Correlation Between Functional and Electrophysiological Recovery in Acute Ischemic Stroke

Chu Vang, MD; David Dunbabin, MBBS, FRACP; David Kilpatrick, MD, FRACP

Background and Purpose—There is still controversy about the prognostic value of motor evoked potentials (MEPs) in the assessment of hemiplegia. The aims of this study are to determine the relationship between functional and electrophysiological recovery and thus the value of MEP as a prognostic indicator of clinical outcome in acute ischemic stroke.

Methods—Seventeen healthy subjects and 38 stroke patients were included in this study. Functional recovery was assessed with the Modified Canadian Neurological Scale (MCNS), the Barthel Activities of Daily Living Index (BI), and the Rankin scale. Transcranial magnetic stimulation was used to determine the change in central motor conduction time (CMCT). Stroke outcome was assessed at the end of 2 weeks. One-way ANOVA with post hoc comparisons using the Scheffé procedure as well as t tests were used to assess the significance of the results in this study.

Results—Unpaired t test showed significantly higher mean scores of the MCNS (2P=0.001), BI (2P=0.002), and Rankin scale (P<0.001) at day 14 in the group of patients with recordable MEP at day 1. A better clinical improvement with a higher mean score of the MCNS (2P<0.001), BI (2P<0.001), and the Rankin scale (2P<0.001) was also observed in the patients in whom the CMCT improved.

Conclusions—These data show that there is a close relationship between clinical and electrophysiological improvement and that MEP is a useful prognostic indicator of clinical outcome. (Stroke. 1999;30:2126-2130.)

Key Words: electrophysiology ■ prognosis ■ stroke outcome ■ stroke, ischemic

It is possible to stimulate the human brain through the intact scalp and skull in conscious alert subjects with transcranial magnetic stimulation (TMS). Central motor pathways can be stimulated by TMS of the motor cortex.

TMS is a technique in which a small transient electrical current in the cerebral cortex is induced by a strong magnetic field. The stimulating coil is held close to the scalp so that the magnetic field is focused and can pass through the skull to produce local electrical currents in the cerebral tissue. Magnetic stimulation of the motor cortex was introduced for the first time by Barker1 and may become a routine and useful method in clinical neurophysiology.2 TMS of the motor cortex has been used successfully to evaluate the motor pathways in many neurological diseases, including stroke.3–12

The relationship between functional and electrophysiological recovery has been studied; however, there is still controversy about the real prognostic value of motor evoked potentials (MEPs) for hemiplegia. Some authors recommend cortical MEP as a prognostic indicator for hemiplegia,3–9 whereas others reported no significant predictive value of MEP in acute hemiplegia.10–12

The aim of this study was to determine the relationship between functional and electrophysiological recovery and thus the value of MEP as a prognostic indicator of clinical improvement in acute ischemic stroke.

Subjects and Methods

Seventeen healthy subjects and 38 consecutive patients, aged 34 to 86 years, with a first acute ischemic stroke involving the middle cerebral artery (MCA) territory, were included in this study. The mean age was 40 years for the healthy subjects and 67 years for the stroke patients. The site of occlusion was in the proximal MCA in 22 cases (59%) and the distal MCA in the other 15 cases (41%). Stroke severity category recorded at day 1, as measured with the Modified Canadian Neurological Scale (MCNS), ranged from moderate (28 cases) to severe (10 cases). Functional recovery was assessed with the MCNS,13 the Barthel Activities of Daily Living Scale (BI), and the Rankin scale.15 TMS was used to determine the presence of MEPs as well as to measure the central motor conduction time (CMCT). Stroke outcome was assessed at the end of 2 weeks.

Assessment of Functional Recovery

The MCNS was used to quantify the degree of neurological impairment or stroke severity. This scale assesses different levels of motor function deficit. Points are awarded according to the degree of neurological deficit and can be added together to provide a total score ranging from 0 to 11.5. The BI14 was used to determine the degree of disability. It assesses 10 different aspects of activities of daily living, most of which indirectly relate to motor function. Points are awarded for different levels of achievement in each category and can be added together to provide a total score ranging from 0 to 20. When possible, the information required was obtained from the principal carer rather than the patient.
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Amplitude of Motor Evoked Potential (AMP) and CMCT Recorded in Healthy Subjects (Controls) and Stroke Patients

<table>
<thead>
<tr>
<th>Difference in Mean CMCT and AMP Between Stroke Patients and Healthy Subjects</th>
<th>Control Subjects</th>
<th>Stroke Patients</th>
<th>2P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left side (n=17)</td>
<td>Affected side (n=22)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMCT</td>
<td>6.0412 (1.014)</td>
<td>7.1636 (1.889)</td>
<td>0.023</td>
</tr>
<tr>
<td>AMP</td>
<td>5.4286 (1.847)</td>
<td>3.0133 (2.431)</td>
<td>0.002</td>
</tr>
<tr>
<td>Right side (n=17)</td>
<td>Affected side (n=22)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMCT</td>
<td>5.5824 (1.104)</td>
<td>7.1636 (1.889)</td>
<td>0.002</td>
</tr>
<tr>
<td>AMP</td>
<td>5.3568 (2.536)</td>
<td>3.0133 (2.431)</td>
<td>0.006</td>
</tr>
<tr>
<td>Left side (n=17)</td>
<td>Normal side (n=38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMCT</td>
<td>6.0412 (1.014)</td>
<td>5.6158 (1.305)</td>
<td>0.239</td>
</tr>
<tr>
<td>AMP</td>
<td>4.5229 (2.139)</td>
<td>4.5229 (2.139)</td>
<td>0.137</td>
</tr>
<tr>
<td>Right side (n=17)</td>
<td>Normal side (n=38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMCT</td>
<td>5.5824 (1.104)</td>
<td>5.6158 (1.305)</td>
<td>0.927</td>
</tr>
<tr>
<td>AMP</td>
<td>5.3568 (2.536)</td>
<td>4.5229 (2.139)</td>
<td>0.213</td>
</tr>
</tbody>
</table>

Side-to-Side Difference in Mean CMCT and AMP

<table>
<thead>
<tr>
<th>Right side (controls) (n=17)</th>
<th>Left side (controls) (n=17)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CMCT</td>
<td>5.5824 (1.104)</td>
<td>6.0412 (1.014)</td>
<td>0.230</td>
</tr>
<tr>
<td>AMP</td>
<td>5.3568 (2.536)</td>
<td>5.4286 (1.847)</td>
<td>0.917</td>
</tr>
<tr>
<td>Normal side (patients) (n=22)*</td>
<td>Affected side (patients) (n=22)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMCT</td>
<td>5.1091 (0.739)</td>
<td>7.1636 (1.889)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AMP</td>
<td>4.7202 (2.114)</td>
<td>3.0133 (2.431)</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Values are given as mean (SD).

*Patients with no recordable MEP from affected side were excluded from this analysis.

The Rankin or Oxford Handicap Scale15 was used to quantify the degree of handicap of the patients. In this assessment 6 categories are recognized, ranging from 0 (no symptoms) to 5 (severe handicap and totally dependent).

Assessment of Electrophysiological Recovery

In this study the Magstim Model 200 with a coil 90 mm in diameter was used to excite the motor cortex and spinal motor roots. This device can stimulate the neuromuscular tissue by inducing small currents in the tissue with a brief pulse electromagnetic energy. Due to the limited availability of the TMS device, the TMS tests could not be performed exactly at days 1 and 14 as planned. The mean day on which the TMS tests were performed on the patients after the onset of stroke (day1) was 1.78±0.98 days for the first test and 12.36±4.05 days for the second test (day14). Patients were seated or lying half supine in bed, with the arm being studied supported by a pillow. An explanation of electromagnetic brain stimulation was printed out on A4 paper so that hand calculations of the CMCT could be performed. The CMCT techniques previously described were also used to measure their CMCT and amplitude of motor evoked responses in active the thenar muscle obtained from these 17 healthy subjects with a mean of 5.5824±1.104 ms was used as normal data to group the CMCT obtained from the stroke patients included in this study as normal, delayed, and absent. The CMCT was considered abnormal if it fell outside the 99% CI limit of these normal CMCT values (mean±2.5 SD), which ranged from 2.7824 ms to 8.4424 ms. The CMCT was defined as delayed when it fell above 8.44 ms and as absent when there was no recordable MEP.

In this study TMS tests were also performed on both sides in 17 healthy subjects to measure their CMCT and amplitude of motor response. The TMS techniques previously described were also used in these healthy subjects. The range of CMCT recorded in active the thenar muscle obtained from these 17 healthy subjects with a mean of 5.5824±1.104 ms was used as normal data to group the CMCT obtained from the stroke patients included in this study as normal, delayed, and absent. The CMCT was considered abnormal if it fell outside the 99% CI limit of these normal CMCT values (mean±2.5 SD), which ranged from 2.7824 ms to 8.4424 ms. The CMCT was defined as delayed when it fell above 8.44 ms and as absent when there was no recordable MEP.
ment was indicated when no motor response was detected at day 1 and day 14 or the CMCT at day 14 worsened and became absent or more delayed. One-way ANOVA with post hoc comparisons using the Scheffé procedure and *t* tests were used to assess the significance of the results in this study.

**Results**

TMS tests were performed on both sides on 17 healthy subjects to measure their CMCT and amplitude of motor response. These data were compared with data of CMCT and amplitude of motor response recorded from 38 stroke patients (Table). There was a significantly lower mean amplitude of MEP on the affected side of the stroke patients compared with data recorded from the left (3.0133 mV versus 5.4286 mV, \(2P=0.002\)) and right (3.0133 mV versus 5.5368, \(2P=0.006\)) sides of the healthy subjects. A longer mean CMCT was found in the affected side of the stroke patients compared with data recorded from the left (7.1636 ms versus 6.0412 ms, \(2P=0.023\)) and right (7.1636 ms versus 5.5824 ms, \(2P=0.002\)) sides of the healthy subjects. No significant difference in mean amplitude of MEP and CMCT was found between the nonparetic side of the stroke patients and data recorded from both left and right sides of the healthy subjects.

There was no significant difference in mean amplitude of MEP and CMCT between the left and right sides in the group of healthy subjects. However, in the stroke patients, the mean amplitude of MEP of the affected side was lower (3.0133 mV versus 4.7202 mV, \(2P=0.025\)), with a greater or more delayed CMCT (7.1636 ms versus 5.1691 ms, \(2P<0.001\)) in comparison with data recorded in the nonparetic side. These data show that nerve conduction through the central motor pathway is severely affected by acute ischemic stroke.

A better clinical outcome was observed at day 14 in the patients in whom there was a recordable MEP at day 1. There were significantly higher mean scores recorded at day 14 of the MCNS (9.9091 versus 7.1250, \(2P=0.001\)), the BI (16.8750 versus 13.7500 versus 8.1538, \(2P=0.0001\)), and the Rankin scale (1.3750 versus 1.7500 versus 3.1538, \(P<0.0001\)) between the normal, delayed, and absent CMCT groups, respectively. In Post hoc comparisons between groups, using the Scheffé procedure, there was a significantly higher or better mean score of the MCNS (\(P<0.001\)), the BI (\(P<0.001\)), and the Rankin scale (\(P<0.001\)) in the normal CMCT group compared with the group in which the CMCT was absent (Figure 2). Clinical improvement was closely associated with the CMCT improvement. Unpaired *t* tests showed a better mean score recorded at day 14 of the MCNS (10.1471 versus 6.9667, \(2P<0.001\)), the BI (16.9420 versus 9.2667, \(2P<0.001\)), and the Rankin scale (1.3529 versus 2.9333, \(2P<0.001\)) in the patients in whom the CMCT improved (Figure 3). These data confirm the usefulness of CMCT change as a powerful prognostic indicator of clinical improvement.

**Discussion**

The results of this study show that there is a close relationship between clinical and electrophysiological recovery, and that MEP is useful as a prognostic indicator of clinical outcome in acute ischemic stroke.

Many studies have dealt with transcranial motor cortex stimulation in stroke patients.\(^7,8,11,12,17,18\) The CMCTs were grouped in these studies as normal, delayed, and absent, and the change in CMCT was assessed according to this classification. According to their reports, no significant change of...
the CMCT was observed in the acute phase of ischemic stroke. In this study, the change in CMCT was assessed with a self-control trial technique, which compared the CMCTs recorded at day 1 and day 14, even though they were within the normal range of CMCT recorded from healthy subjects.\textsuperscript{7,18} This method of assessment showed a significant improvement of the CMCT in the affected side in the reperfused groups at day 14. This electrophysiological improvement may be due to a plastic reorganization in the affected area.

Many animal studies done by neuroscientists such as Bjorklund in Sweden,\textsuperscript{19} Aguayo in Canada,\textsuperscript{20} Raisman in England,\textsuperscript{21} and Steward in the United States\textsuperscript{22} have provided evidence that neurons of the brain and spinal cord also have the same capacity to regenerate as peripheral nerves after injury showing collateral growth or sprouting. Other authors of TMS studies also provided evidence that there was some degree of electrophysiological recovery after the onset of stroke in human beings.\textsuperscript{5,7,8,23,24} Lee and van Donkelaar\textsuperscript{25} reviewed the mechanisms underlying functional recovery after stroke and found relevant evidence from animal experiments indicating that there is considerable potential for reorganization of representations and functions in sensory and motor cortex after the occurrence of localized lesions. Three major mechanisms for this plastic reorganization were suggested: “unmasking of existing but functionally inactive pathways, sprouting of fibers from surviving neurons and formation of new synapses, and redundancy of CNS circuitry allowing alternative pathways to take over functions.”\textsuperscript{25} It has been suggested that when one system breaks down or something goes wrong, the secondary system immediately becomes operational and takes over for the damaged system; this mechanism is called redundancy. Another form of redundancy can be “unmasked.” In the 1970s, Wall and colleagues in London\textsuperscript{26,27} showed that previously silent fiber pathways in the brain stem could become immediately active when the sensory fibers in the spinal cord were cut. Because the appearance of activity occurred so soon after the injury, Wall\textsuperscript{26} proposed that the new pathways were there all the time but their activity was masked or inhibited by the primary sensory fibers.

In this study, clinical improvement was significantly better in the group in which the CMCT improved. In addition, cortical MEPs that were previously absent reappeared in TMS tests repeated at day 14 after the onset of stroke in many of the patients in this group. Clinical improvement of the 38 patients included in this study was significantly associated with the degree of CMCT improvement recorded at day 14 and the MEP recorded at day 1. These data suggest that plastic reorganization occurs in the human brain after the onset of stroke, which leads to a better recovery of the central motor pathway with a better stroke outcome.

On the other hand, the CMCT worsened in many of the patients, which led to a poor clinical improvement. This poor stroke outcome may be due to an increase of neuronal death in the ischemic penumbra area located around the central necrotic core. It is known that there is hypoperfusion and neuronal hypoxia\textsuperscript{28–30} in the penumbra; however, neuronal cells are still viable in this area.\textsuperscript{31} Reduction of oxygen supply to brain tissue results in a cascade of biochemical reactions in the affected cerebral territory, with a massive calcium influx into the cell and breakdown of the membrane, leading to neuronal cell death. If cerebral blood flow is not restored within a short time after the onset of stroke, there may be an extension of neuronal death into the ischemic penumbra, resulting in a clinical and electrophysiological deterioration with a poor stroke outcome. The capacity to regenerate a new set of axon terminals depends on the neurons as well as glial cells that can survive after the onset of stroke. In the earliest phase of the lesion, the injured, dying, and traumatized cells are in a state of shock and release all of their stores of amino acid neurotransmitters (glutamate and aspartate, among others) and the calcium ions needed to activate them.\textsuperscript{32} However, if cerebral reperfusion does not occur and the transport of these critical elements is not quickly restored to normal, further death of affected neurons in the area of injury will occur and result in greater functional disturbance.

Inappropriate activation of apoptosis may be another possible mechanism for clinical and electrophysiological deterioration or poor stroke outcome that occurred in these stroke patients. Apoptosis is a mechanism in which the cell implements its own death in response to a diverse set of signals that...
include physical and genetic damage, oxygen or nutrient deprivation, loss of contact with neighboring cells, and infection by viruses. Previous studies have shown that certain types of nerve cell death in the brain occur by an apoptotic mechanism.23–33 These studies have demonstrated that moderate hypoxic-ischemic episodes can cause DNA fragmentation as well as other morphological features of apoptosis in neurons destined to die, whereas more severe hypoxic-ischemic episodes lead to neuronal necrosis and infarction.

In conclusion, this study provides evidence that there is a close relationship between clinical and electrophysiological recovery, and that MEP is useful as a prognostic indicator of clinical outcome in acute ischemic stroke.

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References

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