Annals of Physical and Rehabilitation Medicine 58 (2015) 225–231

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Update article

Transcutaneous electrical spinal-cord stimulation in humans

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ARTICLE INFO

Article history:
Received 1st May 2015
Accepted 1st May 2015

Keywords:
Painless transcutaneous electrical enabling motor control (pcEmc)
Spinal-cord injury
Neuromodulation
Recovery
Neural plasticity

ABSTRACT

Locomotor behavior is controlled by specific neural circuits called central pattern generators primarily located at the lumbosacral spinal cord. These locomotor-related neuronal circuits have a high level of automaticity; that is, they can produce a "stepping" movement pattern also seen on electromyography (EMG) in the absence of supraspinal and/or peripheral afferent inputs. These circuits can be modulated by epidural spinal-cord stimulation and/or pharmacological intervention. Such interventions have been used to neuromodulate the neuronal circuits in patients with motor-complete spinal-cord injury (SCI) to facilitate postural and locomotor adjustments and to regain voluntary motor control. Here, we describe a novel non-invasive stimulation strategy of painless transcutaneous electrical enabling motor control (pcEmc) to neuromodulate the physiological state of the spinal cord. The technique can facilitate a stepping performance in non-injured subjects with legs placed in a gravity-neutral position. The stepping movements were induced more effectively with multi-site than single-site spinal-cord stimulation. From these results, a multielectrode surface array technology was developed. Our preliminary data indicate that use of the multielectrode surface array can fine-tune the control of the locomotor behavior. As well, the pcEmc strategy combined with exoskeleton technology is effective for improving motor function in paralyzed patients with SCI. The potential impact of using pcEmc to neuromodulate the spinal circuitry has significant implications for furthering our understanding of the mechanisms controlling locomotion and for rehabilitating sensorimotor function even after severe SCI.

1. Introduction

Epidural spinal-cord stimulation is an effective tool for regulating locomotor behavior [1] and can allow for regaining voluntary control of movements by paralyzed patients [2,3]. Here we describe a novel non-invasive technique — transcutaneous electrical spinal-cord stimulation — used to neuromodulate the physiological state of the non-injured and injured spinal cord.

1.1. The concept of the automaticity in understanding the neural control of movement in the non-injured and injured spinal cord

Spinal locomotor neuronal circuitries, called central pattern generators, can induce stepping EMG patterns without supraspinal input and/or peripheral afferent input. This phenomenon came to be called fictive locomotion (i.e., locomotion in the absence of movement). The ability to produce actual locomotion in the absence of brain input can be attributed to a combination of intrinsic properties of the circuitry generating fictive locomotion with the ability to process complex proprioceptive and cutaneous patterns. These features enable the lumbar circuitry to adapt the motor patterns to accommodate different speeds and levels of weight-bearing and sustain successful stepping in a continuously changing environment. To utilize this potential, the spinal circuitry seems to persist in a highly dynamic state, which reflects the immediate and chronic patterns of sensory input being processed by the spinal networks.

The idea that networks of neurons within biological systems can generate cyclic motor output is decades old. Key experiments demonstrating the significance of the automaticity of motor control in the mammalian spinal cord were performed by Brown in 1911 [4] and Shik et al. [5] in the 1960s and 1970s. These

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http://dx.doi.org/10.1016/j.rehab.2015.05.003
1877-0657/

experiments built a strong conceptual basis for the automaticity of the neural control of locomotion and posture. Shik and Orlovsky proposed that one level of control provides nonspecific tonic input that determines the intensity of locomotion (speed and grade), while the other is responsible for fine adjustments for the control of the limbs, including for maintaining equilibrium. This fine control system normally interacts with sources of sensory information, such as proprioceptive and visual inputs, to execute fine adjustments in the locomotor pattern. After the appearance of these key findings [6–8], many studies have attempted to define the mechanisms underlying the phenomenon of automaticity of movement control.

We now know that the spinal circuitry can learn a task that is taught (practiced) [9,10] and that it can forget the task if it is not practiced [11,12]. These and similar observations of the plasticity of the spinal locomotor circuitry provide the fundamental basis for re-examining current concepts and considering new ones that might lead to a greater potential for recovery from spinal-cord injury (SCI).

In the following sections, we describe the development of a novel technique to take advantage of the basic concepts of automaticity in maximizing motor functions in non-injured subjects but more importantly in patients who have lost motor function due to SCI.

1.2. Methodology of transcutaneous electrical spinal-cord stimulation

We introduce a novel non-invasive stimulation strategy of painless transcutaneous electrical enabling motor control (pcEmc) to neuromodulate the physiological state of the spinal cord. This method includes electrically activating the spinal circuitry via electrodes placed on the skin overlying the vertebrae of the lower thoracic and/or lumbosacral vertebrae. One of the innovative features is the use of a specific stimulation waveform that does not elicit pain even when used at energies required to transcutaneously reach the spinal networks. This waveform consists of 0.3- to 1.0-ms bursts with a carrier frequency of 10 kHz administered at 5 to 40 Hz [13]. By modulating the spinal cord with this non-invasive device, we can safely use energies that were previously prohibitive due to pain. In our initial studies, pcEmc stimulation was delivered by a 2.5-cm round electrode (Lead-Lok, Sandpoint, USA) placed midline at the C5, T11, and/or L1 spinous processes as cathodes and two 5.0×10.2 cm^2 rectangular plates made of conductive plastic (Ambu, Ballerup, Germany) placed symmetrically on the skin over the iliac crests as anodes. Biphasic rectangular 0.5- to 1.0-ms pulses with a carrier frequency of 10 kHz and at an intensity ranging from 30 to 200 mA were used.

1.3. Effects of pcEmc on stepping movements

We demonstrated that pcEmc at 30 Hz applied to T11 results in step-like movements in non-injured subjects when their legs are placed in a gravity-neutral position. Such stimulation produced involuntary coordinated, cyclic, oscillatory, locomotor-like steps in 5 of 6 normal subjects when placed in a gravity-neutral position [13]. An example of the kinematics of the hip, knee, and ankle and electromyography (EMG) activity from selected muscles as well as right–left coordinated movements during pcEmc in non-injured subjects is shown in Fig. 1. Furthermore, we refined the technology of pcEmc to involve multi-segmental stimulation to further improve locomotor ability. Use of a three-channel stimulation device permitting independent modulation via 3 different spinal locations at the C5, T11, and L1 vertebrae in a normal subject induced robust oscillatory and coordinated stepping movements that reached maximal excursions and EMG burst amplitudes within 2 to 3 step cycles; these movements were much greater than with stimulation at T11 alone (Fig. 1). Reciprocal, alternating patterns were more evident with multiple- than single-site stimulation. The synergistic and interactive effects of pcEmc suggest a multi-segmental convergence of descending and ascending and most likely propriospinal effects on the spinal neuronal circuitries associated with locomotor activity. These observations are consistent with the concept of differential modulation of the activation levels of combinations of motor

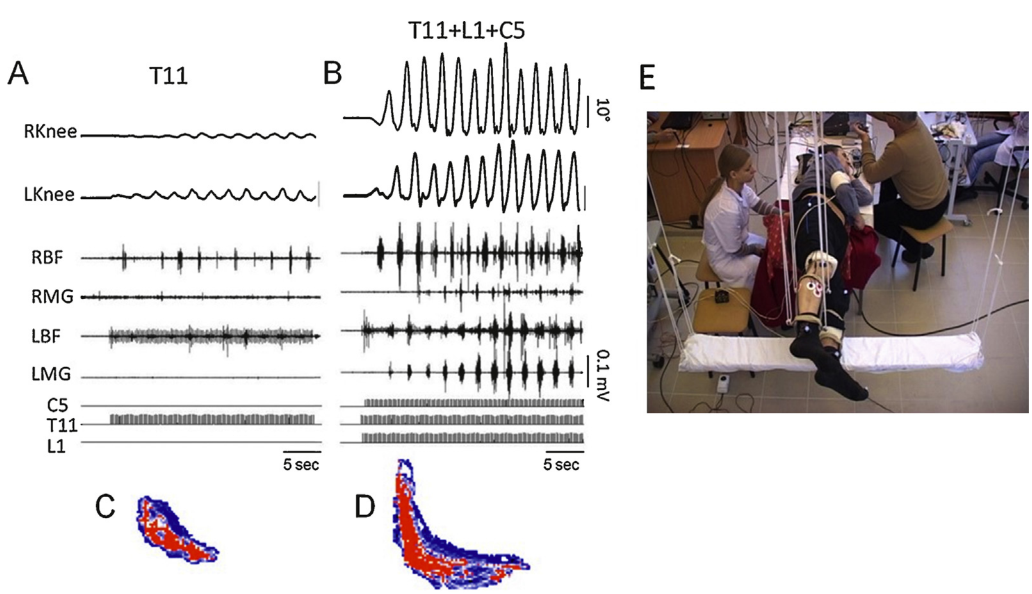

Fig. 1. Angular excursions of the right (R) and left (L) knee joints and electromyography (EMG) activity in the right and left biceps femoris (BF) and right and left medial gastrocnemius (MG) muscles with painless transcutaneous electrical enabling motor control (pcEmc) (5 Hz) at T11 alone (A) and at C5+T11+L1 simultaneously (B). Angle-angle trajectory plots of multiple cycles (50-ms time bins) showing the left (horizontal)-right (vertical) kinematics coupling of the angular movements at the knee with pcEmc at T11 (C) and at C5+T11+L1 (D) as shown in (A) and (B), respectively. Color scheme in (C) and (D) reflects the density of the data points, with red the highest density. E-photo of the subject placed in the gravity-neutral device.
Adapted from Gerasimenko et al. 2015.