“Threshold-level” multipulse transcranial electrical stimulation of motor cortex for intraoperative monitoring of spinal motor tracts: description of method and comparison to somatosensory evoked potential monitoring

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Numerous methods have been pursued to evaluate function in central motor pathways during surgery in the anesthetized patient. At this time, no standard has emerged, possibly because each of the methods described to date requires some degree of compromise and/or lacks sensitivity.

Object. The goal of this study was to develop and evaluate a protocol for intraoperative monitoring of spinal motor conduction that: 1) is safe; 2) is sensitive and specific to motor pathways; 3) provides immediate feedback; 4) is compatible with anesthesia requirements; 5) allows monitoring of spontaneous and/or nerve root stimulus-evoked electromyography; 6) requires little or no involvement of the surgical team; and 7) requires limited equipment beyond that routinely used for somatosensory evoked potential (SSEP) monitoring. Using a multipulse electrical stimulator designed for transcranial applications, the authors have developed a protocol that they term “threshold-level” multipulse transcranial electrical stimulation (TES).

Methods. Patients considered at high risk for postoperative deficit were studied. After anesthesia had been induced and the patient positioned, but prior to incision, “baseline” measures of SSEPs were obtained as well as the minimum (that is, threshold-level) TES voltage needed to evoke a motor response from each of the muscles being monitored. A brief, high-frequency pulse train (three pulses; 2-msec interpulse interval) was used for TES in all cases. Data (latency and amplitude for SSEP; threshold voltage for TES) were collected at different times throughout the surgical procedure. Postoperative neurological status, as judged by evaluation of sensory and motor status, was compared with intraoperative SSEP and TES findings for determination of the sensitivity and specificity of each electrophysiological monitoring technique.

Of the 34 patients enrolled, 32 demonstrated TES-evoked responses in muscles innervated at levels caudal to the lesion when examined after anesthesia induction and positioning but prior to incision (that is, baseline). In contrast, baseline SSEPs could be resolved in only 25 of the 34 patients. During surgery, significant changes in SSEP waveforms were noted in 12 of these 25 patients, and 10 patients demonstrated changes in TES thresholds. Fifteen patients experienced varying degrees and durations of postoperative neurological deficit. Intraoperative changes in TES thresholds accurately predicted each instance of postoperative motor weakness without error, but failed to predict four instances of postoperative sensory deficit. Intraoperative SSEP monitoring was not 100% accurate in predicting postoperative sensory status and failed to predict five instances of postoperative motor deficit. As a result of intraoperative TES findings, the surgical plan was altered or otherwise influenced in six patients (roughly 15% of the sample population), possibly limiting the extent of postoperative motor deficit experienced by these patients.

Conclusions. This novel method for intraoperative monitoring of spinal motor conduction appears to meet all of the goals outlined above. Although the risk of postoperative motor deficit is relatively low for the majority of spine surgeries (for example, a simple disc), high-risk procedures, such as tumor resection, correction of vascular abnormalities, and correction of major deformities, should benefit from the virtually immediate and accurate knowledge of spinal motor conduction provided by this new monitoring approach.
A new device for transcranial stimulation was recently marketed, prompting us to reexamine the feasibility of transcranial electrical stimulation (TES) of the motor cortex during surgery to monitor conduction in central motor pathways. This device, a stimulator (model D185; Digi-timer Ltd., Welwyn Garden City, UK), produces a brief train of stimulus pulses, applied at a rate approximating that of discharging cortical motor neurons (the "upper" motor neurons) during voluntary movements. A recent study using the D185 stimulator reported the successful activation of central motor pathways during spine surgery, in which the primary output parameters were based on the maximum evoked motor responses.

In this study we tested whether the minimum stimulus intensity needed to elicit any response from a given muscle could serve as an indicator of central motor conduction, an approach that we have termed "threshold-level" TES. If successful, this approach would minimize the undesirable consequences of the high stimulus intensities needed to elicit maximal contractions, such as patient movement and an increased risk of skin burns. The goals of the present study were to: 1) establish the safety, advantages, and disadvantages of this threshold-level TES monitoring method; and 2) compare findings of TES monitoring and the more traditional SSEP monitoring to postoperative sensory and motor function in a patient population in which a relatively high rate of postoperative neurological deterioration would be expected.

Clinical Material and Methods

Patient Population

Enrollment was restricted to patients with at least partial neurological preservation caudal to their lesion but who were considered to be at relatively high risk for postoperative neurological deterioration. The extent of motor preservation in segments caudal to the spine or spinal cord lesion was assessed preoperatively in two ways: either through direct recordings of motor responses to transcranial magnetic stimulation in the awake patient1 or through evaluation by a therapist who examined each myotome for voluntary movement capabilities in all tested segments caudal to the lesion site. One muscle that was consistent-ly treated in the prone position. Most patients who underwent surgery while supine were placed in some form of cervical device (such as Gardner–Wells tongs) and traction.

Electromyography Recording

The electrical response of the muscle was recorded by an electromyograph using pairs of noninsulated electroencephalography-type needle electrodes (approximately 27 g, 1.5-cm length), which were placed subcutaneously and overlying each target muscle, with approximately 5-cm spacing between electrodes. This method of electrode placement is considerably faster than that used for surface electrodes, yet it provides results that are comparable. Data from initial experiments were tape-recorded with a custom electrophysiological instrumentation rack, but the majority of studies were conducted using an eight-channel commercially available evoked potential device (Excel; Cadwell Laboratories, Inc., Kennewick, WA). For both approaches, signal amplification and filtering were typically 10 kHz and 100 Hz to 5 kHz, respectively. Electromyographic (EMG) recordings were made from either or 12 muscles simultaneously, concentrating on those target muscles innervated by neurological segments caudal to the lesion site. One muscle that was consistently recorded, even when the lesion was in the thoracic or thoracolumbar cord, was the abductor pollicis brevis, an intrinsic hand muscle at the base of the thumb. Under normal circumstances the abductor pollicis brevis muscle is easily recruited following stimulation over the con-
Potential latencies and amplitudes were determined using software in the Excel monitoring device. Changes in SSEP responses were considered significant for amplitude reductions exceeding 50% of baseline or latency increases exceeding 10% of baseline values. Postoperative changes in motor and/or sensory scores, as judged by a therapist, were only considered significant if a given muscle group score declined by 2 or more, or if a sensory score changed on the 3-point sensory scale (0–2). Single point changes in motor score, particularly when that change was from a 5 to a 4, were not considered significant, because postoperative pain and reduced mobility often contributed to a modest and transient functional deterioration in apparent strength, without being due to neurological deterioration.

Results

Thirty-four patients (20 males and 14 females) aged 9 to 78 years (mean 42.4 years) were studied. Preoperative diagnoses included intradural tumor (21 patients), spinal deformity (scoliosis, kyphosis, or displaced fracture; six patients), arteriovenous fistula (two patients), tethered cord (diastomatomyelia or posttraumatic; two patients), cervical spine tumor (chordoma or metastatic disease; two patients), and posttraumatic cervical syringomyelia (one patient). The anesthetic protocol of N.O, narcotic medication (fentanyl or sufenta) and propofol (constant infusion) was used successfully in every case, although in one case equipment failure necessitated a revision in drug delivery. There were no instances of patient recall and no adverse reactions that could be attributed to the TES.

Baseline responses to TES were evident in at least one target muscle caudal to the lesion in 32 of the 34 patients examined. Both of the two patients who did not demonstrate TES-evoked responses were found to have pronounced lower-limb spasticity and weakness preoperatively but were still able to ambulate without assistance at that time. Nevertheless, TES-evoked responses could not be elicited in any of their lower-limb muscles during surgery, even when using high-intensity stimuli. An example is illustrated in Fig. 1. In the laboratory, evoked responses to transcranial magnetic stimulation could be elicited in lower-limb muscles from this patient (Fig. 1A) when he attempted a voluntary contraction in the target muscle at the time of stimulation. In contrast, during surgery no response could be elicited by TES in any of the six lower-limb muscles studied in this patient. Technical faults or concerns about inappropriate anesthesia were ruled out, given the well-defined intraoperative responses to TES evident in the patient’s abductor pollicis brevis muscles bilaterally (Fig. 1B).

When present, evoked responses to intraoperative TES increased in magnitude and distribution with increasing numbers of stimuli in a train. An example is shown (Fig. 2) in which there was no response in any of the muscles tested to a single stimulus pulse of 400-V intensity (Fig. 2A) delivered between C4 (anode) and C3 (cathode). Addition of a second stimulus pulse 2 msec after the first stimulus (2 @ 2 msec) resulted in a small response in the left quadriceps and the right abductor pollicis brevis muscles (Fig. 2B). A stimulus train of three pulses (3 @ 2 msec; Fig. 2C) resulted in well-defined evoked muscle
responses in all but the right quadriceps muscle group. As expected, the latency increased as the distance of the target muscle group from the brain increased. The right abductor pollicis brevis, ipsilateral to the anode, also showed a large response to a 3 @ 2 msec pattern. The stimulus intensity used in this case (400 V) was well above the threshold determined for this muscle in response to stimulation of the opposite polarity (250 V; data not shown). Preoperative evaluation of this patient by means of transcranial magnetic stimulation indicated that activity from the left tibialis anterior and abductor hallucis muscles was absent; hence, these muscles were not monitored during the surgical procedure.

There was pronounced variability in the amplitude and minimum latency of TES-evoked responses from trial to trial, even when stimulus intensity and configuration were not changed. An example is shown in Fig. 3, which summarizes data from one patient for whom the absolute amplitude (y-axis) and minimum latency (x-axis) of the evoked responses to TES of two intensities were plotted. Note that the range of response amplitudes far exceeds the 50% value traditionally used for SSEP monitoring; similarly, variability in SSEP latencies exceeds the 10% cutoff value typically used. This finding was true of approximately 80% of the muscle responses quantified in this manner, leading us to explore the alternative presented here (that is, threshold-level TES) in lieu of the traditional amplitude and latency criteria for monitoring changes in conduction properties of central axons.

Thresholds for TES-evoked responses to one-, two-, and three-pulse stimulations were determined for the abductor pollicis brevis muscles in 19 of the first 22 patients studied and are summarized in Fig. 4A. Single-pulse cortical stimuli typically required high intensities to elicit responses or sometimes failed to elicit responses at all (Fig. 4A, open circles), even with stimulus intensities as high as 1000 V (approximately 1.5 A current). In marked contrast, addition of a second or third stimulus pulse led to much lower intensities needed to evoke motor responses. Threshold intensities as low as 100 V for a three-pulse train were sometimes observed. Such weak stimuli routinely failed to cause any localized contraction of scalp or neck muscles, and they often went unnoticed by the surgical team. The mean threshold voltages for the five most commonly monitored muscles are shown in Fig. 4B. Individual thresholds for upper-limb muscles were almost

**Fig. 1.** Recording of evoked responses to motor cortex stimulation in the same patient. A: Using a single-pulse magnetic stimulator in the awake patient, bilateral responses to a single stimulus (arrow) are shown in each of the tibialis anterior (TA) and abductor hallucis (ABH) muscles. The patient was attempting to contract his tibialis anterior muscles at the time the stimulus was applied (coil positioned at Cz). B: During surgery the following day, electrical stimulation (3 @ 2 msec) elicited responses in the patient’s abductor pollicis brevis (APB) muscles bilaterally, but did not elicit responses in any of the lower-limb muscles studied. Stimulus intensity = 450 V, C3–C4 (anode–cathode). Vertical bar = 0.25 mV for A, 0.1 mV for B. L = left; Quads = quadriceps; R = right; TMS = transcranial magnetic stimulation.

**Fig. 2.** Electromyogram recorded from six muscles in response to stimulation (delivered at Time 0) with either a single-pulse (A), 2 @ 2 msec (B), or 3 @ 2 msec (C) stimulus pattern. The site of stimulus delivery (C4–C3; anode–cathode) and stimulus intensity (400 V) was the same in all three cases. All records reflect the exact EMG responses recorded, without any type of signal averaging or postacquisition processing. Vertical bar = 0.5 mV. L = left; R = right.

**Fig. 3.** Scatterplot displaying variability in the peak-to-peak amplitude (ordinate) and minimum latency (abscissa) of right abductor pollicis brevis responses evoked by TES in one patient during the entire surgical procedure. The stimulation site (C3–Cz) and pulse train (3 @ 2 msec) were unchanged. Stimulus intensity was either 175 V (circles) or 200 V (squares).
Multipulse transcranial electrical stimulation

always less than those for lower-limb muscles, given that most trials were optimized for activation of the hand area (for example, anode at either C3 or C4).

In contrast to TES-evoked responses that were present at baseline in all but two patients, SSEP responses were absent at baseline evaluation in nine patients. Significant intraoperative changes of SSEP waveforms were seen in 12 patients; these changes were transient in five instances (that is, signals had recovered by the end of the procedure) and prolonged in seven cases. For TES parameters, there were 10 instances in which thresholds of one or more muscles increased by 100 V or more and remained elevated at the conclusion of the procedure. Postoperatively, there was a deterioration in sensation and/or strength noted in 15 patients; this change was transient in three cases (all being related to unilateral motor function and resolving between 1 and 3 hours) and prolonged in 12 cases.

Figure 5 is the first of three summaries chosen to illustrate different aspects of threshold-level TES compared with SSEP monitoring. The patient in this case was a 78-year-old man with a schwannoma at C1–2, who had normal preoperative strength and a primary complaint of pain. Surgery involved suboccipital craniotomy and C-1 and C-2 laminectomies to expose the dura, dural incision, and resection of the mass. Throughout this procedure, median nerve SSEP responses showed no significant change in either latency or amplitude at any time (Fig. 5A–E). Responses to TES can be found in Fig. 5F–H, in which the left-side responses were poorly defined but present at baseline (Fig. 5F). After bone decompression, but before tumor resection (Fig. 5G), muscles on the left side no longer responded to TES, a situation that did not change for the remainder of the surgical procedure. The threshold voltages required to elicit activity in the left flexor carpi radialis, right abductor pollicis brevis, and right abductor hallucis muscles in this case are summarized in Fig. 5I. A rise in the threshold for the left flexor carpi radialis muscles was evident following the craniectomy (approximately 1 hour after incision), well before the dura was opened (Fig. 5I, dashed line at approximately 2.7 hours). The patient awoke with a complete absence of motor function in his left arm and leg but retained normal motor strength in his right limbs. This case had the worst postoperative motor deficit of the 34 patients studied in this protocol. No detailed pre- and postoperative neurological evaluations were performed in this patient, who was one of the first studied using this method.

Figure 6 illustrates data obtained in a 66-year-old woman with an L-1 lipoma and a tethered spinal cord. In this case there was a significant drop in SSEP amplitude in response to right-side stimulation while the mass was being resected (Fig. 6B); this amplitude recovered to baseline levels by the end of the procedure (that is, the change was transient). There were no significant changes in threshold for TES-evoked responses at any time in the muscles studied (Fig. 6D–F; summarized in Fig. 6G). Postoperative sensory scores of dorsal column function showed a complete absence of vibration sensibility within the L-1, L-5, and S-1 dermatomes bilaterally and within the L-2 dermatome on the right side. Motor strength was unchanged postoperatively from preoperative values.

Figure 7 summarizes results obtained in a 52-year-old woman with C-4 metastatic disease, who underwent a C-4 corpectomy followed by strut-graft placement augmented with Steinmann pins and methyl acrylate cement. There was a transient decline in the left-side SSEP amplitude while the patient was undergoing corpectomy, but the amplitude recovered before graft placement (data not shown) and remained within baseline limits at the conclusion of the procedure (Fig. 7C). In marked contrast, TES-evoked responses were stable during the corpectomy (Fig. 7D) but demonstrated a sudden threshold increase immediately following distraction and graft placement. At this time none of the right-side muscles responded to TES as high as 400 V (data not shown; because of the delay [approximately 30 seconds] associated with printing these data, they were not printed or included in Fig. 7G). The surgical team was notified of this sudden change and immediately removed the graft. Within 1 minute after graft removal, TES-evoked responses were again seen in the right-side muscles (Fig. 7E), although the response amplitudes were dramatically reduced and remained lower for the duration of the procedure. By the end of the operation, TES-evoked responses were evident in all muscles studied at thresholds equal to or somewhat higher than baseline values. On awakening, the patient was immediately able to generate voluntary contractions in her left arm, hand, and leg and in her right arm and leg. However, she was
unable to make a fist and squeeze her fingers together in her right hand for approximately 2 hours. By the time the postoperative evaluation was conducted by the therapist (Fig. 7I; testing performed approximately 18 hours post-surgery), the patient’s strength was comparable to preoperative levels. There was no obvious change in clinical sensation after surgery, despite the transient reduction in SSEP amplitude to left-side stimulation during surgery.

We encountered several situations that led to increases in thresholds for TES-evoked responses; however, these could be accounted for by systemic factors unrelated to damaged central motor axons per se. In one example the propofol infusion pump failed at the midpoint of the procedure, forcing the anesthesiologist to switch to an intermittent bolus method of propofol delivery. The TES-evoked responses before and immediately after this transition in drug delivery are illustrated in Fig. 8. While the patient was receiving a steady infusion of propofol,
Fig. 6. Summary data obtained in a 66-year-old woman with an L-1 lipoma and a tethered spinal cord. A–C: The SSEP responses to posterior tibial nerve stimulation; Cz–Fz recording montage. During the surgical procedure there was a significant decrease in the right SSEP amplitude while the mass was being resected (B); after closing the dura (C) this amplitude recovered to baseline levels. Left- and right-side stimulation as shown in Fig. 5. D–F: The TES-evoked responses at different times during the procedure. There were no significant changes in thresholds in this procedure. Stimulation parameters: C3–C4, 200 V, 3 @ 2 msec. Vertical calibration: 2 mV for abductor pollicis brevis, 100 mV for quadriceps, and 500 mV for tibialis anterior and abductor hallucis. G: Scatterplot displaying absolute threshold intensity for TES-evoked responses determined during the course of the surgical procedure. Each symbol represents the threshold of the muscle shown. H and I: Pre- and postoperative neurological evaluation of motor and sensory (dorsal column [DC] and lateral tract [LT]) function. The motor scores determined for each muscle and the sensory scores evaluated for each dermatome on the left and right sides are indicated by filled symbols. Asterisks denote those trials in which the outcome was limited either by pain or orthoses or attempts contravened by doctor’s orders. R = right.
Fig. 7. Summary data obtained in a 52-year-old woman with C-4 metastatic disease. A–C: The SSEP responses to posterior tibial nerve stimulation; Cz–Fz recording montage. There was a decrease in left-side response amplitude during the corpectomy, which recovered to within baseline limits by the conclusion of the procedure. Left- and right-side stimulation as shown in Fig. 5. D–F: The TES-evoked responses at different times during the procedure. A sudden increase in threshold and reduction in response amplitude immediately followed spine distraction and graft placement. Stimulation parameters: C3–C4, 250 V, 3 @ 2 msec. Vertical calibration: 50 mV for all traces except for panel D, abductor pollicis brevis (100 mV). G: Scatterplot displaying absolute threshold intensity for TES-evoked responses determined during the course of the surgical procedure. Each symbol represents the threshold of the muscle shown. Open circles indicate those trials in which no response was evoked by TES for the intensity shown in the right abductor pollicis brevis. H and I: Pre- and postoperative neurological evaluation of motor and sensory (dorsal column [DC] and lateral tract [LT]) function. The motor scores determined for each muscle and the sensory scores evaluated for each dermatome on the left and right sides are indicated by closed boxes. R = right.
Multipulse transcranial electrical stimulation

![Graph depicting the current–voltage relationship of the stimulator determined for a single patient at different times during the surgical procedure. Each symbol represents a different sampling time.](image)

Fig. 8. Electromyogram recorded from different muscles in a single patient in response to three-pulse TES during a steady infusion of propofol (A) and immediately after bolus infusion of 2 ml propofol (B). The same stimulation (3 @ 2msec, 750 V) evoked widespread muscle recruitment (A) while the patient was not deeply anesthetized (that is, “light”) and only low-amplitude responses by the right soleus and abductor hallucis muscles (B) following intravenous infusion of a large bolus dose of propofol. HAMS = hamstring; L = left; R = right.

![Image](image)

Fig. 9. Graph depicting the current–voltage relationship of the stimulator determined for a single patient at different times during the surgical procedure. All measurements were obtained in the same stimulation configuration. For a given preset voltage, the amount of current actually delivered increased by a modest amount during the course of an extended surgical procedure. Each symbol represents a different sampling time.

there was widespread recruitment of muscles in response to the relatively strong stimulus intensity used (Fig. 8A). After the patient received a bolus dose of propofol, however, the same stimulus intensity caused negligible recruitment, with the exception of low-amplitude evoked responses in the right abductor hallucis and soleus muscles (Fig. 8B). The second situation in which threshold levels for TES were elevated was in response to low blood pressures: typical values that affected the responses were 80/50 (systolic/diastolic) or lower (data not shown). Thus when an elevation in thresholds was noted, it was first necessary to rule out issues related to anesthesia before warning the surgical team of this development.

Figure 9 illustrates the current–voltage relationship of the stimulator in one patient, sampled at different times during the surgical procedure for the same stimulation configuration. Using values from this graph and those obtained from other patients (data not shown), the “dynamic” impedance for the stimulating electrodes was calculated using Ohm’s law and found to range between 500 Ω and 725 Ω from patient to patient. These values were virtually identical for surface electrodes (active area approximately 3.5 cm²) and subdermal electrodes (active area approximately 0.45 cm²). Figure 9 also shows that the actual current delivered for a given stimulus tended to increase over the duration of a surgical procedure. This increase between baseline and final values was approximately 10 to 15% for procedures lasting 5 or more hours, such as the procedure summarized in Fig. 9. This increased current delivery suggests a gradual reduction in dynamic impedance of the stimulating electrodes. However, multiple stimuli delivered within a narrow time frame during a procedure led to virtually identical current delivery, showing high reproducibility in stimulator output from trial to trial.

Although the sample size in this study is small, we quantified the ability of the two electrophysiological techniques—SSEP and threshold-level TES—to predict postoperative deterioration in sensory and motor function accurately, as judged in more than 80% of the cases, by a therapist blinded to the intraoperative findings. With either test, there are four possible outcomes: 1) intraoperative electrophysiological deterioration that agrees with postoperative worsening of clinical status (true positive [TP]); 2) intraoperative worsening in the absence of postoperative worsening (false positive [FP]); 3) postoperative worsening in the absence of intraoperative worsening (false negative [FN]); and 4) no intra- or postoperative deterioration (true negative [TN]). The criteria used to indicate a significant deterioration in an SSEP response were based on latency (> 10% increase) and amplitude (> 50% decrement). For threshold-level TES, the criterion was an increase in the threshold of 100 V or more that persisted for more than 1 hour. For both methods, we ruled out anesthesia and blood pressure considerations before indicating whether a change was significant or not.

The incidence of each of the four categories described across the sample population was as follows: TP 11 and 10 cases, TN 11 and 22 cases, FP 2 and 0 cases, and FN 1 and 0 cases for SSEP and threshold-level TES monitoring, respectively. As indicated previously, the population size is smaller for the SSEP group because nine of the 34 patients studied did not have baseline SSEPs against which intraoperative changes could be judged. Calculations of each test’s sensitivity (TP/[TP+FP]) and specificity (TN/[TN+FN]) were made using these numbers. For threshold-level TES monitoring, both the sensitivity and specificity were 1.0 in the sample studied (that is, perfect agreement in all cases between intraoperative findings and postoperative motor status). For SSEP monitoring, sensitivity and specificity values were 0.92 and 0.85, respectively.

Neither SSEP nor threshold-level TES monitoring was very good for predicting clinical deterioration in the opposite test’s neurological counterpart. There were four cases of pure sensory clinical deterioration for which there were no intraoperative changes in TES thresholds. Similarly, there were five cases of pure motor clinical deficit in the absence of any intraoperative change in SSEP records. However, neither instance should be considered a “false negative,” as we argue in the Discussion.
Discussion

This study was conducted to address the need for an intraoperative monitoring technique that provides rapid, accurate information about conduction in central motor pathways, yet is compatible with monitoring of spontaneous and stimulus-evoked EMG responses, as these latter methods are gaining in use during spine surgery. These conditions appear to be met by the method of threshold-level TES described in this paper. Furthermore, this technique can be implemented with relatively limited expense in those programs already using intraoperative SSEP monitoring.

Threshold-Level TES

Comparison With Other Methods. Several methods for direct monitoring of function within central motor pathways during spine surgery have been pursued. Direct stimulation of the spinal cord via epidural or needle electrodes placed within adjacent spinous processes has been studied. Single-pulse transcranial stimulation of primary motor cortex via either electrical or magnetic stimulation has also been pursued. More recently, investigators have used multipulse trains delivered to the motor cortex to elicit activity via both electrical and magnetic stimulation methods. Methods for recording the output of central motor axon activation have been either neural-based or muscle-based (for example, EMG monitoring). Neural-based recordings have been made from peripheral nerves as well as the spinal cord.

Investigators working with the aforementioned methods have used criteria associated with amplitude reduction and/or latency increase in evoked response waveform in deciding whether a significant change (deterioration) in spinal conduction has occurred. Unlike SSEP monitoring, however, the amplitudes of motor responses evoked by transcranial magnetic stimulation have been reported to vary considerably from trial to trial, even when stimulation parameters are identical. Less variability is seen in response latency but only when maximum stimulus intensities are being used. As shown in Fig. 3, excessive variability in latency and amplitude values produced by weaker TES intensities would have made interpretation of intraoperative findings extremely difficult.

Associations have been drawn between the TES threshold and other parameters, including the level of anesthesia and the maturity of the corticospinal tract; however, to our knowledge, the threshold voltage for TES-evoked activity has not been used as the primary indicator of corticospinal tract integrity and function.

The threshold values we observed for upper-limb muscles, approximately 100 to 200 V but as low as 75 V, agree very closely with those numbers reported by Burke and colleagues. These investigators used single-pulse TES and made recordings directly from the spinal cord in patients with normal spinal cord function and found that to elicit the initial response (the “D-wave”) to threshold stimulation, voltages ranging from 75 to 300 V were required. This similarity in values between studies suggests that the primary effect of the additional TES pulses used in the present study is at the spinal cord level, via temporal summation.

The 3 @ 2 msec stimulus pattern used in this study was formulated from preliminary testing in awake volunteers.
(two of the authors) and from confirmation of its efficacy in the first patient we studied with multipulse TES. The interstimulus interval of 2 msec is well suited to enhance temporal summation at the alpha motor neuron level, given the known time course of the postsynaptic potentials reported in primate motor neurons in response to intracortical microstimulation and the recorded discharge rates of cortical motor neurons during voluntary movements in primates. This same 2-msec interval was adopted independently in the only other study of multipulse TES in which the D185 stimulator was used. In several patients we observed that addition of another stimulus pulse (that is, 4 @ 2 msec) caused a further, albeit slight, reduction in threshold compared with that for three pulses. However, the difference in absolute threshold between the three- and four-pulse stimulus patterns rarely exceeded 50 V in the absence of an acute deterioration in spinal conduction and was deemed to be clinically irrelevant.

**Theoretical Basis.** The theoretical basis for the threshold-level TES method studied herein is depicted in Fig. 10. Figure 10A represents the situation in which spinal conduction is normal, such that a stimulus intensity of approximately 150 V is adequate to cause one or more action potentials in the population of cortical motor neurons depicted in red (central axon). Their action leads to depolarization of one or more lower motor neurons (whose membrane potential is measured hypothetically with an intracellular electrode), as depicted by the excitatory postsynaptic potential giving rise to an action potential in this neuron. This action potential is in turn conducted to the target muscle (for example, abductor pollicis brevis) and recorded on an electromyograph. Thus, although the additional corticospinal tract neurons depicted in blue and green are capable of exciting the same spinal motor neuron, the weak stimulus intensity used (150 V) limits the cortical area that is stimulated and they are silent. However, in the case of a partial conduction block affecting the cortical motor neurons shown in red, that same 150-V stimulus may no longer be adequate to depolarize the lower motor neuron, necessitating stimulation of a larger volume of motor cortex (Fig. 10B). In so doing, the axons depicted in green and blue will now be brought into action, and their effect will lead to an EMG response in the same target muscle. An increased stimulus intensity (such as 400 V) will now be necessary to achieve the same “threshold” effect, as judged by the minimum EMG response in the target muscle.

**Advantages and Disadvantages.** Many of the drawbacks associated with the alternative methods for motor tract monitoring outlined previously are avoided using this threshold-level approach. First, the method was effective in the majority of patients studied, even though in many patients the severity of preexisting myelopathy precluded SSEP monitoring. Second, using a minimum amount of stimulus energy reduces the risk of skin burn and seizure associated with efforts to produce maximum response amplitudes and minimum latencies. Moreover, the amount of patient movement associated with threshold-level stimulation is often negligible. Our use of the Mayfield headholder further limits the possibility of head/neck movement, even in those instances in which stimulus intensities are relatively high. Third, because of the high signal-to-noise ratio associated with EMG recordings, signal averaging is not needed, which eliminates the delays typically associated with SSEP monitoring and measures using neural-based averages. Fourth, using EMG responses to represent the output signals allows us to include additional intraoperative methods, such as stimulus-evoked and spontaneous EMG responses, which are often of great value for nerve root and gray matter preservation during such procedures as tumor dissection, nerve root decompression, and spinal instrumentation. Fifth, because EMG responses are the measured signals there can be no concerns about whether the signal of interest represents a motor signal or a waveform originating from antidromically stimulated sensory fibers.

The drawbacks associated with threshold-level TES include a dependence on appropriate anesthesia, particularly avoiding use of halogenated agents such as isoflurane. We used propofol as an alternative to isoflurane in this study and recognize the added expense inherent in this approach (an increase of several hundred dollars in drug costs). The level of neuromuscular blockade cannot be total because the EMG response is the signal being monitored. Even so, a partial block (such as two twitches in a train of four) is acceptable for this method because we are only looking for threshold responses, whereas this partial block would be unsuitable for methods that monitor amplitude and latency parameters of electromyography as the primary outcome measure. In the absence of a total neuromuscular blockade, patient movement is a concern when stronger stimulus intensities are used. In fact, it has been recommended that a bite block be used in patients to prevent tooth damage when the jaws are brought forcefully together by stimulation using multipulse TES. In our experience, contraction of scalp, facial, paraspinal, and trapezius muscles can be vigorous beyond stimulus intensities of approximately 500 V, entirely as a result of peripheral nerve stimulation via current spread. Under these circumstances, care must be taken, particularly for cervical procedures, that a stimulus is not delivered at the same time that a surgical instrument is adjacent to the spinal cord. Our use of threshold-level stimulus intensities largely reduces this risk associated with patient movement. To reduce this risk further, we use a video camera mounted above the surgical field, whose output is shown on a liquid crystal display alongside the stimulator. This allows us to view the position of the surgical instruments relative to the spinal cord to judge more clearly the appropriate time to deliver a stimulus without having to warn the surgical team continually of an impending stimulus.

Finally, we found that, although in cases of severe spinal cord disease the threshold-level TES method was more effective than SSEP monitoring for generating useful signals, we did not experience uniform success in all patients by using the former method. Two patients with volitional movements in their lower limbs preoperatively did not show responses to TES in the same muscle groups during surgery, although we could elicit TES-evoked responses from their hand muscles at thresholds comparable to those of other patients. Patients should be carefully screened before surgery, with the expectation that a muscle group with a manual muscle test score of 2 or less is not likely to respond to TES during surgery.
Safety of the Procedure. The risks associated with our protocol are: 1) patient movement against a surgical instrument (discussed previously); 2) skin burns and/or scalp irritation; and 3) induction of seizures. The emphasis in our protocol on using threshold-level stimulus intensities helps minimize all three risks. We have had no skin burns at the site of stimulating electrodes, including both surface and spiral needle electrodes. The absence of adverse reactions with spiral stimulating electrodes is consistent with other reports.6,13

The risk of seizures associated with single-pulse magnetic or electrical transcranial cortical stimulation has been estimated to be extremely low, even in cases in which the patient has an increased tendency toward seizures.11 Stimulation with a prolonged train of magnetic pulses did cause a seizure in one patient with no history of seizures,40 but the number of stimuli applied prior to the onset of seizure-like activity (approximately 75) far exceeded that used in our study (that is, three pulses).

The initiation of a generalized seizure in the sedated patient is the desired goal of electroconvulsive therapy (ECT). According to the user manual of a commercially available ECT device, a therapeutic stimulus pattern recommended for the “typical” patient is as follows: pulse width 1 msec; frequency 70 Hz; phase biphasic (140 pulses/second); current 800 mA/pulse; duration of stimulus train 1.25 seconds. These parameters lead to a (calculated) charge delivery of 140,000 microcoulombs (µC).44 In marked contrast, the total charge delivered in our protocol for a given maximum stimulus train (that is, 500-V intensity) would not exceed approximately 120 µC (40 µC/pulse ∗ three pulses). In the absence of a conduction block or failure, our stimulus intensities routinely vary between 100 and 250 V, leading to current delivery of 170 to 420 mA/pulse. This results in a total charge delivery for our protocol, within the routine ranges of intensities used, of between 8.5 and 21 µC/pulse or 25 to 65 µC/pulse train. When compared with the charge delivered for a typical ECT session, it is clear that a 3 @ 2 msec pulse train for TES is unlikely to trigger a seizure in the vast majority of patients, particularly if patients with preexisting epilepsy, head injury, or stroke are excluded.

Interpretation of Findings. In the 32 patients studied successfully, there were 10 instances in which thresholds to TES increased by 100 V or more during the surgical procedure and remained elevated for more than 1 hour. In every case, the patient awoke with increased motor weakness compared with the preoperative status. As a consequence of our findings, the surgeon was able to take steps that may have helped minimize the extent of postoperative weakness in six of our patients. One example was detailed in Fig. 7; we believe that this patient’s motor status would have shown pronounced deterioration had the TES monitoring not been in place at the time of cervical distraction and graft placement. In our experience, deterioration in the absence of immediate intervention such as that seen in this patient is typically irreversible.

We did not influence the postoperative outcome of the patient for whom data are depicted in Fig. 5; this patient showed the greatest deterioration in this population. Based on the time at which the thresholds were found to increase, the deficit appeared to be a consequence of the craniotomy and exposure of the cervicomedullary mass. We can only speculate about the mechanism underlying this patient’s deficit. The slow-growing nature of the mass would have allowed a homeostasis among the mass, the central nervous system, cerebrospinal fluid dynamics, and bloodflow (arterial and venous). Decompression could potentially interfere with this balance, resulting in a period of vascular instability. Alternative explanations include the vibration and/or heat from the drilling used in the craniotomy. This patient recovered the ability to walk within 2 months of surgery. Whatever the underlying mechanism for his postoperative deficit, we believe it is fair to state that had TES monitoring not been used in this procedure, one might instead have assumed that the deficit was a consequence of the resection of the mass.

In a patient with diastomatomyelia, the thresholds to TES-evoked responses in the patient’s quadriceps muscles increased during spinal root untethering and removal of a spicule separating the caudal portions of the spinal cord; however, thresholds for her tibialis anterior and abductor hallucis muscles were unchanged (data not shown). Based on this information, the orthopedic surgeon who assisted with this procedure decided against an attempt to correct a scoliotic deformity following the spinal untethering; the surgeon elected instead to fuse the patient’s spine at the existing curvature. On awakening, the patient had only trace movements in the proximal muscles of her lower limbs, whereas prior to surgery she had near-normal strength in her proximal lower-limb muscles. However, distal muscles in her lower limbs had normal strength immediately following surgery. She was discharged from the hospital to a rehabilitation center, where she recovered ambulation (using a walker) by 10 days postsurgery.

Had we not been using threshold-level TES in this procedure, there were two possible outcomes for this patient. First, it is possible that the patient’s postoperative weakness would have been exacerbated by further traction on the proximal spinal roots of the lumbar enlargement, had the planned correction of the scoliotic deformity been performed. Second, even if a correction was performed and it did not cause further deterioration in the already impaired proximal nerve root function, the patient’s postoperative weakness might have led to an immediate reoperation for removal of the instrumentation, at needless risk and expense, because the TES monitoring demonstrated that the deficit preceded spine instrumentation.

The remaining cases in which we believe TES monitoring was helpful involved tumor resection. In general in each of the patients studied, the majority of tumor tissue was resected without affecting the TES-evoked response thresholds. However, as the resection neared completion, there were four patients in whom the thresholds began to increase, often evident in only one or two of the eight to 12 muscles being monitored. When informed of these changes, the surgeon indicated that he was attempting to eliminate all traces of the mass by working around the perimeter of the tumor but that he would stop, given the information of changes in threshold being seen. Each of these patients recovered from anesthesia with muscle weakness confined to the target muscles identified during surgery, and each recovered complete preoperative strength in the muscle(s) within 6 weeks postsurgery.

Several characteristics of TES-evoked responses were observed repeatedly in this study. In those cases in which
Multipulse transcranial electrical stimulation

thresholds for some muscles in a limb were elevated (perhaps to the point at which responses could no longer be evoked) but which were unchanged in other muscles of the same limb, there was invariably short-term (hours to days) weakness in that muscle group, with good recovery of strength and function over the following days and weeks. Moreover, the presence of any response in a given muscle group for the same baseline threshold was consistent with virtually normal motor strength in that muscle group by 24 hours postsurgery, even when the amplitude of the response to much stronger stimuli was dramatically reduced (as seen in Fig. 7, for example). As our experience with threshold-level TES increased, we found that delivery of stimulus intensities exceeding 500 V was not warranted in most cases, because if patients did not show an evoked response in a given muscle to TES intensities of 500 V, they only rarely did so for higher voltages. Clearly, it is possible to evoke responses of higher amplitude with stimuli in excess of 500 V, but as stated earlier, we believed that the advantages of threshold-level TES did not warrant stimulation with such intensities in the majority of patients.

One means of expressing the accuracy of any type of intraoperative monitoring is by measures of its specificity and sensitivity. Although the sample size was relatively small in the present study, both sensitivity and specificity had values of 1.0 for this threshold-level TES method as it relates to postoperative motor deterioration. The equivalent scores for SSEP monitoring as predictors of sensory deficits, 0.92 and 0.85, were somewhat lower and based on a population made smaller still by the absence of baseline SSEP responses in approximately one-fourth of our patient population. Published values for a study of SSEP responses alone, in which the sample size was much larger, were sensitivity and specificity of 0.92 and 0.99, respectively (note assumption made in the Discussion of that study36). However, it is not possible to compare findings of that study directly with those of the present study, because the study of Nuwer and colleagues36 did not break down postoperative deficits into those specific to sensory and motor function as was done in the present study. Indeed, had we used SSEP responses as a predictor of motor deficits or threshold-level TES values as a predictor of sensory deficits, neither test would have fared well with respect to sensitivity and specificity (examples in Figs. 5–7). We believe that it is misleading to refer to these particular instances as “false negatives,” despite the fact that this designation has historically been applied.15 That is, the expectation that a sensory test will reflect abnormalities in motor spinal pathways (or the converse) ignores the clear anatomical and vascular distinctions between fibers within the dorsal columns and lateral corticospinal tracts. Instead, these findings of specificity argue strongly for the inclusion of both sensory (SSEP) and motor (threshold-level TES) monitoring during surgical procedures that place the spinal cord at risk.

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Disclosure Statement

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