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Review of physiological motor outcome measures in spinal cord injury using transcranial magnetic stimulation and spinal reflexes

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Abstract—This article reviews methods that have been developed as part of a clinical initiative on improving outcome measures for motor function assessment in subjects with spinal cord injury (SCI). Physiological motor outcome measures originally developed for limbs—transcranial magnetic stimulation (TMS) of the motor cortex to elicit motor-evoked potentials (MEPs) and mechanical stimulation to elicit spinal reflexes—have been extended to muscles of the trunk. The impetus for this development is the lack of a motor component in the American Spinal Injury Association clinical assessment for the thoracic myotomes. The application of TMS to the assessment of limb muscles is reviewed, followed by consideration of its application to the assessment of paravertebral and intercostal muscles. Spinal reflex testing of paravertebral muscles is also described. The principal markers for the thoracic SCI motor level that have emerged from this clinical initiative are (1) the threshold of MEPs in paravertebral muscles in response to TMS of the motor cortex, (2) the facilitation pattern and latency of MEPs in intercostal muscles during voluntary expiratory effort, and (3) the absence of long-latency reflex responses and the exaggeration of short-latency reflex responses in paravertebral muscles.

Key words: corticospinal function, motor cortex, motor-evoked potentials, motor function outcomes, rehabilitation, reinnervation, spinal cord injury, spinal reflexes, transcranial magnetic stimulation, trunk muscles.

INTRODUCTION

The need to improve clinical, physiological, and functional methods for assessing the level and degree of completeness of spinal cord injury (SCI) is assuming increased importance in light of emerging and realistic proposals to repair spinal cord damage [1]. Approaches to the repair of human SCI will be varied, as is evident from the wide range of successful methodologies in animal experiments [2–5]. However, the hazards of transferring strategies based on animal work to human trials indicate that certain routes may be preferred. To limit the potential risk of damage to surviving connections of the upper limbs in the cervical spinal cord, researchers may have to recruit volunteer subjects with thoracic SCI for any interventive repair measures that

Abbreviations: ASIA = American Spinal Injury Association, ISRT = International Spinal Research Trust, MEE = maximum expiratory effort, MEP = motor-evoked potential, SCI = spinal cord injury, T = thoracic, TMS = transcranial magnetic stimulation.

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are based on the expectation of regeneration across the lesion and beyond. If so, we are faced with an absence of any clinical or physiological tools for the assessment of motor output from the thoracic spinal cord. The American Spinal Injury Association (ASIA) clinical assessment of SCI only provides sensory scores for the second thoracic (T2) to first lumbar segments [6–7]. Another issue is that animal studies of regeneration indicate that reinnervation of musculature may be limited to one or two segments below the original lesion [2,4]. If the initial regeneration trials do not achieve reinnervation of the legs, no motor recovery will be found with the current ASIA assessment criteria. The objective of the clinical initiative commissioned by the International Spinal Research Trust (ISRT) was the development of new tools for the assessment of the level and degree of completeness of SCI in terms of sensory, motor, and autonomic function [8]. This article reviews physiological motor assessments of subjects with SCI for muscles innervated by the thoracic spinal roots and provides details of those methods specifically developed during the clinical initiative. The assessments include transcranial magnetic stimulation (TMS) of the motor cortex that elicits motor-evoked potentials (MEPs) in paravertebral and intercostal muscles and mechanical stimulation that elicits reflex responses of paravertebral muscles.

ASSESSMENT OF CORTICOSPINAL FUNCTION WITH TMS

TMS of the human motor cortex is a painless and non-invasive method of assessing the integrity of corticospinal innervation of muscles. It has been used to map the cortical representation of muscles [9–11] and create recruitment curves of MEPs for increasing stimulation strength or increasing facilitation degree from voluntary contraction in subjects with SCI [12]. Other attributes of cortical control over muscles in subjects with SCI that can be revealed by TMS are central conduction time in the corticospinal tract [13] and the inhibitory circuitry that determines cortical output [14–16]. A fuller review of the application of TMS to the understanding of lesioned pathways and plasticity (reorganization) of central nervous system circuits in subjects with SCI has been published recently [17]. In summary, TMS allows measurement of several attributes of corticospinal function and can reveal deficits resulting from SCI as well as reorganization of cortical motor output (plasticity). If these characteristics of corticospinal action are altered by interventions that promote functional recovery from SCI, then monitoring based on TMS and electromyography of MEPs could be a powerful tool for monitoring efficacy of treatment.

CORTICAL MOTOR-EVOKED POTENTIALS IN ERECTOR SPINAE MUSCLES

To investigate muscles innervated by thoracic and upper-lumbar vertebral spinal roots, researchers have used surface electromyography and TMS to elicit MEPs in paravertebral muscles in control subjects [18] and subjects with SCI [19]. MEPs may be elicited in right and left erector spinae muscles in control subjects with a double cone coil that has the crossover positioned over the vertex. MEPs in different myotomes have progressively increasing latencies in a rostro-caudal direction, but thresholds to TMS were constant at different levels. In subjects with SCI, a confounding issue was that MEPs could routinely be recorded from surface electrodes placed over myotomes of paravertebral muscles at levels apparently well below the lesion level of a complete SCI, a finding not reported in an earlier study by Ertekin et al. [20]. However, unlike control subjects, the TMS threshold strength required to elicit an MEP in erector spinae muscles in subjects with SCI depended on the vertebral level. In comparison with control subjects, subjects with SCI unexpectedly showed reduced thresholds for MEPs above and elevated thresholds for MEPs below the level of a complete SCI. In addition, **Figure 1** shows a reasonably linear dependence of threshold on vertebral level, with a close-to-normal control value occurring at the injury level. A lower threshold above the lesion level may be explained as corticospinal hyperexcitability of those myotomes because of central plasticity resulting from the SCI. Similarly, plasticity of cortical motor function had previously been invoked as an explanation for the downregulation of inhibitory processes following SCI [14]. The raised TMS thresholds below the injury are consistent with a degree of innervation loss from above the lesion. A prediction from this finding is that any recovery of motor function in subjects with SCI below the initial lesion level may shift the TMS threshold pattern in relation to vertebral level. If this proves to be the case, the abnormal threshold pattern should assist in the determination of the lesion level and the tracking of recovery from reinnervation.

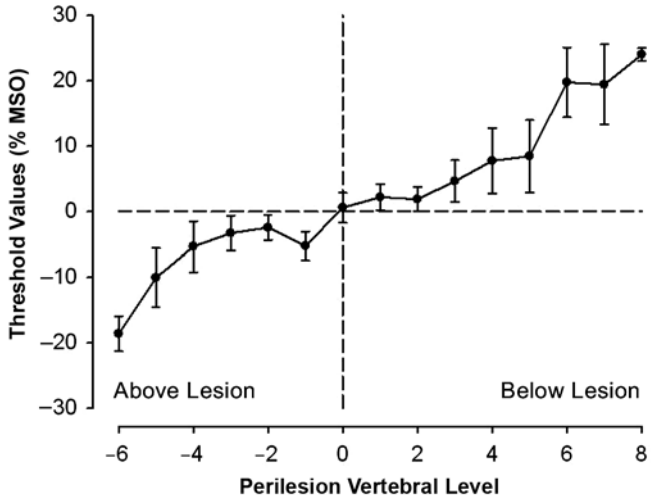

Figure 1.
Threshold values (mean ± standard error) for eliciting motor-evoked potentials (MEPs) of erector spinae muscles using transcranial magnetic stimulation of motor cortex, recorded at different levels in eight subjects with complete spinal cord injury (SCI) (T4–T7). Thresholds expressed as difference in % maximum stimulator output (% MSO) required to elicit MEP in subjects with SCI relative to mean value established in control subjects. Thresholds at individual vertebral levels have been aligned with respect to SCI level. Reprinted with partial alteration by permission from Cariga P, Catley M, Nowicky AV, Savic G, Ellaway PH, Davey NJ. Segmental recording of cortical motor evoked potentials from thoracic paravertebral myotomes in complete spinal cord injury. Spine. 2002;27(13):1438–43. [PMID: 12131743]. T = thoracic.

INTERCOSTAL MUSCLE RESPONSES TO TMS

MEPs from intercostal muscles in response to TMS and the facilitation pattern of MEPs with increasing respiratory effort have been developed as tools that could assist in the differentiation of both the neurological level and degree of completeness of high thoracic SCI. In a group of control subjects, the facilitation pattern with changing voluntary effort was examined at all six intercostal muscle levels [21]. Surface electrodes were placed in each intercostal space approximately 2 cm from the sternal edge (1st–4th spaces), at the midclavicular line (6th space), and halfway between the two (5th space). Using a breathing tube with a slow leak connected to a pressure meter to give respiratory effort feedback, we recorded data from 5 percent of maximum to maximum expiratory effort (MEE). We applied TMS using a circular coil centered over the vertex at an intensity 1.2 times the threshold for evoking an MEP at 10 percent MEE. MEPs could be recorded at all sites in all subjects for each voluntary effort. The latency of MEPs increased from an average of approximately 9 ms for the first three intercostal spaces to 11 ms for the last three intercostal spaces. The magnitude of the MEPs became larger with increasing voluntary effort. In a pilot study, we have applied the technique to a small number of subjects with complete thoracic SCI (T3–T5) [22]. **Figure 2** shows the MEP facilitation patterns from increasing expiratory effort in a subject with a complete injury (T5) at the different intercostal recording sites. As with recordings of MEPs in erector spinae muscles, MEPs appear to be recorded below the level of a complete injury. Above the lesion, the recruitment curves from increasing expiratory effort appear normal. However, in this example (**Figure 2**), the curves are less steep at and below the lesion level. In some cases, the latency of the MEP has been recorded as longer than normal at or below the lesion. At present, the body of data is insufficient for determining whether recruitment curves or MEP latency will provide robust indicators of the level and completeness of SCI.

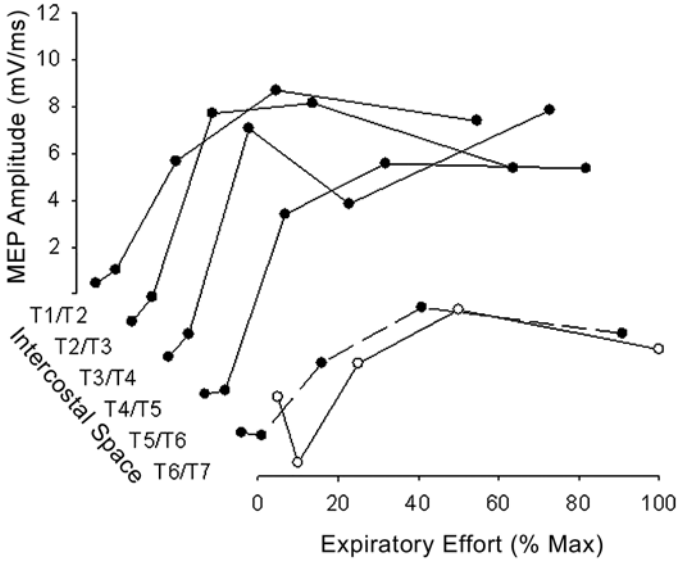

Figure 2.
Three-dimensional recruitment plot of motor-evoked potentials (MEPs) recorded by surface electromyography from intercostal spaces T1/T2 to T6/T7 in subjects with complete spinal cord injury (SCI) (T5: American Spinal Injury Association [ASIA] Grade A) for different degrees of expiratory effort. Filled symbols/continuous line: above lesion. Filled symbols/broken line: at lesion level. Open symbols/continuous line: below lesion. Max = maximum, T = thoracic. ASIA has developed impairment scale for neurological classification of SCI, based on tests of key muscles and levels of dermatomes, that consists of five categories (A to E). A = complete injury with no motor or sensory response below injury.

REFLEX RESPONSES OF ERECTOR SPINAE MUSCLES

As mentioned previously, the current International Standards for Neurological Classification of SCI provide no tests for determining the motor injury level in the trunk [17]. As part of the clinical initiative, we have conducted a physiological study of the reflex responses of back muscles to develop a method for assessing the level of a thoracic spinal cord lesion [23]. We exposed 12 subjects with clinically complete thoracic SCI (T2–T12) and 12 control subjects to repeated, brief mechanical stimulation (prod) using an electromagnetic coil to drive a blunt probe (under servomechanism control of its excursion) against either a vertebral process or erector spinae muscle. Both short- and long-latency reflexes could be recorded electromyographically (**Figure 3**). Short-latency responses could be recorded at vertebral levels within approximately two or three segments of the site of stimulation. These responses are likely segmental in origin and based on a simple mono- or oligosynaptic pathway [24–26]. Short-latency reflexes could be evoked in approximately 80 percent of trials of

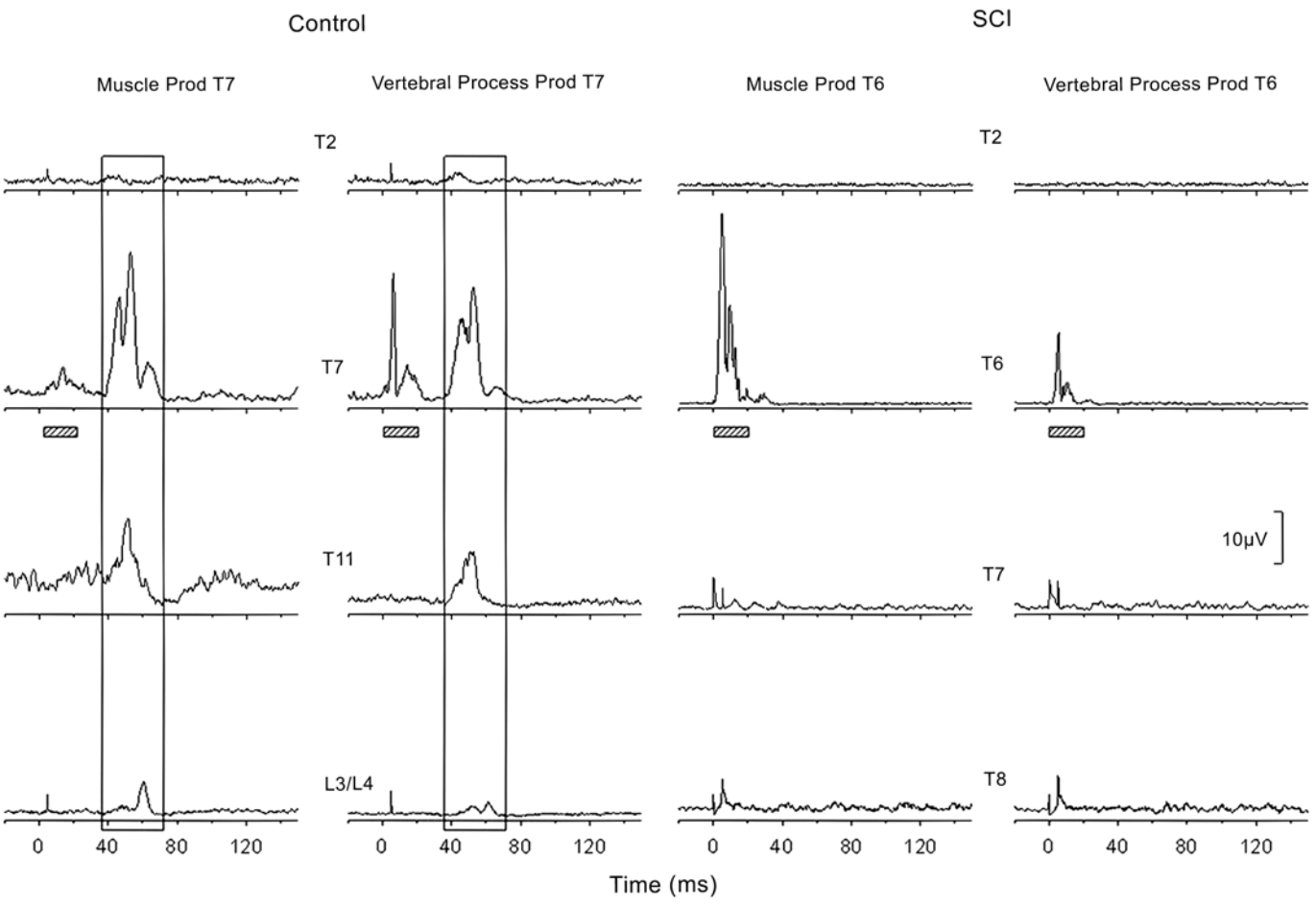

Figure 3.
Reflex responses in erector spinae muscles in response to mechanical stimulation (brief prod) of muscle or adjacent vertebral process. Recordings of surface electromyography at various vertebral levels above, at, and below stimulation level for control subject and subject with complete spinal cord injury (SCI) at T6 (American Spinal Injury Association [ASIA] Grade A). Stimuli applied at T7 for control subject and T6 for subject with SCI. Vertical clear boxes indicate long-latency reflex responses visible at all vertebral levels in control subject only. Horizontal, hatched boxes indicate short-latency reflex responses restricted to stimulation level, but seen in both control and subject with SCI. Note also larger size of short-latency response in subject with SCI. L = lumbar, T = thoracic. ASIA has developed impairment scale for neurological classification of spinal cord injury, based on tests of key muscles and levels of dermatomes, that consists of five categories (A to E). A = complete injury with no motor or sensory response below injury.

control subjects and in 90 to 100 percent of trials of subjects with SCI in the two segments above or below the lesion. Short-latency reflex responses in control subjects had a mean latency (± standard error of the mean) of 5.7 ± 0.5 ms when the vertebral process was prodded and 5.4 ± 0.4 ms when the muscle was prodded. In the subjects with SCI, latencies were slightly longer (up to 0.7 ms) both above and below the lesion. The most noticeable feature of the reflex responses in the subjects with SCI was that the amplitudes were on average 2 to 3 times larger at the three levels spanning the lesion than either above or below the lesion; these short-latency reflexes were also of higher magnitude than in control subjects (**Figure 3**).

Mechanical stimulation of vertebral processes and erector spinae muscles also produced longer latency reflexes (30–40 ms) that could be recorded at vertebral levels distant to the site of stimulation. These longer latency reflexes are thought to involve a supraspinal conduction pathway [25]. The long-latency responses were largely absent in subjects with SCI regardless of whether stimulation was directed above or below the lesion (**Figure 3**).

Our conclusion is that the exaggerated short-latency reflexes recorded close to the lesion site may be useful in determining the level of thoracic SCI. Additionally, the location of the enhanced reflex could be used as an outcome measure for monitoring recovery after any intervention designed to repair or improve function of a damaged spinal cord.

DISCUSSION AND CONCLUSIONS

The specific aim of the work reviewed here was the development of motor function tests for muscles innervated by thoracic and lumbar spinal roots. The two methods of choice were TMS of the motor cortex to elicit MEPs in trunk muscles and brief mechanical stimulation of paravertebral muscles or vertebral processes to elicit reflex responses. Both methods were found to reliably elicit responses in trunk muscles. However, a confounding issue was that MEP responses to TMS in trunk muscles could apparently be recorded at sites below the lesion level in complete SCI. However, subjects in these studies were diagnosed with complete thoracic-level SCI (below T1) solely on the basis of sensory tests: all had upper-limb motor ASIA scores of 50 (one exception at 48), which reflect normal upper-limb motor function, and scores of 0 for all lower-limb muscles (e.g., Cariga et al. [19]). The high frequency with which MEPs were recorded in trunk muscles makes the possibility that they indicate surviving connections below the lesion level extremely unlikely. More likely is that the muscles concerned receive innervation from above the lesion, with the additional possibility that peripheral sprouting and reinnervation of muscle fibers had occurred at some time postinjury.

The question then is whether these motor tests can assist in the determination of the level and completeness of thoracic SCI. The most promising markers were (1) the dependence on vertebral level of MEP threshold to TMS in erector spinae muscles, (2) the facilitation pattern and increased latency in intercostal MEP responses to TMS, and (3) the exaggerated short-latency spinal reflexes in paravertebral muscles. Additionally, the altered patterns of MEP recruitment curves and the downregulated cortical inhibition established earlier for upper-limb muscles [12,14] affected by incomplete lesions appear to also apply to muscles of the trunk and may indicate incomplete motor lesions or zones of partial preservation.

The next step is validation of the tests developed during this clinical initiative. To this end, we will use the tests to assess motor changes in subjects with incomplete SCI who will receive treatment intended to improve functional outcome. This second stage of the clinical initiative will include repetitive TMS [27–28] of the motor cortex and weight-assisted treadmill walking [29–30] as treatments.

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The authors have declared that no competing interests exist.

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