

Recording of Corticospinal Evoked Potential for Optimum Placement of Motor Cortex Stimulation Electrodes in the Treatment of Post-stroke Pain

—Two Case Reports—

Takamitsu YAMAMOTO^{*,**}, Yoichi KATAYAMA^{*,**}, Toshiki OBUCHI^{**},
Toshikazu KANO^{**}, Kazutaka KOBAYASHI^{*,**}, Hideki OSHIMA^{**},
Chikashi FUKAYA^{*,**}, and Ryusuke KAKIGI^{***}

^{*}Division of Applied System Neuroscience, Department of Advanced Medical Science, and

^{**}Department of Neurological Surgery, Nihon University School of Medicine, Tokyo;

^{***}Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki, Aichi

Abstract

The corticospinal motor evoked potential (MEP) evoked by motor cortex stimulation was investigated as an intraoperative index for the placement of stimulation electrodes in the epidural space over the motor cortex for the treatment of post-stroke pain. A grid of plate electrodes was placed in the epidural space to cover the motor cortex, sensory cortex, and premotor cortex employing a magnetic resonance imaging-guided neuronavigation system in two patients with severe post-stroke pain in the right extremities, a 66-year-old man with dysesthesia manifesting as burning and aching sensation, and a 67-year-old woman with dysesthesia manifesting as pricking sensation. The D-wave of the corticospinal MEP was recorded with a flexible wire electrode placed in the epidural space of the spinal cord during anodal monopolar stimulation of each plate electrode under general anesthesia. The grid electrode was fixed in position with dural sutures and the craniotomy closed. The effect of pain reduction induced by anodal monopolar stimulation of the same plate electrodes was examined using the visual analogue scale (VAS) on a separate day in the awake state without anesthesia. Comparison of the percentage VAS reduction and the recorded amplitude of the D-wave employing the same stimulation electrode revealed significant correlations in Case 1 ($r = 0.828$, $p < 0.01$) and Case 2 ($r = 0.807$, $p < 0.01$). The grid electrode was then replaced with two RESUME electrodes over the hand and foot areas, and the optimum positions were identified by D-wave recording before electrode fixation. Both patients reported satisfactory pain alleviation with lower stimulation voltages than usually required for patients with similar symptoms. These results indicate the potential of D-wave recording as an intraoperative indicator for the placement of stimulating electrodes over the motor cortex for pain relief.

Key words: motor evoked potential, post-stroke pain, motor cortex stimulation, corticospinal motor evoked potential, D-wave

Introduction

Motor cortex stimulation therapy was first proposed for the treatment of post-stroke pain,¹⁹⁻²¹ and subsequently numerous studies have examined the effectiveness for neuropathic pain and central pain.^{2-4,7,8,11-13,16,17,22} In the large series, the long-term success rate for pain alleviation was about 50%. The pain control provided by motor cortex depends on stimu-

lation of neuronal circuits mediated by corticospinal tract neurons originating from the motor cortex.⁹ Activation of the thalamic nuclei directly connected with the motor and premotor cortices causes a cascade of synaptic events in pain-related structures receiving afferents from these nuclei, including the medial thalamus, anterior cingulate, and upper brainstem, and motor cortex stimulation attenuates the nociceptive spinal reflexes.⁵ Motor cortex stimulation also produces significant transient inhibition of the responses of the spinal cord dorsal horn neu-

Received January 9, 2007; Accepted July 5, 2007

rons to higher intensity mechanical stimuli without affecting the response to innocuous stimuli.¹⁸⁾ Therefore, at least part of the antinociceptive effect induced by motor cortex stimulation involves the corticospinal tract neurons originating from the motor cortex.

Correct placement of the cortical electrode, which induces the muscle twitches or muscle contractions, is most important to achieve effective pain relief in post-stroke pain.^{9,21)} The recommended position of the cortical stimulation electrode is over the painful area.^{14,17,21)} Various surgical techniques are available for the accurate placement of epidural or subdural electrodes over the motor cortex.^{14,17,21)} However, a standard method has not yet been established. Anatomical identification of the central sulcus by phase reversal of N20 with monitoring of the somatosensory evoked potential or magnetic resonance (MR) imaging-guided neuronavigation may allow exact positioning of the stimulation electrode on the precentral gyrus directly or epidurally. However, the activation of the corticospinal tract neurons originating from the motor cortex cannot be predicted. Moreover, anodal monopolar cortical stimulation activates vertically oriented pyramidal neurons,¹⁾ whereas only cathodal bipolar cortical stimulation, which tends to excite the superficial horizontal fibers and cortical interneurons, is available from the implantable pulse generator approved for clinical use.

The corticospinal motor evoked potential (MEP) evoked by direct stimulation of the motor cortex can be recorded from the epidural space of the spinal cord, and has been used for the intraoperative monitoring of motor function.^{9,23)} The corticospinal MEP response consists of an initial D-wave and a later sequence of volleys termed I-waves.^{1,15)} The D-wave reflects impulses arising from direct activation of the axons of corticospinal tract neurons, whereas the I-waves reflect neurons via synaptic activity.

The present study examined the relationship between pain reduction on the visual analogue scale (VAS) and the recorded amplitude of the D-wave during stimulation of various points of the motor cortex to evaluate the D-wave as an index for the placement of the epidural electrode in the treatment of post-stroke pain.

Patients and Methods

This study included two patients, a 66-year-old man with post-stroke pain in the right extremities caused by left pons bleeding manifesting as dysesthesia with burning and aching sensation for 25 months

(Case 1), and a 67-year-old woman with post-stroke pain in the right extremities caused by thalamic bleeding manifesting as dysesthesia with pricking sensation for 24 months (Case 2). Both patients felt most severe pain in the upper extremity. Both patients could walk unaided, and had grade 4 motor function of the right extremity by the muscle maneuver test (MMT).²³⁾ Both patients gave informed consent for intraoperative monitoring of the corticospinal MEP and test stimulation employing a grid electrode implanted in the epidural space just over the motor cortex. The present study was approved by the Committee for Clinical Trials and Research in Humans of our university and by the Japanese Ministry of Health and Welfare as part of an advanced medical care program.

A flexible four-channel, platinum wire electrode (3487A PISCES-Quad; Medtronic, Inc., Minneapolis, Minn., U.S.A.) was inserted into the epidural space of the cervical vertebrae, at the C2 to C4 levels, on the day before the operation. The patient was placed in the abdominal prone position, and an 18-gauge Touhy needle included in the electrode package was inserted into the midline epidural space at the cervical and thoracic junction under radiographic control. The spinal epidural space was confirmed from the change of resistance observed during saline injection through the Touhy needle. The electrode was inserted into the epidural space with a stylet via the Touhy needle and advanced to the appropriate position under radiographic control. The stylet and Touhy needle were then removed, and the electrode was fixed with adhesive tape and a drape placed on the skin (Fig. 1).

On the next day, a craniotomy sufficient to expose the postcentral gyrus, precentral gyrus, and posterior parts of the superior, middle, and inferior frontal gyri was performed under general anesthesia with muscle relaxant and completely controlled ventilation. The grid electrode, comprising 20 plate electrodes of 5 mm diameter and each separated by 5 mm, with each of the plate electrodes embedded in thin and soft silicone material (Unique Medical Co., Ltd., Komae, Tokyo), was placed in the epidural space over the motor, sensory, and premotor cortices employing an MR imaging-guided neuronavigator (Fig. 2). The ground electrode was placed on the forehead. The cerebral cortex was stimulated utilizing each contact point of the grid electrode. The stimulation was applied as a monophasic square wave pulse of 0.2 msec duration delivered at 2 Hz, and anodal monopolar stimulation with an intensity of 30 mA was selected for monitoring of the D-wave. A recording electrode with four contact points was used for bipolar recording between adjacent contact

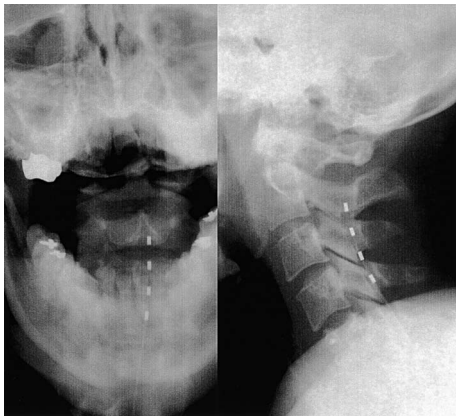


Fig. 1 Radiographs showing a four-channel wire electrode placed within the epidural space of the cervical spinal cord at the C2 to C4 levels.

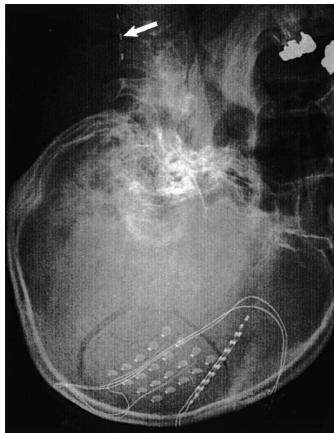


Fig. 2 Radiograph showing an epidural grid electrode implanted in the epidural space for direct cortical stimulation, and the electrode in the epidural space of the cervical spinal cord (arrow). Same orientation as Fig. 4.

points, and the signals were fed into an amplifier with a band pass range of 5 Hz to 5 kHz and averaged for 32 sweeps using Synax 2100 (NEC Co., Tokyo).

After recording the corticospinal MEP, the epidural grid electrode was fixed to the dura with sutures at several points to maintain the grid electrode location, and the wound was closed. The effect on pain induced by monopolar anodal cortical stimulation employing the contact points of the grid electrode was examined using the VAS on another day in the awake state without anesthesia. This test stimulation used a frequency of 25 Hz with a

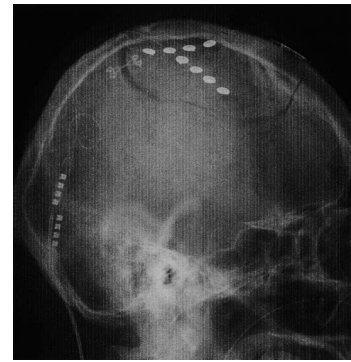


Fig. 3 Radiograph showing the two RESUME motor cortex stimulation electrodes placed on the hand and foot areas.

duration of 0.2 msec, and the best stimulation intensity was selected between 10 to 20 mA. The change of the VAS was expressed as percentage VAS reduction, calculated as $(1 - \text{VAS with stimulation} / \text{VAS without stimulation}) \times 100\%$. The percentage VAS reduction and the recorded amplitude of the D-wave using the same stimulating electrode were then compared by simple regression analysis.

After confirming that pain alleviation was obtained with cortical stimulation, chronic implantation of the electrode for motor cortex stimulation was performed under general anesthesia with muscle relaxant. Until this second operation, the recording electrode was left in the cervical epidural space. The epidural grid electrode was replaced with a four-channel plate electrode (3587A RESUME · II; Medtronic, Inc.), which has four contact points consisting of plate electrodes of 5 mm diameter and spaced 5 mm apart. The optimum location of the two RESUME electrodes for stimulation of the hand and foot areas was identified by monitoring the D-wave with bipolar stimulation of the most distant two contact points of the four (Fig. 3). After confirming the best location for the RESUME electrodes, which evoked the D-wave at the highest amplitude by bipolar stimulation, the edge of the RESUME electrode was sutured to the dura, to prevent movement of the electrode. This procedure was essential to ensure steady attachment between the dura and contact points. An implantable pulse generator was implanted under the anterior chest wall at the same time, and connected to the RESUME electrode with an extension cable.

Results

D-waves were detected after stimulation of 14 of the

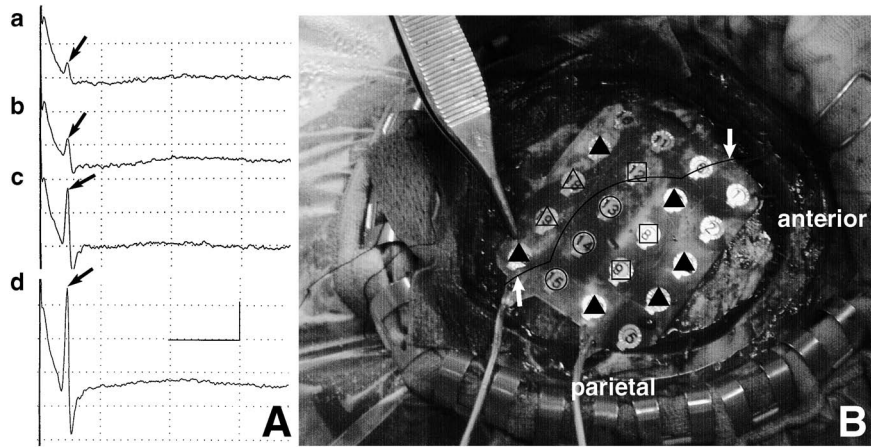


Fig. 4 **A:** Representative D-waves (arrows) classified into amplitudes of under 2 μV (a), 2 to 5 μV (b), 5 to 10 μV (c), and over 10 μV (d). Time scale, 5 msec; amplitude, 5 μV . **B:** Photograph of the intraoperative epidural grid electrode placed over the sensory, primary motor, and premotor cortices in Case 1. The amplitude of the D-wave evoked by the stimulation of each plate electrode was classified as over 10 μV (open circles), 5 to 10 μV (open squares), 2 to 5 μV (open triangles), and under 2 μV (closed triangles). Thick line: Central sulcus estimated by magnetic resonance imaging-guided navigation.

20 contact points of the grid electrode in Case 1, and 11 contact points in Case 2. The recorded amplitudes of the D-waves were classified into over 10 μV , 5 to 10 μV , 2 to 5 μV , and less than 2 μV (Fig. 4A). The evoked amplitudes of the D-waves were plotted on an intraoperative view of the grid electrode (Fig. 4B). The contact points which evoked D-wave amplitudes of over 10 μV were located just anterior to the central sulcus as estimated by MR imaging-guided neuronavigation.

Figure 5 illustrates the relationships between the recorded amplitude of the D-wave and the percentage VAS reduction in Cases 1 and 2. Simple regression analysis showed significant correlations in Case 1 ($r = 0.828$, $p < 0.01$) and Case 2 ($r = 0.807$, $p < 0.01$).

Discussion

The present study used high intensity anodal monopolar stimulation so that both the electrode contact areas and the surrounding cortical areas were stimulated together, thus stimulating a wider area of the cerebral cortex than previously,²³⁾ so we could compare the amplitude of the D-wave with the percentage VAS reduction. The percentage VAS reduction was significantly correlated with the D-wave amplitude, indicating that D-wave recording provides an intraoperative guide for placing the stimulating electrode at the optimum position on the motor cortex.

Chronic implantation of the RESUME electrodes was performed in the epidural space exposed by the craniotomy. The electrodes were placed parallel to the sagittal sinus over the central sulcus in the foot area, and parallel to the central sulcus over the motor strip in the hand area. The optimum positions were identified by searching for the D-wave with the highest amplitude evoked by bipolar stimulation. Both patients complained of most severe pain in the upper extremity, but also of dysesthesia of the lower extremity. Therefore, both hand and foot areas were stimulated together, since it is important to induce muscle contraction or muscle twitch in the painful area for the motor cortex stimulation therapy.^{10,19-22)}

Our previous experience with patients with MMT of 4 suggested that the threshold intensity to induce muscle contraction under stimulation conditions of 25 Hz with 0.2 msec duration is 5.8 ± 0.9 V ($n = 10$). In the present patients, muscle contraction was induced at 2.9 V in Case 1 and 3.3 V in Case 2. Both patients were satisfied by the results of chronic motor cortex stimulation. These findings confirm the importance of identifying the optimum point for motor cortex stimulation therapy in the treatment of post-stroke pain.

Corticospinal MEP monitoring requires insertion of the recording electrode into the cervical epidural space. The recording electrode can be easily and safely placed in the epidural space by the same technique as used for transcutaneous spinal cord stimulation for the treatment of pain, and we have already

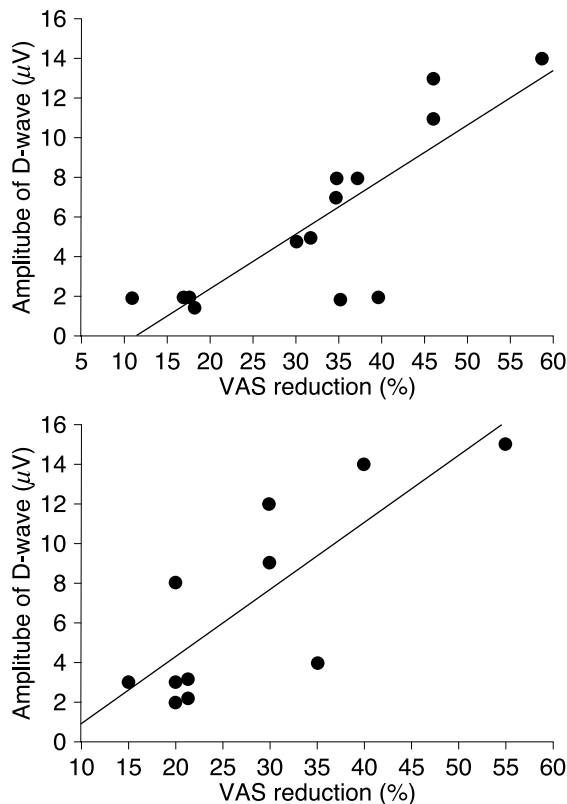


Fig. 5 Correlations of the recorded amplitude of the D-wave and the percentage visual analogue scale (VAS) reduction in Case 1 (upper) and Case 2 (lower). Simple regression analysis showed significant correlations in Case 1 ($Y = -3.033 + 0.274X$, $r = 0.828$, $p < 0.01$) and Case 2 ($Y = -2.575 + 0.339X$, $r = 0.807$, $p < 0.01$). Percentage VAS reduction = $(1 - \text{VAS with stimulation} / \text{VAS without stimulation}) \times 100\%$.

experienced over 250 cases without irreversible complications arising from such electrode insertion. Monitoring of the muscle responses to direct motor cortex stimulation is also useful for the monitoring of cerebral ischemia.⁶⁾ Another advantage is that, unlike muscle responses to motor cortex stimulation, the D-wave of the corticospinal MEP is resistant to surgical doses of anesthetics and is unaffected by muscle relaxants, apart from changes to the excitability of the spinal motor neurons, and so the amplitude can be easily correlated with the site of cortical stimulation.

The present study indicates that monitoring of the D-wave provides a good indicator of the optimum placement of the chronic electrode for the treatment of post-stroke pain, and thus allows implantation of the motor cortex stimulation electrode in a one-stage

operation under general anesthesia.

Acknowledgment

The present work was supported by grants from the Ministry of Education, Culture, Sports, Sciences and Technology of Japan (Grants No. A-15209047 and No. C-18591614) and a grant for the promotion of industry-university collaboration at Nihon University.

References

- 1) Amassian VE, Stewart N, Quirk GJ, Rosenthal JL: Physiological basis of motor effects of transient stimulus to cerebral cortex. *Neurosurgery* 20: 74-93, 1987
- 2) Canavero S, Bonicalzi V: Cortical stimulation for central pain. *J Neurosurg* 83: 1117, 1995
- 3) Carroll D, Joint C, Maartens N, Shlugmann D, Stein J, Aziz TZ: Motor cortex stimulation for chronic neuropathic pain: a preliminary study of 10 cases. *Pain* 84: 431-437, 2000
- 4) Ebel H, Rust D, Tronnier V, Böker D, Kunze S: Chronic precentral stimulation in trigeminal neuropathic pain. *Acta Neurochir (Wien)* 138: 1300-1306, 1996
- 5) Garcia-Larrea L, Peyron R, Mertens P, Gregoire MC, Lavenne F, LeBars D, Lonvers P, Mauquiere F, Sindou M, Laurent B: Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study. *Pain* 83: 259-273, 1999
- 6) Horiuchi K, Suzuki K, Sasaki T, Matsumoto M, Sakuma J, Konno Y, Oinuma M, Itakura T, Kodama N: Intraoperative monitoring of blood flow insufficiency during surgery of middle cerebral artery aneurysm. *J Neurosurg* 103: 275-283, 2005
- 7) Hosobuchi Y: Motor cortical stimulation for control of central deafferentation pain. *Adv Neurol* 63: 215-217, 1993
- 8) Katayama Y, Fukaya C, Yamamoto T: Poststroke pain control by chronic motor cortex stimulation: neurological characteristics predicting a favorable response. *J Neurosurg* 89: 585-591, 1998
- 9) Katayama Y, Tsubokawa T, Maejima S, Hirayama T, Yamamoto T: Cortico-spinal direct response in humans; identification of the motor cortex during intracranial surgery under general anesthesia. *J Neurol Neurosurg Psychiatry* 51: 50-59, 1988
- 10) Katayama Y, Tsubokawa T, Yamamoto T: Chronic motor cortex stimulation for central deafferentation pain: experience with bulbar pain secondary to Wallenberg syndrome. *Stereotact Funct Neurosurg* 62: 295-299, 1994
- 11) Meyerson BA, Lindblom U, Linderöth B, Lind G, Herregodts P: Motor cortex stimulation as treatment of trigeminal neuropathic pain. *Acta Neurochir Suppl (Wien)* 58: 150-153, 1993
- 12) Migita K, Uozumi T, Arita K, Monden S: Transcrani-

- al magnetic coil stimulation of motor cortex in patients with central pain. *Neurosurgery* 36: 1037-1039, 1995
- 13) Nguyen JP, Keravel Y, Feve A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B: Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. *Acta Neurochir Suppl* 68: 54-60, 1997
 - 14) Nguyen JP, Lefaucheur JP, Decq P, Uchiyama T, Carpentier A, Fontaine D, Brugieres P, Pollin B, Feve A, Rostaing S, Cesaro P, Keravel Y: Chronic motor cortex stimulation in the treatment of central and neuropathic pain. Correlations between clinical, electrophysiological and anatomic data. *Pain* 82: 245-251, 1999
 - 15) Patton HD, Amassian VE: Single and multiple-unit analysis of cortical stage of pyramidal tract activation. *J Neurophysiol* 17: 345-363, 1954
 - 16) Peyron R, Garcia-Larrea L, Deiber MP, Cinotti L, Convers P, Sindou M, Mauguière F, Laurent B: Electrical stimulation of precentral cortical area in the treatment of central pain: electrophysiological and PET study. *Pain* 62: 275-286, 1995
 - 17) Saitoh Y, Shibata M, Hirano S, Hirata M, Mashimo T, Yoshimine T: Motor cortex stimulation for central and peripheral deafferentation pain. Report of 8 cases. *J Neurosurg* 92: 150-155, 2000
 - 18) Senapati AK, Huntingten PJ, Peng TB: Spinal dorsal horn neuron response to mechanical stimuli is decreased by electrical stimulation of the primary motor cortex. *Brain Res* 1036: 173-179, 2005
 - 19) Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S: Chronic motor cortex stimulation for the treatment of central pain. *Acta Neurochir Suppl (Wien)* 52: 137-139, 1991
 - 20) Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S: Treatment of thalamic pain by chronic motor cortex stimulation. *Pacing Clin Electrophysiol* 14: 131-134, 1991
 - 21) Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S: Chronic motor cortex stimulation in patients with thalamic pain. *J Neurosurg* 78: 393-401, 1993
 - 22) Yamamoto T, Katayama Y, Hirayama T, Tsubokawa T: Pharmacological classification of central post-stroke pain: comparison with the results of chronic motor cortex stimulation therapy. *Pain* 72: 5-12, 1997
 - 23) Yamamoto T, Katayama Y, Nagaoka T, Kobayashi K, Fukaya C: Intraoperative monitoring of the corticospinal motor evoked potential (D-wave): Clinical index for postoperative motor function and functional recovery. *Neurol Med Chir (Tokyo)* 44: 170-182, 2004

Address reprint requests to: Takamitsu Yamamoto, M.D., Division of Applied System Neuroscience, Department of Advanced Medical Science, Nihon University School of Medicine, 30-1 Ohyaguchi Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan.
e-mail: nusmyama@med.nihon-u.ac.jp