

Epidural Stimulation — Improving Results for Spinal Cord Injury

BY TOM VALEO

ARTICLE IN BRIEF

Investigators report incremental progress in using epidural stimulation to help people with spinal cord injury stand, walk, and move some muscles.

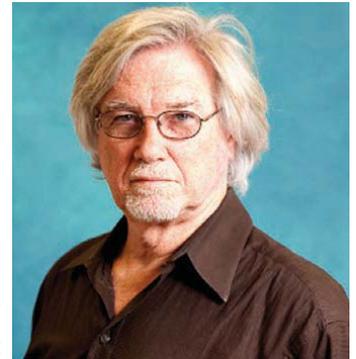
Analysis from a spinal cord injury, once considered permanent and unalterable, now yields somewhat to forms of electrical stimulation that enable paralyzed people to stand and, in some cases, to take a few steps, as researchers in the United States and Europe are demonstrating.

A group led by Susan Harkema, PhD — professor in the department of neurological surgery at the University of Louisville, rehabilitation research director at the Kentucky Spinal Cord Injury Research Center, and research director at Frazier Rehab Institute in Louisville

— and V. Reggie Edgerton, PhD, professor of integrative biology and physiology, and neurobiology at University of California, Los Angeles — made headlines in 2011 with a paper in *The Lancet* that described how they implanted a 16-electrode array between the vertebrae and the dura in the lumbar region of a 23-year-old man left paralyzed in 2006 by a lesion in the C7-T1 region of his spinal cord. Although the man retained some sensation, he had no motor function below



THE SUBJECT OF THE 2011 case report in *The Lancet* shown here stepping on a treadmill.



DR. V. REGGIE EDGERTON: “If you stimulate the spinal cord at high intensities, you can induce movement, but the proprioceptive information is overwhelmed. We stimulate just enough to change the circuitry, but not enough to evoke a motor response.”

A 32-year-old man who had been paralyzed for 4.2 years could move his legs as soon as the stimulator was turned on, and progressed to the point where he could move without stimulation.

the site of the lesion, no voluntary bladder contraction, and a flaccid anal sphincter. [See the *Neurology Today* report on the paper, “After Epidural Stimulation, Spinal Cord Injury Patient Stands and Treadmill Steps,” <http://bit.ly/mDaOx7>.]

Two years of traditional physical therapy failed to change his condition significantly, but after the Medtronic RestoreAdvanced array, normally used to control pain, was implanted in December of 2009, subsequent training enabled the man to stand on his own for up to 25 minutes at a time, and take a few assisted steps on a treadmill. He also developed the ability to move his toes, ankles, knees,

and hips voluntarily while the stimulator was on, and showed improvements in blood pressure, body temperature regulation, and other autonomic functions.

At the recent Society for Neuroscience meeting in New Orleans, Dr. Harkema and colleagues reported on two additional subjects who had been paralyzed for two to four years, who showed an even better response. “When we turned the stimulator on the first time, they both could move a toe,” said Claudia

questionnaires, perhaps skewing the results towards significantly better outcomes for those who received rt-PA,” he wrote in an e-mail.

tPA, Quality of Life

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better functional outcome will improve quality of life.”

That said, “it is still important to perform quality-of-life analyses like this,” he said. “As neurologists, we often focus on the neurological exam, but it is important to remember that to patients, quality of life is just as important.

“Not many treatments have been shown to improve quality of life for patients with acute ischemic stroke,” he added, “although with time and rehabilitation, many do improve.”

The benefits seen in the study — both in the main and the secondary analysis — “are pretty modest,” he said, and that is probably because patients were treated out to six hours, according to study data.

“Most of us don’t think that there is a significant enough improvement out

“The study was an open trial so that patients, relatives and medical provid-

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past 4.5 hours to warrant giving rt-PA,” Dr. Elkind said.

Antonio Culebras, MD, professor of neurology at Upstate Medical University in Syracuse, NY, said that bias may have skewed the results.

ers knew that patients had received the potent and highly admired ‘clot-buster.’

“One cannot eliminate the lingering suspicion that some bias clouded people’s answers to the study

FOR FURTHER READING:

- The IST-3 collaborative group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): A randomised controlled trial. *Lancet* 2012; 379: 2352–2363.

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A. Angeli, PhD, manager of the Human Locomotion Research Center at Frazier Rehab Institute, and assistant professor in the department of neurological surgery at the University of Louisville, who presented a poster on the work.

One patient — a 32-year-old man who had been paralyzed for 4.2 years — could move his legs as soon as the stimulator was turned on, and progressed to the point where he could move without stimulation. All three subjects also developed bladder sensation, and regained the ability to void without a catheter.

ANIMAL MODELS SUPPORT APPROACH

Animal experiments conducted by Dr. Edgerton over three decades have demonstrated that electrical stimulation can drive the spinal cord's own networks, enabling weight bearing and stepping without input from the brain. Such improvement does not require signals from the brain to pass through the lesion because the spinal cord itself is "smart," in Dr. Edgerton's opinion, and capable of "learning" to respond to stimulation which, when combined with therapy, produces some motor ability in the paralyzed legs.

"If you stimulate the spinal cord at high intensities, you can induce movement, but the proprioceptive information is overwhelmed," said Dr. Edgerton. "We stimulate just enough to change the circuitry, but not enough to evoke a motor response."

Dr. Edgerton, whose work on animals led to the development of the type of stimulation used on the subjects, emphasized that feedback provided by

proprioception helps the human subjects stand. If they sit in a chair, move forward until they get some weight on their legs and feel some proprioceptive feedback, the muscle memory in their legs appears to be activated, Dr. Edgerton explained, allowing them to stand up using only signals from the spinal cord.

However, the robust response of the three subjects studied so far leave

open the possibility that some partially damaged but dormant neurons that pass through the lesion may have been "awakened" by the stimulation. With training, the subjects developed an improved ability to move their toes, flex their ankles, and initiate other voluntary movements while the stimulator is on. One subject even regained some voluntary movement without stimulation.

"We don't think it's regeneration," said Dr. Harkema. The biggest obstacle at the moment is the stimulator itself, which was never designed for such use.

"It was good enough to demonstrate proof of principle," Dr. Edgerton said. "We're working on something better. The technology we need is on the shelf,

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DR. SUSAN HARKEMA and colleagues have received FDA approval to proceed with epidural stimulation of two more paralyzed subjects. The biggest obstacle at the moment is the stimulator, she said, which must be modified. The team is developing a new device expected to be available in five years.

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and we're working with engineers to design a unit specifically for this."

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sophisticated enough," said Dr. Harkema. "It could use a feedback system."

She and her colleagues are working with engineers at the California Institute of Technology (Caltech) and the University of Louisville to develop a new device, which she expects to be available to patients within five years.

CHANGES IN CENTER OF GRAVITY

Karen Minassian, PhD, a research associate at the Institute of Analysis and Scientific Computing of Vienna University of Technology, and Center of Medical Physics and Biomedical Engineering at Medical University of Vienna in Austria, said the most remarkable and "surprisingly underestimated" aspect of the work by Dr. Harkema and her colleagues is their demonstration that muscles of paralyzed people respond to changes of the center of gravity when standing. "To my best knowledge this was the first direct demonstration of a spinal mechanism in humans involved in body-posture and equilibrium control," said Dr. Minassian. "To quote Dr. Edgerton, the spinal cord really is 'smart.' Both techniques evoked electrophysiologically identical muscle twitches."

Dr. Minassian, who co-authored a chapter explaining transcutaneous lumbar posterior root stimulation in the recently published textbook, *Restorative Neurology of Spinal Cord Injury* (Oxford University Press), helped design the trial reported by Dr. Harkema and colleagues in the 2011 *Lancet*, but was not involved in their current work. •

FOR FURTHER READING:

- Dimitrijevic MR, Kakulas BA, McKay WB, and Vrbova G, eds. *Restorative Neurology of Spinal Cord Injury*, Oxford University Press 2012.
- Harkema S, Gerasimenko Y, Edgerton VR, et al. 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; 377(9781):1938-1947. E-pub 2011 May 19.
- *Neurology Today* archive on spinal cord injury: <http://bit.ly/T661YF>.

NEWS FROM THE SOCIETY FOR NEUROSCIENCE ANNUAL MEETING

Stimulation to Decrease Muscle Activation in Spinal Cord Injury

BY TOM VALEO

In their most recent work, Aiko K. Thompson, PhD, and Jonathan R. Wolpaw, MD, have been using stimulation to decrease rather than increase muscle activation in people with spinal cord injuries.

Unlike Dr. Harkema and her colleagues, they have been training people with spinal cord damage to suppress the uncontrolled activation that produces spasticity, which disrupts the coordinated muscle contractions that make walking possible.

"We showed many years ago that animals could learn to change the size of a simple spinal reflex — the knee-jerk reflex — that was thought to be fixed," said Dr. Wolpaw, chief of the Laboratory of Neural Injury and Repair at the Wadsworth Center of the New York State Department of Health and State University of New York (SUNY). "Monkeys, rats, and mice could make these reflexes bigger or smaller when given a specific training task and rewarded with a food pellet. What they're learning to control is the descending activity from the brain down to the spinal cord, which can vary widely."

Most of the subjects tested — about 75-80 percent — can learn to do this, too, and thereby improve their walking, according to a poster presented at the Society for Neuroscience meeting in New Orleans by Dr. Wolpaw; Dr. Thompson, associate professor at SUNY at Albany, an assistant professor at Columbia University Medical Center, and a research scientist at Helen Hayes Hospital in West Haverstraw, NY; and Ferne R. Pomerantz, MD, director of the Spinal Cord Injury Program at Helen Hayes Hospital.

The human subjects received mild electrical stimulation to the back of the knee, which elicits an H-reflex in the soleus muscle, one of the calf muscles. Guided by a vertical bar on a video screen that indicates the size of the reflex, they tried to suppress it. If they held it below a specified level they were "rewarded" by the sight of a green bar.

"They figure out by trial and error how to produce the type of descending activity that produces a green bar," Dr. Wolpaw said. "They talk about using imagery, meditation, or other types of mental actions to change the descending activity, but it's not clear how informative these descriptions are. In any case, the important fact is that the reflex changes in the correct direction."

Humans, like monkeys, need about 1,000 trials (about four one-hour training sessions) to learn how to decrease the reflex, and then they continue to perform this feat in subsequent sessions. Control subjects received the same number of trials, but without the feedback indicating reflex size.

The H-reflex pathway, like other reflex pathways, is important for walking. "In walking that's impaired by spinal cord injury, these reflex pathways often become too strong and no longer support locomotion," Dr. Wolpaw said. "If we take a pathway that's too strong and active in people with incomplete partial spinal cord injuries, and we make it weaker using this procedure, will their walking get better?"

The answer is yes, according to the results of the study. "Subjects who managed to reduce the H-reflex to about 70 percent of the original got significantly better at walking," Dr. Wolpaw said. "They weren't limping as much. One went from a walker to a cane. But they all walked faster, and they walked more symmetrically. The muscles in both legs behaved more normally and contributed more strongly to locomotion than before."

Keith Tansey, MD, PhD, research faculty in neurology and physiology at the Emory University School of Medicine, and director of Spinal Cord Injury Research at the Crawford Research Institute Shepherd Center in Atlanta, said suppressing an H-reflex is fundamentally different from the type of lumbar spinal cord stimulation being done by Dr. Harkema and the researchers in Vienna because it relies on input from above the spinal lesion.

Both, however, "could theoretically be used to improve function," he said, especially in patients with incomplete injuries. "Presumably, however, the greater the spinal cord injury, the less corticospinal or other descending tract there is with which to modulate spinal reflexes."

However, by showing that patients with incomplete injuries can suppress the H-reflex, Dr. Wolpaw and his colleagues have provided encouraging evidence by demonstrating that such patients can learn to reduce spasticity, a major obstacle to improved mobility.

"They've built a nice body of work over the last 10-15 years," he said of Dr. Wolpaw and colleagues. "They've shown that spinal circuitry is modifiable. Training patients to use relaxation techniques to reduce spasticity has met with success in some cases. I don't think this group set out to make spinal cord injuries better, but if you can train patients to reduce H-reflexes, that could help reduce spasticity. And maybe it could go the other way — maybe they can be trained to improve voluntary movements."