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Specialty Section on Surgical Neuromonitoring

INTRAOPERATIVE MOTOR EVOKED POTENTIAL MONITORING: OVERVIEW AND UPDATE

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ABSTRACT. Amidst controversy about methodology and safety, intraoperative neurophysiology has entered a new era of increasingly routine transcranial and direct electrical brain stimulation for motor evoked potential (MEP) monitoring. Based on literature review and illustrative clinical experience, this tutorial aims to present a balanced overview for experienced practitioners, surgeons and anesthesiologists as well as those new to the field. It details the physiologic basis, indications and methodology of current MEP monitoring techniques, evaluates their safety, explores interpretive controversies and outlines some applications and results, including aortic aneurysm, intramedullary spinal cord tumor, spinal deformity, posterior fossa tumor, intracranial aneurysm and peri-rolandic brain surgeries. The many advances in motor system assessment achieved in the last two decades undoubtedly improve monitoring efficacy without unduly compromising safety. Future studies and experience will likely clarify existing controversies and bring further advances.

KEY WORDS. transcranial electrical motor evoked potential, intraoperative neurophysiology, aortic aneurysm, intramedullary spinal cord tumor, posterior fossa tumor, intracranial aneurysm, peri-rolandic brain surgery

INTRODUCTION AND OBJECTIVES

Transcranial electric stimulation (TES) has recently emerged as an effective and practical way to perform selective corticospinal motor evoked potential (MEP) intraoperative monitoring (IOM). Direct cortical electric stimulation has a long history of use for motor system mapping during open brain surgery, but recent advances improve and extend this technique to include monitoring. After studying this review, the reader should be able to (1) describe the physiologic basis, indications and methodology of current MEP monitoring techniques; (2) evaluate their safety; (3) assess controversial aspects of intraoperative MEP interpretation and (4) outline some applications and results.

PHYSIOLOGIC BASIS AND METHODOLOGY

Patton and Amassian laid the scientific foundation for MEP monitoring in 1954 by discovering that a single electric pulse applied to monkey motor cortex evokes several descending corticospinal tract volleys [1]. An immediate non-synaptic discharge of corticospinal axons was shown to produce the first and largest volley that was named the D wave, being directly generated by the electric pulse. The following 1–5 volleys were shown to be due to the excitation of cortical synaptic circuits that discharge corticomotor

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neurons with 1.3–2.0 ms periodicity. These were called I waves, being indirectly generated by the electric pulse.

Then in 1980, Merton and Morton found that single-pulse TES produces a muscle MEP in conscious humans [2]. The mechanism is believed to vary with the momentary excitability of alpha motor neurons, determined by their levels of background depolarization from facilitatory synaptic bombardment [3]. Those close to action potential threshold fire in response to the initial D wave excitatory post-synaptic potential (EPSP), others fire after D and I wave EPSP summation and most do not fire. Thus, each successive response represents a varying subpopulation of the recorded muscle's motor units.

Barker et al. developed transcranial magnetic stimulation (TMS) in the mid-1980's, introducing diagnostic MEP testing without the scalp discomfort of TES [4]. This technique generates muscle responses predominantly through I wave volleys, although D waves can be evoked with coil orientations that induce lateral to medial current flow in the brain [5].

Intraoperatively, the synaptic interference of surgical anesthesia normally eradicates single-pulse muscle responses by reducing or abolishing I waves and reducing alpha motor neuron excitability. However, the remaining non-synaptic D wave recorded in the spinal epidural space following TES came into clinical use as a valuable corticospinal tract monitoring technique beginning in the 1980s [6–9].

Efforts to include alpha motor neurons in intraoperative MEP testing turned to invasive spinal cord electrical stimulation with recording from muscle [10–12] or peripheral nerve [13]. However, cord stimulation is non-selective. Consequently, while leg muscle responses evoked by rostral cord stimulation are mediated through alpha motor neurons, these might be activated through any of several spinal cord pathways connecting to them. Theoretically, this could include antidromic volleys in dorsal column 1a afferent axons, whose collateral branches form monosynaptic excitatory synapses with alpha motor neurons. Thus, while lower motor neuron compromise should be reliably detected, the possibility of undetected motor tract damage exists. Even worse, peripheral nerve responses (formerly 'neurogenic MEPs') were eventually shown to mostly be antidromic sensory potentials containing no reliable motor information [14].

Taniguchi et al. made a major breakthrough in 1993 by showing that a short train of 3–5 electric pulses with an inter-pulse interval of 2–4 ms applied directly to human motor cortex evokes a muscle MEP under anesthesia [15]. This is thought to be due to summation of EPSPs from (1) the evoked burst of D waves and (2) any I waves that may be facilitated by the second or third pulse even when absent to a single pulse [16]. Finally, in 1996 three independent groups showed that pulse-train TES is also effective [17–19]. Pulse-train TMS might work, but TES is more practical and its scalp discomfort is irrelevant under anesthesia. Thus, comprehensive tools for selective corticospinal motor system monitoring were finally in place 42 years after the discovery of MEPs. Today, several techniques are in use:

Pulse-train TES with muscle recording

Pulse-train TES muscle MEP monitoring is now widely applied and is indicated for any surgery threatening the motor system except open peri-rolandic brain surgery that removes the skull overlying motor cortex. It allows rapid assessment of motor system integrity from brain to muscle and is available from induction to closure.

Anesthesia and neuromuscular blockade

This monitoring technique appears to be facilitated by intravenous anesthesia such as propofol and remifentanil or other opioids that have proven to be safe, effective and well tolerated [20–24]. Sometimes low-concentration nitrous oxide is added [25], but whether or not this practice detracts from MEP monitoring is unclear. Other examples of reportedly favorable anesthetics include ketamine/sufentanil [26], diazepam/propofol/fentanyl/nitrous oxide [27] and benzodiazepine/fentanyl [28].

The apparent benefits of intravenous agents for muscle MEP monitoring may be due to less interference with alpha motor neuron excitability than from inhalational anesthetics including nitrous oxide [29–34]. Chen recently compared propofol and isoflurane in neurologically intact patients at similar anesthetic depths as judged by bispectral index (BIS) measurement [23]. Muscle MEP monitorability was better with propofol at any given BIS level. About 60% of patients had MEPs with light 0.6% isoflurane. This fell below 20% at 0.8% and even lower at higher concentrations, indicating marked dose-related MEP suppression at surgical anesthesia levels. In contrast, 100% MEP monitorability was found with propofol infusions up to 25 mg/Kg/h, corresponding to deep surgical anesthesia. There was surprisingly no statistically significant dose-related depression, although others have observed this to occur [35]. Similarly, Pelosi et al. found MEPs to be less consistently present, smaller and more variable under isoflurane/nitrous oxide compared to propofol/opioid anesthesia [21]. Nevertheless, the combination of less than 0.5 minimum alveolar concentration desflurane and propofol/opioid infusion may be permissive [36]. Further studies of anesthesia and its effects on the monitorability and

reliability of muscle MEP monitoring will be important and could bring forward new or superior methods. For the time being, there seems to be little concrete reason to avoid intravenous-based approaches that appear to optimize monitoring efficacy.

For obvious reasons, neuromuscular blockade is often omitted after intubation and this does not appear to interfere with monitoring or surgery [28, 37–39]. Otherwise, muscle relaxation must be incomplete and somehow tightly controlled according to the amplitude of muscle responses to peripheral nerve stimulation [26, 27, 40, 41]. This approach increases technical and interpretive complexity and runs the risk of inadvertently disabling muscle MEP monitoring at a critical moment. Note that blockade potentiation occurs with the administration of magnesium and that some blood pressure lowering agents such as alpha2-receptor antagonists and ketanserin can depress MEP amplitudes [42].

Stimulating electrodes and montages

Standard spiral needles, straight needles and EEG cup electrodes are effective and commonly used for transcranial stimulation [37–39, 43]. Average TES impedances for these electrodes are about 500, 800 and 1100 Ohms, respectively and this is relevant because constant voltage MEP thresholds are proportional to impedance above 460 Ohms [43]. Larger electrodes, such as unusually long subdermal needle anodes inserted bilaterally into the central scalp along with a large forehead strip cathode can eliminate this dependence by having less than 460 Ohms impedance [43], but are not commonly used. Metal electrodes screwed into the skull might increase stimulus efficiency [44], but seem unnecessarily invasive [45].

Electrodes are placed at international 10–20 system central (C) sites approximately overlying motor cortex, or at slightly anterior C+1 cm or C+2 cm sites [37–39, 46]; there is currently no evidence for an efficacy difference between these choices. The latter locations may reduce stimulus artifact by increasing the distance from Somatosensory evoked potential (SEP) scalp recording electrodes through which TES voltage reaches the headbox. Using CP SEP sites (midway between central and parietal sites) that are slightly posterior to traditional C′ sites (C − 2 cm) might also help. Disconnecting scalp SEP leads during TES markedly reduces stimulus artifact and may be necessary at high voltages that can otherwise produce excessive artifact obscuring muscle responses [38]. Digitimer (www.digitimer.com) manufactures a switch box to do this automatically when using their external high-voltage D185 stimulator. The switch also disconnects TES electrodes during SEP recording because electrical artifact from the stimulator otherwise interferes with SEPs. These maneuvers are not necessary when using the integrated lower-voltage stimulators of the Nicolet (www.viasyshealthcare.com) Viking or Endeavor monitoring devices [39].

Stimulus montages vary. An electrode array such as C3, C1, Cz−1 cm, C2, C4 and Cz+6 cm [37] or similar arrays using slightly more anterior sites are useful for selecting optimal anode-cathode pairs (Figure 1). Monitoring is most commonly performed with interhemispheric C1/2 or C3/4 TES. The C3/4 montage is more efficient, partly because less current shunts through the scalp between the widely-spaced electrodes [47]. However, it might promote deeper current penetration that may increase the likelihood of not detecting cerebral motor compromise rostral to a deep activation site [48].

Due to preferential subanodal brain activation, recording left and then right MEPs to right anodal (C2−C1 or C4−C3) and then left anodal (C1−C2 or C3−C4) TES is common practice [28, 37–39, 49, 50]. This is reversed in the patient with uncrossed corticospinal tracts that may not be that rare in scoliosis surgery because it is part of the autosomal recessive disorder horizontal gaze palsy and progressive scoliosis (HGPPS) [51]. Hemispheric C3−Cz and C4−Cz TES with bilateral muscle recording effectively assesses decussation because it evokes predominantly or exclusively unilateral MEPs [51]. I have found or confirmed non-decussation in about 3% of scoliosis surgeries at my hospital in Saudi Arabia through post-induction screening with this technique (unpublished data). HGPPS is more common in the Middle East where there is a high rate of consanguinity, but has also been reported in Europe, Japan and North America. Hemispheric montages are also best for facial MEP monitoring because they reduce the likelihood of extracranial stimulation of the targeted contralateral facial nerve [52]. They also readily evoke hand MEPs, but are less effective for leg muscle responses (Figure 2).

Using Cz−C3 or C4 for leg MEP monitoring [21] might produce response asymmetry [17]. Vertex-(Cz+6 cm) TES should promote symmetric leg MEPs but is less effective for hand muscles [37]. In addition, posterior-anterior TES may be generally less efficient since it might not evoke D waves as readily as coronal TES [53]. A vertex anode to circumferential basal cathode array can produce symmetric MEPs [54], but likely promotes deep activation.

Pulse parameters and stimulators

Constant voltage stimulation is commonly used, although controlled current is theoretically preferable, being less dependent on impedance [43]. More intense stimuli than traditionally applied to IOM are necessary to penetrate the

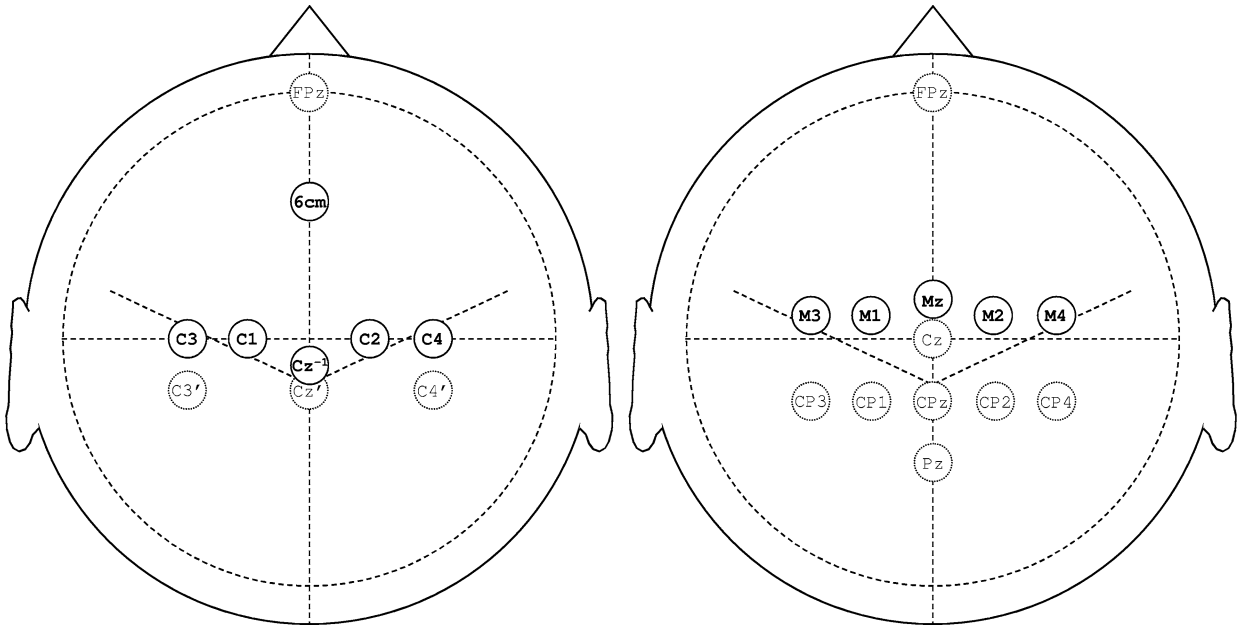

Fig. 1. Two TES arrays. Solid and broken circles are TES and SEP electrode sites. In the left array (Deletis, 2002), Cz^{-1} is 1 cm behind Cz and the frontal site is 6 cm anterior. Anode-cathode combinations can be selected to optimize technique. The author's array on the right increases TES-SEP electrode distance. M sites are 1 cm anterior to C sites except Mz, 2 cm anterior to Cz. Mz is used for hemispheric (e.g. M3-Mz) stimulation. Leg MEPs are usually evoked with M1/2 or M3/4. The additional SEP sites are used for SEP optimization.

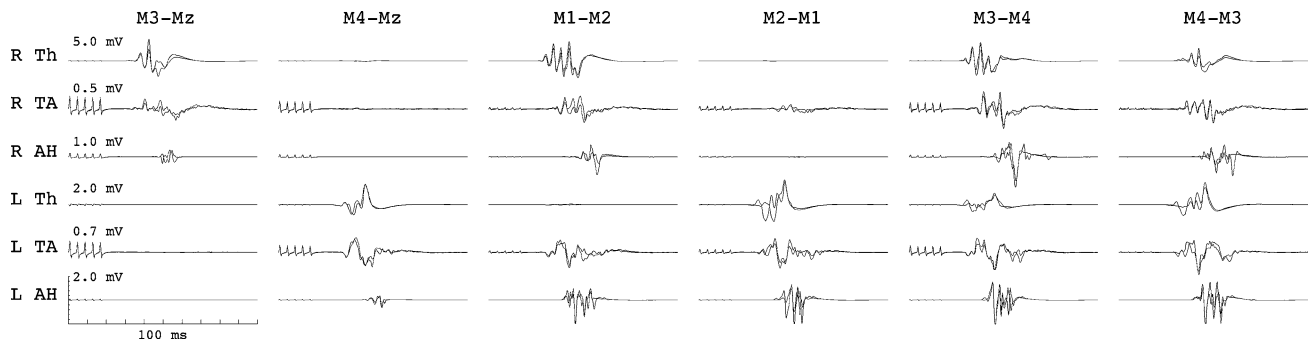

Fig. 2. TES montages. Th, thenar; TA, tibialis anterior; AH, Abductor hallucis. Hemispheric TES produced unilateral MEPs but smaller leg MEPs than interhemispheric montages, of which M3/4 was most efficient. Note anode-contralateral maximal MEPs with each montage. Nicolet Endeavor stimulator, 0.5 ms 300 V pulses, 5-pulse trains, 4 ms inter-pulse interval.

skull and this has been a source of concern and controversy. Either short pulses of 0.05 ms duration (D) and up to 1500-mA current (*I*), or long pulses of up to 0.5 ms and 240 mA are used. The two techniques produce similar charge ($D \times I$) in microcoulombs (μC) that is actually the most relevant stimulus parameter [55]. Thus, they have been referred to as 'fast' or 'slow' charge delivery methods [56]. Both are effective and each has a theoretical advantage: MEP threshold charge appears to be about 35% lower with short pulses [50, 56], while long pulses appear to speed D wave recovery between closely-timed pulses [57].

Constant voltage TES stimulators using 0.05 ms pulses are available from Digitimer (www.digitimer.com) and Cadwell (www.cadwell.com) with maximum 1500 and 800 V settings, respectively. Axon Systems (www.axonsystems.com) produces a TES stimulator using either 0.075 pulses of up to 1000 V or 0.35 ms pulses of lower voltage but comparable charge; double-train facilitation capability is built-in. The 100 mA limit of standard IOM stimulators in constant current mode is too low to consistently evoke TES muscle responses. However, using constant voltage mode instead can drive current

beyond this limit, depending on impedance. For example, standard Nicolet Viking and Endeavor stimulators approach 200 mA output at the maximum 400 V setting when electrode impedance is low and are thus effective when using 0.5 ms pulses [39, 55]. Parallel constant current output from two standard IOM stimulators reaches 200 mA and is consistently effective using 0.5 ms pulses [56]. Deletis et al. described a custom-made constant current long pulse stimulator with up to 240 mA output [57], and Inomed (www.inomed.com) manufactures a 150 or 220-mA variable pulse width constant current stimulator with double train facilitation capability. More advanced and flexible TES devices will likely be integrated into future monitoring systems.

Train parameters

Trains consist of 3–9 rectangular pulses with a 1–5 ms inter-pulse interval. There is presently no clearly superior parameter selection and further studies are needed. Pulse number is adjusted according to need and operator or institutional preference. Reasonable starting points might be 5 pulses for leg MEPs [37, 39] and 3 or 4 pulses when only hand and/or facial responses are monitored [52, 58].

The optimal inter-pulse interval appears to vary with anesthetic depth, stimulus intensity, the targeted muscle(s) and individually. With light anesthesia permitting abundant I waves, unusually long intervals of 8 ms or more can be optimal by allowing full I wave expression before the next pulse [16]. However, under regular surgical anesthesia corticospinal drive depends mainly on D waves that have an absolute and relative refractory period. With medium-intensity TES, D waves do not show full amplitude recovery between pulses until a 4–5 ms interval that should therefore promote corticospinal drive and muscle MEPs [16, 37, 50]. Full D wave recovery may also occur with a 2 ms interval when higher intensity is used [59].

Despite incomplete D wave recovery, a 1 ms interval can produce large hand MEPs and was recently found optimal for hand muscle MEP amplitude to trains of four 0.05 ms pulses at 300 V [48, 58]. However, the same may not be true for leg muscles (Figure 3). This suggests that other factors may be involved, such as segmental alpha motor neuron summation properties, motor unit synchronicity or I wave facilitation. In practice, 4 ms might be a good starting point when leg muscles are included in monitoring, but a shorter interval might be preferable when monitoring only hand and/or facial muscles [52]. Interval adjustments can sometimes optimize individual recordings [36, 38, 39, 60].

Facilitation

Facilitation techniques are often used, especially when single-train MEPs are small, inconsistent or absent. Most commonly, one or more preconditioning trains to build up alpha motor neuron excitability are applied immediately before the test stimulus, or a series of 2 Hz recurrent pulse-trains is applied [36–39, 61]. Generating a subliminal withdrawal reflex through high-frequency foot sole stimulation 50–100 ms before TES facilitates tibialis anterior responses so much that they can be evoked with a single transcranial pulse [62, 63]. While not commonly used, the effects of this spatial facilitation technique show that segmental alpha motor neuron excitability can be modified by local sensory input under anesthesia. The potential use of Ia afferent facilitation [64] remains largely unexplored, but might be valuable.

Recording

Recordings are typically made from hand, tibialis anterior and foot muscles using needle electrodes, an approximately 20–2000 Hz bandwidth, and 100 ms time base. Surface recording electrodes such as adhesive ECG discs are also effective [25]. Other limb and sphincter muscles are monitored as indicated. Bulbar muscle MEPs require attention to filtering and stimulus montage because of short latency and cranial nerve and muscle proximity to scalp TES current [52]. Stimulation is usually adjusted to clear supra-threshold MEPs in all targeted muscles [36–39] or to the threshold of the last recruited muscle [49, 65]. Supra-maximal stimulation has also been described [25], but is not commonly used at this time.

Muscle responses tend to be polyphasic when recorded with needle electrodes and this tendency increases with inter-pulse interval and pulse number. Surface recordings tend to show less polyphasia but smaller amplitude. Curve area should be a more accurate measurement of polyphasic MEPs than peak-to-peak amplitude, but is not commonly used. Responses vary with anesthesia and between patients and muscles, generally – but not always – being largest with lowest threshold in the hands. They are consistently obtained in neurologically intact patients under appropriate anesthesia but may be rendered small, inconsistent or absent by antecedent corticospinal system pathology. Their amplitudes range from μV to several mV and there is often substantial trial-to-trial variability, although relatively stable responses also occur. The high signal-to-noise ratio makes averaging unnecessary, so that single-trial responses are most commonly monitored. Averaging is theoretically undesirable because of facilitation with repetitive trains, but might enhance stability [36, 50].

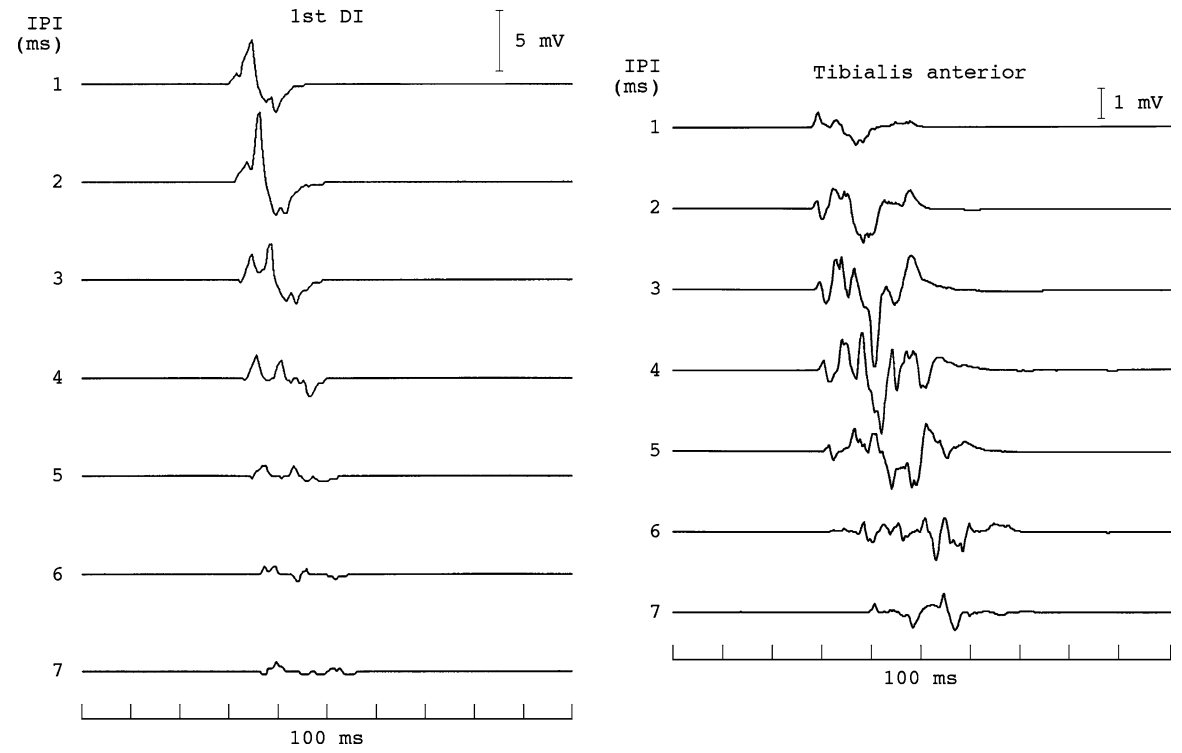

Fig. 3. Inter-pulse interval (IPI). This first dorsal interosseous (1st DI) muscle showed large simple responses to 3-pulse short interval trains. Tibialis anterior MEPs maximized at 3–4 ms intervals (5-pulse trains). Digitimer D185 stimulator.

Pulse-train TES with peripheral nerve recording

Peripheral nerve responses to pulse-train TES are true neurogenic MEPs, but will not likely replace muscle recording because they require averaging and because temporal dispersion may not allow distal peripheral nerve MEP recording (Deletis, personal communication). However, this technique does have a unique role in assessing motor root continuity or avulsion during brachial plexus surgery [66] (Figure 4).

Pulse-train direct cortical/subcortical stimulation with muscle recording

Muscle MEPs to cortical or subcortical pulse-train stimulation are useful during peri-rolandic brain surgery to map and monitor motor cortex and to judge proximity to subcortical motor fibers [46, 67, 68]. Subdural strip or probe electrodes are used for monopolar anodal stimulation, generally with a scalp cathode. Bipolar cortical stimuli should also be effective [69]. Train parameters are the same as TES, except for much lower charge since there is no intervening skull [70].

Single-pulse TES with D wave recording

Monitoring spinal epidural D waves to single-pulse TES allows selective corticospinal tract assessment. Nevertheless, few centers apply this possibly underutilized method. Since the advent of muscle MEPs, the main indication for this technique is spinal cord tumor surgery [37, 71, 72]. Some centers still include D waves during spinal deformity surgery [50].

Stimulation and recording

Pulse parameters, stimulating electrodes and montages are the same as the pulse-train technique. Bipolar recording electrodes with a 2–3 cm inter-electrode distance are inserted into the epidural space by the surgeon after posterior spine exposure or percutaneously by an anesthesiologist. They can also be inserted into the subarachnoid space through lumbar puncture and threaded upward [73]. Single sweeps can be monitored, but averaging a few trials at 0.5–2 Hz clarifies the responses. A 10–20 ms time base is used and low-frequency filtering varies from about 100 Hz [37] to up to 500 Hz to constrain stimulus artifact

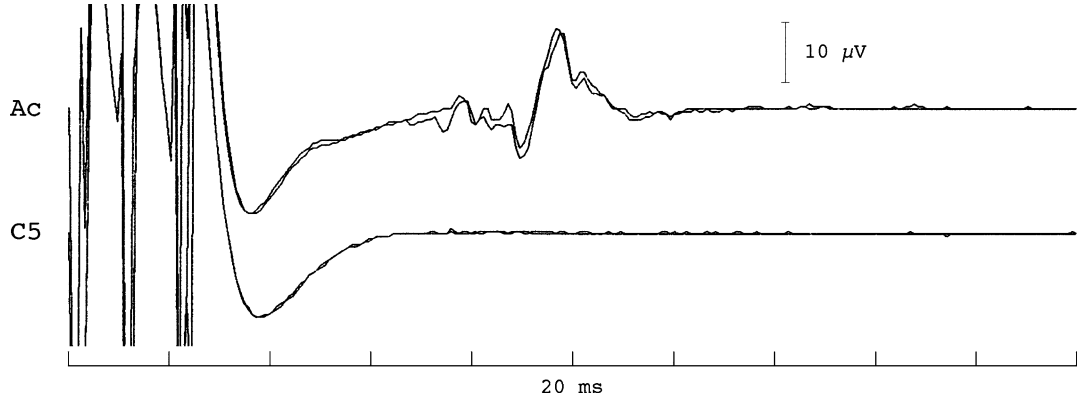

Fig. 4. Pulse train TES with peripheral nerve recording during brachial plexus surgery. The neurogenic MEP confirmed motor root continuity to the accessory (Ac) nerve. The absent C5 root response supported a diagnosis of avulsion. Digitimer D185 stimulator.

[6, 8] while causing some signal attenuation. Sometimes an open low-frequency filter setting of 0.2–2 Hz can produce a level baseline before D wave onset without signal attenuation (unpublished personal experience).

D wave characteristics

With increasing stimulus intensity, D waves grow in amplitude and decrease in latency, indicating recruitment of more corticospinal axons and deepening subcortical activation [6, 9] (Figure 5A). One or more I waves may appear, indicating the recruitment of cortical synaptic circuits [6, 9, 37]. Sometimes with further increments the D wave bifurcates and then trifurcates into distinct earlier components [6] (Figure 5B). This suggests a tendency for activation to jump to deeper preferential sites, perhaps the internal capsule and brainstem [37, 48]. Thus, there may not be a clear supramaximal level, but setting intensity to the largest non-bifurcated D wave or to that selected for pulse-train muscle MEPs is reasonable [37].

Transcranially-evoked D waves at the cervical level can exceed 100-μV and have 2–3 ms peak latency. Toward more caudal levels where the corticospinal tracts become progressively smaller, D wave amplitude decreases and latency increases until the potential disappears at lumbosacral cord where the tracts end [6, 9]. D waves are highly stable and unaffected by neuromuscular block. They are resistant but not immune to anesthesia; modest dose-related threshold elevation and amplitude reduction do occur and might be caused by axonal effects [74] or superficial cortical shunting due to cerebrovascular changes [37].

D waves appear to be unrecordable under 21 months of age, probably because of temporal dispersion due to variable conduction velocity of immaturely myelinated corticospinal tract axons [75]. In contrast, no lower age limit for pulse-train muscle MEP monitorability is presently known. Sala et al reported muscle MEPs in children as young as 11 months [67] and I have monitored them in the legs of a 4-month-old (Figure 6), indicating that incompletely-myelinated corticospinal axons conduct and excite lumbosacral alpha motor neurons at a young age.

Antecedent corticospinal tract pathology can reduce or obliterate D waves due to axonal destruction and conduction block. Sometimes these patients have muscle MEPs without recordable D waves and this might be explained by temporal dispersion ('desynchronization') due to variable conduction velocity of damaged but still conducting corticospinal axons [37].

Lateralization

D waves evoked by TES are not clearly lateralized because of the midline recording and the difficulty of limiting stimulation to one hemisphere [48]. They represent bilateral corticospinal volleys when the same stimulus montage and charge evokes bilateral pulse-train muscle MEPs, but there may be a greater contribution from the sub-anodal hemisphere. They predominantly arise from the sub-anodal hemisphere when there are unilateral pulse-train muscle responses [37]. However, some contribution from the other hemisphere cannot be excluded because D waves have lower thresholds than muscle responses (Figure 7). One approach is to record 'left' and 'right' D waves to right and left anodal TES, while recognizing that these may not be purely lateralized [37, 48].

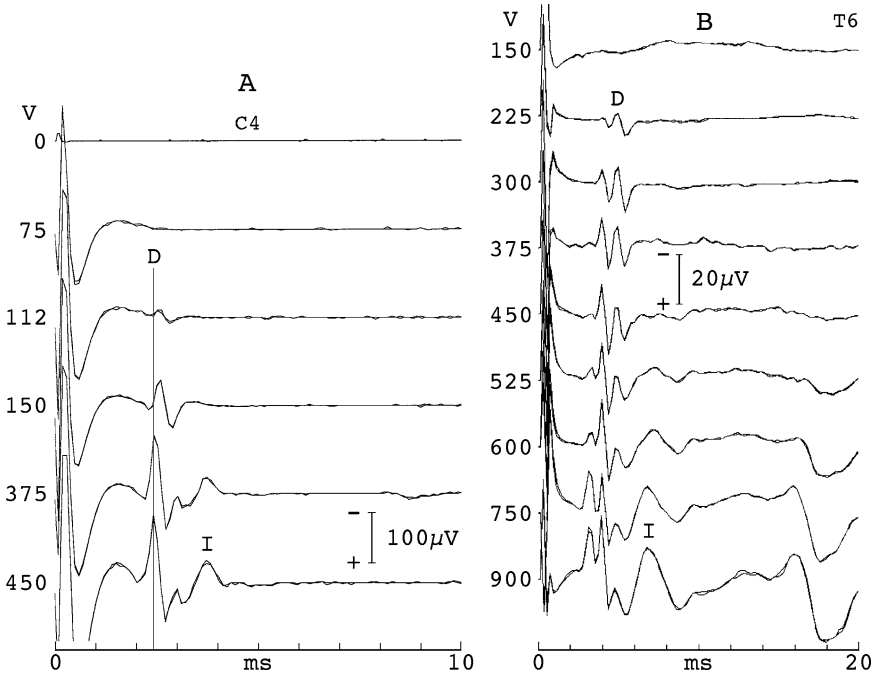

Fig. 5. D waves at increasing stimulus intensity. In A, cervical (C4) D wave amplitude increases and latency decreases. In B, a thoracic (T6) D wave bifurcates and trifurcates. Note the appearance of an I wave at high intensity and the appearance of a late muscle artifact at very high intensity (B). Digitimer D180a stimulator.

Single-pulse direct cortical stimulation with D wave recording

Monitoring D waves to direct cortical single-pulse stimulation can be used to identify motor cortex and assess corticospinal integrity during peri-rolandic brain surgery [69, 76–78]. These D waves are lateralized and focal since they are generated by locally-stimulated cortex. The percutaneous cervical epidural recording electrode will probably limit the use of this method to specialized centers. However, recent evidence suggests that it may be a valuable compliment to muscle MEP monitoring of these surgeries [69, 79].

SAFETY ISSUES

Fundamental principles of electric safety and infection control must be adhered to and are comprehensively addressed elsewhere [80]. Special concerns for MEP monitoring include the possibilities of hazardous stimulator output, movement-induced injury, bite injury or epidural electrode complications as well as contraindications. Note that there is currently no evidence for a significant safety difference between short- and long-pulse TES or between supra-threshold and threshold-level MEP monitoring [55, 56, 74, 80].

Hazardous stimulator output

Excessive electrical stimulation might cause thermal injury (burn) of the scalp or brain and electrochemical or excitotoxic injury to the brain. Stimuli that are not directly injurious to tissue might provoke seizures or cardiovascular alterations.

Thermal injury

The energy in Joules (J) of an electrical pulse is the product of voltage × charge and produces heat. Since voltage = current (I) × resistance (R) and charge = I × pulse duration (D), pulse energy is equivalent to $I^2 \times R \times D$. Therefore, short pulses that require larger current must generate substantially more heat than equivalent-charge long pulses. The International Electrotechnical Commission (IEC) safety standards for evoked potential equipment stipulate that electrical stimulator output shall not exceed 50 mJ through 1000-Ohm load resistance [81]. This is predicated by the assertion that all known clinical applications can be achieved without exceeding this limit and validated by the absence of confirmed skin or neural thermal injuries from electrical stimulation below it. Intraoperative skin burns at monitoring electrode sites do rarely occur, but

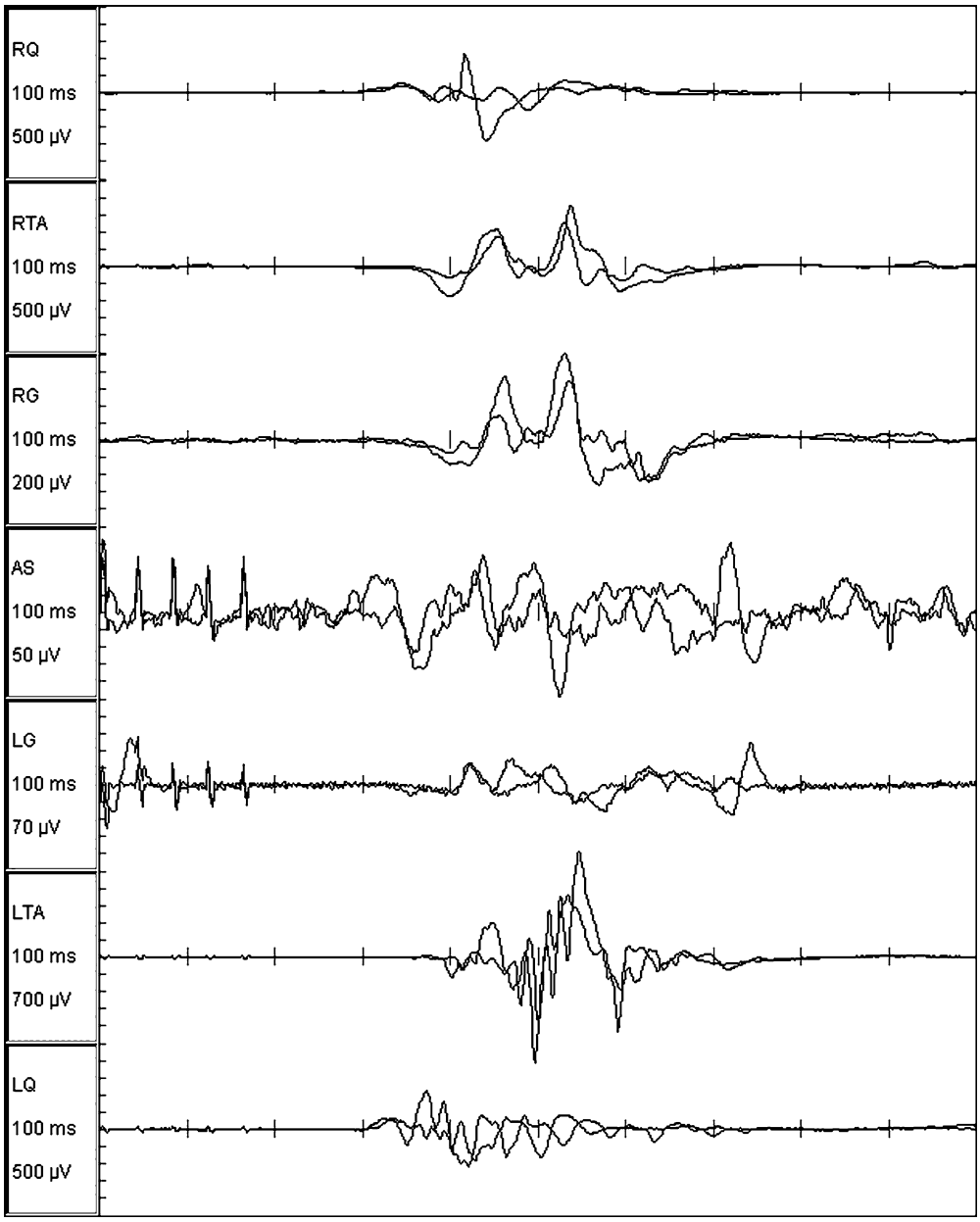

Fig. 6. Intraoperative TES muscle MEPs in a 4-month old undergoing tethered cord release. Q, quadriceps; TA, tibialis anterior; G, gastrocnemius; AS, anal sphincter. Nicolet Endeavor stimulator, 5-pulse trains, 4 ms inter-pulse interval, 400 V.

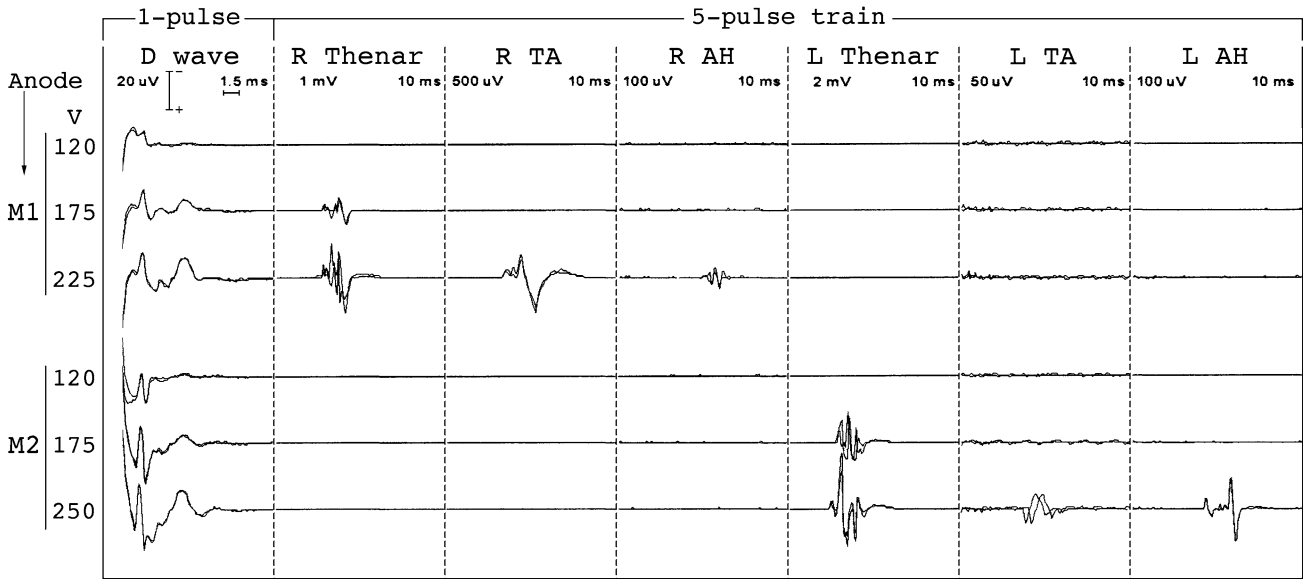

Fig. 7. Lateralized D waves. Unilateral muscle responses indicate that these D waves originate predominantly from the sub-anodal hemisphere. Since D wave threshold was lower than muscle responses, some contralateral contribution cannot be excluded. Nicolet Viking stimulator.

are not limited to stimulating electrodes and when investigated are almost always due to stray high-intensity electrosurgical radiofrequency current or sustained low-intensity direct current from equipment malfunction [80, 82].

Considering direct cortical stimulation for MEP monitoring, the largest maximum pulse parameters reported so far have been 50 mA and 0.5 ms [69]. Assuming 5000-Ohm impedance, maximum pulse energy would be 6.25 mJ and should not cause thermal cortical injury. Note that a 0.05 ms pulse of equivalent charge would generate 62.5 mJ. In fact, early investigators found cortical thermal injury to be possible in animal experiments with short pulses and recommended pulse durations of more than 0.1 ms [83]. Thus, short-pulse stimulators designed for TES must not be directly applied to the brain since an inadvertently moderate to high stimulus setting normally intended for extracranial application might cause cortical thermal injury.

Considering TES, the high charge needed to reach the brain might lead to scalp thermal injury. Maximum long-pulse stimulation (240 mA, 0.5 ms) through 500 Ohms (the average of spiral electrodes) to 1100 Ohms (the average of EEG cup electrodes) would produce 14–32 mJ at the scalp, probably insufficient to cause a burn. However, maximum short-pulse stimulation (1500 mA, 0.05 ms) through 500–667 Ohms (where full Digitimer D185 current output is possible) would generate 56–75 mJ, exceeding the IEC limit and introducing the possibility of scalp thermal injury. Indeed, a review of TES safety identified two vertex electrode burns that might have been due to short-pulse stimulation [55]. Thus, caution is advised when operating short-pulse stimulators near maximum output. Regardless of the stimulator type, it is prudent to assure low scalp electrode impedance and avoid needlessly-high current.

Electrochemical injury

Electrochemical neuronal injury is only possible at the electrode-tissue interface and is therefore not a concern during TES [55]. Nor is it a concern during direct cortical stimulation with single pulses that transfer charge mainly through capacitive current as long as pulse duration is 1-ms or less (thus, direct cortical pulses should probably be between 0.1 and 1 ms) [83, 84]. However, due to the properties of the electrode-tissue interface, direct cortical monophasic pulse-trains can begin to transfer charge through faradic current involving electrochemical reactions causing a local accumulation of various toxic products [80, 84]. A quantity of these can be tolerated or buffered, so that the possibility of injury increases with train duration [84].

Biphasic pulse-trains were introduced in the 1950s to circumvent this problem [83]. Each biphasic pulse consists of two phases of opposite polarity, driving any electrochemical reactions in opposite directions and minimizing the accumulation of toxic products [84]. Therefore, although biphasic stimulation tends to be less effective for neural activation [84], it is recommended for traditional cortical mapping with 50–60 Hz pulse-trains lasting seconds [83,

85]. However, note that early human investigators including Penfield used monophasic trains lasting seconds without clinical signs of toxicity [85].

The 3- to 7-pulse direct cortical trains used for muscle MEP monitoring are monophasic, raising the question of whether they might cause electrochemical injury. However, their extreme brevity, modern capacitive coupling that also limits Faradic current [85] and the lack of reported clinical signs of toxicity argue against a significant hazard, although histologic confirmation is lacking. Thus, it currently appears acceptably safe to apply this technique, pending further information to the contrary.

Excitotoxicity

Animal experiments designed to evaluate the safety of chronic direct cortical stimulation have shown that continuous 50 Hz biphasic pulse-trains lasting many hours can cause excitotoxic neuronal damage [55]. Charge and charge density (charge/electrode area, in $\mu C/cm^2$) are injurious cofactors in these experiments; higher charge can be tolerated with lower charge density and visa versa [86]. Thus, 0.4 μC at 40 $\mu C/cm^2$ and 6 μC at 12 $\mu C/cm^2$ have each been identified as experimental injury thresholds. The severity of histologic damage increases with train duration [86]. Notably, there are no experiments evaluating the safety of brief intermittent pulse-trains analogous to those used intraoperatively.

The only histologic investigation in humans so far was conducted by Gordon et al. who found no damage after 50-Hz intermittent biphasic pulse-trains lasting up to 5 s [85]. They evaluated 3.175 mm diameter disc electrodes and 0.3 ms pulses of up to 15 mA, producing up to 4.5-μC and 57-$\mu C/cm^2$. Traditional 50–60 Hz pulse-trains lasting seconds using smaller 1–2 mm diameter hand held probe electrodes can exceed 300-$\mu C/cm^2$ charge density and are considered safe after decades of clinical experience [55, 85].

In their original report of muscle MEPs to direct cortical 3–7 pulse-trains, Taniguchi et al applied 0.5 ms pulses of up to 20 mA through a 1-cm^2 silver plate electrode [15]. Maximum charge and charge density were 10 μC and 10 $\mu C/cm^2$, without clinical signs of neural injury. Subsequent reports of pulse-train or single-pulse direct cortical stimulation for MEP monitoring describe using 4 or 5 mm diameter subdural strip electrodes and pulses of 0.2–0.5 ms duration. Current has usually been limited to 20–25 mA [46, 67, 68, 79], although up to 33 mA [70] and even 50 mA [69] has been applied. The corresponding maximum charge and charge density values vary between 10–25 μC and 50–130 $\mu C/cm^2$, with no reported clinical signs of excitotoxic cortical injury.

Thus, no injury threshold for brief intermittent pulse-train cortical stimulation has been defined, but histologic confirmation is lacking. Charge and charge density values below experimental injury thresholds should exclude the possibility of excitotoxic injury and staying below those examined by Gordon et al. is likely to be safe. In any case, it would seem prudent to favor larger electrodes producing lower charge density, avoid needlessly high charge and follow published protocols that have not been found harmful.

Considering TES, a review of contemporary stimulus parameters found that experimental animal injury thresholds are not likely to be exceeded at the brain even with maximum stimulator output because of dispersion through the skull [55]. Thus, cerebral excitotoxicity appears to be unlikely and there are no reports of clinical symptoms or signs suggesting such an injury. Again, histologic confirmation is lacking and it seems prudent to avoid needlessly-high intensity.

Seizures

The possibility that brain stimulation could provoke a seizure is clearly a concern. Traditional 50–60 Hz direct cortical pulse-trains lasting 1–5 s frequently induce afterdischarges (seizure patterns) that build to clinical seizures in 5–20% of patients [87]. While most seizures are self limited or readily aborted with a variety of techniques [88], a convulsion could cause serious morbidity or sequelae [55]. Interestingly, it has been found that one way to terminate an afterdischarge is to apply a brief burst of cortical electrical stimulation [89].

Thus, perhaps it is not surprising that very brief pulse-trains have turned out to have a low chance of provoking seizures. Nevertheless, seizures rarely occur during surgeries monitored with pulse-train TES, fortunately without morbidity so far [55, 70]. Their rarity makes it uncertain what proportion is due to stimulation or to anesthesia that can also rarely induce seizures [55]. The direct cortical pulse-train technique does appear to trigger seizures in a few predisposed patients, but much less frequently than longer 50–60 Hz trains [67, 68, 70]. No intraoperative seizures have yet been reported during single-pulse direct cortical or transcranial stimuli [55]. Note that kindling is not believed to occur with any of these techniques [55].

Cardiovascular alterations

Cardiac arrhythmia or blood pressure alteration has been observed rarely during surgery monitored with pulse-train

TES, but the relationship, if any is unclear [55]. Deep current penetration to the hypothalamus or brainstem is one possible mechanism and another reason to avoid needlessly high intensity and widely spaced TES electrodes. A parasitic TES current path from scalp SEP electrodes through the headbox into leg electrodes and then traveling through the heart on the way back to the head is another theoretical mechanism [90]. Using separate monitoring devices for MEPs and SEPs would eliminate this possibility but be impractical. Consequently, it may be advisable to use separate headboxes for scalp and leg recording leads (which is what I do), or to disconnect scalp SEP electrodes during TES [90]. Cardiac arrhythmia must be differentiated from TES artifacts that appear in the ECG [80].

Movement-induced injury

The patient twitch during pulse-train TES could cause injury if a vital structure is jolted into or torn away from a surgical tool, but there are currently no reported incidents [55]. This concern arises mainly during neurosurgery and neck surgery. Technical adjustments may help. For example, omitting leg MEPs that require strong stimuli is helpful during posterior fossa surgery. When this is done, using C3−Cz and C4−Cz TES may reduce the magnitude of movements by producing predominantly unilateral MEPs [52]. When leg MEPs are considered essential, C1/2 or Cz−(Cz+6cm) may produce less movement than C3/4 [37, 46], but tend to be less efficient. Threshold-level TES may lessen movements [49, 65]. Video monitoring, communication and careful stimulus timing are other essential preventive strategies. Partial neuromuscular blockade may dampen but not eliminate movement and complicates interpretation. The spatial facilitation technique of preceding TES by foot sole stimulation may limit movement to an individual leg [62], but is not widely used. Direct cortical pulse-trains generate less movement than TES because of more focal muscle activation [70].

Bite injuries

Bite injuries due to jaw muscle contractions during TES are the most common but still infrequent complication, having an estimated incidence of about 0.2% [55]. The mechanism may involve both corticobulbar activation with pulse-trains and direct muscle or trigeminal nerve stimulation, because jaw-clenching also occurs with single pulses. Thus, C3/4 TES might produce stronger biting than C1/2 TES because the electrodes are closer to facial motor cortex, jaw muscles and trigeminal nerves.

Most tongue or lip lacerations heal spontaneously, but a few have needed surgical repair and one mandibular fracture has been reported with C3/4 threshold-level TES [49, 55]. Soft bite-blocks are recommended, but in ten years TES experience using mostly C1/2, I had not seen any bite injuries and wondered why others had encountered them. After I started exploring C3/4 because of its greater efficiency, there was still only one minor tongue bite. Then one frightening day a patient bit partway through her armored endotracheal tube (Figure 8) and needed emergency re-intubation! This patient required strong repetitive C3/4 TES due to her spinal cord tumor and severe paraparesis. We then tried oral airways, but a patient with jaw malocclusion broke two incisors on the hard airway, again with C3/4. Now we pack gauze between the molars and I have gone back to preferring C1/2, reserving C3/4 for cases needing it.

Epidural electrode complications

Spinal epidural electrode complications have not yet been reported. However, nerve root or spinal cord trauma, infection and especially hematoma are concerns with any spinal epidural invasion [55]. For example, Rodi et al. reported a patient who required emergency laminectomy to relieve cord compression from intraoperative hematoma caused by an epidural anesthetic catheter [91] and the same could occur with an epidural electrode. This patient had ankylosing spondylitis that is a known risk factor, as are anticoagulation, bleeding disorders and difficult or repeated punctures. To put this in perspective, the rate of clinically significant hematoma with epidural anesthesia is about 1/150,000 and infection is rare [55]. Still, about 10% of spinal hematomas are due to epidural or lumbar puncture [92].

Thus, the use of epidural recordings should be justified by need or deferred to non-invasive methods when sufficient [80]. For example, D wave recordings are justified during intramedullary spinal cord tumor surgery because they appear to add important prognostic corticospinal tract information that muscle MEPs alone do not provide [37, 71]. Epidural recordings are more difficult to justify during aortic or spinal deformity surgeries that are now adequately monitored with non-invasive methods using appropriate anesthesia.

TES contraindications

Comprehensive relative contraindications for TES include epilepsy, cortical lesions, convexity skull defects, raised in-

Fig. 8. Ruptured endotracheal tube. A potentially life-threatening TES bite complication.

tracranial pressure, cardiac disease, proconvulsant medications or anesthetics, intracranial electrodes, vascular clips or shunts and cardiac pacemakers or other implanted biomedical devices [55]. Some of these are theoretical or borrowed from TMS and electroconvulsive therapy contraindications [55]. Whether epilepsy, cortical lesions or proconvulsant medications increase the chance of a TES-induced seizure is presently unknown. While convexity skull defects might produce a localized high current density through a low resistance pathway, no particular hazard has yet been reported when TES is performed during craniotomy, on a patient with previous craniotomy or on infants with open fontanels and unclosed sutures (note that spiral needle stimulating electrodes should not be used in infants [67]). It is unknown whether intracranial electrodes, clips or shunts increase TES hazards. While TMS can disrupt cardiac pacemaker function, this seems unlikely with TES that does not generate a strong magnetic field. Thus, each relative contraindication must be weighed against the risk of omitting MEPs and such patients have been monitored uneventfully when the need for MEP monitoring seemed substantial [55]. An intraoperative seizure or cardiac arrhythmia is an indication to consider aborting TES when no other mechanism is apparent.

The benefits of MEP monitoring clearly outweigh the risks and the techniques are thus sufficiently safe for clinical use in expert hands using appropriate precautions [55]. The recent United States Food and Drug Administration (FDA) clearance of TES stimulators affirms this conclusion.

INTERPRETATION

D waves

The D wave is a linear potential: up to a point, its amplitude is proportional to stimulus charge and reflects the number of recruited fast corticospinal axons synchronously conducting through the recorded spinal cord level [3, 37]. This property and its notable stability allow relatively straightforward amplitude interpretation. Whenever possible, a control recording rostral to the level of potential spinal cord injury helps identify confounding factors (Figure 9). These include stimulus failure, marked anesthetic changes, scalp edema and intracranial air during sitting position posterior fossa surgery [37, 38, 48]. Electrode displacements in the longitudinal direction of the spinal cord that alter amplitude are made obvious by peak latency shift.

D wave amplitude reductions unexplained by confounding factors indicate but do not clearly lateralize partial conduction block rostral to the recorded level [37]. Preservation does not exclude injury caudal to the recorded level

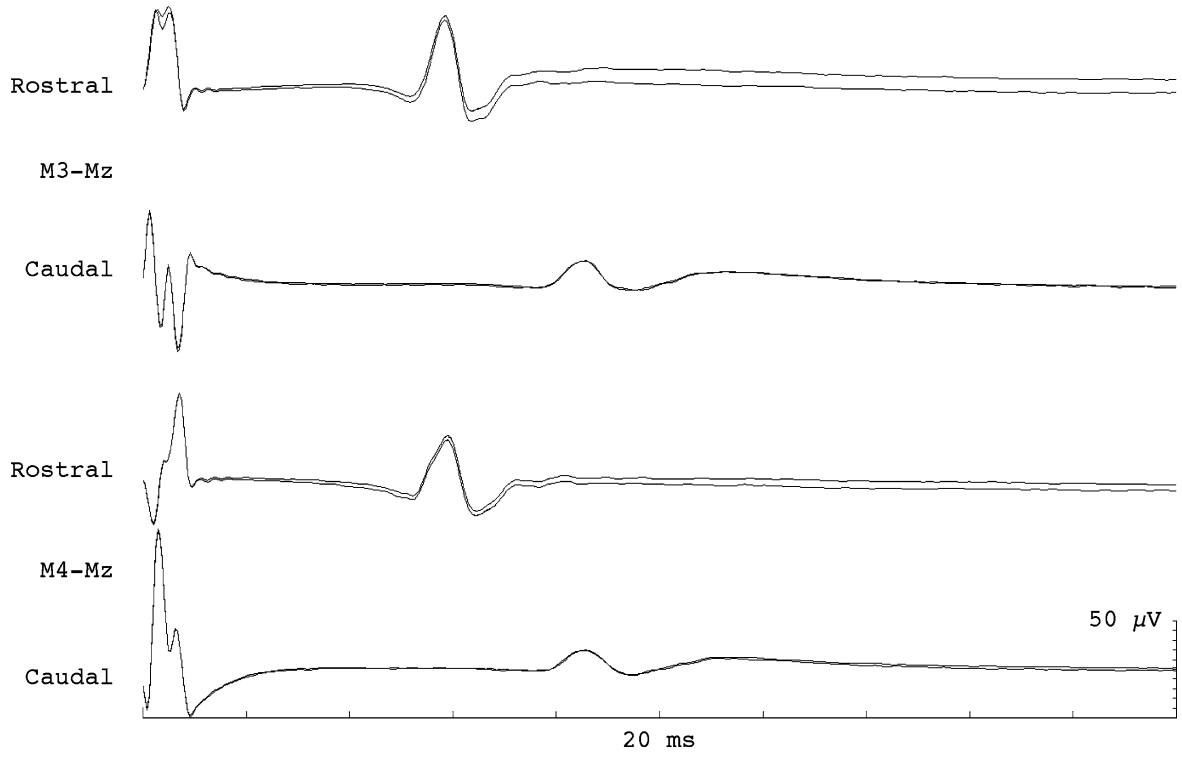

Fig. 9. Rostral and Caudal 'right' and 'left' D waves during thoracic spinal cord tumor surgery. Rostral recordings control for confounding factors. Nicolet Endeavor stimulator.

or rostral to the intracranial activation site [48]. With TES, worsening of an antecedent hemiparesis cannot be excluded by preserved D waves that may originate from the healthy hemisphere [48]. In addition, motor deficits not due to corticospinal tract injury can occur without D wave change [37]. Finally, an animal model of spinal cord ischemia found ischemic D wave reduction delays of up to 22 minutes due to tract resistance [93].

A 50% amplitude reduction seems critical for long-term motor function during intramedullary spinal cord tumor surgery [37, 71]. It appears that greater reduction is associated with permanent motor deficit while preservation is associated with good motor outcome or recovery of any early postoperative weakness. Similarly, initial results with D waves to direct cortical stimulation during peri-rolandic brain surgery suggest that a >30–50% reduction may predict permanent motor deficit, while preservation may predict good long-term outcome [69, 78, 79]. Thus, it presently appears that corticospinal tract preservation allows eventual compensation and recovery of early postoperative weakness due to injury mechanisms other than corticospinal tract or alpha motor neuron destruction.

A 20–30% reduction alarm criterion has been recommended for scoliosis surgery [6, 8, 50]. However, Ulkatan et al have recently observed thoracic D waves to decrease–or increase–by up to 75% after spine straightening without muscle MEP or scalp SEP changes or correlation to outcome [94] (Figure 10). This might be due to altered distance between the epidural electrode and the spinal cord as its position shifts within the newly straightened spinal canal [94]. In support of this explanation, the spinal cord is known to assume a rotated ectopic location toward the concave side of the scoliotic spine [94]. Regardless of the mechanism, these observations contradict previous recommendations, introduce a new possible confounding factor that might not affect a rostral control recording and cast doubt on the reliability of epidural recordings for these surgeries.

Muscle MEPs: Interpretive considerations

Complexity and the alpha motor neuron

Pulse-train muscle MEP recordings are much more complex. They involve: (1) non-synaptic and synaptic corticomotor neuron excitation, (2) corticospinal tract

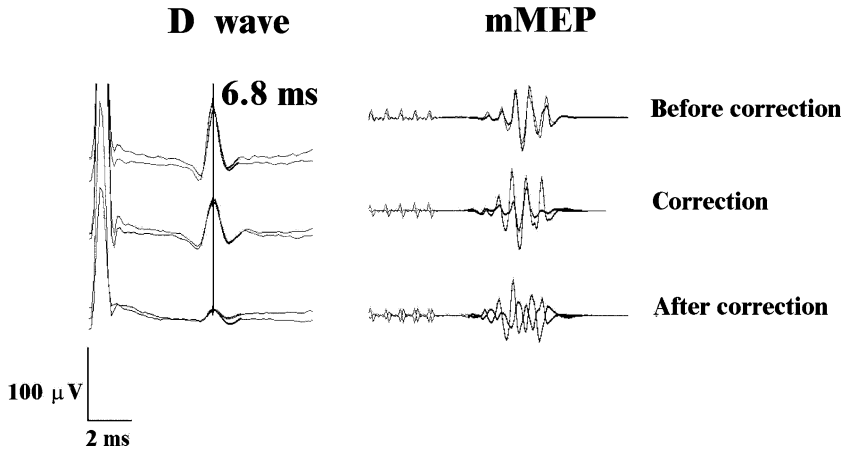

Fig. 10. Benign D wave reduction during scoliosis surgery. Marked D wave reduction occurred after deformity correction without muscle MEP (mMEP) change or deficit. Unchanged peak latency ruled out vertical electrode displacement. From Ulkatan et al. [94], with permission.

conduction, (3) synaptic transfer through alpha motor neurons, (4) spontaneous variability, systemic factors and other systems affecting alpha motor neuron excitability, (5) peripheral conduction and (6) neuromuscular transmission. Anesthesia mainly interferes with synapses, while axonal conduction and neuromuscular transmission are largely unaffected. TES mostly bypasses cortical synapses by directly activating subcortical motor axons. This leaves alpha motor neuron excitability as the most vulnerable–and capricious–link in the chain of muscle MEP generation. If used, neuromuscular blockade further compounds this complexity.

Non-linearity, high sensitivity and instability

The fundamental building blocks of muscle MEPs are motor units, each consisting of one alpha motor neuron and the muscle fibers it supplies. Motor unit output is non-linear: corticospinal EPSP input that sums to or exceeds an alpha motor neuron's firing threshold produces a full unit response while anything below firing threshold produces no response. Compound muscle responses are somewhat more graded as motor units are added or removed, but still exhibit substantial aggregate non-linearity [3]. This makes the technique exquisitely sensitive because a small reduction of corticospinal drive or alpha motor neuron excitability can cause a disproportionately large reduction or loss of muscle response.

Each trial recruits a fraction of the recorded muscle's motor units and individual unit firing depends not only on corticospinal input, but also on the momentary excitability of its alpha motor neuron [3]. This fluctuates and changes of the subpopulation of activated units can produce large response swings because of the many muscle fibers per unit. In contrast, D wave stability indicates consistent corticospinal tract activation although any evoked I wave volleys might vary. Thus, it seems likely that normal muscle MEP trial-to-trial variability predominantly reflects alpha motor neuron excitability fluctuations.

Systemic factors and other systems

Alpha motor neuron excitability is modified by anesthesia and other systemic factors such as hyper- or hypoventilation [95], as well as several non-corticospinal systems. For example, other descending pathways make oligosynaptic connections with alpha motor neurons and sensory inputs have already been pointed out. There are also intrinsic spinal cord motor control systems including propriospinal neurons that project to alpha motor neurons and may provide an indirect disynaptic pathway for corticospinal volleys [96, 97]. Even under anesthesia, these systems likely provide some background alpha motor neuron depolarization that can be changed by systemic and pathologic factors. This might explain why anesthetic increments reduce muscle MEPs, H-reflexes and F-waves, while having little effect on corticospinal volleys [29–34, 98]. It might also partly explain H-reflex and F-wave amplitude decrements after spinal shock caused by acute intraoperative rostral cord injury [99, 100].

Pathologic alterations

It follows that pathologic muscle MEP decrements can be caused by several mechanisms. It is important to realize

that corticospinal tract compromise is only one of these. Corticomotor or alpha motor neuron failure typically due to ischemia is another. It also appears that disturbances of cortex adjacent to but outside primary motor cortex can reduce muscle MEPs by interfering with the transcortical generation of I waves when these are contributing to muscle responses [79]. In addition, root or peripheral nerve trauma, stretch, ischemia or pressure can reduce MEP amplitude. Finally, it is believed that compensable damage to supportive spinal motor system(s) can reduce muscle MEPs during intramedullary tumor surgery [37, 71]. This is based on repeated observations of temporary postoperative paralysis predicted by muscle MEP loss but D wave preservation, indicating the absence of corticospinal tract malfunction. Thus, intramedullary dissection may temporarily render intact alpha motor neurons unexcitable to intact corticospinal input by disrupting background alpha motor neuron depolarization from supportive system(s). Propriospinal system injury has been proposed as one possible mechanism [37]. Edema might explain some temporary paralyses [36], but examples of unaltered D waves and rapid recovery argue against this.

Confounding factors

Control recordings such as hand MEPs during thoracolumbar or facial or trapezius MEPs during cervical surgery can help identify confounding factors. These include anesthesia, stimulus failure, scalp edema, intracranial air and neuromuscular blockade [37–39, 101]. Somatosensory evoked potentials also help control for systemic and peripheral nerve disturbances caused by limb ischemia or pressure [38, 39]. Monitoring EEG patterns during anesthesia might also be helpful. Marked positive fluid balance can cause scalp edema that may increase extracranial shunting, requiring stimulus increments [38] (Figure 11).

Potential fade

Stable anesthesia is clearly important; however, it is critical to understand that gradual muscle MEP amplitude-fading and threshold increase is normal during stable intravenous or inhalational anesthesia without scalp edema [36, 38, 39, 102]. Similar benign SEP amplitude-fading is known to occur [38, 39, 102]. Antecedent myelopathy exacerbates this unexplained phenomenon [102], and pathologically-small or inconsistent MEPs from the beginning may eventually disappear without new injury (unpublished observations). Lyon et al. estimated that the average rate of TES voltage rise necessary to maintain $>50\,\mu$V leg muscle MEPs is about 11 V/h in neurologically-intact patients, and 23 V/h in myelopathic patients [102]. In practice, there seems to be considerable individual variation, from little or no fade to substantial fade, threatening false-positive results. An important point may be the gradual generalized evolution that appears to distinguish this phenomenon from more abrupt focal pathological decrements [38, 39, 102]. Note that leg muscle responses may sometimes be more affected by this phenomenon than hand muscle responses that are therefore imperfect systemic controls (unpublished observations).

Since D waves have not yet been reported to show this pattern, it presently seems that amplitude-fade predominantly reflects decreasing alpha motor neuron excitability, although reductions of any existing I wave volleys might contribute. In practice, variable charge and/or pulse-number increments to increase corticospinal drive are often needed to maintain muscle MEPs. I have also twice seen a switch to C3/4 TES restore leg MEPs that had faded-out to hemispheric or C1/2 stimulation, without injury (unpublished observations).

Expectation adjustment

Muscle MEP monitoring tracks fluctuating aggregate motor unit output that *indirectly* reflects corticospinal input because spontaneous variability, systemic factors and other systems affect alpha motor neuron excitability. Because of complexity, non-linearity, instability and high sensitivity to several pathologic mechanisms and confounding factors including potential fade, this technique does not readily conform to traditional interpretation and requires an expectation adjustment.

Muscle MEP interpretation: Spinal cord and brainstem

"Either the feet twitch, or they don't"

Because of instability and high sensitivity, the only generally-accepted warning sign is the disappearance of a consistently present response unexplained by confounding factors [37]. These events are visually obvious and focal when control recordings are available, and are usually abrupt, typically appearing within seconds or minutes, depending on the time between trials [37–39]. Stimulus increments normally do not reverse them. There may or may not be a retrospectively obvious amplitude reduction or threshold increase preceding disappearance.

Clinical experience shows that reappearance without injury commonly follows intervention during aortic or orthopedic surgery [37, 38, 40, 42]. This indicates that disappearance is not an excessively late sign of ischemia, compression or traction. Of course, restoration is unlikely with fixed lesions due to contusion, coagulation, aspira-

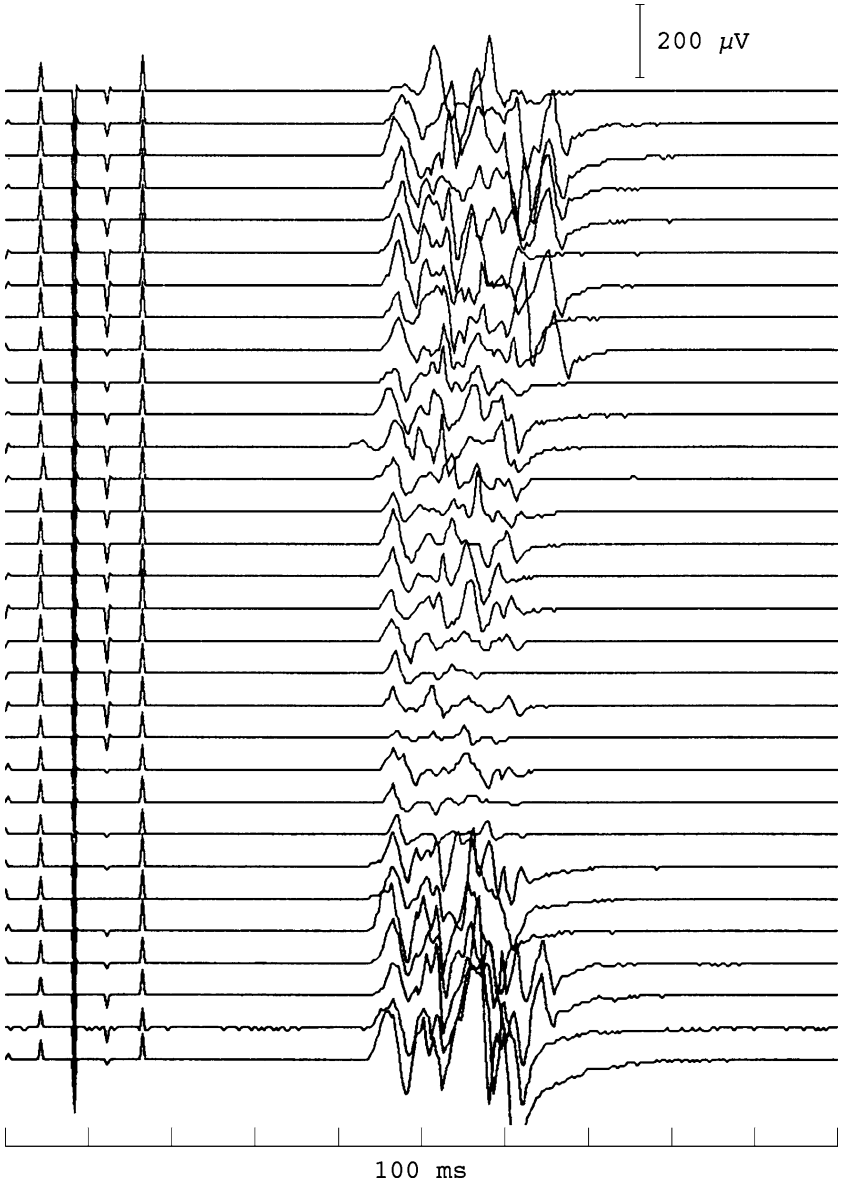

Fig. 11. Scalp edema. There was hemorrhaging and massive fluid administration with 3-liter positive fluid balance and scalp pitting edema during this scoliosis surgery. A 300–400 V increment restored fading tibialis anterior MEPs. Digitimer D 185 stimulator.

tion or laceration, but reappearance can follow a pause with warm saline irrigation or papaverine application during spinal cord tumor surgery [71]. Although clearly significant, there is concern that disappearance may be overly specific and insufficiently sensitive [36].

"The feet twitch less than before or need stronger stimuli"

Intuitively, partial central motor compromise should cause partial muscle MEP decrement. On the other hand, the definition of significant partial alterations remains elusive and there is concern that these approaches could be overly sensitive and insufficiently specific [71]. Instability and polyphasia make percentage of baseline amplitude criteria problematic. Most consider a 50% level [40, 50] to be too sensitive. One report supports an 80% level amounting to virtual disappearance [25], but did not specify the number with disappearance, and >80% reductions without injury have been observed [103].

Two reports support a >100 V threshold elevation for more than 1 hour criterion [49, 65]. This method applies Digitimer D185 3- or 4-pulse trains, a 2 or 3 ms inter-pulse interval, C3/4 spiral electrodes, and

propofol/opioid/nitrous oxide anesthesia. The reported theoretical basis attributes threshold elevation to partial corticospinal tract conduction block, analogous to simple motor nerve threshold testing that can expect one axonal discharge per stimulus and certain neuromuscular transmission of any conducted nerve action potentials. However, one should consider several other possible mechanisms. Furthermore, this theory does not account for the greater complexity of MEP testing that should expect variable corticospinal axonal discharges per stimulus (D±I waves) and uncertain transmission of any conducted corticospinal volleys through alpha motor neurons. These properties likely affect threshold and can be altered by other systems and systemic factors, including potential fade that may cause >100 V threshold elevations without injury [102]. Scalp electrode impedance also affects voltage threshold and varies with electrode and scalp factors that can change [43]. Thus, there is concern that threshold increase may lack specific pathologic significance in itself [71]; perhaps the results are methods-dependent. It may be important to consider the time course of potentially-relevant threshold changes, with greater emphasis given to acute elevations [36, 102].

One report supports transformation from long-duration polyphasic MEPs evoked by supra-threshold 6- to 8-pulse trains to short-duration biphasic waveforms as a sign of impending corticospinal tract injury during intramedullary spinal cord tumor surgery [36]. This pattern certainly indicates a visually obvious reduction of activated motor units that could be significant, but will have several possible causes, including supportive system disruption, fade, and even random variability (Figure 12). This report also supported a 100 V threshold criterion, but used pulse-number increments that also increase corticospinal drive and therefore make <100 V elevations meaningless.

Simple visual analysis of muscle MEPs considering systemic variables, spontaneous variability and gradually evolving patterns may be as effective as and more rapid than measurement [38, 39]. Whatever the approach, sharp focal response decrements or threshold elevations clearly exceeding trial-to-trial variability do raise concern and may be the first sign of compromise. They might reasonably prompt interventions such as pausing, raising blood pressure, repositioning retractors, irrigation, removing the last sublaminar hook, etc. However, in my own view it presently seems that disappearance might best guide decisions irrevocably altering the patient's surgical result. For example, one recent personal experience with cervical intramedullary spinal cord tumor surgery was marked by substantial potential fade, requiring an increase of pulse number from 5 to 9 and voltage increase of over 100 in order to maintain the mere presence of leg MEPs that were anxiously small by the end of surgery. The D wave and SEPs were absent due to antecedent pathology. There was no postoperative worsening of the patient's antecedent quadriparesis, and she enjoyed subsequent neurological improvements as well as gross total tumor resection that might have been prevented by amplitude or threshold criteria. Intraoperative muscle MEP interpretation is definitely not for the faint of heart.

Outcome correlation

Consistently-present muscle MEPs have been correlated with the absence of significant central motor injury [37–39, 71, 72, 103]. However, still-present but substantially reduced MEPs or elevated thresholds have been correlated with partial and often–but not always–temporary central motor deficits [25, 36, 49, 65, 104]. It is currently difficult to explain these different experiences, and the truth probably lies somewhere in-between. Partial weakness that can be difficult to assess in the acute postoperative patient might sometimes be overlooked by the first camp and overstressed by the second. Note that partial central motor deficit is possible even without any appreciable intraoperative muscle MEP alteration [17] (Figure 13).

Muscle MEP presence does not exclude individual nerve root injury because of overlapping radicular innervation, but these injuries sometimes cause a visually obvious step reduction of MEP amplitude that may not exceed any criteria (Figure 14). Injuries to peripheral nerves not represented by monitored muscles may be undetected. For example, I have seen two radial nerve compression injuries unpredicted by hand muscle MEP monitoring. Persistent muscle MEP loss unexplained by confounding factors normally predicts postoperative weakness, but not necessarily complete or permanent paralysis [36–38, 49, 65, 71] (Figure 15). Transient loss with reappearance following intervention suggests prevention, usually–but not always–without a new central motor deficit.

Muscle MEP interpretation: Hemisphere and facial nerve

A further expectation adjustment is needed for supratentorial surgery because partial reductions or transient loss of muscle MEPs appear to be more frequently associated with permanent motor deficits [46, 67, 68, 105]. Perhaps this could be explained by a greater likelihood of focal damage to the fanned-out corticospinal fibers in the hemispheres.

Partial facial nerve injuries can cause facial MEP amplitude reductions without disappearance; it appears that

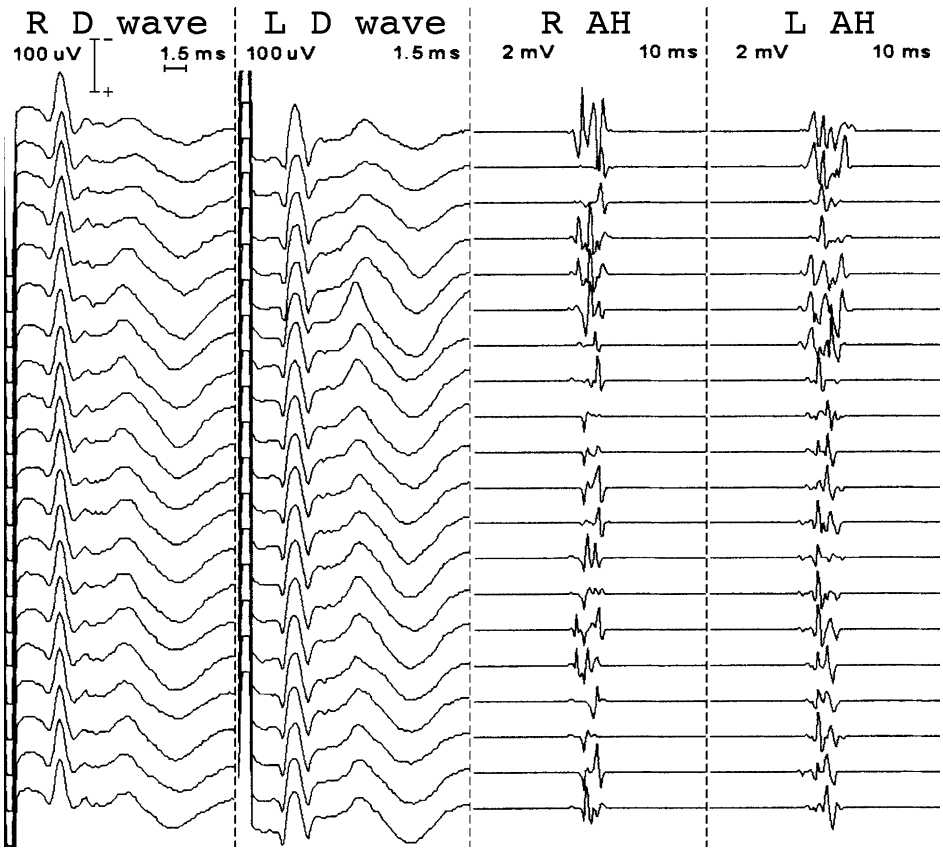

Fig. 12. Normal spontaneous muscle MEP variability. Stable D waves showed that abductor hallucis (AH) variations were not due to corticospinal tract alterations during this spinal cord tumor surgery. There was no alarm or injury. Without D waves, amplitude or morphology muscle MEP criteria might have caused false alarms. Nicolet Viking stimulator, 5-pulse trains, 4 ms inter-pulse interval.

moderate injury becomes possible after a consistent >50% reduction and more likely but not certain after a >65% reduction [52]. Furthermore, because the facial MEP is generated by a subpopulation of facial nerve axons, mild injuries may not produce a decrement and MEP loss that always occurs with paralysis can also occur with some residual function, depending on which axons are damaged [52].

SOME APPLICATIONS AND RESULTS

Aortic surgery

Because spinal cord blood supply is derived from the aorta and its major branches, unmonitored descending aortic aneurysm repair has a 5–16% risk of paraplegia due to spinal cord infarction usually involving the lumbosacral segments [106]. Attempts to improve this with SEP or evoked spinal cord potential monitoring have been disappointing. This is because spinal cord ischemia and infarction is a central cord process beginning in and sometimes limited to the anterior horn gray matter that is not assessed by these techniques [106]. In contrast, TES muscle MEPs that are mediated through anterior horn cells have turned out to be highly sensitive for cord ischemia [28, 38, 42, 106–110]. D waves are ineffective because they are difficult to record from the at-risk lumbosacral cord and because of white matter ischemia resistance [38, 93, 106].

Leg muscle MEP loss or marked attenuation in about 2 min is the usual manifestation of acute cord ischemia and infarction could begin after about 10 min during normothermia [106]. Thus, there is a window of opportunity to restore perfusion and prevent infarction, given sufficiently rapid surgical feedback. Although SEPs may be unaffected or show delayed and transient changes, their inclusion helps to control for confounding factors such as leg ischemia that also affect leg MEPs [38, 106].

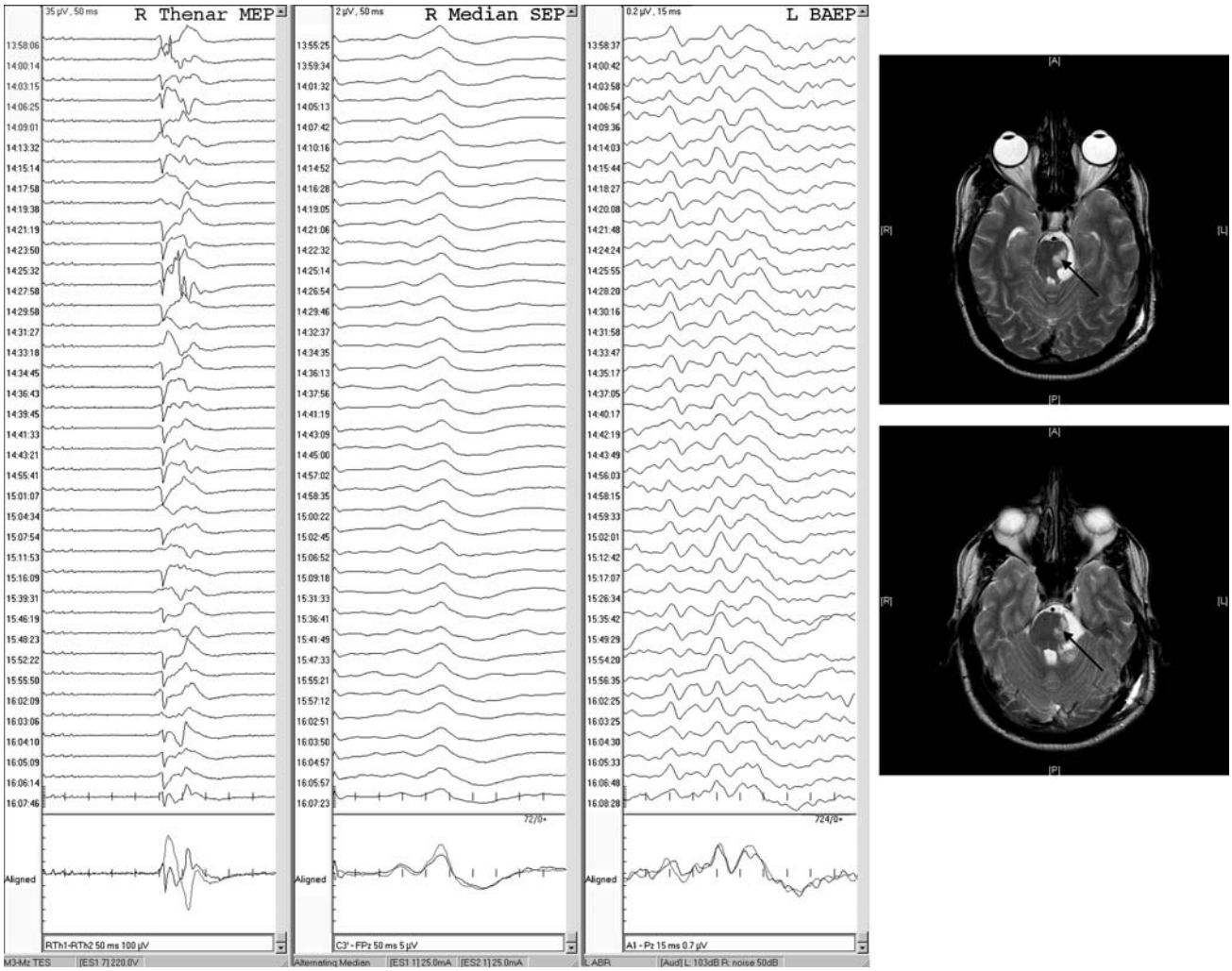

Fig. 13. Unpredicted motor deficit during left cerebello-pontine angle tumor surgery. There was temporary right arm and face partial weakness and diplopia due to left pons injury (arrows). Left BAEP, right median SEP and right thenar MEP recordings did not change. Final MEP amplitude (black) was 61% of 'baseline' (gray). No stimulus increment was required (Nicolet Endeavor, M3-Mz, 220 V, 4-pulse trains).

In these surgeries, persistent leg MEP loss unexplained by confounding factors usually predicts paraplegia [106]. Interventions such as raising distal aortic pressure and anastomosing segmental arteries to the graft frequently restore MEPs [106] (Figure 16). When no clear strategy exists, the selective use of deep hypothermia may avoid infarction. More than 40 min MEP absence or incomplete amplitude restoration may be associated with partial infarction and paraparesis [106]. Theoretically, infarction of anterior horn inhibitory interneurons with alpha motor neuron sparing could cause spastic paraparesis despite full MEP restoration, but only one possible and unproven clinical example has been reported [111].

Aortic surgery currently provides the clearest evidence for injury prevention through MEP monitoring because the cumulative rate of spinal cord infarction in over 450 reported surgeries is only 3.5%, many occurring postoperatively [106]. In one remarkable series of 260 high-risk surgeries, Jacobs et al. reported an infarction rate of only 2.4% (1.4% intraoperative) [109].

Intramedullary spinal cord tumor surgery

Gross total tumor removal is often the goal of intramedullary spinal cord tumor surgery. Dorsal myelotomy frequently causes SEP loss and proprioceptive deficit that will not and should not stop the surgery [71]. While undesirable, mild or even more severe but temporary motor deficits may be acceptable, whereas residual tumor risking recurrence is often an unreasonable price for a perfect im-

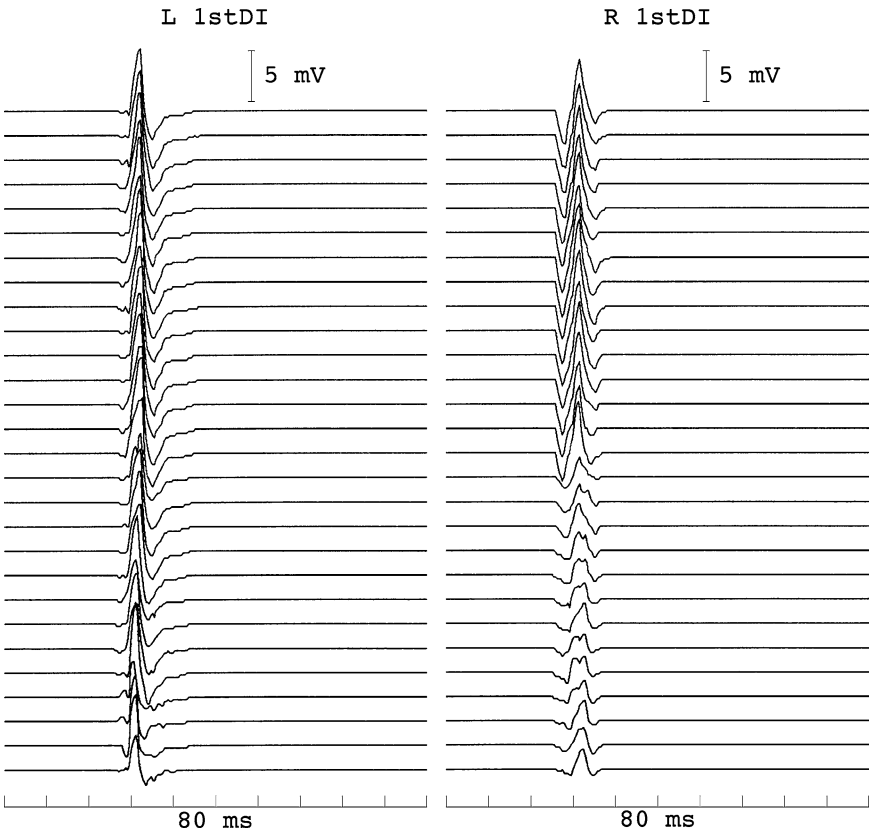

Fig. 14. Root injury. A visually obvious but not >50% focal decrement of the right 1st dorsal interosseous (1stDI) muscle MEP occurred with C8 biopsy during this malignant nerve sheath tumor surgery. There was permanent post-operative right hand intrinsic muscle weakness. Digitimer D185 stimulator, 3-pulse trains, 1 ms inter-pulse interval.

mediate functional outcome. At the same time, permanent paraplegia is an excessive price for gross total resection and its prevention provides strong motivation for monitoring. These considerations vary with tumor histology as well as the patient's preoperative neurological status and desires [71].

Tremendous advances in the integration of MEPs into these surgeries have been made over the last decade [37, 71, 72]. Involved surgeons believe that these techniques allow more aggressive spinal cord manipulation and tumor removal than would otherwise be dared [71]. Bipolar electrosurgery and ultrasonic aspiration that disable monitoring during use have also been identified as dangerous so that alternatives such as contact laser cautery that does not disable monitoring have been recommended [71, 112].

Because combined muscle MEP and D wave monitoring seems to predict immediate and long-term motor outcome, it appears that decisions to abort resection should not be based on muscle MEPs alone whenever possible [37, 71, 72] (Figure 17). This makes surgeries without D waves due to omission, antecedent pathology or lumbosacral tumor location particularly challenging because in these circumstances, muscle MEP loss does not distinguish between temporary or permanent motor deficits [72].

Monitoring patients with substantial antecedent pathology degrading or obliterating evoked potentials and aggravating potential fade can be difficult. Furthermore, improving overall outcome is a challenge because many–but not all–injury mechanisms are irreversible so that monitoring more often documents than avoids injury. However, surgeons might thereby identify dangerous maneuvers and use this information to improve the safety of subsequent surgeries. Recently, 50 patients with muscle MEP and D wave monitoring showed a McCormick functional grade (1–4) mean improvement of +0.28 at follow-up compared to −0.16 mean deterioration for 50 unmonitored matched historical controls ($P = 0.0016$) [72]. There was no significant difference in the completeness of tumor removal between the two groups. This represents the first formal evidence for outcome improvement through MEP monitoring of these surgeries.

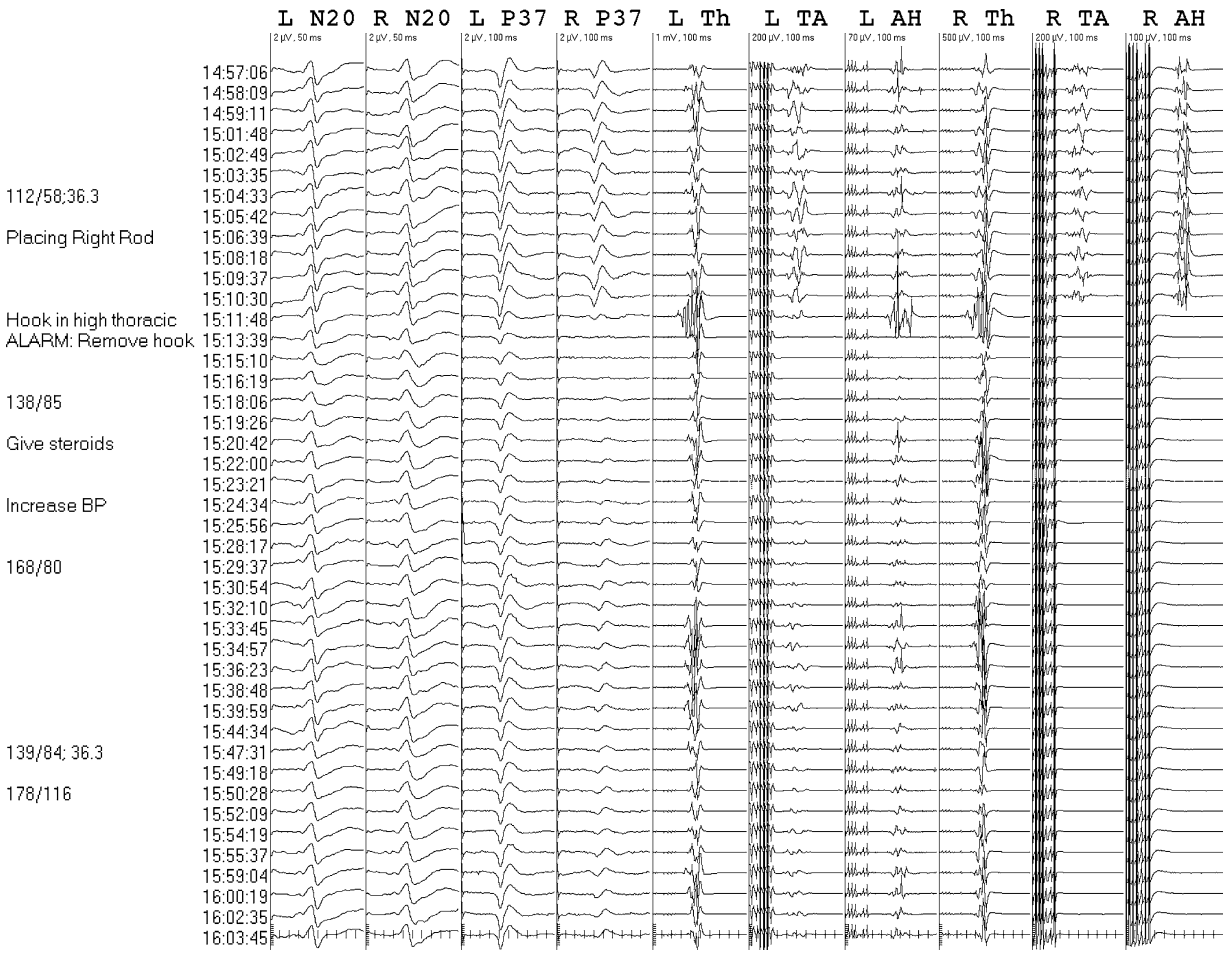

Fig. 15. Persistent MEP loss during scoliosis surgery. N20 and P37, median and tibial cortical SEPs; Th, thenar; TA, tibialis anterior; AH, abductor hallucis. Right leg MEP loss and incomplete tibial SEP restoration predicted right Brown-Sequard syndrome with leg paresis but not paralysis. The patient could walk and enjoyed complete clinical recovery. Probable spinal cord contusion during sublaminar hook placement.

Spinal deformity surgery

Although the overall incidence of cord injury in scoliosis surgery is only 0.6 percent [113], the devastation of paraplegia in even a few patients has motivated tremendous IOM development. Indeed, spinal deformity remains one of the most frequent indications for monitoring.

In many respects, these surgeries are ideal for monitoring. Most patients are neurologically intact so that evoked potentials are often easily obtained, although some patients with neuromuscular scoliosis can be challenging or impossible to monitor. In addition, the majority of injury mechanisms such as ischemia, compression or distraction are reversible through sufficiently prompt recognition and intervention. While contusion is not reversible, its effects might be minimized if the responsible mechanism is quickly identified and corrected.

Based on the premise that transverse cord compromise could be detected by SEPs while still reversible, a large experience with SEP monitoring has evolved and halved the risk of paraplegia [113]. However, selective injury of the unassessed motor system still occurs without SEP warning. Thus, muscle MEP monitoring should favorably impact outcome. Recall that D wave monitoring might be misleading for these surgeries [94]. The FDA clearance of TES stimulators will lead to the large numbers needed to test the hypothesis of improved outcome. Certainly, initial results strongly suggest that muscle MEP monitoring is likely to further reduce paraplegia risk [25, 37, 40] (Figure 18).

Posterior fossa tumor surgery

Muscle MEPs might enhance brainstem and cranial nerve protection during surgery for tumors in the posterior fossa.

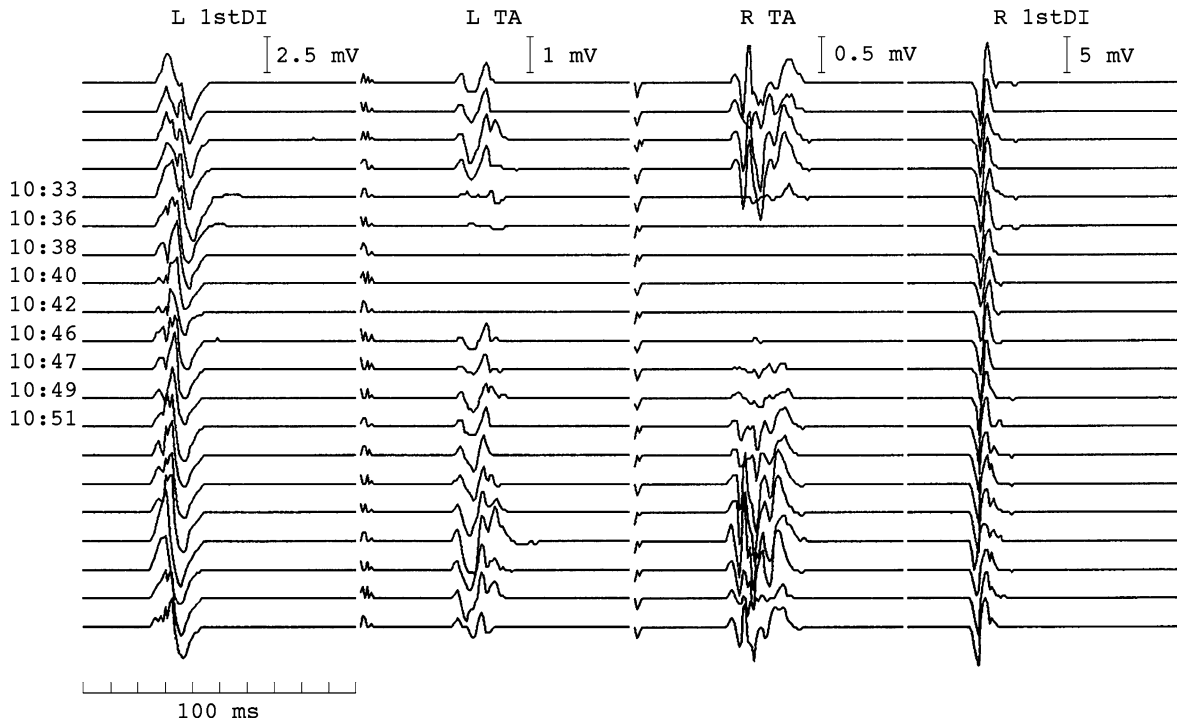

Fig. 16. Aortic surgery. 1stDI, 1st dorsal interosseus; TA, tibialis anterior. The aorta was clamped at 10:33, unclamped at 10:39 and re-clamped at a lower level at 10:50. There was no spinal cord infarction. Note the abrupt leg MEP loss and rapid reappearance. Digitimer D185 stimulator. Modified from MacDonald and Janusz [38], with permission.

Applying C3−Cz and C4−Cz TES to evoke right and left facial and hand muscle responses provides bilateral corticospinal and corticobulbar tract as well as facial nerve assessment. These montages limit movement and reduce the possibility of confounding distal facial nerve excitation from extracranial current spread [52]. Long facial MEP onset latency and the absence of single-pulse responses confirm central origin (Figure 19). Facial MEPs extend traditional facial nerve EMG monitoring techniques by providing a surgeon-independent ongoing measure of functional integrity [52] (Figure 20). However, since the initial report [52] I have not found the technique to be successful in all patients. It might also be possible to monitor other cranial muscle MEPs, but further studies are needed. There is currently insufficient data to decide whether these techniques can improve overall outcome.

Intracranial aneurysm surgery

Intracranial aneurysm surgery can cause cerebral infarction in the distribution of major cerebral arteries supplying cortex and superficial subcortical structures or of perforating arteries feeding deep subcortical structures. Early ischemia detection through evoked potential monitoring might lead to intervention preventing infarction [46, 114–117].

Depending on the vascular territories at risk, median and/or tibial SEP monitoring is often considered reliable for the detection of cortical ischemia [46]. However, this depends on ischemia in the distribution of the middle cerebral artery's posterior division and/or the distal anterior cerebral artery. Cortical ischemia in other vascular territories might go undetected. For example, Szelényi et al. reported a patient with infarction in the territory of the anterior division of the middle cerebral artery and consequent hemiplegia who did not exhibit intraoperative median SEP alteration or sensory deficit [118]. Ischemia of the medial lemniscus in the brainstem, the thalamus or the thalamocortical projections rising through the posterior limb of the internal capsule and corona radiata should cause SEP attenuation. However, infarction of other deep structures including motor pathways can go undetected [115, 117].

Consequently, MEP monitoring has been introduced to evaluate motor cortex and corticospinal pathways descending through the corona radiata, internal capsule, cerebral peduncle, basis pontis and pyramids. Because craniotomy for these surgeries normally does not uncover motor cor-

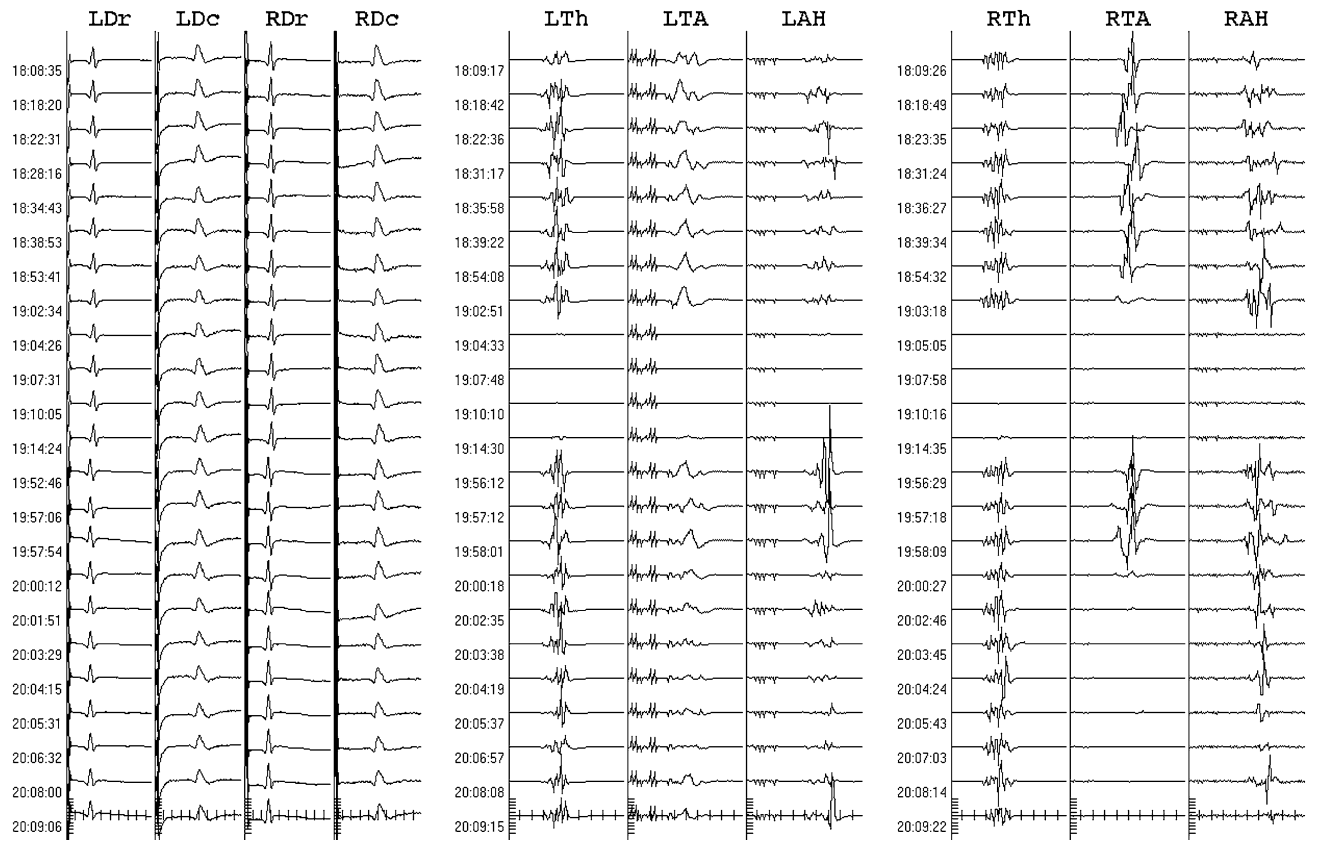

Fig. 17. Intramedullary spinal cord tumor surgery. Dr and Dc, rostral and caudal D waves; Th, thenar; TA, tibialis anterior; AH, abductor hallucis. Erroneous neuromuscular blockade caused transient generalized MEP loss. Later, RTA MEPs abruptly disappeared during resection. Tumor removal continued to completion because D waves showed corticospinal tract integrity. Mild postoperative right leg weakness lasted hours. Nicolet Endeavor stimulator.

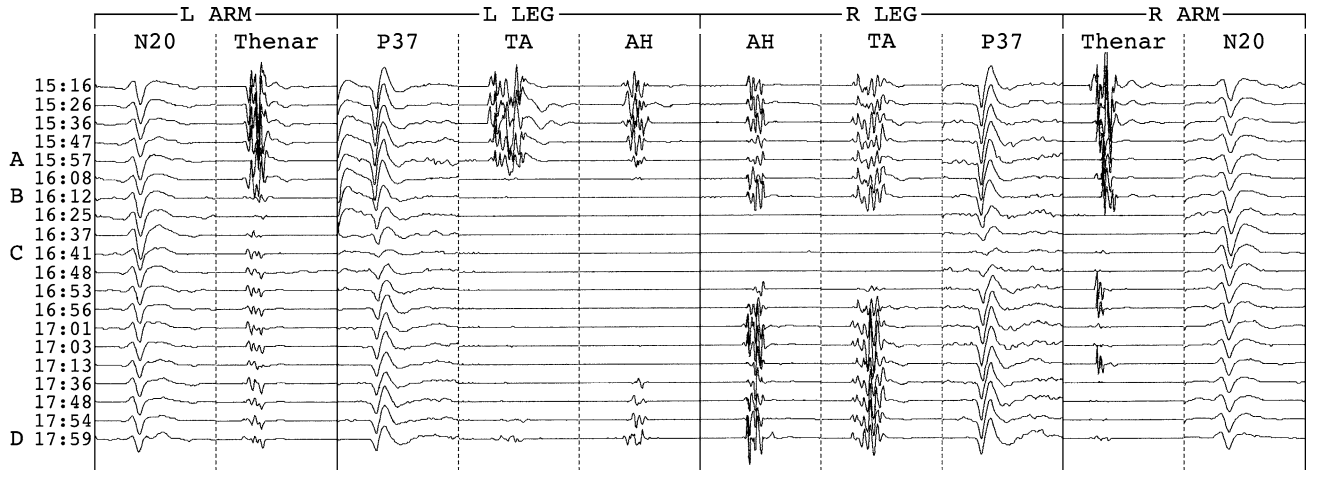

Fig. 18. Scoliosis surgery. N20 and P37, median and tibial cortical SEPs; TA, tibialis anterior; AH, abductor hallucis. Selected traces; the intraoperative recording had greater time resolution. Left leg MEP loss immediately followed left T1 hook placement (**A**)*. Despite blood pressure elevation* (**B**)*, bilateal MEP decrements and finally, tibial SEP reductions followed. SEP recovery but incomplete MEP restoration followed hook removal* (**C**)*, most delayed in the left leg. All potentials were 'present' at closure* (**D**)*. Left dorsiflexion weakness resolved in two days; there were no other deficits. All MEPs were large at reoperation a few days later. Earlier hook removal might have avoided the minor deficit. Greater MEP sensitivity and motor specificity should improve scoliosis monitoring. Nicolet Viking stimulator.*

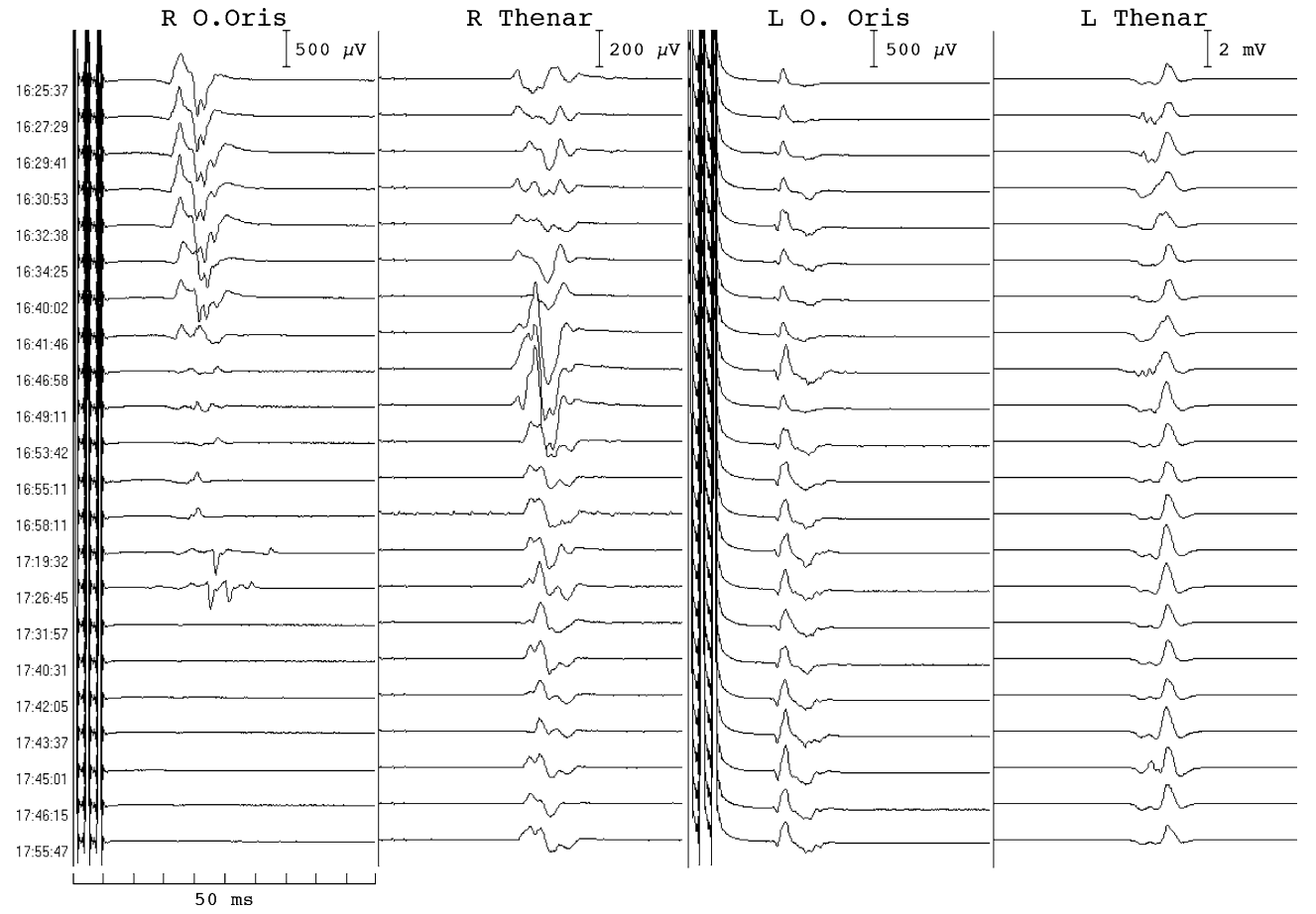

Fig. 20. Acoustic neuroma surgery. The first intracranial proximal/distal facial CMAP ratio was 1.0. There were no EMG discharges. At 16:41, there was abrupt left facial MEP reduction and the CMAP ratio was then 0.32. Resection continued until left facial MEPs abruptly disappeared. The CMAP ratio was then 0.27 and the nerve was in continuity. There was total facial paralysis with partial recovery beginning at 9 months. Nicolet Endeavor stimulator.

tex, TES with standard scalp electrode locations can be performed [46, 70, 116]. However, this raises the important issue about the depth of subcortical motor axon activation with TES. If activation is occurring at the internal capsule, then motor cortex and superficial subcortical motor pathway ischemia could go undetected. While this has not yet been clinically reported, TES MEP monitoring has been considered reliable for deep subcortical ischemia detection only [46, 70].

If activation is occurring even deeper (possibly as caudal as the pyramidal decussations), then there is the chance of missing deep subcortical motor pathway ischemia as well [70]. For example, in 1998 I encountered a patient who suffered left hemiplegia due to midbrain injury during posterior fossa tumor surgery whose left MEPs disappeared to C2−C1 TES despite increasing intensity, but reappeared with C2/z/1-FPz TES, giving false reassurance (Figure 21). The latter montage that I used only this one time likely activated corticospinal axons below the injured midbrain. This type of montage might be appropriate for spinal [25] or aortic surgery [54], but not for intracranial surgery. Thus, when TES is applied to intracranial aneurysm (or posterior fossa) surgery, widely spaced stimulating electrodes and needlessly high intensity promoting deep activation should be avoided. Short inter-electrode distance montages such as C1/2, C3−Cz/C4−Cz and Cz−(Cz + 6cm) should be preferred. An increase in MEP stimulus requirements might indicate deepening of activation to below an ischemic level [70].

To avoid these problems, direct cortical stimulation through subdural strip or grid electrodes slid underneath the craniotomy to motor cortex has been advocated [70, 114, 115, 117]. This technique produces focal muscle activation, less movement and superficial stimulation that should detect cortical and superficial subcortical ischemia and avoid false negatives [70, 117]. However, there is about a 2% incidence of bridging vein rupture with subdural bleeding during the blind electrode insertion and the leg

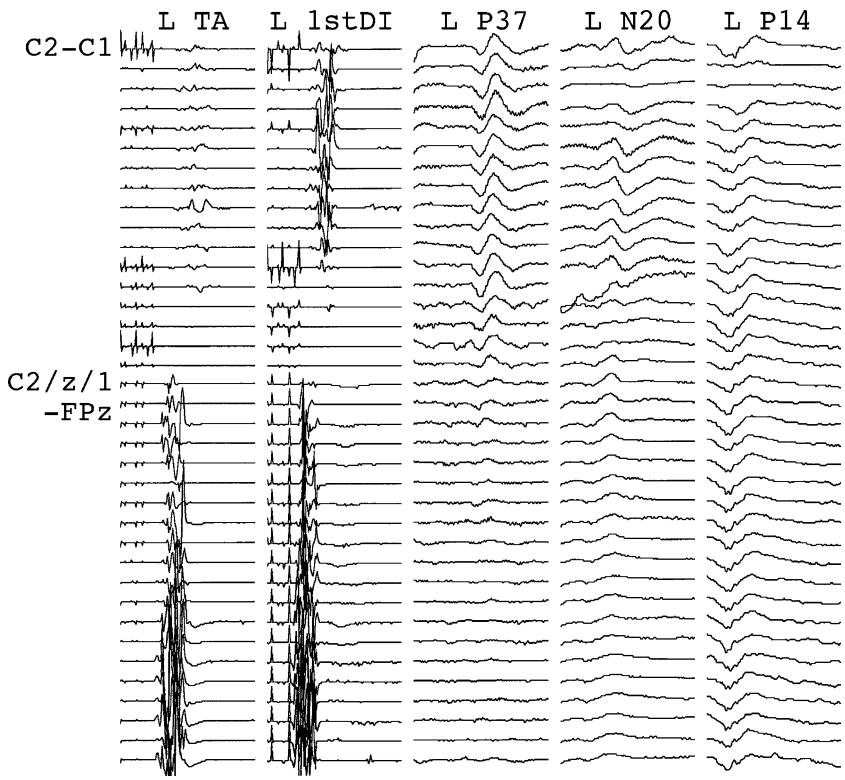

Fig. 21. Midbrain injury during clivus chondrosarcoma surgery. TA, tibialis anterior; 1stDI, first dorsal interosseous; P37 and N20, tibial and median cortical SEP; P14, median subcortical SEP. Left muscle MEPs to C2-C1 TES were lost despite increasing intensity and left cortical but not subcortical SEPs were lost. There was midbrain injury with left hemiplegia, but large short-latency left MEPs reappeared to same-intensity C2/z/1-FPz TES, presumably due to motor pathway activation below the injured midbrain.

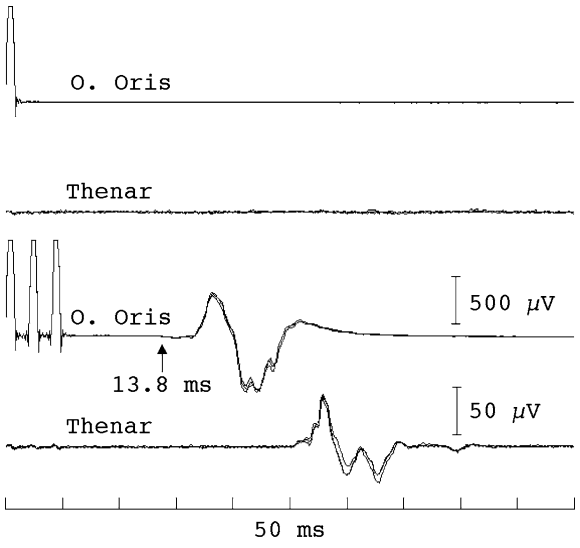

Fig. 19. Left facial MEP. M4-Mz TES, Nicolet Endeavor stimulator. The absence of single pulse responses (top two traces) and the long orbicularis oris MEP onset latency indicate central corticobulbar origin.

area can be hard to reach [70]. Infrequent seizures may occur with either technique in these predisposed patients [70].

Whichever technique is used, initial results are promising. Muscle MEPs have been shown to detect motor pathway ischemia or infarction undetected by SEPs, and to provide greater sensitivity and earlier warning when both are affected [46, 114–117]. Several patients have had MEP loss reversed after intervention and it seems likely that an overall improvement in patient outcome will eventually be demonstrated. Note that infarctions outside of the sensorimotor systems could still occur without warning.

Peri-rolandic brain surgery

Electrically evoked motor activity has been essential during peri-rolandic brain surgery for decades. Classical mapping applies 50–60 Hz 1–5 s pulse-trains while observing the conscious patient for movement. During general anesthesia, higher stimulus intensities are needed and the success rate diminishes. Electrocorticography is needed to detect afterdischarges that can produce misleading signs by spreading to non-stimulated cortex.

The new direct cortical muscle MEP techniques use general anesthesia [15, 46, 67, 68]. Having the lowest MEP threshold identifies motor cortex. Total charge is markedly reduced, seizures seem to be much less frequent, localization appears to be accurate when combined with cortical SEP mapping and electrocorticography is not required. In addition, the technique appears to be successful in young children in whom the traditional method may fail [67]. Furthermore, it allows MEP monitoring during resection and subcortical testing for corticospinal tract localization. This technique clearly advances patient comfort and safety. Language mapping still requires the more hazardous classical 50–60 Hz stimulation methods and awake craniotomy.

Recent evidence suggests that D wave monitoring of these surgeries may enhance muscle MEP interpretation by predicting long-term outcome, analogous to spinal cord tumor surgery [69, 79]. It appears that surgically induced cortical disturbances outside primary motor cortex may cause muscle MEP reduction and postoperative weakness by interfering with the transcortical generation of I waves when these are contributing to muscle responses [79]. However, D wave preservation indicating primary motor cortex and corticospinal tract integrity seems to predict postoperative compensation and recovery [69, 79].

These observations suggest a possible unifying view for D wave monitoring. Specifically, D waves may differentiate muscle MEP decrements due to intrinsic motor cortex or corticospinal tract compromise threatening permanent motor deficit from extrinsic cortical I wave or spinal cord supportive system disruptions that tend to produce temporary deficits. Surgeries in which the latter two mechanisms are unlikely may be adequately or perhaps even better served by non-invasive muscle MEPs alone.

CONCLUSION

Remarkable motor system monitoring advances have been achieved over the last two decades. Certainly, further investigation and experience are needed to resolve existing controversies and bring forward technical improvements. Nevertheless, in their current state pulse-train and single-pulse MEP monitoring techniques provide unprecedented motor specificity with sufficient safety and undoubtedly improve the efficacy of IOM.

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