purinergic transmission [7] [8], whereas in humans, cholinergic transmission is the major excitatory mechanism [13]. Combined, 3) and 4) supports this, and is further evidence of the biological nature of the signal in this guinea pig model.

As also outlined by Ballaro *et al.* [12], the current view on bladder EMG is that in healthy persons, contraction is mediated by cholinergic transmission [14]. There is some evidence that in pathological conditions, purinergic transmission emerges, or has emerged [15] [16]. However, the evidence is indirect, and is still debated [17]. In guinea pigs, cholinergic and purinergic neurotransmission coexist. It was shown, that cholinergic activation does not cause membrane depolarization [18] [19], but that purinergic activation does [20]. By analogy, it is hypothesized that in pathological states, emerged purinergic activation causes membrane depolarization also in humans. Thus, measurement of bladder EMG may be theoretically possible in patients with NDO, but not in healthy persons.

Given that this hypothesis is true, and given an implantable system capable of measuring bladder EMG, it might be used to control stimulation in a conditional stimulation scheme. However, the presence of the signal needs to be verified in situ, and a chronically stable implantable electrode and recording system needs to be devised.

2.2. Anal Sphincter EMG

In the absence of bladder EMG, it has been suggested to use either the urethral sphincter EMG or the anal sphincter EMG as a proxy of that signal.

Most patients with NDO show either a synergic or dyssynergic response to involuntary detrusor contractions. A synergic response reduces the tone of the entire pelvic floor, including the anal sphincter, during contractions. A dyssynergic response increases the tone of the pelvic floor, during contractions. In either case, a change in the amplitude of the anal sphincter EMG can be expected as a result.

In a study by Wenzel *et al.* [21], acute experiments in cats were conducted, and retrospective analysis of human data was performed. For the acute experiments 9 cats were used. Wire electrodes were placed in the external anal sphincter (EAS). A transurethral catheter was used to occlude the urethra, and used for artificial filling of the bladder. A second fluid-filled catheter was inserted into the bladder through the bladder wall, and connected to a pressure transducer. The bladder was slowly filled until distention evoked reflexive bladder contractions occurred.

In six cats a dyssynergic response was observed; a synergic in the remaining three. From these groups, 1.333 and 293 contractions were recorded, respectively. In the dyssynergic group, 202 false negatives and 547 false positives were identified, and a mean pressure increase at detection of 15.7 ± 13.8 cmH$_2$O. For the synergic group, there were 17 false negatives and 336 false positives, and a mean pressure increase at detection of 4.4 ± 8.9 cmH$_2$O.

The analysis of human data was based on cystometrograms of 41 patients with spinal cord injury and NDO. The time since injury ranged from 1 to 25 years. The average baseline pressure was 11 ± 7 cmH$_2$O and the average pressure during contractions was 66 ± 30 cmH$_2$O based on 92 contractions. The patients were divided into 3 groups, based on the ratio of EMG activity during contractions and the EMG activity during the intercontraction interval. A ratio greater than one was defined as a dyssynergic response (n = 25), a ratio less than one a synergic response (n = 5), and a ratio equal to one meant a non-modulating sphincter (n = 11). Using data from the synergic and dyssynergic groups, 12 and 52 contractions were analyzed, respectively. In the synergic group there were no false negatives, but 40 false positives. In the dyssynergic group, there were 9 false negatives and 66 false positives.

In summary, more false positives than true positives were detected in three of the four analyzed groups. Only in one group was the sensitivity higher than 95%, but in this group the specificity was as low as 23%. The fact that these results are obtained under ideal conditions in the lab, suggests that improvements in recording or signal processing are required to use EAS EMG as a reliable trigger for conditional stimulation.

Another study was done by Craggs *et al.* on a small group of SCI patients [22] [23]. A device was placed in the anal canal, and included both recording and stimulation electrodes, connected to circuitry for closed loop control of stimulation. Stimulation was triggered based on an EMG envelope threshold value, and was delivered as trans-rectal bilateral stimulation of the mixed pudendal nerves. 12 male SCI patients were initially included in the study, of which 6 were found to possibly be able to benefit from the system (4 did not show NDO, 2 showed no or adverse effects). In these patients, cystometries were performed with the system. During these six cystometries, 52 true positive and 14 false positive contractions were detected. On average, that is 8.7 ± 5.1 true positive and 2.3 ± 2.1 false positive detections over a period of 26 ± 9.5 min [24]. There were no reports of false

negative detections (missed contractions). With the system, there was a mean increase in bladder capacity from 115 ml to 386 ml; continence was achieved in all 6 patients. Studies of the performance of the device in activities of daily living were planned, but no further reports about the system are known to the authors. Further, there seems to be some inconsistencies in the publication ([24]) particularly regarding the number of true positives, so caution in interpreting the numbers is warranted. However, if the system proves to function as well as stated above during normal activities of daily living, it seems to be a relatively simple yet feasible treatment option.

2.3. Urethral Sphincter EMG

Based on similar principles as using EAS EMG to detect bladder contractions, it was proposed by Hansen *et al.* to use external urethral sphincter EMG (EUS EMG) [25]. Wire electrodes were placed in the EUS for EMG recording. Vesical and rectal pressures were obtained, and the detrusor pressure computed as $P_{det} = P_{ves} - P_{abd}$. 23 patients were enrolled in the study, of which 9 had NDO with DSD and EUS modulation during contractions. In these 9 patients two classification schemes were applied, a simple threshold and a kurtosis-based algorithm. The mean pressure at onset detection was 2.2 ± 2.6 and 3.2 ± 3.4 cmH$_2$O, for method 1 and 2, respectively. The number of false positives were 14.8 ± 12.8 and 0.8 ± 0.8, respectively. Thus, method 2 performs much better than method 1, albeit it is a bit slower. Still, if the 0.8 ± 0.8 false positive detections can be extrapolated to a conditional stimulation system, a rate of almost one false positive detection for each true positive detection seems too high. In this study conditional stimulation was not applied; hence only one detrusor contraction was recorded for each subject.

A similar study was conducted by Opisso *et al.* [26]. The same kurtosis-based algorithm was used, but it was applied online to control a stimulator connected to surface electrodes placed near the dorsal genital nerve. 12 subjects were enrolled, of which ten had NDO with DSD. In one of the ten subjects, EMG controlled stimulation failed. In the remaining nine subjects, a bladder capacity increase of 84% was seen. In the ten filling cystometries with stimulation enabled, 34 contractions were registered; 30 of these could be suppressed by conditional stimulation. One was not detected, and two occurred after filling had ceased at an end volume of 400 ml. False positives occurred in two of the ten patients. Five occurred in the patient where the actual contraction was missed, and four in another patient. Thus, for each cystometry a mean of 3 ± 3 contractions were suppressed, and 1 ± 2 false positive detections occurred. While the performance of this system seems somewhat below that using EAS EMG, it also seems to be a feasible approach to pursue. The robustness of this system, however, also needs to be verified against the test of normal activities of daily living.

2.4. Sacral Root and Pelvic Nerve ENG

Studies in cats have shown that increased firing rates of bladder afferents occur in response to both bladder distention and bladder contractions [27] [28]. These afferents are believed to run through the pelvic nerve, and enter the spinal cord at the S2 and S3 level. As a consequence, onset detection based on both sacral root ENG and pelvic nerve ENG has been investigated in animals and humans.

A study with pigs was conducted by Jezernik *et al.*, to investigate the feasibility of using whole nerve recordings of bladder afferents to detect bladder contractions [29]. 10 female pigs were used for the study; bladder pressure was recorded by a microtipcatheter, and rectal pressure by a perfused catheter. Cuff electrodes were placed on the preganglionic pelvic nerve, and on the S2 and S3 sacral roots.

The artificial stimuli that were examined were slow bladder filling (to explore volume monitoring), fast bladder filling (to simulate pressure increases similar to contractions), manually applying pressure to the bladder (to simulate contractions). In addition, small spontaneous detrusor contractions were observed. In response to both fast filling and manual application of pressure to the bladder, increases in pelvic nerve and S3 ENG could be seen. The responses were primarily phasic in nature, which is desired for detecting contractions. Small spontaneous contractions with amplitude of 3 cmH$_2$O and a period of approximately 50 s were observed in three pigs. During these contractions, clear responses were seen in the pelvic nerve ENG (2 pigs) or the S3 ENG (1 pig). The low SNR of the "raw" ENG signals, and the poor repeatability of the results are identified as the two main problems by the authors. In summary, this option does not seem feasible given the current recording techniques, due to the very low SNR and selectivity.

A similar experimental setup was used in cats by Jezernik, Grill and Sinkjaer [30]. Bladder and rectal pressures were monitored, and cuff electrodes were placed on the the extradural S1 and S2 roots in 6 cats (in one cat

also on the intradural ventral and dorsal S1 roots). Slow saline infusion was initiated and maintained until the distention evoked contractions began to occur. ENG was recorded during filling, and during at least 5 bladder contractions. In addition, ENG was recorded during rapid injections at different volumes. Bladder contractions could be evoked in 5 cats.

In all cats, there was a strong correlation between bladder pressure and rectified averaged S1 ENG. Automatic detection of bladder contractions was explored using two algorithms. One was a threshold applied directly to the rectified averaged ENG; the other applied the CUSUM algorithm to the ENG and then a threshold. Contractions could be detected using the simple threshold, but this also resulted in several false positives. Using the CUSUM algorithm, 29 of 30 contractions were detected, with only one false positive. Time of detection was 6 ± 8 s (range 0.2 to 42 s) and pressure increase at time of detection was 9 ± 8 cmH$_2$O (range 0.3 to 29.5 cmH$_2$O). During rapid saline injections, a similar strong correlation between bladder pressure and rectified averaged ENG was seen. Several measures were taken to determine if the recorded activity was efferent or afferent, e.g. cutting the nerve proximal to the cuff electrode. All observations indicate that the activity was indeed afferent, presumably from tension receptors in the bladder.

Kurstjens *et al.* measured sacral root ENG in 6 human subjects who underwent implantation of an extradural FineTech-Brindley system [31] [32]. Since the patients were under general anesthesia, it was only possible to record responses to different artificial stimuli. The following stimuli were applied: electrical stimulation of the dorsal penile/clitoral nerve, mechanical stimulation of the relevant sacral dermatome, rectal distention using a rectal balloon, bladder filling using transurethral catheter and bladder contractions evoked by electrical stimulation of the contralateral sacral root.

The strongest response was due to mechanical stimulation of the dermatome. Responses to rectal distention were small, and mainly phasic. Bladder filling was done by 50 ml bolus injections. Typically, the was no response during the first 7 injections, thereafter a peak was seen in the ENG during injection, and the increasing bladder pressure (35 to 105 cmH$_2$O) resulted in a tonic ENG response. Maximum attained SNR was between 0.3 and 0.5 in all patients, depending on infused volume. Regarding bladder stimulation, the pressure response was generally an increase of 60 cmH$_2$O, that decreased almost linearly to 40 cmH$_2$O during a 30 s period. ENG increased significantly just after stimulation was turned off (amplifier was saturated during stimulation), and this response showed an approximate exponential decrease during the following 10 s, until baseline was reached. SNR in the three patients where contralateral sacral root stimulation was applied was 0.47 ± 0.27.

The authors conclude that although "the phasic nature of nerve responses favors the application of detecting bladder contractions… improvements in recording quality and more sophisticated signal processing methods are needed to reliably detect bladder contractions in a chronic application."

2.5. Pudendal Nerve ENG

Wenzel *et al.* investigated whether bladder contraction onset could be detected from the pudendal nerve ENG in 8 cats [33]. They used a setup which was also later used to study EAS EMG [21]. A transurethral catheter was used to occlude the urethra, and used for artificial filling of the bladder. A second fluid-filled catheter was inserted into the bladder through the bladder wall, and connected to a pressure transducer. The bladder was slowly filled until distention evoked reflexive bladder contractions occurred. The pudendal nerve was accessed through a lateral approach, and a tripolar cuff electrode (contact distance 5 mm) was placed either on the whole nerve trunk (n = 3) or distal to the urethral sensory branch (n = 5). A total of 781 contractions and 757 baseline intervals were recorded across the 8 cats. Data was split in a calibration and a validation set, and three different algorithms were applied to detect contractions. These were a constant threshold algorithm, a dynamic threshold algorithm, and the CUSUM algorithm. The cost function for setting the trigger level included number of false negatives, detection delay, pressure increase at detection, and number of false positives is a 4:2:2:1 weighting. The best results were obtained using the CUSUM algorithm. Using this, the calibration sensitivity was 98% with a specificity of 68%; in the corresponding validation, a sensitivity of 82% with a specificity of 60% was obtained. Taking the very small amplitude of these signals, the validation sensitivity of 82% and the specificity of 60% into account, this method does not seem viable for use in a system to treat incontinence.

2.6. Pressure Based Sensors

The first experiments using pressure sensors to monitor the urinary bladder were conducted by Brindley [34]. A

fluid-filled capsule was sewn onto the bladder wall, such than it invaginated the bladder. No results from this experiment have been published. Nearly a decade later, a similar study was conducted by Brindley and Donaldson [35]. The pressure measurement system was completely mechanical. Two fluid-filled capsules were placed back to back, and sewn onto the bladder wall. If the pressure of the sensor facing the bladder lumen exceeded the pressure of the sensor facing the abdominal cavity, a switch would turn on and trigger electrical stimulation of the pudendal nerve. The system was implanted in 4 patients, and initially worked as intended. However, in all four patients the pressure sensors became detached from the bladder in less than one year [36].

In a study concerned more with ambulatory monitoring of bladder pressure than controlling a neuroprosthesis, Takayama *et al.* implanted catheter-tip pressure sensors in 5 dogs [37]. The catheter tip was placed between the detrusor and the urothelium. The catheter was tunneled subcutaneously to the neck of the dog, from where it was connected to an external control box and recorder. The left external jugular vein was cannulated with an 8F tube; the other end was tunneled subcutaneously to the neck, similarly to the catheter. Experiments were performed from the 7th to the 64th day after surgery. To provoke spontaneous urination, 500 ml of 5% glucose and 20 mg frusemide were injected through the tube. Recordings were done without the use of anesthesia, the only restraint on the dog being a leash. Recordings were performed during various physiological states, e.g. respiration, postural changes, coughing, defecation and urination. The recorded pressures were higher than expected, with tail-shaking resulting in increases of 60 to 100 cmH$_2$O, coughing resulting in 25 to 75 cmH$_2$O increases (n = 17) and voiding resulting in 44 to 257 cmH$_2$O increases (n = 28). Because of the high pressures recorded, sensors from two dogs were explanted and placed in a water gauge, where correct pressure readings were verified. The duration of the experiments was not sufficiently long to show permanent chronic stability.

Acknowledging the problems of sensor detachment experienced by Brindley and Donaldson, Koldewijn *et al.* investigated chronic implantation of pressure sensors in an animal model. Experiments were performed in 12 goats, divided into two groups. Group 1 consisted of eight goats, and each goat was implanted with three sensors: one was sewn intra-abdominally on the peritoneum of the bladder dome (A), one was positioned in a pouch between the muscular layer and the peritoneum (B), and one was positioned in a pouch between the bladder and the vesicovaginal septum (C). In four goats, vicryl (absorbable) sutures were used, and in four goats prolene (non-absorbable) sutures were used. Group 2 consisted of four goats, all of which had three sensors implanted between the urothelium and the detrusor. The goats of group 2 were sacrificed after 12 months. At this time, two goats had one sensor in place and two sensors missing; in the other two goats all sensors were missing. In group 1, there was more variation. Sensors at position A and C were detached at time of sacrifice after 12 months. This was also the case for sensors at position B anchored with vicryl sutures. However, three of four sensors at position B and anchored with prolene sutures stayed in place for as long as 25 months. One was missing in one of the two goats sacrificed after 12 months, and both were in place in the two goats sacrificed after 25 months. Based on this, it was concluded that it is feasible to implant pressure sensors in the bladder wall. The authors suggest placing the sensors in a pouch between the muscular layer and the peritoneum, and to use non-absorbable suture material for anchoring the implant.

In order to investigate whether sensors placed in the bladder wall could be used to trigger conditional stimulation, Melgaard and Rijkhoff conducted a study with pigs [38]. An implantable sensor was made for this purpose. The sensor was based on a resistive sensing die, and was considerably smaller than the mechanical sensors used by Brindley [35] and Koldewijn [36] (13 mm in diameter and 2 mm thick, compared to 30 mm in diameter and 3 mm thick). Experiments were performed in 6 pigs, where sensors were placed in pouches in the middle of the detrusor. Several pouch locations were examined, as was orienting the membrane both towards and away from the bladder lumen. Bladder contractions were evoked by unilateral stimulation of the pelvic nerve. In total, 114 recordings were made from 70 contractions (two sensors were placed at once during several contractions). It was found that when the sensing membrane faced away from the bladder lumen, contractions could not be detected reliably. However, with the membrane facing the lumen, 96 of 102 contractions were detected by an automatic detection algorithm. The 6 missed contractions were in two pigs with three occurring in each. In both pigs the sensor was placed in a pouch near the bladder base, where surgical access was restricted, and correct placement of the sensor was difficult. Since the contractions were evoked by electrical stimulation, it was not possible to assess the specificity. In conclusion, it is feasible to use a pressure sensor placed in the bladder wall to detect contractions. However, chronic studies are needed to verify that the sensor stays in place, and to assess the sensitivity and specificity during physiological conditions.

2.7. Detrusor Blood Flow Changes

Laser Doppler Flowmetry (LDF) is a method where a laser beam is directed at a volume of tissue. Movement within the volume of the tissue, typically movement of red blood cells, will cause a shift in frequency of the reflected and scattered light, proportional to the speed of the moving particles. This is known as the Doppler Effect.

Blood flow changes during the micturition cycle were investigated by Greenland and Brading [39]. Previous to this study, there was conflicting evidence of the effects of bladder filling on blood flow, and no studies were performed in conscious subjects. Greenland and Brading used a pig model, consisting of 7 pigs all subjected to chronically implanted vascular access, urodynamic catheters, and an intramural laser Doppler probe. LDF does not give an absolute value of blood flow, but is able to show any flow changes not perpendicular to the laser beam.

Minimal sedation of the pigs was used, and bladder contractions were evoked by distention due to artificial filling. The authors chose 4 epochs from each filling and compared these to each other. The first epoch is 30 s immediately before filling is started, then 30 s immediately before the voiding contraction, an epoch covering the voiding contraction is its full duration (not fixed time), and a 5 s epoch centered around peak pressure. Pre-filling pressure was 2.5 ± 0.5 cmH$_2$O (mean $\pm$ SD), and blood flow was normalized to 100. Prevoid pressure was 4.1 ± 0.4 cmH$_2$O, and blood flow was 96.3 ± 2.5. Average pressure of the entire contractions was 18.6 ± 1.3 cmH$_2$O, with peak pressure 21.9 ± 1.1 cmH$_2$O. Average blood flow during the entire contractions was 50.2 ± 2.3, and during the period of peak pressure is was 37.9 ± 2.1.

The purpose of the study was not to control a conditional stimulator, rather it was to develop a model that could be used to investigate the changes in blood flow during normal micturition cycles and in various disease states.

Since there is no data on the delay of the blood flow decrease with respect to the detrusor pressure, it is not possible to judge the potential for using the technique to detect the onset of bladder contractions. However, from the relatively small standard deviations of the prevoid blood flow, it seems plausible that the technique could be used. However, a stable long-term chronic interface is still needed. The authors' state that is was possible to perform measurements for up to 3 weeks, they did not note the reason for this limit. It may well have been vascular access that set this limit, but this is only speculation.

2.8. Detrusor Blood O$_2$ Changes

In a comprehensive study, Azadzoi *et al.* measured arterial blood flow, systemic blood pressure, detrusor blood flow and detrusor O$_2$ tension in an acute animal model [40]. 18 male mongrel dogs were used. The internal iliac artery was exposed, the caudal gluteal branch identified and ligated, and a perivascular flow sensor was placed around the artery. The pelvic and hypogastric nerves were exposed, and electrodes were placed in turn on each of them. Intravesical pressure was measured via a catheter placed through a cystotomy in the bladder dome. Bladder blood flow was measured by laser Doppler flowmetry using a probe placed in the detrusor muscle; oxygen tension was measured with a polarographic oxygen sensing electrode contained in a 20-gauge needle placed directly in the detrusor muscle. Responses to both passive filling and contractions induced by electrical stimulation of the pelvic nerve were measured. Responses to electrical stimulation of the hypogastric nerve were also measured. In addition, responses to some spontaneous contractions were recorded. Finally, a ligation of the bladder neck was used to investigate all the same parameters in an obstructed model. The obstructed model may mimic patients with DSD best.

Following pelvic nerve stimulation, intravesical pressure was slightly higher in the obstructed model (46 ± 8 mmHg) compared to the unobstructed model (38 ± 3 mmHg). In both models, wall perfusion and oxygen tension decreased, with the largest decreases in the unobstructed model. Oxygen tension was $74\% \pm 3\%$ and $58\% \pm 8\%$, for the obstructed and unobstructed model, respectively. Blood flow was $58\% \pm 5\%$ and $48\% \pm 5\%$, respectively. However, the rate at which the signals changed was different. The decrease in perfusion occurred in a manner similar to an exponential decay, and could be detected after 5 to 10 s. Oxygen tension changed much more slowly and linearly, and maximal decay occurred after 20 to 80 s relative to intravesical pressure. The slowly changing nature of this signal makes it infeasible as means for detecting bladder contractions.

During spontaneous bladder contractions, the situation was different. In the obstructed model, intravesical pressure was similar to stimulated contractions, 42 ± 5 mmHg. In the unobstructed model, however, pressure remained relatively low (17 ± 2 mmHg), reportedly due to leakage during the contractions. In the obstructed

model, oxygen tension decreased to 74% ± 6%, and blood flow decreased to 58% ± 5%. In the unobstructed model, oxygen tension fell to 86% ± 6% of precontraction value, while blood flow increased to 161% ± 11% of baseline.

The discrepancy in intravesical pressure between spontaneous and stimulated contractions in the unobstructed model was not explained, and neither was the inverse relation between oxygen tension and wall perfusion in the two conditions.

Opposite the study of Greenland and Brading [39], an increase in blood flow was reported during spontaneous bladder contractions. Additional studies are required to reveal the true nature of this signal. In both studies a delay of approximately 10 s relative to intravesical pressure was reported. This delay makes it questionable if blood flow signal can be used to trigger conditional stimulation, independent of whether an increase or decrease occurs. Changes in oxygen tension occur too slowly for the signal to be feasible as a trigger for conditional stimulation.

2.9. Near-Infrared Spectroscopy

Near-Infrared Spectroscopy (NIRS) measures the amount of so-called tissue chromophores such as oxyhemoglobin and deoxyhemoglobin. Thus, a change in blood perfusion or blood O_2 levels can be detected using this technique. It is a noninvasive technique, and the wavelength used is able to penetrate some centimeters into the body. Like other noninvasive measurement techniques, the exact spatial selectivity is difficult to determine exactly.

In a prospective cohort study, Farag *et al.* investigated whether NIRS could accurately and reproducibly be used to detect detrusor overactivity (DO) episodes [41]. Note that the aim of the study was to detect DO episodes, not the contraction onset. 41 patients with OAB symptoms underwent cystometry. They were diagnosed by aurodynamicist and divided into two groups, one with 18 control subjects not having DO, and one with 23 patients having DO. Cystometry was repeated for all subjects, but this time with concurrent NIRS. After excluding 29 curves because of motion artifacts, this resulted in 34 control curves, and 34 DO curves, all containing both cystometry and NIRS signals. The cystometry and NIRS curves were separated and anonymized, and subsequently evaluated by three experienced urodynamicists. All curves were evaluated at two sessions with 3 weeks in between. In the 6 review sessions of the 34 signals, 2 DO episodes were missed when using the cystometrogram; there were 16 false positives (n = 204). Using NIRS, 30 DO episodes were missed and there were 67 false positives.

In another paper by the group it is mentioned that deflection in the NIRS signal was delayed by a median of 3 s (n = 14) [42]. Only in one case did the NIRS deflection precede DO, in four cases it was delayed by more than 10 s. Although this was only a small pilot study, this speaks against using NIRS to detect contractions.

Given the current technology, the signal does not seem suited for triggering conditional stimulation. In the study, where NIRS was recorded under optimal conditions, 13 out of 47 recordings (28%) were dismissed due to motion artifacts, and in the remaining "good" recordings, there was no deviation in the signal during 15% of DO episodes. Adding to this the varying temporal relationship with intravesical pressure, NIRS may be a viable option to detect detrusor contractions in select patients, but does not seem suited as a general reliable trigger for conditional stimulation.

2.10. Skin Potential Changes

Skin potentials (SP) are one specific type of signals in a group of signals collectively termed electrodermal activity (EDA). It is a potential generated by sweat glands during the production of sweat, although there is no established relation between the magnitudes of the SP and the amount of sweat. To investigate autonomic mechanisms associated with bladder contractions, Prévinaire *et al.* recorded skin potentials from 32 SCI patients [43]. 29 had complete lesions, while 3 were incomplete. The authors looked at SPs below and above the level of the lesion. In all 29 patients with complete lesion, SPs were elicited below the lesion concurrently with reflex bladder contractions. In the 3 patients with incomplete lesions, no SP responses were observed during bladder contraction. Above the level of lesion, no SP responses were seen during bladder contractions in either group. The authors also measured SPs from 2 healthy subjects during cystometry. Here the timing was reversed; during baseline and filling, large SPs were seen, but during micturition there were no SP responses.

While SP responses were seen in all 29 patients with complete lesions, there was no fixed temporal relation

between the contraction and the response. In some patients SPs were elicited at the onset of contraction, in others during the course of the contraction, and in some only at the peak of the contraction. Despite SPs were elicited in all patients with complete SCI, this signal source does not seem suitable for use as a trigger for conditional neuromodulation. In the patients where SPs are elicited concurrently with detrusor contractions, it might be feasible. However, the use of surface electrodes are prone to noise and movement artifacts, and maintaining a good low-impedance electrode contact for a full day every day could pose a problem. Also, the applicability is limited to patients with complete SCI, and hence other systems are still desired.

2.11. Bladder Sounds

It has been hypothesized that since sound is pressure waves, bladder "sounds" could be used to detect the onset of contractions [44]. The idea is that by using an implantable microphone (the difference towards an ordinary pressure sensor being unclear), bladder sounds may be recorded. The patent application goes further and suggests placing the microphone in the bladder wall, and using it to control an implanted stimulator for stimulating e.g. the pudendal nerve.

The application contains only schematic diagrams of the system, neither experimental data demonstrating the feasibility nor examples of bladder sounds.

2.12. Capacitive "Flexor"

An anatomical sensor consisting of "Flexor's" was proposed in a patent by the company Urovid [45]. Flexors are variable capacitors, consisting of two intertwined spring-like structures (similar to the structure of DNA). The shorter the assembly is, the closer the spring windings are, and the larger the capacity is (similarly to moving two capacitor plates closer together). Conversely, when the assembly is stretched, the capacity decreases. Two methods of monitoring the bladder, both employing flexors, are proposed in the patent application. The first method is to sew a flexor across the bladder dome. During filling the volume can be estimated by the slowly decreasing capacity of the flexor. During contractions a transient increase in capacity is believed to be present. The second method is to make a cage of flexors and wrap it around the bladder. Volume could then be monitored by the gradual lengthening of the flexors. During contractions the bladder is believed to obtain a more spherical form than when relaxed. This would cause some flexors to lengthen and others to shorten, enabling a method for detection of contractions as well.

The rather rigid and invasive nature of the system is, however, likely to cause damage to the bladder. The flexors would be prone to both migration and encapsulation that would decrease their mechanical response.

2.13. Patient Controlled Stimulation

In the absence of a sensor capable of detecting the onset of bladder contractions, two studies have investigated whether patient reported bladder sensation could be used to control a neuroprosthesis. Opisso et al. compared automatic and patient controlled stimulation cystometries in 33 patients [46]. In 16 of the 33 patients automatic stimulation was applied successfully, but these had no sensation and could not perform patient controlled stimulation. In the remaining 17 patients, patient controlled stimulation worked as well as automatic stimulation, although a mean delay of 5.7 s compared to automatic stimulation was noted. Martens et al. performed conventional and ambulatory (using a portable device) urodynamics in 26 patients, but did not apply any stimulation [47]. In conventional cystometries, detection rate based on patient sensation was 73%, while it was only 23% during ambulatory urodynamics. Further, the mean detection delays were 16 s and 57 s, respectively. The low sensitivity and long delay during ambulatory urodynamics is hypothesized to be due to the lack of "penalty" for missed contractions. Still, contradictory conclusions were reached in the two studies. Opisso et al. concluded that patient controlled stimulation is feasible is select patients, although they recommend training of these patients. Martens et al. conclude that bladder sensation is not a suitable trigger for conditional stimulation. In select patient groups with preserved well-defined sensation, this could be a solution, although drawbacks such as the delay and the requirement for user interaction may limit the use.

3. Discussion

Despite demonstrating feasibility in acute or even chronic settings, none of the methods or devices described in

this review appear in clinical practice. The explanations differ between each group of methods.

Generally, ENG signals have small amplitudes, and employing currently existing recording techniques yield poor signal-to-noise ratio. Cuff electrodes used for obtaining pudendal nerve or sacral root ENG is a good example of this. Cuff electrodes provide a stable chronic nerve interface, but by the nature of the cuff, only whole nerve recordings can be made. It is very difficult to distinguish the bladder related activity from non-bladder related activity in the mixed pudendal or sacral nerves. Adding to this difficulty is that the mechanoreceptors of the bladder are innervated by small myelinated (Aδ) or unmyelinated (C) fibers, while the cutaneous mechanoreceptors are innervated by larger myelinated (Aβ) fibers. One way to improve SNR from the small fibers is to use velocity-selective recording. This can be achieved by placing a multi-ring cuff, and sample the rings at intervals corresponding to the desired propagation velocity. However, this requires a long cuff, which can only be implanted on the dorsal sacral roots. This makes the surgical procedure both difficult and very invasive.

It is likely, although it has not been shown, that bladder EMG can be recorded in pathological conditions such as NDO [48]. However, bladder EMG has very small amplitude, and since recording requires the use of suction electrodes [12], is not likely to appear as part of in an implantable system.

Most promising within the group of naturally occurring signals seems to be urethral or anal sphincter EMG, which show adequate signal, but, using current detection algorithms, also show a large number of false positive detections. Provided that the intramuscular electrode interface is chronically stable, improvements in detection algorithms may enable the clinical use of such systems.

Koldewijn *et al.* [36] showed that the precise anatomical position of implanted devices in the bladder may be crucial in determining the chronic success or failure of the implant. Even large sensors ($2.5 \times 2.3 \times 0.3$ cm) connected by relatively rigid tubes were shown to stay in place for as long as 25 months, provided the optimal position and suture. This shows the feasibility of sensors that are implanted in or around the bladder. Melgaard and Rijkhoff showed that using the signal obtained from a pressure sensor placed in the bladder wall is feasible for controlling a conditional neuroprosthesis [38]. Further research is necessary to verify the chronic stability of such implants, and to investigate the performance of implanted sensors in chronic settings.

Common for the techniques using blood-related parameters (blood pressure, arterial blood flow, detrusor blood flow (including the NIRS technique) or detrusor oxygen tension) is that the response is delayed at least 5 - 20 seconds compared to contraction onset [40]. No studies have investigated whether the signals were timely enough to automatically control a stimulator unit. The few examples shown of the temporal relation between the signals indicate that the delay of these signals is too large for automatic control (e.g., it took 10 s before bladder wall perfusion had decreased from 33 ml/min/100g tissue to 28 ml/min/100g tissue. During this period intravesical pressure increased from 4 cmH$_2$O to 29 cmH$_2$O. Manual readings from graph in [40]). The detrusor pressure will most likely have increased to undesired levels at the time a contraction can be unambiguously detected from these signals.

4. Conclusion

In conclusion, the most promising techniques seem to be urethral or anal sphincter EMG, or intravesical pressure. These signals have a good SNR; the challenge is to make a chronically stable interface, and to some extent improve detection algorithm specificity.

Acknowledgements

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