Transoesophageal spinal cord stimulation for motor-evoked potentials monitoring: feasibility, safety and stability†

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Abstract

OBJECTIVES: Specificity of transcranial motor-evoked potentials (MEPs) is low because amplitude fluctuation is common, which seems due to several technical and fundamental reasons including difficulty in electrodes positioning and fixation for transcranial stimulation and susceptibility to anaesthesia. This study aimed to investigate the feasibility, safety and stability of our novel technique of transoesophageal spinal cord stimulation to improve the stability of MEPs.

METHODS: Ten anaesthetized adult beagle dogs were used. Transoesophageal stimulation was performed between the oesophageal luminal surface electrode (cathode) and a subcutaneous needle electrode (anode) at the fourth to fifth thoracic vertebra level. Stimulation was achieved with a train of five pulses delivered at 2.0-ms intervals. Compound muscle action potentials were recorded from four limbs and external anal sphincter muscles. Stability to anaesthetic agents was tested at varying speeds of propofol and remifentanil, and effects of varying concentration of sevoflurane inhalation were also evaluated.

RESULTS: Transoesophageal MEPs could be recorded without difficulty in all dogs. Fluoroscopic evaluation showed that electrodes misalignment up to 5 cm cranially or caudally could be tolerated. Stimulus intensity to achieve maximum amplitude of hindlimb muscle potentials on both sides was significantly lower by transoesophageal stimulation than by transcranial stimulation (383 ± 41 vs 533 ± 121 V, P = 0.02) and had less interindividual variability. Latency of transoesophageal MEPs was shorter than that of transcranial MEPs at every recording point. No arrhythmia was provoked during stimulation. Animals that were allowed to recover showed no neurological abnormality. In the two sacrificed animals, the explanted oesophagus showed no mucosal injury. Stability to varying dose of anaesthetic agents was similar between transoesophageal and transcranial stimulation, except for the potentials of forelimbs by transoesophageal stimulation that were resistant to anaesthetic depression.

CONCLUSIONS: Transoesophageal stimulation for MEPs monitoring was feasible without difficulty and safe. Although its stability to anaesthetic agents was similar to that of transcranial stimulation, its technical ease and small interindividual variability warrants further studies on the response to spinal cord ischaemia.

Keywords: Motor-evoked potentials • Aortic surgery • Spinal cord ischaemia • Anaesthesia • Oesophageal electrode

INTRODUCTION

Ischaemic spinal cord injury remains one of the most serious complications of aortic surgery. To minimize its risk, monitoring of spinal cord function by several neuro-electrophysiological methods, such as transcranial motor-evoked potentials (Tc-MEPs) [1], somatosensory-evoked potentials (SSEPs) [2] and evoked spinal cord potentials (ESCPs) [3], has been proposed as a component of a multidisciplinary approach, to enable prompt action to spinal cord ischaemia during surgery. Among these methods, Tc-MEPs have gained widespread acceptance, because it monitors the functional integrity of motor pathway and its response to ischaemia is quick and highly sensitive [4, 5].

Despite these advantages, however, instability of Tc-MEPs has been a clinical problem, which seems due to several technical and fundamental reasons. It may sometimes be difficult to achieve and maintain correct positioning of the transcranial stimulation...
electrodes. It is more vulnerable to various anaesthetic drugs than the other techniques and therefore requires special anaesthetic considerations to obtain consistent results [5, 6]. In addition to these technical problems, the use of compound muscle action potentials (CMAPs) itself may also be a reason for baseline fluctuation of the elicited responses, because excitability of the alpha motor neurons is modulated by many factors [5]. This instability results in the low specificity of Tc-MEPs when the cut-off value is set high, which trades off specificity against sensitivity, and may explain why the cut-off amplitude of the evoked potentials varies considerably from 25 to 75% of baseline among the investigators [4, 7].

To solve this problem of instability, we conceived of transoesophageal direct spinal cord stimulation. Technically, we expected that correct positioning and fixation of the transoesophageal stimulation electrodes was much easier than that of transcranial electrodes. Stability to anaesthesia may also be improved by the use of direct spinal cord stimulation, because synaptic transmission is the most vulnerable part to the influence of anaesthesia, and transcranial electrical stimulation partly involves synaptic transmission via interneuronal neurons within the motor cortex [5, 6]. It is well known that influence of anaesthesia is the smallest with ESCP, which is stimulated and recorded through lumbar and cervical epidural electrodes and therefore does not involve synaptic transmission at all [8]. The use of epidural electrodes, however, is not desirable during aortic surgery with heparin administration because of the risk of epidural haematoma [5]. In addition, response of ESCP to spinal cord ischaemia is slow [9] because it monitors the function of spinal tracts but not that of alpha motor neurons, the most vulnerable part to ischaemia in the spinal cord. From these considerations, we planned the combination of transoesophageal direct spinal cord stimulation and recordings of myogenic potentials (transoesophageal MEPs: Te-MEPs), to avoid the use of epidural electrodes and to retain the merits of Tc-MEPs to include alpha motor neuron in the monitored pathway.

The purpose of the present study is to establish the method of transoesophageal spinal cord stimulation for MEPs monitoring and to evaluate its safety in a canine model. We also examined whether or not our novel technique of Te-MEPs is more stable to anaesthesia than conventional Tc-MEPs.

**MATERIALS AND METHODS**

All animals received humane care in compliance with the ‘Guide for the Care and Use of Laboratory Animals’ published by the National Institutes of Health (NIH publication 85–32, revised 1985). The institutional ethics committee on the use and care of animals approved the experimental protocol (No. 2013014).

**Experimental settings**

Ten adult beagle dogs (weight 15.8–21.2 kg) were anaesthetized with intravenous infusion of propofol (12–24 mg/kg/h) and remifentanil (12–24 μg/kg/h), and were intubated and maintained on mechanical ventilation. Baseline dose of these drugs was determined on each dog to fulfill the following conditions: apnoea, disappearance of eyelash reflex and unresponsiveness to painful stimulation. No muscle relaxant was used. The electrocardiogram was continuously monitored throughout the experiment.

For MEPs measurement, we used a Neuropak MEB-2200 system for data acquisition, processing and analysis, with a SEN-4100 equipment for electrical stimulation (Nihon Kohden, Tokyo, Japan). For transcranial stimulation of the brain motor area, a cathode was placed on the C4 position and an anode on the C3 position of the international 10–20 system. A train of five rectangular pulses was used with a 2.0 ms inter-stimulus interval in a constant voltage mode with a 0.05-ms pulse width. MEPs were recorded at the bilateral abductor pollicis brevis muscles, anterior tibial muscles and external anal sphincter muscles. Needle electrodes were used to record CMAPs from the limbs and a plug-type electrode (a special order product, Nihon Kohden, Tokyo, Japan) was used to record external anal sphincter muscle potentials [10]. The latency and amplitude of MEPs were measured.

Transoesophageal stimulation of the spinal cord was performed between the hand-made oesophageal luminal surface electrode (cathode) and a nuchal subcutaneous needle electrode (anode) (Fig. 1). The former was inserted to a 20-cm depth from the corner of mouth. This depth was determined by fluoroscopic control in the feasibility study, so that the electrode tip was placed at the fourth to fifth thoracic vertebra level. The latter was placed 5 cm cranially from the shoulder joint level. This positioning was also

**Figure 1:** A fluoroscopic image and a schematic drawing of the settings of the stimulation electrodes for transcranial and transoesophageal motor-evoked potentials. In the fluoroscopy, which was used in the feasibility study, oesophageal luminal surface electrodes are shown by arrows. The tip electrode was always used and the second one was a backup. The C position is the standard site for a nuchal subcutaneous electrode.
determined in the feasibility study. The settings for recording were common to both transcranial and transoesophageal stimulation.

Feasibility study

The first two animals were used for this study. After the position of the oesophageal luminal electrode was determined under fluoroscopic control, five subcutaneous electrodes were inserted into the nuchal region at a 2.5-cm distance (Fig. 1). All of these five subcutaneous electrodes were tested for stimulation.

As for the transoesophageal stimulation method, a single pulse and trains of two to nine pulses were evaluated, with the intensity varied from 100 to 600 V and inter-stimulus interval varied from 1.0 to 3.0 ms. Other conditions of pulse-train stimulations were equivalent to those for transcranial stimulation, as described above.

Establishment of stimulation condition and normal responses

We used a train of five pulses for both transcranial and transoesophageal stimulations. Measurements were repeated three times on each stimulation condition, and the data were averaged. In the seven animals including the first two undergoing the feasibility study, stimulation intensity was varied from 100 to 600 V to determine the lowest level that produced maximum amplitude of MEPs. Practically, the amplitude elicited by 600-V stimulation was considered maximum, and the stimulation intensity that produced more than 90% of this maximum amplitude on both sides was determined as the lowest stimulation intensity to produce maximum response.

Evaluation of stability to anaesthesia

A total of 14 experiments were performed on the eight dogs. After baseline measurements, anaesthetic depth was varied according to one of the following three protocols, and the measurements were repeated. In the protocol P (n = 5), the infusion speed of propofol was increased to double, triple and quadruple of baseline in a step-by-step manner, while that of remifentanil was kept unchanged. In the protocol R (n = 5), the speed of remifentanil was similarly increased as double, triple and quadruple, while the dose of propofol was fixed to baseline. In the protocol S (n = 4), sevoflurane inhalation at incremental concentrations of 2, 3 and 5% was added to the baseline doses of propofol and remifentanil. Measurements were repeated 15 and 30 min after cessation of sevoflurane. For these measurements, a fixed stimulation intensity at 500 V was used. This value was higher than the lowest stimulation intensity to produce maximum response (supramaximal stimulation intensity) for Te-MEPs in all dogs, while it was not so (suprathreshold stimulation intensity) for Tc-MEPs in four animals. Injections of atropine sulphate (50–100 μg) and ephedrine hydrochloride (4–8 mg) were used as necessary to avoid haemodynamic compromise under deep anaesthesia.

Evaluation of safety

The electrocardiograms during stimulation were retrieved and arrhythmias were analysed in all dogs. The first two animals used in the feasibility study were sacrificed by anaesthetic overdose for histological evaluation of the oesophagus. The remaining dogs were allowed to recover and the motor function of the four limbs was evaluated.

Statistical analysis

Each value was expressed as the mean ± standard deviation. Statistical analyses for comparisons of the continuous variables were performed using one-way analysis of variance (ANOVA) test with IBM SPSS Statistics software (version 21, IBM Japan, Tokyo, Japan). Dunnett’s test was used as a multiple comparison procedure. Repeated-measurements ANOVA was used for comparisons of the influence of varying dose of anaesthetic agents between the groups. A P-value less than 0.05 was considered significant.

RESULTS

Feasibility study

Te-MEPs could constantly be recorded without difficulty at every recording site by a train of three or more stimulations of 500-V intensity and 2-ms intervals. Each of the five subcutaneous anodes for transoesophageal stimulation yielded identical waveforms and amplitudes. On the other hand, a train of four or more stimulations was required for Tc-MEPs to be consistently recorded at every site.

Change in the inter-stimulus interval from 1.0 to 3.0 ms did not influence the amplitudes of Te-MEPs at 500 and 300-V stimulation intensity. On the other hand, while Tc-MEPs were not influenced by changes in inter-stimulus interval at 500-V intensity, use of 1.0-ms interval at 300 V resulted in amplitude decrease.

The waveforms of Te-MEPs were similar to those of Tc-MEPs except for those recorded on the forelimbs (Fig. 2). Single-pulse transoesophageal stimulation can always elicit CMAPs on the forelimbs but not on the hindlimbs. The waveforms of forelimbs by transoesophageal stimulation were identical either by single-pulse stimulation or by pulse-train stimulation.

Stimulation condition and normal responses

The relationship between stimulation intensity and MEP amplitudes is shown in Fig. 3. The lowest stimulation intensity to produce maximum MEP amplitude and the latency on each recording site are given in Tables 1 and 2. Stimulation intensity to achieve maximum amplitude of anterior tibial muscle potentials was significantly lower by transoesophageal stimulation than by transcranial stimulation, with less interindividual variability by transoesophageal stimulation. Latency of Te-MEPs was shorter than that of Tc-MEPs at every recording point. The difference in latency between Tc-MEPs and Te-MEPs was significantly greater on the forelimbs than on the other two recording sites.

Stability to anaesthesia

The relationship between the dose of anaesthetic agents and MEP amplitudes is shown in Fig. 4. Amplitudes of both Te-MEPs and
Tc-MEPs decreased with increasing doses of anaesthetic drugs, except for Te-MEPs on the forelimbs. There was no difference between Te-MEPs and Tc-MEPs of the hindlimb muscles and anal sphincter muscles in this aspect, while Te-MEPs of the forelimbs were not influenced by anaesthesia.

It is noteworthy that Te-MEPs could be recorded at the first trial with no difficulty in all of the eight animals, while it was sometimes difficult to set the stimulation electrodes for Tc-MEPs.

Simultaneous recordings from the four limbs and anal sphincters were especially difficult by transcranial stimulation because of the presence of polarity.

**Safety of transoesophageal stimulation**

No arrhythmia was provoked during transoesophageal stimulation. All animals that were allowed to recover showed no
neurological abnormality. In the two sacrificed animals, the explanted oesophagus showed no evidence of mucosal injury.

DISCUSSION

The present study showed that transoesophageal electrical stimulation of the spinal cord can safely evoke CMAPs on the limbs and external anal sphincters (Te-MEPs), which can be used for intra-operative monitoring of spinal cord motor function. Furthermore, setting and fixation of the stimulation electrodes for Te-MEPs was simple and easy, which was in clear contrast to those for Tc-MEPs. This is important because setting up the transcranial stimulation is a technique which is cult and time-consuming in clinical practice, and migration of the stimulation electrodes for Te-MEPs was easy, which was in clear contrast to those for Tc-MEPs. This is why we used myogenic potentials to include neurogenic potentials in this setting. Together with the use of partial neuromuscular blockade [5], if it is applied in a clinical situation.

Another potential limitation of this technique is the concern that antidromic activation of the sensory fibres would stimulate motor neurons at lower spinal levels through the channels that connect dorsal column to the anterior horn and produce a myogenic response, bypassing the descending motor tracts [5]. If this is the case, selective injury of the motor tract that spares alpha motor neurons will not be detected by this technique. It has been shown that antidromic activation of the sensory fibres by direct spinal cord stimulation can be recorded on the peripheral nerve [11]. This is why we used myogenic potentials to include neurogenic junction and not the neurogenic potentials recorded from the peripheral nerves. Mochida et al. [12], using selective spinal cord transection technique in cats, have shown that CMAPs evoked by a single-pulse stimulation of the spinal cord showed remarkable reduction in amplitude after dorsal column transection, which suggests the activation of alpha motor neurons through the channels that connect dorsal column to the anterior horn and produce a myogenic response. However, they also showed that CMAPs evoked by single-pulse stimulation were not influenced by dorsal column transection but were vanished by lateral column transection, and the CMAP amplitudes were 10-fold higher after dorsal column transection than with single-pulse stimulation. From these results, the authors concluded that CMAPs evoked by single-pulse spinal cord stimulation purely reflect the motor pathway function, and the contribution of alpha motor neuron activation through the antidromic dorsal column potentials is not big enough to influence the myogenic potentials in this setting. Together with the

Another important finding was the safety of transoesophageal stimulation. There was no evidence of arrhythmia, oesophageal mucosal injury and neurological abnormality. The only concern is strenuous movement of the forelimbs during transoesophageal stimulation. A special care should therefore be taken to protect the upper limbs and to avoid unwanted shift in position, such as the use of partial neuromuscular blockade [5], if it is applied in a clinical situation.

Our expectation that Te-MEPs are more resistant to anaesthesia than Tc-MEPs was not supported by the present results. This can be explained by the fact that transcranial electrical stimulation can directly activate sub-cortical motor axons. Even though indirect activation of sub-cortical motor axons through the cortical synapses is completely suppressed by anaesthetic agents, direct activation of the sub-cortical motor axons is not depressed [5, 6], and the excitatory post-synaptic potentials of the spinal anterior horn cells can be summed by the use of pulse-train stimulation to evoke the myogenic potentials. Therefore, although direct spinal cord stimulation bypasses synaptic transmission within the motor cortex, transcranial electrical stimulation also does not depend on cortical synapses as far as adequate pulse-train stimulation was used, and the resistance to anaesthetic depression was not significantly different between the two techniques.

Judging from the waveforms and latency data, it seems that Te-MEPs of the forelimbs were elicited by direct stimulation of the alpha motor neurons and not through the synaptic transmission after activation of the spinal motor tract. The result that single-pulse stimulation could evoke CMAPs on the forelimbs may also support this speculation. This may explain why Te-MEPs of the forelimbs were resistant to anaesthesia, because activation of the alpha motor neurons by direct electrical stimulation should be resistant to anaesthetic depression, just like activation of the sub-cortical motor axons as discussed previously. This may be a limitation of Te-MEPs, because recordings from the upper limbs cannot be used as a real-time control to preclude the influence of anaesthesia.

Another potential limitation of this technique is the concern that antidromic activation of the sensory fibres would stimulate motor neurons at lower spinal levels through the channels that connect dorsal column to the anterior horn and produce a myogenic response, bypassing the descending motor tracts [5]. If this is the case, selective injury of the motor tract that spares alpha motor neurons will not be detected by this technique. It has been shown that antidromic activation of the sensory fibres by direct spinal cord stimulation can be recorded on the peripheral nerve [11]. This is why we used myogenic potentials to include neurogenic junction and not the neurogenic potentials recorded from the peripheral nerves. Mochida et al. [12], using selective spinal cord transection technique in cats, have shown that CMAPs evoked by a single-pulse stimulation of the spinal cord showed remarkable reduction in amplitude after dorsal column transection, which suggests the activation of alpha motor neurons through the connecting channels. However, they also showed that CMAPs evoked by pulse-train stimulation were not influenced by dorsal column transection but were vanished by lateral column transection, and the CMAP amplitudes were 10-fold higher with pulse-train stimulation than with single-pulse stimulation. From these results, the authors concluded that CMAPs evoked by pulse-train spinal cord stimulation purely reflect the motor pathway function, and the contribution of alpha motor neuron activation through the antidromic dorsal column potentials is not big enough to influence the myogenic potentials in this setting. Together with the

### Table 1: The lowest stimulation intensity on each recording site to produce more than 90% of the maximum amplitude of transoesophageal and transcranial motor-evoked potentials on both sides

<table>
<thead>
<tr>
<th></th>
<th>Te-MEPs (V)</th>
<th>Tc-MEPs (V)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forelimb (n = 7)</td>
<td>340 ± 152</td>
<td>500 ± 100</td>
<td>0.08</td>
</tr>
<tr>
<td>Anal sphincter (n = 7)</td>
<td>383 ± 75</td>
<td>483 ± 117</td>
<td>0.11</td>
</tr>
<tr>
<td>Hindlimb (n = 7)</td>
<td>383 ± 41</td>
<td>533 ± 121</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Te-MEPs: transoesophageal motor-evoked potentials; Tc-MEPs: transcranial motor-evoked potentials.

### Table 2: Latency of transoesophageal and transcranial motor-evoked potentials on each recording site

<table>
<thead>
<tr>
<th></th>
<th>Te-MEPs (ms)</th>
<th>Tc-MEPs (ms)</th>
<th>Tc-MEPs minus Te-MEPs (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forelimb</td>
<td>3.4 ± 0.7</td>
<td>9.4 ± 1.3</td>
<td>6.0 ± 1.2*</td>
</tr>
<tr>
<td>Anal sphincter</td>
<td>11.4 ± 1.9</td>
<td>13.4 ± 1.4</td>
<td>2.0 ± 1.6</td>
</tr>
<tr>
<td>Hindlimb</td>
<td>12.3 ± 0.7</td>
<td>15.3 ± 1.6</td>
<td>3.0 ± 1.6</td>
</tr>
</tbody>
</table>

Data are shown as an average of both sides. Te-MEPs: transoesophageal motor-evoked potentials; Tc-MEPs: transcranial motor-evoked potentials. *P < 0.001 from other recording sites.
The fact that the most vulnerable part of the spinal cord to ischaemia is alpha motor neurons and selective injury of the spinal motor tract with no alpha neuron damage is not likely to occur as a complication of aortic surgery, antidromic dorsal column potentials will not be a clinical problem of Te-MEPs as far as we use the pulse-train supramaximal stimulation during aortic surgery.

**Study limitations**

We used varying speeds or concentrations of anaesthetic agents to evaluate the influence of anaesthetic depth on Te-MEP, but we did not monitor bispectral index to control it. This may be a limitation of this study because we did not know the depth of anaesthesia objectively and whether or not the study condition was clinically relevant. This may be the reason for the marked anaesthetic suppression of both Te-MEPs and Tc-MEPs by propofol and remifentanil. Unlike the inhalation anaesthetics, effects of these drugs on Tc-MEPs are reported to be small [5, 6]. Nevertheless, the conclusion that Te-MEPs are influenced by anaesthetic agents will not be changed because the observed influence of anaesthesia was similar between Te-MEPs and Tc-MEPs.

Another potential limitation of this study is that we did not evaluate the effect of muscle relaxants on Te-MEPs and the time required to regain the ability to monitor. Because of the occasional clinical need for short-time paralysis during the key portions of the operation, it may be interesting to evaluate them. Considering the mechanism of action of these drugs, however, their effect on Te-MEPs does not seem different from that on Tc-MEPs, which has been extensively studied.

**CONCLUSIONS**

Results of the present study show that Te-MEPs monitoring is feasible and safe. Although our expectation that it is more resistant to anaesthesia was not supported, its technical ease and small inter-individual variability warrants further studies on the response to spinal cord ischaemia, which is now underway using a temporary descending aortic occlusion model.

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**Conflict of interest**: none declared.
REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr V. Mosquera: I have just two questions.

Dr Pacini: We performed our experiment without myorelaxant.

Dr Tsuda: And are you planning to try this technique with this kind of drug?

Dr Pacini: Yes. I plan to use small amounts of myorelaxant in future clinical trials.

Dr Tsuda: Because it could be interesting to know if this can be affected by these drugs.