Case Report

Impact of long-term epidural electrical stimulation enabled task-specific training on secondary conditions of chronic paraplegia in two humans

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Introduction: Spinal cord injury (SCI) often results in chronic secondary health conditions related to autonomic and metabolic dysfunction. Epidural electrical stimulation (EES) combined with task-specific training has been shown to enable motor function in individuals with chronic paralysis. The reported effects of EES on secondary health conditions, such as bladder function and body composition, are limited. We report the impact of EES on SCI-related secondary health changes in bladder function and body composition.
Methods: Two participants with motor and sensory complete SCI performed 6 months of rehabilitation without EES followed by 12 months of task-specific training with EES after implantation of a 16-electrode array on the surface of the lumbosacral spinal cord. Participants performed three days of training per week in the laboratory, and additionally performed task-specific activities with EES at home during this time frame. Changes in bladder and body composition were recorded via clinically-available testing of neurogenic bladder functionality and dual-energy X-ray absorptiometry, respectively.
Results: In one participant, we observed an increase in episodes of urinary incontinence with worsening bladder compliance and pressures at the end of the study. Bone mineral density changes were insignificant in both participants; however, one participant showed a substantial increase in lean mass (+9.1 kg; 6 months of training) via redistribution of body fat through an android/gynoid ratio reduction (−0.15; 6 months of training).
Conclusion: EES optimized for standing and stepping may negatively impact neurogenic bladder functionality. Close monitoring of bladder health is imperative to prevent undesirable bladder compliance, which can lead to upper urinary tract deteriorations. Conversely, EES may serve as an adjunct tool with regular exercise modalities to improve body composition through activation of musculature innervated by spinal segments that are below the SCI.

Keywords: Neuromodulation, Spinal cord injury, Neurorehabilitation, Epidural stimulation, Chronic paraplegia

Introduction

Neuromodulation of lumbosacral circuitry, in the form of epidural electrical stimulation (EES), has been shown to restore motor and autonomic function in

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humans with chronic paralysis due to spinal cord injury (SCI).[1] More specifically, recent reports have shown that EES in combination with task-specific training has enabled independent stepping in humans with complete,[2,3] as well as partial,[4] paraplegia. Darrow *et al.*[5] describe volitional lower limb movement, and anecdotal evidence of improved bladder, bowel and sexual function with EES use only. However, the effects on SCI-related secondary health conditions, such as bladder function and body composition, during EES enabled task-specific training has not been thoroughly characterized. Herein, we describe changes in bladder function and body composition of two participants in a clinical trial exposed to 12 months of EES and task-specific training.

Methods

Two male participants had sustained traumatic thoracic AIS-A (American Spinal Injury Association Impairment Scale, A) SCIs, participant 1 (P1; 26 years old) at T6 and participant 2 (P2; 37 years old) at T3, more than 3 years prior to clinical trial participation. Pre-intervention activities consisted of six months of locomotor training (LT) without any form of neuromodulation, via a bodyweight support treadmill and overground activities three times per week. LT was followed by implantation of a 16-contact epidural electrode array (Specify 5-6-5, Medtronic, Fridley, MN) on the dorsal surface of the spinal cord between T12 and L1, and 12 months of EES enabled task-specific training, which we termed multi-modal rehabilitation (MMR). Both participants responded to EES with motor activation of the lower extremities to achieve independent seated, standing and stepping activities during daily MMR sessions. Measures of body composition and bladder function were collected over the 18-month study timeline including neurogenic bladder symptom score (NBSS), urodynamic studies, body composition and bone mineral density. Prior to enrolling the second participant, additional body composition outcome measures were included for further analysis.

Approach to EES enabled task-specific training

After EES surgical implantation an optimization period of three weeks was used to determine initial side-lying, seated, standing and stepping parameters to use during MMR sessions. These parameters were adjusted throughout the 12 months of MMR to enhance motor performance for each task-specific activity. Once stimulation optimization details were aligned for each participant they began MMR sessions for 12 months. Detailed descriptions of LT used prior to implantation, EES implantation procedure, optimization of EES parameters, and MMR training sessions have been previously published.[2,6,7] EES parameter optimization focused mainly on the recovery of motor performance and not autonomic functions. Both participants were asked to attend three sessions a week of MMR at the laboratory following implantation of the epidural stimulation device. The participants were allowed to use the device at home to complete supine, seated and standing activities on days they did not participate in activities in the laboratory, and for no more than 3 hours a day.

Assessment of urologic function

Urodynamic studies (UDS) consisted of a filling phase and a voiding phase cystometrogram along with perineal patch muscle electromyography (EMG) performed with EES off. Complete UDS were performed with catheters in the rectum, bladder and patch EMG electrodes at a fill rate of 25 mL/min. Bladder function and satisfaction was assessed using the Neurogenic Bladder Symptom Score (NBSS) survey, a 24 item validated instrument with three domains (incontinence, storage and voiding, and urinary complications) and one general question regarding satisfaction with urinary function.[8] UDS were collected prior to implant and completion of study, and NBSS assessments were performed at 5 time points throughout the study. Urine microbiology and urinalysis were normal for both participants prior to UDS.

Assessment of body composition

Bone densitometry, dual-energy X-ray absorptiometry (DXA) [enCORE iDXA Table, software version 15], was used to measure whole body bone and soft tissue composition in one participant. For the same participant, thigh circumference was measured 10 and 20 cm above the superior patellar border for both legs. At all locations mean values were calculated from measurements that were repeated 3 times.

Results

EES usage over the course of the study

P1 used the stimulator an average of 15.7 hours per week during the initial 6 months of MMR and home exercise program, and increased to an average for 22.9 hours per week the following 6 months of MMR and home exercise program. P2 used the stimulator for an average of 13.0 hours a week for the initial 6 months of MMR and home exercise program, and decreased to an average of 10.1 hours a week thereafter.

Table 1 Urodynamic studies summary for both participants.

Participant 1	**Pre-implantation**	**Post-treatment**
Detrusor Function	Overactive; low contractility; tonic external sphincter activity	Overactive; tonic activity external sphincter
Urodynamic reading	EFDP 8 cm H2O/500 mL MBC	
Intermittent low amplitude poorly sustained detrusor contractions to 18 cm H_20 occurring during bladder filling	EFDP 40 cm/500mL MBC	
Intermittent sustained detrusor contractions to 75 cm H_20 occurring throughout bladder filling		
Compliance: Normal >20mL/cmH_2O	Excellent: 62.5	Poor: 12.5
Participant 2	**Pre-implantation**	**Post-treatment**
Detrusor Function	Overactive; low contractility; tonic external sphincter activity	Underactive; tonic external sphincter activity
Urodynamic reading	EFDP 6 cm H2O/500 mL	
Intermittent low amplitude poorly sustained detrusor contractions to 15 cm H_2O occurring during bladder filling	EFDP 10 cm H2O/700 mL	
No detrusor instability		
Compliance: Normal >20mL/cmH_2O	Excellent: 83.3	Excellent: 70

EDFP: End-filling detrusor pressure; cm: centimeter; mL: millimeter.

Impact of EES on urologic function

Throughout the study, both participants' neurogenic bladder was managed by self-intermittent catheterization 4–6 times per day, with P2 taking anticholinergic medications as well. A summary of UDS recordings suggest conflicting changes between participants (Table 1). Prior to EES, P1 was noted to have an underactive bladder with excellent compliance, and did not require any pharmacologic intervention. Although there was not a detectable change in voiding habits at the completion of the study, his UDS revealed a substantial alteration from a compliant, underactive bladder to an overactive, poorly compliant bladder with sustained detrusor pressure during the filling phase that reached a peak of 75 cmH_2O (Table 1). Upon enrollment, P2 had a history of overactive bladder with associated detrusor sphincter dysynergy, however well controlled with anticholinergics medication. He maintained on anticholinergics throughout the study, and during end of study cystometry testing. P2 had minimal change in compliance and maximum detrusor pressures at the completion of the study. Finally, The NBSS sub-scores show conflicting results, especially related to urinary incontinence as the study progressed, with P1 noting increase episodes of incontinence, and P2 with reduced occurrence of incontinence and consequences such as urinary tract infection (UTI). P2 developed an additional symptomatic UTI at the 6-month time point of MMR sessions, and was treated with antibiotics. Both participants were symptomatic of UTI within two weeks after EES surgical implant; P2 did receive antibiotic treatment. No further symptomatic UTIs were identified while receiving EES treatment for either participant.

Body composition

Body composition and bone mineral density (BMD) values are summarized in Table 2. Throughout the 12 months of the MMR both participants' BMD remained relatively unchanged with minor changes in their *t*-score values. Both participants showed a substantial increase in body mass over the course of 12 months of MMR. Upon noticing substantial increase in lower leg girth for P1, a protocol modification was approved to include detailed body composition measures for P2. Additional testing for P2 revealed improvements in lean body mass, body fat mass, and android/gynoid ratio for the initial 6 months of MMR. However, P2 also showed regression in all of these values following the completion of the remaining 6 months of MMR. Furthermore, P2 saw increases in thigh circumference at the 10 and 20 cm locations for both legs for the initial 6 months of MMR, and again showed regression in the following 6 months of MMR (Table 2).

Discussion

We report varied results in bladder function and body composition in two participants in a clinical trial initiated to investigate the effect of EES and motor rehabilitation in individuals with paraplegia. Of concern, we identified increased and sustained bladder pressures during the fill phase of UDS of P1, which we did not observe in P2. Additionally, a notable difference between the participants is the continuation of anticholinergic medications for P2 that potentially prevented dangerous bladder pressures and maintained compliance. The change in bladder pressures noted during the UDS correlates with the NBSS of P1, as he experienced increased episodes of urinary incontinence.

Table 2 Body composition, bone mineral density t-score summaries and thigh circumference.

Participant 1	**Post-Surgery**	**Month 6 of MMR**	Δ^1	**Month 12 of MMR**	Δ^1
Total body mass (kg)	76.8	80.7	+ 3.9	81.8	+5.0
BMD L Hip	−3.2	−3.2	0.0	−2.8	+0.4
BMD R Hip	−2.8	−2.9	−0.1	−2.9	−0.1
Participant 2	**Post-Surgery**	**Month 6 of MMR**	Δ^1	**Month 12 of MMR**	Δ^1
Total mass (kg)	84.8	92.7	+7.9	93.3	+8.5
Lean body mass (kg)	52.8	61.9	+9.1	59.6	+6.8
Bone mineral mass (kg)	2.85	2.8	−0.5	2.7	−1.85
Fat mass (kg)	29.1	28.0	−1.1	30.9	+1.8
Body fat (%)	35.5	31.2	−4.3	34.1	−1.4
Android (%)	46.6	37.1	−9.5	44.5	−2.1
Gynoid (%)	38.0	34.3	−3.7	33.4	−4.6
Android/Gynoid ratio	1.23	1.08	−0.15	1.33	+0.1
BMD L Hip	−1.5	−1.6	−0.1	−1.8	−0.3
BMD R Hip	−1.8	−1.9	−0.1	−1.7	+0.1
Right Thigh 10cm	42.6	44.8	+2.2	45	+2.4
Right Thigh 20 cm	48.8	52.7	+3.9	51.9	+3.1
Left Thigh 10cm	43.0	45.1	+2.1	44.3	+1.3
Left Thigh 20cm	49.0	53.1	+4.1	51.9	+2.9

BMD: bone mineral density; MMR: multi-modal rehabilitation; kg: kilogram; L: left; R: right; Δ^1 change since baseline.

However, due to the small sample size reported here, it is not possible to determine if EES alone or MMR had any influence on P1's bladder compliance. P1 had been followed clinically at our facility 3 years prior to study enrollment, and his bladder management and compliance was stable during this time. A previous case study by Harkema *et al.*[9] reported improvements in autonomic function, including the ability to voluntarily void with minimal residual volume, following EES with intense rehabilitation. Recent studies have targeted EES parameters to modulate autonomic circuits responsible for bladder and bowel function near the pelvic parasympathetic outflow using the caudal parts of the electrode array.[10,11] These studies have shown the ability to modulate the external anal sphincter, pelvic floor muscle tone, and detrusor pressures, noting the potential to enhance function. Our participants reported here did not attempt bladder voiding or bowel function with stimulation during 12 months of MMR sessions.

To our knowledge this is the first description of bladder function over the course of EES with motor rehabilitation in a patient that was not taking anticholinergic medications. Specifically, due to the concerns for side effects and possible long-term concerns regarding the use anticholinergic agents, we do not use, nor would we recommend, the use of pharmacologic agents to control bladder dynamics unless indicated.[12,13] The alterations in bladder storage pressures found in this isolated incidence does raise concerns regarding risks that may arise in patients with neurogenic bladders while undergoing long term EES, and fuels the need for additional studies, focused on autonomic functions, to determine the true incidence of the alterations that can occur within these parameters while undergoing EES use alone, or in combination with MMR sessions. Walter *et al.*[10] investigated EES when specifically mapped to the caudal region of a person with C5 AIS B, their time needed for bowel care reduced by 55%, from 58 minutes to 26 minutes. In both of our participants, there were no noted changes in frequency, management or timing of their bowel program, however, stimulation was not specifically mapped to achieve this goal. Subjectively, both noted the ability to manage their respective bowel program in less than 30 minutes at the start and throughout study.

As soon as two months following an SCI, an individual typically begins to show an increase in body fat mass, and this mostly occurs in the abdominal region.[14] This shift can be attributed to the dramatic decrease in energy expenditure, and/or from the over consumption of nutrients. Furthermore, there typically is a substantial increase in muscle atrophy in paralyzed muscles.[15] Unfortunately, detailed body composition data was not collected on P1. DXA data collected on P2 showed an impressive increase in lean muscle mass of nearly 10 kg for the first 6 months of MMR. Additionally, P2's android-gynoid ratio improved from 1.23 to 1.08, which supports the finding of an increase in lean muscle mass and loss of fat mass. Similar to findings noted by Terson de Paleville *et al.*,[15] we found that P2 had considerable positive changes to his body composition during the initial 6 months of combining intense task specific training and stimulation use. During the final 6 months of MMR, lean body mass decreased, fat mass increased, body fat percent increased and the android/gynoid ratio increased to beyond baseline values. The regression of these positive changes could be related to the decline in stimulation use by the participant, and therefore, a decline in physical activity from a reduction in MMR participation.

A recent study by Solinsky *et al.*[16] surveyed SCI physicians within the United States Spinal Cord Injury Model System. Several barriers were cited related to the clinical implementation of EES for persons with SCI, yet the majority of physicians surveyed felt the intervention to be safe. Additionally, the authors called for future efficacious studies with defined qualitative endpoints to move this technology into clinical practice. We concur with the authors for the need to report and characterize potential risks to allow patients to make informed decisions. EES may affect bladder pressures, as noted here. Careful monitoring is warranted to avoid undue risks to the upper urinary tracts and function. The importance of regular exercise to improve cardiovascular risk factors, body composition and metabolic profiles continues to grow for individuals with SCI. A potential adjunct exercise modality for improvements in body composition is through the use of EES to activate musculature below the level of injury in order to complete a variety of seated, standing and stepping activities to a higher intensity. Regularly participating in higher intensity exercise will generate greater energy expenditure in shorter duration when compared to moderate intensity steady state exercise, but more importantly has the potential to improve cardiorespiratory fitness, improve cardiometabolic risk factors and prevent cardiometabolic disease in SCI.[17] Long-term effects of EES has yet to be deciphered regarding overall benefits versus risks to establish this as a clinical treatment modality.

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Conflicts of interest KL has previously served as a consultant to Medtronic's Department of Technology Development focused on deep brain stimulation.

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References

1 Calvert JS, Grahn PJ, Zhao KD, Lee KH. Emergence of epidural electrical stimulation to facilitate sensorimotor network functionality after spinal cord Injury. Neuromodulation. 2019;22(3):244–52. doi:10.1111/ner.12938.

2 Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, *et al.* Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nat Med. 2018. doi:10.1038/s41591-018-0175-7.

3 Angeli CA, Boakye M, Morton RA, Vogt J, Benton K, Chen Y, *et al.* Recovery of over-ground walking after chronic motor complete spinal cord Injury. N Engl J Med. 2018. doi:10.1056/NEJMoa1803588.

4 Wagner FB, Mignardot JB, Le Goff-Mignardot CG, Demesmaeker R, Komi S, Capogrosso M, *et al.* Targeted neurotechnology restores walking in humans with spinal cord injury. Nature. 2018. doi:10.1038/s41586-018-0649-2.

5 Darrow D, Balser D, Netoff TI, Krassioukov A, Phillips A, Parr A, Samadani U. Epidural spinal cord stimulation facilitates immediate restoration of dormant motor and autonomic supraspinal pathways after chronic neurologically complete spinal cord injury. J Neurotrauma. 2019. doi:10.1089/neu.2018.6006.

6 Grahn PJ, Lavrov IA, Sayenko DG, Van Straaten MG, Gill ML, Strommen JA, *et al.* Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. Mayo Clin Proc. 2017. doi:10.1016/j.mayocp.2017.02.014.

7 Calvert JS, Grahn PJ, Strommen JA, Lavrov IA, Beck LA, Gill ML, *et al.* Electrophysiological guidance of epidural electrode array implantation over the human lumbosacral spinal cord to enable motor function after chronic paralysis. J Neurotrauma. 2019. doi:10.1089/neu.2018.5921.

8 Welk B, Morrow S, Madarasz W, Baverstock R, Macnab J, Sequeira K. The validity and reliability of the neurogenic bladder symptom score. J Urol. 2014. doi:10.1016/j.juro.2014.01.027.

9 Harkema S, Gerasimenko Y, Hodes J, Burdick J, Angeli C, Chen Y. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet. 2011. doi:10.1016/S0140-6736(11)60547-3.

10 Walter M, Lee AHX, Kavanagh A, Phillips AA, Krassioukov AV. Epidural spinal cord stimulation acutely modulates lower urinary tract and bowel function following spinal cord injury: a case report. Front Physiol. 2018. doi:10.3389/fphys.2018.01816.

11 Herrity AN, Williams CS, Angeli CA, Harkema SJ, Hubscher CH. Lumbosacral spinal cord epidural stimulation improves voiding function after human spinal cord injury. Sci Rep. 2018. doi:10.1038/s41598-018-26602-2.

12 Dray EV, Cameron AP. Identifying patients with high-risk neurogenic bladder: beyond detrusor leak point pressure. Urol Clin N Am. 2017. doi:10.1016/j.ucl.2017.04.010.

13 Chancellor MB, Watanabe T. Making a case for not prescribing antimuscarinic drugs to treat overactive bladder in older adults. J Urol. 2019. doi:10.1016/j.juro.2018.09.061.

14 Maher JL, McMillan DW, Nash MS. Exercise and health-related risks of physical deconditioning after spinal cord injury. Top Spinal Cord Inj Rehabil. 2017. doi:10.1310/sci2303-175.

15 Terson de Paleville DGL, Harkema SJ, Angeli CA. Epidural stimulation with locomotor training improves body composition in individuals with cervical or upper thoracic motor complete spinal cord injury: a series of case studies. J Spinal Cord Med. 2019. doi:10.1080/10790268.2018.1449373.

16 Solinsky R, Specker-Sullivan L, Wexler A. Current barriers and ethical considerations for clinical implementation of epidural stimulation for functional improvement after spinal cord injury. J Spinal Cord Med. 2019. doi:10.1080/10790268.2019.1666240.

17 Nightingale TE, Metcalfe RS, Vollaard NB, Bilzon JL. Exercise Guidelines to promote cardiometabolic health in spinal cord Injured humans: time to raise the intensity? Arch Phys Med Rehabil. 2017. doi:10.1016/j.apmr.2016.12.008.