BRIEF REPORT

Recovery of Over-Ground Walking after Chronic Motor Complete Spinal Cord Injury

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SUMMARY

Persons with motor complete spinal cord injury, signifying no voluntary movement or sphincter function below the level of injury but including retention of some sensation, do not recover independent walking. We tested intense locomotor treadmill training with weight support and simultaneous spinal cord epidural stimulation in four patients 2.5 to 3.3 years after traumatic spinal injury and after failure to improve with locomotor training alone. Two patients, one with damage to the mid-cervical region and one with damage to the high-thoracic region, achieved over-ground walking (not on a treadmill) after 278 sessions of epidural stimulation and gait training over a period of 85 weeks and 81 sessions over a period of 15 weeks, respectively, and all four achieved independent standing and trunk stability. One patient had a hip fracture during training. (Funded by the Leona M. and Harry B. Helmsley Charitable Trust and others; ClinicalTrials.gov number, NCT02339233.)

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There are estimated to be 1,275,000 persons with paralysis from spinal cord injury in the United States.[1] These patients indicate in surveys that walking and standing are highly desirable goals.[2] We have previously shown that epidural stimulation of the spinal cord and simultaneous intense rehabilitation may allow the restoration of some volitional movement below the level of spinal injury[3,4] and may result in the ability to stand independently.[5,6] We report here recovery of independent walking over ground, not on a treadmill, in two of four patients with motor complete paralysis, with the use of a program that combines customized epidural spinal cord stimulation and intense training in standing and stepping.

The study was approved by the institutional review board at the University of Louisville and was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent. All the authors vouch for the completeness and accuracy of the data and the reporting of adverse events and for the adherence of the study to the protocol, available with the full text of this article at NEJM.org. Medtronic provided the epidural electrode arrays, neurostimulators, programming devices, and recharging units to the Kentucky Spinal Cord Injury Research Center at the University of Louisville. There was no other industry involvement, and no funds were given by Medtronic to the institution, investigators, or research participants. The delay between active intervention for the first patient (November 11, 2014) and registration of the study (January 12, 2015) is explained in the Supplementary Appendix, available at NEJM.org.

PATIENT CHARACTERISTICS

Four participants with traumatic, motor complete spinal cord injury, meaning the absence of voluntary movement below the level of injury with or without some preserved sensation, began study treatment 2.5 to 3.3 years after their injury (Table 1). The participants are numbered in the order of their enrollment into the program. They are the only patients who have been treated under this protocol as of September 7, 2018. The spinal cord segmental level of injury, or neurologic level, was identified by the highest level above which there was normal motor and sensory function. The American Spinal Injury Association Impairment Scale (AIS) was used to classify the completeness of the spinal cord injury.[7] In brief, motor complete injury (AIS grade A) is defined as loss of sensory and motor function below the level of injury, including at the S4–S5 level, and sensory incomplete injury (AIS grade B) is defined as loss of motor function, including an inability to contract the anal sphincter, but some spared sensation below the level of injury. Motor function was assessed by the ability to move a joint voluntarily for five joints, representing motor segments from C5 to T1 (arms) and L2 to S1 (legs), with a score of 0 (no muscular contraction) to 5 (normal power) for each segment and a total score of 0 to 25 for each arm or leg (Table 1). Sensation was assessed by response to pinprick and separately to light touch, with a score of 0 (absent) to 2 (normal sensation) for each sensory segment (T10 to S5, with S4 and S5 counted as one dermatome) and a total score of 0 to 48 for each side (left or right).

Participants 1 and 2 had a T4 spinal cord injury level with no movement or sensation below that level (AIS grade A), Participant 3 had a C5 spinal cord injury level and partially retained sensation to light touch, but not pinprick, below that level (AIS grade B), and Participant 4 had a T1 spinal cord injury level with partially retained sensation to light touch and pinprick below that level (AIS grade B) (Table 1). None had voluntary sphincteric control.

STUDY PROCEDURES

After recovery from their injury and conventional clinical rehabilitation, the participants were unable to stand, walk, or voluntarily move their legs. Each then received intense locomotor training in our program for 5 days per week for 2 hours, over a period of 8 or 9 weeks before implantation of an epidural stimulator (Fig. 1). This training was performed on a treadmill with body-weight support and manual facilitation of stepping (for details of rehabilitation preceding epidural stimulation, see the Supplementary Appendix), and it resulted in no changes to locomotor ability, as gauged by the lack of ability to stand or walk independently either on the treadmill or over ground. The neurologic level, voluntary movement, and sensation below the level of injury did not change after this period of training.[7] Neurophysiological assessments that used surface electromyographic (EMG) recording during attempted voluntary muscle contraction did not detect activation of muscles below the neurologic motor level.[8]

INITIATION OF EPIDURAL STIMULATION

Participants had a 16-electrode array (see the Supplementary Appendix) implanted epidurally over spinal segments L1 to S1–S2 and a spinal cord stimulator implanted surgically in the anterior abdominal wall. The electrode array was inserted over the midline of the exposed dura and positioned by determination of the minimal amplitude of stimulation necessary to activate the soleus, medial gastrocnemius, tibialis anterior, medial hamstring, rectus femoris, and vastus lateralis muscles, as detected by EMG recording electrodes. Stimulation was at a frequency of 2 Hz, and EMG was recorded with surface electrodes over the muscles, but with wire electrodes in the iliopsoas muscles. Multiple bipolar stimulation configurations were tested with the use of midline and left and right electrode pairs within the array. After positioning and placement of the array, wire leads were tunneled subcutaneously to the abdomen and connected to the stimulator.

STIMULATION SETTINGS

After an approximately 20-day postsurgical period to allow healing around the electrode array and the abdominal incision, we used EMG to identify the extensor and flexor muscle groups that were activated by stimulating each epidural anode and cathode combination at 2 Hz while the patient was supine (see the Supplementary

Table 1. Clinical Characteristics of Four Participants Trained under the Same Training Paradigm.*

Participant No.	Age in Years	Years since Injury	Neurologic Level	AIS Grade	AIS Component									
					Sensory Score				Motor Score				Anal Sensation	Anal Contraction
					LT, Left Side	PP, Left Side	LT, Right Side	PP, Right Side	Left Leg	Right Leg	Left Arm	Right Arm		
At time of epidural electrode implantation														
1	26	2.5	T4	A	0	0	0	0	0	0	25	25	No	No
2	23	3.1	T4	A	0	0	0	0	0	0	25	25	No	No
3	32	3.3	C5	B	8	0	10	0	0	0	11	12	Yes	No
4	22	3.3	T1	B	17	5	17	9	0	0	25	25	Yes	No
At end of training with epidural stimulation														
1	29	5.0	T4	A	0	0	0	0	0	0	25	25	No	No
2	24	4.2	T4	A	0	0	0	0	0	0	25	25	No	No
3	34	5.9	C4	C	7	0	11	0	0	1	11	12	Yes	No
4	23	3.8	T1	B	15	0	17	0	0	0	25	25	Yes	No

* The neurologic level was derived from sensory and motor scores on the American Spinal Injury Association Impairment Scale (AIS). AIS grades can be A (motor and sensory complete injury), B (motor complete and sensory incomplete injury), and C or D (motor and sensory incomplete injury). AIS grades C and D are differentiated by the percent of muscles below the level of injury that can move against gravity (grade C, <50%; grade D, ≥50%). Scores for sensation to light touch (LT) and pinprick (PP) range from 0 to 48 for each side (left or right), with each of 12 segments (T10 to S5, with S4 and S5 counted as one dermatome) scored as 2 (normal sensation), 1 (impaired sensation), or 0 (absent). Scores for motor function in the legs range from 0 to 25 for each leg, with each of five segments (L2 to S1) scored as 0 (total paralysis), 1 (palpable or visible muscle contraction), 2 movement with gravity eliminated, 3 movement against gravity, 4 less than full power, or 5 normal. Scores for motor function in the arms range from 0 to 25 for each arm, with each of five segments (C5 to T1) scored as 0 (total paralysis), 1 (palpable or visible muscle contraction), 2 movement with gravity eliminated, 3 movement against gravity, 4 less than full power, or 5 normal.

	Participant 1	Participant 2	Participant 3	Participant 4
Training and Implantation	Standing and stepping, both same day for 8 wk	Standing and stepping, both same day for 9 wk	Standing and stepping, both same day for 9 wk	Standing and stepping, both same day for 8 wk
	Implantation			
	Standing with stimulation or stepping with stimulation, twice daily for 1 wk	Standing with stimulation or stepping with stimulation, once daily for 24 wk	Standing with stimulation or stepping with stimulation, once daily for 23 wk	Standing with stimulation or stepping with stimulation, once daily for 5 wk
	Medical hold for 52 wk		Standing with stimulation and stepping with stimulation, both same day for 15 wk	
	Standing with stimulation, once daily for 10 wk		Stepping with stimulation, once daily for 47 wk	Standing with stimulation and stepping with stimulation, both same day for 19 wk
	Standing with stimulation or stepping with stimulation, once daily for 39 wk	Standing with stimulation and stepping with stimulation, both same day for 17 wk		
	Standing with stimulation and stepping with stimulation, both same day for 13 wk			
Outcome	Independent swing, only on treadmill	Unilateral independent stepping on treadmill	Independent over-ground walking	Independent over-ground walking

Figure 1. Training and Outcome for Participants Enrolled in the Study.

Shown is a graphic representation of the training. Participants received training on over-ground standing (1-hour session) and stepping on the treadmill (1-hour session), both on the same day, before implantation of epidural electrodes and after standard clinical rehabilitation. After implantation, a training session on standing or on stepping with epidural stimulation was performed once a day, or training sessions of both types were performed on the same day. Dark gray shading indicates training sessions involving epidural stimulation. Outcomes were achieved only with epidural stimulation. Independent swing (for Participant 1) is defined as the advancement phase of the leg during each step.

Appendix for details). We then tested multiple anode and cathode stimulation combinations of amplitude and frequency to obtain quantitative information on which ones caused rhythmic activation of ensembles of leg muscles that simulated walking movements. Combinations were selected that enhanced standing and stepping movements while participants focused on each of these tasks. Quantitative EMG activity from these assessments was used to select the final configurations of stimulation settings for standing or stepping (see the Supplementary Appendix).

LOCOMOTOR TRAINING WITH EPIDURAL STIMULATION

A session denotes training with the epidural stimulator turned on. Trials were also conducted in an unblinded fashion to determine whether motor achievements were sustained with the epidural stimulator turned off. There were three types of training sessions: stepping on a treadmill, over-ground standing, and over-ground walking, with each type of session performed daily, except for over-ground walking, which occurred only if the preceding skill was attained. Each session lasted 1 hour, and there were one or two training sessions per day; stepping sessions were interspersed with over-ground walking sessions when appropriate. For training sessions on standing, participants were placed in a custom-built apparatus that allowed weight bearing and the ability for the participants to use their arms to aid in posture and balance. Manual assistance at the knees and hips was provided by trainers when needed. Training sessions on stepping used body-weight support on a treadmill and manual assistance by trainers to move the legs through the step cycle if needed, during which the participant made voluntary attempts to perform elements of the step cycle.

Videos showing training and outcomes are available at NEJM.org

Both standing and stepping stimulation configurations were modified every 2 to 4 weeks to determine whether adjustments resulted in better standing and stepping, on the basis of observation and EMG activity. During over-ground walking sessions, speed was calculated over a distance of 10 m and averaged over three trials, and the total distance walked in a session was recorded.

RESULTS

Two of the four participants (Participants 3 and 4, both AIS grade B) were able to walk over ground with assistive devices after intensive physical training with electrical stimulation of the lower spinal cord. The other two (Participants 1 and 2, both AIS grade A) achieved some components of independent stepping on the treadmill with body-weight support but not over-ground walking. All four participants could not do these actions in trials when the stimulator was off. Motor and sensory scores for three participants did not change from the scores before implantation. In Participant 3, the motor score improved from 23 to 24 and the sum of the sensory scores from 83 to 86 (Table 1, and Fig. S1 in the Supplementary Appendix).

Participant 1 had a spontaneous hip fracture (he was stepping on the treadmill with body-weight support) after 1 week of training, without a fall, and resumed training 1 year later. He had a total of 176 sessions over a period of 62 weeks, after which he could stand with a walker. Participant 2 was able to produce continuous steps on the treadmill with one leg at a time after 40 sessions over a period of 14 weeks with 60% body-weight support and treadmill speeds of 0.22 to 0.67 m per second. He achieved unsupported sitting and standing with a walker but not over-ground walking after a total of 159 sessions over a period of 41 weeks.

Participant 3 was able to step the right leg independently on the treadmill with 35% body-weight support after 160 sessions over a period of 36 weeks. The transition to over-ground walking occurred after achievement of independent stepping of the right leg and an independent extension of the left leg on the treadmill after 278 total training sessions over a period of 85 weeks. This participant was able to walk over ground during epidural stimulation while using horizontal poles for balance or when holding hands with two persons (one on each side) (Fig. 2A, and Video 1, available at NEJM.org). Muscle activation during walking was timed appropriately to the step cycle, as detected by surface EMG recording (Fig. S2A in the Supplementary Appendix). During epidural stimulation, he could walk over ground only when he intended to walk, not otherwise, and the pattern of EMG activation was different when he intended to step on the treadmill than when he did not intend to (Figs. S3 and S4 in the Supplementary Appendix). When this participant stopped his mental intention to walk, he was unable to move his legs.

Walking speed (Fig. S2B in the Supplementary Appendix) and continuous walking distance improved in Participant 3 during the next 80 over-ground walking sessions, reaching 90.5 continuous meters without a rest and a total of 362 m during an interrupted 1-hour session. He reached a maximum speed of 0.19 m per second and was limited in speed and distance by imbalance and fatigue. He also regained the ability to stand independently using a walker during epidural stimulation (Fig. 2B and Video 2) and to sit independently for 5 minutes (Fig. 2C and Video 2, and Fig. S5 in the Supplementary Appendix).

Participant 4 achieved independent right-leg stepping on the treadmill with 50% body-weight support after 5 sessions over a period of 1 week. She transitioned to over-ground walking after 81 sessions over a period of 15 weeks and was able to achieve independent stepping of the right leg and an independent extension of the left leg on the treadmill (Fig. 2A and Video 3). At session 147, she was able to walk over ground with a walker and with no contact assistance from trainers. She also achieved independent standing for approximately 50 minutes at a time while holding on to elastic bands during epidural stimulation only (Fig. 2B and Video 4). She was completely independent during standing, without balance support by the arms, for 7 to 10 seconds at a time (Fig. 2B).

The only serious adverse event was a hip fracture in Participant 1, noted earlier. On the participant's return to the study, after 68 sessions,

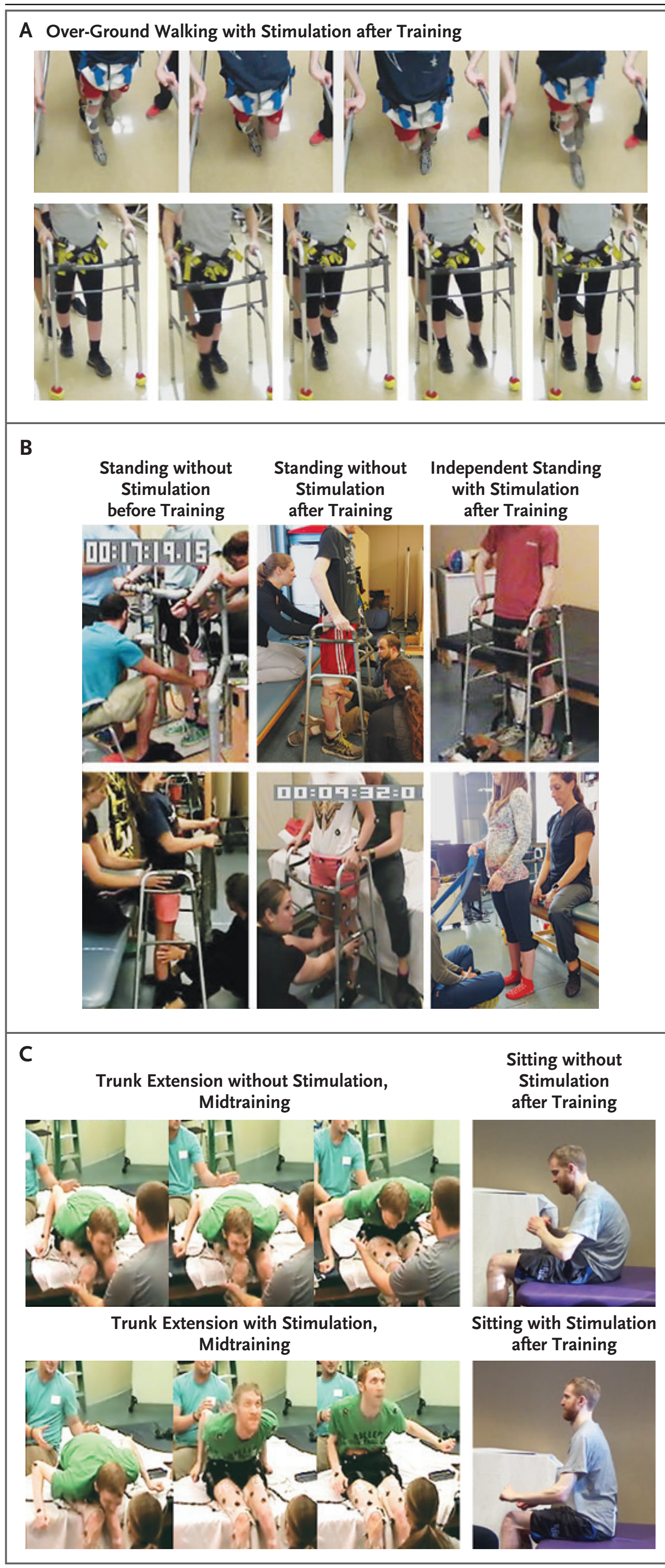

Figure 2. Walking over Ground.
Panel A shows a series of photographs of independent walking. Participant 3 (top) is walking with parallel poles for trunk stability. Participant 4 (bottom) is walking using a rolling walker. Panel B shows standing without stimulation (before and after training) and with stimulation (after training) for Participant 3 (top) and Participant 4 (bottom). Panel C shows Participant 3 performing trunk extension without and with stimulation after 89 locomotor training sessions and sitting without and with stimulation.

ankle edema developed on the right side. Adverse events are reported in Table S1 in the Supplementary Appendix.

DISCUSSION

We report the recovery of intentional walking over ground with programmed epidural spinal cord stimulation coupled with intense locomotor training in two of four persons who had chronic motor complete cervical or thoracic spinal cord injury. Walking had not been achieved with weight-supported locomotor training alone and was possible only when the stimulator was on and the patient intended to walk. Both persons had partially spared sensation below the level of neurologic injury. Walking over ground occurred after 278 locomotor training sessions over a period of 85 weeks and after 81 sessions over a period of 15 weeks. The other two participants, with motor and sensory complete thoracic injuries, did not achieve independent bilateral stepping after 176 sessions and could not transition to over-ground walking after 159 sessions; however, they were able to stand[5,6] and sit independently, milestones that were reported previously by our group and by others when epidural stimulation was used. The differences in outcomes between the two participants who were able to walk and the two who were not may have been due to sensory sparing or to other factors we are studying.

The execution of walking in persons with chronic motor complete spinal cord injury took place only during the combination of epidural stimulation and the participant's intention to engage in walking. This suggests that interneuronal networks in the lumbosacral spinal cord may be activated by the electrical stimulation through dorsal nerve roots and by direct stimulation of the parenchyma of the cord.[9] Furthermore, the complex, coordinated, and sequential activation of motor neurons, as reflected in rhythmic EMG activity in leg muscles, was appropriate for the step cycle and not entrained to the frequency of stimulation, which indicates that ensembles of neurons in the cord were activated. Standing[5,6,10] and voluntary movement[3,10] were not driven solely by electrical stimulation but occurred only with the intention to move and when the sensory information of weight bearing during standing was provided, which suggests that broad segmental and suprasegmental excitation of spinal networks is entrained for walking after cord injury by the technique we describe.[9,11-25]

The current study showed that recovery of walking, standing, and trunk mobility can occur under special circumstances with intensive training and electrical stimulation years after a spinal cord injury that caused complete leg paralysis. Persons with some degree of spared sensation below the level of injury may be more suitable candidates than those with no sensation, but this, and the durability of over-ground walking, requires investigation in larger groups of patients with spinal cord injury.

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