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Spinal cord epidural stimulation to control bladder in spinal cord injury patients V.1

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Abstract

Aim was to investigate the effects of spinal cord epidural stimulation (scES) to improve bladder storage and emptying, seven individuals (32.1 ± 4.6 years of age; 6 males, 1 female) with motor complete spinal cord injury (SCI) (average time since injury at 9.1 ± 2.5 years at C3-T2 spinal cord level) previously implanted with a 16-electrode array (5–6–5 Specify, Medtronic, Minneapolis, MN, USA.) at the T11–L1 vertebral levels over spinal cord segments L1–S1 (Initial time frame of enrollment in this study following implant surgery of 3.3 ± 2.8 years) and connected to the pulse generator (Restore ADVANCED (B21, B23), or Intellis (A101, A96, A68, B24, B07), Medtronic, Minneapolis, MN) placed ventrally in the abdomen, participated in a research study conducted at the University of Louisville. Following enrollment, each participant completed a baseline Urodynamics without stimulation, followed by approximately 8 weeks of bladder mapping. Each participant completed a minimum of 20 urodynamic sessions (10 for storage; 10 for void initiation) mapping the detrusor and urethral pressure responses as well as sphincter EMG responses during both filling and emptying cystometry phases while scES parameters (anode, cathode selection; frequency and amplitude, and the number of cohorts) were modulated to isolate successful configurations. The goal for bladder capacity (BC)-scES was to target volumes between 400–500 mL based on average normal capacity and avoiding over-distention in those individuals performing intermittent catheterization 4–6 times/day (including average fluid intake). Also targeted were filling pressures (< 10 cmH_20) to improve overall bladder compliance and detrusor leak-point pressures (< 40 cmH_2O). Maintaining normative systolic pressures during filling, within a range of 110–120 mmHg, was a further goal. All enrolled participants completed prior scES mapping studies for cardiovascular function and thus, the cardiovascular cohort was integrated if blood pressure (BP) was elevated. All simulations accounted for any cardiovascular cohorts.

Materials

	A	B	C	D
	ITEM	Company	catalog number	website link
	16-electrode array	Medtronic	5-6-5 Specify	
	pulse generator (Restore ADVANCED)	Medtronic	97713	https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/spinal-cord-stimulation-systems/legacy-scs-products.html
	pulse generator or Intellis	Medtronic	97715	https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/spinal-cord-stimulation-systems/intellis-platform.html
	blood presure machine Carescape V100	General Electric		https://www.gehealthcare.com/products/patient-monitoring/patient-monitors/carescape-v100
	Aquarius ‰ LT system	Laborie	AQS1000	https://www.laborie.com/product/aquarius-range-2/
	dual-channel catheter	Laborie	CAT880	https://www.laborie.com/product/t-doc-air-charged-urodynamic-catheters-2/
	rectal catheter	Laborie	CAT875	https://www.laborie.com/product/t-doc-air-charged-urodynamic-catheters-2/
	surface patch EMG electrodes	Conmed	NeoTrode II cat#1741-003	https://mms.mckesson.com/product/210558/Conmed-1741-003
	MATLAB	Mathworks		https://www.mathworks.com/products/matlab.html
	Siemens 3.0 Tesla Magnetom Skyra	Siemens	Magnetom Skyra	https://www.siemens-healthineers.com/en-us/magnetic-resonance-imaging/3t-mri-scanner/magnetom-skyra

	A	B	C	D
	Siemens 1.5 Tesla ESPREE	Siemens	Tesla ESPREE	https://www.siemens-healthineers.com/en-us/refurbished-systems-medical-imaging-and-therapy/ecoline-refurbished-systems/magnetic-resoncance-imaging-ecoline/magnetom-espree-eco
	T2 Turbo Spin Echo	Siemens		https://www.siemens-healthineers.com/en-us/magnetic-resonance-imaging/options-and-upgrades/clinical-applications/tgse
	SAS 9.4	SAS, Inc	SAS 9.4	https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.5/pgmsashome/home.htm

Troubleshooting

Clinical Evaluation

1 The patients' injuries were classified by two independent clinicians using the ASIA (American Spinal Injury Association) Impairment Scale (AIS)[1].

2 The patients underwent a physical examination for medical clearance, ensuring participation safety using the following **inclusion criteria**:

1. Stable medical condition
2. No painful musculoskeletal dysfunction, unhealed fracture, contracture, pressure sore, or urinary tract infection that might interfere with training.
3. No untreated psychiatric disorders or ongoing drug abuse.
4. Clear indications that the period of spinal shock is concluded, determined by the presence of muscle tone, deep tendon reflexes, or muscle spasms, and discharged from standard inpatient rehabilitation.
5. Non-progressive supra-sacral spinal cord injury (SCI).
6. Epidural stimulator implanted at the lumbosacral spinal cord.
7. Not ever having received Botox injections for management of bladder dysfunction.
8. Not ever having received anti-spasticity medication (e.g., Baclofen).

3 The patients underwent a bladder/kidney ultrasound by the study physician and study urologist, respectively.

Urodynamic evaluation

4 Baseline blood pressure (BP) and heart rate (HR) were obtained in the supine and seated positions from the brachial artery and measured by oscillometric technique (Carescape V100, GE Healthcare, Milwaukee, WI) prior to urodynamic testing and throughout the urodynamic session.

5 The patients underwent a baseline urodynamic evaluation following the standard urodynamic evaluations recommended by the International Continence Society (ICS).

- **Cystometry** was performed using the Aquarius ® LT system (Laborie, Williston, VT)with the patient in the seated position via a single sensor, dual-channel catheter (7 Fr, T-DOC ® Air-Charged™, Laborie, Williston, VT) with the continuous filling of sterile, body-temperature saline (37 °C) at a fixed rate of 10 mL/min, more closely reflecting physiological filling.

- **Abdominal pressure** was measured via a rectal catheter (7 Fr, T-DOC ® Air-Charged™, Laborie, Williston, VT).

- **Pelvic floor electromyography (EMG)** (Neotrode II, Laborie, Williston, VT) was recorded using surface patch EMG electrodes and a grounding pad was placed on a bony prominence, usually the hip or knee.

5.1 During the filling phase of the experiment, participants were instructed to communicate:

- bladder sensations (first sensation);
- the desire to urinate (first urge to void);
- the strong desire to void,
- the feeling that voiding/leaking cannot be delayed (maximum capacity).

Given that many SCI participants may have a loss of bladder sensation, indirect sensations were also used.

5.2 Uninhibited bladder contractions were identified.

5.3 During the voiding phase, a “permission to void” was commanded to the patient followed by stopping the infusion pump (at approximately 80% of leak point volume). Detrusor pressure was monitored during the void attempt and expelled urine was measured.

5.4 Voided volume was measured by the gravimetric system attached to the urodynamic equipment. Post-void residual (PVR) volume was measured by taking the urine remaining into the bladder through the urethral catheter to evaluate the extent of bladder emptying.

6 Bladder capacity was calculated as the volume of leaked and/or voided fluid plus any residual amount removed from the bladder.

7 Voiding efficiency (VE) was calculated as:

- VE = [volume voided/(volume voided + residual volume) × 100].

8 Compliance was calculated by dividing the volume change (ΔV) by the change in detrusor pressure (ΔPdet) during that change in bladder volume and was expressed in mL/cmH_2O.

9 The intravesical pressure (Pves) at which involuntary expulsion of water/urine from the urethral meatus was observed was considered the detrusor leak point pressure (DLPP).

10 Maximum detrusor pressure (MDP) was identified as the peak detrusor pressure during the voiding phase of the cystometrogram. Detrusor pressures were calculated by subtracting the intra-abdominal pressure from the intra-vesical pressure. If a participant did not leak during the filling cycle, MDP was used in place of DLLP.

11 All analyses were performed with customized software in MATLAB (MathWorks, Natick, MA, 2017A).

12 A post-fill BP recording was captured to ensure BP values returned to baseline.

13 Bladder filling was ceased, and the bladder was emptied if any of the following conditions were observed:

- Spontaneous urine leakage,
- Filling volume ≥ 600 mL or reaching maximum bladder capacity as evidenced by a rise in
  the compliance curve.
- High sustained intravesical pressure ≥ 40 cmH_2O.
- Autonomic dysreflexia as evidenced by a sustained systolic blood pressure recording of ≥ 20 mmHg from baseline and/or intolerable symptoms.

Mapping

14 Bladder mapping was performed by selecting electrode configurations with cathodes positioned caudally, targeting the sacral micturition center and parasympathetic pathways, then with cathodes positioned in the mid-array to target the purported lumbar spinal coordinating center with presynaptic connections to sphincter motoneurons, and then with cathodes positioned rostrally, to target sympathetic pathways (location selection order varied for each mapping session).

15 Changes in detrusor pressure, sphincter activation/relaxation, and blood pressure responses were monitored during bladder filling while conducting a gradual ramp-up of stimulation frequency and intensity until a near-motor threshold stimulation amplitude that did not elicit direct lower limb movements was selected.

16 The increase in stimulus amplitude was applied once frequency was fixed for the specific trial, which was at approximately 80% bladder capacity/80% of leak point volume and in response to participant sensations of bladder fullness or the desire to void. The aim was to increase sensory feedback and the participant's intent during mapping to augment either storage (increase in sphincter EMG and urethral pressure and reduction of detrusor pressure) or void effects (increase in detrusor pressure, decrease in urethral pressure, and quiescence of sphincter EMG activity).

17 The effects of varying frequency at a fixed pulse width (μs) were applied in both an ascending (low to high frequency, 15–90 Hz) and descending order (high to low frequency, 90–15 Hz) in increments of 5 Hz for both BC-scES (Bladder compliace-spinal cord epidural stimulation) and BV-scES (Bladder voiding-spinal cord epidural stimulation) mapping at the initiation of filling cystometry (to register changes in sphincter EMG

activity) and at 80% capacity/80% of leak point volume (to increase the storage or void effect).

18 Void initiation was attempted without stimulation.

19 Stimulation frequency and intensity were modulated synergistically in order to isolate an optimal frequency that elicited an overall continuous low detrusor pressure filling profile with a synchronized sphincter EMG pattern effective for bladder continence.

20 The participants' sensations of bladder fullness marked the transition from continence to micturition by activating the electrodes in the caudal, middle, and rostral regions of the array while the frequency was kept fixed and amplitude adjusted in order to isolate an optimal intensity that drove the initiation of voiding activity (simultaneous increase in detrusor pressure with a decrease in upper urethral pressure and quiescence of sphincter EMG responses).

21 Electrode location and selection refinement were further modified to adjust for sensory and autonomic symptoms during mapping.

22 Lower extremity and trunk EMG was monitored continuously throughout mapping to identify those parameters that modulate detrusor pressure and coordination with the external anal sphincter muscle (mirroring external urethral sphincter) and blood pressure but do not elicit motor activity in the lower extremity or trunk.

23 Stimulation amplitude was lowered and electrode selection was modified to inhibit lower extremity/trunk activity.

24 All mapping urodynamic sessions were conducted at least two days apart.

Mapping parameters analysis

25 To determine the most optimal stimulation configuration among those tested within participants, we quantified the degree of improvement (Imp_{coeff}) as a function of bladder capacity (BC) and detrusor pressure (DP) as follows:

$$Imp_{coeff} = \frac{BC}{BC_{BL}} \times \frac{1}{\left(\frac{DP}{DP_{BL}}\right)}.$$

Optimal stimulation configuration formula

An increase in bladder capacity and a decrease in detrusor pressure compared to pre-interventionvalues will lead to an increase in the improvement coefficient, with a value greater than 1 being improved function, less than 1 being a decrease in function, and 1 suggesting no overall change in function.

26 Ellipses were calculated using quartiles determined by a chi-square distribution with a 0.95 confidence interval after outliers more than 1.5 interquartile ranges below the lower quartile and above the upper quartile were removed for both bladder capacity and detrusor pressure.

High-resolution spinal cord MRI and X-ray images

27 MRI 2-D scans of all levels of the spine with high spatial resolution were recorded using either Siemens 3.0 Tesla Magnetom Skyra or Siemens 1.5 Tesla ESPREE in sagittal and axial planes. Sagittal images were obtained in two or three separate sequences (depending on the height of the participant) to cover the whole spine from the foramen magnum to the end of the sacral region. These images were reviewed by the radiologist and neurosurgeon to screen for syrinxes, significant stenosis, scoliosis, level of injury and stabilizing treatment, and related surgical changes over time.

28 Axial images were obtained using T2 Turbo Spin Echo in 4 to 5 separate sequences (depending on the height of the participant) with a focused field of view typically from cervical, upper thoracic, mid thoracic, lower thoracic-upper lumbar, and lower lumbosacral levels. Axial images were obtained with 3 mm slice thickness and zero mm gap. The axial images were used to measure the cross-sectional area of the spinal cord at different vertebral levels.

29 Anterior–posterior and lateral X-ray images of the spinal cord at the location of the scES paddle electrode implant, obtained after implantation from each participant, were used to identify the T12 vertebra based on the location of the last floating rib, and identify the exact location of the rostral and caudal ends of the paddle electrode with respect to the vertebral body.

30 The location of the paddle was estimated with respect to the spinal cord by integrating the lateral X-ray with the sagittal and axial MRI scans 97. Based on the length of the

paddle electrode (46.5 mm for Medtronic Specify® 5–6–5 lead), 15 MRI axial slices (total of 15 × 3 mm = 45 mm in length) that best describe this location were identified.

Statistical Analysis

31 Bladder outcomes, all normally distributed per Kolmogorov–Simonov test, were evaluated using paired t test. All tests were 2-sided with a significance set to 5%. Statistical analyses were performed in SAS 9.4 (SAS Inc., Cary, NC).

Protocol references

1. Roberts TT, Leonard GR, Cepela DJ. Classifications In Brief: American Spinal Injury Association (ASIA) Impairment Scale. Clin Orthop Relat Res. 2017 May;475(5):1499-1504. doi: 10.1007/s11999-016-5133-4. Epub 2016 Nov 4. PMID: 27815685; PMCID: PMC5384910.