Ipsilateral Motor Responses to Focal Transcranial Magnetic Stimulation in Healthy Subjects and Acute-Stroke Patients

Giovanna Alagona, MD; Valérie Delvaux, MD; Pascale Gérard; Victor De Pasqua; Giovanni Pennisi, MD; Paul J. Delwaide, PhD; Francesco Nicoletti, MD; Alain Maertens de Noordhout, PhD

Background and Purpose—Prevalence and characteristics of ipsilateral upper limb motor-evoked potentials (MEPs) elicited by focal transcranial magnetic stimulation (TMS) were compared in healthy subjects and patients with acute stroke.

Methods—Sixteen healthy subjects and 25 patients with acute stroke underwent focal TMS at maximum stimulator output over motor and premotor cortices. If present, MEPs evoked in muscles ipsilateral to TMS were analyzed for latency, amplitude, shape, and center of gravity (ie, preferential coil location to elicit them). In stroke patients, possible relationships between early ipsilateral responses and functional outcome at 6 months were sought.

Results—With relaxed or slightly contracting target muscle, maximal TMS over the motor cortex failed to elicit ipsilateral MEPs in the first dorsal interosseous (FDI) or biceps of any of 16 normal subjects. In 5 of 8 healthy subjects tested, ipsilateral MEPs with latencies longer than contralateral MEPs were evoked in FDI muscle (in biceps, 6 of 8 subjects) during strong (>50% maximum) contraction of the target muscle. In 15 of 25 stroke patients, ipsilateral MEPs in the unaffected relaxed FDI (in biceps, 6 of 25 stroke patients) were evoked by stimulation of premotor areas of the affected hemisphere. Their latencies were shorter than those that MEPs evoked in the same muscle by stimulation of the motor cortex of the contralateral unaffected hemisphere. Such responses were never obtained in normal subjects and were mostly observed in patients with subcortical infarcts. Patients harboring these responses had slightly better bimanual dexterity after 6 months.

Conclusions—Ipsilateral MEPs obtained in healthy individuals and stroke patients have different characteristics and probably different origins. In the former, they are probably conveyed via corticoreticulospinal or corticopropriospinal pathways, whereas in the latter, early ipsilateral MEPs could originate in hyperexcitable premotor areas. (Stroke. 2001; 32:1304-1309.)

Key Words: cerebral cortex ■ neuronal plasticity ■ stroke, ischemic ■ transcranial magnetic stimulation

The existence of an uncrossed corticospinal tract has long been established in humans. It may consist of only a few isolated fibers, or it may be a compact tract,1 representing 8% to 10% of the global population of pyramidal axons,2 the majority of which ultimately cross in the segmental cord.3 Only a small proportion of fibers make synaptic connections with ipsilateral spinal motoneurons.

For Davidoff,1 the function of uncrossed pyramidal axons remains unknown, but others4 suggest that it exerts some control on bilateral proximal limb movements. The presence of functional ipsilateral corticospinal connections appears to be a normal state in infants and children aged <10 years,5 but their presence in adult humans is still debated. Besides the uncrossed corticospinal tract, other descending pathways could also convey motor cortex output to ipsilateral muscles, for instance, bilaterally branching corticomotoneuronal axons or corticoreticulospinal or corticopropriospinal pathways, but anatomic evidence is largely missing in humans.

The development of transcranial magnetic stimulation (TMS) offered new possibilities in the investigation of the functional role of such pathways in humans. Although some authors have failed to observe ipsilateral excitatory responses (motor-evoked potentials [MEPs]) to TMS in adults,5,6 others mention that ipsilateral responses can occasionally be recorded in healthy individuals. Wassermann et al,7 who recorded from proximal (deltoid and biceps) upper limb muscles, found such responses to TMS in 3 of 6 normal subjects. In another report, Netz et al8 found small ipsilateral responses in thenar muscles of 2 of 12 subjects examined. More recently, Ziemann et al,9 using a focal 8-shaped coil, showed that ipsilateral MEPs can also be recorded in several upper limb muscles of most healthy subjects under strong background contraction of the target muscles and with high-intensity TMS. Such responses were usually more prominent in proximal muscle, and their latencies were variable but consistently longer
than those of contralateral MEPs. Because their amplitudes could be modulated by neck rotations, the authors proposed that such ipsilateral responses could correspond to the activation of corticoreticulospinal or corticopropriospinal pathways, which are known to be under strong control of sensory afferents. Although such ipsilateral MEPs seemed to occur in most healthy individuals, they were always of low amplitude and were obtained only under particular experimental conditions.

Ipsilateral MEPs have been observed more frequently in patients than in healthy subjects. Some authors have suggested that ipsilateral projections may be one of the substrates for functional restoration after stroke. Conversely, others have concluded that the presence of ipsilateral responses to TMS is an indicator of poor motor recovery. Bastings found early ipsilateral hand responses after focal magnetic stimulation of the undamaged hemisphere in only 1 of 28 patients. Fries et al have observed bilateral MEPs after stimulation of the affected hemisphere in 5 patients despite MRI signs of pyramidal tract degeneration secondary to capsular infarcts.

Ipsilateral responses have also been found in other neurological conditions, such as cerebral gliomas, congenital mirror movements, X-linked Kallmann’s syndrome, or Klippel-Feil syndrome. In the case of patients with congenital mirror movements, evidence has been obtained for bilateral branching of corticomotorneuronal axons.

The aim of the present study was to compare the prevalence and characteristics of ipsilateral upper limb MEPs in a population of healthy subjects and acute-stroke patients studied with the same technique and to determine whether the presence of ipsilateral responses in acute-stroke patients plays a role in recovery.

Subjects and Methods

The study was approved by the local ethics committee, and informed consent was obtained from all healthy volunteers and stroke patients.

Normal Subjects

We studied 16 healthy volunteers (10 men and 6 women) aged 19 to 80 years (median 53 years). All were right-handed, had a normal neurological examination, and were free of medications that could induce cortical or spinal excitability changes. They were recruited among laboratory staff or relatives and patients hospitalized in a nonneurological department.

Stroke Patients

Twenty-five first-ever stroke patients (14 men and 11 women, aged 17 to 88 years, median 57 years) were studied within the first 48 hours from symptom onset. All patients were right-handed and showed a complete hand palsy that was due to an infarct in the area of the left (14 patients) or right (11 patients) middle cerebral artery (MCA) (n = 18) or deep perforating branches (n = 7). Eleven of them exhibited a corticosubcortical infarct; in 7 patients, the lesion was subcortical; and 7 patients exhibited a limited capsular infarct. General clinical status on admission was rated on NIH and Rankin stroke scales. The median NIH score of the 25 patients was 12; the median Rankin scale was 5. Patients were excluded if they were comatose or unable to understand simple orders. Only 22 patients were reexamined clinically after 6 months (1 died, and 2 were lost to follow-up) and retested on the Barthel index and Medical Research Council (MRC) scale (from 0 to 5, where 0 indicates no movement; 1, movement only if gravity is removed; 2, movement against gravity; 3, movement against slight resistance; 4, movement against stronger resistance but some weakness; and 5, full strength). Patients’ clinical and radiological findings are summarized in Table 1.

Focal TMS Procedure

Surface recording adhesive electrodes were placed bilaterally over first dorsal interosseous (FDI) and biceps brachii muscles. In 8 normal subjects, responses were also recorded from both finger extensor and triceps brachii muscles. TMS was performed with a Magstim 200 stimulator (Magstim Ltd) connected to a butterfly-shaped coil (2 x 70-mm diameter). The coil was placed tangentially to the scalp with the handle held backward, and TMS intensity was initially set at maximal stimulator output (100%). Scalp coordinates were determined on a cap placed over the patient’s head with a 1-cm² grid drawn from the vertex. Stimulation was first applied at the “hot spot” (ie, the scalp position from which a contralateral MEP of maximal amplitude and lowest threshold was obtained) and then displaced to various positions, not only over motor cortex but also over more frontal and more posterior regions of both hemispheres. When ipsilateral responses were elicited, their hot spots and centers of gravity were calculated. All normal subjects were tested at rest and with weak (10% to 20% maximum) voluntary isometric contraction of the target muscles, first contralaterally to the side of TMS and then ipsilaterally and bilaterally. Responses were amplified with CED 1902 amplifiers (Cambridge Electronic Design). Signals were collected through a CED Micro 1401 interface and fed into a personal computer by use of a data collection and averaging program (Signal 1.85). In 8 normal subjects (5 men and 3 women), TMS series at maximal stimulator output were repeated under strong (>50% maximum) voluntary contraction. When ipsilateral responses were present, TMS intensity was reduced to measure their thresholds. Onset latency, amplitude, and shape of ipsilateral responses were compared with those of contralateral MEPs. Influences of neck rotation and of coil orientation were also examined. Amplitudes of MEPs are expressed as percentage of the response to maximal nerve stimulation (Mmax).

Statistical Analysis

When not specified, values are given as mean ± SD. The paired Student t test was used for analysis of contralateral and ipsilateral MEP responses. The Mann-Whitney U test was used to establish correlations between the presence or absence of ipsilateral responses in stroke patients and functional outcome at 6 months on the MRC scale and Barthel index.

Results

Healthy Volunteers

In all 16 subjects tested, responses elicited in contralateral muscles by focal TMS at maximum stimulator output had normal latencies, amplitudes, and shapes (Table 2). In all, such stimuli failed to produce any ipsilateral MEP in relaxed or slightly (10% to 20% maximum) contracting muscles, even in the biceps. Moving the coil 4 to 5 cm frontally over premotor regions resulted in the progressive disappearance of contralateral MEPs without eliciting any ipsilateral response. Among the 8 subjects tested under strong background contraction and maximal TMS intensity, ipsilateral MEPs were found in the FDI in 5 subjects, in the biceps in 6, in the finger extensors in 2, and in the triceps in only 1. Responses were inconstant and of small amplitude (6±3% of contralateral MEPs for FDI and 12±4% for biceps) and variable shapes and had latencies 3.5 to 7 ms longer than those of contralateral responses (P = 0.003 for FDI, P = 0.001 for biceps, paired t test). Some of these responses were followed by short silent periods (Figure 1). In 1 subject, 90° rotation of the coil (from posteroanterior to lateromedial orientation) caused latency shortening of ipsilateral (1.3 ms) as well as contralateral (1.4 ms) FDI MEPs. The amplitude of ipsilateral MEPs was...
reduced during head rotation toward the side of TMS, whereas no change was noted with the opposite head rotation.

**Stroke Patients**

In all 25 patients tested within 48 hours from stroke onset, responses elicited in contralateral muscles by focal TMS over the unaffected hemisphere had normal latencies and amplitudes, which were comparable to those of healthy subjects (Table 2). In 21 of the patients, TMS over the affected motor cortex at maximal output failed to evoke responses in contralateral paralyzed hand muscles. In 4 patients, small MEPs with normal latencies were present in the affected FDI (6 in the biceps). Ipsilateral MEPs were observed in the unaffected FDI on stimulation of the affected hemisphere in 15 of 25 patients (5 of 11 with corticosubcortical MCA territory infarct, 3 of 7 with limited subcortical MCA territory lesion, and 7 of 7 with capsular infarcts; see Table 1). The mean center of gravity of the area producing such ipsilateral responses was significantly shifted forward (4.4 ± 0.3 cm, P < 0.003, paired t test) and medially (2.2 ± 0.3 cm, P < 0.01, paired t test) when compared with the area producing contralateral MEPs from the opposite (unaffected) hemisphere (Figure 2). In all but 1 patient, such ipsilateral MEPs could be obtained in relaxed FDI, and their

### TABLE 2. Characteristics of Biceps and FDI MEPs of 16 Healthy Subjects and 25 Stroke Patients

<table>
<thead>
<tr>
<th></th>
<th>Latency Biceps, ms</th>
<th>Amplitude Biceps, % Mmax</th>
<th>Latency FDI, ms</th>
<th>Amplitude FDI, % Mmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>12.7±0.6</td>
<td>22±8</td>
<td>22.9±0.5</td>
<td>25±10</td>
</tr>
<tr>
<td>Ipsilateral, strong contraction</td>
<td>14.3±0.9 (n=6)</td>
<td>2.7±2.3 (n=6)</td>
<td>25.9±1.2 (n=5)</td>
<td>1.4±2.3 (n=5)</td>
</tr>
<tr>
<td>Stroke patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest, unaffected side</td>
<td>12.9±0.6</td>
<td>21±9</td>
<td>23.3±0.6</td>
<td>27±9</td>
</tr>
<tr>
<td>Rest (ipsilateral), frontal stimulation</td>
<td>12.1±2.1 (n=6)</td>
<td>6±5</td>
<td>21.8±0.8 (n=15)</td>
<td>12±6</td>
</tr>
</tbody>
</table>

L indicates left; R, right; lost, lost to follow-up; Y, yes; and N, No.
mean latencies were significantly shorter (21.83 versus 23.56 ms, \(P=0.025\), paired Student's \(t\) test) and their amplitudes were significantly smaller (12\(\pm\)6\% versus 27\(\pm\)9\% of maximum, \(P=0.001\), paired Student's \(t\) test) than were the responses evoked in the same muscle by stimulation of the unaffected motor cortex at rest and at 100\% of stimulator output. Voluntary contraction slightly shortened the latencies (0.93 ms on average) and markedly increased the amplitudes of these ipsilateral MEPs (Figure 3). Maximal amplitude of ipsilateral FDI responses during voluntary contraction was, on average, 33\(\pm\)8\% of that evoked by stimulation of the unaffected motor cortex. In 5 patients tested for this parameter, 90° rotation of the coil (from posteroanterior to latero-medial) resulted in the disappearance of these early ipsilateral responses (Figure 3). Ipsilateral responses to TMS over frontal regions of the affected hemisphere were also observed in the biceps of 6 patients. On average, their latencies were also slightly shorter than those of MEPs evoked in the same muscle by stimulation of the unaffected motor cortex (Table 2). However, the latency difference was not significant for the biceps, because of the higher latency variability of these responses. In most cases, ipsilateral biceps MEPs were inconstant and of small amplitude (Table 2). The cortical region from which these responses were elicited was similar to that for FDI. Thirteen patients were retested 3 months later; ipsilateral responses were still present in FDI in 5 of 11 patients and in the biceps in 2 of 5 patients who exhibited them at first visit.

In acute-stroke patients, no ipsilateral MEPs were recorded in relaxed FDI or biceps of the paralyzed arm on TMS over any region of the unaffected hemisphere at 100\% of stimulator output. In FDI, the effects of voluntary contraction could not be tested because of paralysis, but strong contraction of the unaffected hand did not modify the results. In 6 of 25 patients who could still activate the biceps on the affected side, no ipsilateral responses were elicited by maximal stimulation of the unaffected hemisphere. However, the level of voluntary contraction was insufficient to allow study of “late” ipsilateral responses observed in normal subjects.

Figure 1. Ipsilateral (Ipsi) MEPs (traces 1 and 3) recorded in biceps and FDI of a normal subject on focal TMS of the motor cortex (100\% maximum) during strong (50\% maximum) background contraction of the target muscles compared with responses evoked in the same muscles (traces 2 and 4) by TMS at the same intensity over the opposite motor cortex. Note the high variability, small amplitude, and longer latency of Ipsi responses recorded in FDI, whereas Ipsi responses evoked in biceps have nearly the same amplitude as contralateral (Contra) responses. This subject was chosen because she had particularly ample Ipsi responses.

Figure 2. Left, Ipsi responses evoked in relaxed left FDI on TMS over premotor areas on the affected side of 1 patient with left capsular infarct (upper traces) compared with responses evoked in the same muscle by stimulation of the intact (right) primary motor cortex (bottom traces). Stimulus intensities were adjusted to evoke responses of similar amplitudes (55\% maximum for Contra stimulation, 75\% maximum for Ipsi stimulation). Ipsi responses have a shorter latency than do Contra responses. Right, Mean center of gravity of cortical areas (in cm from the vertex [Cz]) whose stimulation produced such Ipsi responses in 15 stroke patients compared with the center of gravity of Contra (“normal”) responses.
Of the 22 patients reexamined clinically at 6 months, 8 had no ipsilateral FDI responses initially, and 14 showed such responses. Mean MRC scores for hand muscles were 3.4±1.4 and 3.6±1.1 in the 2 respective groups, and median Barthel index scores were 83.1±16.1 and 89.6±15.4, respectively. Although mean MRC and Barthel values were slightly higher in the group with early ipsilateral responses, the differences were not significant (P=0.66 and 0.33, Mann-Whitney test). Interestingly, when considering only the Barthel items reflecting upper limb and bimanual motor function (feeding, personal toilet, and dressing, ie, “Barthel motor” on Table 1), the difference reaches nearly statistical significance (15.6±7 versus 22.1±3.8, P=0.06, Mann-Whitney test). All 4 patients who presented FDI MEPs on the paralyzed side on stimulation of the affected motor cortex in the acute phase made full hand-strength recovery (MRC 5).

**Discussion**

The anatomic substrate and function of ipsilateral motor projections to distal upper limb muscles in humans remain debated; their possible role in motor recovery from brain insults also remains to be determined. Activation of ipsilateral motor cortex during hand movement has been demonstrated by imaging techniques such as PET or functional MRI. In the present work, ipsilateral MEPs were obtained in normal subjects with characteristics similar to those observed by Ziemann et al. Interestingly, in 1 subject who showed very reproducible responses, their latencies could be shortened by 1 to 2 ms by rotating the stimulating coil from the posteroanterior to the lateromedial direction, as has been observed previously for contralateral MEPs. This suggests that these responses involve the motor cortex itself and are not due to activation of deep structures by strong TMS. However, these ipsilateral responses of normal subjects were usually small and inconstant. They seem unlikely to play a significant functional role and are probably an evolutionary relic.

The ipsilateral MEPs on stimulation of the unaffected hemisphere observed in previous studies were usually very small, with latencies 5 to 14 ms longer than those of contralateral MEPs, and were more frequent in patients with poor motor outcome. Such responses are probably similar to those described in normal subjects. That such responses were not observed in the present study can probably be explained by the fact that only patients with severe upper limb paralysis, who could not achieve voluntary contraction, were included. The ipsilateral MEPs observed by Fries et al on stimulation of the damaged hemisphere in patients with capsular stroke had slightly shorter latencies than did those elicited in the same muscle by stimulation of the intact hemisphere. Because of MRI signs of pyramidal tract degeneration, these authors concluded that these responses could be conveyed by noncorticospinal pathways. In the present study, ipsilateral responses observed in FDI of 15 of 25 stroke patients had very similar characteristics. However, their most striking characteristic was the fact that they could be evoked only when the stimulating coil was displaced 4 to 5 cm frontally and 2 cm mediially to the normal motor cortex representation of the hand muscles (see Figure 2), a position that never induced such responses in normal subjects or in stroke patients on stimulation of the unaffected hemisphere. For this reason, we believe that current spread over the opposite hemisphere cannot be the explanation for such responses. Because its latency is shorter than that of normal responses, transcallosal activation also seems unlikely, which would require 5 to 10 additional milliseconds. These short-latency ipsilateral responses to stimulation of the damaged hemisphere could be the result of activation of deep brain structures. Modifications of physical properties of the damaged brain, in particular, the increase of water content, could favor the spread of induced current. This hypothesis cannot be ruled out but seems unlikely for the following reasons: Such responses were evoked more frequently in patients with very limited deep infarcts than in those with large cortical strokes. They were not only present for a short period after stroke, but they could also be found several months later in some patients. Moreover, changing the coil orientation (from posteroanterior to lateromedial) caused a complete disappearance of these ipsilateral MEPs (Figure 3). This suggests that current orientation is crucial in obtaining these responses, implying the activation of particularly oriented cortical or subcortical structures. The present findings are consistent with the activation of premotor areas, among which are the lateral premotor cortex and the supplementary motor area (SMA). Such areas are known to have largely bilateral output projections to the spinal cord, and intracortical microstimulation techniques have shown that “surprisingly fast connections exist between SMA and spinal cord, with latencies consistent with monosynaptic connections.” We hypothesize that in stroke patients with damage to the mainstream of the corticospinal pathway, there could be a compensatory hyperexcitability of lateral premotor cortex and SMA on the affected side, whose output would be reflected only by short-latency
ipsilateral responses, whereas a lesion of the crossed cortico-
spinal fibers prevents the appearance of contralateral re-
ponses. Thus, the slightly earlier latency of ipsilateral responses could be explained by the activation of a fast-
conducting uncrossed output pathway from these brain areas. This hypothesis is reinforced by metabolic studies with PET, showing that in subcortical stroke, there is particular activa-
tion of SMA and prefrontal cortex ipsilateral to the stroke during passive forearm movements that is not observed in healthy control subjects. Moreover, all patients harboring these ipsilateral responses in the present study had intact premotor areas on CT scans (see Table 1). The functional role of SMA is not fully understood in humans, but it seems to play an important role in the execution of bimanual move-
ments, as shown by ablation procedures. This role could be
reflected in the present study by the fact that stroke patients displaying ipsilateral responses on stimulation of premotor areas seemed to make better recovery on the Barthel items involving bimanual coordination. That the difference on “motor” Barthel items did not reach significance between patients showing such responses and others might indicate that these items very imperfectly address the function of premotor areas. Only a few patients had such ipsilateral responses in the biceps. It may appear surprising, because premotor areas seem to exert an important control over proximal upper limb muscles. At present, we have no straightforward explanation for this difference of responsiveness between distal and proximal muscles on stimulation over premotor regions, but this is yet another argument against induced current spread to deep brain structures, which would probably have caused more global muscle activation.

The present study sheds a new light on the origin of ipsilateral responses to TMS after stroke. In patients with severe upper limb deficit, weak ipsilateral projections from the unaffected motor cortex to the paralyzed limb probably exist as they do in normal subjects but could not be activated in our patients because of severe motor deficit at stroke onset. These ipsilateral responses probably resulted from activation of the cortico-recticulospinal or corticopropriospinal pathways. The small amplitude of such ipsilateral responses to TMS, even in normal subjects, suggests that their role in functional recovery is negligible, as pointed out by Turton et al., who observed that they were more often recorded in patients with poor motor outcome. On the other hand, the majority of our stroke patients showed short-latency responses in upper limb muscles ipsilateral to the side of stroke on weak TMS applied over premotor areas only, and not over primary motor regions; these responses occurred more often in patients with deep infarcts. They are probably the result of hyperexcitability of SMA and lateral premotor regions and might reveal the existence of an otherwise silent fast-conducting uncrossed pathway from these areas to spinal motoneurons. The presence of these responses did not seem to influence the global recovery at 6 months but was positively correlated with better scores on Barthel index items reflecting bimanual coordination. Finally, in the present study, we found no evidence for activation of fast-conducting uncrossed corticospinal pathways from the unaffected cortex to the paralyzed upper limb.

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