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Conditional Electrical Stimulation in Animal and Human Models for Neurogenic Bladder: Working Toward a Neuroprosthesis

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Abstract

Sacral neuromodulation has had a tremendous impact on the treatment of urinary incontinence and lower urinary tract symptoms for patients with neurologic conditions. This stimulation does not use real-time data from the body or input from the patient. Incorporating this is the goal of those pursuing a neuroprosthesis to enhance bladder function for these patients. Investigators have demonstrated the effectiveness of conditional (also called closed-loop) feedback in animal models as well as limited human studies. Dorsal genital nerve, pudendal nerve, S3 afferent nerve roots, S1 and S2 ganglia have all been used as targets for stimulation. Most of these have also been used as sources of afferent nerve information using sophisticated nerve electrode arrays and filtering algorithms to detect significant bladder events and even to estimate the fullness of the bladder. There are problems with afferent nerve sensing, however. Some of these include sensor migration and low signal to noise ratios. Implantable pressure sensors have also been investigated that have their own unique challenges, such as erosion and sensor drift. As technology improves, an intelligent neuroprosthesis with the ability to sense significant bladder events and stimulate as needed will evolve.

Keywords

Sacral Neuromodulation; Neurogenic Bladder; Neuroprosthesis; Urinary Incontinence

Introduction - Why does this matter?

Urinary incontinence affects an estimated 200 million people worldwide [1], at a total annual cost of US $19.5 billion in 2000 in the United States alone [2]. Neurologic disease contributes to a significant amount of this. It significantly decreases the quality of life in those it affects. For decades research has brought advances in diagnosis and treatment, consisting of dietary modification, oral medication, and neuromodulation, the most common interventions. Despite these advances, a significant number of patients remain frustrated by the lack of improvement in the symptoms that prompted them to seek care in the first place.

Compliance with Ethics Guidelines: ***Human and Animal Rights and Informed Consent***: This article does not contain any studies with human or animal subjects performed by the author.

Significant advances have been achieved with regard to treating neurogenic bladder, with the mainstay consisting of Clean Intermittent Catheterization (CIC) and anticholinergic medication to improve continence and decrease resting bladder pressures. The death rate from sepsis after a spinal cord injury at one time was 82 times higher than expected based on age-matched controls [3]. High pressures in the bladder are thought to contribute to damage to the urinary system, renal failure, and incontinence [4]. Detrusor sphincter dyssynergia and detrusor overactivity can lead to a high pressure situation. Because of advances in the management of the urinary tract after spinal cord injury, urologic problems are no longer the leading cause of death after spinal cord injury [5]. In fact, mortality in the first 2 years after spinal cord injury has declined by 40%. Despite this success, further improvements in quality of life and longer term survival remain elusive [6].

Early experience with sacral neuromodulation for those with neurogenic bladder was disappointing, with one early series noting a loss of benefit over a follow up of 54 months in all but 1 of 12 patients [7]. Since then, techniques and technology have changed, and now multiple authors have demonstrated that neuromodulation is effective in treating neurogenic bladders [8-11]. All of these trials, however, employ continuous, or in some cases intermittent stimulation that does not take real time data or patient-driven input into account. Taking patient data into consideration to modulate therapy is known as “closed-loop feedback” and has a long history of success in the field of cardiac pacemakers. The cardiac pacemaker was the first electrical stimulator to enjoy widespread implantation in the human body. Significant improvements were achieved in cardiac pacing when devices became responsive to real-time data from the heart, making therapies such as implantable cardiac defibrillation possible [12]. This “closed-loop feedback”, also called conditional stimulation, does not currently exist for the bladder and carries significant promise.

There are many reasons that closed loop feedback has not yet been successfully achieved in the bladder for treatment of urinary incontinence and neurogenic bladder disease. The first and most important is that current sacral neuromodulation therapy has achieved reasonable long term success of 81-98% for neurogenic lower urinary tract symptoms (LUTS), and it continues to improve[9, 13]. There remains room for improvement, however. Closed loop feedback carries many technical challenges, such as how to sense a significant bladder event, how to determine the best target for electrical stimulation, and how to stimulate it. One might even ask if the increased complexity truly improves outcomes.

Background

Understanding prior work helps to inform contemporary investigators so they can avoid duplicating past failures and build on past accomplishments.

Brindley Finetech Stimulator

Introduced in 1978 for patients with neurogenic voiding dysfunction due to complete spinal cord injury, the Brindley stimulator has enjoyed moderate success at a limited number of centers. The continence comes from the surgical rhizotomy of the dorsal root of the sacral nerves and the ability to void comes from stimulation of the anterior roots of S2, S3, and S4

(known as Sacral Anterior Root Stimulation, SARS) using a surgically implanted cuff electrode. The most recent report on the Brindley stimulator was from the Netherlands. When compared with matched spinal cord injured controls, 53% of the 46 patients who responded reported urinary continence, compared with 14% of 28 patients who did not undergo the procedure. 37% of those with the stimulator reported they no longer used it for volitional voiding, but 33% of them still enjoyed improved continence secondary to the rhizotomy. Those still using it reported significantly higher quality of life scores [14]. This stimulator did not use closed loop feedback, but since the user pressed a button to void it does incorporate on-demand patient input effectively, and can serve as a model for future devices.

Does Closed-Loop Feedback improve outcomes over continuous stimulation?

The earliest appearance of this in the literature involved on-demand penile squeeze or anal dilation, which appeared effective at suppressing detrusor overactivity in the majority of patients in the 1980s, and serves as the basis for some pelvic floor muscle exercises [15]. Still, it not surprising investigators continue to seek an alternative method to improve continence.

Early efforts to compare closed-loop feedback directly to continuous stimulation involved cats anesthetized with alpha-chloralose. Investigators found that stimulating the pudendal nerve after a bladder “event” increased bladder capacity to 38mL, compared to 33mL when stimulated continuously ($p=0.027$), and 28mL with no stimulation. A bladder contraction “event” was triggered by a recording of the contralateral pudendal nerve using a cuff electrode. A bladder event was defined using a mathematical algorithm and could be achieved autonomously, making the technique appealing for an implantable device. Using the pudendal nerve electroneurogram as a trigger, however, reduced the reliability of the technique, as 2 of the 6 cats tested did not exhibit a bladder “event” despite obvious leakage from the urethra [16]. In responders, this effectively increased the bladder capacity by 36% and decreased the stimulation time (saving power) by 67%.

The fact that alpha-chloralose was used may be significant because it has been noted to cause irritability in the bladder and may decrease the inhibitory effects of neurostimulation [17].

Closed loop feedback has also been tested in humans with spinal cord injury, demonstrating some improvements in bladder capacity and compliance when compared with continuous (conventional) stimulation (173mL increase in capacity vs. 230mL). The dorsal penile nerve was stimulated in 6 men with complete spinal cord injury and the bladder ‘event’ to trigger stimulation was a 10cm H2O rise in detrusor pressure during urodynamic study. These men were compared with 6 other men who underwent urodynamic evaluation with continuous penile nerve stimulation, which also reduced Overactivity, but this difference failed to achieve statistical significance [18].

A very similar experiment compared continuous as well as conditional stimulation to lack of stimulation of the dorsal genital nerve in 9 spinal cord injured patients and found that although maximum cystometric capacity increased by 63cc and 74cc respectively, the difference between continuous and conditional stimulation was insignificant [19]. Stimulation in this trial was automatic, triggered on a fixed rise in bladder pressure by 8-12cmH2O. These two are the only human trials thusfar investigating conditional stimulation, and only involved the dorsal genital nerve and spinal cord injury.

Recently this concept has also been demonstrated in dogs with improved efficacy, including an increase in bladder warning time from 10 seconds to 213 seconds. The continuous group received sacral neuromodulation (continuous afferent stimulation), but the conditional stimulation group received pudendal stimulation only in response to a bladder contraction event. A tripolar cuff electrode was placed around the pudendal nerve which was stimulated only in response to a bladder contraction. This was the conditional stimulation group and the trigger was a rise in bladder pressure of 5 cmH2O. A moving average calculated over 5 seconds was used to smooth the signal. Acetic acid 0.4% was used as the irritant to induce bladder contractions. Bladder capacity improved from 64mL to 70mL in the dogs receiving continuous afferent stimulation and 64mL to 98mL in the dogs receiving only conditional electrical stimulation to the pudendal nerve. A third group of dogs was stimulated with both continuous afferent stimulation and conditional pudendal stimulation. That group saw an increased capacity to 103mL, suggesting a synergy can be achieved by combining continuous sacral nerve (S3) stimulation and conditional pudendal stimulation[20]. The afferent stimulation was stopped momentarily to apply the pudendal stimulation.

Subject controlled, on-demand Dorsal Genital Nerve Stimulation is one variant of closed loop feedback in which the subject triggers the stimulation based on urgency to urinate. Investigators enrolled 7 neurologically intact patients to undergo 1 week of stimulation via an in-office dorsal genital nerve needle electrode placement. To qualify, subjects had to have at least 4 episodes of urge urinary incontinence per day. Not all subjects followed the protocol, but 6/7 reported a mean 73% subjective improvement, and heavy incontinence episodes (soaked pads) were reduced by 100% in two subjects and by at least 80% in four others [21]. Only six patients completed the trial, as one suffered migration of the electrode. The stimulation was set to the maximum tolerable amplitude, 20Hz and a 300 microsecond pulse width.

By comparison, continuous dorsal genital nerve stimulation was investigated by Goldman and colleagues during a 2008 study of 21 women, in which 47% had a >=50% reduction in incontinence episodes. Pad weight decreased (76% of those completing the study had a >= 50% reduction) as well, but 4 did not complete the 24h pad testing [22].

Martens and colleagues applied conditional stimulation of Dorsal Genital Nerve to a group of eight spinal cord injured patients. Successful engagement with the nerve was confirmed by an anal wink reflex. Three of eight patients did not demonstrate this, but two of these still exhibited suppressed detrusor contractions, defined by urodynamic pressure tracing returning to “near baseline”. Stimulation was triggered manually by a rise in detrusor

pressure of 10cm H2O. Not all detrusor contractions were suppressed, and success was considered the ability to suppress one detrusor contraction [23].

Needle electrodes are unattractive to patients, and prior to the study described above, Opisso and colleagues examined self-adhesive surface electrodes for on-demand Dorsal Genital Nerve stimulation. Their 11 patients experienced an increase in bladder capacity from 147mL to 204mL, and an increase in mean voided volume as well [24]. These patients suffered from neurogenic bladder but had sensation. The cause of the neurogenic bladder ranged from multiple sclerosis, to traumatic brain injury, to myelitis, and spinal cord injury.

How do we detect an unwanted detrusor contraction? Using Afferent Nerve Activity

The paucity of clinical trials exploring closed loop feedback may be due to the technical difficulty in sensing a significant bladder event.

The pudendal nerve has long been a target of sensory algorithms to detect a detrusor contraction using afferent nerve information. Investigators in 2004 observed that a cuff electrode placed around the pudendal nerve in cats would be able to detect a bladder contraction at a mean of 1.2 seconds after it began, allowing the contraction to reach a mean amplitude of 7cmH2O. Using a cumulative sum algorithm they were able to achieve 98% sensitivity and 55% specificity, suggesting an excellent detection of “bladder events” but also a lot of false positives [25]. They used simultaneous urodynamic pressure values to validate the pudendal electroneurograms, and the highly processed and filtered signal using the cumulative sum algorithm outperformed the signal using a constant threshold and one employing a dynamic threshold, which changed as the baseline electroneurogram signal increased or decreased, essentially a moving average value.

The pudendal nerve carries more than just bladder information, and it is difficult to detect the desired signal from the noise, which in engineering terms leads to a low signal to noise ratio. Some have attempted to increase the signal to noise ratio for pudendal sensing with a more sophisticated electrode array. The Utah Slanted Electrode Array is designed to obtain intra-fasicular recordings and stimulation of the pudendal nerve by perforating the nerve with micro-electrodes of varying lengths. The authors note that in the seven cats investigated, only a few electrodes exhibited increased firing responses to bladder filling. This required a roughly 10 hour implantation technique and a long characterization process (about 30 hours total). Histologic examination revealed that the nerve in the cat was only about 39% axonal tissue, the rest was empty space, adding to the complexity of implantation. Once identified, the electrodes did not consistently sense the stimulus, which the authors speculated was due to motion and not nerve damage caused by the electrodes [26]••.

Like the pudendal nerve cuff electrode, cuff electrodes placed extradural on the S3 nerve root in humans have been hampered by low signal to noise ratios, making it difficult to distinguish bladder pressure information from other information carried in this nerve bundle [27]. The S1 and S2 dorsal root ganglia are one area where sensory afferents are separated

from motor fibers, and in theory, a higher signal to noise ratio can be obtained by sampling from this area. Investigators from Pittsburgh, USA explored the feasibility of this by implanting neuroelectrode arrays in the S1 and S2 dorsal root ganglia of 3 cats to determine if bladder filling could be detected. As the bladder was filled certain dorsal root ganglia units could be sensed by the electrode array manifested by an increase in firing rate as the bladder was filled, some of which were quiet when the bladder was empty, and some with baseline firing activity that increased with filling. This was dependent on the specific position of the electrode array and the animal examined. Of the bladder-responsive ganglion units identified, firing rate generally began to increase once bladder pressure reached 11cm H2O. Once bladder pressure reached 20cmH2O, 92% of the responsive units were registering, suggesting that higher pressures might recruit more nerve units, and different populations of nerve units might begin to respond at different pressures [28]•.

Using the body's afferent nerves to quantify bladder fullness

Mendez, Wyndaele, and colleagues were able to use pelvic nerve afferent activity to distinguish between 3 levels of bladder fullness in rats. They found that after a training period, in which nerve units were identified that appeared to respond to bladder fullness, they could use those nerve units to distinguish between 25%, 50%, and 100% maximum cystometric capacity. This process involved a surgical laminectomy to dissect L6 filaments from which the pelvic nerve arises and lay them in a microelectrode array. The complicated process may not be practical for widespread use, and the electrode array might damage the nerve filaments over time, but this demonstrates that if responsive nerve units can be identified then quantitative measurement of bladder fullness is possible using sensory afferents[29]••.

Some have taken the approach that bladder pressure is more practical for chronic detection of bladder events because there are problems with afferent nerve sensing techniques such as instability of the electrode-nerve interface and problems with decoding the information, which has yielded variable results[25, 28, 29]. This makes direct sensing of bladder pressure more desirable. Unfortunately, early attempts to develop an implantable bladder pressure sensor were frustrated by sensor migration and infection in dogs and goats [30, 31]. Recent short term results appear encouraging, however. Investigators from Denmark designed a 13mm implantable pressure sensor and tested it in 6 pigs. They placed it in the wall of the bladder and compared it to an intraluminal urodynamic catheter. They found that the wall sensor detected a contraction earlier than the urodynamic catheter by an average of 307 miliseconds. Not all contractions were detected by the wall sensor but the correlation coefficient was >0.90. Bladder contractions were evoked by unilateral stimulation of the pelvic nerve, and so a precise onset of the contraction was obtained [32]. Sensor drift, or loss of accuracy over time, is another significant problem with chronic monitoring of bladder pressure, that investigators have improved on recently by encapsulating a sensor in silicone oil, isolating the pressure sensing membrane from the physiologic environment [33].

Clinical urodynamic studies typically employ a second pressure sensor placed in the rectum to help distinguish abdominal artifact from a true detrusor contraction. Some authors have turned to sophisticated algorithms to reliably detect this without the use of a rectal (second)

sensor. This type of adaptive event sensing algorithm might be necessary in the future before implementation of a true closed-loop feedback system is practical. With this in mind, Karam, Damaser, and collegues have refined this work and developed a novel Real-time Classification algorithm for detection of bladder contraction that has some ability to distinguish artifact from a real event. It has been termed “context aware thresholding”, and the authors note a 97% true positive rate, 1.3% false positive rate, using stored urodynamic data on 14 human subjects diagnosed with neurogenic bladder [34]. Some other potential event triggers investigated included static detection of bladder pressure above a certain threshold, such as 10 cm H2O, and the authors note that using this type of detection scheme they achieve an inferior rate true positive rate of 76%. The urodynamic data was from humans, and included only one contraction per filling phase which was determined by an expert observer.

Unconventional ways to sense bladder fullness

Ultra wideband radar has been investigated to sense bladder fullness since it can sense the dielectric interface between urine and the bladder wall. A k-Nearest Neighbor learning algorithm is trained with a phantom bladder model. It was able to distinguish “full” from “medium” to “small” with 91-95% accuracy [35].

Target for stimulation: Pudendal Nerve

Electrodes have been placed on the surface of the skin to stimulate pudendal nerve with some decrease in bladder contractions in animal models [36, 37].

Direct stimulation of the pudendal nerve has been done in multiple animal studies, and the body of literature in this area is growing. Wark and colleagues use a sophisticated microelectrode array (the “Utah” electrode array discussed earlier) placed within the fascicules of the pudendal nerve trunk to stimulate as well as inhibit reflexive detrusor contractions, as well as restore continence in a denervated model for stress incontinence. They describe successfully stimulating contractions in 5/13 neurologically intact animals after a long (30 hour) mapping procedure utilizing anesthesia and urodynamic catheters. They selectively stimulate combinations of 48 electrodes and map them to muscle responses including external anal sphincter contraction, external urethral sphincter contraction, and detrusor contraction. The authors were able to induce reflexive voiding contractions by filling the bladder in alpha-choralose anesthetized cats in 6/13 animals. In 2 animals, the authors were able to inhibit reflex contraction by stimulating the electrode array. A model for stress incontinence was created by transecting the right and left pudendal nerves proximal to the electrode array and then filling the bladder until a reflexogenic detrusor contraction occurs [38]. Unfortunately the leak point pressure did not vary significantly from the neurologically intact animals, calling into question the validity of the model. Once leakage began, however, it stopped immediately after stimulation was applied, suggesting the external urethral sphincter was able to be stimulated via the pudendal electrode array.

There is strong evidence that stimulating the pudendal nerve can both inhibit volume-induced bladder contractions in spinal cord injured cats and stimulate the bladder to contract

without causing a simultaneous contraction in the external urethral sphincter. This provides an advantage over sacral afferent root stimulation (SARS), as it does not simultaneously contract the sphincter and inhibit voiding as the bladder contracts. Investigators were able to reproduce contractions in 14/14 cats stimulated at 33Hz, and inhibition of volume triggered detrusor contractions in 8/8 cats stimulated at 10Hz [39].

Anecdotal evidence exists that pudendal nerve stimulation can elicit detrusor contractions in humans with spinal cord injury. Two individuals with spinal cord injury were able to achieve urodynamic proven detrusor contractions when stimulated at frequencies of 20-50 Hz [40].

Target: S3 Nerve Root

Some investigators have demonstrated that it is possible to distinguish between 3 levels of bladder fullness in rats by attaching cuff electrodes to nerve roots carrying primary afferent neural activity from bladder mechanoreceptors[29]. Others have developed implantable pressure sensors that may one day be used to provide feedback to stimulation devices [41, 42].

Taken a step further, in theory more selectivity can be achieved by targeting the S1 and S2 dorsal root ganglia using microelectrode arrays, which have only afferent fibers and are more protected from motion by their proximity to the spine. Sensing activity from the ganglia was described by Bruns, Weber, and Gaunt in 2011 and they investigate stimulation in their 2015 investigation. They succeeded in eliciting reflex voiding in 5/6 cats by stimulating select nodes on a microelectrode implanted in the S1 dorsal root ganglia and another in the S2 dorsal root ganglia. Unlike some prior investigations, these animals had an intact spinal cord. These were long procedures, ranging from 22 to 40 hours, involving a long characterization process to determine which microelectrode channels would elicit a urodynamic response. Once effective single-channel and multi-channel schemes were identified, the average evoked rise in pressure was 16cmH2O, but the investigators found that bursts of stimulation could lead to greater evoked potentials [43]•.

Target: Intraspinal Stimulation

Investigators described a novel stimulation technique in which a microelectrode array was placed in the dorsal gray commissure at the level of S1 using 22 cats. They noted that monthly stimulation over 14 months was able to achieve a strong bladder contraction of at least 20cm H2O and a relaxation of the external urinary sphincter of at least 40mmH2O [44]. Older data in humans exists where authors describe implanting the electrode in the conus medularis of 14 spinal cord injured patients in the USA and 9 in France, but results were difficult to achieve, with a laminectomy necessary to place a needle electrode in the conus medularis. Patients responded in 60% of the cases, and one might speculate that the invasiveness of the procedure coupled with modest results has led to no further papers since 1981 [45, 46].

Conclusion

Conditional stimulation, or closed loop feedback, offers the promise of longer battery life, more effective prevention of urinary incontinence, and more effective voiding efficiency, including initiation of a voiding contraction. The animal literature has demonstrated that stimulation can be more effective, but human data is sparse. A reliable method for sensing a bladder event remains elusive, but the most promising technologies involve direct bladder pressure sensing or recording afferent nerve activity and processing the data with sophisticated algorithms to distinguish artifact from a true bladder event. Stimulation has been effective when applied to pudendal nerve, dorsal genital nerve, and S3 afferent nerve roots. The future of this field is still being written and will be exciting to watch as a neuroprosthesis emerges.

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