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Guidelines

Intraoperative motor evoked potential monitoring – A position statement by the American Society of Neurophysiological Monitoring

D.B. MacDonald [a,*], S. Skinner [b], J. Shils [c], C. Yingling [d]

[a] Section of Clinical Neurophysiology, Department of Neurosciences, King Faisal Specialist Hospital & Research Center, MBC 76, PO Box 3354, Riyadh, Saudi Arabia
[b] Intraoperative Monitoring, Department of Neurophysiology, Abbott Northwestern Hospital, 800 E 28th Street, Minneapolis, MN 55407, USA
[c] Intraoperative Monitoring, Department of Neurosurgery, Lahey Clinic, 41 Mall Rd., Burlington, MA 01805, USA
[d] ION IntraOperative Neurophysiology, Otolaryngology at Stanford University School of Medicine, USA

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HIGHLIGHTS

- This article comprehensively reviews intraoperative motor evoked potentials.
- It then forms summary recommendations based on current evidence and expert opinion.
- The International Society of Intraoperative Neurophysiology collaborated and endorses this position statement.

ABSTRACT

The following intraoperative MEP recommendations can be made on the basis of current evidence and expert opinion: (1) Acquisition and interpretation should be done by qualified personnel. (2) The methods are sufficiently safe using appropriate precautions. (3) MEPs are an established practice option for cortical and subcortical mapping and for monitoring during surgeries risking motor injury in the brain, brainstem, spinal cord or facial nerve. (4) Intravenous anesthesia usually consisting of propofol and opioid is optimal for muscle MEPs. (5) Interpretation should consider limitations and confounding factors. (6) D-wave warning criteria consider amplitude reduction having no confounding factor explanation: >50% for intramedullary spinal cord tumor surgery, and >30–40% for peri-Rolandic surgery. (7) Muscle MEP warning criteria are tailored to the type of surgery and based on deterioration clearly exceeding variability with no confounding factor explanation. Disappearance is always a major criterion. Marked amplitude reduction, acute threshold elevation or morphology simplification could be additional minor or moderate spinal cord monitoring criteria depending on the type of surgery and the program's technique and experience. Major criteria for supratentorial, brainstem or facial nerve monitoring include >50% amplitude reduction when warranted by sufficient preceding response stability. Future advances could modify these recommendations.

Contents

* Corresponding author. Tel.: +966 11 464 72772x32827; fax: +966 11 442 4763.
E-mail addresses: dbmacdon@yahoo.com (D.B. MacDonald), drskinnermd@yahoo.com (S. Skinner), jay.shils@lahey.org (J. Shils), cy@brainmon.com (C. Yingling).

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1. Introduction

This position statement reviews and forms recommendations for intraoperative motor evoked potentials (MEPs) that are a relatively new and increasingly important part of intraoperative neurophysiologic monitoring (IONM). It recognizes that there may be alternative approaches and that future advances could modify subsequent recommendations. The International Society of Intraoperative Neurophysiology collaborated and endorses this document.

1.1. History

The origin of MEP monitoring dates to 1870 when Fritsch and Hitzig found that direct electrical stimulation of frontal cortex produces contralateral movement in dogs (Fritsch and Hitzig, 2009). Subsequently, Ferrier (1874) electrically mapped the motor gyrus of dogs and monkeys. Sir Victor Horsley and Otfrid Foerster pioneered human direct cortical stimulation (DCS) during brain surgery around the turn of the century, but it was Penfield and Jasper (1954) who later established routine intraoperative DCS using a probe to explore cortex with 50–60 Hz pulse trains lasting seconds while observing patient responses. The 'Penfield technique' became standard for cortical mapping, but worked best with local anesthesia and could not be used for monitoring.

The next step was Amassian's discovery that single-pulse DCS evokes several corticospinal tract volleys consisting of a direct 'D-wave' followed by a group of indirect 'I-waves' (Patton and Amassian, 1954). Subsequently, Merton and Morton (1980) and Barker et al. (1987) described transcranial electric stimulation (TES) and transcranial magnetic stimulation (TMS) muscle MEPs. However, neither technique worked under anesthesia. Consequently, a few groups developed TES D-wave monitoring (Fig. 1) (Boyd et al., 1986; Burke et al., 1992; Deletis, 1993). This provided corticospinal tract monitoring, but required an invasive recording electrode and excluded lower motor neurons (LMNs).

Then Taniguchi et al. (1993) discovered that brief pulse train DCS evokes muscle MEPs under anesthesia, thus allowing motor cortex mapping and monitoring during brain surgery. Finally, three groups demonstrated pulse train TES muscle MEPs under anesthesia (Fig. 1), thus providing muscle MEP monitoring for any surgery (Jones et al., 1996; Pechstein et al., 1996; Rodi et al., 1996). Safety concerns limited use until governmental approval of a TES stimulator in 2002 and MacDonald (2002) documented sufficient clinical safety; an escalation of practice and research followed.

1.2. Previous guidelines

Previous review articles have made recommendations (Deletis, 1993, 2002; Burke and Hicks, 1998; MacDonald, 2006; Burke, 2008; Deletis and Sala, 2008) and the American Clinical Neurophysiology Society recently issued an importantspinal cord monitoring guideline update including MEPs, but focusing on deficit prediction rather than methodology (Nuwer et al., 2012). We are not aware of any previous MEP monitoring guidelines per se.

2. Rationale and clinical basis for MEP monitoring

Somatosensory evoked potential (SEP) monitoring was used in the past to reduce the risk of motor system injury. This was based on sensory and motor pathway proximity: one hoped that major pathophysiology affecting motor pathways would also disturb sensory pathways, thereby causing SEP deterioration prompting intervention at a reversible stage. It had merit because SEP monitoring halved paraplegia risk during scoliosis surgery (Nuwer et al., 1995). However, cases of motor injury without SEP warning and of SEP deterioration without motor injury accumulated (Lesser et al., 1986; Ben-David et al., 1987; Chatrian et al., 1988; Dawson et al., 1991; Nuwer et al., 1995). This was inevitable because the two systems have distinct anatomy and vascular supply so that smaller lesions can damage only one or the other. Thus, the rationale for MEP monitoring is to directly test the motor system during surgery.

The neurophysiologist's expertise, anesthetist's collaboration and surgeon's desire and intention to utilize the results form the clinical basis for successful MEP monitoring.

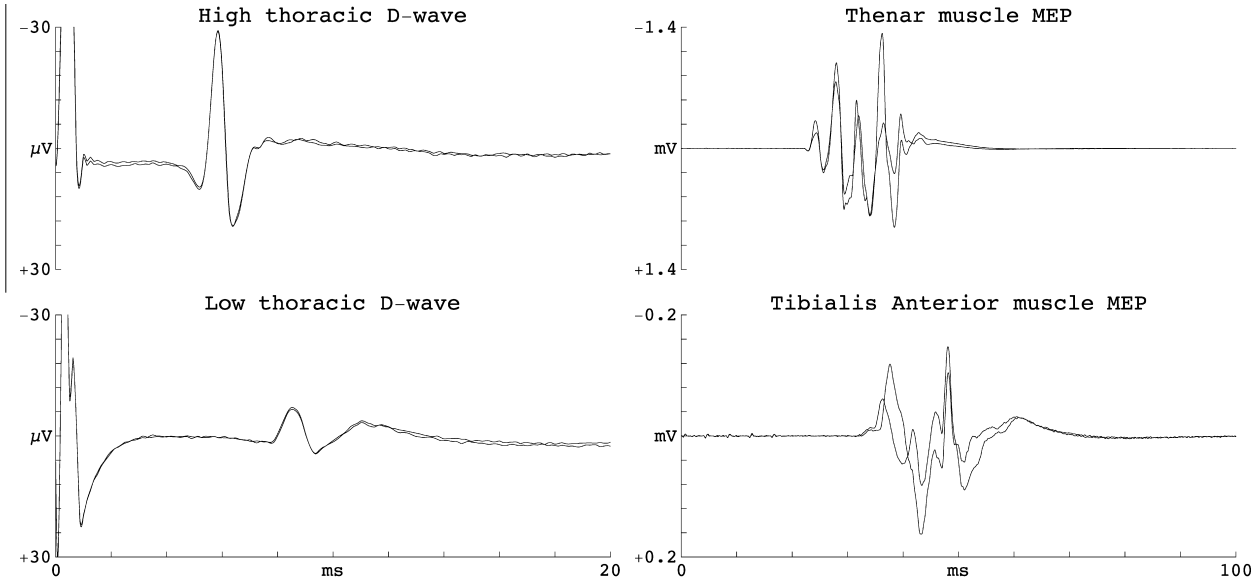

Fig. 1. Single-pulse D-wave and pulse train muscle MEP recordings during intramedullary spinal cord tumor surgery under propofol/opioid anesthesia. The plots exemplify D-wave stability and muscle MEP variability by superimposing two sequential trials. Transcranial electric stimulation was done with C3–C4 collodion-fixed EEG cups. Pulse duration was 0.5 ms and intensity 250 V. Trains had 5 pulses with a 4-ms interstimulus interval. D-waves were recorded from spinal epidural electrodes rostral and caudal to the tumor; muscle MEPs were recorded with intramuscular needles.

3. Anatomy and physiology

3.1. Anatomy

This section collates information from authoritative sources (Ghez and Krakauer, 2000; Krakauer and Ghez, 2000; Loeb and Ghez, 2000; Melvill Jones, 2000; Ropper and Brown, 2005a,b; Crossman and Griffiths, 2008; Crossman and Molnar, 2008; Crossman and Neary, 2008).

3.1.1. Motor cortex

The primary motor cortex is the pre-central gyrus containing corticomotor neurons; it is critical for voluntary movement and its destruction produces permanent weakness. Primary motor cortex has the lowest threshold for eliciting simple movements with electrical stimulation. It is somatotopically organized with tongue and face motor neurons near the sylvian fissure, hand and arm neurons in its middle convexity, and leg and foot neurons from its crest to mesial parasaggital region. The volume of motor gyrus innervating distal limb, tongue, and lower facial muscles is much greater than for less precisely controlled muscles. This is one reason supporting distal limb muscles as MEP recording sites.

Premotor, supplemental motor and prefrontal cortex contribute to the organization and initiation of movement. Electrical stimulation of these regions can produce positive or negative motor phenomena and discrete lesions of them may cause motor disturbances (e.g., transient mutism and motor neglect with supplemental motor area damage), but not permanent weakness.

3.1.2. Corticospinal tract

The corticospinal tract is the only direct descending connection between the cortex and spinal cord and is important for voluntary movement. Pure corticospinal tract lesions cause paralysis that over time partially resolves to permanently impaired strength and fine control of distal limb muscles and positive Babinski sign.

Corticospinal axons descend the corona radiata from primary motor and other frontoparietal cortex. They converge at the internal capsule into a tract that continues down the cerebral peduncle, basis pontis, medulla pyramid (hence the alternate name 'pyramidal tract') and the spinal cord. Most axons terminate on interneurons from which impulses reach LMNs through intermediary synapses, but about 2% synapse directly on LMNs, especially those innervating distal limb muscles, which is a second reason supporting distal MEP recording. The direct fibers are mostly large thickly myelinated axons from primary motor cortex.

Normally 75–90% of corticospinal fibers cross the midline at the pyramidal decussation and then descend the lateral or to a lesser extent, ventral corticospinal tract; uncrossed fibers descend the ventral or to a lesser extent, lateral corticospinal tract. The lateral corticospinal tract is more important for MEPs because it controls mainly distal limb muscles and descends the entire cord, while the ventral corticospinal tract controls mainly axial muscles and ends in the mid-thoracic cord. Decussation makes MEP thresholds lower and amplitudes larger contralateral to the stimulated hemisphere. However, this can be surprisingly reversed with 'horizontal gaze palsy and progressive scoliosis' in which the corticospinal and dorsal column sensory pathways are congenitally uncrossed; IONM methods to detect and adjust for non-decussation benefit these rare patients (MacDonald et al., 2003, 2007; Vulliemoz et al., 2005).

3.1.3. Corticobulbar tract

The corticobulbar tract is the direct descending connection between the cortex and brainstem motor nuclei and is critical for voluntary cranial muscle movements. Its axons descend alongside corticospinal fibers before diverging into the brainstem. Most terminate on interneurons, but a few form direct connections, especially with lower facial and tongue motor neurons.

Projections to most motor nuclei are bilateral. Hence, unilateral cortical stimulation tends to produce bilateral movements and unilateral lesions produce mild if any weakness. However, projections to lower face and tongue motor nuclei are mostly contralateral so that unilateral cortical stimulation produces contralateral movement and unilateral lesions produce contralateral weakness of these muscles.

3.1.4. Indirect motor pathways

There are also indirect motor pathways consisting of corticobrainstem-spinal relays. Their axons descend with corticospinal

fibers before diverging to synapse in the brainstem. From there, rubrospinal, vestibulospinal, reticulospinal and tectospinal tracts travel down the ventral and lateral spinal cord white matter. Their axons mostly terminate on interneurons; a small fraction may form direct LMN connections (Rekling et al., 2000).

Indirect motor pathways serve axial and integrated body–limb movements, posture and muscle tone. They probably do not directly contribute to MEPs, but might influence muscle MEPs through background synaptic facilitation (Rekling et al., 2000; Amassian, 2002; MacDonald, 2006).

3.1.5. Upper motor neuron system

The corticospinal and indirect pathways together comprise the upper motor neuron (UMN) system. Pathology generally involves both, so that UMN lesions typically cause a mixture of corticospinal deficits along with antigravity weakness, spasticity and hyperreflexia attributed to indirect pathway damage.

3.1.6. Propriospinal system

The propriospinal system is a network of spinal interneurons interconnected by inner white matter axons. It receives input from UMN, sensory and other systems, projects to LMNs and contributes to polysynaptic reflexes and central pattern generation. It may indirectly influence muscle MEPs through background synaptic facilitation (Amassian, 2002; Deletis, 2002; MacDonald, 2006).

3.1.7. Neuromodulatory pathways

Neuromodulatory pathways from the brainstem project diffusely to LMNs and powerfully modulate their excitability. (Rekling et al., 2000; Heckman et al., 2009). Abrupt neuromodulatory interruption may contribute to the initial flaccid arreflexia seen with acute cord injuries, and subsequent neuromodulatory denervation hypersensitivity may contribute to long-term spasticity (Rekling et al., 2000; Heckman et al., 2009). Thus, neuromodulatory pathways and receptors might influence muscle MEPs by facilitating or inhibiting LMN excitability.

3.1.8. Lower motor neuron system

The LMN system consists of spinal and brainstem motor neurons and their peripheral axons. It is the final common pathway for muscle innervation. The clinical signs of a LMN lesion are weakness, atrophy and hyporeflexia.

Lower motor neurons integrate UMN, propriospinal, sensory and neuromodulatory synapses. Each LMN has one axon that divides into multiple terminal branches, each forming an excitatory synapse on a single muscle fiber. A motor unit consists of one LMN, its arborized axon and innervated fibers. The number of muscle fibers in a motor unit varies from a few in finely controlled muscles (e.g., extraocular) to a thousand or more in less precisely controlled muscles (e.g., quadriceps). Each muscle contains hundreds of motor units occupying overlapping regions of about 5–11 mm in diameter (Leppanen, 2005).

Motor axons coalesce into cranial motor nerves or spinal anterior roots. Cranial nerves traverse the subarachnoid space and exit through skull base foramina. Spinal anterior roots join with sensory posterior roots to form mixed roots that traverse the subarachnoid space and exit through intervertebral foramina. Cervical and thoracic roots have an approximately horizontal trajectory to their foramina. Because the spinal cord normally ends at the L1–L2 vertebral level, lumbosacral roots descend the spinal canal as the cauda equina before reaching their foramina.

With some variability, nerve roots innervating limb muscles intermingle in the brachial or lumbosacral plexi that branch into peripheral nerves. Thus, muscles receive somewhat variable dominant radicular supply from one or two major roots and lesser supply from adjacent roots; radicular overlap may be more extensive than depicted in myotomal charts (Schirmer et al., 2011; MacDonald et al., 2012).

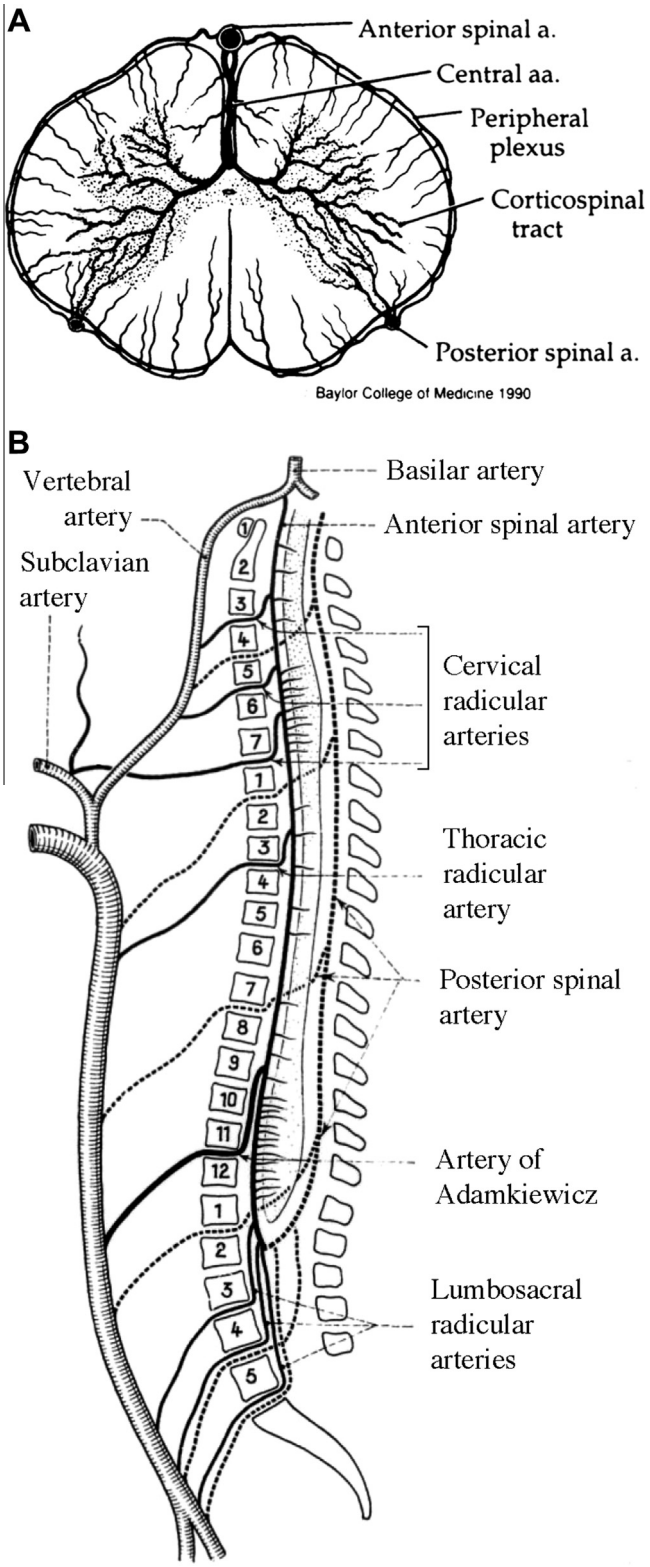

Fig. 2. Spinal cord blood supply. (A), Axial view, from Mawad et al. (1990), with permission. (B), longitudinal view, modified from Connolly (1998), with permission.

3.1.9. Neuromuscular junction

The neuromuscular junction is a monosynaptic excitatory synapse between a LMN terminal branch and its muscle fiber.

Normally each motor axon action potential results in a muscle fiber action potential and contraction. Perisynaptic inhibitory agents or neuromuscular junction disease can disturb transmission.

3.1.10. Muscle

A skeletal muscle consists of many muscle fibers sheathed together. The belly tapers to fibrous tendons attaching to bone and crossing a joint so that contraction produces movement. Single muscle fiber contraction produces no visible twitch or movement. Single motor unit contraction may cause a visible focal muscle belly twitch, but usually no joint movement. Movement generally requires the activation of several motor units; faster firing and recruitment of more and larger units increases contraction strength.

3.1.11. Cerebral blood supply

The middle cerebral artery supplies the lateral motor cortex and its descending axons in the lateral corona radiata; ischemia produces contralateral UMN lower face and arm paralysis. The anterior cerebral artery supplies the parasaggital motor cortex and its descending axons in the mesial corona radiata; ischemia produces contralateral UMN leg paralysis. Lenticulostriate perforators and the anterior choroidal artery supply the internal capsule; ischemia produces contralateral UMN hemiplegia. Vertebral and basilar artery branches supply the brainstem. Unilateral ischemia can produce contralateral UMN hemiplegia and ipsilateral LMN cranial muscle paralysis. Bilateral ischemia can produce UMN quadriplegia and bilateral LMN cranial muscle paralysis.

There is a concern that TES MEP monitoring may not detect ischemia (or other pathology) in these territories if deeply penetrating current were to continue to generate MEPs by activating unaffected corticospinal axons in the internal capsule or brainstem (Szelényi et al., 2005, 2006; MacDonald, 2006). Consequently, near-threshold intensity and penetration-limiting stimulus montages such as C1/2 or C3–Cz and C4–Cz have been advised for surgery risking cerebral ischemia or other pathology, but theoretically might still miss cortical disturbances; DCS might maximize the likelihood of detecting motor cortex failure (Szelényi et al., 2005, 2006, 2010).

3.1.12. Spinal cord blood supply

The anterior spinal artery running down the ventral median fissure supplies the anterior horns, intermediate gray, inner dorsal horns and inner white matter including the corticospinal tracts (Fig. 2). It receives vital collateral supply from neck arteries, a few radicular arteries arising from the descending aorta, and the iliac arteries. The two posterior spinal arteries run down the dorsolateral cord, receive similar collateral supply, and perfuse the dorsal columns and outer dorsal horns. A circumferential anastomotic plexus supplies outer white matter.

Spinal cord blood flow is distributed according to metabolic need (MacDonald and Dong, 2008). Resting flow is four times greater in gray than white matter because neurons have higher metabolic rate than axons. The lumbosacral and cervical enlargements have 40% greater flow than the thoracic cord containing less gray matter. Autoregulation stabilizes perfusion across a range of systemic blood pressure and increases flow with spinal neuron activity.

Spinal cord ischemia and infarction are multi-segmental processes most often affecting the lumbosacral and low thoracic cord, followed by the cervical segments; isolated thoracic ischemia is infrequent (MacDonald and Dong, 2008). In accordance with metabolic rate, ischemia begins in and may remain confined to gray matter, particularly the anterior horns. Thus, affected segments show rapid muscle MEP deterioration (Fig. 3).

White matter conduction may be unaffected or eventually fail depending on duration and severity. Thus, potentials mediated through white matter (D-waves, SEPs) and muscle MEPs generated in segments below an ischemic level may be unaltered or show delayed deterioration (Lips et al., 2002; MacDonald and Dong, 2008). For instance, ischemia limited to the thoracic cord might not affect leg MEPs or do so after some delay. This may be relevant during thoracic spine surgery because abrupt leg MEP disappearance in this setting would tend to suggest compression that can more quickly block long tract conduction (MacDonald et al., 2007).

3.2. Physiology

3.2.1. Spinal cord stimulation

Spinal cord stimulation non-selectively activates tracts. Spinally elicited peripheral nerve potentials formerly proposed as ‘neurogenic motor evoked potentials’ are now known to be

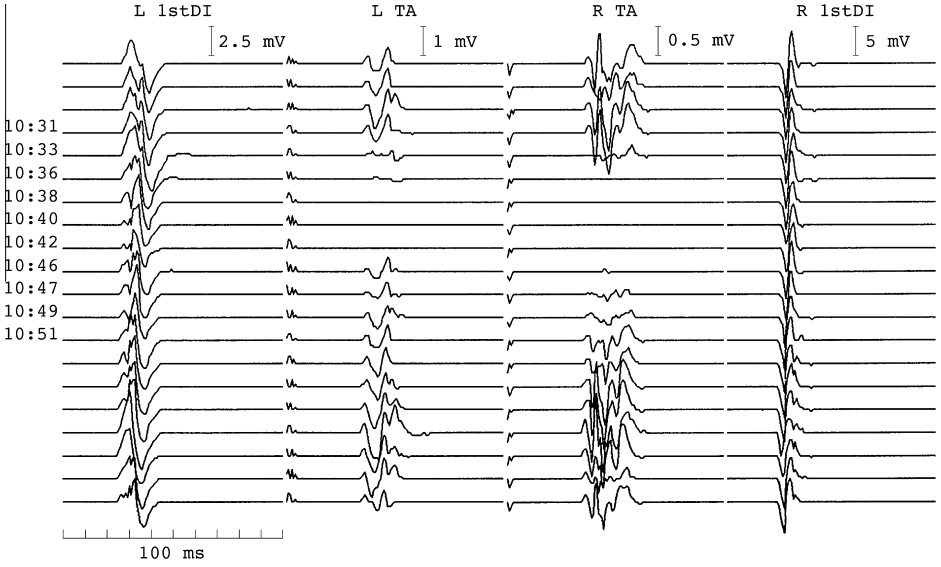

Fig. 3. Acute lumbosacral spinal cord ischemia during thoracoabdominal aneurysm surgery under propofol/opioid anesthesia. 1stDI, first dorsal interosseous; TA, tibialis anterior. Abrupt leg MEP deterioration rapidly progressing to disappearance followed aortic cross clamping at 10:32. Restoration followed clamp release at 10:42. There was no motor deficit. Modified from MacDonald and Janusz (2002), with permission.

predominantly antidromic dorsal column sensory potentials (Leppanen et al., 1999; Toleikis et al., 2000; Minahan et al., 2001). Spinally evoked muscle responses demonstrate LMN firing, but could be mediated through several tracts including antidromic impulses in dorsal column axons making collateral synapses on LMNs (Langeloo et al., 2007). Consequently, spinal cord stimulation is generally discouraged for central motor pathway monitoring.

However, there may still be valid roles when specific tracts are less critical. For example, testing for thoracic pedicle breach with pulse train pedicle screw stimulation (Donohue et al., 2008). Also, spinally elicited muscle responses might be a valid way to monitor cauda equina motor axons when central motor tracts are not at risk. Finally, stimulating the spinal cord at one end and monitoring evoked spinal cord potentials at the other might be considered for patients with pathologically absent MEPs and SEPs. Inadvertent physical stimulation of the spinal cord can evoke EMG discharges that may provide a passive warning, but this is not an electrical stimulation technique (Skinner et al., 2009).

3.2.2. Brain stimulation

Brain stimulation also activates several neuronal systems, but effectively selects corticospinal and corticobulbar pathways that uniquely conduct action potentials to LMNs without intervening synapses. The large thickly myelinated axons from primary motor cortex are likely the principal fibers underlying MEPs because (1) their relatively synchronous fast conduction velocities enable D- and I-wave recording, and (2) they directly excite LMNs (Amassian, 2002; Deletis, 2002; MacDonald, 2006). Thus, brain stimulation is recommended for MEP monitoring. Electrical stimulation is more practical and effective for IONM than TMS because it is simpler to fix in position and more directly excites corticospinal axons.

3.2.3. D-waves

D-waves are compound corticospinal action potentials initiated by direct axonal activation and having approximately 50 m/s conduction velocity (Patton and Amassian, 1954; Amassian, 2002). Threshold activation occurs in superficial subcortical white matter. Suprathreshold stimuli increase amplitude and decrease latency through axonal recruitment and deeper activation. With strong TES, the D-wave may jump to shorter latency or bifurcate and then trifurcate into earlier components, most likely representing internal capsule and brainstem corticospinal fiber activation (Fig. 4) (Burke et al., 1990; Rothwell et al., 1994).

D-wave amplitude is greatest when the bipolar recording electrode is near the spinal cord, which is the reason for invasive recording. A 2–3 cm inter-electrode distance is satisfactory; shorter distance reduces amplitude and longer distance introduces noise.

For fixed spinal cord-electrode and inter-electrode distances, D-wave amplitude is proportional to the number of synchronously conducting corticospinal axons at the recorded level (Deletis, 1993, 2002; Amassian, 2002). Since there are fewer axons down the cord, amplitude progressively decreases to zero at the lumbosacral cord where the tracts end; latency increases with brain-electrode distance (Fig. 1).

D-waves are highly stable, visible in single sweeps and require little averaging (Burke et al., 1995). They provide corticospinal tract information, but are not useful at or below the lumbosacral cord. It may be reasonable to record ‘left’ and ‘right’ D-waves to right and left scalp anodal stimuli, but some bilateral activation makes purely lateralized TES D-waves unlikely (MacDonald, 2006).

3.2.4. I-waves

A set of later I-waves having a 1.3–2.0 ms periodicity follows the D-wave in conscious humans (Amassian, 2002; Di Lazzaro et al., 2010). Their generation involves the activation of frontoparietal oscillatory intracortical circuits that incite additional corticomotor neuron discharges (Amassian, 2002; Di Lazzaro et al., 2010). Epidural I-wave amplitude may underestimate the number of descending impulses (Patton and Amassian, 1954).

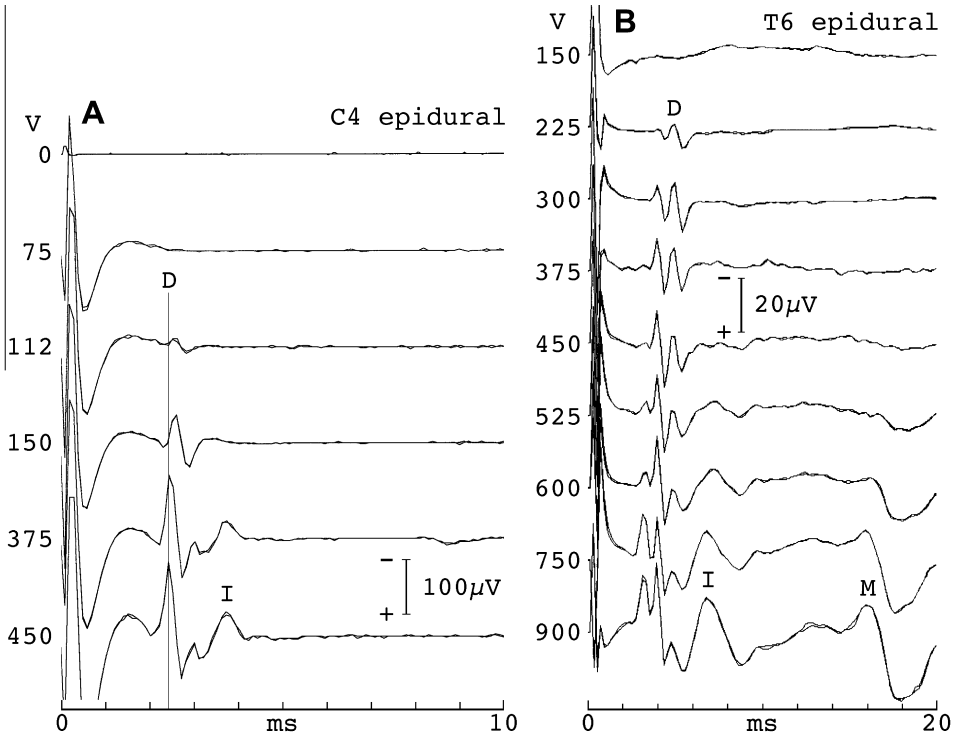

Fig. 4. Spinal epidural responses with increasingly strong C1/2 constant voltage (V) 0.05-ms pulses under propofol/opioid anesthesia. In (A), D-wave amplitude increases and latency suddenly decreases. In (B), the D-wave bifurcates and trifurcates into earlier components. Note I-wave recruitment at high intensity. Late muscle artifact (M) appears in (B) at very high intensity. Modified from MacDonald (2006), with permission.

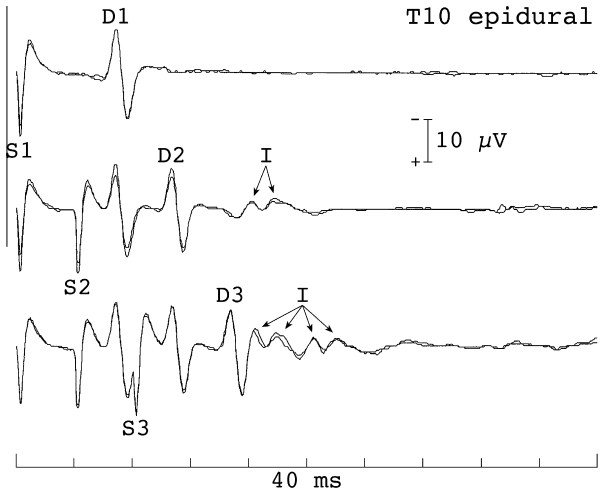

Fig. 5. Pulse train I-wave recruitment during scoliosis surgery under propofol/opioid anesthesia. C1/2 stimulation used 0.05-ms pulses and a 4-ms interstimulus interval. Each stimulus (S1–3) produced a D-wave (D1–3). Single pulses evoked no I-waves, but double pulses recruited two and 3-pulse trains recruited four.

Anesthesia suppresses intracortical synapses so that intraoperative recordings often show mainly D-waves (Fig. 1) (Boyd et al., 1986; Burke et al., 1992; Deletis, 1993, 2002; Amassian, 2002). Nevertheless, there can be one or more I-waves with strong stimuli or light anesthesia (Fig. 4). Also, I-wave recruitment follows the second or third and subsequent pulses of train stimuli (Fig. 5) (Deletis, 2002; MacDonald, 2006).

Anesthetic suppression of I-waves limits their use as a monitor. An exception may be DCS cervical I-wave monitoring during peri-Rolandic brain tumor resection (Fujiki et al., 2006).

3.2.5. Non-synchronous corticospinal action potentials

There may normally be some non-synchronous corticospinal impulses exciting LMNs but not contributing to D- and I-wave volleys (Di Lazzaro et al., 2010). Also, infants below 18 months have muscle MEPs but no D-wave because immature myelination disperses conduction velocity (Szelényi et al., 2003). In addition, some patients with spinal cord lesions have muscle MEPs but no D-wave, suggesting pathologic desynchronization of damaged but still conducting corticospinal axons (Deletis, 2002).

3.2.6. Muscle MEPs

The basic mechanism of muscle MEP generation is temporal and spatial summation of LMN excitatory postsynaptic potentials (EPSPs) (Taylor et al., 1993; Taniguchi et al., 1993; Amassian, 2002; Deletis, 2002; MacDonald, 2006). In conscious humans, single-pulse D- and I-wave action potentials produce sequential LMN EPSPs summating toward firing threshold. A few LMNs, having sufficient excitability at the time, reach threshold and fire, thereby generating a muscle response.

Anesthesia inhibits I-waves and LMN excitability; usually there is insufficient EPSP summation and no muscle MEP; there may be small responses with light anesthesia. Pulse trains evoke a series of D-waves and recruit some I-waves, thereby generating enough EPSP summation to make some LMNs fire (Figs. 5 and 6) (Amassian, 2002; MacDonald, 2006).

The number of motor units firing at threshold is unknown; one could be enough if the recording electrode were near its muscle fibers. Suprathreshold stimuli increase amplitude, polyphasia and duration by recruiting more motor units until supramaximal intensity (Langeloo et al., 2003).

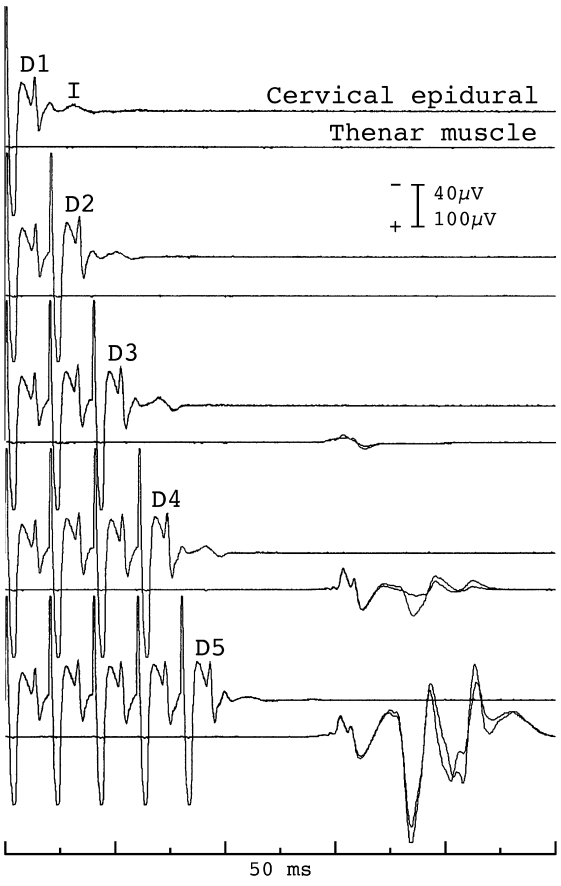

Fig. 6. Spinal epidural and muscle MEPs during cervical tumor surgery under propofol/opioid anesthesia. D1 through D5 are D-waves evoked by one through five C1/2 pulses (0.5-ms duration, 4-ms ISI, 250 V). An I-wave followed each D-wave. Temporal summation of D- and I-wave excitatory postsynaptic potentials produced non-linear progressive thenar motor unit recruitment with 3- to 5-pulse trains. Modified from MacDonald (2002), with permission.

3.2.7. Muscle MEP variability

Despite stable D-waves, muscle MEPs exhibit considerable trial-to-trial amplitude and morphology variability (Fig. 1). This is attributed to fluctuating LMN background facilitation from UMN, propriospinal, and sensory synapses, as well as neuromodulatory synapses releasing transmitters such as norepinephrine and serotonin that powerfully affect excitability (Rekling et al., 2000; Amassian, 2002; Heckman et al., 2009). To what extent I-wave fluctuations might contribute is unknown.

3.2.8. Muscle MEP sensitivity

Motor units exhibit on–off behavior: EPSP summation reaching or exceeding firing threshold produces a full response, while anything less produces no response (Amassian, 2002). Muscle MEPs show more graduated modulation as individual units add to or drop out of the compound potential. Nevertheless, being built from motor units they are still non-linear, so that a disproportionately large reduction can follow a small decrease of corticospinal drive or LMN excitability (Amassian, 2002; MacDonald, 2006). This high sensitivity makes muscle MEP deterioration an imperfect predictor of motor deficit severity or permanence. On the other hand, preservation provides good evidence for central motor pathway integrity.

3.2.9. Muscle MEP fade

Despite stable anesthesia, muscle MEPs tend to exhibit gradually falling amplitudes and rising thresholds during the hours of

surgery (Lyon et al., 2005; MacDonald, 2006; MacDonald et al., 2007). Fade varies from none to marked and may be greater with antecedent myelopathy (Lyon et al., 2005).

It seems likely that fade reflects falling LMN excitability (MacDonald, 2006). However, it could be that D- or I-wave fade contributes, but has not yet been recognized. The important clinical point is that fade can progress to marked reduction or disappearance unless stimulus increments are made (Lyon et al., 2005; MacDonald, 2006; MacDonald et al., 2007).

3.2.10. Muscle MEP deterioration without corticospinal tract or LMN injury

A syndrome consisting of D-wave preservation, but muscle MEP loss with transient paralysis has been repeatedly observed with intramedullary spinal cord tumor (IMSCT) surgery (Fig. 7) (Deletis, 2002; Kothbauer, 2002; Sala et al., 2006a). This suggests that intramedullary dissection can temporarily reduce intact LMN excitability to intact corticospinal tract input by disrupting background facilitation systems (Deletis, 2002; MacDonald, 2006). When D-wave amplitude is reduced, but by less than 50%, recovery might also be due to secondary systems compensating for the loss of some corticospinal tract fibers (Deletis and Sala, 2001).

A similar syndrome consisting of cervical D-wave preservation, but I-wave and thenar MEP deterioration with temporary paralysis has been reported during peri-Rolandic brain surgery (Fujiki et al., 2006). This suggests that peri-Rolandic manipulation may temporarily reduce corticospinal drive by disrupting I-wave circuits.

3.2.11. Peripheral conduction, neuromuscular transmission and nerve roots

Peripheral motor axons conduct action potentials with no anesthetic interference, while neuromuscular blockade (NMB) can reduce or obliterate muscle MEPs. A varying sub-population of motor axons generates the muscle MEP. Because of radicular overlap, the effect of intraoperative conduction failure in one root varies according to the proportion of axons it was contributing to the response. If it were contributing few or no axons there could be no change. If it were contributing enough axons there could be a visible step-like decrement that might or might not exceed a given warning criterion. If it were a dominant root contributing most of the axons, then the response could markedly decrease. Thus, muscle MEP monitoring has uncertain reliability for predicting nerve root integrity (MacDonald et al., 2012).

4. Methodology

4.1. Stimulating electrodes

Spiral 'corkscrew' needles, straight needles and EEG cups are effective for TES. Spiral needles are self-securing, while straight needles must be secured by other means. Collodion-fixed EEG cups can be securely applied with <2-kΩ impedance prior to entering the operating room, saving intraoperative time (MacDonald et al., 2003, 2007). Direct cortical stimulation is done with subdural strips, or with probe or wick electrodes that can also be used for subcortical stimulation.

4.2. Stimulus montages

Anodal stimuli evoke MEPs more efficiently than cathodal stimuli when applied to the scalp or cortex, whereas cathodal stimuli are more efficient for subcortical stimulation (Amassian, 2002; Szelényi et al., 2011). Consequently, TES and DCS montages are

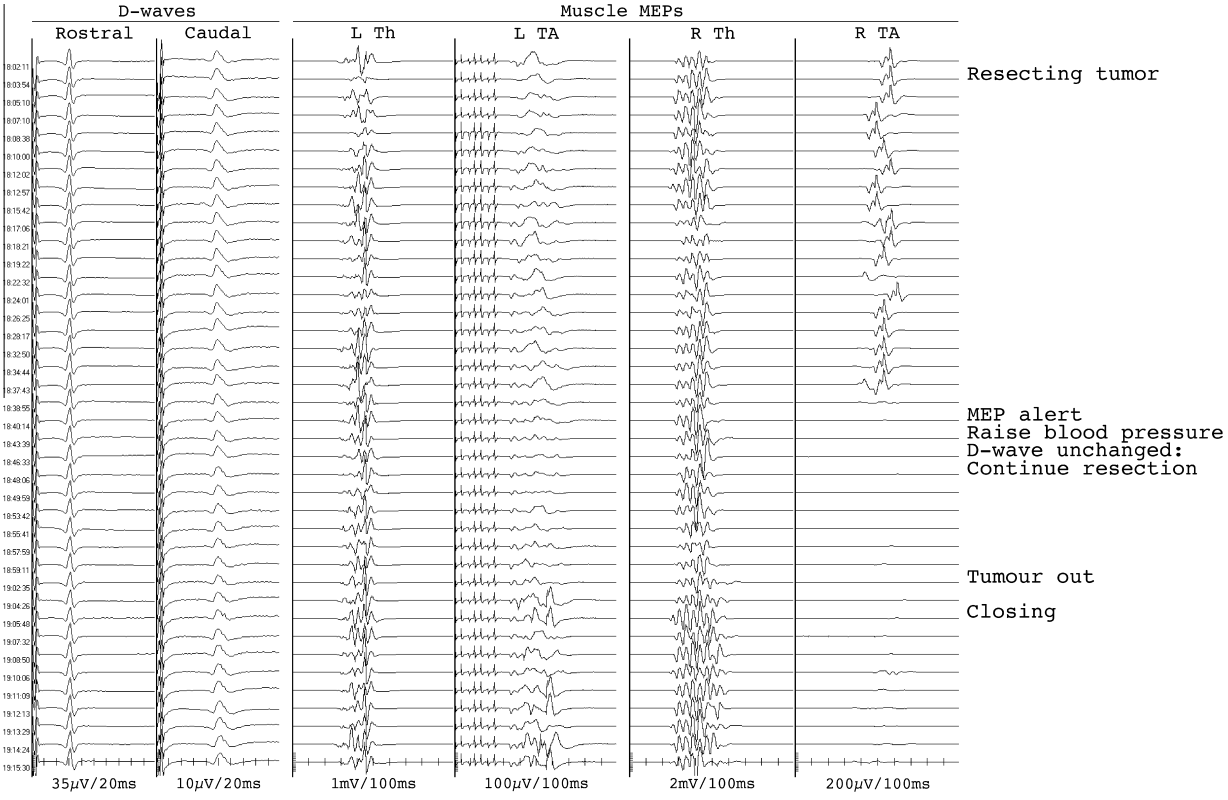

Fig. 7. D-wave and muscle MEP monitoring during thoracic intramedullary spinal cord tumor surgery under propofol/opioid anesthesia. Th, thenar; TA, tibialis anterior. Abrupt right TA MEP disappearance during resection prompted ineffective blood pressure elevation. Despite this, tumor resection continued to completion because D-waves were preserved. Small right TA MEPs reappeared during closure. Postoperative right leg paresis recovered within hours.

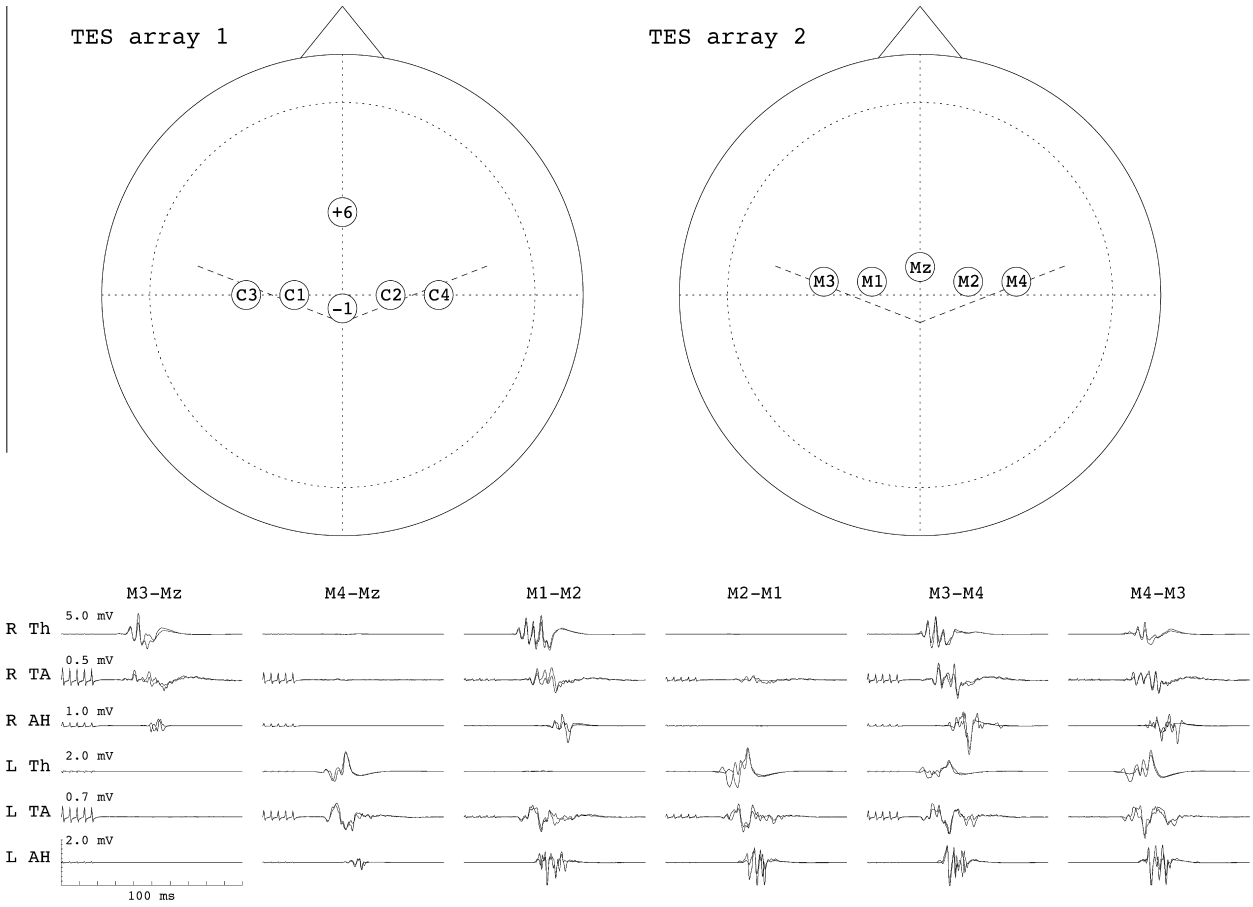

Fig. 8. Transcranial electric stimulation (TES) arrays and montages. In array 1 (Deletis, 2002), -1 is Cz − 1 cm and + 6 is Cz + 6 cm. In array 2 (MacDonald et al., 2007), sites are labeled 'M' for motor and are at C + 1 cm locations, except Mz at Cz + 2 cm to make room for Cz SEP recording. In the bottom panel, hemispheric TES montages (M3–Mz, M4–Mz) produced unilateral MEPs and smaller leg MEPs than inter-hemispheric montages, of which M3/4 was more potent. Anode-contralateral maximal MEPs confirmed normal motor decussation, most clearly with hemispheric TES. Th, thenar; TA, tibialis anterior; AH, abductor hallucis. Propofol/opioid anesthesia; five 0.5-ms 300 V pulses with 4-ms ISI. Modified from MacDonald (2006), with permission.

designated anode–cathode, while subcortical stimulation is cathode–anode.

4.2.1. TES electrode arrays

Scalp stimulating arrays are placed at measured sites over motor cortex (Fig. 8). One array is C3, C1, C2, C4, Cz − 1 cm and Cz + 6 cm (Deletis, 2002). Some practitioners use slightly anterior arrays, such as C + 1 cm sites designated M3, M1, Mz, M2 and M4 to distinguish them as motor (MacDonald et al., 2007). These sites might constrain TES artifact because of greater distance from scalp SEP electrodes through which stimuli reach the headbox. There is no known efficacy difference between C and slightly anterior sites; C refers to either in this document.

4.2.2. TES montages

Common TES montages are hemispheric, inter-hemispheric or midline (Table 1 and Fig. 8).

4.2.2.1. Hemispheric. The hemispheric montages are C3–Cz and C4–Cz (Deletis, 2002; MacDonald et al., 2004, 2007; Dong et al., 2005; MacDonald, 2006; Szelényi et al., 2007). They stimulate predominantly the left and right hemisphere and generate mostly

Table 1
Summary of common stimulation montages for motor evoked potential (MEP) monitoring. CST, corticospinal tract; TH, threshold.

Technique	Type	Montage	Application	Response symmetry	Induced movement	Current penetration depth
Transcranial	Hemispheric	C3–Cz, C4–Cz	Decussation testing, facial and arm MEPs	Mainly unilateral	Moderate	Moderate
	Inter-hemispheric	C1/C2	Arm and leg MEPs	Asymmetric	Moderate	Moderate
		C3/C4	Arm and leg MEPs	Asymmetric	Strong	Deep
	Midline	(Cz − 1)–(Cz + 6)	Leg MEPs	Symmetric	Moderate	Moderate
Intracranial	Direct cortical	Anode–cathode	Motor cortex mapping	Unilateral	Mild	Minimal near TH
	Direct subcortical	Cathode–anode	CST mapping	Unilateral	Mild	Minimal near TH

Table 2
Mean abductor pollicis brevis MEP thresholds (n = 10) to 5-pulse TES under propofol and opioid anesthesia (Szelényi et al., 2007) with corresponding rheobase and chronaxie. TH, threshold.

ISI (ms)	Pulse duration (ms)			Pulse duration (ms)			Rheobase (mA)	Chronaxie (ms)
	0.1	0.2	0.5	0.1	0.2	0.5		
	TH current (mA)			TH charge (μC)				
2	158	105	76	15.8	21.0	38.0	55.8	0.180
3	140	97	64	14.0	19.4	32.0	44.3	0.225
4	126	91	61	12.6	18.2	30.5	43.9	0.199
5	179	120	83	17.9	24.0	41.5	58.8	0.206

unilateral MEPs. They are recommended for decussation assessment (contralateral responses confirm decussation, while ipsilateral responses disclose non-decussation) and for facial and arm, but not leg MEPs. They constrain pulse train patient movement and may limit current penetration depth.

4.2.2.2. Inter-hemispheric. The inter-hemispheric montages are C1/C2 and C3/C4 (Deletis, 2002; MacDonald, 2006; MacDonald et al., 2007; Szelényi et al., 2007). They evoke arm, leg and sphincter MEPs, but are inadvisable for facial MEPs because of confounding facial nerve excitation (Dong et al., 2005). They often produce bilateral responses with lower threshold and higher amplitude contralateral to the anode (ipsilateral with non-decussation). Anode switching allows symmetric assessment, for example C1–C2 and then C2–C1 for right and then left MEPs (reversed for non-decussation). Using biphasic pulses may produce symmetric MEPs, but cannot assess decussation and might generate stronger patient movements.

C1/C2 is less potent than C3/C4, probably because more current shunts through the scalp (Holdefer et al., 2006). However, it produces less patient movement and may limit current penetration. C3/C4 may be needed for some patients, but causes stronger movement and may promote deeper current penetration. Switching to C3/4 during surgery may occasionally be needed to restore fading C1/2 MEPs (MacDonald et al., 2007).

4.2.2.3. Midline. The midline montage is Cz − 1 cm to Cz + 6 cm (Deletis, 2002; Szelényi et al., 2007). It evokes symmetric leg MEPs with constrained patient movement, but has lower efficacy than inter-hemispheric stimuli and is inadvisable for arm or facial MEPs. It might be advantageous during sitting position posterior fossa surgery when intracranial air over the hemispheric convexities can interfere with coronal TES.

4.2.2.4. Alternatives. Some practitioners apply only C1/C2 or C3/C4, which limits opportunities to optimize. A few reports describe a Cz anode and circumferential basal cathode array (Ubags et al., 1996), or using two long subdermal needles over both motor strips as a combined anode with a large forehead surface cathode (Langeloo et al., 2003). These approaches produce symmetric four-limb MEPs, but cannot assess decussation and could promote deep current, so may be inadvisable for intracranial surgeries.

4.2.3. Intracranial montages

Direct cortical and subcortical stimuli are most commonly monopolar with an exploring electrode and scalp or distant cortical return, although bipolar stimuli can also evoke MEPs (Yamamoto et al., 2004; Szelényi et al., 2011). Intracranial stimuli produce unilateral MEPs and minimal patient movement. Current penetration or spread is minimal near threshold, but increases with intensity; monopolar stimuli are non-localizing at high intensity.

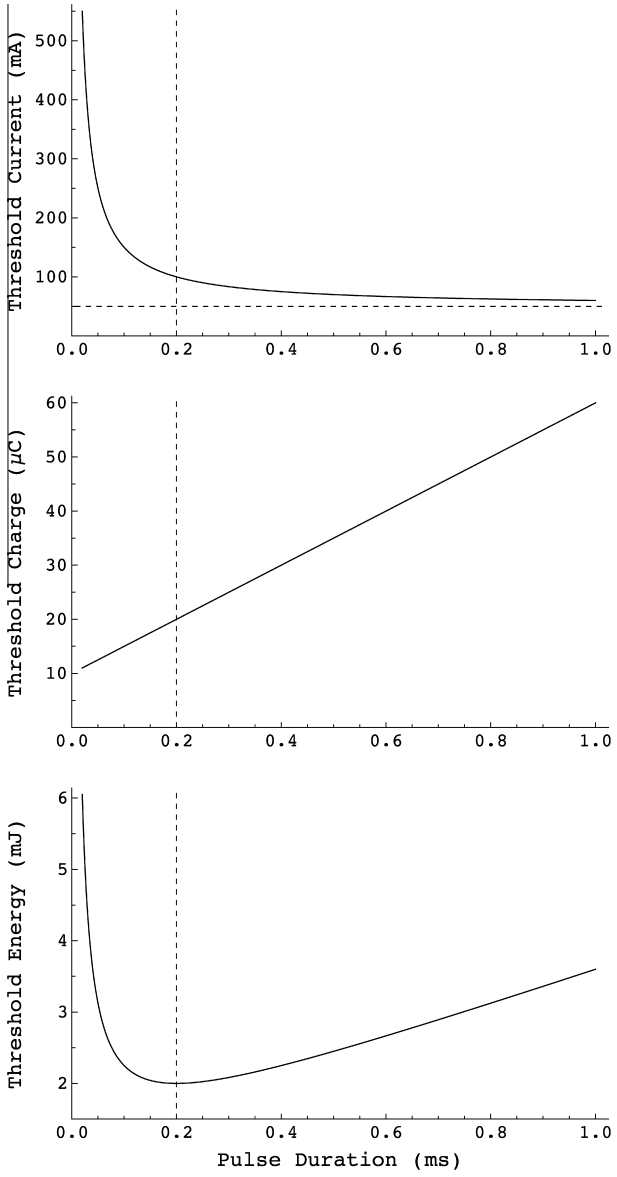

Fig. 9. Threshold current, charge and energy across a 0.02–1.0 ms pulse duration range for a 50 mA rheobase (horizontal dashed line), 0.2 ms chronaxie (vertical dashed lines) and 1 kΩ resistance.

4.3. TES pulse parameters

Rectangular stimulus parameters are pulse width or duration D in milliseconds (ms), current I in milliamps (mA), charge Q in microcoulombs (μC) and energy E in millijoules (mJ). Charge $Q = I \times D$ is the amount of electricity and the most relevant parameter for stimulation and excitotoxicity. Energy $E = I^2 \times D \times R \times 0.001$, where R is

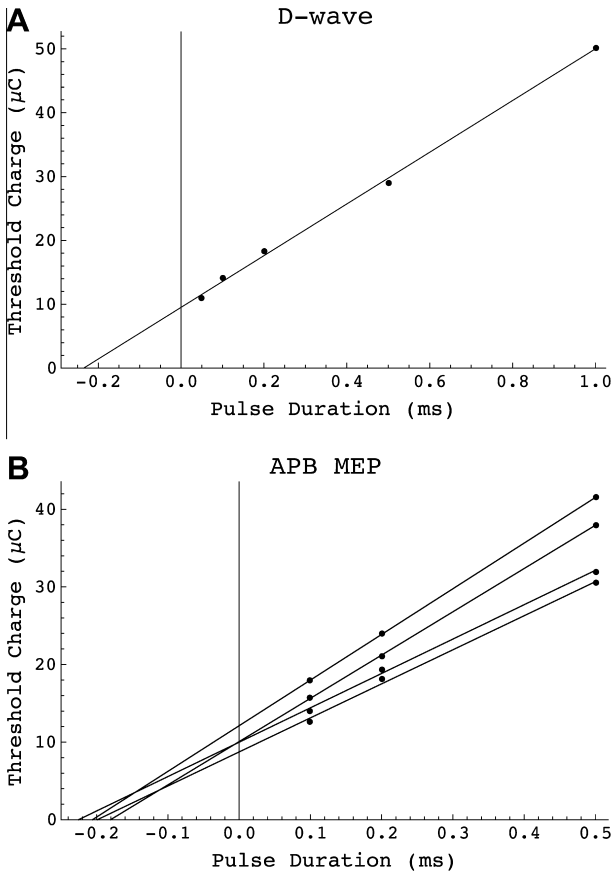

Fig. 10. Published mean charge-duration data for D-waves (Bartley et al., 2002) and abductor pollicis brevis (APB) MEPs (Szelényi et al., 2007). By the classical formulation of Weiss (1901), rheobase = slope and chronaxie = −X-intercept. In (A), the corresponding rheobase and chronaxie are 40.5 mA and 0.235 ms. In (B), regression lines from top to bottom correspond to ISIs of 5, 2, 3 and 4 ms; while rheobase varies with ISI, the chronaxie is near 0.2 ms for each ISI.

resistance in kΩ and 0.001 is needed to have the result in mJ when the other variables are in the above units. Energy produces heat and is the most important parameter for thermal injury. The International Electrotechnical Commission (IEC) safety limit is 50 mJ through 1 kΩ resistance (IEC, 1998).

The pulse strength needed to evoke an excitable tissue response varies with duration and the tissue's excitability threshold properties known as rheobase and chronaxie. Rheobase is threshold current at infinite D and chronaxie is D having a threshold current two times the rheobase. The threshold current (I_{th}), charge (Q_{th}) and energy (E_{th}) equations are (Prutchi and Norris, 2005):

$$I_{th} = rheobase \times \left(1 + \frac{chronaxie}{D}\right)$$

$$Q_{th} = rheobase \times \left(1 + \frac{chronaxie}{D}\right) \times D$$

$$E_{th} = rheobase^2 \times \left(1 + \frac{chronaxie}{D}\right)^2 \times D \times R \times 0.001$$

Fig. 9 plots these functions over the range of D from 0.02 to 1 ms for realistic rheobase, chronaxie and resistance values of 50 mA, 0.2 ms and 1 kΩ. It is evident that: (1) threshold current drops sharply from very high values at very short pulse widths and levels off toward rheobase at long pulse widths, (2) threshold charge rises linearly with pulse width, and (3) threshold energy drops sharply from high values at very short pulse widths to reach a minimum at the chronaxie and then rises again toward longer pulse widths. Thus, short pulses constrain charge at the expense of high current and energy and long pulses constrain current at the expense of high charge and energy, but pulse width equal to the chronaxie minimizes energy while balancing current and charge, so could be considered optimal.

One can derive rheobase and chronaxie by fitting strength-duration measurements to the threshold charge equation (Weiss, 1901; Burke et al., 2000). Bartley et al. (2002) determined mean TES D-wave thresholds at several pulse durations under sevoflurane anesthesia (0.05 ms, 217.8 mA; 0.1 ms, 140.5 mA; 0.2 ms, 91.5 mA; 0.5 ms, 58.1 mA; 1 ms, 50.2 mA). The corresponding rheobase and chronaxie work out to 40.5 mA and 0.235 ms (Fig. 10A). Similarly, Szelényi et al. (2007) determined mean abductor pollicis brevis (APB) muscle MEP thresholds to C3/4 5-pulse TES under propofol/opioid anesthesia at three pulse durations and four ISIs. The corresponding rheobase and chronaxie work out to 44–59 mA and 0.18–0.23 ms, depending on ISI (Fig. 10B, Table 2). Thus, based on published strength-duration data, mean APB muscle MEP rheobase is about 50 mA under common intraoperative conditions and TES MEPs have an approximately 0.2 ms mean chronaxie.

To allow for threshold variations, maximum output of about four times the mean APB threshold while not exceeding the 50 mJ safety limit would be a reasonable stimulator design. The corresponding maximum current, charge and pulse energy for D from 0.02 to 1 ms can be estimated with the three threshold equations, using the derived 0.2 ms mean chronaxie and substituting 4 × mean APB rheobase = 200 mA for rheobase. Fig. 11 plots the resulting curves and Table 3 lists maximum parameters at selected durations. Based on this analysis, the desired maximum output could respect the IEC 50 mJ limit within the pulse duration range of 0.05–0.80 ms. Also, pulse duration near the mean 0.2 ms chronaxie might be optimal.

Nevertheless, for mainly historical and government approval agency restriction reasons the monitoring community is divided between 0.05 ms or 0.5 ms pulses. Both are effective, but represent the extremes. What is lacking is a variable pulse width stimulator with maximum output logically graduated to pulse duration. Instead, commercial stimulators have fixed maximum output with either fixed or variable duration. In the later case, practitioners tend to use long duration because maximum output becomes insufficient to consistently elicit MEPs at shorter durations. In particular, there are no approved stimulators with sufficient maximum output near the estimated 0.2 ms chronaxie. Hopefully, future studies will provide additional strength-duration data to refine rheobase and chronaxie estimates and stimulator designs will begin to incorporate these considerations.

4.4. Intracranial pulse parameters

There are no published strength-duration data for intracranial MEPs. One might expect a similar chronaxie, but lower rheobase because current directly enters the brain rather than dispersing though the skull. Thus, thresholds and maximum currents are lower, as illustrated by four representative monopolar pulse train DCS muscle MEP studies:

Two studies applied variable duration pulses of up to 20 mA using a 1-cm diameter anode and inhalational anesthesia. Taniguchi et al. (1993) applied 2–4 ms ISI and 0.2–0.5 ms duration. Motor gyrus threshold was 6–12 mA and varied with duration, but strength-duration was not systematically analyzed. Cedzich et al. (1996) used 2 ms ISI and 0.2–0.4 ms pulse duration. Mean motor gyrus threshold was 12 mA.

Two studies applied 0.5 ms duration, 4 ms ISI and 25 mA maximum current. Szelényi et al. (2007) used 5-pulse trains and a

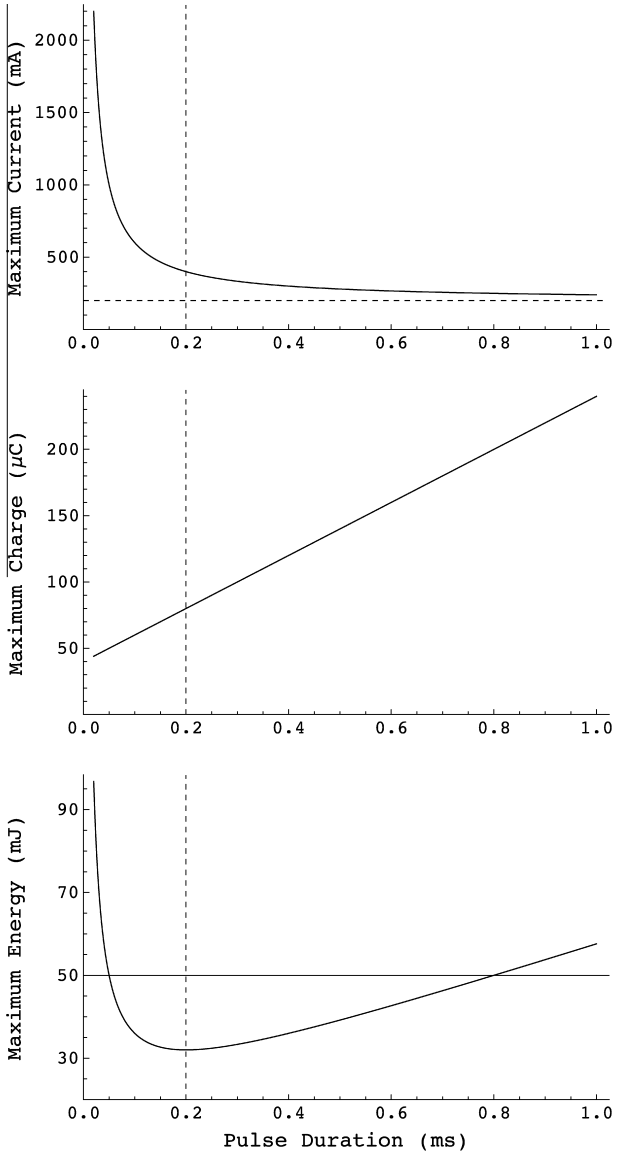

Fig. 11. Theoretical maximum pulse current, charge and energy (1 kΩ resistance) to have maximum stimulator output of four times estimated mean APB muscle MEP threshold across a 0.02 to 1.0 ms pulse duration range, based on 50 mA rheobase and 0.2 ms chronaxie (vertical dashed lines) estimates derived from published strength-duration data. The horizontal dashed line in the top plot represents 4× estimated mean APB rheobase. The horizontal solid line in the bottom plot is the IEC 50 mJ safety limit.

Table 3
Theoretical maximum current (I_{max}), charge (Q_{max}) and energy (E_{max}) to have up to four times estimated mean APB MEP threshold stimulator output at several pulse widths and not exceed 50 mJ (1 kΩ resistance). Based on 50 mA rheobase and 0.2 ms chronaxie estimates derived from published strength-duration data (Bartley et al., 2002; Szelényi et al., 2007).

D (ms)	I_{max} (mA)	Q_{max} (μC)	E_{max} (mJ)
0.05	1000	50	50
0.10	600	60	36
0.20	400	80	32
0.30	333	100	33
0.50	280	140	39
0.80	250	200	50

0.4 cm diameter anode from an 8-contact strip slid underneath the skull. Mean threshold was 15 mA, but stimuli may not have always been on motor cortex. Simon et al. (2010) studied 6-pulse trains using a probe anode of unspecified diameter. Mean motor gyrus threshold was 8.5 mA. Compared to the conscious state, mean thresholds were 1.3 mA higher under propofol and 4.8 mA higher under inhalational anesthesia. Thresholds increased with anesthetic depth.

4.5. Constant voltage, current or charge?

For historical and government approval agency restriction reasons, constant voltage stimulators are most commonly used for TES MEP monitoring today. However, stimulating current depends on resistance that varies with multiple factors and may change during surgery. Consequently, a delivered current read out is desirable.

Constant current stimulators adjust voltage to deliver selected current independent of resistance (within compliance limits). They are preferred for intracranial stimulation because of this advantage and are becoming more common for TES.

Since charge is the most relevant parameter for stimulation and threshold charge is linearly related to pulse duration, a constant charge design would be logical. Such a device would adjust voltage to deliver the current necessary for the pulse width used in order to make the selected charge; maximum charge could be linearly graduated according to selected duration.

4.6. Pulse train parameters

Train pulse number and ISI in ms, or frequency in Hz (ISI = 1000/frequency) are not standardized and each program must decide its approach. Adding pulses reduces MEP threshold and increases amplitude, duration and polyphasia (Fig. 6). Generally at least 3 pulses are necessary to evoke muscle MEPs. Consequently, some practitioners use 3 or 4 pulses (Calancie et al., 1998, 2001). Others find that more pulses may be needed, particularly for leg MEPs. Thus, 5 pulses are another reasonable starting point, although fewer may be sufficient for some patients and more may be needed for others (Deletis, 2002; MacDonald, 2006; MacDonald et al., 2003, 2007). Some practitioners apply 6–8 pulses for long duration polyphasic MEPs (Quiñones-Hinojosa et al., 2005).

Three pulses seem to be a reasonable starting point for facial MEPs, but more may be needed (Dong et al., 2005). Note that moderate TES can spread to the facial nerve itself, thereby generating confounding short latency (5–7 ms) peripheral responses that also occur with single pulses. One avoids this by ensuring there are no single-pulse responses at monitoring intensity and that the pulse train facial MEPs have >10 ms onset latency consistent with a central origin (Dong et al., 2005).

Some practitioners use a 2-ms ISI (Calancie et al., 1998, 2001). However, this may be within the D-wave relative refractory period whereas a 4-ms ISI allows full D-wave recovery, minimizes muscle MEP threshold and may be a good general starting point (Table 2) (Deletis et al., 2001a,b; Bartley et al., 2002; Szelényi et al., 2007). Still, hand (but not leg) MEPs have greatest amplitude and simplest morphology with a 1–2 ms ISI, which can also separate stimulus artifact from short latency facial MEPs (Dong et al., 2005; Scheufler et al., 2005). Therefore, this may be a reasonable starting point when monitoring only facial and/or hand MEPs. Individual ISI adjustments may enhance MEPs in certain patients or anesthetic conditions (Deletis et al., 2001b; Deletis, 2002; MacDonald, 2006).

4.7. Facilitation

Muscle MEP facilitation techniques use preconditioning stimuli to raise excitability before the test stimulus (Journée et al., 2007).

Some practitioners apply them regularly (Deletis, 2002; MacDonald et al., 2007).

Double train facilitation increases MEP amplitude at short inter-train intervals (ITIs) of 10–20 ms and at long ITIs of 100–1000 ms (Journée et al., 2004, 2007). Programmable double train stimulators can exploit short or long ITI facilitation, and stimulators that allow manual triggering at any frequency can exploit long ITI facilitation: the operator builds up responses with one or more preconditioning trains (MacDonald et al., 2007). Recurrent 1–2 Hz pulse trains can provide rapid facilitated MEP feedback during critical surgical maneuvers (Deletis, 2002).

Another largely unexplored technique employs peripheral nerve stimulation to produce sensory afferent LMN facilitation. The effect is segmental and lateralized, so that one might be able to focally enhance MEPs (Andersson and Ohlin, 1999; Journée et al., 2007).

4.8. D-wave recording

One records D-waves with sterile electrodes having three or four contacts so that different bipolar recording pairs can be selected. It is advisable to place caudal monitoring and rostral control electrodes for spinal cord surgery (e.g., Figs. 1 and 7).

The surgeon can insert epidural electrodes after opening, or the anesthetist can insert them through a tuohy needle before surgery (Boyd et al., 1986; Burke et al., 1992; Deletis, 1993). Subdural electrodes are threaded upward from a lumbar puncture or inserted after opening (Iwasaki et al., 2003; Sutter et al., 2007a). Percutaneous placements require radiographic confirmation.

Typical recordings use 10–20 ms time base, 5–20 sweep averaging, and 0.2–2 Hz to 1500–3000 Hz filtering (Deletis, 1993, 2002). Some reports recommend 500 Hz low frequency filtering, although this attenuates amplitude (Burke et al., 1992).

4.9. Muscle MEP recording

One records muscle MEPs with surface, subdermal needle, intramuscular needle, or intramuscular hookwire electrodes (Deletis, 2002; MacDonald, 2006; Langeloo et al., 2003). Intramuscular recordings show greatest amplitude (Skinner et al., 2008). Limb MEPs are recorded from muscle belly electrode pairs about 2–3 cm apart, or from belly-tendon derivations, although long inter-electrode distance can increase noise. For cranial MEPs, <0.5 cm inter-electrode distance is advisable to minimize volume conducted signals from untargeted muscles; double hookwires may be advantageous (Deletis et al., 2009).

Muscle MEPs have high signal-to-noise ratios and require no averaging; some practitioners try to counteract variability by averaging a few epochs. A 100 ms time base is appropriate for limb MEPs; a longer epoch may be needed for pathologically delayed responses. The time base may be shortened for cranial MEPs. Filter settings of 10–100 Hz to 1500–3000 Hz are appropriate for limb muscles. Stimulus artifact may obscure cranial MEPs with these settings; opening the low frequency filter to 0.2–2 Hz or constraining it to 150–300 Hz can help (Dong et al., 2005).

Arm MEP recordings typically include the abductor pollicis brevis (thenar muscle); the 1st dorsal interosseous and hypothenar muscles are alternatives. Leg MEP recordings typically include the tibialis anterior and abductor hallucis. Additional muscles spanning more cord segments, roots or nerves may be added according to the surgical circumstances.

Facial MEP recordings include the orbicularis oris and sometimes other muscles (Dong et al., 2005; Fukuda et al., 2008). Vagal nerve MEPs can be recorded from the vocalis or cricothyroid muscles (Deletis et al., 2009). Some practitioners record other cranial nerve MEPs according to the surgical circumstances (Shils et al., 2005).

5. Anesthesia and systemic factors

Anesthesia and other systemic factors can profoundly affect MEPs and could lead to misinterpretation if unrecognized.

5.1. Anesthesia

Anesthetics reduce I-waves, but have little effect on D-waves that are monitorable with any anesthetic, although high concentration inhalational agents modestly reduce their amplitude (Boyd et al., 1986; Burke et al., 1992; Deletis, 1993).

Propofol causes less suppression of LMN excitability than inhalational agents (Zentner et al., 1992, 1997; Zhou et al., 1998; Zhou and Zhu, 2000; Kerz et al., 2001; Rehberg et al., 2004). Consequently, muscle MEP monitoring is consistently successful in neurologically intact patients under propofol and opioid total intravenous anesthesia (TIVA) that is widely recommended as optimal (Calancie et al., 1998, 2001; Deletis, 2002; Langeloo et al., 2003; Chen, 2004; Szelényi et al., 2005, 2007; MacDonald, 2006; Sala et al., 2006a; MacDonald et al., 2007; Sutter et al., 2007b). Other favorable intravenous agents include ketamine, etomidate and benzodiazepines (van Dongen et al., 2001; Jacobs et al., 2002; Weigang et al., 2005; Sutter et al., 2007b). Muscle MEP thresholds are higher and success rates lower with inhalational anesthesia that is therefore suboptimal (Pelosi et al., 2001; Chen, 2004; Deiner et al., 2010; Simon et al., 2010).

Deepening anesthesia and administering boluses reduces or obliterates muscle MEPs, whereas lightening anesthesia increases them. Stable anesthesia is desirable, but adjustments may be medically indicated and it is necessary to track them.

5.2. Neuromuscular blockade

Neuromuscular blockade is best omitted for muscle MEPs (Deletis, 2002; MacDonald, 2006; Sutter et al., 2007b). Otherwise it must be partial and controlled, which may be difficult and complicates interpretation. Transient NMB is permissible for intubation when neck extension and patient positioning are not critical (Sutter et al., 2007b). When these maneuvers risk cord compression, they are best done without NMB to allow concurrent MEP monitoring.

5.3. Blood pressure

The relationship between blood pressure and MEP amplitude needs careful analysis.

5.3.1. Autoregulation

Brain and spinal cord autoregulation persists under anesthesia and maintains physiological perfusion across a range of mean arterial pressure (MAP), traditionally considered to be 50–60 to 120–150 mmHg (Hickey et al., 1986; Paulson et al., 1990; Strebel et al., 1995; Rasulo et al., 2002). Thus, neurons should get the blood flow they need and their potentials should not get larger or smaller simply because of blood pressure changes within the patient's autoregulation range.

5.3.2. Dysautoregulation

However, the lower limit of autoregulation (LLA) varies from as low as 33 mmHg to rarely, as high as 113 mmHg and some anesthetists recommend that 'average' human LLA should be 70 mmHg (Drummond, 1997; Patel and Drummond, 2010). In addition,

advanced age, hypertension and diabetes may elevate the LLA or dampen autoregulation, rendering tissue perfusion more linearly dependent on MAP (Paulson et al., 1990; Toyoda et al., 1997). Furthermore, preoperative pathology such as arterial stenosis, tumor or compression can derange local autoregulation (Paulson et al., 1990).

Thus, blood pressure becomes critical when too low to maintain adequate perfusion. This can occur with severe hypotension overwhelming autoregulation, or with modest MAP reduction in certain patients with a high LLA or dampened autoregulation. Nervous tissue becomes ischemic and MEPs deteriorate; this effect is usually generalized. Similarly, localized pathologic dysautoregulation can produce localized ischemia and focal MEP deterioration with modest MAP reduction. In both situations, raising blood pressure could restore blood flow and MEPs if ischemia due to insufficient MAP is the primary cause.

5.3.3. Third factors

On the other hand, congruent MAP and MEP amplitude changes do not necessarily imply ischemia. Instead, a third factor having a same-direction effect on both may change. Most commonly, to raise blood pressure anesthetists turn down anesthesia, thereby

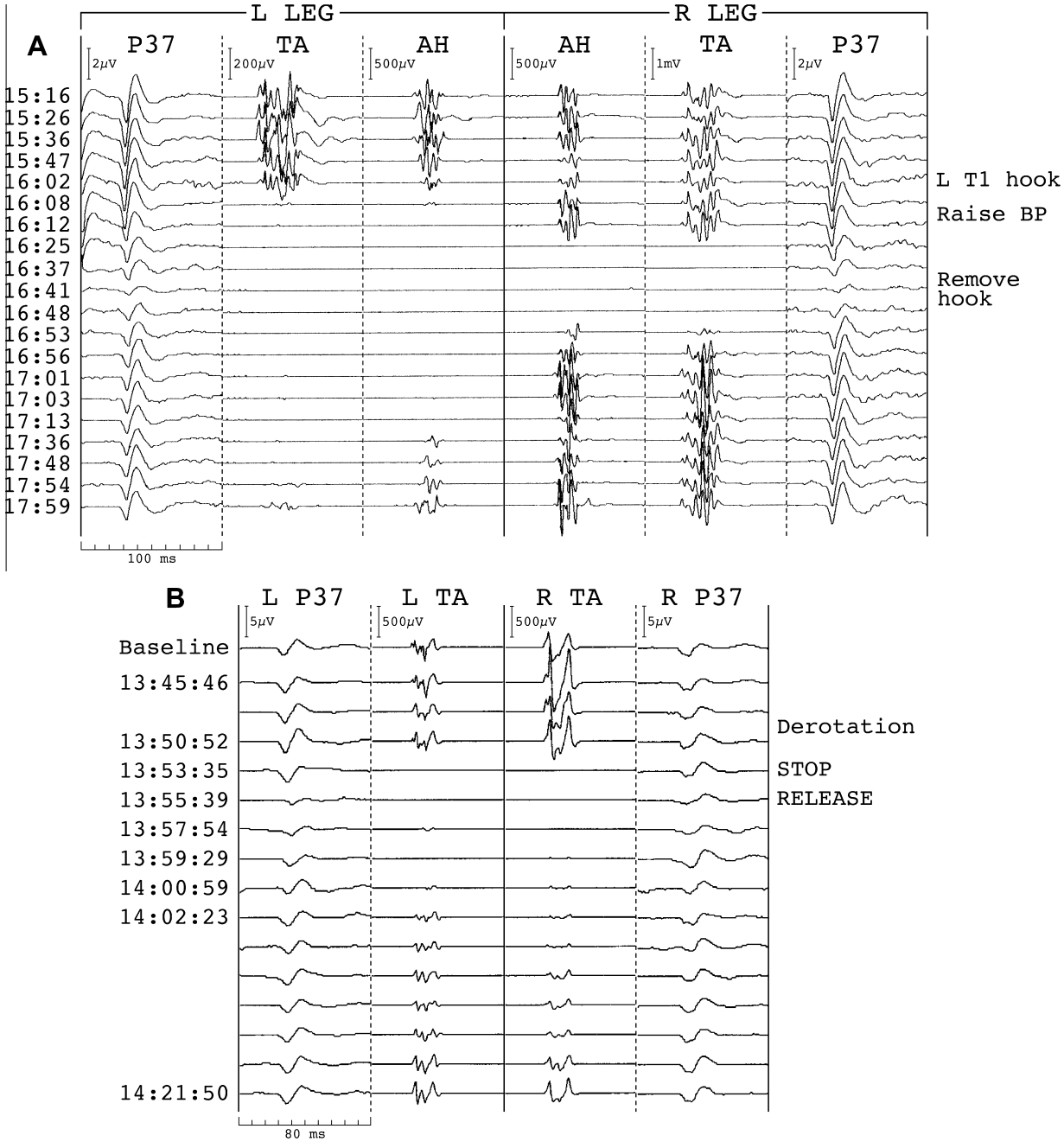

Fig. 12. Two examples of intervention for MEP disappearance during scoliosis surgery. P37, tibial nerve cortical SEP; TA, tibialis anterior; AH, abductor hallucis; BP, blood pressure. In (A), raising blood pressure had no beneficial effect on abrupt left leg MEP loss after sublaminar hook insertion. Instead, deterioration progressed to right leg MEP loss and bilateral SEP reduction. The hook was finally removed and evoked potential restoration followed, but left leg MEP absence was protracted (>40 min) and there was left leg paresis lasting a few days. Immediate hook removal might have been a more effective initial intervention. In (B), immediate instrumentation release without raising blood pressure was quickly followed by restoration of abrupt bilateral leg MEP loss and subsequent SEP deterioration during derotation. There was no deficit. Modified from MacDonald et al. (2007) and MacDonald et al. (2003), with permission.

also increasing MEPs, or to lower blood pressure they increase anesthesia, thereby also reducing MEPs. Some other drugs given to change blood pressure might alter MEP amplitude through neuromodulatory receptor affinity. For example, alpha-2 antagonist or ketanserin antihypertensives can reduce MEPs (de Haan and Kalkman, 2001) and the hypertensive agent phenylephrine might increase them by elevating motor neuron excitability; theoretically, similar considerations might apply to ephedrine or vasopressin (Rekling et al., 2000). Magnesium sulfate reduces blood pressure and might reduce MEPs by potentiating neuromuscular blockade (de Haan and Kalkman, 2001). As a pathophysiologic example, acute spinal cord compression can produce transient hypertension due to a noradrenergic surge that might also transiently increase MEPs above the compressed segment (Eidelberg, 1973; Rawe and Perot, 1979; Young et al., 1980; Guha and Tator, 1988).

5.3.4. Other injury mechanisms

Furthermore, there are other injury mechanisms and an overemphasis on raising MAP in response to MEP deterioration could delay specific intervention. For example, acute spinal cord compression quickly blocks conduction and initiates time-dependent structural damage if unrelieved (Grill, 2005; Carlson et al., 1997). There may also be secondary ischemia and posttraumatic neurogenic hypotension could follow (Guha et al., 1987), but waiting to see the effect of raising MAP may not alleviate the primary cause and could waste valuable time (Fig. 12A). In such circumstances, immediately undoing the implicated surgical maneuver can be effective without raising MAP (Fig. 12B) (MacDonald et al., 2007). It may be reasonable to simultaneously raise MAP, but it could be inadvisable to omit or delay primary treatment. The interpreter tries to decide the most likely cause for MEP deterioration based on the context and directs intervention accordingly.

5.4. Temperature

Modestly low temperatures increase latencies and higher temperatures reduce them. The effect can be generalized according to body temperature, or localized to a limb cooled by exposure or intravenous infusion, or to a spinal cord segment exposed to air or cool irrigation. Deep hypothermia obliterates muscle MEPs (MacDonald and Janusz, 2002).

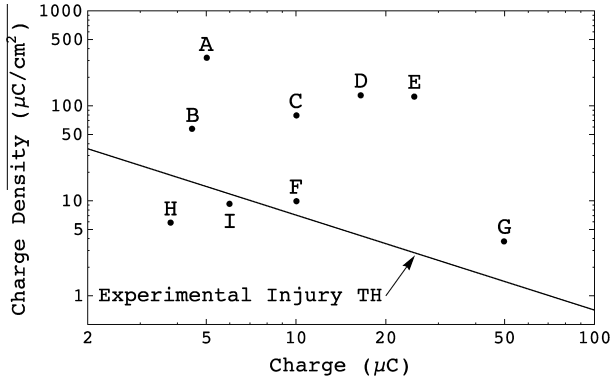

Fig. 13. Maximum published cortical charge (Q) and charge density (QD) of several clinical applications in relation to the excitotoxic injury threshold (TH) in experimental animals. The threshold follows $\log(QD) = 1.85 - \log(Q)$. (A) Penfield method with handheld probe (MacDonald, 2002); (B) Penfield method with subdural grid (Gordon et al., 1990); (C–F) direct cortical stimulation for MEP monitoring (C), Sala and Lanteri, 2003; (D) Szelényi et al., 2005; (E) Yamamoto et al., 2004; (F) Taniguchi et al., 1993); (G) transcranial electroconvulsive treatment (MacDonald, 2002); (H and I) transcranial stimulation for MEP monitoring (MacDonald, 2002).

5.5. Other systemic factors

Other systemic factors are less common but important causes of MEP alteration. Marked positive fluid balance can cause scalp edema that reduces MEPs by interfering with TES (MacDonald and Janusz, 2002). Severe electrolyte disturbances, hypoxemia, hypercapnia, hypocapnia or anemia can produce MEP deterioration.

6. Safety

Intraoperative MEP monitoring is sufficiently safe for clinical use in expert hands using appropriate precautions, but could inadvertently cause harm. Safety issues include hazardous output, bite injuries, seizures, invasive electrode complications, movement-induced injury, arrhythmia, and relative contraindications.

6.1. Hazardous output

There was initially concern that TES could cause excitotoxic, electrochemical or thermal injury of the brain or scalp.

6.1.1. Excitotoxicity

Excitotoxic injury occurs when neurons are damaged by excessive stimulation. Our understanding of excitotoxicity comes from prolonged DCS animal experiments. These apply continuous 50 Hz pulse trains lasting hours and produce histological damage beyond an injury threshold. Pulse charge (Q) and charge density (QD) in $\mu C/cm^2$ are reciprocal cofactors that determine the injury threshold (McCreery et al., 1990; Merrill et al., 2005). Below the threshold, cortex tolerates stimulation indefinitely; above it, damage severity increases with hours of stimulation.

The relevance of these experiments to brief IONM stimuli is questionable. In fact, maximum published Penfield (points A and B, Fig. 13) and DCS MEP parameters (points C to F, Fig. 13) exceed the experimental injury threshold, but appear safe based on the absence of clinical or histological evidence of injury (Gordon et al., 1990; MacDonald, 2002; MacDonald and Deletis, 2008). It may be advisable to stay within published parameters and consider larger electrodes to limit charge density.

The high charge needed for TES could be toxic if applied directly to cortex. However, the scalp and skull disperse charge by about 1:20 (MacDonald, 2002). For perspective, electroconvulsive therapy could produce intracranial charge and charge density above the experimental injury threshold (point G, Fig. 13), but scientific opinion argues against injury. Maximum published TES MEP parameters (points H and I, Fig. 13) should produce intracranial charge and charge density below the experimental injury threshold. Therefore, approved TES stimulators are exceedingly unlikely to cause excitotoxicity, but are inadvisable for DCS.

6.1.2. Electrochemical injury

Electrochemical injury occurs at the electrode-tissue interface and is a therefore a concern with DCS, but not TES. It can occur with >1-ms pulse durations or prolonged monophasic trains; biphasic trains avoid electrochemical injury (Girvin, 1978; Merrill

Table 4
Correlation of TES MEP results to postoperative motor function during intramedullary spinal cord tumor surgery (Deletis, 2002; Kothbauer, 2002; Sala et al., 2006a). Lost signifies disappearance.

D-wave amplitude	Muscle MEP	Postoperative motor function
Preserved	Present	Unchanged
Preserved	Lost	Transient new deficit
>50% reduction or lost	Lost	Permanent new deficit

et al., 2005). Therefore, DCS pulse duration should not exceed 1-ms and Penfield technique should use biphasic pulses (Girvin, 1978; MacDonald and Deletis, 2008). The brief monophasic pulse trains used for DCS MEP monitoring are considered safe (MacDonald and Deletis, 2008).

6.1.3. Thermal injury

Thermal injury could occur if pulse energy were to dissipate too much heat. The very high threshold energy of 0.005–0.015 ms pulses damaged cortex in early animal experiments and this is the basis for a longstanding recommendation that direct cortical pulses have at least 0.1 ms duration (Girvin, 1978).

To avoid scalp burns, TES stimulators should respect the 50 mJ IEC safety limit. In practice, scalp burns have been rare with an estimated 0.01% incidence and might have been due to stray electrosurgery current (MacDonald and Deletis, 2008). Caution is advised when operating high energy short-pulse TES stimulators near maximal intensity.

6.2. Bite injuries

Bite injuries are the most common pulse train TES complication with an estimated 0.2% incidence (MacDonald, 2002; MacDonald and Deletis, 2008). They are caused by jaw muscle contractions likely mediated through corticobulbar pathways and trigeminal nerve and/or jaw muscle stimulation. All published bite injuries involve C3/4 (Jones et al., 1996; Calancie et al., 1998; MacDonald, 2006; Duma et al., 2009). This might be due to common use, but also implies elevated bite injury risk that would match the tendency for C3/4 to generate strong twitches and the proximity of C3/4 to the trigeminal nerves and temporalis muscles. However, one cannot presume that other montages are free of risk.

Most injuries are self-healing tongue or lip contusions or lacerations; some need surgical repair. One jaw fracture and two instances of armored endotracheal tube rupture have been reported (Calancie et al., 1998; MacDonald, 2006; Duma et al., 2009). Soft bite-blocks are a standard precaution, but do not necessarily eliminate injuries (Duma et al., 2009). They may be dental blocks, or rolled-up gauze between the molars. Hard bite blocks might promote tooth or jaw injury. The C3/4 montage may require particular care; other montages might be preferred when effective. Bite injury may be an informed consent consideration.

6.3. Seizures and afterdischarges

Cortical stimulation can incite afterdischarges that may build up to a seizure. A minute or two delay between stimulus and seizure does not exclude causation.

Fifty to 60 Hz trains lasting seconds are particularly epileptogenic (MacDonald, 2002). They are the basis of electroconvulsive therapy and the Penfield technique regularly produces afterdischarges and incites seizures in 5–20% of patients (Sartorius and Wright, 1997).

Seizures are less likely with brief high-frequency pulse trains and have not been reported with single pulses. They are rare with pulse train TES, having an estimated 0.03% incidence; the few reported seizures have been self-limited and free of morbidity (MacDonald, 2002). Direct cortical brief pulse trains have an estimated seizure incidence of 1% (Szelényi et al., 2005).

It is advisable to be prepared for a seizure with anti-convlusants and ice-cold irrigation during DCS. Seizures may be an informed consent consideration.

6.4. Invasive electrode complications

Invasive spinal electrodes carry a small but potentially serious risk of hemorrhagic, traumatic or infectious complications (MacDonald, 2002; MacDonald and Deletis, 2008). D-wave benefits appear to outweigh these risks for IMSCT surgery (Sala et al., 2006a). However, this may not be the case for scoliosis surgery (Ulkatan et al., 2006). Subdural stimulating electrodes slid underneath the skull may cause bleeding, but no morbidity has been reported and the technique might enhance monitoring (Szelényi et al., 2005). There may be other justifiable indications for invasive techniques that may be an informed consent consideration.

6.5. Movement-induced injury

The possibility of injury due to pulse train patient movement is a generally recognized surgical concern, although no adverse events have been reported. There are strategies to minimize or manage movement (MacDonald, 2002; MacDonald and Deletis, 2008): When craniotomy permits, DCS produces focal MEPs with no generalized twitch. C3–Cz, C4–Cz, C1/2 and midline TES montages limit movement compared to C3/4. Near-threshold intensity might help. When disturbing movements remain, one relies on careful timing guided by surgical field video and surgeon communication.

6.6. Arrhythmia

There are rare reports of cardiac arrhythmia with pulse train TES (MacDonald, 2002; MacDonald and Deletis, 2008). There are two theoretical mechanisms: (1) deep current penetration to autonomic centers and (2) a 'parasitic' current pathway through scalp SEP electrodes to leg electrodes via the headbox and then through the heart on the way back to the head (Journée, 2003; MacDonald and Deletis, 2008). Strategies to limit current penetration and the use of separate head boxes for scalp and leg leads to limit parasitic current may be advisable. It is also advisable to be alert for arrhythmia and differentiate it from TES artifact in the ECG (MacDonald and Deletis, 2008).

6.7. Relative contraindications

Relative TES contraindications include epilepsy; cortical lesions; skull defects; intracranial vascular clips, shunts, or

Table 5
Correlation of muscle MEPs to motor outcome during supratentorial and posterior fossa surgery (Neuloh et al., 2008). Deterioration signifies >50% amplitude reduction or reduction clearly below earlier amplitudes when preceding trial-to-trial variability is more than 50%; loss signifies disappearance.

Muscle MEPs	Postoperative motor function		
	Permanent new deficit	Transient new deficit	No new deficit
Unaltered	Never	Never	Always
Reversible deterioration or loss	Rare	Frequent	Frequent
Irreversible deterioration	Frequent	Frequent	Rare
Irreversible loss	Always	Never	Never

electrodes; and pacemakers or other implanted bioelectric devices (MacDonald, 2002; MacDonald and Deletis, 2008). There is no proof that any of them increase TES complications and many patients with one or more of these conditions have undergone uneventful MEP monitoring. One applies risk–benefit analysis: if the risk of motor deficit without MEP monitoring outweighs the uncertain additional risk of a relative contraindication, then it is justifiable to proceed with informed consent.

7. Indications

Indications for MEP monitoring include any surgery risking motor system injury. However, patients with chronic paralysis and no useful function are unlikely to benefit (Kombos et al., 2003; Sala et al., 2006a; Chen et al., 2007; MacDonald et al., 2007). The most common indications arise during neurosurgical, orthopedic and vascular interventions.

Neurosurgical indications include tumor or epileptic focus resections near the motor cortex or corticospinal tract, intracranial aneurysm clipping, posterior fossa surgery, craniocervical junction and spinal operations, spinal cord procedures and tethered cord or cauda equina surgeries (Taniguchi et al., 1993; Deletis, 2002; Kombos et al., 2003; Sala and Lanteri, 2003; Neuloh et al., 2004, 2010; Yamamoto et al., 2004; Dong et al., 2005; Sala et al., 2006a; Szelényi et al., 2005, 2006, 2007). Orthopedic indications include spinal deformity or fracture surgery, vertebral tumor resections, and anterior cervical discectomy (MacDonald et al., 2008). Vascular indications include descending aortic procedures, spinal arteriovenous malformation interventions and carotid endarterectomy (Niimi et al., 2004; MacDonald and Dong, 2008; Malcharek et al., 2013).

8. Correlation with and impact on outcome

The monitoring community is presently accumulating data about the correlation of MEP monitoring to outcome, which is challenged by inherent difficulties in classifying results and requires careful outcome description.

8.1. Classifying results

Test-condition analysis determines the probability that a positive or negative static test (the surrogate) predicts the presence or absence of a static condition (the gold standard). However, this fits poorly because the MEP tests and the motor deficit condition are dynamic and assessed at different times. Intraoperative MEPs cannot be defined as motor condition and postoperative motor condition does not necessarily equate to its intraoperative state, and can also change from early to later periods.

Unchanged MEPs could be true negative when there is no deficit and false negative when there is. However, they could be true negative for monitored structures (e.g., spinal cord) and false negative for unmonitored deficits (e.g., radial nerve palsy). Similarly, *irreversible* MEP deterioration could be true positive when there is a deficit and false positive when there is not, but there might still be unmonitored structure discrepancies.

It is impossible to suitably classify *reversible* MEP deterioration. It cannot be classified reversible true positive because motor condition is unknown at the time. It might be true positive when there is a postoperative deficit and false positive when there is not. However, it is never known whether such a false positive truly indicated reversible deficit – in which case 'false' is unsatisfactory. This dilemma is compounded by evidence that deficits may be more likely with protracted (e.g., >40 min) than quickly reversible MEP deterioration (e.g., Fig. 12) (Calancie et al., 1998; MacDonald et al., 2007; MacDonald and Dong, 2008).

Thus, if test-condition analysis is applied, there might be separate analyses for quickly reversible, protracted reversible and irreversible MEP deterioration with careful explanations (e.g., MacDonald et al., 2007). Alternatively, one might simply report the incidence of monitored and unmonitored deficits with unchanged MEPs and the three types of deterioration (e.g., Neuloh et al., 2008).

8.2. Outcome description

Anatomical localization and grading of deficits is encouraged. Early outcome is important, but might be subject to cursory assessment overlooking minor deficits or overemphasis of mild weakness influenced by pain and/or sedation. Including intermediate and long-term outcome is encouraged because they are more objectively assessable and relevant to patients' lives and because some early deficits resolve. Delayed postoperative deficits should be identified as a monitoring limitation.

8.3. Outcome correlations

8.3.1. D-waves

There is consistent evidence that D-waves correlate with long-term postoperative motor function in IMSCT surgery (Table 4) (Deletis, 2002; Kothbauer, 2002; Sala et al., 2006a) and peri-rolandic brain surgery (Yamamoto et al., 2004; Fujiki et al., 2006).

8.3.2. Muscle MEPs

Available evidence indicates that intraoperative muscle MEPs show good although imperfect correlations to early postoperative motor function. This is true for IMSCT surgery (Table 4) (Deletis, 2002; Kothbauer, 2002; Quiñones-Hinojosa et al., 2005; Sala et al., 2006a), orthopedic spine surgery (Calancie et al., 1998, 2001; Langeloo et al., 2003; Costa et al., 2007; MacDonald et al., 2007; Schwartz et al., 2007; Sutter et al., 2007a), descending aortic surgery (van Dongen et al., 2001; MacDonald and Janusz, 2002; Dong et al., 2002; Jacobs et al., 2002; Weigang et al., 2005; MacDonald and Dong, 2008), spinal cord monitoring in general (Nuwer et al., 2012), supratentorial and posterior fossa surgery (Table 5) (Kombos et al., 2003; Neuloh et al., 2004, 2007, 2008, 2009, 2010; Quiñones-Hinojosa et al., 2004; Szelényi et al., 2010), and facial nerve monitoring (Dong et al., 2005; Fukuda et al., 2008).

8.4. Impact on outcome

Most reports cited in section 8.3 contain examples of reversible MEP deterioration with no new motor deficits that provide circumstantial evidence for injury prevention. They also contain consistent evidence that muscle MEP deterioration often occurs before and sometimes without SEP changes. This suggests a greater chance for early detection, intervention and motor deficit prevention.

Proving a positive impact on outcome will be more difficult because of practical and ethical barriers to randomized clinical trials (Sala et al., 2006a). Nevertheless, convincing evidence could be obtained from surveys, systematic reviews, meta-analyses or case-control studies. A well-designed historical case-control study of IMSCT surgery demonstrated significantly better long-term outcome with combined muscle MEP/D-wave monitoring compared to no monitoring (Sala et al., 2006a). Also, a review of descending aortic surgery provided evidence for reduced paraplegia rates with muscle MEP monitoring compared to other monitoring techniques or unmonitored surgery (MacDonald and Dong, 2008).

9. Interpretation and criteria

9.1. Confounding factors

Confounding factors may cause MEP reduction or loss and need to be considered before attributing deterioration to surgical compromise. Rostral or contralateral control MEPs can help identify some of these factors (MacDonald et al., 2003, 2007).

Gradual generalized MEP reductions suggest systemic factors such as anesthesia or fade (MacDonald and Janusz, 2002; MacDonald et al., 2003, 2007, 2008; Lyon et al., 2005; MacDonald, 2006). More abrupt generalized reduction may be seen with stimulus failure, drug boluses, abrupt hypotension, NMB or bilateral intracranial air during sitting position posterior fossa surgery. Cortical SEP and EEG traces can provide clues about systemic changes. Train-of-four testing identifies NMB. Scalp examination discloses pitting edema. Skull X-ray identifies intracranial air.

Focal MEP deterioration is the hallmark of surgical neurologic compromise, but can also be due to localized confounding factors (MacDonald, 2006; MacDonald et al., 2007). For example, caudal D-wave amplitude reduction could be caused by downward electrode displacement; a shift to longer peak latency would suggest this. In addition, straightening a scoliotic spine can produce spurious thoracic epidural D-wave reduction of up to 70% (Fig. 14) (Ulkatan et al., 2006). This has been attributed to increased spinal cord-electrode distance as the cord's position shifts within the newly straightened spinal canal.

Confounding focal muscle MEP deterioration can be caused by brachial plexus or peripheral nerve conduction failure due to shoulder malpositioning or limb pressure or ischemia (MacDonald and Janusz, 2002; MacDonald et al., 2003, 2007). Peripheral SEPs can help to identify these problems (MacDonald et al., 2007, 2008). Confounding lateralized deterioration could be caused by asymmetric intracranial air during sitting position posterior fossa surgery; skull X-ray can demonstrate it. With DCS, one has to consider displacement of the stimulating electrode away from motor cortex.

Some confounding factors are potentially injurious, such as severe hypotension or causes of peripheral conduction failure. Correcting these problems might prevent injury.

9.2. D-wave interpretation

Because the standard deviation of trial-to-trial D-wave amplitude variation is only 8%, interpretation based on amplitude change is relatively straightforward (Burke et al., 1995). D-wave preservation provides good evidence for corticospinal tract integrity. However, it does not necessarily exclude (1) corticomotor neuron failure or cortical I-wave circuit disruption, (2) Conduction failure above the intracranial corticospinal axon activation site or below the recording electrode, (3) LMN failure, (4) peripheral conduction failure, (5) worsening of an antecedent hemiparesis if TES D-waves come predominantly from the healthy side, or (6) delayed post-operative motor deficits (Deletis, 2002; MacDonald, 2006).

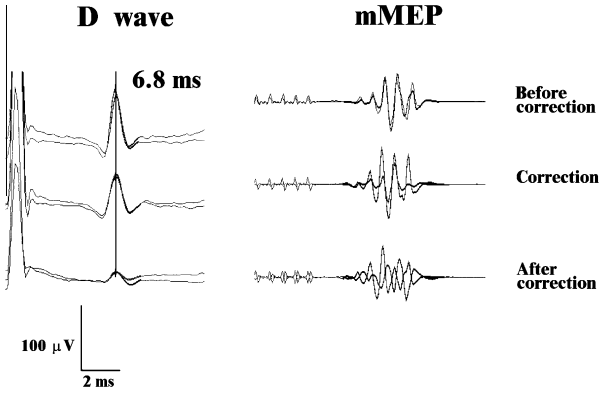

Fig. 14. Spurious D-wave reduction following scoliosis correction. There was no leg muscle MEP (mMEP) deterioration or motor deficit. An increase of spinal cord-epidural recording electrode distance due to vertebral column straightening might explain this result. Modified from Ulkatan et al. (2006), with permission.

D-wave reduction unexplained by confounding factors indicates partial corticospinal tract conduction failure above the recorded level (Deletis, 2002). The warning criterion for IMSCT surgery is 50% reduction because this appears to be critical for long-term motor outcome based on retrospective studies (Deletis, 2002; Kothbauer, 2002; Sala et al., 2006a). The criterion for peri-Rolandic surgery with DCS cervical D-wave monitoring is 30–40% reduction for the same reason (Yamamoto et al., 2004; Fujiki et al., 2006).

A 20–30% reduction criterion was an early recommendation for scoliosis surgery based on simultaneous D-wave and spinal SEP recordings from the same electrode to guard against false positives (Burke et al., 1992; Burke and Hicks, 1998; Burke, 2008). However, Iwasaki et al. (2003) recommended 50%, Sutter et al. (2007a) did not specify a criterion and Ulkatan et al. (2006) observed spurious >50% reductions after curve correction. Consequently, there is presently no consistent criterion for scoliosis surgery.

9.3. Muscle MEP interpretation

Variability, anesthetic vulnerability, fade and high sensitivity make muscle MEP interpretation more difficult and controversial (MacDonald, 2006). One difficulty involves guarding against false results. Another difficulty consists of the variety of proposed criteria and evidence that different criteria may be needed for different monitoring situations.

9.3.1. Avoiding false results

Possibly due to high muscle MEP sensitivity, false negatives are infrequent in expert hands and usually due to limitations, such as injuries of unmonitored peripheral nerves or single roots and delayed postoperative deficits (MacDonald et al., 2007; Sutter et al., 2007a). Thus, it is advisable to avoid making predictions about inadequately monitored structures or postoperative complications and to ensure that surgeons are aware of these limitations.

Disastrous false negatives are exceedingly rare (Nuwer et al., 2012). One report of false negative paraplegia (Modi et al., 2009) was due to technical and interpretive errors of inadequate personnel using a semi-automated IONM device (Lieberman et al., 2010a,b). Expertise and proper instrumentation are likely to guard against such disasters.

False positive irreversible MEP deterioration is uncommon in expert hands. However, a few IMSCT patients have had irreversible disappearance without new weakness (Kothbauer, 2002). In addition, some false positives have been reported with amplitude (Langeloo et al., 2003) or threshold criteria (Calancie and Molano, 2008). In an atypical report, Kim et al. (2007) found that five of six irreversible MEP disappearances during cervical myelopathy surgeries were false positive. However, they used inhalational anesthetics and exclusive C1/2 TES, had no neurophysiologist and did not recognize or adjust for fade that particularly affects myelopathic patients. This report may underscore the importance of expertise and optimal methodology that are likely to guard against false positives, and illustrates a concern that inhalational anesthesia might promote them.

False positives are serious from a surgical point of view because they could interfere with surgical treatment and undermine surgeons' confidence in MEP alerts, possibly leading to disastrous failure to intervene for truly pathological MEP deterioration.

Interpretive criteria might also influence false results. It is advisable to select criteria appropriate for the type of surgery based on published evidence. A sense of responsibility not only for avoiding deficits, but also for helping to achieve successful surgical treatment without undue monitoring interference is recommended.

9.3.2. Mechanisms of pathological muscle MEP deterioration

Pathologic muscle MEP deterioration could be caused by several mechanisms, including (1) cortical I-wave circuit disruption, (2) corticomotor neuron failure, (3) corticospinal tract conduction failure, (4) background facilitation system disruption, (5) LMN failure, and (6) peripheral conduction failure.

9.3.3. Muscle MEP interpretive criteria

9.3.3.1. Preservation. Preservation (no appreciable deterioration) generally makes new weakness unlikely. However, there are limitations, including injury above the intracranial activation site, radiculopathy, mild facial nerve injury, unmonitored peripheral nerve injury and delayed postoperative motor deficits (Dong et al., 2005; MacDonald, 2006; Szelényi et al., 2006; MacDonald et al., 2007).

9.3.3.2. Presence. The presence of a muscle response indicates a functional connection between the motor tract activation site and muscle. This makes *paralysis* unlikely, subject to the limitations noted for preservation. However, it does not exclude *paresis* due to partial injuries of the brain, brainstem, facial nerve, roots or peripheral nerves. There is contradictory spinal cord data: some studies report that consistently present MEPs exclude new spinal cord motor deficits (Deletis, 2002; Dong et al., 2002; Kothbauer, 2002; MacDonald and Janusz, 2002; Sala et al., 2006a; Ulkatan et al., 2006; MacDonald et al., 2007; MacDonald and Dong, 2008), while others find that deterioration of still-present MEPs can correlate with partial cord injury and weakness (Langeloo et al., 2003, 2007; Quiñones-Hinojosa et al., 2005; Calancie and Molano, 2008). This discrepancy is currently unresolved.

9.3.3.3. Disappearance. Disappearance is the visual loss of a response at the same display sensitivity that had contained consistently present MEPs and is always a major alarm criterion because irreversible disappearance is a strong predictor of new weakness, although not necessarily severe or permanent (Kothbauer, 2002; Quiñones-Hinojosa et al., 2005; Sala et al., 2006a; MacDonald et al., 2007).

Disappearance as the main warning criterion has been proposed only for spinal cord monitoring. This is based on (1) variability that challenges other criteria, (2) high sensitivity to central motor disturbances, (3) the likelihood that pathophysiology will affect many corticospinal axons because the tract is very small in the spinal cord, and (4) the rapid failure of ischemic LMNs. In fact, abrupt disappearance is frequent compared to other evoked potentials and is commonly the first spinal cord warning sign, although can be preceded by retrospectively apparent deterioration (Figs. 3 and 12) (MacDonald and Janusz, 2002; Calancie and Molano, 2008; MacDonald et al., 2007).

Several reports support disappearance as sufficiently specific and sensitive for IMSCT, descending aortic and orthopedic spine surgery and there are many published examples of reversible disappearance with no deficit (Deletis, 2002; Dong et al., 2002; Kothbauer, 2002; MacDonald and Janusz, 2002; Sala et al., 2006a; MacDonald et al., 2007; MacDonald and Dong, 2008). The critique supported by some other reports is that partial cord injury may cause deterioration without disappearance (Langeloo et al., 2003, 2007; Quiñones-Hinojosa et al., 2005; Calancie and Molano, 2008). Again, this discrepancy is currently unresolved.

9.3.3.4. Amplitude reduction. Criteria based on peak-to-peak amplitude falling below a percentage of a baseline have been proposed for all types of monitoring. Criticisms point to variability, systemic sensitivity and fade that make it unclear how or when to select a valid baseline and how to identify a pathological decrement. There is no agreement on limits that range from >50% to >80%, and even an 80% limit produces false positives in expert hands (van Dongen et al., 2001; Jacobs et al., 2002; Langeloo et al., 2003, 2007; Dong et al., 2005; Schwartz et al., 2007; Neuloh et al., 2008; Szelényi et al., 2010).

Efforts to mitigate these problems include selecting representative or average baselines, requiring consistent reduction over several trials, including control recordings and emphasizing focal amplitude decrements. An unquantified approach applies unequivocal decrement clearly exceeding trial-to-trial variability: with high variability, only disappearance may be unequivocal, but with less variability an amplitude decrement may be obvious (MacDonald et al., 2003).

9.3.3.5. Threshold elevation. Criteria based on threshold (TH) reaching or exceeding a predefined limit above baseline have been proposed for several types of monitoring. The theoretical basis is that the largest corticospinal axons have lowest TH and greatest susceptibility to damage so that TH elevation should provide highest sensitivity (Calancie et al., 1998).

The most developed TH criterion consists of a 100 V or greater elevation, using 3–4 C3/4 constant-voltage 0.05 ms pulses with a 2-ms ISI and propofol/opioid/nitrous oxide anesthesia without NMB (Calancie et al., 1998, 2001). The largest series reported 100% sensitivity and 99.7% specificity for early postoperative weakness in orthopedic and neurosurgical spine surgeries (Calancie and Molano, 2008). Threshold elevation correlated with mild weakness, while concurrent or delayed disappearance correlated with greater weakness. Two of 93 elevations were false positive.

There are technical critiques: Testing TH takes about a minute, which delays feedback compared to other methods. Proportional increase varies with each muscle's baseline TH and percentage elevation has not been evaluated. Other pulse and train parameters that affect TH must be kept constant and it is unclear how to translate the criterion to other methods.

Other critiques consider factors that could undermine TH tracking: Thresholds exhibit some variability (Calancie et al., 1998), are higher with inhalational anesthesia than TIVA and increase with anesthetic depth (Simon et al., 2010). Also, fade can gradually increase THs by 100 V or more without injury, especially in myelopathic patients (Lyon et al., 2005).

Based on the published results, one would expect more false negatives than have been reported with other criteria and this discrepancy is presently difficult to reconcile. In addition, since very sensitive tests generally produce more false positives, the high specificity may seem surprising.

9.3.3.6. Morphology simplification. A criterion based on long-duration polyphasic to short-duration biphasic morphology simplification has been described in one IMSCT study (Quiñones-Hinojosa et al., 2005). The theoretical basis is that pathologic loss of motor units could reduce polyphasia without affecting amplitude. The study used C1/2 constant-voltage 0.05 ms pulses, facilitation, 2–3 trial averaging, desflurane/propofol/opioid anesthesia without NMB, 2.8–4 ms ISI and 6–8 pulse trains to produce long-duration polyphasic MEPs. Alarm criteria were acute simplification with 100 V or greater TH elevation, or disappearance.

Morphology simplification with TH elevation correlated to mild early weakness and long-term recovery. Disappearance correlated to greater early and long-term weakness including paralysis, but mild weakness and recoveries were also observed. There were

two false negatives for unmonitored muscles, but no false positives. A high 43% subtotal resection rate suggests that some removals may have been prematurely stopped by the criteria.

Critiques point to factors that could undermine morphology tracking: Muscle MEP morphology differs between patients and muscles and varies with stimulus parameters (MacDonald, 2006; Langeloo et al., 2007). Spontaneous variability can include polyphasic/biphasic shifts and some MEPs are biphasic from the start (Langeloo et al., 2007). Finally, amplitude decrements without morphology change have been reported during orthopedic surgery and with nerve root injury (Langeloo et al., 2003; MacDonald et al., 2012).

9.3.4. Monitoring situations

Based on available evidence, different MEP criteria may be needed for different situations. The goals of monitoring include helping to prevent deficits without unnecessarily compromising surgical treatment. To this end, criteria should be neither overly specific nor overly sensitive for the circumstances.

9.3.4.1. Intramedullary spinal cord tumor surgery. Because complete IMSCT removal can determine survival, early paralysis may be acceptable if long-term recovery ensues. Thus, the goals of monitoring are to help avoid long-term deficits, while not unnecessarily limiting resection. Combined muscle MEP and D-wave monitoring is recommended because it improved long-term outcome without limiting tumor removal (only 24% subtotal) in a historical case control study and no similar efficacy data presently exist for other monitoring techniques (Deletis, 2002; Kothbauer, 2002; Sala et al., 2006a). When D-waves are unavailable, one must rely on muscle MEPs while realizing that even their disappearance is compatible with good long-term function.

The following criteria are recommended on the basis of current evidence: (1) >50% D-wave reduction is a major criterion mandating restorative efforts and can justify stopping resection. (2) Muscle MEP disappearance is a major criterion mandating restorative efforts, but resection may continue while D-wave amplitude remains above 50%; irreversible disappearance can justify stopping if D-waves are unavailable. (3) Depending on the monitoring program's technique and experience, marked muscle MEP amplitude reduction, acute TH elevation or morphology simplification could be minor criteria prompting restorative efforts, but might not justify stopping resection and might increase false positives.

9.3.4.2. Orthopedic spine surgery. The main goal of monitoring during orthopedic spine surgery is to help avoid cord injury while not unnecessarily compromising the patient's surgical result. Based on current evidence (Langeloo et al., 2003, 2007; MacDonald et al., 2003, 2007; Calancie and Molano, 2008), the following muscle MEP criteria can be recommended: (1) Disappearance is a major criterion mandating restorative efforts, including undoing surgical maneuvers and modifying or even abandoning instrumentation. (2) Depending on the monitoring program's technique and experience, marked amplitude reduction or acute TH elevation could be moderate criteria prompting restorative efforts, but might not justify major surgical modifications and might increase false positives. There are currently no published studies of morphology criteria for orthopedic surgery.

9.3.4.3. Descending aortic surgery. The goal of monitoring descending aortic surgery is to help avoid spinal cord infarction. Based on current evidence (MacDonald and Dong, 2008), the following muscle MEP criteria are recommended: (1) Disappearance is a major criterion mandating efforts to restore perfusion or limit the effects of ischemia. (2) Depending on the monitoring program's technique and experience, marked amplitude reduction could be a moderate criterion prompting restorative efforts, but might increase false positives. There is no published support for TH or morphology criteria.

9.3.4.4. Supratentorial and brainstem surgery. The goals of monitoring supratentorial and brainstem surgery include localizing motor cortex, judging proximity to subcortical corticospinal fibers and helping avoid motor deficits while not unnecessarily compromising surgical treatment.

For cortical mapping, lowest MEP TH reliably localizes motor cortex (Taniguchi et al., 1993; Cedzich et al., 1996; Kombos et al., 2003, 2009; Sala and Lanteri, 2003; Sala et al., 2006b; Neuloh et al., 2004, 2008, 2009; Szelényi et al., 2006, 2010, 2011; Simon et al., 2010). For subcortical mapping, muscle MEP TH is approximately 1 mA per mm distance to the corticospinal tract using trains of five monopolar 0.2–0.5 ms pulses and 3–4 ms ISI (Kamada et al., 2009; Nossek et al., 2011; Szelényi et al., 2011).

For monitoring DCS cervical D-waves, >30–40% amplitude reduction is a major criterion (Yamamoto et al., 2004; Fujiki et al., 2006). For muscle MEP monitoring, major criteria include disappearance or consistent >50% amplitude reduction when trial-to-trial variability permits, or consistent reduction below earlier amplitudes when variability exceeds 50% (Neuloh et al., 2004, 2008, 2009; Szelényi et al., 2006, 2010, 2011). Acute TH elevation might be relevant (Quiñones-Hinojosa et al., 2004; Szelényi et al., 2010). There is no published support for morphology criteria.

The reason for different muscle MEP criteria than for spinal cord monitoring might be the large size of cortical and superficial subcortical motor structures making partial injury and moderate deterioration more likely. Lesions of the smaller corticospinal tract at the internal capsule might cause more dramatic deterioration similar to the spinal cord. This hypothesis is supported by MRI evidence that superficial lesions generally reduce amplitude whereas deep lesions typically cause disappearance (Szelényi et al., 2010).

9.3.4.5. Facial nerve monitoring. Facial nerve MEP monitoring aims to compliment EMG techniques by providing a surgeon-independent test of facial nerve integrity (Fig. 15). Based on available evidence, major criteria include disappearance or consistent >50% amplitude reduction when preceding stability permits, or consistent reduction below earlier amplitudes when variability exceeds 50% (Akagami et al., 2005; Dong et al., 2005; Liu et al., 2007; Fukuda et al., 2008; Matthies et al., 2011). There is no published support for TH or morphology criteria.

This situation differs from central motor pathway or nerve root monitoring because the intraoperative injury is distal to the LMN and the facial nerve is the only nerve supplying the recorded muscle. Consequently, amplitude reduction approximately proportional to the number of damaged motor axons might be anticipated. In fact, greater reductions correlate with greater facial weakness likelihood and severity. However, facial MEPs test a subpopulation of motor axons and partial injuries could affect axons that may or may not have been contributing to the response. Thus, correlations are imperfect. For example, preservation does not exclude mild weakness and disappearance does not necessarily predict paralysis.

9.3.4.6. Nerve root monitoring. Section 3.2.11 discusses the difficulties of predicting nerve root integrity with muscle MEPs. Nerve root injuries can cause myotomal MEP amplitude reduction (Sutter et al., 2007a,b; Lieberman et al., 2008; Mok et al., 2008; MacDonald et al., 2012). However, due to radicular innervation overlap, limited sampling, confounding factors and variability the effects range from none to variable amplitude reduction to disappearance and

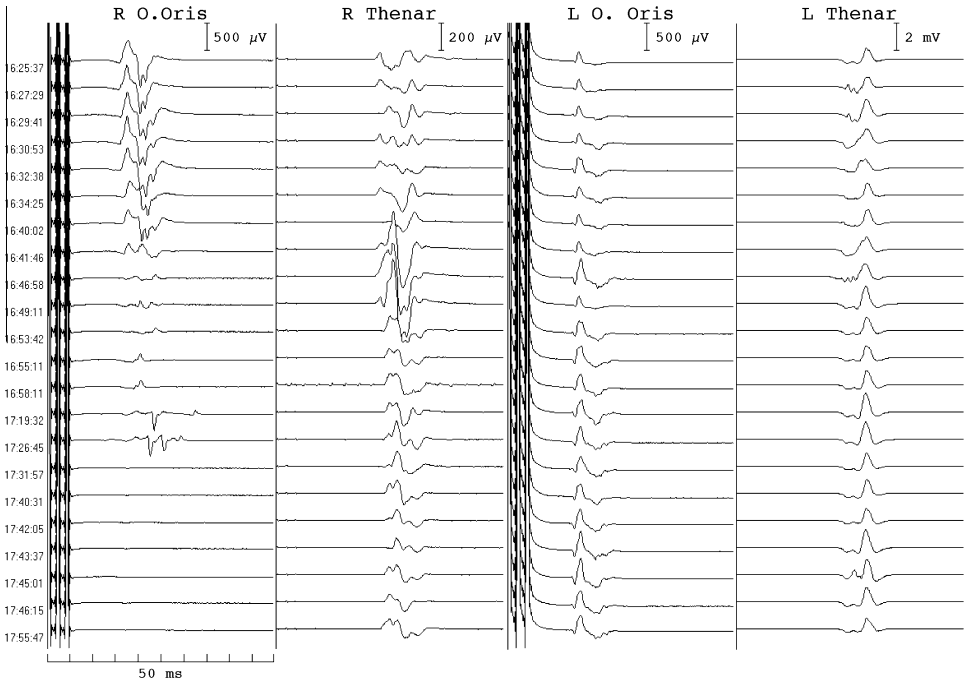

Fig. 15. Facial MEPs during right acoustic neuroma surgery under propofol/opioid anesthesia. O. Oris, orbicularis oris. C3–Cz and C4–Cz TES with three 0.5-ms pulses and 2-ms ISI. Abrupt right facial MEP reduction during tumor resection prompted restorative efforts (pause, irrigation) that were followed by partial amplitude restoration, but irreversible disappearance followed further resection. There were no free-running EMG discharges. The patient had complete facial palsy with partial recovery beginning at 9 months. From MacDonald (2006), with permission.

some false results are expected (MacDonald et al., 2012). There is no established criterion.

10. Staffing and credentials

Based on consensus expert opinion and clinical evidence (Section 9.3.1), personnel doing MEP monitoring should have appropriate education, training, experience and qualifications (Isley and Pearlman, 2006; Sutter et al., 2007b). A professional level person (physician or Ph.D. neurophysiologist) should be responsible for supervision and interpretation and a technical level person can perform acquisition.

Relevant certification is recommended according to community norms for acceptable practice in each country. The development of specific IONM credentials where none presently exist may be a consideration. As potentially useful models, the American Board of Clinical Neurophysiology and the American Board of Neurophysiologic Monitoring offer professional IONM certification, and the American Board of Registration for Electroneurodiagnostic Technologists offers technical IONM certification. These (or equivalent) credentials are recommended in the US; interested international candidates may be eligible.

Continuing education and the development of institutional MEP monitoring policies and procedures are also recommended.

11. Documentation

Documentation should comply with hospital and governmental record retention policies. It is advisable to include demographic data, diagnosis and preoperative neurologic status, type of surgery, equipment, procedures and personnel, waveforms, anesthetic agents and levels, relevant physiological variables, MEP warnings, interventions, and clinical outcome, if known. A timely written report prepared by the responsible interpreter should be entered in the medical record and is generally a hospital requirement.

12. Evidence and recommendation definitions

Quality of evidence and strength of recommendation ratings are based on clinical and scientific evidence and expert opinion (Leppanen, 2005).

12.1. Quality of evidence

Class I: One or more well-designed, prospective, blinded, controlled studies.

Class II: One or more well-designed, clinical studies such as case control, cohort studies, etc.

Class III: Expert opinion, non-randomized historical controls or case reports.

12.2. Strength of recommendation

Type A: Strong positive recommendation based on Class I, or overwhelming Class II evidence.

Type B: Positive recommendation based on Class II evidence.

Type C: Positive recommendation based on strong consensus Class III evidence.

Type D: Negative recommendation based on inconclusive or conflicting Class II evidence.

Type E: Negative recommendation based on evidence of ineffectiveness.

Type U: No recommendation, based on divided expert opinion or insufficient data.

12.3. Practice option

A practice option is a patient management strategy for which there is favorable evidence, but which the community still considers an option to be decided upon by individual practitioners.

13. Summary recommendations

A. Appropriately qualified personnel should acquire and interpret intraoperative MEPs (Class III, Type C).
B. Intraoperative MEP techniques are sufficiently safe for clinical use in qualified hands using appropriate precautions (Class II and III, Type B).
C. Intraoperative MEPs are an established practice option for localizing motor cortex, judging subcortical proximity to corticospinal tract fibers and monitoring motor pathways during surgical procedures that risk motor system injury in the brain, brainstem, spinal cord or facial nerve (Class II and III, Type B).
D. Total intravenous anesthesia usually based on propofol and opioid infusion is optimal for muscle MEP monitoring. Benzodiazepines, ketamine and etomidate may be suitable intravenous alternatives. Inhalational anesthetic agents are suboptimal and discouraged unless medically necessary. This does not exclude the development of new anesthetic protocols. (Class II and III, Type B).
E. Interpretation should consider limitations and confounding factors (Class III, Type C):
   1. Commonly used anesthetic drugs, physiological parameters and other confounding factors affect MEPs. Monitoring should include tracking of anesthetic dosages and physiological parameters, and rostral or contralateral control MEPs when possible.
   2. Muscle MEPs exhibit substantial intrinsic variability and a tendency to gradual amplitude fade and threshold elevation.
   3. Intraoperative MEPs cannot predict motor deficits of inadequately monitored structures or arising postoperatively.
F. Warning criteria for D-waves are based on amplitude reduction having no apparent confounding factor explanation.
   1. Intramedullary spinal cord tumor surgery: >50% reduction (Class II and III, Type B).
   2. Brain surgery with DCS cervical D-waves: >30–40% reduction (Class III, Type C).
   3. Orthopedic spine and other surgeries: No established criterion (Class III, Type U).
G. Warning criteria for muscle MEPs may need to be tailored to monitoring situations and are based on deterioration clearly exceeding spontaneous variability with no apparent confounding factor explanation.
   1. Spinal cord: Disappearance is always a major criterion (Class II and III, Type B). Depending on the monitoring program's technique and experience:
      i. For IMSCT surgery, marked amplitude reduction, acute threshold elevation or morphology simplification could be additional minor criteria (Class II and III, Type C).
      ii. For orthopedic spine surgery, marked amplitude reduction or acute threshold elevation could be additional moderate criteria (Class II and III, Type C).
      iii. For descending aortic surgery, marked amplitude reduction could be an additional moderate criterion (Class II and III, Type C).
   2. Brain and brainstem: Major criteria include disappearance or consistent >50% amplitude reduction when warranted by sufficient response stability, or amplitude reduction clearly exceeding variability when responses are less stable (Class III, Type C). Acute threshold elevation might be relevant (Class III, Type U).
   3. Facial nerve: Major criteria include disappearance or consistent >50% amplitude reduction when warranted by sufficient response stability (Class III, Type C).
   4. Nerve roots: No established criterion (Class III, Type U).

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