

The Role of Transcranial Motor Evoked Potentials in Predicting Neurologic and Histopathologic Outcome after Experimental Spinal Cord Ischemia

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Background: Monitoring of myogenic motor evoked potentials to transcranial stimulation (tcMEPs) is clinically used to assess motor pathway function during aortic and spinal procedures that carry a risk of spinal cord ischemia (SCI). Although tcMEPs presumably detect SCI before irreversible neuronal deficit occurs, and prolonged reduction of tcMEP signals is thought to be associated with impending spinal cord damage, experimental evidence to support this concept has not been provided. In this study, histopathologic and neurologic outcome was examined in a porcine model of SCI after different durations of intraoperative loss of tcMEP signals.

Methods: In 15 ketamine-sufentanil-anesthetized pigs (weight, 35–45 kg) the spinal cord feeding lumbar arteries were exposed. tcMEP were recorded from the upper and lower limbs. Under normothermic conditions, animals were randomly allocated to undergo short-term tcMEP reduction (group A, < 10 min, n = 5) or prolonged tcMEP reduction (group B, 60 min, n = 10), resulting from temporary or permanent clamping of lumbar segmental arteries. Neurologic function was evaluated every 24 h, and infarction volume and the number of eosinophilic neurons and viable motoneurons in the lumbosacral spinal cord was evaluated 72 h after induction of SCI.

Results: In all animals except one, segmental artery clamping reduced tcMEP to below 25% of baseline. All but one animal in group A had reduced tcMEP for less than 10 min and had normal motor function and no infarction at 72 h after the initial tcMEP reduction. Seven animals in group B (70%) had reduced tcMEP signals for more than 60 min and were paraplegic with massive spinal cord infarction at 72 h. Two animals (one in both groups) had tcMEP loss for 40 min, with moderate infarction and normal function. In general, histopathologic damage and neurologic dysfunction did not occur when tcMEP amplitude recovered within 10 and 40 min after the initial decline, respectively.

Conclusion: Prolonged reduction of intraoperative tcMEP amplitude is predictive for postoperative neurologic dysfunction, while recovery of the tcMEP signal within 10 min after the initial decline corresponds with normal histopathology and motor function in this experimental model. This finding confirms that intraoperative tcMEPs have a good prognostic value

for neurologic outcome during procedures in which the spinal cord is at risk for ischemia.

PROLONGED spinal cord ischemia (SCI) during surgery on the aorta or the spine can result in irreversible neurologic deficit. Although recent reports indicate that the incidence of neurologic complications has declined, resection of thoracoabdominal aneurysms is still associated with a 5–15% incidence of spinal cord injury.^{1–6} Loss of motoneuron function that occurs during temporary reduction of spinal cord perfusion pressure resulting from, e.g., occlusion of critical segmental arteries that are located within the excluded aortic segment, can be detected with myogenic transcranial motor evoked potentials (tcMEPs).^{7–9} This technique provides continuous assessment of motor tract conduction integrity,^{10–12} and the amplitude of tcMEPs recorded from the lower limb was minimized almost instantaneously after aortic cross-clamping.^{13–15} The early detection of SCI by tcMEPs allows prompt institution of measures to restore spinal cord perfusion, such as increasing distal aortic perfusion pressure and reattachment of critical segmental arteries to the graft.^{16,17} A considerable body of evidence indicates a good agreement between intraoperative motor evoked potentials and postoperative neurologic status.^{11,16,18,19} However, a prospective evaluation that indicates that tcMEP consistently detects SCI before irreversible spinal cord injury occurs, and that a prolonged reduction of tcMEPs predicts postoperative neurologic deficit has been lacking. In the current study, SCI was induced in a porcine model with segmental artery clamping. This method reduced spinal cord blood flow (SCBF) to a level similar to that observed after aortic occlusion, sufficient to result in tcMEP loss.^{20–23} A similar prolonged reduction of SCBF can result in spinal cord infarction and neurologic dysfunction.²⁴ The purpose of this study was to investigate the predictive value of myogenic tcMEPs for short-term neurologic and histopathologic outcome.

Materials and Methods

Animal care and experimental procedures were performed in compliance with The National Guidelines for Care of Laboratory Animals in the Netherlands. The study protocol was approved by the Animal Research Committee of the Academic Hospital at the University of

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Amsterdam, the Netherlands. Fifteen pigs, weighing 47 ± 5 kg, were included in the study.

Anesthesia

Premedication consisted of ketamine 15 mg/kg intramuscularly. Anesthesia was induced with inhalation by mask of 2.0% isoflurane in a mixture of 50% O₂ in air. Two intravenous catheters (18 gauge) were placed in an ear vein, and normal saline was infused at a rate of $15 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. After induction of anesthesia, sufentanil 15 $\mu\text{g}/\text{kg}$ and clonidine 2 $\mu\text{g}/\text{kg}$ were given intravenously, isoflurane was discontinued, and anesthesia was maintained with a continuous infusion of ketamine ($15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), sufentanil ($5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), and clonidine ($1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). The tracheas were intubated, and animals were ventilated using intermittent positive pressure ventilation. End-tidal carbon dioxide concentration was measured by a mainstream capnograph (Hewlett-Packard, Boeblingen, Germany), and PaCO₂ was maintained between 36 and 40 mmHg. Adequacy of ventilation was confirmed by blood gas analysis at 37°C. The level of neuromuscular blockade was monitored electromyographically using a Datex Relaxograph (Datex-Ohmeda, Helsinki, Finland) placed at the animal's wrist equivalent after stimulation of the median nerve. A closed loop infusion system with pancuronium was used to maintain 40% relaxation as referenced to the control situation. This level of muscle relaxation was chosen to provide an optimal trade off between spontaneous movements of the animal and the minimal requirements for myogenic evoked potential recording and assessment of adequate depth of anesthesia. Arterial blood pressure and central venous pressure were measured from catheters placed in the right popliteal artery and the left cephalic vein, respectively. Oxygen saturation was continuously assessed by pulse oximetry. Nasopharyngeal temperature was monitored and kept at 38°C by means of a heating lamp. Urinary output was measured throughout the experiment. Before incision, the skin of the animal was pinched with a forceps, and absence of spontaneous movement or an increase of arterial blood pressure was an indication for adequate depth of anesthesia. Before the start of ischemic manipulations, arterial pH, PaO₂, PaCO₂, hemoglobin concentration, and hematocrit were measured.

Operative Procedure

Animals were placed in the right decubitus position. Under sterile conditions a laparotomy was made through a midline incision, and the viscera were transposed to the right. The abdominal aorta, the arising lumbar arteries, and the sacral artery were exposed. The thoracic duct, which in pig is much larger compared to the thoracic duct in humans, is at risk during the exposure of segmental arteries. Rupture may result in development of severe dyspnea during the postoperative phase, as

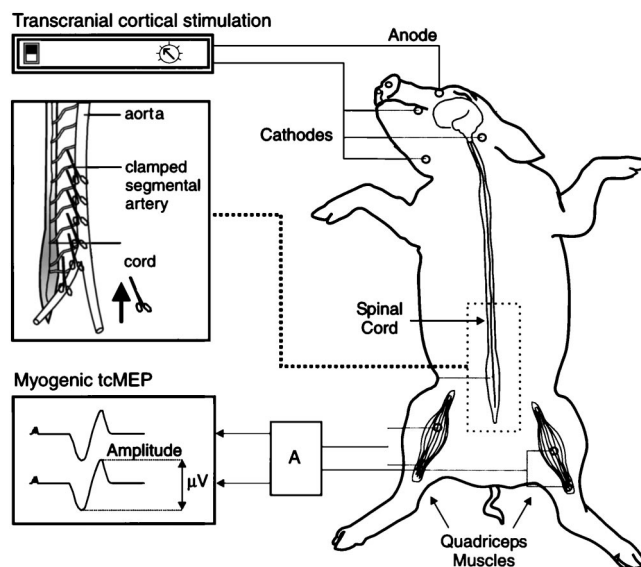


Fig. 1. Schematic representation of the experimental set up. (Top to bottom) Transcranial stimulation of the motor cortex, sequential clamping of segmental arteries, and myogenic recording of evoked potentials is shown, respectively.

observed in a pilot study. To avoid damage, we separated the entire lumbar part of the duct from the aorta. Incidental leaks were meticulously sutured, and all animals in the study remained free from pulmonary complications. Permanent occlusion of segmental arteries (group B) was carried out with a clip application instrument (ligaclip MCA; Ethicon, Somerville, NJ). After induction of SCI (see Experimental Design), the abdomen was closed in layers. The spinal cord was harvested at 72 h, during which procedure the interior of the aorta was inspected to determine whether all lumbar and intercostal segmental arteries (SAs) had been identified.

Experimental Design

Figure 1 shows the experimental setup. Fifteen minutes before ischemic manipulations, baseline values for tcMEP were obtained. Animals were randomized to undergo either transient tcMEP reduction (group A, $n = 5$) or prolonged tcMEP reduction (group B, $n = 10$). The target period of tcMEP loss was less than 10 min in group A and 60 min in group B. To induce SCI, SAs were clamped in a caudal-to-cranial direction. A time interval of 5 min was applied between the occlusion of two successive arteries. In group A, a number of SAs were occluded sequentially with removable arterial clamps, which was sufficient to abolish tcMEP completely. One or several clamps were then sequentially released, starting at the most cranial arterial clamp, until tcMEP returned to values greater than 75% of baseline. The remaining clamps were replaced by vascular clips that permanently occlude an artery. Permanent clipping of these arteries was performed to approach the clinical situation of aortic aneurysm repair, during which only

SAs that are critical for spinal cord perfusion (as identified by tcMEP recording) are reattached to the graft.¹⁷ tcMEP monitoring was discontinued at 60 min after the initial loss of the tcMEP signal. In group B, all arteries were sequentially occluded with permanent vascular clips. tcMEP monitoring was discontinued at 60 min after the primary loss of tcMEP signals. After termination of tcMEP recording, anesthesia was discontinued in all animals. At 72 h after the initial tcMEP loss, animals underwent the final neurologic scoring, and spinal cords were harvested after the animals were killed.

Evoked Potential Recording

Transcranial motor evoked potential stimuli were applied with a transcranial electrical stimulator (Digitimer D 185 cortical stimulator; Welwyn Garden City, UK) through four needle electrodes attached to the scalp. A train-of-four square wave pulses (peak voltage 600–1,200 V), with a duration of 50 μ s and an interstimulus interval of 2 ms, was distributed over the motor cortex *via* an anode located at the occiput and three interconnected cathodes placed behind the ears and in the soft palate. Compound muscle action potentials were recorded from the skin over the right upper limb triceps muscle and bilaterally over the lower limb quadriceps muscles using adhesive gel Ag/AgCl electrodes. The signals were amplified 5,000–20,000 times (adjusted to obtain maximum vertical resolution) and filtered between 30 and 1,500 Hz using a 3T PS-800 biologic amplifier (Twente Technology Transfer, Twente, the Netherlands). Stimulus intensity was adjusted to acquire maximal responses, and recording was performed at a setting of 10% above the stimulus level that obtained maximal amplitude. Amplitude of the compound muscle action potentials was defined as the peak-to-peak distance in microvolts. A reduction of tcMEP amplitude on the muscle groups monitored to less than 25% of the baseline value was considered an indication of ischemic spinal cord dysfunction. This criterion is based on the assumption that an amplitude decrease below three times the SD should provide optimal detection of ischemia while limiting the rate of false-positive monitoring results and our previous observation of a 26% within-patient variability of the tcMEP.¹⁶ Loss of tcMEP signal was defined as reduction of the amplitude to below 40 μ V (this value represented approximately 2 times the peak-to-peak noise level in waveforms acquired without stimulation). This complete reduction of tcMEP amplitude is presented in Results as tcMEP absence. Baseline motor evoked potentials were obtained during laparotomy by averaging 10 consecutive responses before the clamping of SAs. Responses were displayed and stored on a MacIntosh Quadra computer (Apple Computer, Cupertino, CA) with 12-bit A/D conversion and acquisition software written in the LabVIEW programming environment (National Instruments, Austin, TX).²⁵

Postoperative Period

Before extubation animals received buprenorphine 0.01 mg/kg intramuscularly and a nonsteroidal anti-inflammatory drug (flunixin 2 mg/kg intramuscularly) for analgesia. During the night following surgery, the animals received buprenorphine 0.01 mg/kg intramuscularly at 8 and 16 h after awaking, and flunixin 2 mg/kg intramuscularly at 12 h after awaking. All animals received total parenteral nutrition (Intralipid 20%; Fresenius, Homburg, Germany) 100 ml, during the first hours after awaking.

Neurologic Evaluation

Twenty-four, 48, and 72 h after the ischemic insult, the neurologic status of the animals was assessed by an observer blinded to the surgical intervention. After stimulation of the animals with the placement of food rewards several feet away from their resting location, neurologic function was evaluated according to a modified Tarlov score (five-point scale of motor function)²⁶: 0 = paraplegic with no lower extremity function; 1 = poor lower extremity function, weak antigravity movement only; 2 = good movement, not able to stand; 3 = able to stand, not to walk; 4 = normal motor function.

Spinal Cord Pathology

After final scoring of neurologic function at 72 h, the animals were premedicated (ketamine 15 mg/kg intramuscularly) and anesthetized with ketamine (15 mg \cdot kg⁻¹ \cdot h⁻¹), sufentanil (5 μ g \cdot kg⁻¹ \cdot h⁻¹), and clonidine (1 μ g \cdot kg⁻¹ \cdot h⁻¹), and 2.0% isoflurane in a mixture of 50% O₂ in air. After administration of heparin, animals were killed with pentobarbital (100 mg intravenously) and KCL (10 ml intravenously), and the vertebral column containing the vertebral bodies L2–S1 was perfusion fixated with formalin 3.6%. The lumbosacral segment of the spinal cord was removed *en bloc* and immersed in formalin for at least 10 days. The whole lumbosacral portion of the spinal cord was sampled systematically.²⁷ Twelve equidistant transverse slices (1 mm thick) were dissected and embedded in paraffin. From each paraffin block, randomly selected 4- μ m thick sections were cut and stained with hematoxylin and eosin. In the resulting series of sections, the spinal cord segment that gives rise to the lumbosacral plexus (L4–L6 and S1–S4) in pig²⁸ was located between the 5th and the 11th section.

Infarction Volume

At a low magnification, all of the sections were digitized and the areas of total gray matter and infarcted gray matter were measured interactively using image analysis software (Qwin; Leica, Cambridge, UK) by two observers who were blinded to the experimental results. The areas (millimeters squared) were then integrated with the known distance between each transverse level to provide an estimate of the infarction volume of the

Table 1. Physiologic Parameters

Group	pH	Paco ₂ (mmHg)	PaO ₂ (mmHg)	Ht (%)	Hb (g/dl)	Temp (°C)
Intervention (A, n = 4)	7.46 ± 0.03	37.6 ± 2.8	202 ± 25	30.6 ± 2.2	9.7 ± 0.3	38.3 ± 0.4
Ischemia (B, n = 10)	7.49 ± 0.08	35.2 ± 3.6	237 ± 27	31.7 ± 1.0	10.3 ± 0.3	38.7 ± 0.5

All values are mean ± SD.

Paco₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension; Ht = hematocrit; Hb = Hemoglobin; temp = rectal temperature during the last hour of tcMEP recording; intervention = group A, short tcMEP reduction; ischemia = group B, prolonged tcMEP reduction.

spinal cord. In each animal, the extent of infarction was expressed as the percentage of necrotic tissue of the total gray matter volume. To further specify the localization of infarctions, gray matter area was separated into dorsal, intermediate, and ventral zones by dividing the dorsoventral axis of gray matter into three equal parts.

Selective Neuronal Necrosis

To quantify selective necrosis, eosinophilic neurons were counted in every section of the spinal cord using light microscopy (Leica). Individual counts were added to give an aggregate of eosinophilic neurons for all 12 sections. The effective magnification was 100×.

Ventral Horn Motoneurons

The total number of apparently viable ventral horn (α) motoneurons was determined in each section. Morphologic viability was defined according to the following criteria: fine granular cytoplasm with basophilic stippling (presence of Nissl substance), prominent nucleoli, and a soma diameter of 30–60 μ m.²⁹ Results were expressed as aggregates of 12 counts for each animal, one count being the total number of motoneurons for one section.

Group Size and Presentation of Results

Power analysis was used to calculate the minimal group size that allowed for detection of significant differences in neurologic outcome between the two groups. We wished to have sufficient power ($1-\beta = 0.8$, $\alpha = 0.05$) to be able to detect a reduction of the incidence of paraplegia from 80% in the permanently clamped group to 0% in the intervention group (transient tcMEP reduction). This required a group size of 5 in the intervention group (group A) and 10 in the permanently clamped group (group B). We assumed that the expected difference in neurologic events would agree with a relevant difference in duration of tcMEP loss between the groups. This would allow for a reliable determination of the predictive value of short and prolonged tcMEP loss for postoperative neurologic function. Because the degree of postoperative neurologic injury was the dependent variable in this study, the expected outcome in the intervention group (100% normal motor function) was less informative. Therefore, the number of animals in the intervention group was limited, resulting in unequal group sizes.

Arterial blood pressure, blood gases, weight, and temperatures are expressed as means ± SD. Neurologic

Table 2. tcMEP Reduction Times and Neurologic Status after 72 h

Group	Animal	Interval (min)	tcMEP < 25% (min)	tcMEP Absent (min)	Motor Score (0–4)	Infarction Volume (%)
Partial reperfusion after tcMEP loss (A)	1	18	3	2	4	0
	2	36	2	0	4	0
	3	13	61	43*	4	11.6
	4	13	7	2	4	0
Permanent segmental artery occlusion (B)	1	18	47	42	3	95.1
	2	7	60	60	0	38.9
	3	19	60	60	0	92.4
	4	12	60	60	0	100
	5	22	25	8	4	9.6
	6	40	37	10*	4	31.3
	7	8	63	60	0	43.7
	8	21	62	60	0	73.8
	9	17	62	60	0	92.7
	10	20	62	60	0	54.1

Absolute and relative values for individual animals are shown.

* In these animals, three short periods of waveform absence were observed, of which the summation is given.

Interval = time in minutes between clamping the first segmental artery and reduction of tcMEP to below 25%; tcMEP < 25% = time in minutes that tcMEP were reduced to below 25% of baseline; tcMEP absent = time in minutes that tcMEP waveform was absent (< 40 μ V); motor score = neurologic function at 72 h, with 0 being total paraplegic and 4 normal motor function; infarction = relative infarction volume of the lumbosacral spinal cord.

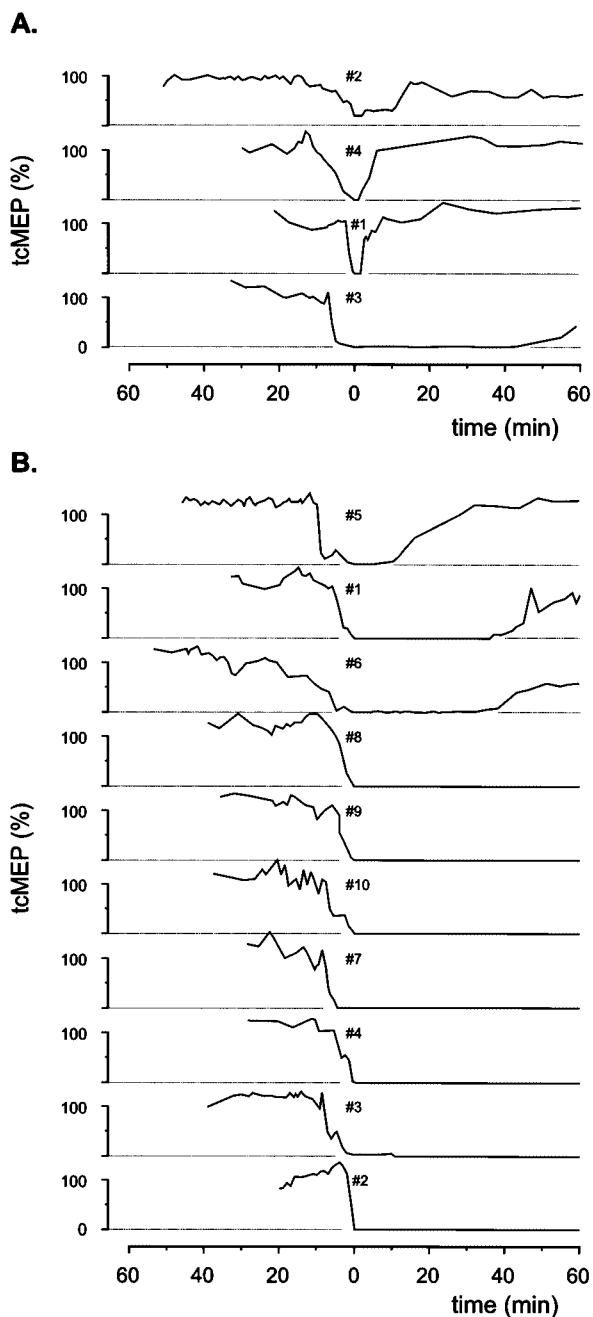


Fig. 2. The time course of transcranial motor evoked potentials (tcMEPs) during sequential clamping of segmental arteries and 60 min of recording after the initial tcMEP reduction is shown in all animals (n = 14). On the x-axis, the time in minutes is shown, with zero being the initial disappearance of tcMEP. Individual graphs are arranged according to the moment of initial tcMEP loss. On the y-axis, the relative amplitude of tcMEP compared to baseline is shown. The thin horizontal lines at the bottom of each graph represent the value 0 for relative tcMEP. A = group A; B = group B. The animal number is depicted on the top of each graph and corresponds with outcome parameters in table 2. Dichotomous neurologic outcome at 72 h is indicated (N = normal motor function, P = paraplegic).

scores, tcMEP amplitude, infarction volumes, and neuron counts are presented as medians and interquartile ranges. The physiologic variables were analyzed with a

one-way analysis of variance, and when significant differences were identified, Student *t* tests for intergroup comparisons with appropriate correction for multiple comparisons were carried out. Neurologic scores, infarction volumes, and neuron counts were analyzed with the use of a rank-sum statistical test (Mann-Whitney U test). A *P* value < 0.05 was considered significant. Sensitivity (true positive/true positive + false negative), specificity (true negative/true negative + false positive), positive predictive values (true positive/true positive + false positive), and negative predictive values (true negative/true negative + false negative) of different reduction times of tcMEP for postoperative spinal cord injury were calculated.

Results

There were no differences in animal weight between group A (40 ± 4 kg) and group B (41 ± 6 kg). Table 1 summarizes the hemodynamic and blood gas data before the onset of arterial clamping and rectal temperature after placement of the clamps. No differences in pH, PaO₂, PaCO₂, hemoglobin, hematocrit, and rectal temperature were observed between the groups. Mean arterial blood pressure during and after tcMEP reduction was the same for animals in group A (82 ± 3 mmHg) and group B (83 ± 5 mmHg). Six lumbar SAs and the medial sacral artery were identified. Complete loss of the hind-limb tcMEP signal was established after clamping of 7 ± 1 (SD) arteries during sequential clamping. In group A, motor transmission recovered after declamping of 2-4 arteries following the initial tcMEP loss. The viscera were repositioned after termination of tcMEP recording to avoid the possible influence of increased circulating volume and subsequent reduction of the intensity of the induced ischemia.

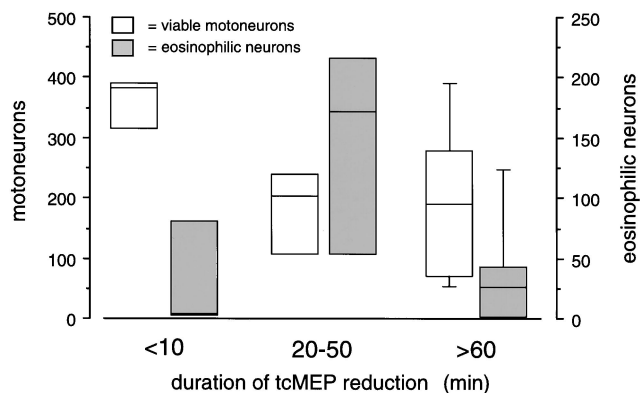


Fig. 3. Neuronal counts, with animals group according to the total period of transcranial motor evoked potential (tcMEP) reduction. Three periods are shown: < 10 = tcMEP recovery within 10 min; 20-50 = tcMEP reduction between 20 and 50 min, after which recovery was observed; > 60 = tcMEP reduction for more than 60 min. The y-axis for the total number of eosinophilic neurons is shown on the right side of the diagram.

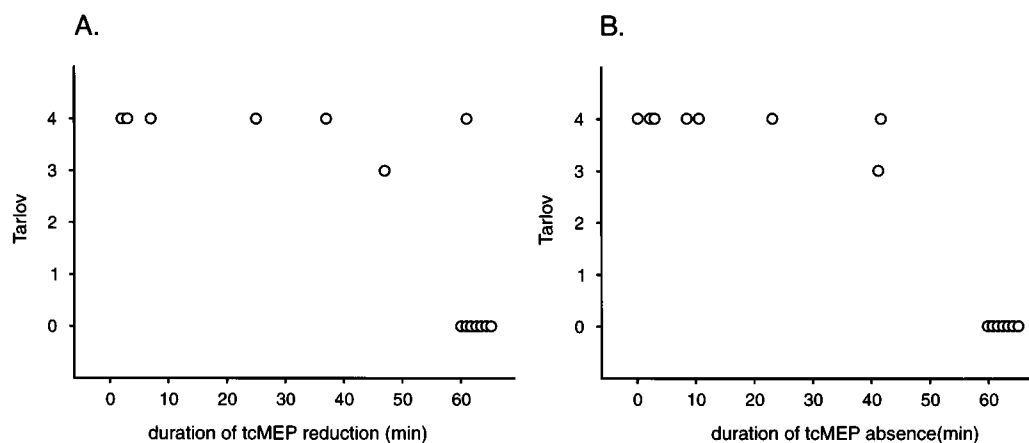


Fig. 4. The Tarlov motor score as a function of duration of transcranial motor evoked potential (tcMEP) reduction (A) or tcMEP absence (B).

Reproducible tcMEP were recorded in all animals. The median amplitude before ischemic manipulations was $1,934 \mu\text{V}$ (interquartile range: $1,498$ – $2,727 \mu\text{V}$). In one animal (group A), tcMEP could not be reduced to below 25% of baseline with the maximum numbers of SAs clamped. Staged aortic clamping was used to determine if all arteries were found. Postmortem observation showed one segmental artery that was not identified during the first surgical procedure. Because repeated aortic clamping was used, this animal was not included in the analysis. The time interval between the start of segmental artery clamping and reduction of tcMEP to below 25% of baseline was the same in group A (median, 16 min; interquartile range, 13–23 min) and group B (median, 19 min; interquartile range, 12–21 min). The subsequent interval, between the initial reduction of tcMEP to 25% of baseline and complete loss of tcMEP waveform, was not different in group A (median, 4 min; interquartile range, 3–5 min) and group B (median, 2 min; interquartile range, 1–5 min).

Figure 2 shows the tcMEP for every successive segmental artery clamping stage for both groups. In group A, the declamping of segmental arteries after an initial reduction of tcMEP amplitude resulted in prompt recovery (within 10 min) of tcMEP signals to baseline values in three animals. No spinal cord infarction was present in these animals, and motor function was normal at 72 h after tcMEP reduction. In one animal of group A, tcMEP reduction was more prolonged (animal No. 3, tcMEP < 25%: 61 min, tcMEP absence: 43 min). This animal showed minimal infarction of the lumbosacral spinal cord and had a normal motor function at 72 h after tcMEP reduction. In seven (70%) animals in group B, the tcMEP waveform was rapidly abolished and remained absent. These animals had massive infarction of the spinal cord segments giving rise to the lumbosacral plexus, and were all paraplegic 72 h after the initial tcMEP loss. In three animals (30%) of group B, tcMEP returned to

values above 25% of baseline after the primary decrease within 8, 10, and 42 min, despite the permanent occlusion of all lumbar SAs. Their total infarction volumes were 9.6%, 31.3%, and 95.1%, respectively, and their Tarlov scores were 4, 4, and 3, respectively. No additional SAs were found during postmortem observations at 72 h after tcMEP reduction.

The period of tcMEP reduction, neurologic score, and infarction volumes for individual animals are shown in table 2. Both in groups A and B, reduction of tcMEP to below 25% of baseline was a continuous period. Continuous absence of tcMEP waveform occurred in all animals except one in both groups (animal No. 3 in group A and animal No. 6 in group B). In these animals, three short periods of waveform absence were observed, the summation of which is given in table 2. Neuronal counts for three different periods of tcMEP reduction are shown in figure 3. The total number of viable motoneurons and eosinophilic neurons was not different among these groups. In animals with massive infarction of the spinal cord, individual neurons could often not be identified in the penumbral region of the lesion. In figure 4, the relation is shown between the time of tcMEP reduction and neurologic function at 72 h after the initial loss of tcMEP amplitude.

To determine the diagnostic characteristics of intraoperative tcMEP reduction for postoperative spinal cord damage, animals were regrouped according to their tcMEP reduction times. Four different periods of tcMEP reduction were defined, and the respective diagnostic characteristics for paraplegia and spinal cord infarction are shown in table 3. The positive and negative predictive values of fast recovery of tcMEP signals (within 10 min) for normal postoperative motor function were 1.00 and 0.64, respectively. The positive and negative predictive values of fast recovery of tcMEP for absence of spinal cord infarction were 1.00 and 1.00, respectively.

Table 3. Diagnostic Characteristics for Different Periods of tcMEP Loss for Postoperative Paraplegia and Spinal Cord Infarction

	Paraplegia				Infarction > 20%			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Critical > 30	1.00	0.57	0.70	1.00	1.00	0.80	0.90	1.00
Critical > 60	1.00	0.86	0.88	1.00	0.78	0.80	0.88	0.67
Absent > 30	1.00	0.71	0.78	1.00	0.89	0.80	0.89	0.80
Absent > 60	1.00	1.00	1.00	1.00	0.78	1.00	1.00	0.71

Four different tcMEP reduction times are shown and their corresponding predictive powers for paraplegia and spinal cord infarction at 72 h after ischemic manipulations.

Paraplegia = Tarlov 0; infarction > 20% = more than 20% infarction of the total gray matter volume of the lumbosacral spinal cord; critical > 30, 60 = reduction of tcMEP for more than 30, 60 min; absent > 30, 60 = complete loss of tcMEP for more than 30, 60 min; PPV = positive predictive value; NPV = negative predictive value.

Discussion

In the present study, intraoperative absence of tcMEP signals for more than 1 h consistently resulted in paraplegia and extensive spinal cord infarction 72 h later, while SCI followed by prompt restoration of tcMEP signals corresponded with normal histopathology and normal motor function. The data indicate that tcMEPs predict neurologic outcome after short and permanent intraoperative loss of the responses.

The present results are in agreement with observations following aortic occlusion in dogs, where loss of intraoperative spinal tcMEP correlated with worse neurologic outcome 24 h after reperfusion.³⁰ The authors concluded that neurogenic motor evoked potentials were too sensitive to use as an indicator of spinal cord damage, because the responses disappeared within 1 min after the onset of SCI. However, to reduce adverse outcome, it is imperative that an intraoperative spinal cord monitoring technique detects ischemia before the occurrence of irreversible neuronal damage. The present data indicate that prolonged loss of myogenic tcMEPs predicts postoperative neurologic dysfunction, and that detection of acute SCI with tcMEPs before irreversible damage has occurred is feasible. In a porcine model of SCI, 10-min reduction of spinal cord evoked potentials recorded from the lumbar spine, followed by reperfusion, was associated with paraplegia in 2 of 4 animals at 3 h after reperfusion.³¹ In contrast, recovery of myogenic tcMEP within 10 min was associated with normal motor function in the present study. Our data support the hypothesis that myogenic tcMEPs provide a more sensitive and clinically relevant assessment of both ischemia and irreversible damage of the spinal cord in comparison with spinal cord evoked potentials. In a previous study we used tcMEP to assess adequacy of SCBF when SAs were selectively perfused during aortic cross-clamping.³² In all animals ($n = 5$) where SAs were not perfused, tcMEPs were permanently lost and paraplegia was observed 72 h later. Although a good correlation between intraoperative loss of tcMEP amplitude and postoperative neurologic deficit was present, that study was

not designed to prospectively evaluate the validity of tcMEP criteria for the prediction of neurologic outcome.

Because the consequences of iatrogenic paraplegia are so devastating, spinal cord monitoring techniques should have a high sensitivity for the detection of intraoperative spinal cord dysfunction, in order to allow prompt intervention. In addition, false-negative monitoring results should be absent. For the prediction of adverse outcome, tcMEP can be regarded as a repetitive application of a diagnostic test, so that the prognostic power of a sequence of positive monitoring results is important. Loss of neurogenic motor evoked potentials recorded in dogs that were subjected to permanent segmental artery ligation predicted postoperative neurologic injury in 67% of the cases.³³ Unfortunately, the difference in evoked potentials recording site and the extensive collateral circulation in dogs as compared to pig and humans³⁴ hampers the comparison with the present data.

In the current study, a high positive predictive value and sensitivity of tcMEP loss for postoperative paraplegia were observed after loss of the responses for more than 60 min, while 30 min of tcMEP loss was already highly predictive of spinal cord infarction involving more than 20% of the total gray matter volume. The total number of paraplegic animals was less than expected, and one animal was excluded from the analysis, resulting in a smaller-than-proposed group size in the intervention group. However, it is unlikely that this influenced the predictive power of the present data because the overall incidence of paraplegia remained constant.

In some animals in group B (animal Nos. 1, 5, and 6; fig. 2), tcMEP did not remain absent during the entire study period, but gradually recovered. These animals had less extensive histopathologic damage and better neurologic score at 72 h after the initial tcMEP reduction. One possible explanation is the recruitment of collateral blood vessels that partially restored SCBF to a level sufficient for recovery of tcMEP signals. The postoperative motor score and histopathologic damage in these animals was similar to that observed after fast restoration of tcMEP signals in the animals of group A, which under-

went reperfusion of the spinal cord through declamping of the most cranial lumbar SAs. In general, a good correlation was observed between histopathologic damage and neurologic function. However, in two animals (animal No. 3 in group A, No. 1 in group B) a similar intermediary duration of tcMEP loss resulted in normal motor function in both animals, while histopathologic damage was less in the animal of group A. A possible explanation for this discrepancy is the higher number of permanently clamped segmental arteries that was present in the animal in group B (seven compared to five in the animal of group A). The greater number of occluded SAs in the animal of group B might have resulted in a more compromised SCBF and subsequent more extensive neuronal loss during the postoperative period.

We reduced SCBF by sequential clamping of segmental arteries. Compared to aortic cross-clamping, this model minimizes the risk of false-positive responses due to ischemia of the peripheral nerve and muscles and avoids the major cardiovascular changes associated with aortic occlusion and the subsequent reperfusion period. The spinal cord blood supply of the pig resembles that of humans because it comprises a plurisegmental artery supply of a continuous anterior spinal artery.^{35,36} The vulnerable region of the spinal cord with regard to SCBF is located in the lower thoracic region, facilitating flow in the lumbar region, because of a large decrease in diameter of the anterior spinal artery in the cranial direction and the presence of extensive collateral circulation in the lumbar spinal cord.^{35,36} In a previous study we confirmed with laser Doppler flowmetry that SCBF of the anterior horn is severely reduced after segmental artery clamping.²³ However, because placement of the flow probes on the ventral aspect of the spinal cord involved extensive removal of vertebral bone, this would preclude survival of the animals, and we therefore chose not to measure SCBF in the present study.

The rationale for the 25% tcMEP amplitude decrease criterion that is used clinically to detect SCI is based on theoretical considerations and has been confirmed empirically.³⁷ In general, the criterion for SCI during somatosensory evoked potentials monitoring is a decrease of amplitude to less than 50% of baseline or a 10% latency increase.³⁸ The more restrictive criterion for spinal cord dysfunction during tcMEP monitoring was based on the larger amplitude variability of tcMEP signals compared to somatosensory evoked potentials.¹⁶ The cortical and spinal motoneuronal components of tcMEP are vulnerable to agents that reduce neuronal excitability, and the myogenic component of tcMEP is severely depressed by agents that possess muscle-relaxing properties. The combination of ketamine-sufentanil anesthesia in the current study is used clinically^{16,39} and probably depresses myogenic tcMEP less than total intravenous anesthesia, such as low-dose propofol-opioid.⁴⁰

The present experimental data support the validity of the empirical criterion (25% tcMEP amplitude reduction) for initiating interventions to maintain spinal cord perfusion pressure during surgical procedures on the thoraco-abdominal aneurysm or the spine.

Conclusions

The present observations in this porcine model demonstrate that prolonged reduction of intraoperative tcMEP amplitude predicts spinal cord injury following SCI. In contrast, immediate restoration of SCBF after tcMEP amplitude loss results in full tcMEP recovery and prevents spinal cord neuronal damage even in the presence of permanent occlusion of several segmental arteries. Our finding supports the concept that prompt restoration of spinal cord perfusion after disappearance of the tcMEP signal may prevent neurologic deficit.

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