Published in final edited form as:

Curr Bladder Dysfunct Rep. 2016 December ; 11(4): 346–349. doi:10.1007/s11884-016-0391-2.

Using the Native Afferent Nervous System to Sense Bladder Fullness: State of the Art

Lauren E. Tennyson, MD,

Department of Urology, University of Pittsburgh, 700 Kaufmann Building, 3471 Fifth Ave.,
Pittsburgh, PA 15213, USA

Changfeng Tai, PhD, and

Department of Urology, University of Pittsburgh, 700 Kaufmann Building, 3471 Fifth Ave.,
Pittsburgh, PA 15213, USA

Christopher J. Chermansky, MD

Department of Urology, University of Pittsburgh, 700 Kaufmann Building, 3471 Fifth Ave.,
Pittsburgh, PA 15213, USA

Abstract

The regulation of micturition involves complex neurophysiologic pathways, and its understanding has grown immensely over the past decade. Alternative approaches and applied technologies in the treatment of bladder dysfunction have minimized the complications that result from neurogenic bladder. The use of natural bladder mechanoreceptors and electroneneurographic (ENG) signal recordings from afferent nerves to chronically monitor bladder volume is a promising concept, but the technology to accomplish this has proven to be a great biomedical engineering challenge. The focus of this paper will be to describe the current state of ENG signal recording as a method to detect bladder fullness.

Keywords

Electroneneurographic (ENG); Native Afferent Nervous System; natural bladder mechanoreceptors; Bladder Dysfunction

Introduction

The regulation of micturition involves complex neurophysiologic pathways, and its understanding has grown immensely over the past decade. A neurologic insult, occurring anywhere along the neural axis from the brain to the pelvic ganglia innervating the bladder disrupts autonomic reflex pathways and results in bladder dysfunction. If unrecognized,

Corresponding author: chermanskycj2@upmc.edu.

Conflict of Interests

Drs Tennyson, Tai and Chermansky declare no conflicts of interest

Compliance With Ethics Guidelines

Human and Animal Rights and Informed Consent:

This article does not contain studies with human or animal subjects performed by the author.

renal failure can develop and cause deterioration of both health and quality of life. Alternative approaches and applied technologies in the treatment of bladder dysfunction have minimized renal failure resulting from neurogenic bladder. Continuous monitoring of bladder volume has been proposed as a way to obtain insight into bladder function and guide treatment options. Clinical scenarios where this would be helpful include determining when maximum bladder capacity has been reached or when post void residual volume is abnormally elevated. Furthermore, continuous bladder monitoring would also allow for the observation of patterns over time rather than isolated measurements. Lastly, this monitoring could improve existing neuroprosthetic technology by allowing for closed-loop control and auto-regulation based on sensory information (1) ••.

Unfortunately, chronic monitoring of bladder volume has proven to be a great biomedical engineering challenge, and the complexity of bladder neurophysiology and the limitations of current technology have proven unsuccessful. Two general bladder sensing techniques have been tried. The first uses artificial sensors such as intravesical pressure transducers, electrical impedance plethysmography and wearable ultrasonography. The second technique uses natural bladder mechanoreceptors and electroneurographic (ENG) signal recordings from afferent nerves (2). Artificial sensors function independently of a patient's condition, and this offers potential advantages; however, issues with sensor biocompatibility and long-term reliability have halted interest. Consequently, the focus has shifted to tapping the bladder's natural sensors as a more reliable alternative. Mendez and Sawan recently performed a detailed review and quantitative analysis of the different techniques used for monitoring of chronic bladder activity, and they sought to select the best technique with minimal bias (2). ENG recording from bladder afferents was deemed the most suitable option for chronic bladder monitoring because it scored well most consistently, but with the caveat that improvements and more studies are necessary to prove its feasibility.

Individual neurons, whole pelvic nerves, sacral nerve roots, and dorsal root ganglion (DRG) have all been utilized for ENG recordings, with each approach presenting unique advantages and challenges. The focus of this paper will be to describe the current state of ENG signal recording as a method to detect bladder fullness. To achieve clinical translatability, ENG recording from bladder afferents has challenges that will need to be overcome.

Background

The pelvic, hypogastric, and pudendal afferent nerves continuously monitor the bladder. They are comprised of myelinated A δ and unmyelinated C fibers that transmit sensory information from the lower urinary tract to the lumbosacral spinal cord. In humans the cell bodies of the pelvic and pudendal afferent nerves are located in the S2-S4 dorsal root ganglion (DRG), and the cell bodies of the hypogastric nerve are located at the T11-L2 levels (3). Animal models have demonstrated the existence of bladder mechanoreceptors that respond specifically to changes in bladder pressure and volume (4, 5). The information these mechanoreceptors transmit can be recorded based on action potential firing frequency as an ENG recording, where the signal is created by superimposed action potentials firing from multiple neurons (see figure 1). There is also evidence that C fibers, which have a slower conduction velocity, respond to gradual bladder distension at physiologic volumes and are

solely volume receptors that do not respond to bladder contraction (4). Yu and de Groat placed bipolar cuff electrodes on the pelvic nerve in rats and recorded activity during bladder filling. Both phasic and tonic afferent activity increased gradually as these rat bladders distended. Phasic firing occurred during bladder contractions, and tonic firing occurred with bladder stretch and reflected fiber recruitment within the pelvic nerve (6). Several studies have debated whether it is possible to accurately detect bladder fullness from tonic responses. Kurstjens et al evaluated afferent activity of the bladder, rectum, and skin dermatomes in 6 anesthetized spinal cord injury (SCI) patients (7). They placed a tri-polar cuff electrode on the S3 nerve root and found that phasic responses favored the detection of bladder contractions; however, detecting bladder volume was more difficult due to the high threshold needed with tonic responses. Also, Jezernik et al concluded that it was not feasible to monitor bladder fullness with cuff electrode placement on the sacral nerve root in a cat model (8). In contrast, Mendez et al created and tested a method that successfully estimated bladder volume using ENG signal recording in a rat model (1). Rather than record from the sacral nerve root, they isolated 25 bladder afferent nerve fibers (seven classified as Aδ fibers, 18 as C fibers) and quantified both phasic and tonic bladder responses during slow filling and isovolumetric measurements. Unlike the aforementioned studies, Mendez et al estimated bladder volume with a low margin of error, thereby lending further evidence to the existence of volume-specific mechanoreceptors.

Technical limitations of nerve recordings

Researchers have isolated and tested bladder-specific afferent neurons. Yet, problems with this approach preclude clinical translatability. Sensory neurons responding to bladder distension often share innervation with other visceral and cutaneous regions (9). Additionally, chronically recorded axons fatigue over time and their signals decline (10). Finally, the wire or hook electrodes needed with this approach cannot be used long-term and are not clinically applicable.

Cuff electrodes placed around the pelvic nerve or sacral nerve root has been performed in multiple studies (11). Cuff electrodes have demonstrated good long-term outcomes for implantation in humans, and they can be used for both nerve recording and electrical stimulation. Their placement allows for a more secure interface; however, volume-sensing afferents comprise only a small percentage of the thousands of fibers found within pelvic or sacral nerves. This results in lower amplitudes and lower signal-to-noise ratios (8). The amplitude of the recorded nerve signal also decreases with the larger cuff sizes required in humans, and this is important when considering clinical applicability. Another factor making cuff placement challenging in humans is the plexus-like nature of the pelvic nerve, which contrasts to the distinct pelvic nerve seen in animals (12). Furthermore, Kurstjens et al noted that whole nerve cuff electrode recordings appeared biased towards more superficial axons and larger diameter fibers (7). They ultimately concluded that "...improvements in recording quality and more sophisticated signal processing methods are needed...".

To attain long-term stability while selectively recording bladder afferent fibers, researchers have begun implanting microelectrode arrays into sacral dorsal root ganglia (DRG). DRGs contain the cell bodies of afferent neurons projecting into the spinal cord, and they offer

unique access to hundreds of neurons that can be recorded with a higher signal-to-noise ratio (13) •. Large numbers of neurons in DRGs can be isolated and recorded simultaneously, although it remains impossible to definitively know which neurons are being recorded. DRG are shielded by the spinal column, which offers protection from mechanical forces compared to peripheral nerves; however, access to DRG requires a laminectomy, making this approach much more invasive. Bruns et al was the first group to demonstrate that DRG neural activity could be used to estimate bladder pressure (13) •. They have since created the first cat model that uses sacral DRG microelectrodes to measure reflex bladder responses that control micturition and continence (14) ••. They concluded that their findings could contribute to neuromodulation advancement through the coupling of neural recordings from the same microelectrodes to provide closed-loop control, thereby allowing for highly selective control over bladder function. Sacral DRG recordings have yet to be studied in humans or evaluated for long-term efficacy.

Potential for clinical applicability

To better sense bladder fullness, one could create a neuroprosthesis that couples sensory feedback with applied stimulation based on the bladder state. This principle is known as conditional stimulation. Current methods for long-term neuromodulation such as InterStim® (Medtronic, Minneapolis, MN, USA), apply continuous, rather than conditional, stimulation because the device lacks the feedback and processing capability necessary to create a closed-loop circuit (15). Conditional stimulation systems have theoretical advantages. Since conditional stimulation is applied only when necessary, electrode and battery life are increased and the risk of habituation of the reflex loop is decreased. (16). Also, and perhaps most importantly, conditional stimulation allows a warning signal to be delivered when a bladder contraction is suppressed or when a certain volume has been reached indicating it is time to empty the bladder. Patients with neurogenic bladder from SCI or other neurologic conditions are a target population for such technology advancements because of the potential for urinary tract deterioration if inadequately managed. In addition, patients with underactive bladder, characterized by prolonged urination time with or without a sensation of incomplete bladder emptying and reduced sensation on filling, could benefit from advancements in detecting bladder fullness (17).

Although there are currently no commercially available products that utilize the native afferent nervous system to monitor bladder volume, it is well acknowledged that this application would improve neuromodulation devices. Mendez et al recently designed a feedback sensor capable of detecting, discriminating and decoding real-time information about bladder volume utilizing afferent nerves (18). These authors plan on studying this sensor with neuroprosthetic implants that utilize conditional stimulation, hopefully restoring bladder function. This technology is far from clinical application; however, investigations continue and significant advancements are being made. It is hoped that better sensory feedback from bladder afferent nerves will soon transform the treatment of lower urinary tract dysfunction.

Conclusion

Technology that uses the native afferent nervous system to sense bladder fullness is far from clinical application; however, investigations continue and significant advancements are being made. It is hoped that better sensory feedback from bladder afferent nerves will soon transform the treatment of lower urinary tract dysfunction.

References

Papers of particular interest, published recently, are highlighted as:

- Of importance
- Of major importance
- 1. Mendez A, Sawan M, Minagawa T, et al. Estimation of Bladder Volume From Afferent Neural Activity. *IEEE Trans Neural Syst Rehabil Eng*. 2013 Sep; 21(5):704–15. The authors record nerve activity from the Dorsal Root Ganglion taking advantage of the segregated nerve fibers, prove this is feasible, and accurately decode the signal to estimate bladder volume. [PubMed: 23771346]
- 2. Mendez A, Sawan M. Chronic monitoring of bladder volume: a critical review and assessment of measurement methods. *Can J Urol*. 2011; 18(1):5504–16. [PubMed: 21333041]
- 3. Kanai A, Andersson KE. Bladder Afferent Signaling: Recent Findings. *J Urol*. 2010; 183(4):1288–95. [PubMed: 20171668]
- 4. Morrison J. The activation of bladder wall afferent nerves. *Exp Physiol*. 1999; 84(1):131. [PubMed: 10081713]
- 5. Habler HJ, Janig W, Koltzenburg M. Activation of unmyelinated afferent fibers by mechanical stimuli and inflammation of the urinary bladder in the cat. *J Physiol*. 1990; 425:545–62. [PubMed: 2213588]
- 6. Yu Y, de Groat WC. Sensitization of the pelvic afferent nerves in the in vitro rat urinary bladder—pelvic nerve preparation by purinergic agonists and cyclophosphamide pretreatment. *Am J Physiol Renal Physiol*. 2008; 294(5):F1146–56. [PubMed: 18322018]
- 7. Kurstjens G, Borau A, Rodriguez A, et al. Intraoperative Recording of Electroneurographic Signals from Cuff Electrodes on Extradural Sacral Roots in Spinal Cord Injured Patients. *J Urol*. 2005; 174:1482–87. [PubMed: 16145476]
- 8. Jezernik S, Grill WM, Sinkjaer T. Detection and inhibition of hyperreflexia-like bladder contractions in the cat by sacral nerve root recording and electrical stimulation. *Neurourol Urodynam*. 2001; 20(2):215–30.
- 9. Ness TJ, Castroman P. Evidence for two populations of rat spinal dorsal horn neurons excited by urinary bladder distension. *Brain Res*. 2001; 923(1–2):147–56. [PubMed: 11743982]
- 10. Bruns TM, Gaunt RA, Weber DJ. Multielectrode array recordings of bladder and perineal primary afferent activity from the sacral dorsal root ganglia. *J Neural Eng*. 2011; 8(5)
- 11. Sinkjaer, T., Haugland, M., Struijk, J., et al. Long-term cuff electrode recordings from peripheral nerves in animals and humans. In: Windhorst, U., Johansson, H., editors. *Modern Techniques in neuroscience*. New York, New York: Springer-Verlag; p. 787-802.
- 12. Wozniak W, Skowronska U. Comparative anatomy of pelvic plexus in cat, dog, rabbit, macaque and man. *Anat Anz*. 1967; 120(5):457–73. [PubMed: 4970410]
- 13. Bruns TM, Gaunt RA, Weber DJ. Estimating Bladder Pressure from Sacral Dorsal Root Ganglia Recordings. *Conf Proc IEEE Eng Med Biol Soc*. 2011; 2011:4239–42. The authors use a cat model to prove feasibility in measuring pressure using a complex microelectrode array placed in the S1 and S2 dorsal root ganglion. The authors' detailed methods section should facilitate other investigators interested in reproducing their results. [PubMed: 22255275]
- 14. Bruns TM, Weber DJ, Gaunt RA. Microstimulation of afferents in the sacral dorsal root ganglia can evoke reflex bladder activity. *Neurourol Urodyn*. 2015; 34(1):65–71. The authors leverage

their experience and skill with cats to stimulate, not just listen, to the S1 and S2 dorsal root ganglion. They achieve bladder contraction by modulating the electrode stimulated and the frequency of stimulation. Similarly, by altering these parameters they demonstrated relaxation of the bladder in some, but not all, experimental animals. [PubMed: 24464833]

15. Spinelli M, Sievert KD. Latest technologic and surgical developments in using InterStim Therapy for sacral neuromodulation: impact on treatment success and safety. *Eur Urol.* 2008; 54(6):1287–1296. [PubMed: 18336992]
16. Melgaard J, Rijkhoff NJM. Detecting Urinary Bladder Contractions: Methods and Devices. *Journal of Sensor Technology.* 2014; 4:165–76.
17. Chapple CR, Osman NI, Birder L, et al. The underactive bladder: a new clinical concept? *Eur Urol.* 2015; 68(3):351–3. [PubMed: 25770481]
18. Mendez A, Belghith A, Sawan M. A DSP for Sensing the Bladder Volume Through Afferent Neural Pathways. *IEEE Trans Neural Syst Rehabil Eng.* 2014; 8(4):552–64.

Figure 1.