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Myogenic transcranial motor evoked potentials monitoring cannot always predict neurologic outcome after spinal cord ischemia in rats

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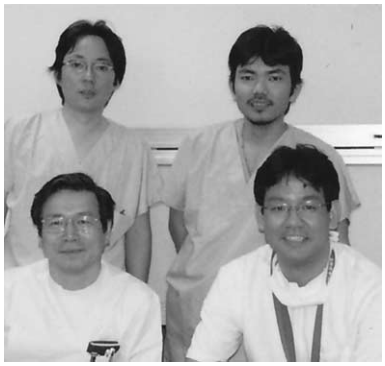

Miyata, Kawabata *(top, from left)*; Sugahara, Kakinohana *(bottom, from left)*

Objectives: A day after undergoing an operation of the thoracic aorta, a patient showed signs of spastic paraplegia, but on myogenic transcranial motor evoked potential monitoring, the myogenic transcranial motor evoked potentials recorded from the left anterior tibial muscle appeared normal. We sought to confirm these observations by using a rat spinal ischemia model to define the possibility of false-negative results in myogenic transcranial motor evoked potential monitoring by motor function behavior and spinal histopathology.

Methods: Spinal ischemia was induced for 6 minutes (group A, n = 6) or 10 minutes (group B, n = 6) with an intra-aortic balloon. After ischemia, motor function was assessed periodically by using the motor deficit index (0, complete recovery; 6, complete paraplegia). Myogenic transcranial motor evoked potentials were recorded from the right soleus muscle before ischemia, 2 and 6 minutes after the start of spinal ischemia, and at 30 minutes, 24 hours, and 72 hours of reperfusion.

Results: All group A rats showed normal motor function at 72 hours of reperfusion, whereas all group B rats displayed complete spastic paraplegia (motor deficit index = 6) at 72 hours of reperfusion. However, transcranial motor evoked potential was preserved in both group B and group A. Histopathologic analysis in group B revealed the presence of extensive necrotic changes of the gray matter distributed between laminae V through VII in the L3 to L5 segments but normal appearance of α motor neurons.

Conclusion: According to our data, in using myogenic transcranial motor evoked potential monitoring during thoracic or thoracoabdominal aneurysm repair, we should be aware that transcranial motor evoked potentials cannot always be used to predict neurologic outcome after the operation.

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Spinal cord ischemic injury remains the most devastating complication after descending thoracic or thoracoabdominal aneurysm repair. The risk of spinal cord ischemia and neurologic deficit has not changed much since it was first reported in 1956 by Adams and Van Geertruyden[1]; its incidence varies between 4.4% and 16% in large series of patients undergoing thoracic or thoracoabdominal aortic aneurysm repair.[2-4] One of the main limitations of protective strategies is the inability to assess the adequacy of spinal cord perfusion and spinal cord function intraoperatively. In the orthopedic field somatosensory evoked potentials (SEPs) recorded from the cerebral sensory area by stimulating the peripheral nerve or skin have been used since the early 1970s in Europe and North America.[5] In the cardiovascular surgery field, Coles and colleagues[6] and Cunningham and associates[7] demonstrated an earlier detection of spinal cord ischemia by using SEPs that were generated by

means of intraoperative stimulation of peripheral nerves. Although many reports were published in the mid-1980s on SEP monitoring during aortic surgery, use of SEP monitoring was drastically reduced after false-negative results were reported.[8-11] In contrast, because myogenic transcranial motor evoked potentials (tc-MEPs) monitor the descending motor system located in the anterior and lateral corticospinal tracts and the anterior horn motor neuronal system, including the function of the ischemia-sensitive α motor neurons, tc-MEP monitoring can reflect motor tract function. Thus, it is a highly sensitive technique to assess spinal cord integrity, identifying insufficient blood flow to the spinal cord through excluded segmental arteries that make a critical contribution to spinal cord perfusion.[12] In addition, from experimental data with a porcine spinal cord ischemic model, Lips and coworkers[13] concluded that tc-MEPs can be sued to predict spinal cord injury after spinal cord ischemia. In this article, however, we report the appearance of myogenic tc-MEPs in a patient in spite of paraplegia after descending thoracic aortic surgery (see the Appendix) and experimental data suggesting that myogenic tc-MEPs cannot always be used to predict paraplegia after spinal cord ischemia.

Materials and Methods

Studies described in this report were performed according to a protocol approved by the Animal Subjects Committee of the University of the Ryukyus. Animals were allowed free access to food and water until they were anesthetized. Male Sprague-Dawley rats (350-400 g) were used in the present study. Animals were anesthetized in a Plexiglas box with 4% isoflurane in room air. After induction, rats were maintained with 1% to 2% isoflurane delivered through an inhalation mask. An intravenous catheter (PE-10) was inserted into the right external jugular vein for continuous infusion of ketamine (2-5 $mg \cdot kg^{-1} \cdot h^{-1}$). After tissue infiltration with 1% lidocaine, the trachea was intubated through a tracheostomy, and the lungs were ventilated with 100% oxygen by using a small-animal respirator (Harvard Apparatus) to maintain arterial carbon dioxide tension between 35 and 45 mm Hg. After achievement of stable ventilation, infusion of ketamine was started after isoflurane was stopped. Anesthetic depth was determined by noting the withdrawal reflex when pinching the tail and was supplemented with intravenous doses of ketamine (usually 1 mg/kg per dose) as necessary. After the end of the operation, ketamine infusion was ceased. The tracheal tube was removed, followed by closure of the tracheostomy with 5-0 nylon sutures after confirming adequacy of spontaneous breathing. In recording tc-MEPs at 24 and 72 hours of reperfusion, the same procedure as described above was performed.

Recording of Myogenic Motor Evoked Potentials

Tc-MEPs were applied with a transcranial electrical stimulator (SEN 3301; Nihon Kohden) through 2 needle electrodes attached to the scalp. A train of 5 square wave pulses (voltage, 80-100 V), with a duration of 50 μs and an interstimulus interval of 2 ms, was distributed over the motor. Compound muscle action potentials were recorded from the right soleus muscle by using needle electrodes. A grounding electrode was placed over the tail. The signals were amplified 5000 to 20,000 times and filtered between 30 and 1500 Hz with a Neuropack II (Nihon Kohden). Stimulus intensity was adjusted to acquire maximal amplitude (supramaximal stimulation), and recording was performed at a setting 10% greater than the stimulus level that obtained maximal amplitude. Amplitude of the compound muscle action potentials was defined as the peak-to-peak distance in millivolts.

After preischemic tc-MEP recording, spinal cord ischemia was induced. Tc-MEPs were recorded before ischemia, at 2 and 6 minutes after the start of spinal cord ischemia, and at 30 minutes, 24 hours, and 72 hours of reperfusion. A reduction of tc-MEP amplitude on the muscle groups monitored at less than 25% of the baseline value was considered an indication of ischemic spinal cord function.[14]

Induction of Spinal Cord Ischemia

Details of the aortic occlusion model have been reported previously.[12] In brief, a polyethylene catheter (PE-50) was inserted into the tail artery for monitoring of distal arterial pressure and for injection of heparin. For induction of spinal ischemia, the left femoral artery was isolated, and a 2F Fogarty catheter was placed into the descending thoracic aorta so that the tip of the catheter reached the level of the left subclavian artery. A 20-gauge Teflon catheter connected to an external blood reservoir (37.5°C) was inserted into the left carotid artery to control the proximal arterial blood pressure at 40 mm Hg during the period of aortic occlusion. Water (38.0°C-38.3°C) was perfused through the heat exchanger at 100 mL/min to control and maintain the degree of spinal cord normothermia during aortic occlusion.[15] At the completion of all cannulations, heparin (200 U) was injected into the tail artery. A balloon catheter was inflated with 0.05 mL of saline to induce spinal ischemia, and the blood was allowed to flow into an external reservoir. The efficiency of the occlusion was evidenced by an immediate and sustained loss of any detectable pulse pressure and a decrease of distal arterial pressure. After ischemia, the balloon was deflated, and the blood was reinfused over a period of 60 seconds. In the sham-operated rats all surgical procedures were performed as described; however, the balloon catheter was not inflated. Protamine sulfate (4 mg) was then administered subcutaneously. All arterial lines were then removed, incisions were closed, and the animals were allowed to recover.

Assessment of Neurologic Function

During reperfusion, recovery of motor function was assessed with the grading system described as follows. Motor function was quantified on the basis of assessment of ambulation and placing and stepping responses. For statistical purposes, ambulation (walking with lower extremities) was graded as follows: 0, normal; 1, toes flat under the body when walking but ataxia present; 2, knuckle walking; 3, movement in lower extremities but unable to knuckle walk; or 4, no movement, drags lower extremities. Placing-stepping reflex was assessed by dragging the dorsum of the hind paw over the edge of a surface. This normally evokes a coordinated lifting and placing response (eg, stepping) that was graded as follows: 0, normal; 1, weak; or 2, no stepping. A motor deficit index (MDI) was calculated for each rat at each time

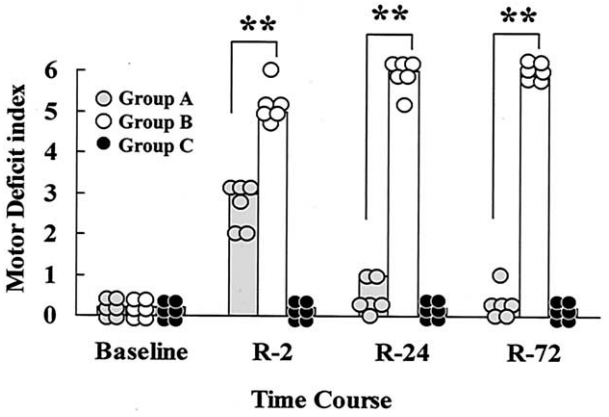

Figure 1. Changes in neurologic function after spinal cord ischemia, as assessed by the motor deficit index. Data were expressed as medians. A significant motor dysfunction induced by 10 minutes of spinal cord ischemia (group B) can be seen ($P <$ .01 compared with group A). *R-2,* Two hours of reperfusion; *R-24,* 24 hours of reperfusion; *R-72,* 72 hours of reperfusion.**

interval. The final MDI was the sum of the scores (walking with lower extremities plus placing and stepping reflex). The MDI was calculated by an observer without knowledge of the treatment group (M.K.).

Experimental Groups and Design

The animals were assigned to one of the following 2 groups according to the interval of aortic occlusion (n = 6 per group): group A, a short interval of occlusion (6 minutes); group B, a longer, injurious interval (10 minutes); and group C, a sham operation.

Perfusion Fixation and Histopathologic Analysis

Rats were terminally anesthetized with pentobarbital (100 mg/kg administered intraperitoneally) and phenytoin (25 mg/kg administered intraperitoneally) 72 hours after spinal cord ischemia. The animals were then transcardially perfused with 100 mL of heparinized saline, followed by 150 mL of 4% paraformaldehyde in phosphate buffer (pH = 7.4). Twenty-four hours later, the spinal cords were removed and postfixed in the same fixative for 2 to 14 days. After this period, the spinal cords were removed from the fixative, and L3, L4, and L5 spinal segments were dissected and cryoprotected in 30% sucrose solution. Frozen transverse sections (20-30 μm) were then prepared and stained by using the Nissl method. For analysis, 10 representative sections taken from segments L3 through L5, respectively (total, 30 sections from each spinal cord), were coded for each animal and then subjected to a systematic examination. The number of normal-appearing and dark-stained α motor neurons were counted by an observer without knowledge of the treatment group (M.K.).

Statistical Analysis

Statistical analyses of physiologic data were performed by using the unpaired Student *t* test. In analysis of neurologic function, testing of overall neurologic function was performed with the Kruskal-Wallis test. Significance of results was probed further by using the Mann-Whitney test for comparisons. In the study of tc-MEPs, comparisons between groups were performed by using 2-factor analysis of variance for repeated measures. When overall differences were detected, individual comparisons between groups after each time period that indicated either ischemia or reperfusion were performed with the unpaired Student *t* test. In addition, comparisons between baseline values and values at each time point were made within each group by using 1-factor analysis of variance for repeated measures, and post hoc comparisons were made by use of the Dunnett test with the baseline value.

Results

Preischemic and Intraischemic Observations

During the preischemic and intraischemic periods, body temperature ranged between 38.4°C and 37.6°C. Baseline distal arterial pressure was 71 ± 15 mm Hg and decreased to 6 ± 3 mm Hg at the end of aortic occlusion. No significant differences among experimental groups were detected.

Neurologic Function after Aortic Occlusion

Data on neurologic function after aortic occlusion are shown in Figure 1. In group A (6 minutes of aortic occlusion) all rats showed modest and transient motor weakness (MDI, 2-3) at 2 hours after reperfusion, followed by recovery to normal motor function at 72 hours of reperfusion. In group B 10 minutes of aortic occlusion resulted in an almost complete loss of the ability to stand, walk, or step at 2 hours of reperfusion. All rats in group B displayed a gradual development of spasticity between 2 and 24 hours of reperfusion, resulting in complete spastic paraplegia (MDI, 6) at 72 hours of reperfusion. In group C all rats showed normal motor function throughout the experiments.

Transcranial Motor Evoked Potentials

Data on tc-MEPs are shown in Figures 2 and 3. Reproducible tc-MEPs were recorded in all animals. In both groups the amplitude of tc-MEPs disappeared completely at 2 minutes after aortic occlusion ($P < .0001$ compared with baseline). Then tc-MEP signals recovered to the baseline level at 30 minutes of reperfusion. Although all group B rats displayed complete paraplegia at 24 and 72 hours of reperfusion, tc-MEPs could be seen; amplitude was about 250% of baseline at 24 and 72 hours of reperfusion. There were significant differences in the amplitude of tc-MEPs between groups A and B at 24 hours ($P < .01$) and 72 hours ($P < .01$) of reperfusion.

Histopathologic Analysis

In group A (6 minutes of spinal cord ischemia) most neurons, including interneurons and α motor neurons, had a normal appearance (Figure 4, *A* and *B*). In contrast, histopathologic changes in group B (10 minutes of spinal cord ischemia) were characterized by the presence of extensive necrotic changes of the gray matter distributed between

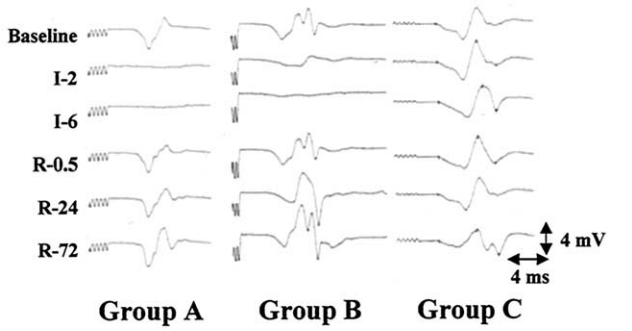

Figure 2. Myogenic tc-MEPs recorded from the right soleus muscle. Tc-MEPs in group A (almost normal motor function during reperfusion) appeared at 30 minutes of reperfusion. In group B (10 minutes of spinal cord ischemia) tc-MEPs appeared consistently in a paraplegic rat. In group C (sham operation) tc-MEPs did not change throughout the experiment. *I-2,* Two minutes of spinal cord ischemia; *I-6,* 6 minutes of spinal cord ischemia; *R-0.5,* 30 minutes of reperfusion; *R-24,* 24 hours of reperfusion; *R-72,* 72 hours of reperfusion.

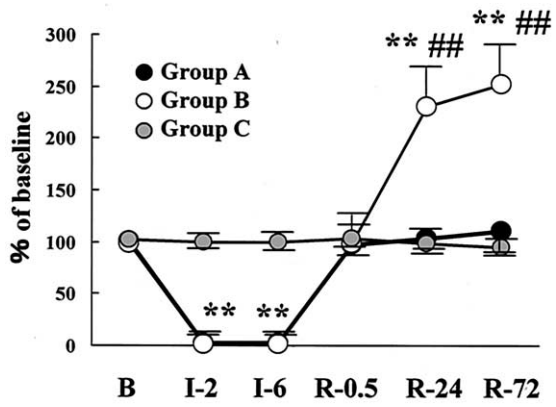

Figure 3. Time course changes in the amplitude of myogenic tc-MEPs. Data were expressed as means ± SD. The amplitudes of tc-MEPs decreased significantly and disappeared during spinal cord ischemia. Disappearance reversed to baseline level at 30 minutes of reperfusion in both groups. Note that tc-MEPs can be seen during reperfusion in group B (spastic paraplegia after 10 minutes of spinal cord ischemia). The amplitudes in group B were significantly higher than in group A at 24 and 72 hours of reperfusion (,##$P < .01$, **compared with group A, ##compared with baseline level.). *I-2,* Two minutes of spinal cord ischemia; *I-6,* 6 minutes of spinal cord ischemia; *R-0.5,* 30 minutes of reperfusion; *R-24,* 24 hours of reperfusion; *R-72,* 72 hours of reperfusion.**

laminae V through VII in the L3 through L5 segments (Figure 4, *C*). Corresponding to the presence of spasticity, the majority of α motor neurons had a normal structure (Figure 4, *C* and *D*). Histopathologic results of this study are consistent with previously published data[16] using this ischemic model.

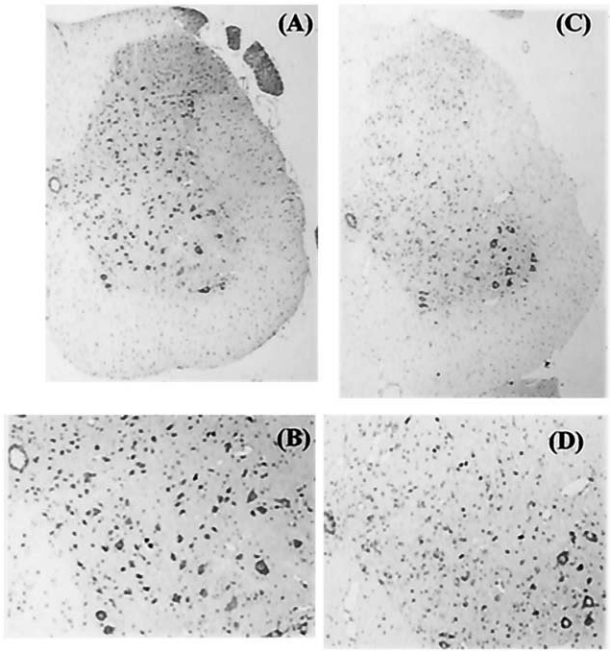

Figure 4. Light microphotograph of transverse sections. A and B, Transverse section of spinal cord taken from the lumbar spinal segment from an animal that underwent 6 minutes of spinal cord ischemia, with normal motor function at 72 hours of reperfusion. Normal appearance of α motor neurons and medium-size interneurons can be seen. C and D, Transverse section of spinal cord taken from the lumbar spinal segment from a rat subjected to 10 minutes of spinal cord ischemia with spastic paraplegia at 72 hours of reperfusion. Although α motor neurons appeared nearly normal, complete loss of medium-size interneurons in the intermediate zone (laminae VII) can be seen.

Discussion

The present study demonstrated that the rats undergoing 10 minutes of aortic occlusion displayed complete paraplegia at 24 and 72 hours of reperfusion, although their tc-MEPs were clearly preserved. To our knowledge, this is the first case report in which MEPs evoked by means of transcranial electrical stimulation appeared in a patient with complete paraplegia after emergency thoracic aortic aneurysm repair (Appendix). In addition, our experimental study also demonstrated that MEPs evoked by means of transcranial electrical stimulation could be detected even in rats with spastic paraplegia. These experimental data suggested that recovery of tc-MEP signals to baseline values after reperfusion does not always indicate postoperative normal motor function after a spinal cord ischemia.

Although exact criteria for indications of ischemic spinal cord dysfunction do not exist for myogenic tc-MEP monitoring, an amplitude of less than 25% of baseline value is considered an indication of ischemic spinal cord dysfunction.[13] In our case (Appendix) we could not monitor the

intraoperative MEP because of the patient's urgent shock status before surgical intervention. The amplitude of myogenic MEP recorded in the intensive care unit (ICU) might have been significantly less than preoperative values. However, in our clinical data (data not published) the baseline amplitude of myogenic MEPs recorded from 10 patients undergoing aortic surgery without the effect of a muscle relaxant was 725.3 μV (range, 371.8-1288.3 μV). Therefore, the amplitude in this case (1023 μV) could be considered within the normal range (Appendix Figure).

We produced spinal cord ischemia by means of balloon occlusion of the descending thoracic aorta. This technique is likely to induce ischemia of the peripheral nerve and muscle, resulting in a false-positive response during ischemia and reperfusion. In a preliminary study with a rat aortic occlusion model, we had confirmed that amplitude of compound muscle action potentials recorded from the soleus muscle evoked by the sciatic nerve recovered to the control level approximately 15 to 20 minutes after 10 minutes of aortic occlusion in this model. Because of the risk for a false-positive response within approximately 20 minutes of reperfusion, we therefore chose to measure the amplitude of tc-MEPs at 30 minutes after reperfusion.

Perioperative monitoring of myogenic MEPs in response to transcranial stimulation of the motor cortex provides a method to monitor the functional integrity of descending motor pathways. The main descending fiber tract is the corticospinal tract, which arises predominantly from the precentral gyrus. The fibers descend to the pyramid of the medulla and terminal, directly or by means of inhibitory interneurons, on to the motor neurons from which axons emerge from the spinal cord as the ventral root to the muscles. In normal motor function balanced tonic activity of excitation and inhibition is needed; excitation can be induced by the fiber terminal directly on the motor neurons, and inhibition can be induced by the inhibitory interneurons.[17] In spastic paraplegia or paraparesis, excitatory tonic activity in the spinal motor neurons might predominate as the result of a decrease in inhibition mediated by inhibitory interneurons. In this case report (Appendix) it could be speculated, on the basis of physical findings in the ICU, that inhibitory interneurons in the spinal cord would be damaged predominantly by intraoperative manipulation (thoracic aortic crossclamping).

Because the blood supply in rats has been reported to resemble closely that in the human spinal cord, thus providing a good model for study of spinal cord ischemia,[15] our model is appropriate to study the pathophysiology of spinal cord damage as a result of circulatory disturbances. In this animal model withdrawal of arterial blood from the left carotid artery controlled systemic blood pressure proximal to the aortic occlusion, and this could effectively decrease collateral perfusion, thus producing a near-total elimination of collateral flow to the spinal cord. In our case collateral perfusion to the spinal cord was likely to have been eliminated to a degree because of slight hypotension during the aortic crossclamping. This pathophysiologic condition can be considered similar to that in the rat model. In the present study all rats in group B displayed complete spastic paraplegia at 72 hours of reperfusion, and histopathology revealed a normal appearance of the α motor neurons and a loss of the medium-sized interneuronal pool localized predominantly in laminae V through VII. An immunohistochemical study[18] showed that medium-sized interneurons in laminae V through VII are likely to be inhibitory interneurons. The similarity between our case and our animal model supports our speculation that most of the spinal inhibitory interneurons in this patient were damaged, resulting in the spastic paraplegia seen in the ICU.

Perioperative monitoring of myogenic MEPs in response to transcranial stimulation of the motor cortex provides a method to monitor the functional integrity of descending motor pathways. In rats MEPs elicited by means of bipolar electrical stimulation to the motor cortex arise from activation of the spinal pyramidal pathway.[19-21] Although de Haan and Kalkman[22] mentioned that intraoperative myogenic tc-MEPs have a good prognostic value for neurologic outcome during the reperfusion period, our experimental data are not completely in agreement with their conclusion. From the histopathologic results of the experiment, the structure of α motor neurons was normal, despite complete damage to the spinal interneurons after 10 minutes of spinal cord ischemia. Marsala and colleagues[23] demonstrated that the corticospinal tract terminal connected through normal synapses to α motor neurons in an ischemic lumbosacral segment taken from rats with irreversible spastic paraplegia. Considering that spinal interneurons are not included in the pyramidal motor pathway from which the MEPs arise, it is understandable that myogenic tc-MEPs could appear even in spastic paraplegia resulting from damage to a predominant number of spinal inhibitory interneurons.

We do not mean to imply that myogenic tc-MEPs are unworthy as monitors of spinal cord ischemia during aortic crossclamping. Indeed, our experimental data demonstrated rapid disappearance of myogenic tc-MEPs after aortic occlusion and their reappearance after reperfusion, providing rapid assessment of the adequacy of spinal cord blood flow. This rapid assessment of spinal cord blood flow offers several advantages in a surgical approach that includes spinal cord protection (eg, identification of critical segmental arteries during aortic crossclamping and assessment of adequate blood supply through reattachment of segmental arteries).[22] Therefore, it is believed that myogenic tc-MEP monitoring can provide useful information to clinicians for making decisions with regard to timely interventions aimed

at correcting ischemic conditions and preserving spinal cord blood flow.

In conclusion, we experienced a recording of myogenic tc-MEPs in a patient with spastic paraplegia after aortic surgery. The present results, using a rat spinal cord ischemia model, demonstrated that MEPs evoked by means of transcranial electrical stimulation can be recorded during reperfusion after an injurious interval of spinal cord ischemia, resulting in spastic paraplegia. In using myogenic tc-MEP monitoring during thoracic or thoracoabdominal aneurysm repair, we should be aware that the reappearance of tc-MEPs does not mean the return of normal neurologic function in thoracic or thoracoabdominal aneurysm repair surgery.

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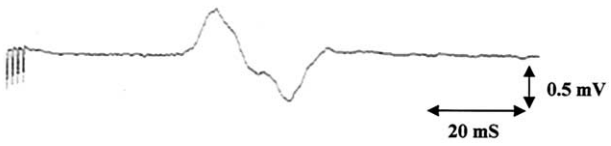
Appendix

Clinical Summary

A 66-year-old 45-kg man was admitted to the University of the Ryukyus Hospital for elective thoracic aortic aneurysm repair. He had been well until the previous day, when he experienced sudden intense chest pain and subsequently went into shock. Tracheal intubation was performed immediately, and his systolic blood pressure was maintained at 90 to 100 mm Hg without support by any inotropic agents. Chest computed tomography revealed widening of a descending thoracic aortic aneurysm and left intrapleural space, and rupture of the thoracic aortic aneurysm was suspected. Surgeons decided to perform an urgent thoracic aortic aneurysm repair and transferred the patient to the operating room. After induction of anesthesia with 50 μg of fentanyl and 6 mg of vecuronium bromide with ketamine infusion at 1 $mg \cdot kg^{-1} \cdot h^{-1}$, the patient was placed in a right semilateral position. After completion of the positional change, arterial blood pressure, recorded



Appendix Figure. MEPs evoked by means of transcranial electrical stimulation recorded from the left anterior tibial muscle in a patient with spastic paraplegia a day after thoracic aortic surgery. This MEP showed amplitude of 1023 μV.

from the right radial artery, suddenly decreased from 96/62 mm Hg to 64/45 mm Hg. Blood pressure was decreasing gradually, and bolus injections of norepinephrine (0.5 or 1 mg) could not maintain a systolic blood pressure of greater than 50 mm Hg. Under the diagnosis of ruptured aneurysm, both a right femoral venous and a right femoral arterial cannula were inserted immediately, and partial cardiopulmonary bypass was started to maintain systolic blood pressure at 50 mm Hg after systemic heparinization (14,000 U). Thoracotomy was performed at the fifth intercostal space, and an aneurysmal rupture into the pericardial lumen was confirmed by findings of bloody pericardial effusion. The thoracic aorta proximal to the aneurysm was crossclamped at the level of Th 7, and thereafter systolic blood pressure at the right radial artery could be controlled between 70 and 90 mm Hg. A descending thoracic aneurysm repair (level between Th 7 and Th 9) was performed with a 20-mm graft (Gelweave, Sulzer Vascutek). The durations of aortic crossclamping and surgical intervention were 70 minutes and 6 hours, respectively. In the intensive care unit this patient awoke, was alert, and followed our commands but was unable to move his legs the day after the operation. Neurologic findings by a neurologist revealed spastic paraplegia, indicating ischemic spinal cord injury. Under sedation with propofol infusion (2-3 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}), myogenic tc-MEP monitoring, however, demonstrated a reproducible waveform recorded from the left anterior tibial muscle in spite of his paraplegia (Figure). This paraplegia continued for 3 days after the operation, and his motor function recovered slightly, but neurologic findings one month after the operation revealed the continued presence of paraparesis.