The Performance of Neurophysiologic Monitoring to Predict Postoperative Deficits in a Porcine Model of Spinal Cord Injury

LIU, Quanmeng

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of
Doctor of Philosophy
in
Anaesthesia and Intensive Care

The Chinese University of Hong Kong
September 2010

Thesis/Assessment Committee

Professor Lester Critchley (Chair)

Professor Matthew Chan (Thesis Supervisor)

Professor Leungkim Hung (Committee Member)

Professor Vincent Mok (Committee Member)

Professor Adrian Gelb (External Examiner)

DECLARATION OF ORIGINATION

The work contained in this thesis was carried out by the author in the department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong between September 2007 and May 2010. All work in the thesis is my own original research under the supervision of Professor Matthew Chan. No part of the work described in this dissertation has already been or is being submitted to any other degree, diploma or other qualification at this or any other institutions.

ABSTRACT

Abstract of thesis entitled: **The Performance of Neurophysiologic Monitoring to Predict Postoperative Deficits in a Porcine Model of Spinal Cord Injury**

Submitted by **LIU, Quanmeng**
For the degree of Doctor of Philosophy in Anaesthesia and Intensive Care
At The Chinese University of Hong Kong in June, 2010.

The spinal cord is at risk of injury during complex operations of the spine or aorta, and may result in catastrophic long term disability. Intraoperative monitoring with somatosensory evoked potential (SEP) and transcranial electric motor evoked potential (TceMEP) are commonly performed to assess the integrity of the sensory and motor pathways, respectively. The purpose of this study was to identify the minimum changes in signal amplitudes, beyond which postoperative neurologic deficit may occur.

In a porcine model of direct compression and distraction of the exposed spinal cord, we measured the perioperative changes in SEP and TceMEP. This was correlated with postoperative motor function using the modified Tarlov scale. Magnetic resonance diffusion tensor imaging of the spinal cord was also performed to assess the anatomical extent of injury three days after surgery.

During stable anesthesia, experiments were completed in 31 pigs. A decrease in SEP amplitude > 25% and / or TceMEP amplitude > 65% was associated with substantial risk of postoperative motor deficit. In addition, rapid deterioration of signal within 5 min of an event, and / or a lack of signal recovery within 30 min after the initial deterioration were also predictors of postoperative paraplegia or weakness. These findings also correlated well with radiological changes in the spinal cord. The sensitivity and specificity for TceMEP to predict adverse neurologic outcome were 100% and 90.5%, respectively.

By observing these warning criteria, surgery can be safely carried out if changes of signal amplitudes are within the threshold boundary. Future studies should aim to validate and refine the "warning criteria" for intraoperative neurophysiologic monitoring in different surgery.

CHINESE ABSTRACT (中文摘要)

在關於脊柱和主動脈的復雜手術中，脊髓有損傷的風險，並可以導致災難性的長期殘疾。術中監測如軀體感覺誘發電位（SEP）和經顱電刺激運動誘發電位（TceMEP）常被分別用來評估感覺和運動通路的完整性。本次研究的目的是辨別出信號幅度的最小改變，超過了這個改變則會出現術後的神經功能缺陷。

在豬只的模型中，暴露的脊髓被直接壓迫和牽拉，我們測量圍手術期 SEP 和 TceMEP 的變化。這個變化與基於修正的 Tarlov 評分的術後運動功能聯系起來。脊髓的磁共振彌散張量成像被用來評定手術後三天脊髓解剖結構的損傷範圍。

在穩定的麻醉狀態下，共完成了 31 只豬的實驗。SEP 的幅度降低超過 25% 和/或者 TceMEP 的幅度降低超過 65%，術後有相當大的風險出現運動功能缺陷。此外，某種操作或其他幹預後 5 分鐘內信號的迅速惡化，和/或者最初惡化的 30 分鐘內信號沒有恢復，也是術後癱瘓或者功能弱化的預測因子。這些結果也同脊髓的影像學改變具有很好的關聯性。TceMEP 預測不利神經功能狀態的敏感度和特異度分別為 100% 和 90.5%。

通過觀察確認這些警告標準，如果信號幅度變化在閾值範圍之內，手術則可以安全地進行。未來的研究應該立足於在不同的手術中進一步確認和改進這些術中神經生理監測的警告標準。

ACKNOWLEDGMENT

Firstly, I am grateful to my supervisor, Professor Matthew Chan, for his encouragement, invaluable guidance and continuous support throughout my study. I really appreciate his erudition, diligence, generosity, zealousness and endless patience. I would also like to take this opportunity to express my deepest gratitude to his family for their kindness.

I would like to thank Professor Tony Gin, Chairman of the Department of Anesthesia and Intensive Care, for his support in my research. I thank Professor Christopher Cheng, Department of Biochemistry for his thoughtful guidance. I thank Professor Yixiang Wang, Department of Imaging and Interventional Radiology for his help in the imaging part of the study.

I would like to thank Mr Kevin Leung in the Laboratory Animal Services Centre for their assistance in this complex animal experiment. I would also thank Ms So-so Chang in the electrodiagnostic unit for her teaching in neurophysiology method. I am indebted to my colleagues in the department for their secretarial and technical assistance, especially, Nancy Chung, Ruby Ng, Rebecca Luk, Connie Pang, Janet Ngan, Dora Wong, YH Tam, Bryan Ng, Alex Lee and Thomas Lo.

I am grateful to Drs Heather Ma, Wenzhou Yu and Hong Qiu for their guidance in data analysis. There are also friends and fellow students who have been helping me in my study during the past three years: Ni Wei, Qi Tian, Qing Shang, Amy Meng, Xiaodong Liu, Qinzhou Wang, Sammy Chen, Jason Li and Teresa Hu. This study cannot be accomplished without their help.

Finally, I must express my deepest gratitude to my beloved family, my dearest wife, Wang Lei, my daughter, Helin for their unfailing support. I thank my grandmother, parents and dearest brother, who are willing to help me in all aspects at any time.

This study was supported, in part, by a research grant (10/025) of the Australian and New Zealand College of Anaesthetists and an academic equipment grant from the Chinese University of Hong Kong (#3029499). The project was awarded the Harry Daly Research Fellowship by the Australian and New Zealand College of Anaesthetists.

TABLE OF CONTENTS

LIST OF TABLES

Appendix

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADC	Apparent diffusion coefficient
ASNM	American Society of Neurophysiological Monitoring
CI	Confidence intervals
CMAP	Compound muscle action potential
DTI	Diffusion tensor (magnetic resonance) imaging
EEG	Electroencephalogram
$ETCO_2$	End-tidal carbon dioxide
FA	Fractional anisotropy
FOV	Field of view
Hz	Hertz
IoC	Index of consciousness
ISI	Interstimulus interval
LASEC	Laboratory Animal Services Centre
MEP	Motor evoked potential
mFFE	multi-echo fast field echo
ml/kg/h	Millilitre per kilogram per hour
MRI	Magnetic resonance imaging
NPV	Negative predictive value
NR	Not reported
NSA	Number of signals averaged
PPV	Positive predictive value
SEP	Somatosensory evoked potential
SPSS	Statistical Package for the Social Sciences
SS-EPI	Single shot echo-planar imaging
T	Tesla
TceMEP	Transcranial electrical motor evoked potential
TE	Echo time
TR	Repetition time
TSE	Turbo spin-echo
µg/kg	Microgram per kilogram
µg/kg/h	Microgram per kilogram per hour
µg/kg/min	Microgram per kilogram per minute

PART 1 INTRODUCTION

Chapter 1. Intraoperative Neurophysiologic Monitoring

The spinal cord is at risk of injury during correction of complex spinal deformities, resection of intramedullary spinal cord tumor, and repair of aortic aneurysm. Although intraoperative spinal cord injury is considered uncommon (0.2-1.0 %), the consequence of severe postoperative neurologic deficit is devastating (Chan et al., 2004). Damage of the spinal cord may result in complete paraplegia or partial limb weakness, leading to long term disabilities (Chiodo et al., 2007; Dobkin and Havton, 2004; Priebe et al., 2007), and patient sufferings (Kelleher et al., 2008; Nuwer et al., 1995; Schwartz et al., 2007; Smith et al., 2007). Since repair of the spinal cord injury has long been regarded as difficult, if not impossible; a monitoring technique that can detect impending injury will be invaluable. Appropriate interpretation of these monitoring signals will guide surgical decisions, and allow surgeons to perform timely surgical interventions before permanent damage occurs.

Intraoperative neurophysiologic monitoring with somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) are widely practiced in spinal surgery (Devlin and Schwartz, 2007; Pelosi et al., 2001). SEP records the ascending "signals" that travel along the dorsal sensory column as the distal tract is being stimulated electrically (Deletis and Sala, 2008). These signals can be recorded from the spinal cord, either epidurally or subdurally, or at the somatosensory cortex. In contrast, MEP is the evoked response following stimulation of the motor cortex. MEP signals can be recorded from the distal descending motor tract, including the spinal cord, peripheral nerve, and the muscle groups involved. Currently, the most popular and practical method to elicit MEP is by delivering high voltage electrical

stimulation to the motor cortex through the intact skull i.e. transcranial electrical motor evoked potential (TceMEP).

Injury to the motor and sensory pathways during trauma or ischemia is associated with pathognomonic changes in SEP and MEP. In general, as injury becomes severe, there is progressive increase in the signal latency, a decrease in peak-to-peak amplitude and a loss of waveform complexity. By quantifying these changes, it is therefore possible to provide real-time information on the functional status of the ascending sensory and descending motor tracts.

The clinical utility of neurophysiologic monitoring depends on the threshold changes in waveform signals recorded. In this regard, expeditious response to the warning signals may prevent or reverse potential injury. Similarly, continuous monitoring of evoked potentials may guide the surgeon in deciding the extent of surgery that can be achieved. Thus, optimal tumor removal and correction of spinal deformities may be safely carried out if changes of signals are within the threshold boundary. Clearly, a precise definition of these warning signals is critical to the success of intraoperative neurophysiologic monitoring. The purpose of my study was to define the threshold changes in SEP and MEP, in a porcine model of spinal cord injury, beyond which the type and amount of changes in the evoked potentials may indicate neurologic deficit.

Chapter 2. Review of Warning Signals in Intraoperative Neurophysiologic Monitoring

2.1. Warning signals for somatosensory evoked potential monitoring

Few studies have determined the critical threshold of SEP that is associated with postoperative neurologic deficit. In their early experiment, Nordwall and co-workers (1979) evaluated the changes of SEP during longitudinal distraction of the spinal column in 6 mongrel cats. SEP was recorded from the multiple spinous processes above to the site of injury. Hind limbs movement and withdrawal to deep pinch were tested during brief wake-up tests. Although a complete disappearance of the SEP signals was always associated with limb paralysis and flaccidity, there was substantial variation in the changes of amplitude (72-96% decrease from baseline) among cats with limb weakness. Nevertheless, a decrease in SEP amplitude > 70% was considered significant.

Data regarding changes in waveform latency was less well defined. Brown et al. (1984) reported the surgical outcome in 300 patients undergoing neurosurgical or orthopedic procedures. Three patients (1%) had postoperative neurological deficits. Careful review of the intraoperative SEP recordings showed that all three patients had a 50% decrease in amplitude and an increase in latency > 3 ms (4-12% increase from baseline). They also identified another four patients with similar changes during surgery but recovered at the end of the procedures. None of these patients had postoperative neurologic deficits. This study suggested that a decrease in peak-to-

peak amplitude of ≥ 50% and/or an increase in latency of ≥ 10% would require urgent attention.

Although the early guidelines had emphasized the lack of scientific data and that an absolute boundary of abnormality is unavailable (1987; 1994; Cross, 1999), it is commonly believed that the threshold changes in SEP are 50% decrease in amplitude and/or 10% increase in latency. In their national survey between 1989 and 1990, the Scoliosis Research Society reported that 70.5% of all surgeons participated in the study adopted the amplitude criteria (> 50%) and that 63.5% used the latency criteria (> 10%) (Dawson et al., 1991). A comparable proportion of surgeons accepted the same amplitude (72%) and latency (44%) criteria in the subsequent survey between 1991 and 1995 (Nuwer et al., 1995).

The American Society of Neurophysiological Monitoring (ASNM) recently published a position statement advocating an *empirical* criteria of > 50% decrease in the peak-to-peak amplitude of the primary SEP cortical response (N20 or P37) or ≥ 10% increase in latency as an indication of significant surgical event (Toleikis, 2005).

A number of studies in spinal surgery have reported the diagnostic accuracy of these warning criteria to predict postoperative neurologic outcomes (Table 2.1). Majority of the studies use only the amplitude criterion. While this is considered specific in detecting intraoperative events, the sensitivity in a few studies was low. In this regard, sensitivity is the proportion of postoperative neurologic deficits that are correctly identified by SEP monitoring. Given that there are only few postoperative neurologic events, sensitivity is substantially influenced by the number of patients

who suffer postoperative neurologic weakness despite an uneventful course of SEP monitoring during surgery (i.e. false negative). The incidence of false negative findings ranges from 0.127% to 4.1% (Chan et al., 2004; Hsu et al., 2008; Kelleher et al., 2008; Manninen, 1998; Nuwer et al., 1995; Schwartz et al., 2007; Wiedemayer et al., 2002; Wiedemayer et al., 2004). These studies suggested that threshold changes for SEP amplitude could be much less than 50% of baseline, and the inaccuracy in the threshold may have accounted for the false negative results.

Table 2.1. Predictive accuracy of intraoperative somatosensory evoked potential monitoring.

Author, Year	Type of surgery	No. of cases	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Dawson et al., 1991	Scoliosis correction	33,000	72%	99%	97%	100%
Forbes et al., 1991	Scoliosis correction	1,168	100%	95%	97%	100%
Manninen, 1998	Degenerative spine surgery	309	70%	96%	95%	99%
May et al., 1996	Cervical spine degenerative disease	191	90%	99%	91%	99%
Noonan et al., 2002	Scoliosis correction	134	100%	95%	96%	100%
Nuwer et al., 1995	Scoliosis correction	51,263	82%	90%	95%	99%
Wiedemayer et al., 2002	Degenerative spine surgery	423	81%	96%	90%	95%
Wiedemayer et al., 2004	Degenerative spine surgery	658	79%	88%	92%	96%
Hilibrand et al., 2004	Cervical spine degenerative disease	427	25%	99%	88%	96%
Bose et al., 2004	Cervical spine degenerative disease	119	70.4%	99.6%	99%	98%
Leung et al., 2005	Degenerative spine surgery	871	100%	98%	19%	77%
Khan et al., 2006	Cervical spine degenerative disease	508	77%	100%	100%	100%
Schwartz et al., 2007	Scoliosis correction	1,121	43%	100%	95%	100%
Eggspuehler et al., 2007	Cervical spine degenerative disease	246	83%	99%	90%	99%
Hsu et al., 2008	Spine deformity correction	172	100%	97%	67%	100%
Kelleher et al., 2008	Cervical spine degenerative disease	1,055	52%	100%	100%	97%

2.2. Warning signals for transcranial electrical motor evoked potentials monitoring

The threshold changes in TceMEPs are less clear. A number of decision rules have been proposed.

2.2.1. Amplitude criteria

Similar to SEP monitoring, amplitude analysis of TceMEP are often used to assess spinal cord integrity.

In a case report, Lang et al. (1996) proposed a 50% decrease in amplitude as the warning criterion for TceMEP. It is unclear how the threshold was derived, but it appeared that it was extrapolated from the experience in SEP monitoring. This threshold however produced a high rate of false positive alarm (0.8-11%) (Table 2.2), leading to premature and unnecessary interruptions in the procedures (Langeloo et al., 2007; Pelosi et al., 2002).

In order to avoid false positive alarm, Langeloo et al., proposed a threshold of > 80% decrease in amplitude as the warning signal in TceMEP monitoring (Langeloo et al., 2007; Langeloo et al., 2003). In a review of 145 patients undergoing corrective surgery for spinal deformity, the proposed criterion has a sensitivity of 100% and a specificity of 91%. Nevertheless, there were 10 patients (6.9%) in the cohort who has abnormal TceMEP changes but without postoperative neurologic deficits (i.e. false positive).

Given that TceMEP amplitudes in any individual are variable, there are also suggestions that TceMEP should be considered as an "all-or-none" response (Bednarik et al., 1998; Cioni et al., 1999; Fujiki et al., 2006; Jallo et al., 2001; Jones et al., 1996; Kothbauer, 2007; Kothbauer and Novak, 2004; Lang et al., 1996a; Legatt, 2004; MacDonald, 2002; MacDonald et al., 2003; Mochida et al., 1997; Osburn, 2006; Quinones-Hinojosa et al., 2004; Sala et al., 2007; Sala and Lanteri, 2003; Szelenyi et al., 2005; Szelenyi et al., 2007; Tanaka et al., 2006; Zentner et al., 1989). A number of investigators have proposed that in patients undergoing intramedullary tumor excision, surgery may proceed until there was disappearance of TceMEP signals (Deletis V, 1998; Jones et al., 1996; Kothbauer, 2007; Kothbauer et al., 1998; Lang et al., 1996a; Woodforth et al., 1996; Zentner, 1989, 1991). In a series of patient cohorts from the same group of investigators, there was no false negative report and < 10% rate of false positive results (Kothbauer, 2007; Kothbauer et al., 1998; Sala et al., 2007). However, others have demonstrated permanent paraplegia when TceMEP was abolished (Burke et al., 1995; Quinones-Hinojosa et al., 2005).

Table 2.3 shows the number of published reports demonstrating satisfactory prediction accuracy for different warning criteria in various types of surgery. It is unclear how to choose the various decision rules, but it appears that the choice could be surgery specific. For instances, most investigators will use a 50% decrease in amplitude as the warning criteria for spinal corrective surgery or intracranial procedures (Neuloh et al., 2004; Sala et al., 2006). In contrast, the all-or-none criteria are commonly used for intramedullary tumor excision. Nevertheless, high quality

data is currently unavailable, and there is no consensus on the warning signals for TceMEP monitoring.

Table 2.2. Predictive accuracy of intraoperative transcranial electrical motor evoked potential monitoring.

Author, Year (reference)	Type of surgery	No. of patients	Sensitivity	Specificity	PPV	NPV
50% amplitude decrease						
Sutter et al., 2007*	Spine surgery	1017	89.%	99%	89%	99%
Bose et al., 2007	Anterior cervical spinal surgery	238	91%	89%	29%	99%
Hsu et al., 2008	Spinal deformity surgery	144	100%	97%	67%	100%
Kelleher et al., 2008	Cervical spine surgery	1055	100%	96%	96%	100%
80% amplitude decrease						
Padberg, 1998**	Idiopathic scoliosis surgery	500	99%	100%	22%	98%
Langeloo et al., 2003	Thoracolumbar and cervical spine surgery	142	100%	91%	62%	100%
Hilibrand et al., 2004	Cervical spine surgery	427	100%	100%	100%	100%
Kim et al., 2007	Cervical myelopathy surgery	52	100%	90%	17%	100%
Lieberman et al., 2008	Fixed sagittal plane deformity surgery	35	100%	90%	40%	100%
100% amplitude decrease (all-or-none rule)						
Kothbauer et al., 1998	Intramedullary spinal cord tumor surgery	100	100%	91%	89%	100%
Sala et al., 2007	Intramedullary spinal cord tumor surgery	NR	100%	90%	NR	NR

*Combined with multimodal monitoring; **Note: Combined with an SEP criterion of 60% decrease in amplitude; PPV = positive predictive value; NPV = negative predictive value; NR = not reported.

Table 2.3. The number of reports using different type of amplitude criteria in different types of surgery.

Types of surgery	Amplitude decrease criteria		
	50%	80%	100% (i.e. all or none)
Correction of spinal deformity	19	13	2
Intramedullary tumor excision	4	4	6
Brain surgery, including microsurgical clipping of aneurysm	13	11	5
Miscellaneous	9	5	4

2.2.2. Threshold-level criterion

Apart from the amplitude criteria, the amount of voltage required to elicit TceMEPs may have predictive value. The threshold criterion is based on the principle that higher voltage is required to recruit a larger volume of motor cortex in order to restore muscle response when the motor tract is being damaged. In this regard, Calancie and co-worker (2001, 2008) proposed that a 100 V or more increase in the voltage that lasted for more than one hour correlated with neurologic deficit 24-48 hours after surgery.

The threshold criterion is however limited because its use is restricted to constant voltage generator, it requires a significant period of time (> 1 hour) before the warning criteria can be declared (Langeloo et al., 2007), and other factors such as changing anesthetic dosage during the test period, may have confounded test interpretation. Anecdotal data have suggested that the threshold criterion produced high rate of false positive results and its implication remains uncertain (Pelosi et al., 2002; Pelosi et al., 2001).

2.2.3. Waveform criterion

Finally, a change in the morphology of compound muscle action potential (CMAP) may be important in TceMEP monitoring. In patients undergoing excision of spinal cord tumors, changes of TceMEP waveform from polyphasic to monophasic was thought to be useful in predicting motor outcomes after surgery (Quinones-Hinojosa et al., 2005). Although waveform complexity can be measured by quantifying the duration of the CMAP response, the start and finish of the waveform are often subjective and difficult to determine. Nonetheless, the addition

of waveform data to the amplitude criterion and changes in stimulation threshold may be useful to predict neurologic outcome, but validation data is required (Hsu et al., 2008).

Chapter 3. Pooling Data from Case Reports

3.1. Introduction

In the previous discussion, I have outlined the various methods to determine the warning signals of SEP and MEP during intraoperative neurophysiologic monitoring. Although a number of decision rules have been proposed, the changes in amplitude have been the most popular approach (Banoub et al., 2003; Lam et al., 1991). However, it is unclear whether there is a threshold value, beyond which postoperative neurologic deficit may occur. I have therefore attempted to pool the cases reported in the literature in order to define the threshold changes in the amplitudes of SEP and/or TceMEP to predict postoperative motor outcome.

3.2 Methods

I have included the following database in my literature search: MEDLINE, EMBASE, Cochrane Controlled Trials Register, Google Scholar, DARE, and CINAHL. Full manuscript, case reports, cohort of cases or abstracts published after 1980 were included. I used the following keywords in my search:

Evoked potential or neurophysiologic monitoring;

Cut-off: Indicative warning criteria / deterioration criteria / significant decrease / deterioration / clinically significant / threshold value;

Postoperative findings or motor outcome / motor function or neurologic deficit / outcome / deterioration;

Clinical analysis; Review; Historical control study; Prospective/retrospective study

In this analysis, I have included reports of both adults and children > 12 years. Cases were excluded if there was no explicit statement stating the changes of intraoperative evoked potential monitoring and/or postoperative neurologic outcome. All cases used similar monitoring technique. Thus, SEP was recorded from the scalp after stimulation of a peripheral nerve, MEP was performed after high voltage transcranial electrical stimulation and CMAP was recorded from muscles of extremities.

Two individuals screened the title and abstract of each report identified in my search. We selected any report that we suspected had any possibility of fulfilling our eligibility criteria to undergo full review. Disagreements were resolved by a consensus process of having discussions on the rationale regarding the eligibility of the cases, and when this did not resolve differences, an independent third individual made a final decision on the eligibility.

We defined postoperative neurologic deficit as patients with paraplegia, monoplegia and severe muscle weakness, whereas those with mild weakness or normal muscle power were regarded as having no deficit.

3.3. Statistics

Changes in SEP and TceMEP amplitudes were compared between groups (patients with or without neurologic deficit) using Wilcoxon rank-sum test. The relationship between amplitude changes and postoperative neurologic deficit was determined by logistic regression. A P value less than 0.05 was considered significant.

3.4. Results

A total of 360 cases, from 33 reports (Accadbled et al., 2006; Bose et al., 2007; Costa et al., 2007; Dong et al., 2002; El-Hawary et al., 2006; Fan et al., 2002; Fujiki et al., 2006; Hayashi et al., 2008; Hilibrand et al., 2004; Hsu et al., 2008; Jacobs et al., 2006; Khan et al., 2006; Kim et al., 2007; Kitagawa et al., 1989; Kothbauer et al., 1998; Krassioukov et al., 2004; Langeloo et al., 2003; Lieberman et al., 2008; May et al., 1996; More et al., 1988; Nagle et al., 1996; Neuloh et al., 2004; Neuloh and Schramm, 2004; Noonan et al., 2002; Papastefanou et al., 2000; Paradiso et al., 2005; Pelosi et al., 2002; Pelosi et al., 2001; Smith et al., 2007; Szelenyi et al., 2006; Weinzierl et al., 2007; Wilson-Holden et al., 1999; Zhou and Kelly, 2001), published since 1980's, satisfied the eligibility criteria and were included in this analysis. Figure 3.1 shows the changes in SEP and MEP amplitudes with postoperative motor function. There was substantial overlap in the changes of SEP and MEP amplitudes among patients with different neurologic outcomes. Although there was a trend towards worsening deficit with larger decrease in signal amplitudes, this did not reach statistical significance. It was however possible to construct logistic regression models to illustrate the relationship between amplitude change and postoperative neurologic deficit (Figure 3.2). Nevertheless, the confidence intervals were wide and a threshold change in SEP or TceMEP amplitude could not be accurately determined.

3.5. Discussions

The present analysis is confounded by publication bias. This is because the literature tends to report outlier cases with false positive and false negative findings.

Nevertheless, this study demonstrates the feasibility to determine threshold changes in a prospective cohort.

Figure 3.1. Distribution of amplitude changes in A: somatosensory evoked potential (SEP) and B: transcranial electrical motor evoked potential (TceMEP) in patients with postoperative neurologic events. False positive and false negative cases are highlighted by solid and dashed arrows, respectively.

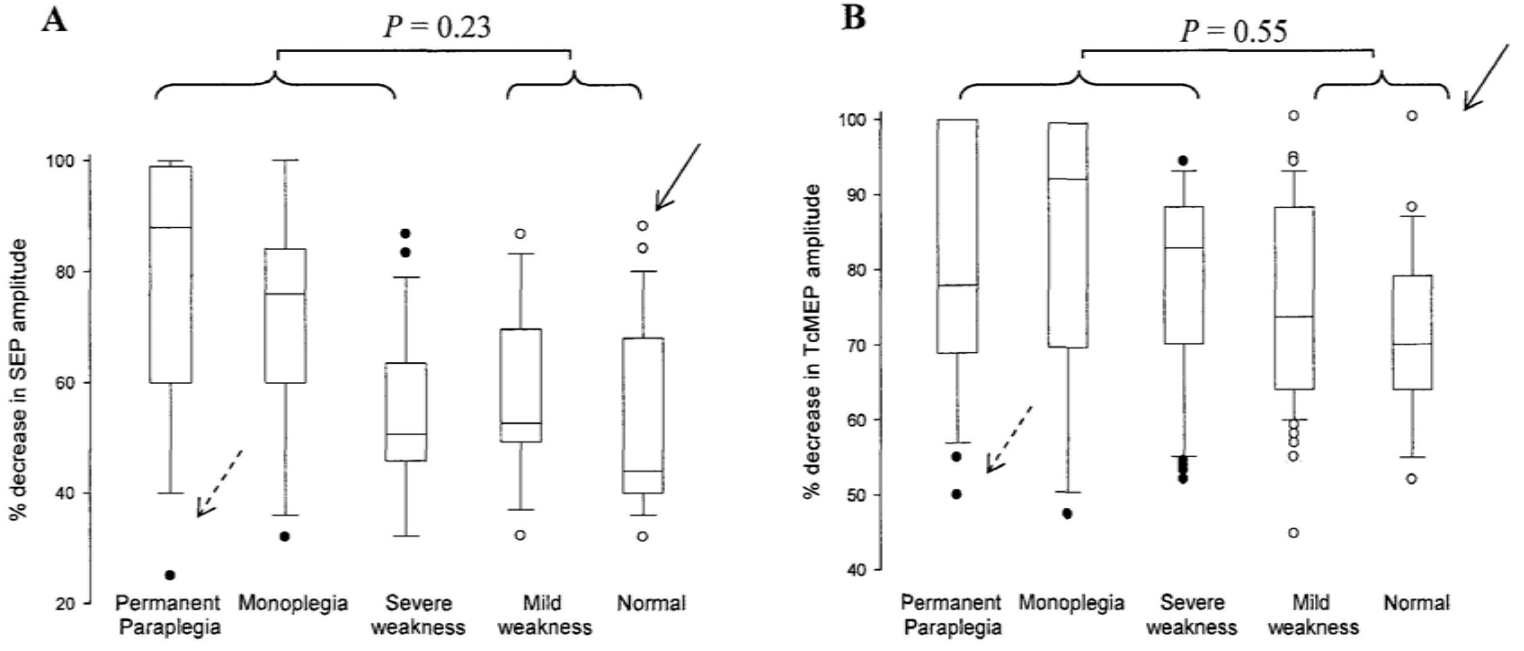
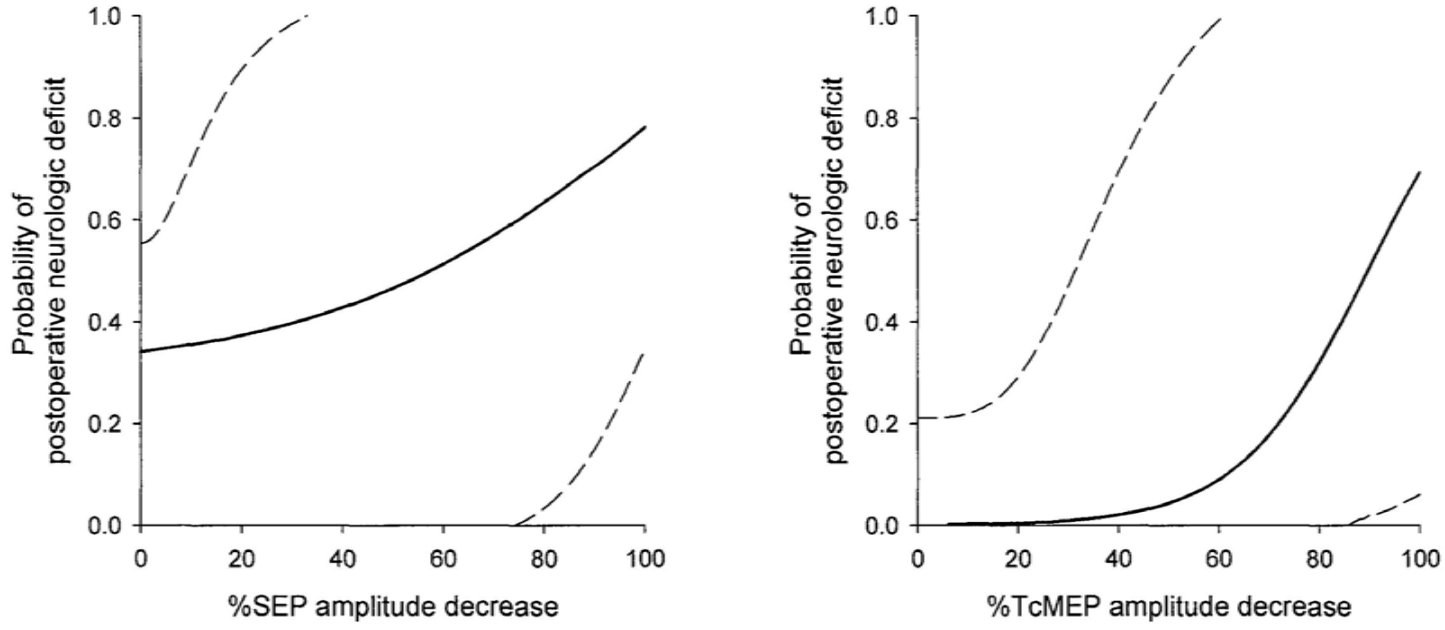


Figure 3.2. Correlation of A: somatosensory evoked potential (SEP) and B: transcranial electrical motor evoked potential (TceMEP) with postoperative neurologic outcome. Dotted lines show the 95% confidence intervals.



3.6. Conclusions

Based on my literature search, I believe that the current recommendations for warning criteria during intraoperative neurophysiologic monitoring are largely empirical (1987; 1994; Calancie et al., 2001; Cross, 1999; Deletis V, 1998; Lang et al., 1996b; Langeloo et al., 2003; Quinones-Hinojosa et al., 2005). The predictive performances of these criteria also vary widely. There are striking variations in the opinions among monitoring professionals and this reflects the paucity of data evaluating the threshold value of neurophysiologic signals (Dawson et al., 1991; Nuwer et al., 1995), beyond which spinal cord injury may occur.

In order to guide surgical decision with intraoperative neurophysiologic monitoring, there must be a valid set of warning criteria that can reliably predict postoperative outcome. Until such threshold can be defined, it is difficult to determine the utility of neurophysiologic monitoring.

PART 2 EXPERIMENTS

Chapter 4. Experimental Design

In order to define the warning criteria of intraoperative neurophysiologic monitoring, I planned to perform a prospective observational cohort study to correlate the changes in SEP and MEP with postoperative neurologic outcomes.

The ideal study should be performed in patients undergoing a wide range of surgery at risk of spinal cord injury. This will maximize the generalizability of the results and allow us to extrapolate the findings to other scenarios (Tunis et al., 2003). There are however a number of problems with this design:

(1) The incidence of neurologic event after spinal surgery is generally low (0.2-1.0%). Given that 10 to 12 events are required to produce stable estimates in regression analysis (Peduzzi et al., 1996), the cohort should include 1,000 to 5,000 patients. More patients will be required when heterogeneity of patient and surgery are considered.

(2) I believe it is ethically difficult to ignore potential deterioration in neurophysiologic recordings while waiting for postoperative evaluation. Although some of the bad signals are false positives, most physicians will try hard to correct for the recordings. This may include leaving residual tumor behind or accepting suboptimal correction for deformity. The results are therefore biased with most of the recordings concentrated at one end of the spectrum, leaving few events for the regression models.

I believe a human experiment cannot be accomplished within a short period of time. I have therefore designed a porcine experiment of controlled spinal cord injury with distraction and compression to evaluate changes in neurophysiologic signals.

I realized that the porcine model is not a perfect representation of human spinal cord injury because it is impossible to detect pure sensory deficit in pigs with an isolated injury to the dorsal column. In this scenario, changes in SEP will not correlate with postoperative neurologic outcome. However, as the experiment included distraction and compression of the spinal cord, it is unlikely that the motor column can be spared. In order to overcome this problem, I have included magnetic resonance imaging of the spinal cord in the study. Therefore, changes of neurophysiologic signals can be correlated with radiological and anatomical changes in spinal cord injury.

There is also concern that data in pigs cannot be translate to clinical practice in human. However in the absence of valid human data, and the difficulties in human experiment, the porcine model provides the best possible alternative.

Chapter 5. Methods

5.1. Animal preparation

We used healthy large white pigs, weighing 25-30 kg in this experiment. All animals were free from neuromuscular disorder or epilepsy. Pigs were obtained from the Sheung Shui Slaughter Center. The care of all animals and experimental protocol were approved by the Department of Health, the Government of the Hong Kong SAR, (Ref: DH.HA&P/8/2/1 Pt.10), and the Animal Experimentation Ethics Committee of the Chinese University of Hong Kong (Ref: 07/087/MIS)

5.2. Anesthesia, monitoring and intraoperative management

Anesthesia was induced with tiletamine-zolazepam 4.0 mg/kg, xylazine 2.0 mg/kg, and atropine 0.04 mg/kg intramuscularly (Mok et al., 2008). This was followed by tracheal intubation and mechanical ventilation of the lungs with an air/oxygen mixture and an inspiratory oxygen concentration of 0.5. Neuromuscular blocking agent was not used to facilitate TceMEP recording (Adams et al., 1993).

Intravenous catheter was then placed in one of the ear veins. Anesthesia was maintained with propofol infusions (100-120 μg/kg/min), ketamine (10-20 μg/kg/min) and fentanyl (2-5 μg/kg/h). Infusion was adjusted to keep a stable processed EEG with an IoC index of 50 (IoC-View Veterinary, Morpheus-Medical, Barcelona, Spain).

The animal was placed in prone position. Oxygen saturation, rectal temperature and urinary output were monitored. Forced air warming was provided. The femoral artery was cannulated for arterial pressure monitoring, but additional

measurement of plasma glucose examination was done. The mean arterial blood pressure was maintained between 60 and 80 mmHg with phenylepherine and labetalol infusions as required. The end-tidal carbon dioxide ($ETCO_2$) concentration was kept between 35 and 40 mmHg by adjusting the minute volume.

All animals received warmed normal saline 10 ml/kg/h during surgery to maintain normal volume status. Standardized treatment was provided. Physiologic parameters were displayed and recorded in 5 seconds intervals using a data acquisition program (PC monitor*).

*The PC Monitor software is available for non-commercial use from Mr YH Tam at http://www.cuhk.edu.hk/med/ans.

5.3. Spinal cord injury model

In the experiment, I induced controlled compression-distraction spinal cord injury at T12 using a purposely designed weight-loading compression device. We choose T12 because the forelimbs can be used as a control during neurologic assessment.

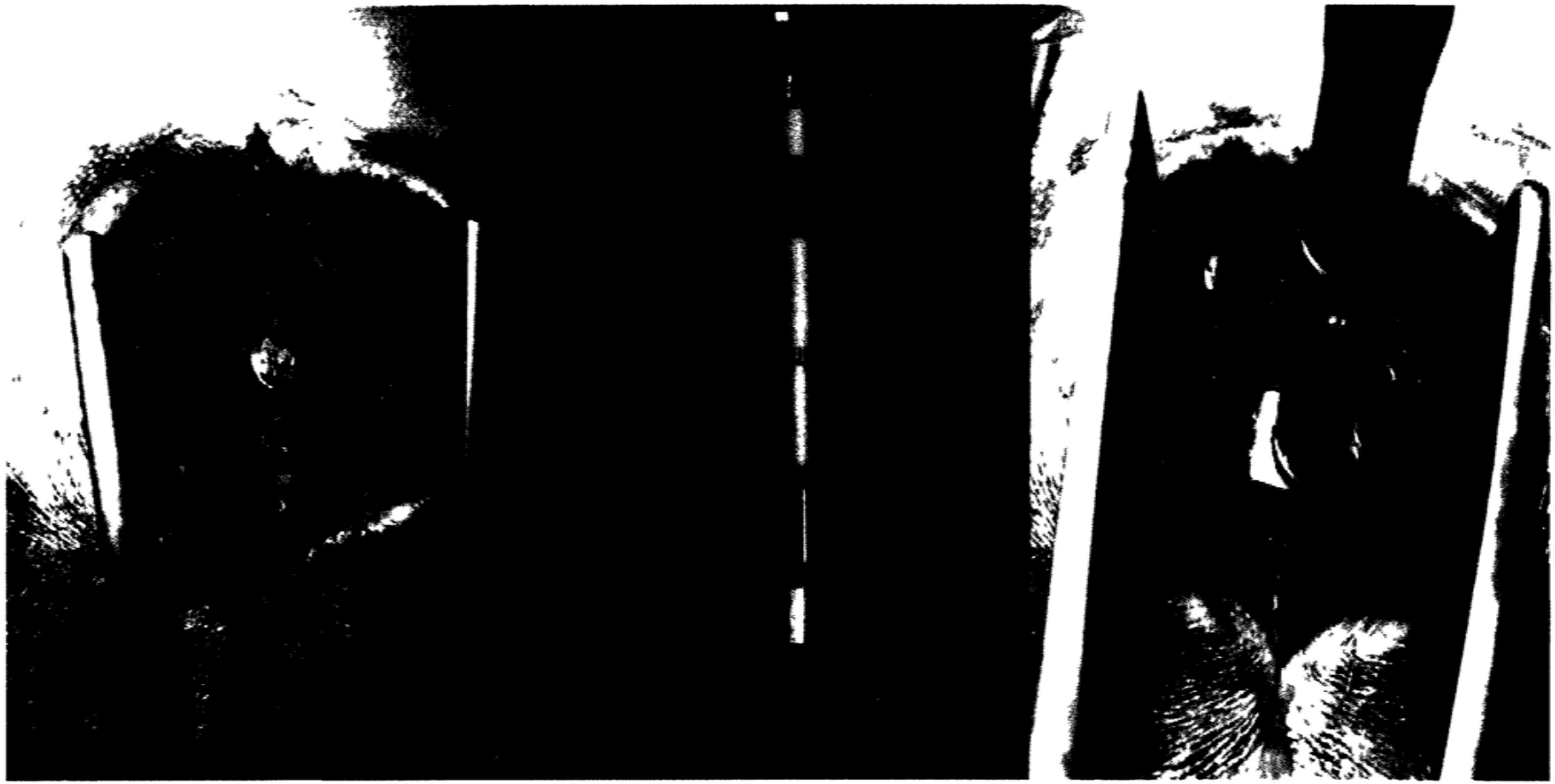
The device contained a screw piston that produces different compression pressure. It consisted of a flat circular tip that was connected to the head of the screw. The tip has a diameter of 6 mm and matched with the average width of the thoracic spinal cord at this level (5.5 - 6.5 mm). By turning the head of screw, the circular tip was lower down and exerted pressure over the spinal cord. For every turn of the screw head, the device produced a pressure of approximately 10 kPa. A maximum pressure of 50 kPa could be induced. This model simulated the form of spinal cord injury during correction of spinal deformity.

Under sterile condition, laminectomy was performed to expose the intact spinal cord at T12. The compression device was then suspended over the dura and mounted to adjacent transverse processes (Figure 5.1). Following establishment of baseline hemodynamic and neurophysiologic recordings, injury was produced by applying pressure to the spinal cord using the compression device.

Pigs were randomly assigned to receive different compression pressure so that a spectrum of postoperative motor deficit (from normal motor function to complete paraplegia) and perioperative changes in neurophysiologic signals (from 0 to 100% decrease in amplitude) can be produced. The details of the pressure induced

in each experiment are listed in Table 8.2. I did not measure the actual pressure because the pressure gauge was not sterilized. Instead, the number of turns was used to estimate the pressure produced. Compression was maintained for 30 min. After compression was released, another 30 min was allowed for possible recovery of neurophysiologic signals. The wound was then closed in layers.

Figure 5.1. Exposed spinal cord at the twelfth thoracic segment (left panel). Hydraulic piston (middle panel) mounted over the spine for producing compression and distraction injury of the cord (right panel).



5.4. Postoperative care

All animals were allowed to recover from anesthesia, and were nursed in the Laboratory Animal Services Centre (LASEC) for postoperative care. Intramuscular injection of gentamicin 5 mg/kg was given before skin incision and oral cloxacillin 10 mg/kg was given daily after surgery.

Following surgery, animals were allowed to move freely in their cages. Standard chow feeds were given. Supplemental intravenous fluid was also administered in animals who did not resume diet well. All animals were reviewed three times daily after surgery. Carprofen 50-100 mg mixed with feeds was given for postoperative analgesia. Subcutaneous buprenorphine 10-50 μg/kg was given, every 8 hours, to animals with inadequate pain relief (defined as brisk response accompanied by vocalization to gentle wound palpation).

Following surgery, animals were allowed to move freely in their cages. Standard chow feeds were given. Supplemental intravenous fluid was also administered in animals who did not resume diet well. All animals were reviewed three times daily after surgery. Carprofen 50-100 mg mixed with feeds was given for postoperative analgesia. Subcutaneous buprenorphine 10-50 μg/kg was given, every 8 hours, to animals with inadequate pain relief (defined as brisk response accompanied by vocalization to gentle wound palpation).

5.5. Magnetic resonance imaging examination

On the third postoperative day, animals were anesthetized again for magnetic resonance imaging of the entire thoracolumbar spine to determine the extent of spinal

cord injury, using a 3 Tesla machine (Achieva 3.0T TX, Philips Healthcare, Andover, Netherlands). The following imaging sequences were applied:

(1) Axial T2-weighted images were acquired using a 3D turbo spin-echo (TSE) sequence (TSE factor = 64, Repetition time (TR) = 2300 ms, Echo time (TE) = 120 ms, slice thickness = 3 mm, Field of view (FOV) = 120×106 mm, slab thickness = 75 mm, acquisition matrix = 240×176, reconstruction pixel size = 0.36×0.36 mm, number of signals averaged (NSA) = 1).

(2) Sagittal T2-weighted images were acquired using 3D TSE sequence (TSE factor = 30, TR = 3026 ms, TE = 120 ms, slice thickness = 2 mm, slice gap = 0.25mm, FOV = 160×221×29 mm, slab thickness = 29mm, acquisition matrix = 268×300, reconstruction voxel size = 0.35×0.35 mm, NSA = 4).

(3) Sagittal T1-weighted images were acquired using multislice TSE sequence (TSE factor = 4, TR = 542 ms, TE = 7.9 ms, slice thickness = 2 mm, number of slice = 13, slice gap = 0.25 mm, FOV = 160×221 mm, acquisition matrix = 228×256, reconstruction matrix = 640×640, reconstruction voxel size = 0.35×0.35 mm, NSA = 4)

(4) Axial T2*-weighted images were acquired using 3D multi-echo fast field echo (mFFE) sequence (echos = 3, TR = 25 ms, TE = 6.9 ms, thickness = 1.5 mm, FOV = 100×100 mm, slab thickness = 90mm, acquisition matrix = 152×115, reconstruction matrix = 336×336, reconstruction voxel size = 0.3×0.3 mm, NSA = 6)

In addition, diffusion tensor imaging (DTI) was performed for mapping of damaged and intact fiber tracks. Briefly, sagittal images were obtained using a single

shot echo-planar imaging (SS-EPI) sequence: EPI factor = 87, TR = 3030 ms, TE = 60 ms, slice thickness = 2 mm, slice gap = 0 mm, slice number = 20, FOV = 160×160 mm, acquisition matrix = 80×78, reconstruction matrix = 256×256, NSA = 1, number of gradient orientation = 33, b = 0,1000 s/mm^2, reconstruction voxel size = 0.63×0.63 mm, halfscan factor = 0.678. The fold over direction was anteroposterrior, and the fat shift direction was posterior.

At the end of the MRI examination, all animals were given an overdose of thiopentone for euthanasia.

Chapter 6. Measurements for the Experimental Parameters

6.1. Neurophysiologic measurements

All neurophysiologic measurements were recorded using a 16-channel Endeavor™CR IOM system (Viasys Healthcare, Madison, WI) (Figure 6.1).

6.2. Somatosensory evoked potential

SEP was elicited by trains of 200 μs square-wave electrical stimulation to the tibial nerve in the hind limb using a pair of subdermal electrodes placed along the nerve 5 cm apart. The stimulation frequency was set as 4.1 Hz, and the intensity was adjusted to produce a visible plantar flexion of the hind limb. This was typically achieved at 30 - 50 mA. Recordings were obtained from the scalp of the contralateral sensory cortex (over the parietal bone) using subdermal electrode. The reference electrode was placed 10 cm away from the recording electrode towards the snout (Figure 6.2). Bandpass filters were set at 10-1,000 Hz (Calancie et al., 2001).

6.3. Transcranial electrical motor evoked potential

TceMEPs are recorded by stimulating the motor cortex with 2 insulated 1.8 cm screws placed 1 cm lateral to the sagittal suture and 1 cm anterior and posterior to the coronal suture (Figure 6.2), using a multi-pulse high voltage cortical stimulator (D185, Digitimer, Welwyn Garden City, UK). Screws instead of needles were used to overcome the large impedance due to the thickness of the skull (nearly 1 cm thick) (Mok et al., 2008; Strauch et al., 2004). The screws were carefully placed so that the inner table of the skull was not breached. CMAP was recorded from the contralateral

quadriceps muscles using subdermal needle electrodes. Bandpass filters were set at 30-1,000 Hz and the time base was 100 ms.

6.4. TceMEP: Stimulation protocol

6.4.1. Background

The stimulation protocol however requires further discussion. It is well known that TceMEP cannot be elicited by single pulse stimulation (Inoue et al., 2002; Ubags et al., 1997; van Dongen et al., 1999; Woodforth et al., 1996; Zentner et al., 1989). Clinically, multi-pulse stimulation is commonly performed. However there is no consensus on the most optimal protocol. Technically, TceMEP amplitude can be altered with different number of electrical stimuli delivered and the interstimulus interval (ISI) chosen. Earlier studies in human (Bartley et al., 2002; Calancie et al., 1998; Kalkman et al., 1995) suggested that a train of 2-3 stimuli and an ISI of 2 ms produced maximum waveform amplitude, but other protocols have been reported (Table 6.1). Certainly, there is no accepted protocol for pig experiment. We therefore conducted a study to determine the optimal number of stimuli and ISI that maximized the TceMEP waveform amplitude.

Table 6.1. Stimulation parameters for transcranial electrical motor evoked potential.

Author	Year	No. of stimuli	Interstimulus interval (ms)
Kalkman et al.	1995	2	2-5
Jones et al.	1996	1-6	1-6
de Haan et al.	1997	2	2-5
Calancie et al.	1998	3-4	2
Meylaerts et al.	2000	5	2
Zhou and Kelly	2001	5	NR
Calancie et al.	2001	3	2
Lips et al.2002a)	2002a	4	2
Kunisawa et al.	2002	5	2
Lips et al., 2002b	2002b	4	2
Langeloo et al., Langeloo et al.	2003	3-5	NR
Bose et al.	2007	3-5	NR
Quinones-Hinojosa et al.	2005	5-6	2.5-3.5
Quinones-Hinojosa et al.	2005b	6-8	2.8-4.0
Jameson and Sloan	2006	4-6	2
Macdonald	2006	3-9	1-5
Pajewski et al.	2007	4-6	2
Sutter et al.	2007b	5 (2-6)	2.5 (2-3)
Sala et al.	2007	5-7	4
Weinzierl et al.	2007	4	2
Zaarour et al.	2007	5	1.1
Mok et al.	2008	5	2
Hsu et al.	2008	3-6	3.5
Lieberman et al.	2008	5	-
Calancie and Molano	2008	3-4	2

NR = not reported, number in parenthesis are range of values.

6.4.2. Methods

I have included 14 pigs in this experiment. Animals were excluded if preoperative neurologic abnormality was identified. Following anesthesia with propofol, ketamine and fentanyl infusions, stimulating screws and recording electrodes were placed as previously described (section 6.3). Transcranial electrical stimulation, of 50 μs duration, was initially delivered with a train of 3 stimuli at an ISI of 2 ms. I began the experiment with a stimulus intensity of 100 V and this was increased in steps of 20 V until a maximum amplitude was observed. This was taken as the maximal stimulus intensity, and was typically in the range of 200 to 500 V. In the subsequent tests, a constant supramaximal stimulus at 120% of the maximum value was used.

Transcranial electrical stimulation was delivered using a combination of ISI (ranged from 1 to 9 ms) and varying number of stimuli (ranged from 1 to 9). The test sequence was randomly assigned. At least two minutes was allowed to elapse before next stimulus was delivered in order to avoid refractoriness of the system (Jones et al., 1996). If TceMEP could not be detected in any given set of parameters, two additional stimuli using the same combination of parameters were delivered at a later stage to confirm the finding (Pechstein et al., 1996). Throughout the experiment, body temperature, anesthetic delivery and hemodynamic stability were maintained (Quinones-Hinojosa et al., 2005). Since the TceMEP amplitude varied between individual animal, I calculated the normalized amplitude as the percentage of the largest amplitude elicited in each animal for subsequent analysis.

All 14 animals were sacrificed at the end of the experiment. Neurological assessment was not performed. Data were not included in the main study.

6.4.3. Results

Figure 6.4 shows the surface plot of TceMEP amplitude when stimulation protocol was varied by different combinations of ISI and number of stimuli delivered. I was unable to detect recognizable TceMEP signal with single pulse stimulation. TceMEP could be elicited in only 9 out of the 14 animals (64%) when a train of two stimuli was delivered (see also Appendix Table 1). There was an increase in TceMEP amplitude when the train of stimuli was increased to 5, beyond which, there was little change in amplitude. Furthermore, stimulus artifact might merge with signal waveform when ≥ 6 pulses were delivered (Figure 6.5). This created problems with *post hoc* measurements. It is important to note that two animals had convulsion when 8 pulses of stimuli was delivered. Experiments were stopped in these incidents, additional doses of propofol was given and was effective to terminate seizures. Both animals recovered uneventfully. In contrast, signal amplitude reduced when stimuli with ISI ≥ 3 ms were delivered (Figure 6.4).

6.4.4. Discussions

The data suggested that the optimal stimulation protocol was a train of 5 stimuli, at an ISI of 2 ms (Figures 6.4 and 6.6). Signal amplitude increased when more pulses were delivered, this is due to recruitment of neurons in the motor cortex (Inoue et al., 2002; Ubags et al., 1997; van Dongen et al., 1999; Woodforth et al., 1996; Zentner et al., 1989). Summative effect with multi-pulse stimulation was

however reduced when ISI was increased (Bartley et al., 2002; Burke et al., 2000; Deletis et al., 2001).

6.5. Definitions of neurophysiologic measurements

Since amplitude criterion is commonly used in clinical practice, the following measurements are defined:

(1) SEP amplitude was measured from the first negative peak and the following positive peak of the cortical waveform;

(2) TceMEP amplitude was the maximum peak-to-peak of the waveform elicited.

Figure. 6.1. Operating room setup. Anesthetic and physiological monitoring (A), and neurophysiologic monitoring system (B) are shown.

Figure. 6.2. Placement of stimulating screws (connected to green alligator electrodes) for the transcranial electrical motor evoked potential and recording electrodes (blue) for somatosensory evoked potential recording. Reference electrode was inserted to the snout (red). Surface marking of the sagittal (dashed line) and coronal (dotted line) sutures are also shown.

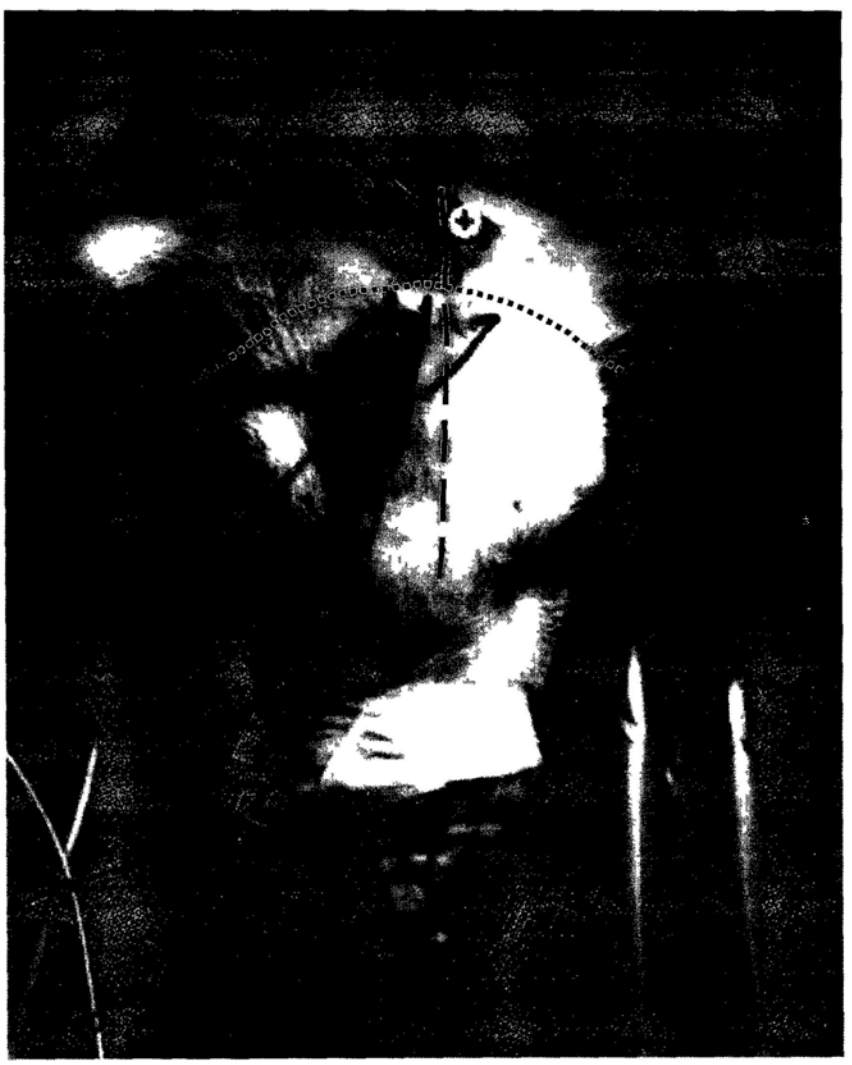


Figure 6.3. Schematic diagram showing the experimental setup. T12 laminectomy was done and the cord was compressed and distracted using a purposely designed hydraulic piston. The resultant damage was revealed by a postoperative magnetic resonance imaging (highlighted by the red arrow).

TceMEP = Transcranial electrical motor evoked potential, SEP = Somatosensory evoked potential.

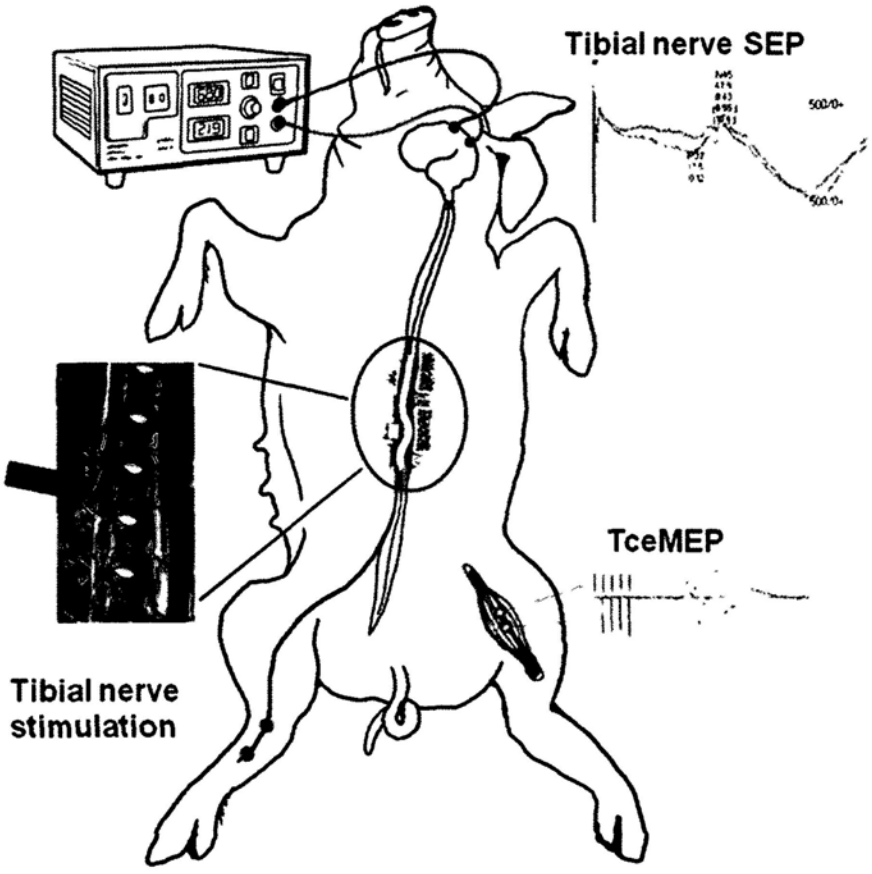


Figure 6.4. Surface plot of transcranial electrical motor evoked potential amplitude when stimulation protocol was varied by different combinations of interstimulus intervals and number of stimuli delivered (Raw data are taken from appendix Table 1).

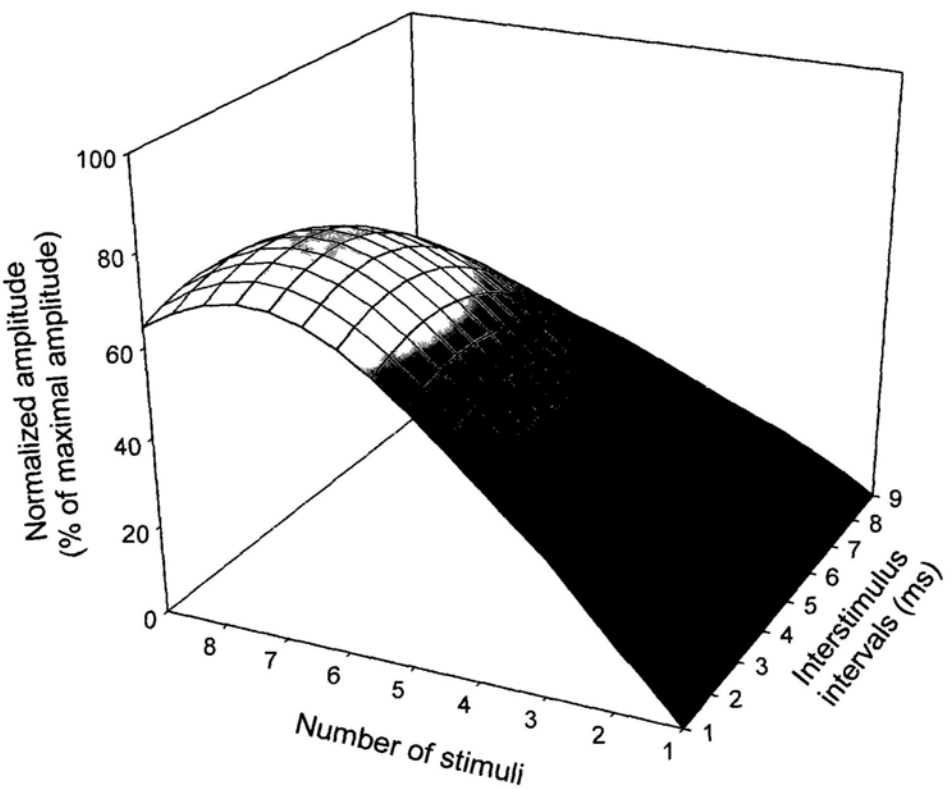


Figure 6.5. Stimulation artifacts (arrow) merged with transcranial electrical motor evoked potential (number of stimuli = 9; interstimulus interval = 8 ms). Time base = 100 ms.

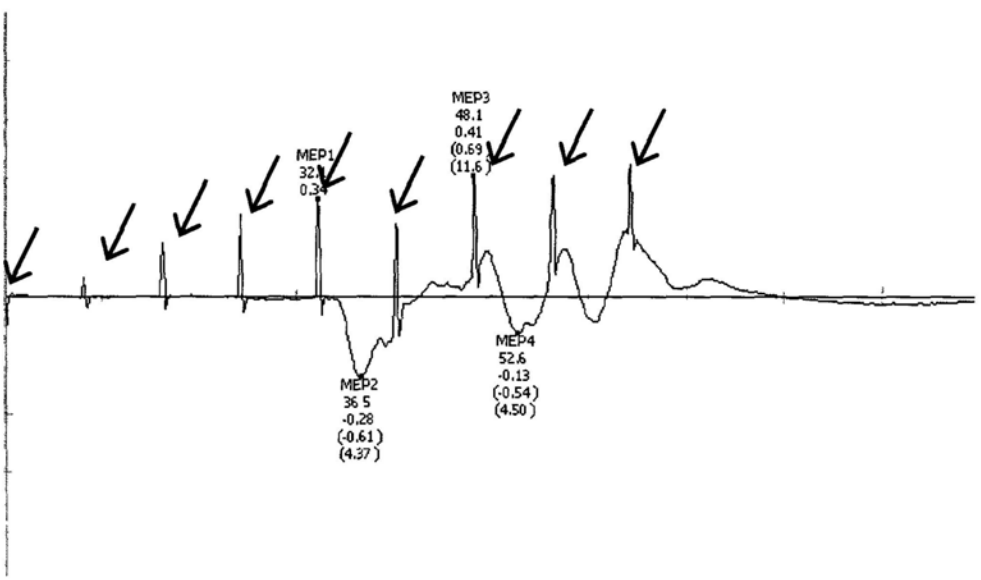
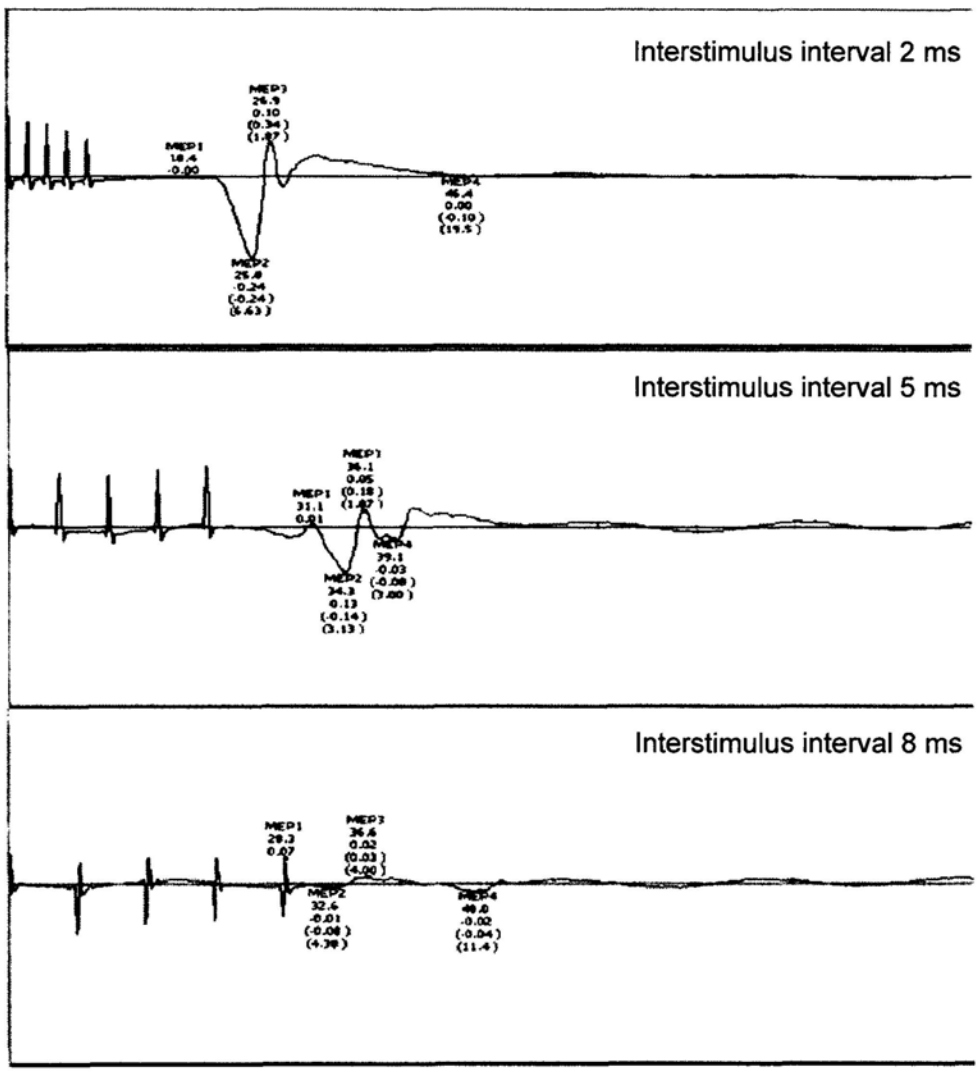


Figure 6.6. Changes of transcranial electrical motor evoked potential when interstimulus interval was increased from 2 ms (A), 5 ms (B) to 8 ms (C). The stimulus intensity was 310 V, number of stimuli was 5, Time base = 100 ms.



6.6. Clinical assessment

Postoperative clinical assessments were conducted by Dr NI Wei, who was blinded to the neurophysiologic recordings (Calancie et al., 2001; Calancie et al., 1998).

The best postoperative motor performance was recorded using the modified Tarlov motor scale (Table 6.2). This is rated when animals were stimulated with placement of food rewards two feet away from their resting position, in an open field.

Table 6.2. Modified Tarlov motor scale (Carlson et al., 2003; Tarlov, 1954)

Score	Standard
0	no movement, paraplegic with no lower extremity function
1	animal has barely perceptible movement of the hind limbs, weak / no antigravity movement only; poor lower extremity function
2	animal has frequent and/or vigorous movement of the hind limbs, some movement in the lower limbs, but not able to stand
3	animal can be able to stand, walk a few steps; and often bears weight on the top of the feet
4	animal is fully weight-bearing, consistently takes steps using the distal portions of the hind limbs, has limited hip flexion and poor balance, and occasionally bears weight on the dorsum of the foot and the pelvis falls repetitively
5	animal walks with only a mild deficit, the hind limbs follow with minimal deviation from the midline, and the animal can stand on the hind limbs alone
6	normal walking, good balance, and recovery from foot slip

Neurologic outcome was further classified as unfavorable (poor) outcome in animals with Tarlov score ≤ 2 and those with favorable (good) outcome when Tarlov score was 3 or more.

I classified the outcome in this fashion because it has been previously reported (Tarlov, 1954). Although a patient who can walk a few steps after spinal cord injury cannot be considered as having ideal recovery; this will suggest that the patient is not wheelchair bound. The socioeconomic burden of these patients would be entirely different from those who cannot tolerate weight bearing tasks.

6.7. Magnetic resonance imaging

The cross-section of the spinal cord was measured at three levels (Figure 6.7) as previously described by Lee and co-workers (Lee et al., 2008).

(1) Lesion level was defined as the region of spinal cord that showed maximal compression.

(2) Cranial normal appearing spinal cord was defined as the region above to the lesion that showed no abnormal signal intensity in structural images.

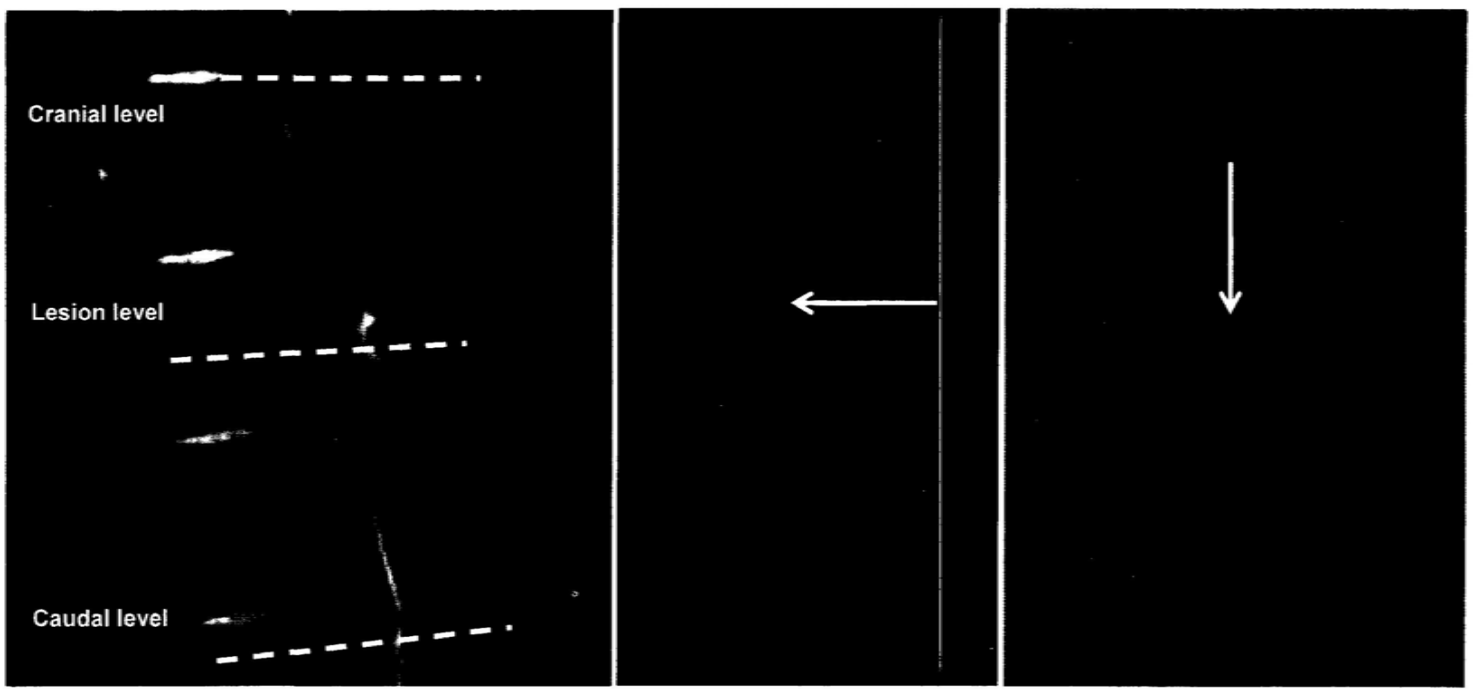
(3) Caudal normal-appearing spinal cord was defined as the region below to the lesion that showed no abnormal signal intensity in structural images.

In order to determine the degree of spinal cord compression, I calculated the area compression ratio using to the following equation:

$$\text{Area compression ratio} = \frac{\text{Area at lesion level} \times 2}{\text{Area at cranial level} + \text{Area at caudal level}}$$

To characterize the anatomical extent of injury, a map of apparent diffusion coefficient (ADC) was generated based on diffusion weighted imaging. Briefly, ADC quantifies the mobility of water molecules within the voxel of interest (Le Bihan et al., 1988). Compression injury limits diffusion of water molecules and results in a low ADC value (Hoehn-Berlage et al., 1995; Moseley et al., 1990; Wang and Lam, 2008). In addition, information from diffusion tensor imaging was used to assess the integrity of fiber tracts at the lesion. In this regard, water molecules in the spinal cord diffuse along the axonal tract. This process of directional diffusion is known as anisotropy. In contrast, when the fiber tract is disrupted, water molecules diffuse in different directions, and is termed isotropy (Basser et al., 2000; Cercignani et al., 2001; Mori et al., 2001). Therefore, it is feasible to quantify the continuity of spinal cord axonal tract, by calculating the directions and diffusibility of water molecules in the spinal cord tissue. This is expressed as fractional anisotropy (FA). An FA value of 1 indicates total anisotropy, and confirms integrity of the fiber tracts in the cord, whereas FA of 0 suggests complete disruption of the tract (isotropy).

Figure 6.7. Sagittal T2-weighted imagine showing compressed (lesion level) and normal appearing (cranial and caudal levels) spinal cord (left panel). Sagittal view of corresponding tractogram indicates axonal tracts (blue) running in the cephalocaudal direction (middle panel). Lesion level is shown by arrow. Fractional anisotropy (FA) map reconstructed in the axial plane shows compression of the spinal cord at the lesion level (right panel).



Chapter 7. Statistics

7.1. General statistics

Baseline characteristics of the animals were tabulated using appropriate summary statistics. Categorical data was analyzed using χ^2 test or Fisher's exact test, as appropriate. Continuous data was assessed with Wilcoxon rank sum test, or signed rank test, as appropriate.

The optimal thresholds for the changes in SEP and TceMEP amplitudes to predict neurologic deficit after surgery were calculated using logistic regression. 95% confidence intervals for the estimates were calculated using bootstrap method.

Apart from the percentage change in SEP and TceMEP after spinal cord injury, I prespecified a number of derived parameters to predict neurologic deficits after surgery. They include:

(1) The rate of change in SEP and TceMEP signals during spinal cord surgery: rapid deterioration ($\leq$ 5 min) *versus* insidious change (> 5 min);
(2) Recovery of SEP and TceMEP signals after spinal cord injury. This is defined as recovery of signal amplitude > 20% of the minimum value after injury;
(3) Duration of decrease in SEP and TceMEP amplitudes more than thresholds: $\leq$ 60 min *versus* > 60 min. This is 30 min compression and 30 min recovery. By looking the changes of signals over time, Figure 8.1, poor outcome is expected if there is no recovery after 30 min.

Sensitivity, specificity and positive and negative predictive values were calculated for each of above parameters.

The extent of damaged spinal cord identified in the magnetic resonance imaging was correlated with the changes in neurophysiologic signals using linear regression.

7.2. Sample size

I calculated the sample size to detect a false-positive and false-negative rates of < 1%. Assuming the area under the curve for the changes of neurophysiologic signals to predict neurologic deficit was > 0.9, 12-15 animals with postoperative deficit were required to minimize the bias of the estimates ($\alpha = 0.05$; $\beta = 0.1$). Since I anticipated about half the animals would have significant limb weakness after surgery, 30 pigs were used in this experiment.

7.3. Statistical software and significance level

Statistical analysis was performed using Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, Illinois). A *P* value of less than 0.05 was considered significant. All *P* values were two sided, unless otherwise specified.

PART 3 RESULTS AND DISCUSSIONS

Chapter 8. Results

The experiments were performed between November 2007 and June 2009. A total of 34 pigs (male : female = 18 : 16), aged 85-104 days, were included in the study. Three experiments were excluded because of machine problems. The final dataset contained 31 pigs that completed all experimental procedures.

8.1. Physiologic data

Table 8.1 summarizes the physiologic data of all animals at baseline, during spinal cord injury and at recovery. There was no change in parameters at different time periods.

Table 8.1. Physiologic and hemodynamic data of the experiment.

Parameters	Baseline	During spinal cord injury	Recovery	Day 3 after surgery	*P* Value*
Age (days)	90.9 ± 3.7	---	---	---	---
Body weight (kg)	28.1 ± 0.9	---	---	28.3 ± 3.8	0.06
Rectal temperature (°C)	34.6 ± 1.7	34.3 ± 2.1	36.0 ± 2.1	34.1 ± 1.6	0.18
Pulse (beats/min)	70.9 ± 12.1	66.7 ± 13.3	69.4 ± 16.9	63. 5 ± 15.5	0.25
Respiratory rate (breaths/min)	12.6 ± 1.9	12.5 ± 1.6	13.4 ± 1.9	12.9 ± 2.3	0.63
Mean arterial pressure (mmHg)	86.0 ± 10.5	82.2 ± 14.4	70.4 ± 33.1	81.7 ± 14.3	0.17
Blood glucose concentration (mmol/L)	8.4 ± 0.3	8.4 ± 0.4	8.2 ± 0.5	8.5 ± 0.5	0.08
Arterial oxygen saturation (%)	98.7 ± 1.8	98.7 ± 1.5	99.7 ± 0.7	98.9 ± 1.7	0.33
End-tidal carbon dioxide concentration (mmHg)	35.3 ± 8.8	34.1 ± 8.8	34.3 ± 9.0	32.8 ± 7.0	0.72
Urinary output (ml/hour)	37.9 ± 7.7	---	---	---	---
IoC index	51.2 ± 4.4	47.6 ± 3.9	50.2 ± 5.8	48.1 ± 5.5	0.27

Values are means ± standard deviation. IoC = index of consciousness (IoC-View Veterinary, Morpheus-Medical, Barcelona, Spain).

*Analysis of variance with repeated measures.

8.2. Changes in neurophysiologic signals during spinal cord injury

Reproducible SEPs and TceMEP signals were recorded in 29 (93.5%) and 31 (100%) animals, respectively. Figure 8.1 shows the changes in SEP and TceMEP amplitudes during spinal cord injury.

By varying the compression pressure and distraction injury, there was a decrease in SEP and TceMEP amplitudes. During injury, the average (± standard deviation) decrease in the SEP amplitudes, 52.7 ± 30.3%, was less than that for TceMEP, 86.4 ± 21.7%, $P = 0.0001$.

The rate of change in signal amplitudes may have prognostic implication. In this regard, a decrease in amplitude to its minimum value within 5 min was considered as a rapid deterioration of monitoring signals. In this dataset, neurologic outcome in animals with rapid decrease in SEP amplitude, (7/9, 78%), was worse compared with those running a more insidious course, (2/9, 22%), $P = 0.01$, Fisher's exact test. Similarly, a rapid decrease in TceMEP amplitude (9/10, 90%) also predicted unfavorable outcome, $P = 0.002$. Nevertheless, rate of changes in SEP amplitude was similar to that of TceMEP (Wilcoxon signed rank test, $P = 0.59$).

A number of animals had recovery of neurophysiologic signal during spinal injury and after removal of compression device. Animals with SEP amplitudes that recovered at least 20% from its minimum value, demonstrated more favorable

neurologic outcome (19/20, 95%), $P < 0.001$. Similarly, recovery of TceMEP (19/21, 90.5%) was associated with favorable outcome, $P < 0.001$.

At the end of the experiment, the maximum decrease in SEP amplitudes, 32.9 ± 29.9%, was less than that of TceMEP, 56.6 ± 37.3%, $P = 0.0015$ (Table 8.2).

Figure 8.1. Amplitude change of (left panels) somatosenory evoked potential (SEP) and (right panels) transcranial electrical motor evoked potential (TceMEP) during 30 min compression and distraction injury of the spinal cord (marked by the grey area). This figure continues for the next 10 pages.

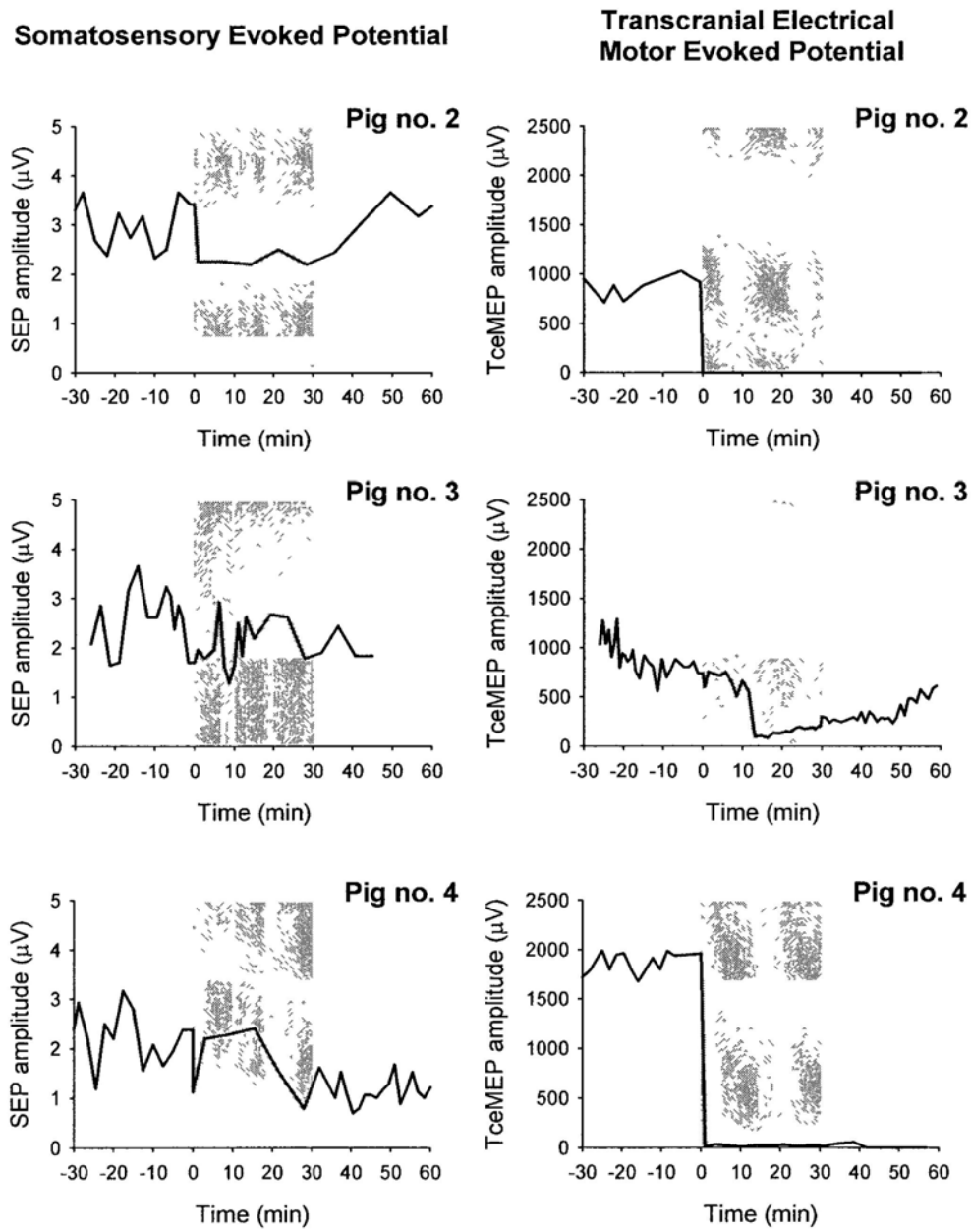


Figure 8.1. (continued).

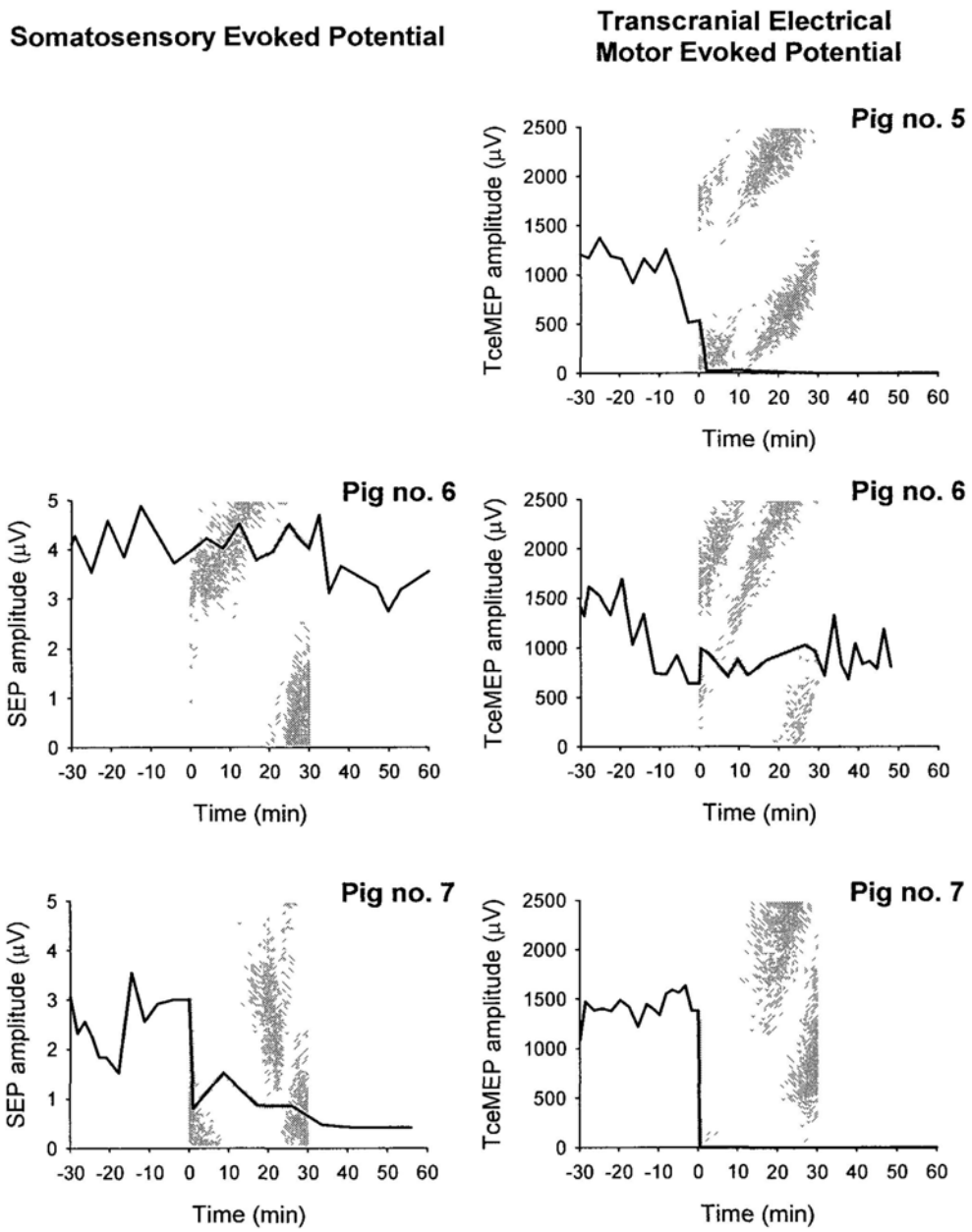


Figure 8.1. (continued).

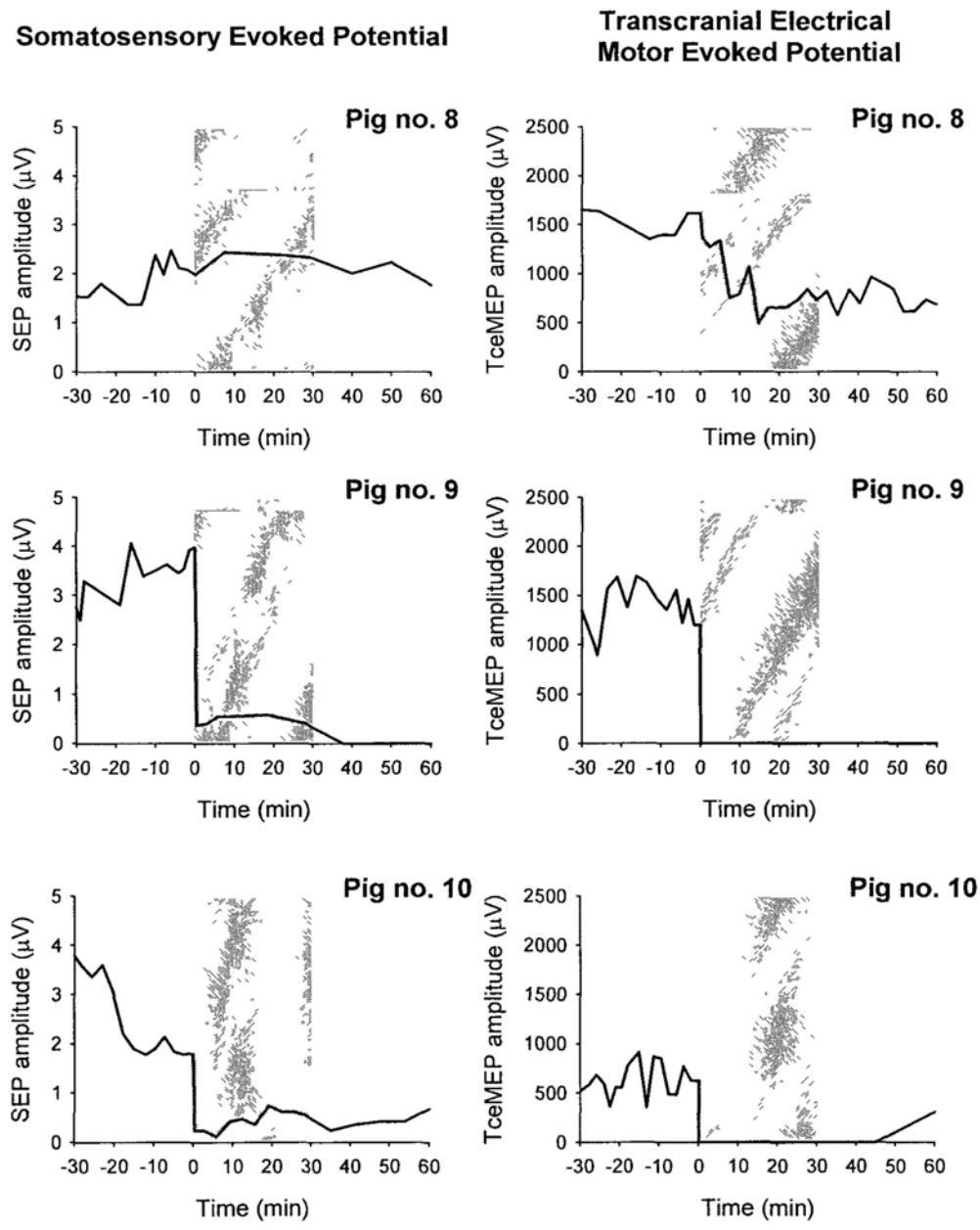


Figure 8.1. (continued).

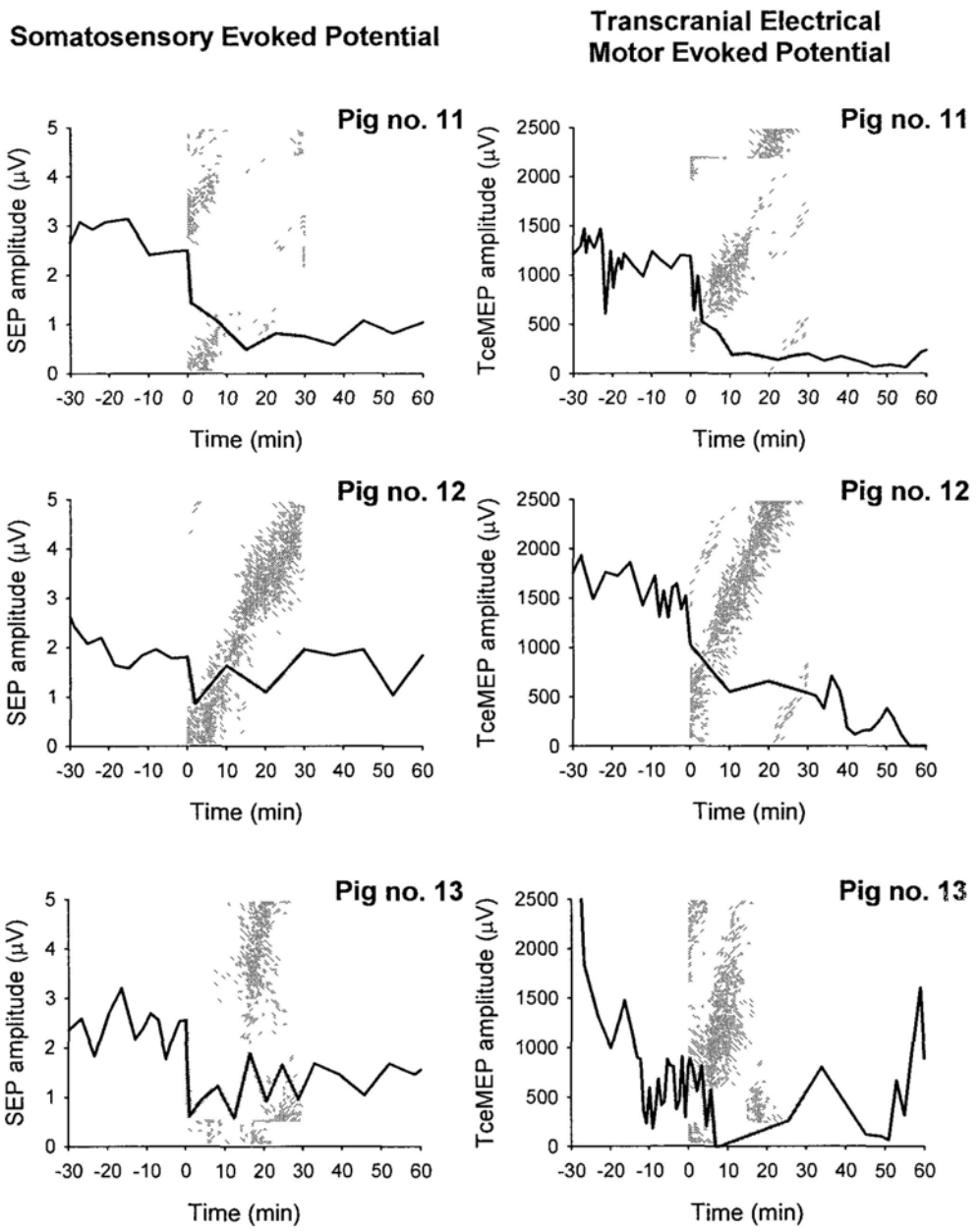


Figure 8.1. (continued).

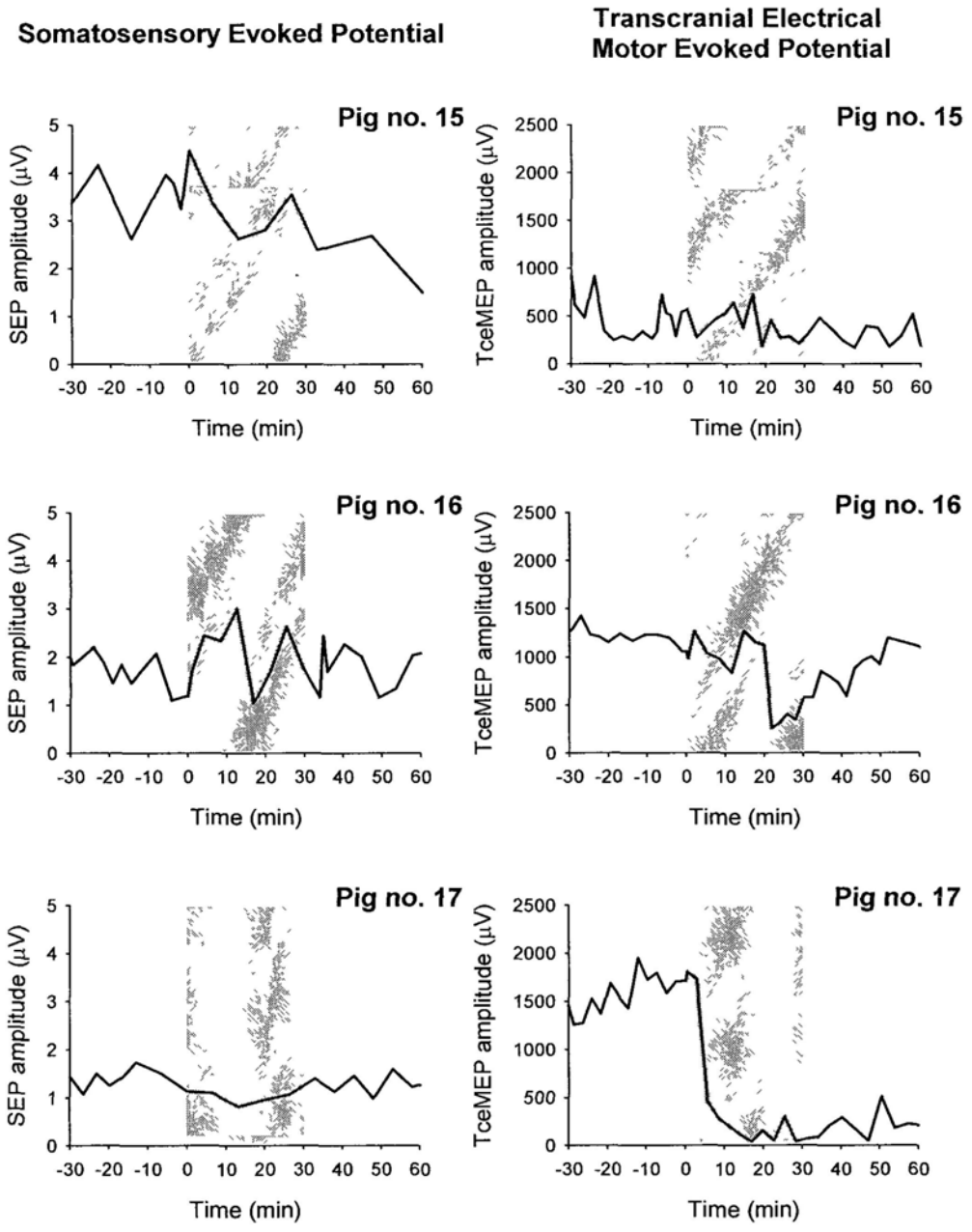


Figure 8.1. (continued).

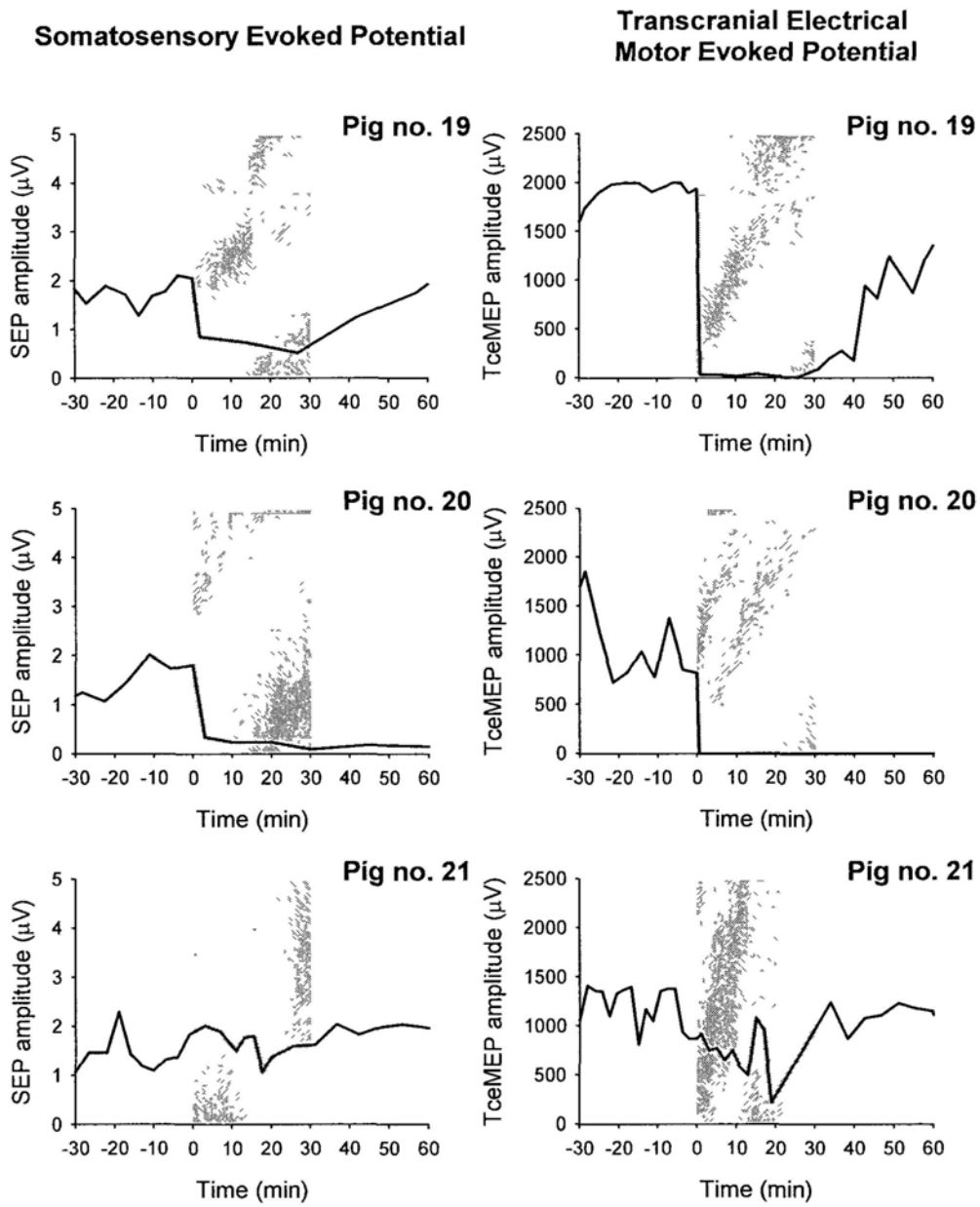


Figure 8.1. (continued).

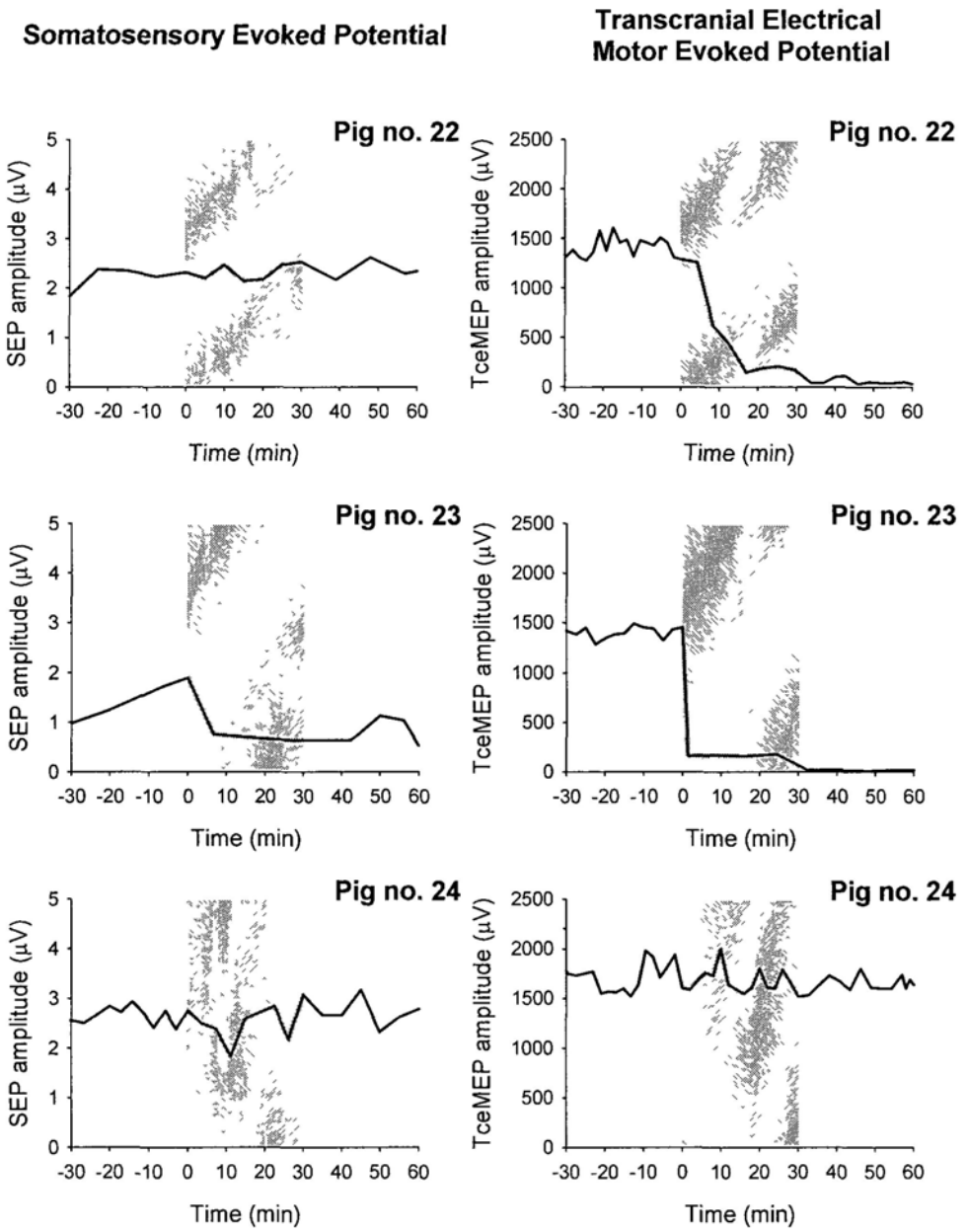


Figure 8.1. (continued).

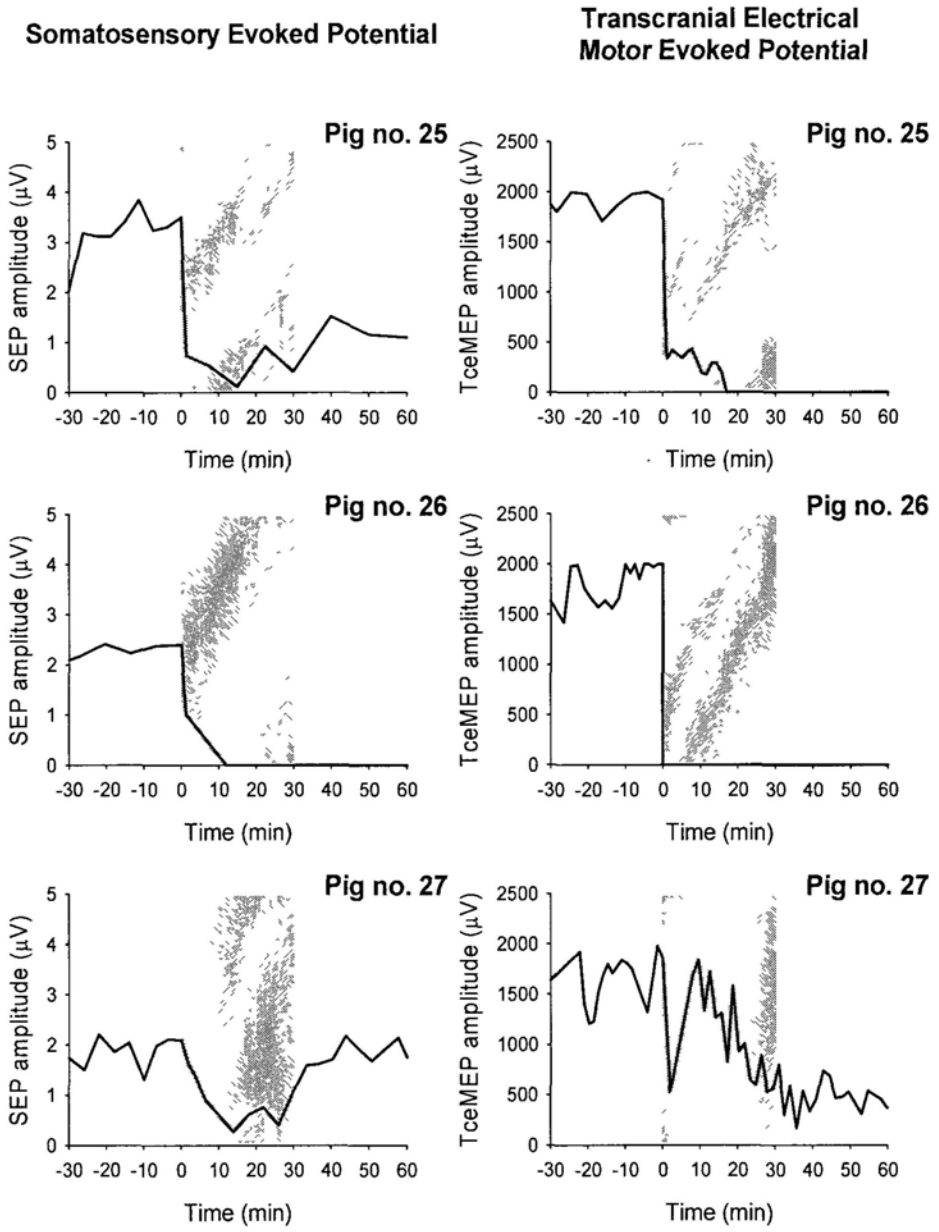


Figure 8.1. (continued).

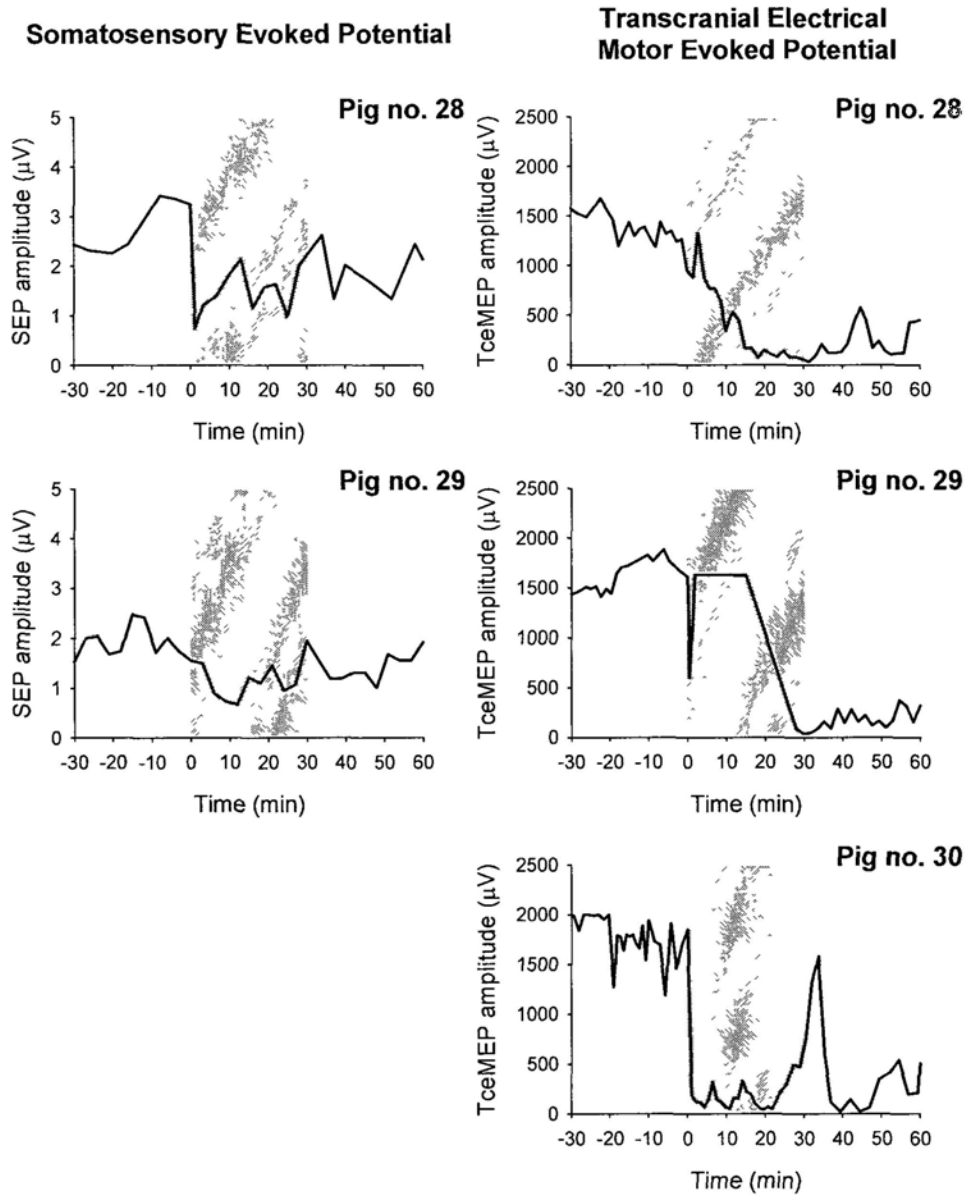


Figure 8.1. (continued).

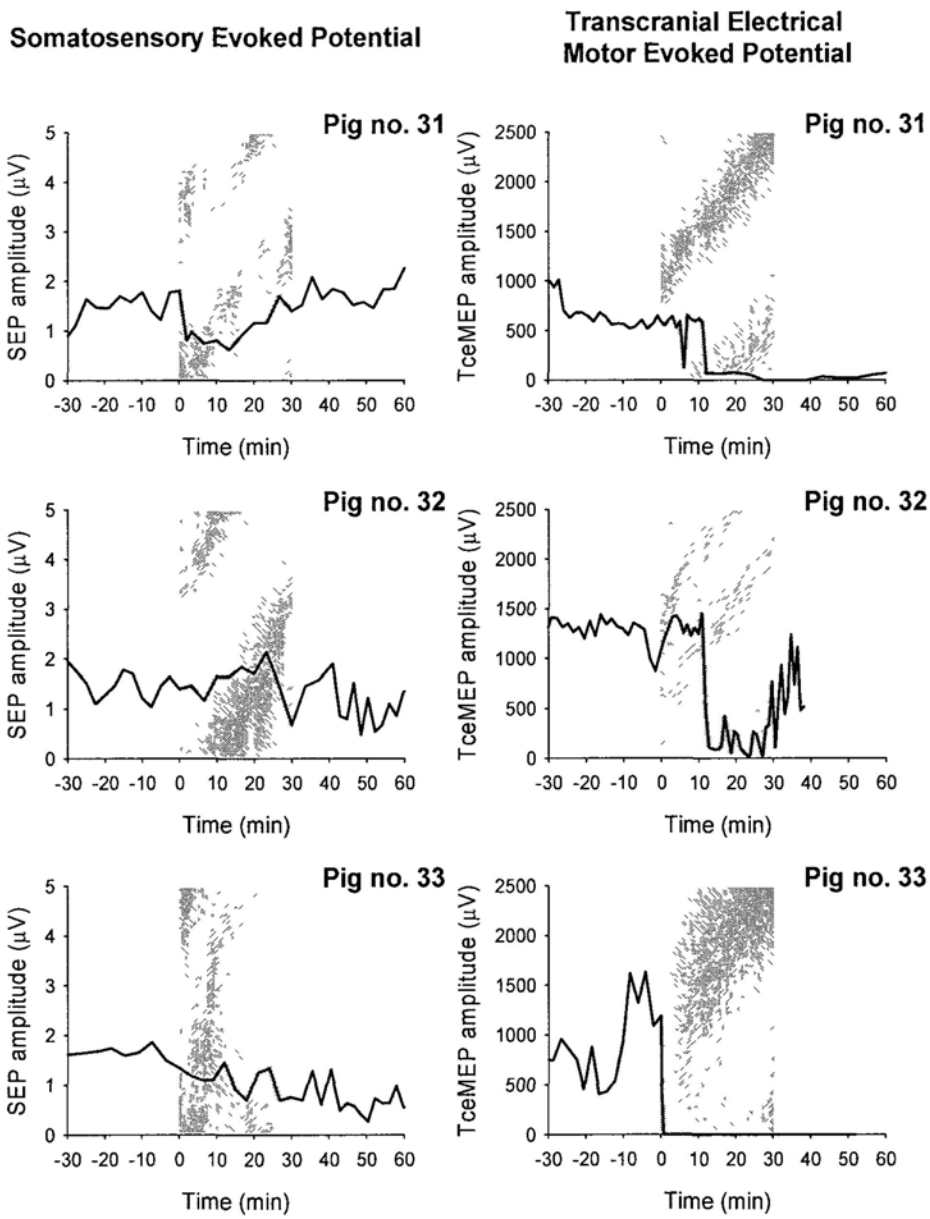


Figure 8.1. (continued).

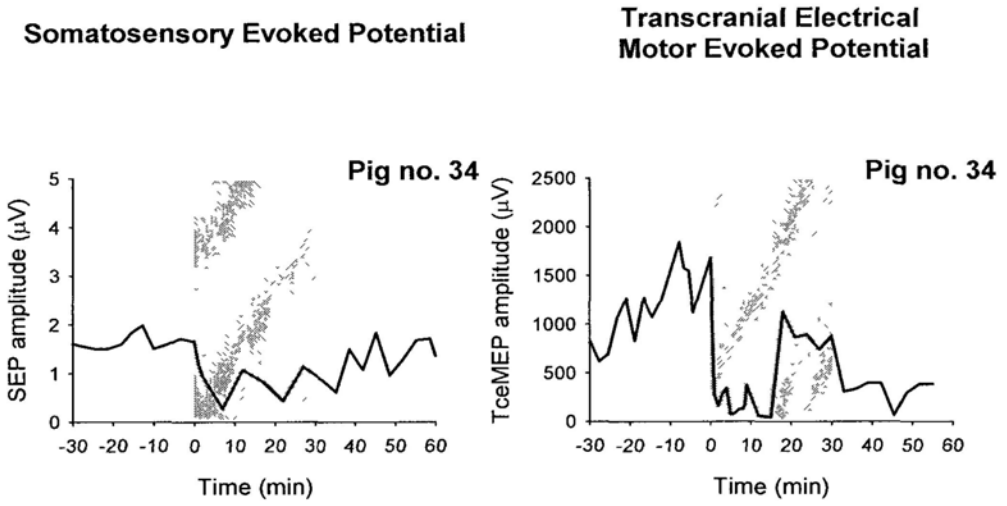


Table 8.2. Amplitude changes in somatosensory evoked potential and transcranial electrical motor evoked potential following spinal surgery.

Pig no.	Estimated pressure (kPa)	Somatosensory evoked potential				Transcranial electrical motor evoked potential				Postoperative motor function (Tarlov score)
		Time to maximum amplitude decrease (min)	Maximum amplitude decrease (%)		Total duration of amplitude decrease (min)	Time to maximum amplitude decrease (min)	Maximum amplitude decrease (%)		Total duration of amplitude decrease (min)	
			During injury	Following recovery			During injury	Following recovery		
2	40	12	24.4	4.9	35	1	100.0	100.0	>60	1
3	35	15	31.1	22.0	8	13	88.2	50.1	16	5
4	40	22	6.6	49.9	>60	1	99.5	98.9	>60	3
5	40	---	---	---	---	2	100.0	94.9	>60	3
6	40	18	5.5	17.1	0	>30	35.8	19.4	30	5
7	40	2	71.2	84.3	>60	1	100.0	100.0	>60	1
8	40	>30	12.4	2.40	0	13	65.7	37.1	30	5
9	40	1	89.4	86.9	>60	1	100.0	100.0	>60	2
10	30	4	91.8	32.2	85	1	100.0	62.9	45	4
11	30	15	85.2	21.9	40	11	87.6	6.9	64	6
12	30	8	78.4	75.4	>60	11	69.4	81.7	>60	1
13	30	2	77.7	47.1	60	2	96.9	83.1	>60	2
15	40	14	23.3	30.7	>60	>30	64.3	69.9	>60	3
16	40	18	48.1	4.5	0	22	78.6	5.9	6	6
17	30	13	41.1	5.7	26	16	97.4	9.6	50	5
19	30	3	72.1	8.5	40	11	99.3	27.4	34	5

Table 8.2. (continued).

Pig no.	Estimated pressure (kPa)	Somatosensory evoked potential				Transcranial electrical motor evoked potential				Postoperative motor function (Tarlov score)
		Time to maximum amplitude decrease (min)	Maximum amplitude decrease (%)		Total duration of amplitude decrease (min)	Time to maximum amplitude decrease (min)	Maximum amplitude decrease (%)		Total duration of amplitude decrease (min)	
			During injury	Following recovery			During injury	Following recovery		
20	40	4	83.2	85.5	>60	1	100.0	100.0	>60	1
21	45	19	24.2	11.9	0	19	73.8	16.3	6	4
22	40	>30	6.0	3.2	0	18	98.5	4.8	56	5
23	40	4	58.3	57.9	>60	2	88.0	98.5	>60	1
24	40	12	32.2	8.4	0	>30	9.4	3.1	0	5
25	30	2	83.1	68.0	>60	2	100.0	100.0	>60	2
26	50	1	100.0	84.8	>60	1	100.0	100.0	>60	0
27	40	14	85.5	2.4	16	2	52.4	67.6	0	5
28	40	1	66.6	12.6	50	18	97.6	19.9	40	5
29	50	12	67.1	45.2	18	28	93.1	57.7	31	4
30	40	---	---	---	---	2	97.7	39.2	47	4
31	35	2	64.4	6.4	20	13	100.0	2.9	53	5
32	45	>30	6.1	11.9	22	13	97.8	54.2	17	4
33	50	25	37.8	55.2	>60	1	100.0	100.0	>60	3
34	40	4	55.8	10.0	28	2	88.7	42.2	8	5

8.3. Changes in neurophysiologic signals and postoperative neurologic outcome

The basic characters and neurophysiologic parameters of pigs having favorable outcome (Tarlov score ≥ 3) and unfavorable outcome (Tarlov score < 3) were compared (Table 8.3). There is significant difference in most parameters between favorable and unfavorable outcome groups.

Logistic regression models were constructed to determine the correlation between the changes in SEP and TceMEP amplitudes with neurologic outcome after surgery. Figures 8.2 and 8.3 show the probability of postoperative neurologic deficit (Tarlov score < 3) following a decrease in signal amplitudes with direct spinal cord injury, respectively.

A wide range of values in the changes of SEP amplitude (4.9-86.9%) was associated with postoperative neurologic deficit. Consequently, the slope outlining the relationship between amplitude change and adverse postoperative neurologic outcome was flat ($P = 0.003$). The median (95% confidence intervals, CI) decrease in SEP amplitude that predicted postoperative deficit was 50.3 (41.3-59.5) %. However, a substantial proportion (10%) of animals might have postoperative deficit when there was as little as 25% decreases in SEP amplitude, but the confidence intervals were wide 11.1-37.7%. Almost all animals have deficit when there was 90% decrease in SEP amplitude.

In contrast, the correlation between the decrease in TceMEP amplitude and postoperative deficit was much steeper ($P = 0.011$). The median (95% CI) decrease in TceMEP amplitude for postoperative deficit was 83.7 (76.5-90) %. The risk of

postoperative deficit became significant (10%) when TceMEP amplitude was decreased by 65%.

Taken together, the threshold changes in SEP and TceMEP amplitudes, beyond which there was a substantial risk of postoperative neurologic deficit, were 25% and 65%, respectively.

Table 8.3. The basic characters and neurophysiologic parameters of pigs having favorable outcome (Tarlov score ≥ 3) and unfavorable outcome (Tarlov score < 3).

	Parameters		Favorable outcome group	Unfavorable outcome group	P value
SEP	Pig amount		20	9	
	Estimated pressure (kPa)		39.1 ± 5.7	37.8 ± 6.7	0.5832
	Time to maximum amplitude decrease (min)		28.6 ± 39.9	4.0 ± 3.7	0.0133
	Maximum amplitude decrease (%)	During injury	43.1 ± 29.0	73.9 ± 21.9	0.0086
		Following recovery	18.1 ± 16.3	66.1 ± 26.8	<0.0001
	Total duration of amplitude decrease		35.7 ± 42.1	103.9 ± 32.6	0.0002
TceMEP	Pig amount		22	9	
	Estimated pressure (kPa)		39.3 ± 4.6	37.8 ± 6.7	0.5412
	Time to maximum amplitude decrease (min)		25.7 ± 39.1	2.4 ± 3.2	0.0113
	Maximum amplitude decrease (%)	During injury	83.0 ± 24.2	94.9 ± 10.4	0.0642
		Following recovery	40.5 ± 32.1	95.9 ± 7.7	<0.0001
	Total duration of amplitude decrease		46.0 ± 40.2	120.0 ± 0.0	<0.0001

Figure 8.2. Probability of postoperative neurologic deficit after a decrease in somatosensory evoked potential amplitude with compression and distraction injury of the spinal cord. Dotted lines indicate 95% confidence intervals.

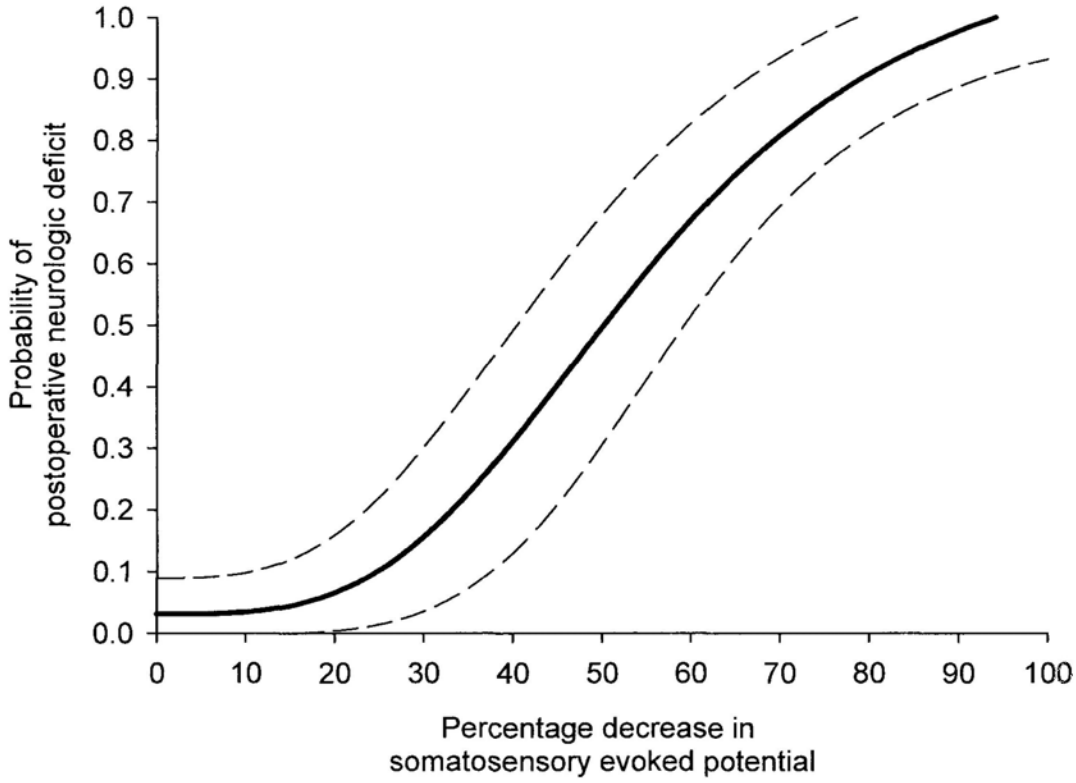
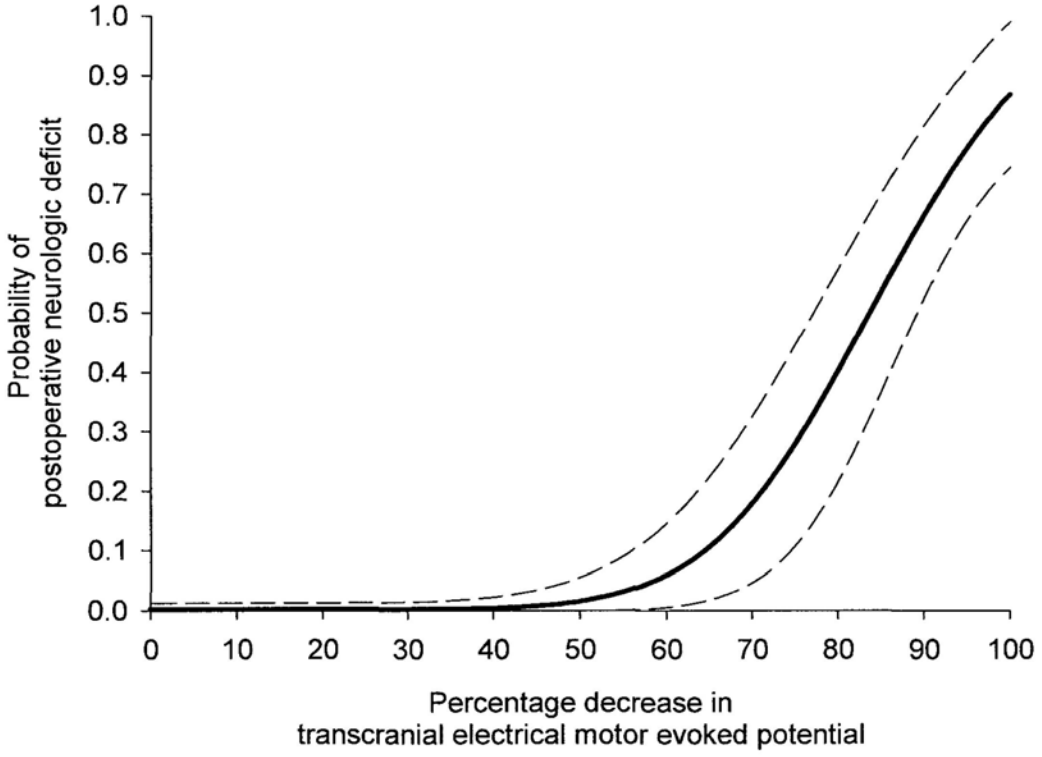


Figure 8.3. Probability of postoperative neurologic deficit after a decrease in transcranial electrical motor evoked potential amplitude with compression and distraction injury of the spinal cord. Dotted lines indicate 95% confidence intervals.



8.4. Performance of signal amplitude change to predict postoperative neurologic deficit

In order to determine the diagnostic accuracy of the threshold criteria identified in the earlier section, I have calculated the sensitivity, specificity, positive and negative predictive values for the minimum decrease in SEP and TceMEP to predict neurologic deficit after spinal cord injury. Based on my dataset, I have performed additional calculations for a number of potential parameters (the items of the 3 numbered paragraphs to calculate the diagnostic accuracy) to predict unfavorable postoperative neurologic outcome. The parameters are listed as below:

(1) The more commonly quoted warning criteria in neurophysiologic monitoring, i.e. 50% decrease in SEP amplitude, 80% decrease in TceMEP amplitude;
(2) The association between rapid deterioration of signal amplitudes and postoperative neurologic outcome. This was defined as a decrease in signal amplitude within 5 min of injury;
(3) A significant recovery of signal amplitudes (> 20% of its minimum value) within 30 min after spinal cord injury.

Table 8.4 summarizes the diagnostic performance of changes in SEP and TceMEP amplitudes to predict postoperative neurologic deficit. TceMEP performed better than SEP in predicting neurologic outcome. By lowering the threshold value from the 80% to 65%, there was substantial improvement in the diagnostic accuracy. Furthermore, a rapid deterioration and a lack of recovery in signal amplitude proved to be a satisfactory predictor for adverse neurologic outcome.

In contrast, the performance of changes in SEP was less accurate. A decrease in amplitude threshold from 50% to 25% did not substantially change the diagnostic accuracy. The main reason for difference in specificity is that our threshold (25%) was based on experimental animal data while the 50% threshold was based on the clinical documents. Although rapid deterioration of SEP signals did not always predict deficits, our data suggested that a recovery of signals > 20% of minimum appeared to be reassuring.

Table 8.4. Diagnostic accuracy of changes in somatosensory evoked potential and transcranial electrical motor evoked potential amplitudes to predict postoperative neurologic deficits.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Somatosensory evoked potential				
Amplitude decrease > 25% of baseline	88.9%	65.0%	53.3%	92.9%
Amplitude decrease > 50% of baseline*	88.9%	85.0%	72.7%	94.4%
Rapid deterioration in signal (< 5 min)	77.8%	80.0%	63.6%	88.9%
A lack of signal recovery**	77.8%	95.0%	87.5%	90.5%
Transcranial electrical motor evoked potential				
Amplitude decrease > 65% of baseline	100%	90.5%	83.3%	100%
Amplitude decrease > 80% of baseline*	100%	76.2%	66.7%	100%
Rapid deterioration in signal (< 5 min)	90.0%	71.4%	60.0%	93.8%
A lack of signal recovery**	100%	90.5%	83.3%	100%

*Warning criteria according to current guidelines. **This was defined as <20% recovery from minimum amplitude for > 30 min.

Chapter 9. Changes in Neurophysiologic Signals and Magnetic Resonance Imaging

Neurophysiologic signals were also correlated with spinal cord damages shown on postoperative magnetic resonance scans. Area compression ratio, apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were compared with SEP and TceMEP changes.

With increasing spinal cord damage, there was a significant increase in area compression ratio and ADC, FA was however reduced (Figure 9.1). These findings suggested that changes in SEP and TceMEP amplitudes correlated with the radiological (and anatomical) appearance as well as functional performance after spinal cord injury (Figures 9.2 and 9.3).

Figure 9.1. Whisker box plots of apparent diffusion coefficient (left panel), fractional anisotropy (middle panel) and area compression ratio (right panel) in animals with and without postoperative neurologic deficit.

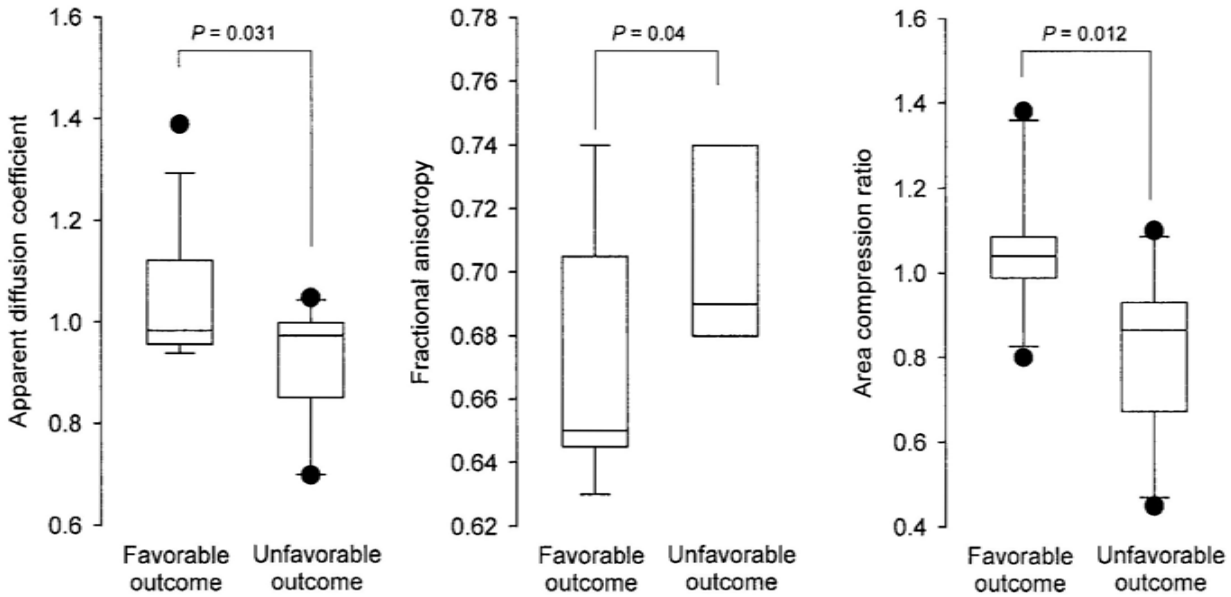


Figure 9.2. Correlation of apparent diffusion coefficient (left panel), fractional anisotropy (middle panel) and area compression ratio (right panel) with changes in somatosensory evoked potential (SEP). Dashed lines are the 95% confidence intervals.

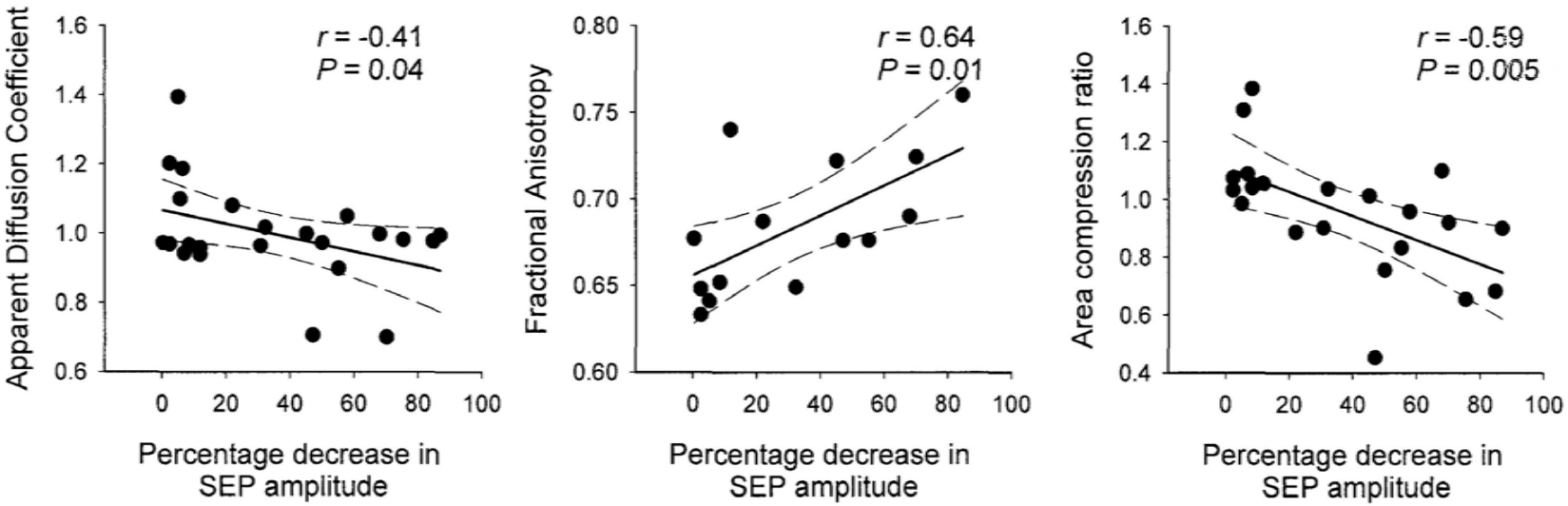
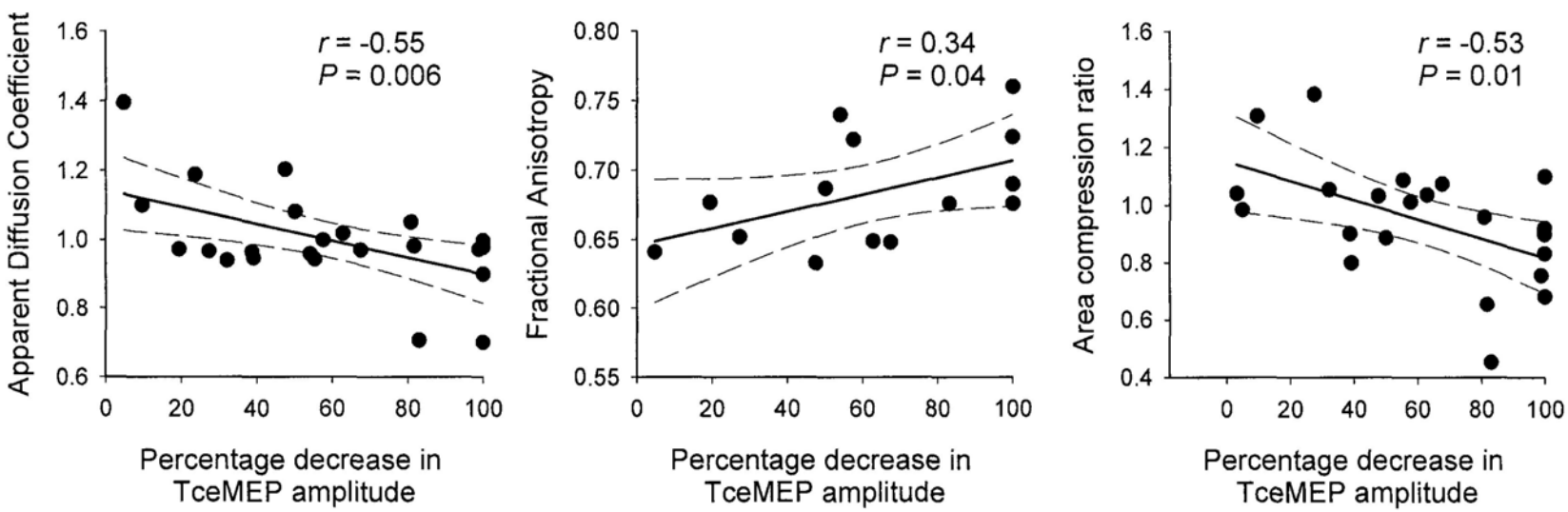


Figure 9.3. Correlation of apparent diffusion coefficient (left panel), fractional anisotropy (middle panel) and area compression ratio (right panel) with changes in transcranial electrical motor evoked potential (TceMEP). Dashed lines are the 95% confidence intervals.



Chapter 10. Discussions

In this study, a set of threshold criteria was defined for the changes in the amplitudes of SEP and TceMEP, beyond which postoperative neurologic deficit occurred. The study suggested that when the amplitude of SEP was reduced by 25% and that of TceMEP by 65%, there was substantial risk of neurologic deficit after surgery. In addition, a rapid deterioration in monitoring signals, reaching its minimum value within 5 min of an event, or a lack of signal recovery for more than 30 min after injury implied poor prognosis with unfavorable postoperative neurologic outcome.

Although the confidence intervals for the estimates were relatively narrow, the diagnostic accuracy of these predictors was more variable. In general, the performance of TceMEP and its derived parameters were better than that of SEP. Amplitude of TceMEP as a predictor has a sensitivity and specificity approaching 100%. In contrast, significant decrease in SEP amplitude was found in 2 animals without postoperative weakness (false negative).

10.1. Somatosensory evoked potential monitoring

Given that SEP measures sensory function in the spinal cord (de Haan and Kalkman, 2001; Khan et al., 2006; Padberg and Bridwell, 1999; Pelosi et al., 2002), it is not surprising that it fails to predict motor events accurately. Arguably, a model permitting examination of the sensory system will produce better results.

Nonetheless, radiologic examination indicated significant correlation between SEP changes and spinal cord damage.

The estimate on the warning criteria for SEP (25% amplitude decrease) is much lower than that recommended in current guidelines (50% amplitude decrease) (American Electroencephalographic Society 1987 and 1994; Cross 1999; Sloan and Jameson 2007; Amantini, Amadori et al., 2008; Tobias, Goble et al., 2008; American Society of Neurophysiological Monitoring). While this appeared to be conservative, it may explain the vast majority of "false negative" cases, where patients suffer postoperative neurologic deficits despite an uneventful course of intraoperative SEP monitoring. Clearly, this criterion may produce false positive alarms. Based on this information, the surgeon may decide to leave behind residual tumor, and to accept suboptimal correction of spinal deformity. Therefore, it is important to incorporate other monitoring modalities that are physiologically specific for the motor tract with high positive and negative predictive values. This study suggested that the warning criteria of a decrease in TceMEP amplitude by 65% might achieve these goals.

10.2. Transcranial electrical motor evoked potential monitoring

The use of TceMEP monitoring however, has been hampered with the lack of appropriate electrical stimulator in the past. With the introduction of multi-pulse, high voltage (up to 1,000V) generator, it is now feasible to establish TceMEP monitoring in almost all patients. Nevertheless, there are other caveats that may require further considerations.

Since the motor tract involves large number of synapses (Pajewski et al., 2007; Sloan, 2002), TceMEP is exquisitely sensitive to anesthetics. In clinically relevant dosage, volatile anesthetics, such as isoflurane, sevoflurane may abolish signal waveform (Haghighi, 1998; Kawaguchi et al., 1998). On the other hand, propofol and ketamine, have been shown to preserve signal amplitude. However, fluctuation in anesthetic doses may decrease signal amplitude by 50-60%, and this may be sufficient to trigger a false positive alarm according to our criteria (65% decrease in amplitude). We have therefore sorted to titrate anesthetic dosage according to an EEG index - the Index of Consciousness (IoC).

The IoC is a hybrid of parameters extracted from the raw EEG signals. Fast Fourier analysis was first used to calculate the power of different frequency bands (1-6 Hz, 6-12 Hz, 10-20 Hz, 30-45 Hz). This is then correlated with the state of consciousness with a non-linear analysis. The IoC uses symbolic dynamic to facilitate this analysis. In this approach, time series events are transformed into a symbol sequence which provides a model for the orbits of the dynamical system via a space of sequences. The IoC also includes EEG suppression rate to indicate deep levels of anesthesia or during hypothermia (data on file, Morpheus Medical, Llacuna, Barcelona, Spain). In this experiment, IoC was used to quantify the depth of anesthesia. Since the IoC values were comparable among pigs (Table 8.1), I therefore believed the changes in neurophysiologic signals were not due to changes in anesthetic dosages..

There are also other factors that may influence TceMEP monitoring. Hypothermia, hypotension, anemia and hypoglycemia may decrease signal amplitude

(Seyal and Mull, 2002; Sloan and Heyer, 2002; Wang et al., 2009), and should be avoided. Bolus doses of neuromuscular blocking agent produced varying degree of relaxation and may interfere with signal interpretation. In my experiment, measures were taken to ensure stable hemodynamics, temperature, plasma glucose concentrations. Muscle relaxation was not given, so that the changes in TceMEP cannot be attributed to factors other than the injury itself.

There are also issues of extrapolating the results to other form spinal cord injury. Libs and co-workers studied changes in TceMEP with spinal cord ischemia in pigs. In their experiment, ischemia was produced by sequential clipping of the lumbar segmental arteries. Neurological function was assessed 24 hours after surgery. They showed that a 75% decrease in TceMEP amplitude for > 10 min predicted postoperative motor deficit and spinal cord infarction (Libs et al., 2002, 2002b). This finding is comparable to the present study. Nevertheless, there are also focal spinal cord injuries during excision of intramedullary tumor. In these cases, TceMEP signal may not be changed with disruption of isolated tracts.

Clearly, it is inappropriate to apply the results directly to human physiology, but this experiment highlights the discrepancy and potential problems with the current guidelines. Given the variation in clinical practice identified in our review, and in the absence of other high quality data, I believe it is important and ethically feasible to validate and perhaps to re-define the "warning criteria" for intraoperative neurophysiologic monitoring in humans.

Chapter 11. Summary of the Study

In a porcine model of spinal cord injury, I have evaluated the threshold limit for the changes in neurophysiologic signals that predicted postoperative neurologic deficit.

Following compression and distraction of the exposed spinal cord, a decrease in SEP amplitude > 25% of baseline and / or a decrease in TceMEP > 65% of baseline, is associated with significant risk of motor deficit after surgery. These findings correlated with radiological (and anatomical) changes in magnetic resonance diffusion tensor imaging. Furthermore, a rapid deterioration in signal amplitude and a lack of signal recovery, for more than 30 min after an injury, indicated poor prognosis.

The findings are clinically relevant. During correction of complex spinal deformity, where compression and distraction injury may occur, surgeons should be alerted when the reduction in signal amplitudes is approaching to these threshold values. This is particularly important, when the deterioration is rapid after an event. Potential surgical interventions should be attempted and hemodynamic stability must be restored in order to avoid permanent damage of the spinal cord. A recovery of signal amplitude by 30 min would be encouraging.

PART 4 REFERENCES AND APPENDIX

References

(1987). American Electroencephalographic Society guidelines for intraoperative monitoring of sensory evoked potentials. J Clin Neurophysiol 4, 397-416.

(1994). Guideline eleven: guidelines for intraoperative monitoring of sensory evoked potentials. American Electroencephalographic Society. J Clin Neurophysiol 11, 77-87.

Accadbled, F., Henry, P., de Gauzy, J.S., and Cahuzac, J.P. (2006). Spinal cord monitoring in scoliosis surgery using an epidural electrode. Results of a prospective, consecutive series of 191 cases. Spine 31, 2614-2623.

Adams, D.C., Emerson, R.G., Heyer, E.J., McCormick, P.C., Carmel, P.W., Stein, B.M., Farcy, J.P., and Gallo, E.J. (1993). Monitoring of intraoperative motor-evoked potentials under conditions of controlled neuromuscular blockade. Anesth Analg 77, 913-918.

Amantini, A., Amadori, A., and Fossi, S. (2008). Evoked potentials in the ICU. Eur J Anaesthesiol Suppl 42, 196-202.

Banoub, M., Tetzlaff, J.E., and Schubert, A. (2003). Pharmacologic and physiologic influences affecting sensory evoked potentials: implications for perioperative monitoring. Anesthesiology 99, 716-737.

Bartley, K., Woodforth, I.J., Stephen, J.P., and Burke, D. (2002). Corticospinal volleys and compound muscle action potentials produced by repetitive transcranial stimulation during spinal surgery. Clin Neurophysiol 113, 78-90.

Basser, P.J., Pajevic, S., Pierpaoli, C., Duda, J., and Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. Magn Reson Med 44, 625-632.

Bednarik, J., Kadanka, Z., Vohanka, S., Novotny, O., Surelova, D., Filipovicova, D., and Prokes, B. (1998). The value of somatosensory and motor evoked evoked potentials in pre-clinical spondylotic cervical cord compression. Eur Spine J 7, 493-500.

Bose, B., Sestokas, A.K., and Schwartz, D.M. (2007). Neurophysiological detection of iatrogenic C-5 nerve deficit during anterior cervical spinal surgery. J Neurosurg Spine 6, 381-385.

Burke, D., Bartley, K., Woodforth, I.J., Yakoubi, A., and Stephen, J.P. (2000). The effects of a volatile anaesthetic on the excitability of human corticospinal axons. Brain 123 (Pt 5), 992-1000.

Burke, D., Hicks, R., Stephen, J., Woodforth, I., and Crawford, M. (1995). Trial-to-trial variability of corticospinal volleys in human subjects. Electroencephalogr Clin Neurophysiol 97, 231-237.

Calancie, B., Harris, W., Brindle, G.F., Green, B.A., and Landy, H.J. (2001). Threshold-level repetitive transcranial electrical stimulation for intraoperative monitoring of central motor conduction. J Neurosurg 95, 161-168.

Calancie, B., Harris, W., Broton, J.G., Alexeeva, N., and Green, B.A. (1998). "Threshold-level" multipulse transcranial electrical stimulation of motor cortex for intraoperative monitoring of spinal motor tracts: description of method and comparison to somatosensory evoked potential monitoring. J Neurosurg 88, 457-470.

Calancie, B., and Molano, M.R. (2008). Alarm criteria for motor-evoked potentials: what's wrong with the "presence-or-absence" approach? Spine 33, 406-414.

Carlson, G.D., Gorden, C.D., Oliff, H.S., Pillai, J.J., and LaManna, J.C. (2003). Sustained spinal cord compression: part I: time-dependent effect on long-term pathophysiology. J Bone Joint Surg Am 85-A, 86-94.

Cercignani, M., Inglese, M., Pagani, E., Comi, G., and Filippi, M. (2001). Mean diffusivity and fractional anisotropy histograms of patients with multiple sclerosis. AJNR Am J Neuroradiol 22, 952-958.

Chan, M.T., Gin, T., and Goh, K.Y. (2004). Interventional neurophysiologic monitoring. Curr Opin Anaesthesiol 17, 389-396.

Chiodo, A.E., Scelza, W.M., Kirshblum, S.C., Wuermser, L.A., Ho, C.H., and Priebe, M.M. (2007). Spinal cord injury medicine. 5. Long-term medical issues and health maintenance. Arch Phys Med Rehabil 88, S76-83.

Cioni, B., Meglio, M., and Rossi, G.F. (1999). Intraoperative motor evoked potentials monitoring in spinal neurosurgery. Arch Ital Biol 137, 115-126.

Costa, P., Bruno, A., Bonzanino, M., Massaro, F., Caruso, L., Vincenzo, I., Ciaramitaro, P., and Montalenti, E. (2007). Somatosensory- and motor-evoked potential monitoring during spine and spinal cord surgery. Spinal Cord 45, 86-91.

Cross, C. (1999). International organisation of societies for electrophysiological technology (OSET). Guidelines for performing EEG and evoked potential monitoring during surgery. . American Journal of Electroneurodiagnostic Technology 39, 21.

Dawson, E.G., Sherman, J.E., Kanim, L.E., and Nuwer, M.R. (1991). Spinal cord monitoring. Results of the Scoliosis Research Society and the European Spinal Deformity Society survey. Spine 16, S361-364.

de Haan, P., and Kalkman, C.J. (2001). Spinal cord monitoring: somatosensory- and motor-evoked potentials. Anesthesiol Clin North America 19, 923-945.

de Haan, P., Kalkman, C.J., de Mol, B.A., Ubags, L.H., Veldman, D.J., and Jacobs, M.J. (1997). Efficacy of transcranial motor-evoked myogenic potentials to detect spinal cord ischemia during operations for thoracoabdominal aneurysms. J Thorac Cardiovasc Surg 113, 87-100; discussion 100-101.

Deletis, V., Isgum, V., and Amassian, V.E. (2001). Neurophysiological mechanisms underlying motor evoked potentials in anesthetized humans. Part 1. Recovery time of corticospinal tract direct waves elicited by pairs of transcranial electrical stimuli. Clin Neurophysiol 112, 438-444.

Deletis V, K.K., ed. (1998). Intraoperative neurophysiology of the corticospinal tract (Vienna, Springer-Verlag).

Deletis, V., and Sala, F. (2008). Intraoperative neurophysiological monitoring of the spinal cord during spinal cord and spine surgery: a review focus on the corticospinal tracts. Clin Neurophysiol 119, 248-264.

Devlin, V.J., and Schwartz, D.M. (2007). Intraoperative neurophysiologic monitoring during spinal surgery. J Am Acad Orthop Surg 15, 549-560.

Dobkin, B.H., and Havton, L.A. (2004). Basic advances and new avenues in therapy of spinal cord injury. Annu Rev Med 55, 255-282.

Dong, C.C., MacDonald, D.B., and Janusz, M.T. (2002). Intraoperative spinal cord monitoring during descending thoracic and thoracoabdominal aneurysm surgery. Ann Thorac Surg 74, S1873-1876; discussion S1892-1878.

El-Hawary, R., Sucato, D.J., Sparagana, S., McClung, A., Van Allen, E., and Rampy, P. (2006). Spinal cord monitoring in patients with spinal deformity and neural axis abnormalities: a comparison with adolescent idiopathic scoliosis patients. Spine 31, E698-706.

Fan, D., Schwartz, D.M., Vaccaro, A.R., Hilibrand, A.S., and Albert, T.J. (2002). Intraoperative neurophysiologic detection of iatrogenic C5 nerve root injury during laminectomy for cervical compression myelopathy. Spine 27, 2499-2502.

Fujiki, M., Furukawa, Y., Kamida, T., Anan, M., Inoue, R., Abe, T., and Kobayashi, H. (2006). Intraoperative corticomuscular motor evoked potentials for evaluation of motor function: a comparison with corticospinal D and I waves. J Neurosurg 104, 85-92.

Haghighi, S.S. (1998). Influence of isoflurane anesthesia on motor evoked potentials elicited by transcortical, brainstem, and spinal root stimulation. Neurological research 20, 555-558.

Hayashi, H., Kawaguchi, M., Yamamoto, Y., Inoue, S., Koizumi, M., Ueda, Y., Takakura, Y., and Furuya, H. (2008). Evaluation of reliability of post-tetanic motor-evoked potential monitoring during spinal surgery under general anesthesia. Spine 33, E994-E1000.

Hilibrand, A.S., Schwartz, D.M., Sethuraman, V., Vaccaro, A.R., and Albert, T.J. (2004). Comparison of transcranial electric motor and somatosensory evoked potential monitoring during cervical spine surgery. J Bone Joint Surg Am 86-A, 1248-1253.

Hoehn-Berlage, M., Eis, M., Back, T., Kohno, K., and Yamashita, K. (1995). Changes of relaxation times (T1, T2) and apparent diffusion coefficient after permanent middle cerebral artery occlusion in the rat: temporal evolution, regional extent, and comparison with histology. Magn Reson Med 34, 824-834.

Hsu, B., Cree, A.K., Lagopoulos, J., and Cummine, J.L. (2008). Transcranial motor-evoked potentials combined with response recording through compound muscle

action potential as the sole modality of spinal cord monitoring in spinal deformity surgery. Spine 33, 1100-1106.

Inoue, S., Kawaguchi, M., Kakimoto, M., Sakamoto, T., Kitaguchi, K., Furuya, H., Morimoto, T., and Sakaki, T. (2002). Amplitudes and intrapatient variability of myogenic motor evoked potentials to transcranial electrical stimulation during ketamine/N2O- and propofol/N2O-based anesthesia. J Neurosurg Anesthesiol 14, 213-217.

Jacobs, M.J., Mess, W., Mochtar, B., Nijenhuis, R.J., Statius van Eps, R.G., and Schurink, G.W. (2006). The value of motor evoked potentials in reducing paraplegia during thoracoabdominal aneurysm repair. J Vasc Surg 43, 239-246.

Jallo, G.I., Kothbauer, K.F., and Epstein, F.J. (2001). Intrinsic spinal cord tumor resection. Neurosurgery 49, 1124-1128.

Jones, S.J., Harrison, R., Koh, K.F., Mendoza, N., and Crockard, H.A. (1996). Motor evoked potential monitoring during spinal surgery: responses of distal limb muscles to transcranial cortical stimulation with pulse trains. Electroencephalogr Clin Neurophysiol 100, 375-383.

Kalkman, C.J., Ubags, L.H., Been, H.D., Swaan, A., and Drummond, J.C. (1995). Improved amplitude of myogenic motor evoked responses after paired transcranial electrical stimulation during sufentanil/nitrous oxide anesthesia. Anesthesiology 83, 270-276.

Kawaguchi, M., Inoue, S., Kakimoto, M., Kitaguchi, K., Furuya, H., Morimoto, T., and Sakaki, T. (1998). The effect of sevoflurane on myogenic motor-evoked potentials induced by single and paired transcranial electrical stimulation of the motor cortex during nitrous oxide/ketamine/fentanyl anesthesia. Journal of neurosurgical anesthesiology 10, 131-136.

Kelleher, M.O., Tan, G., Sarjeant, R., and Fehlings, M.G. (2008). Predictive value of intraoperative neurophysiological monitoring during cervical spine surgery: a prospective analysis of 1055 consecutive patients. J Neurosurg Spine 8, 215-221.

Khan, M.H., Smith, P.N., Balzer, J.R., Crammond, D., Welch, W.C., Gerszten, P., Sclabassi, R.J., Kang, J.D., and Donaldson, W.F. (2006). Intraoperative somatosensory evoked potential monitoring during cervical spine corpectomy surgery: experience with 508 cases. Spine 31, E105-113.

Kim, D.H., Zaremski, J., Kwon, B., Jenis, L., Woodard, E., Bode, R., and Banco, R.J. (2007). Risk factors for false positive transcranial motor evoked potential monitoring alerts during surgical treatment of cervical myelopathy. Spine 32, 3041-3046.

Kitagawa, H., Itoh, T., Takano, H., Takakuwa, K., Yamamoto, N., Yamada, H., and Tsuji, H. (1989). Motor evoked potential monitoring during upper cervical spine surgery. Spine 14, 1078-1083.

Kothbauer, K.F. (2007). Intraoperative neurophysiologic monitoring for intramedullary spinal-cord tumor surgery. Neurophysiol Clin 37, 407-414.

Kothbauer, K.F., Deletis, V., and Epstein, F.J. (1998). Motor-evoked potential monitoring for intramedullary spinal cord tumor surgery: correlation of clinical and neurophysiological data in a series of 100 consecutive procedures. Neurosurg Focus 4, e1.

Kothbauer, K.F., and Novak, K. (2004). Intraoperative monitoring for tethered cord surgery: an update. Neurosurg Focus 16, E8.

Krassioukov, A.V., Sarjeant, R., Arkia, H., and Fehlings, M.G. (2004). Multimodality intraoperative monitoring during complex lumbosacral procedures:

indications, techniques, and long-term follow-up review of 61 consecutive cases. J Neurosurg Spine 1, 243-253.

Kunisawa, T., Takahata, O., Sengoku, K., Suzuki, A., and Iwasaki, H. (2002). [Anesthetic management of four cases of craniotomy with alternate monitoring of motor and somatosensory evoked potentials]. Masui 51, 1233-1237.

Lam, A.M., Manninen, P.H., Ferguson, G.G., and Nantau, W. (1991). Monitoring electrophysiologic function during carotid endarterectomy: a comparison of somatosensory evoked potentials and conventional electroencephalogram. Anesthesiology 75, 15-21.

Lang, E.W., Beutler, A.S., Chesnut, R.M., Patel, P.M., Kennelly, N.A., Kalkman, C.J., Drummond, J.C., and Garfin, S.R. (1996a). Myogenic motor-evoked potential monitoring using partial neuromuscular blockade in surgery of the spine. Spine 21, 1676-1686.

Lang, E.W., Chesnut, R.M., Beutler, A.S., Kennelly, N.A., and Renaudin, J.W. (1996b). The utility of motor-evoked potential monitoring during intramedullary surgery. Anesth Analg 83, 1337-1341.

Langeloo, D.D., Journee, H.L., de Kleuver, M., and Grotenhuis, J.A. (2007). Criteria for transcranial electrical motor evoked potential monitoring during spinal deformity surgery A review and discussion of the literature. Neurophysiol Clin 37, 431-439.

Langeloo, D.D., Lelivelt, A., Louis Journee, H., Slappendel, R., and de Kleuver, M. (2003). Transcranial electrical motor-evoked potential monitoring during surgery for spinal deformity: a study of 145 patients. Spine 28, 1043-1050.

Le Bihan, D., Breton, E., Lallemand, D., Aubin, M.L., Vignaud, J., and Laval-Jeantet, M. (1988). Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 168, 497-505.

Lee, J.W., Park, K.S., Kim, J.H., Choi, J.Y., Hong, S.H., Park, S.H., and Kang, H.S. (2008). Diffusion tensor imaging in idiopathic acute transverse myelitis. AJR Am J Roentgenol 191, W52-57.

Legatt, A.D. (2004). Ellen R. Grass Lecture: Motor evoked potential monitoring. Am J Electroneurodiagnostic Technol 44, 223-243.

Lieberman, J.A., Lyon, R., Feiner, J., Hu, S.S., and Berven, S.H. (2008). The efficacy of motor evoked potentials in fixed sagittal imbalance deformity correction surgery. Spine 33, E414-424.

Lips, J., de Haan, P., Bouma, G.J., Jacobs, M.J., and Kalkman, C.J. (2002a). Delayed detection of motor pathway dysfunction after selective reduction of thoracic spinal cord blood flow in pigs. J Thorac Cardiovasc Surg 123, 531-538.

Lips, J., de Haan, P., de Jager, S.W., Vanicky, I., Jacobs, M.J., and Kalkman, C.J. (2002b). The role of transcranial motor evoked potentials in predicting neurologic and histopathologic outcome after experimental spinal cord ischemia. Anesthesiology 97, 183-191.

MacDonald, D.B. (2002). Safety of intraoperative transcranial electrical stimulation motor evoked potential monitoring. J Clin Neurophysiol 19, 416-429.

Macdonald, D.B. (2006). Intraoperative motor evoked potential monitoring: overview and update. J Clin Monit Comput 20, 347-377.

MacDonald, D.B., Al Zayed, Z., Khoudeir, I., and Stigsby, B. (2003). Monitoring scoliosis surgery with combined multiple pulse transcranial electric motor and

cortical somatosensory-evoked potentials from the lower and upper extremities. Spine 28, 194-203.

Manninen, P.H. (1998). Monitoring evoked potentials during spinal surgery in one institution. Can J Anaesth 45, 460-465.

May, D.M., Jones, S.J., and Crockard, H.A. (1996). Somatosensory evoked potential monitoring in cervical surgery: identification of pre- and intraoperative risk factors associated with neurological deterioration. J Neurosurg 85, 566-573.

Meylaerts, S.A., De Haan, P., Kalkman, C.J., Jaspers, J., Vanicky, I., and Jacobs, M.J. (2000). Prevention of paraplegia in pigs by selective segmental artery perfusion during aortic cross-clamping. J Vasc Surg 32, 160-170.

Mochida, K., Komori, H., Okawa, A., and Shinomiya, K. (1997). Evaluation of motor function during thoracic and thoracolumbar spinal surgery based on motor-evoked potentials using train spinal stimulation. Spine 22, 1385-1393.

Mok, J.M., Lyon, R., Lieberman, J.A., Cloyd, J.M., and Burch, S. (2008). Monitoring of nerve root injury using transcranial motor-evoked potentials in a pig model. Spine 33, E465-473.

More, R.C., Nuwer, M.R., and Dawson, E.G. (1988). Cortical evoked potential monitoring during spinal surgery: sensitivity, specificity, reliability, and criteria for alarm. J Spinal Disord 1, 75-80.

Mori, S., Itoh, R., Zhang, J., Kaufmann, W.E., van Zijl, P.C., Solaiyappan, M., and Yarowsky, P. (2001). Diffusion tensor imaging of the developing mouse brain. Magn Reson Med 46, 18-23.

Moseley, M.E., Cohen, Y., Mintorovitch, J., Chileuitt, L., Shimizu, H., Kucharczyk, J., Wendland, M.F., and Weinstein, P.R. (1990). Early detection of regional

cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. Magn Reson Med 14, 330-346.

Nagle, K.J., Emerson, R.G., Adams, D.C., Heyer, E.J., Roye, D.P., Schwab, F.J., Weidenbaum, M., McCormick, P., Pile-Spellman, J., Stein, B.M., et al. (1996). Intraoperative monitoring of motor evoked potentials: a review of 116 cases. Neurology 47, 999-1004.

Neuloh, G., Pechstein, U., Cedzich, C., and Schramm, J. (2004). Motor evoked potential monitoring with supratentorial surgery. Neurosurgery 54, 1061-1070; discussion 1070-1062.

Neuloh, G., and Schramm, J. (2004). Monitoring of motor evoked potentials compared with somatosensory evoked potentials and microvascular Doppler ultrasonography in cerebral aneurysm surgery. J Neurosurg 100, 389-399.

Noonan, K.J., Walker, T., Feinberg, J.R., Nagel, M., Didelot, W., and Lindseth, R. (2002). Factors related to false- versus true-positive neuromonitoring changes in adolescent idiopathic scoliosis surgery. Spine 27, 825-830.

Nuwer, M.R., Dawson, E.G., Carlson, L.G., Kanim, L.E., and Sherman, J.E. (1995). Somatosensory evoked potential spinal cord monitoring reduces neurologic deficits after scoliosis surgery: results of a large multicenter survey. Electroencephalogr Clin Neurophysiol 96, 6-11.

Osburn, L.L. (2006). A guide to the performance of transcranial electrical motor evoked potentials. Part 1. Basic concepts, recording parameters, special considerations, and application. Am J Electroneurodiagnostic Technol 46, 98-158.

Padberg, A.M., and Bridwell, K.H. (1999). Spinal cord monitoring: current state of the art. Orthop Clin North Am 30, 407-433, viii.

Pajewski, T.N., Arlet, V., and Phillips, L.H. (2007). Current approach on spinal cord monitoring: the point of view of the neurologist, the anesthesiologist and the spine surgeon. Eur Spine J 16 Suppl 2, S115-129.

Papastefanou, S.L., Henderson, L.M., Smith, N.J., Hamilton, A., and Webb, J.K. (2000). Surface electrode somatosensory-evoked potentials in spinal surgery: implications for indications and practice. Spine 25, 2467-2472.

Paradiso, G., Lee, G.Y., Sarjeant, R., and Fehlings, M.G. (2005). Multi-modality neurophysiological monitoring during surgery for adult tethered cord syndrome. J Clin Neurosci 12, 934-936.

Pechstein, U., Cedzich, C., Nadstawek, J., and Schramm, J. (1996). Transcranial high-frequency repetitive electrical stimulation for recording myogenic motor evoked potentials with the patient under general anesthesia. Neurosurgery 39, 335-343; discussion 343-334.

Peduzzi, P., Concato, J., Kemper, E., Holford, T.R., and Feinstein, A.R. (1996). A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 49, 1373-1379.

Pelosi, L., Lamb, J., Grevitt, M., Mehdian, S.M., Webb, J.K., and Blumhardt, L.D. (2002). Combined monitoring of motor and somatosensory evoked potentials in orthopaedic spinal surgery. Clin Neurophysiol 113, 1082-1091.

Pelosi, L., Stevenson, M., Hobbs, G.J., Jardine, A., and Webb, J.K. (2001). Intraoperative motor evoked potentials to transcranial electrical stimulation during two anaesthetic regimens. Clin Neurophysiol 112, 1076-1087.

Priebe, M.M., Chiodo, A.E., Scelza, W.M., Kirshblum, S.C., Wuermser, L.A., and Ho, C.H. (2007). Spinal cord injury medicine. 6. Economic and societal issues in spinal cord injury. Arch Phys Med Rehabil 88, S84-88.

Quinones-Hinojosa, A., Gadkary, C.A., Gulati, M., von Koch, C.S., Lyon, R., Weinstein, P.R., and Yingling, C.D. (2004). Neurophysiological monitoring for safe surgical tethered cord syndrome release in adults. Surg Neurol 62, 127-133; discussion 133-125.

Quinones-Hinojosa, A., Lyon, R., Zada, G., Lamborn, K.R., Gupta, N., Parsa, A.T., McDermott, M.W., and Weinstein, P.R. (2005). Changes in transcranial motor evoked potentials during intramedullary spinal cord tumor resection correlate with postoperative motor function. Neurosurgery 56, 982-993; discussion 982-993.

Sala, F., Bricolo, A., Faccioli, F., Lanteri, P., and Gerosa, M. (2007). Surgery for intramedullary spinal cord tumors: the role of intraoperative (neurophysiological) monitoring. Eur Spine J 16 Suppl 2, S130-139.

Sala, F., and Lanteri, P. (2003). Brain surgery in motor areas: the invaluable assistance of intraoperative neurophysiological monitoring. J Neurosurg Sci 47, 79-88.

Sala, F., Palandri, G., Basso, E., Lanteri, P., Deletis, V., Faccioli, F., and Bricolo, A. (2006). Motor evoked potential monitoring improves outcome after surgery for intramedullary spinal cord tumors: a historical control study. Neurosurgery 58, 1129-1143; discussion 1129-1143.

Schwartz, D.M., Auerbach, J.D., Dormans, J.P., Flynn, J., Drummond, D.S., Bowe, J.A., Laufer, S., Shah, S.A., Bowen, J.R., Pizzutillo, P.D., et al. (2007). Neurophysiological detection of impending spinal cord injury during scoliosis surgery. J Bone Joint Surg Am 89, 2440-2449.

Seyal, M., and Mull, B. (2002). Mechanisms of signal change during intraoperative somatosensory evoked potential monitoring of the spinal cord. J Clin Neurophysiol 19, 409-415.

Sloan, T.B. (2002). Anesthetics and the brain. Anesthesiol Clin North America 20, 265-292.

Sloan, T.B., and Heyer, E.J. (2002). Anesthesia for intraoperative neurophysiologic monitoring of the spinal cord. J Clin Neurophysiol 19, 430-443.

Sloan, T.B., and Jameson, L.C. (2007). Electrophysiologic monitoring during surgery to repair the thoraco-abdominal aorta. J Clin Neurophysiol 24, 316-327.

Smith, P.N., Balzer, J.R., Khan, M.H., Davis, R.A., Crammond, D., Welch, W.C., Gerszten, P., Sclabassi, R.J., Kang, J.D., and Donaldson, W.F. (2007). Intraoperative somatosensory evoked potential monitoring during anterior cervical discectomy and fusion in nonmyelopathic patients--a review of 1,039 cases. Spine J 7, 83-87.

Strauch, J.T., Lauten, A., Spielvogel, D., Rinke, S., Zhang, N., Weisz, D., Bodian, C.A., and Griepp, R.B. (2004). Mild hypothermia protects the spinal cord from ischemic injury in a chronic porcine model. Eur J Cardiothorac Surg 25, 708-715.

Sutter, M., Eggspuehler, A., Muller, A., and Dvorak, J. (2007). Multimodal intraoperative monitoring: an overview and proposal of methodology based on 1,017 cases. Eur Spine J 16 Suppl 2, S153-161.

Szelenyi, A., Kothbauer, K., de Camargo, A.B., Langer, D., Flamm, E.S., and Deletis, V. (2005). Motor evoked potential monitoring during cerebral aneurysm surgery: technical aspects and comparison of transcranial and direct cortical stimulation. Neurosurgery 57, 331-338; discussion 331-338.

Szelenyi, A., Langer, D., Beck, J., Raabe, A., Flamm, E.S., Seifert, V., and Deletis, V. (2007). Transcranial and direct cortical stimulation for motor evoked potential monitoring in intracerebral aneurysm surgery. Neurophysiol Clin 37, 391-398.

Szelenyi, A., Langer, D., Kothbauer, K., De Camargo, A.B., Flamm, E.S., and Deletis, V. (2006). Monitoring of muscle motor evoked potentials during cerebral aneurysm surgery: intraoperative changes and postoperative outcome. J Neurosurg 105, 675-681.

Tanaka, N., Nakanishi, K., Fujiwara, Y., Kamei, N., and Ochi, M. (2006). Postoperative segmental C5 palsy after cervical laminoplasty may occur without intraoperative nerve injury: a prospective study with transcranial electric motor-evoked potentials. Spine 31, 3013-3017.

Tarlov, I.M. (1954). Spinal cord compression studies. III. Time limits for recovery after gradual compression in dogs. AMA Arch Neurol Psychiatry 71, 588-597.

Tobias, J.D., Goble, T.J., Bates, G., Anderson, J.T., and Hoernschemeyer, D.G. (2008). Effects of dexmedetomidine on intraoperative motor and somatosensory evoked potential monitoring during spinal surgery in adolescents. Paediatr Anaesth 18, 1082-1088.

Toleikis, J.R. (2005). Intraoperative monitoring using somatosensory evoked potentials. A position statement by the American Society of Neurophysiological Monitoring. J Clin Monit Comput 19, 241-258.

Tunis, S.R., Stryer, D.B., and Clancy, C.M. (2003). Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 290, 1624-1632.

Ubags, L.H., Kalkman, C.J., Been, H.D., and Drummond, J.C. (1997). Differential effects of nitrous oxide and propofol on myogenic transcranial motor evoked responses during sufentanil anaesthesia. Br J Anaesth 79, 590-594.

van Dongen, E.P., ter Beek, H.T., Schepens, M.A., Morshuis, W.J., de Boer, A., Aarts, L.P., and Boezeman, E.H. (1999). Within patient variability of lower extremity muscle responses to transcranial electrical stimulation with pulse trains in aortic surgery. Clin Neurophysiol 110, 1144-1148.

Wang, A.C., Than, K.D., Etame, A.B., La Marca, F., and Park, P. (2009). Impact of anesthesia on transcranial electric motor evoked potential monitoring during spine surgery: a review of the literature. Neurosurg Focus 27, E7.

Wang, Y.X., and Lam, W.W. (2008). Characterisation of brain disorders and evaluation of therapy by functional and molecular magnetic resonance techniques. Hong Kong Med J 14, 469-478.

Weinzierl, M.R., Reinacher, P., Gilsbach, J.M., and Rohde, V. (2007). Combined motor and somatosensory evoked potentials for intraoperative monitoring: intra- and postoperative data in a series of 69 operations. Neurosurg Rev 30, 109-116; discussion 116.

Wiedemayer, H., Fauser, B., Sandalcioglu, I.E., Schafer, H., and Stolke, D. (2002). The impact of neurophysiological intraoperative monitoring on surgical decisions: a critical analysis of 423 cases. J Neurosurg 96, 255-262.

Wiedemayer, H., Sandalcioglu, I.E., Armbruster, W., Regel, J., Schaefer, H., and Stolke, D. (2004). False negative findings in intraoperative SEP monitoring: analysis of 658 consecutive neurosurgical cases and review of published reports. J Neurol Neurosurg Psychiatry 75, 280-286.

Wilson-Holden, T.J., Padberg, A.M., Lenke, L.G., Larson, B.J., Bridwell, K.H., and Bassett, G.S. (1999). Efficacy of intraoperative monitoring for pediatric patients with spinal cord pathology undergoing spinal deformity surgery. Spine 24, 1685-1692.

Woodforth, I.J., Hicks, R.G., Crawford, M.R., Stephen, J.P., and Burke, D.J. (1996). Variability of motor-evoked potentials recorded during nitrous oxide anesthesia from the tibialis anterior muscle after transcranial electrical stimulation. Anesth Analg 82, 744-749.

Zaarour, C., Engelhardt, T., Strantzas, S., Pehora, C., Lewis, S., and Crawford, M.W. (2007). Effect of low-dose ketamine on voltage requirement for transcranial electrical motor evoked potentials in children. Spine (Phila Pa 1976) 32, E627-630.

Zentner, J. (1989). Noninvasive motor evoked potential monitoring during neurosurgical operations on the spinal cord. Neurosurgery 24, 709-712.

Zentner, J. (1991). Motor evoked potential monitoring during neurosurgical operations on the spinal cord. Neurosurg Rev 14, 29-36.

Zentner, J., Kiss, I., and Ebner, A. (1989). Influence of anesthetics--nitrous oxide in particular--on electromyographic response evoked by transcranial electrical stimulation of the cortex. Neurosurgery 24, 253-256.

Zhou, H.H., and Kelly, P.J. (2001). Transcranial electrical motor evoked potential monitoring for brain tumor resection. Neurosurgery 48, 1075-1080; discussion 1080-1071.

Appendix

Table 1. Average normalized amplitude of transcranial electrical motor evoked potential with different stimulation protocol.

Interstimulus interval (ms)	Number of stimulus								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1	0	17.72	13.35	26.76	38.39	56.25	72.53	70.47	76.26
2	0	37.97	31.81	51.78	71.33	77.71	76.98	82.51	75.71
3	0	8.31	36.38	54.27	66.30	70.63	78.32	81.22	75.69
4	0	7.77	45.67	50.87	65.76	64.23	67.67	70.51	62.09
5	0	23.60	37.28	53.44	68.97	68.43	62.13	55.26	56.72
6	0	15.07	27.58	44.14	55.34	55.61	45.73	56.54	48.73
7	0	18.56	30.10	32.17	38.15	36.28	41.96	47.54	50.75
8	0	28.98	29.02	34.50	35.22	37.76	43.94	38.38	52.12
9	0	16.08	17.50	22.16	28.03	34.93	37.47	31.88	39.99