Effects of Spontaneous Recanalization on Functional and Electrophysiological Recovery in Acute Ischemic Stroke

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Background and Purpose—Transcranial Doppler ultrasound (TCD) studies have shown that spontaneous recanalization results in a better clinical improvement after the onset of stroke. However, its effect on electrophysiological recovery is still unknown. The aim of this study was to determine the effects of spontaneous recanalization on the change in central motor conduction time (CMCT) in acute ischemic stroke.

Methods—Seventeen healthy subjects and 38 consecutive patients with a first acute ischemic stroke involving the middle cerebral artery territory were included. TCD was used to detect spontaneous recanalization. Transcranial magnetic stimulation was used to determine the change in CMCT on days 1 and 14. Improvement of the CMCT at day 14 was indicated if it decreased in comparison with previous data recorded at day 1 or when a nonrecordable motor response at day 1 reappeared at day 14. No CMCT improvement was indicated when there was no recordable motor response at day 1 and day 14 or the CMCT at day 14 worsened, becoming absent or more delayed. The Pearson $\chi^2$ test was used to assess the statistical significance of the results in this study.

Results—Spontaneous recanalization was observed in 62% of the patients: 24% before 24 hours and 38% after this period. No recanalization was observed in 14 patients. The CMCT improved in 87% of the patients who had recanalized before 24 hours and 62% in the recanalized after 24 hours group ($P = 0.005$). In contrast, CMCT improved in only 17% of the patients in the non-recanalized group.

Conclusions—These data show that spontaneous recanalization results in a better recovery of the central motor pathway leading to a better CMCT improvement in acute ischemic stroke. (Stroke. 1999;30:2119-2125.)

Key Words: electrophysiology • reperfusion • stroke, ischemic • stroke outcome

Many angiographic and transcranial Doppler ultrasound (TCD) studies have shown that spontaneous recanalization occurs after the onset of stroke and results in a better clinical improvement. However, the effect of spontaneous recanalization on electrophysiological recovery in acute ischemic stroke is still unknown.

It is possible to detect delays or lack of conduction in descending motor pathways in intact human beings by use of single-pulse high-voltage magnetic stimulation of the cortex and the cervical spine segments. Transcranial magnetic stimulation (TMS) of the motor cortex painlessly stimulates only the largest motor neuron and the fastest conduction axons. Cervical cord stimulation is believed to activate the anterior roots. The difference in time between the motor cortex and cervical activation of hand or forearm muscles represents the conduction velocity of the cortical–cervical cord motor neurons and is known as the central motor conduction time (CMCT).

Magnetic stimulation of the motor cortex, introduced for the first time by Barker, may become a routine and useful method in clinical neurophysiology. This technique has been widely used to evaluate the integrity of the central motor pathways in patients with motor disturbances in many neurological disorders, including stroke. Most of the authors reported that there was some degree of electrophysiological improvement after the onset of stroke. However, none of the studies that have been completed were designed to determine whether there is an association between spontaneous recanalization and the improvement of the CMCT. The aim of this study is to determine the effects of spontaneous recanalization on the improvement of the CMCT in acute ischemic stroke.

Subjects and Methods
Seventeen healthy subjects and 38 consecutive patients, aged 34 to 86 years, with 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 in the distal MCA in the other 15 cases (41%). Stroke severity category recorded at day 1, as measured using the Modified Canadian Neurological Scale, ranged from moderate (28 cases) to severe (10 cases). TCD was used to detect spontaneous recanalization. TMS of the motor cortex was used to determine the CMCT. Stroke outcome was assessed at the end of 2 weeks.
Assessment of Spontaneous Recanalization by TCD

In this study TCD measurements were performed using the Medasonics Transpect TCD device, with a hand-held transducer in a range-gated, pulsed-wave mode at a frequency of 2 MHz. A series of TCD tests was performed on the patients. Blood flow velocities of the MCAs, anterior cerebral arteries (ACAs), and posterior cerebral arteries (PCAs) were recorded on both sides through the transcranial Doppler (TCD) device. Data for MV and PI from each 5-mm step were recorded into a videotape for comparison with further changes of blood flow velocity that occurred in each of the following sections of TCD tests. The relevant color Doppler shifts recorded in each patient were later printed out so that hand calculations of the CMCT could be performed.

Insonation of the MCAs, ACAs, and PCAs

The blood flow signal from the MCA was detected starting with the posterior portion of the window near the ear and then the probe was moved slowly anteriorly and superiorly. At the same time the probe was angled to get the strongest and clearest signal. The depth was set at 55 mm. When the blood flow signal from the MCA with flow direction toward the probe was detected, it was traced up to 30 or 35 mm. Doppler shifts were recorded in each 5-mm step. To detect a blood flow signal from the ACA the depth was set at 65 mm. The probe angle was set anteriorly and superiorly. The flow direction of the ACA was away from the probe. The probe was traced down to 75 or 80 mm in steps of 5 mm. To detect a blood flow signal from the PCA, the probe was aimed posteriorly and inferiorly. The blood flow signal from the PCA usually was detected at 65 mm and could be traced from a 60- to 70-mm depth, and its flow direction was toward the probe.

The Doppler shifts with mean blood flow velocity (MV), peak systolic velocity (PSV), and the Goslung Pulsatility Index (PI) were calculated and displayed automatically by the Medasonics Transpect TCD device. Data for MV and PI from each 5-mm step were recorded into a videotape for comparison with further changes of blood flow velocity that occurred in each of the following sections of TCD tests. The relevant color Doppler shifts recorded in each patient were later printed out so that hand calculations of the CMCT could be performed.

Criteria for Spontaneous Recanalization

In this study an occlusion at the proximal MCA was indicated when there was no motor response. The CMCT was considered abnormal if it fell outside the 99% CI limit of these normal CMCT values (mean ± 2.5 SDs) that ranged from 2.8224 ms to 8.3425 ms. The CMCT was defined as delayed when it fell above 8.34 ms and as absent when there was no motor response.

Assessment of Electrophysiological Recovery

In this study the Magstim Model 200 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 of electromagnetic energy. Due to the limited availability of the TMS device, the TMS tests could not be performed exactly at day 1 and day 14 as planned. The mean day in which the TMS tests were performed on the patients after the onset of stroke (day 1) was 1.78 ± 0.98 days for the first test and 12.36 ± 2.05 days for the second test (day 14). 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 given to all patients before the investigation.

Cortical Stimulation

To stimulate the motor cortex, a circular coil (Magstim 9 cm) was placed in the tangential plane above the vertex. The left hemisphere was stimulated by a counterclockwise current, with side A of the coil visible from above and side B facing the vertex, while the right hemisphere was stimulated by a clockwise current, with side B of the coil visible from above and side A facing the vertex.

The stimulus intensity was set at 100% power for all patients. To document the presence of a response and to obtain appropriate values of CMCT, facilitation was provided by a gentle voluntary contraction of the thenar muscle being studied. If no voluntary contraction of the thenar muscle could be achieved in the paretic side, the patient was asked to contract the thenar muscle of the normal side. An absent response to stimulation was documented if no response was obtained after 4 stimuli with 100% power output of the stimulator and with facilitation from muscle contraction. Patients were stimulated twice from the vertex, and the shortest cortical latency was noted, because this has been shown to provide the basis for the best estimate of the CMCT.

Cervical Stimulation

To stimulate the cervical motor roots the same coil was closely applied to the skin over the seventh cervical spine (C7) and centered in the coronal plane. Counterclockwise current was used to stimulate roots to the right arm and clockwise current for the left arm. During stimulation of the spinal roots the muscles were relaxed. As for stimulation of the cortex, the stimulus intensity used was 100% power, and responses were recorded in a surface electromyogram of the thenar muscle. Two responses were recorded, and the longest latency obtained was noted.

Recording of the Surface Electromyogram

The surface electromyogram was recorded with use of miniature skin-mounted preamplifiers from the thenar muscle (abductor pollicis brevis), with electrodes over the thenar eminence in the direction of the first metacarpal bone. The ground electrode was attached to the back of the hand being studied. The recording electrode comprised 2 silver discs 5 mm in diameter set 20 mm apart. All motor evoked potential (MEP) response signals from the cortical and cervical stimulation were recorded and displayed automatically on the screen of the Nicolet Viking IV recording device. The results of MEP responses recorded on both sides were later printed out so that hand calculations of the CMCT could be performed.

Measurement of the CMCT

TMS tests were also performed on both sides on 17 healthy subjects to measure their CMCT. The same TMS techniques previously described were also used in the healthy subjects. The CMCT was provided by subtraction of the longest cervical latency from the shortest cortical latency. The range of CMCT recorded in active thenar muscle obtained from the 17 healthy subjects with a mean of 5.824 ± 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 SDs) that ranged from 2.8224 ms to 8.3425 ms. The CMCT was defined as delayed when it fell above 8.34 ms and as absent when there was no motor response.

In this study, improvement of the CMCT was indicated when there was a decrease of the CMCT at day 14 in comparison with previous data recorded at day 1 (CMCT decreased) or when a nonrecordable motor response at day 1 reappeared at day 14 (CMCT reappeared). On the other hand, no CMCT improvement was indicated when there was no recordable motor response at days 1 and 14 (CMCT absent at day 1 and day 14) or the CMCT at day 14 worsened and became absent (CMCT normal or delayed at day 1 but absent at day 14) or increased (CMCT increased at day 14). The Pearson χ² test and the
Mantel-Haenszel $\chi^2$ test were used to assess the statistical significance of the results in this study.

**Results**

The CMCTs recorded on active thenar muscle were $5.58 \pm 1.10$ ms (mean $\pm$ SD) for the right side and $6.04 \pm 1.01$ ms for the left side in the group of healthy subjects. These data were compared with the range of normal CMCT reported by other authors,\textsuperscript{19,23} and are completely normal. The CMCT recorded at day 1 was severely affected in the group of stroke patients. No motor response was recorded in 42%, and an additional 10% had a very delayed CMCT recorded on the paretic side. Even the nonparetic side the CMCT was delayed in 8% of the stroke patients (Table 1). These data show that nerve conduction through the motor pathway is severely affected by ischemic stroke.

TMS tests were performed on both sides at day 1 on 38 stroke patients and were repeated on 33 of them at day 14. No significant variation of the CMCT was observed in the normal side; however, on the affected side the CMCT suffered a dramatic change. The earlier spontaneous recanalization occurred, the better the CMCT (Figure 1). At day 14 the CMCT of the affected side decreased in 62% of the patients. In the nonrecanlized group the CMCT did not show any change (58%) or even worsened, becoming absent (8%) or more delayed (16%).

TMS tests were performed on 12 of the 14 patients in whom recanalization did not occur. No improvement of the CMCT of the affected side was observed in 10 (83%) of them. The CMCT of the affected side worsened in 3 of these patients at day 14. It became absent (Figure 1) in 1 (case 017) and more delayed in the other 2. In addition, no change was observed in any of the 7 patients in whom there was no recordable MEP at day 1 in this group.

Pearson $\chi^2$ tests showed a significantly better CMCT improvement in the patients in whom spontaneous recanalization occurred ($P=0.005$). The CMCT improved in 87% of the patients in whom spontaneous recanalization occurred before 24 hours and in 62% in the group in which it occurred after 24 hours (Figures 2 and 3A). In contrast, this electrophysiological outcome was poor (17%) in the nonrecanlized group (Figures 2 and 3B). These findings show that spontaneous reperfusion of cerebral blood flow results in a better CMCT in acute ischemic stroke.

The influence of leptomeningeal collateral blood supply on the improvement of the CMCT is shown in Table 2. For the group in which no collateral blood flow was detected, the CMCT at day 14 improved in 64% of the patients in whom recanalization occurred, whereas no CMCT improvement was observed in any of the patients from the

![Figure 1. Effects of spontaneous recanalization on the change in central motor conduction time on the affected side at day 14 (n=33).](http://stroke.ahajournals.org/)

**Table 1. CMCT Groups Recorded at Day 1 in Healthy Subjects (n=17) and Stroke Patients (n=38)**

<table>
<thead>
<tr>
<th>CMCT Groups</th>
<th>Normal</th>
<th>Delayed</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects (controls)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMCT groups in left side</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>CMCT groups in right side</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

| Stroke patients                          |        |         |        |       |
| CMCT groups recorded at day 1            |        |         |        |       |
| Normal side in stroke*                   | 35     | 92.1    | 3      | 38    |
| Affected side in stroke†                 | 18     | 47.4    | 4      | 22    |
| CMCT groups recorded at day 14           |        |         |        |       |
| Normal side in stroke                    | 31     | 93.9    | 2      | 33    |
| Affected side in stroke                  | 16     | 48.5    | 4      | 20    |

* $\chi^2=1.39, P=NS$ (control versus normal side of the stroke patients at day 1).
† $\chi^2=14.06, P=0.0008$ (control versus affected side of the stroke patients at day 1).
‡ $\chi^2=21.60, P=0.00002$ (normal side versus affected side at day 1).
nonrecanalized group \((2P=0.01)\). On the other hand, for the group in which an efficient collateral blood flow supply was detected, the CMCT improved in both groups, whether or not spontaneous recanalization occurred, with a better outcome in the recanalized group (80% versus 40%).

Results of the Mantel-Haenszel \(\chi^2\) test shown in the stratified table (Table 2) suggest that there is a significant interaction between spontaneous recanalization and leptomeningeal collateral circulation, and both affect the improvement of the CMCT. In addition, these data confirm that spontaneous recanalization results in a better electrophysiological recovery in acute ischemic stroke (Mantel-Haenszel \(\chi^2=6.76, P=0.009\)).

Discussion

This study provides evidence for the first time that spontaneous recanalization results in a better recovery of the cortical motor pathway, with a better CMCT improvement in acute ischemic stroke.

Many studies have dealt with transcranial motor cortex stimulation in stroke patients.\(^{13,18,19,23,27,28}\) 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. 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 have demonstrated that neurons of the brain and spinal cord also have the same capacity to regenerate as peripheral nerves after injury by collateral growth or sprouting.\(^{35}\) There are relevant evidence from animal experiments indicating that there is considerable potential for reorganization of representations and functions in sensory and motor cortex after 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 path-

Figure 2. Influence of the time course of spontaneous recanalization on CMCT improvement \((n=33)\).

![Figure 2](image)

Figure 3. Influence of spontaneous recanalization on the change in CMCT in the acute phase of ischemic stroke. A, Change in CMCT in a patient (case 021) with left MCA infarction. Recanalization occurred at 3 hours after the onset of stroke. There were no recordable MEPs on TMS tests performed at day 1; however, the TMS tests performed at day 14 showed a delayed CMCT (18.4 ms), with an excellent functional recovery at day 14. B, Change in CMCT in a patient (case 017) with left MCA infarction. No recanalization was observed until day 14. The first TMS test performed at day 1 showed a CMCT of 7.0 ms; however, at day 14 there were no recordable MEPs.
ways to take over functions."36 These changes in neural plasticity occur over a period of weeks. More acutely, others have suggested that previously silent fiber pathways in the brain stem could become immediately active when the sensory fibers in the spinal cord were cut.35 A similar process could also occur in the cerebral cortex. Our data (for example, the case shown in Figure 3A with an absent motor response at day 1 that reappeared at day 14) supports this hypothesis. When worsening of neurological impairment with cell death occurs due to permanent occlusion of cerebral artery, the ischemic penumbra around the central necrotic core may be detected only during the acute phase of stroke (<14 days). A clear example of this deterioration is the case shown in Figure 3B, in which the recordable MEP detected at day 1 disappeared completely in the TMS test repeated at day 14.

In this study the CMCT improved in most of the patients in whom spontaneous recanalization occurred. 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 the reperfused groups. These data suggest that plastic reorganization occurs in the human brain after the onset of stroke, and cerebral reperfusion influences this process positively, leading to a better recovery of the central motor pathway.

On the other hand, the CMCT worsened in most (80%) of the patients from the nonreperfused group. This poor outcome may be due to an increase of neuronal death in the ischemic penumbra area located around the central necrotic core. It is well known that there is a critical hypoperfusion and neuronal hypoxia; however, neuronal cells are still viable in this area.40 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.

Another possible mechanism of this electrophysiological deterioration in the nonreperfused group may be an inappropriate activation of apoptosis. Previous studies have shown that certain types of nerve-cell death in the brain occur by an apoptotic mechanism.41–43 The authors of 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. Therefore, apoptosis may be the mechanism involved in further neuronal death in the ischemic cerebral area around the central necrotic core due to delayed degeneration when cerebral reperfusion does not occur.

In this study, even though there was a better CMCT improvement with a better stroke outcome in the group in which an early efficient collateral blood flow supply was detected, the result did not reach statistical significance when the change in CMCT was analyzed according to the presence of leptomeningeal collateral circulation alone. When both spontaneous recanalization and collateral blood supply were present, the stroke outcome was significantly better than what was observed in the group in which collateral blood supply alone was detected. These data show that leptomeningeal collateral circulation alone is not sufficient to obtain a good clinical and electrophysiological recovery, despite the fact that it contributes to minimize the catastrophic effect of stroke.

The CMCT recorded at day 1 from the normal or nonparetic side in active thenar muscle was delayed in 3 of the stroke patients included in this study. All of them were in the severe stroke severity group. Berardelli and colleagues also reported an abnormal delay in CMCT in the unaffected side in 2 of the 20 stroke patients with hemispheric infarction on whom they used transcranial electrical stimulation of the motor cortex to study the change in CMCT in hemiplegia. These data show that ischemic stroke affects the CMCT not only of the compromised cerebral hemisphere but also of the contralateral side.

This delay in CMCT of the nonparetic side in these stroke patients may be due to a compression of the motor pathway from the affected side due to cerebral edema. It is well known that cerebral edema is one of the most important clinical complications in acute ischemic stroke.44–47 Slivka and coworkers examined rats with temporary and permanent occlusion of the right MCA. They found that hemispheric volume, water, and sodium from the infarcted right hemisphere were significantly greater than those from the left hemisphere, beginning 6 hours after MCA occlusion and continuing for 48 hours, with a peak at 24 hours.

<table>
<thead>
<tr>
<th>TABLE 2. Influence of Leptomeningeal Collateral Blood Flow Supply on the Central Motor Conduction Time at Day 14 (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMCT Improvement, No LCBS*</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>No recanalization</td>
</tr>
<tr>
<td>Recanalization</td>
</tr>
</tbody>
</table>

LCBS indicates leptomeningeal collateral blood flow supply.
*2P<0.01; †2 P<0.25; Mantel-Haenszel summary $\chi^2$: 6.76, $P=0.009$. 

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This delay in CMCT in the nonparetic side may also be due to a distant neurological disturbance from the compromised cerebral territory called diachisis.25 Diachisis was thought to be a temporary block of function or inhibition produced by shock of damage or irritation to brain tissue. When a part is disturbed by injury or disease, that trauma can affect other parts quite far from the site of the original damage.

Another possible cause of the delay in CMCT in the nonparetic side may be associated with an inadequate facilitation of the thenar muscle studied in some of the patients included in this study, who suffered a left stroke with comprehension deficit. Ferbert and his colleagues23 reported different ranges of normal CMCT with TMS tests performed in passive and active thenar muscles. They found a more delayed CMCT in TMS tests performed on healthy subjects with passive thenar muscle, with a higher 99% CI upper limit than data recorded in active thenar muscles.

In conclusion, this study provides evidence for the first time that spontaneous recanalization results in a better recovery of the central motor pathway, which leads to a better CMCT improvement in acute ischemic stroke.

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