Association of Epidural Stimulation With Cardiovascular Function in an Individual With Spinal Cord Injury

The application of epidural electrical stimulation to the lumbosacral spinal cord in individuals with a spinal cord injury (SCI) facilitates supraspinal control of paralyzed limbs. There is a growing interest in studying whether epidural stimulation can be leveraged to also abrogate cardiovascular dysfunction, as evidenced by ongoing randomized clinical trials on this topic (NCT02037620; NCT03026816). Here, we investigated whether lumbosacral epidural stimulation could be optimized to control cardiovascular functions in the short term, at a top health priority and primary cause of death, in 1 individual with a motor-complete cervical SCI.

Methods | A man in his early 30s with a chronic C5 motor-complete SCI (ASIA impairment scale B) who was previously (12 months prior) fitted with an epidural spinal cord stimulation unit and 16-electrode array (Restore-ADVANCED and Specify 5-6-5; Medtronic) at T11-L1 vertebral levels was assessed. The placement was confirmed via radiography (Figure 1A). The participant gave his written informed consent. This study was approved by the University of British Columbia Clinical Research Ethics Board.

We first conducted a series of tests (over 2 weeks) to determine the optimum stimulation parameter to increase blood pressure (BP) in the seated position, ultimately selecting a wide-field stimulation configuration (Figure 1A; frequency, 35 Hz; pulse width, 300 milliseconds; intensity, 3.5 V). On the main experimental day, we assessed beat-by-beat BP via finger photoplethysmography (Finometer PRO; Finapres Medical Sy...
tems) corrected to brachial BP (Dinamap Pro 300V2; General Electric), cardiac function using transthoracic echocardiography (Vivid7; General Electric Healthcare), cerebral blood flow/neurovascular coupling by transcranial Doppler (ST3; Spencer Technologies), and trunk/lower-limbelectromyography (Bagnoli; Delsys Inc). All procedures were initially assessed in the supine position and then in response to a 60° head-up tilt, with and without epidural stimulation. To confirm the reliability of our findings, we reassessed the blood pressure response to a 60° head-up tilt (with and without epidural stimulation) on 3 separate days.

Results | The stimulation resolved the orthostatic hypotension (Figure 1B), which is a debilitating and prevalent condition in SCI.3 The rise in BP in response to stimulation was well-controlled and did not increase uncontrollably, as it does during autonomic dysreflexia (Figure 1B).4 In the brain, the stimulation prevented the orthostatic-induced 30% decrease in middle cerebral artery blood flow (Figure 1B), improved neurovascular coupling (Figure 1C), and resolved orthostatic-induced symptoms, including light-headedness, dizziness, and poor concentration, that were self-reported without stimulation. The stimulation also prevented the reduction in cardiac filling (ie, end-diastolic volume) during tilt (Figure 1D), thereby preserving stroke volume and cardiac output. The general lack of lower-limb electromyography during stimulation indicates that the skeletal muscle contraction was not leading to venous pump-mediated increases in BP and venous return (Figure 1E).

Discussion | To our knowledge, this study is one of the first to demonstrate the acute cardiovascular benefits of lumbosacral epidural stimulation in an individual with SCI that spanned the systemic vasculature, heart, and brain. That we found an immediate benefit in integrated cardiovascular responses raises the possibility that epidural stimulation can excite sympathetic circuitry and instantaneously modulate cardiovascular function in individuals with SCI. The possi-

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**Figure 2. Theoretical Mechanisms by Which Epidural Stimulation Affects Cardiovascular Function**

A. Descending sympathetic pathways from the rostral ventrolateral medulla (RVLM) in an intact spinal cord, leading to efficacious action potentials (ie, depolarization) in sympathetic circuitry, allow for supraspinal control over vascular tone (ie, vasoconstriction) and blood pressure. B. Interrupted descending sympathetic pathways due to an anatomically incomplete spinal cord injury (SCI), in which a few preserved descending sympathetic fibers crossing the site of injury are not capable of eliciting action potentials in sympathetic circuitry caudal to injury. C. Epidural spinal electrical stimulation (Stim) may increase the resting membrane potential of sympathetic circuitry caudal to the spinal cord injury, allowing for the previously nonefficacious preserved descending sympathetic fibers crossing the site of injury to actively regulate caudal sympathetic circuits and thereby restore control of vascular tone and blood pressure. D. Epidural electrical stimulation stimulates dorsal afferent relays, which likely affect the membrane potential of intersegmental and intrasegmental neurons that (1) receive direct input from descending sympathetic pathways and (2) directly and indirectly lead to depolarization of sympathetic preganglionic neurons, leading to regulation of vascular tone. The dotted lines indicate the depolarization threshold and the arrowheads indicate the response in the blood vessel (ie, when depolarization occurs then constriction of the artery occurs).
bility of using electrical spinal cord stimulation to modulate hemodynamics in isolated vascular beds and/or organs has been investigated in various settings and species, with the primary intent of alleviating pain, but to our knowledge, this is one of the first demonstrations that acute lumbosacral epidural stimulation modulates multiple facets of the cardiovascular system concomitantly, following motor-complete cervical SCI. We postulate that epidural stimulation can specifically modulate cardiovascular function by increasing the resting membrane potential of sympathetic fibers which one of the first demonstration that acute lumbosacral epidural stimulation modulates multiple facets of the cardiovascular system concomitantly, following motor-complete cervical SCI. We postulate that epidural stimulation can specifically modulate cardiovascular function by increasing the resting membrane potential of sympathetic fibers (Figure 2).

These preliminary data suggest that epidural neuroprosthetics may be a viable approach to manage cardiovascular dysfunction in individuals with chronic SCI and provide an important complement to pharmacological agents that are often slow-acting with undesirable adverse effects.

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COMMENT & RESPONSE

Assessing Tremor and Adverse Events in Patients With Tremor-Dominant Parkinson Disease Undergoing Focused Ultrasound Thalamotomy

To the Editor We read with interest the article of Bond et al1 regarding focused ultrasonographic thalamotomy for the treatment of patients with Parkinson disease.1 In our experience,2-4 which was not referenced in this article, Unified Parkinson Disease Rating Scale scores and Parkinson Disease Questionnaire—39 scores are significantly improved with this procedure as compared with the baseline.2,3 In all of the procedures we performed there was improvement in arm tremor as well as in coexisting tremors of the head, chin, and leg. The results of Bond et al1 seem to emanate from either not having enough power to reveal the association or having a not rigorous enough patient selection; the authors state that they recruited patients with tremor-dominant Parkinson disease that were “medication refractory, severe and disabling.” It is not clear from this statement or from the supplement material that the disability was due to the tremor and not to “on” and “off” phenomenon. This might have adversely biased their results. Furthermore, because the levodopa dosage was not kept constant throughout the study, changes in the levodopa dosage may have affected the study results. In addition, because the Clinical Rating Scale for Tremor score was the primary end point of the study, the authors should have explained how re-emergent tremor was rated, as the Clinical Rating Scale for Tremor score was developed for assessing essential tremor and does not take this kind of tremor into account. We were surprised by the high rate of adverse events in these 2 treatment centers, probably due to inexact lesion localization, including lesioning of the internal capsule, which we have not seen in the patients in our treatment center. In our experience, sensory and gait disturbances were, at most, transient, and none of the patients had any adverse event that lasted for more than...