Central Compensation at Short Muscle Range Is Differentially Affected in Cortical Versus Subcortical Strokes

Caroline I.E. Renner, MD; Hartwig Woldag, MD; Horst Hummelsheim, MD

Background and Purpose—The active force generated by a single muscle fiber is greatest in midrange. In healthy subjects, the reduced muscle force at short muscle length is partially compensated by modified patterns of muscle activation, probably central in origin. These patterns are presumed to be deficient after stroke. We examined the excitability muscle-length relation in stroke patients and healthy controls and hypothesized about its alteration in stroke patients.

Methods—Corticospinal excitability was assessed in 31 stroke patients (19 subcortical, 12 cortical) and 19 healthy volunteers by transcranial magnetic stimulation. We recorded the motor evoked potentials (MEPs) simultaneously from the biceps brachii and the triceps brachii muscles at 0°, 20°, 40°, 60°, 80°, 100°, and 120° degrees of elbow flexion (0° being full elbow extension).

Results—Normal subjects revealed a significant increase in MEP amplitudes at shortened muscle lengths for both the flexor and extensor muscles ($P<0.001$). Multivariate variance analysis revealed that the MEP-angle curves of cortical stroke patients were significantly different from those of the control group for both muscles, lacking an increase of corticospinal excitability at short muscle length. Yet the MEP-angle curves for the subcortical stroke patients did not show a statistically significant difference from the control group for either muscle.

Conclusion—Cortical and subcortical strokes differentially affect the corticospinal excitability muscle-length relation. This may account for the reported disproportionate decrease in muscle strength at shortened range after stroke. (Stroke. 2006; 37:000-000.)

Key Words: cerebral infarction ■ hemiparesis ■ motor cortex ■ transcranial magnetic stimulation

Loss of muscle strength is a major aspect of physical disability after stroke: When elbow flexor and extensor torque in healthy controls are plotted against muscle length, most torque is generated in the muscle’s midlength, resulting in a classic inverted U-shaped curve, thus reflecting the mechanical advantage of the optimal actin and myosin filament overlap at midlength.1,2 It has been demonstrated in neurologically normal subjects that during maximum voluntary contractions at short muscle lengths, there is a reduction in twitch duration to achieve fusion of the twitches accompanied by increased motor unit firing rates.3,4

A common functional problem observed after stroke is that individuals can perform reaching movements that activate the triceps muscle in midrange but often not with the elbow close to full extension. Ada et al2 discovered that stroke subjects were relatively stronger when both flexors and extensors were in their lengthened range and relatively weaker when the muscles were in their shortened ranges. However, the contractile capacity of the paretic muscle itself is not altered after stroke;3 rather, there may be a deficient central recruitment of motor units. Some investigators have suggested that after stroke, impairment of voluntary strength is associated with deficient motor unit recruitment and firing frequencies insufficient to generate a fused tetanus of the involved motor units.3,6 Additionally, the upregulated input from cervical propriospinal motoneurons after stroke, especially in people with poor recovery, may be partially responsible for the altered motoneuronal output.7,8

Transcranial magnetic stimulation (TMS) has introduced the possibility of examining the excitability of the corticospinal tract in humans. Proprioceptive afferent information has been shown to modulate motor evoked potential (MEP) amplitudes.9 The concept of the present study is based on the finding that excitatory or inhibitory factors that modulate the corticospinal system are appropriately reflected by TMS.

The aim of this study was to determine the effect of muscle length on the excitability of the corticospinal projections to the elbow flexor and extensor muscles. That is, we wanted to examine the excitability muscle-length relation in stroke patients and healthy controls and to hypothesize about its alteration in stroke patients as an explanation for the selective weakness at short muscle length. We further differentiated...
between subcortical and cortical strokes to determine the effect of lesion location, as there may be different mechanisms for motor recovery.7,8

Methods

Subjects
Thirty-one stroke patients (18 male, 13 female) aged between 20 and 78 years (mean, 63 years) and 19 healthy, right-handed (Edinburgh Inventory of Handness10) subjects (9 male, 10 female) aged between 20 and 47 years (mean, 32 years) were recruited for the study. All stroke patients except 1 were right handed10 and met the following inclusion criteria: (1) They had 1 ischemic subcortical (ie, corona radiata, internal capsule, basal ganglia) or cortical infarction following inclusion criteria: (1) They had 1 ischemic subcortical (ie, corona radiata, internal capsule, basal ganglia) or cortical infarction in the territory of the middle cerebral artery as revealed by computed tomography or magnetic resonance imaging scan; (2) they lacked any additional neurological disease; and (3) they demonstrated no severe deficits in communication, memory, understanding or attention. Fifteen had a stroke that affected their right side and 16 had a stroke that affected their left side. The mean latency between stroke and enrollment into the study was 38 days (range, 16 to 150 days), and 29 patients had a stroke affecting their left side. The mean latency between stroke and enrollment into the study was 38 days (range, 16 to 150 days), and 29 patients had a stroke affecting their left side. 

TMS
TMS was performed with a flat circular coil (90-mm diameter inside and 140-mm diameter outside) connected to a Magstim 200 magnetic stimulator (Magstim Company Ltd). The maximum magnetic field generated by the stimulator was 1.5 T (according to the manufacturer’s specification). The center of the coil, positioned over the vertex at Cz (international 10–20 system of electrode placement) and by small displacements (1 cm or less) tangentially in an anteroposterior and a mediolateral direction, the optimal scalp site for evoking MEPS of maximal peak-to-peak amplitudes in both the contralateral biceps brachii and triceps brachii muscles simultaneously, was established. The coil position was marked on the scalp and maintained throughout the study. With the elbow fully extended (0°), the resting motor threshold was determined for the biceps brachii and triceps brachii muscles simultaneously. All subjects were instructed to completely relax the arm muscles. By means of continuous auditory feedback of the surface electromyogram (EMG), complete relaxation of the muscles was ensured. Trials “contaminated” with voluntary muscle activity were rejected. For each of the 7 elbow angles, 10 consecutive stimuli with an intensity of 120% of the individual resting threshold were applied over the affected (stroke group) or nondominant (control group) hemisphere and recorded contraterally. MEP signals were amplified, bandpass filtered (20 Hz to 2 kHz; programmable 4-channel amplifier, Jaeger/Toennies) and stored on hard disk for offline analysis. At least 30 seconds elapsed between each stimulus. The order of the elbow angles was randomized. After visual inspection to exclude MEPS contaminated by artifacts or by prior voluntary EMG activity, MEPS were averaged, and the peak-to-peak amplitude was measured (MP 100A, Biopac Systems Inc).

Statistical Analysis
The average MEP amplitude of the biceps muscle at an elbow angle of 0° and the average MEP amplitude of the triceps muscle at an elbow angle of 120° were set to 100%. The average MEPS in the other 6 elbow angle positions were expressed as percentage ratios. Biceps and triceps muscles were analyzed separately, and mean MEP–elbow angle curves were calculated for the control group by 1-way repeated-measures ANOVA. To determine the effect of group (healthy subjects versus cortical or subcortical stroke patients), elbow angle (0°, 20°, 40°, 60°, 80°, 100°, and 120°), and the interaction of both, MEP amplitudes were compared by a multivariate ANOVA from the SPSS program (SPSS). In addition, because of the small sample size, a multivariate analysis for

Recordings
Subjects were seated on a high-backed chair with the affected arm (stroke group) or the nondoniminate arm (control group) firmly secured in an arm splint. The arm splint was attached to a height-adjustable table that allowed the arm to be placed at 90° shoulder flexion. The arm splint completely immobilized the proximal and distal arm and hand. The forearm was secured in pronation. A movable joint at the height of the elbow allowed rotation and fixation of the forearm in 7 elbow angles (0°, 20°, 40°, 60°, 80°, 100°, and 120°). An elbow angle of 0° with a completely extended arm caused the elbow flexor to be maximally lengthened and the elbow extensor to be maximally shortened, whereas a 120° angle caused the elbow flexor to be maximally shortened and the extensor to be maximally lengthened.

MEPs were recorded with Ag/AgCl electrodes (Medtronic L0202) mounted in a belly tendon fashion over the biceps brachii and triceps brachii muscles simultaneously. All subjects were instructed to completely relax the arm muscles. By means of continuous auditory feedback of the surface electromyogram (EMG), complete relaxation of the muscles was ensured. Trials “contaminated” with voluntary muscle activity were rejected. For each of the 7 elbow angles, 10 consecutive stimuli with an intensity of 120% of the individual resting threshold were applied over the affected (stroke group) or nondominant (control group) hemisphere and recorded contraterally. MEP signals were amplified, bandpass filtered (20 Hz to 2 kHz; programmable 4-channel amplifier, Jaeger/Toennies) and stored on hard disk for offline analysis. At least 30 seconds elapsed between each stimulus. The order of the elbow angles was randomized. After visual inspection to exclude MEPS contaminated by artifacts or by prior voluntary EMG activity, MEPS were averaged, and the peak-to-peak amplitude was measured (MP 100A, Biopac Systems Inc).

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Biceps muscle

Triceps muscle

Mean MEP–joint angle curves rescaled to MEP at maximal length for the biceps brachii (A) and the triceps brachii (B) muscles in cortical stroke subjects (filled squares, n = 12), subcortical stroke subjects (empty squares, n = 18), and healthy subjects (triangles, n = 19). Lines of fit from second-order polynomial equations have been added to aid visual inspection.
linear contrast pertaining to the angle × group interaction was also performed to compare the MEP–angle curves of the cortical and subcortical stroke and control group.

Results

Table 1 shows characteristics of the stroke patients in each group. The subgroups were matched for the side of paresis and age. Table 2 describes the lesions in detail for each patient. The mean resting motor threshold to produce MEPs of at least 50 μV in both the biceps and triceps muscles simultaneously was (mean ± SD) 64 ± 11% of the maximal stimulator output for the control group and 70 ± 14% for the stroke group. Group means of the MEPs and standard deviations measured at each angle are presented in Table 3.

The stroke and control groups were not matched for age, but we did not expect the excitability of the corticospinal system, modified by afferent input, to be age dependent. Wassermann demonstrated14 in 151 subjects that age does not affect the resting or active threshold. Pitcher et al15 similarly described the same peak slope of the stimulus-response curves in older and younger subjects.

Because of the high variability of MEP amplitudes between subjects, also reported in the literature,14,15 each subject’s data were normalized by expressing the individual data points as a percentage MEP of his/her MEP at maximal length of the target muscle.

Control Group

The MEP–elbow angle curves of the biceps and triceps muscles for the control group are represented in the Figure, A and B. In a comparison of the different muscle lengths of the biceps muscle with maximal length (0°) in the control group, there was a statistically significant increase of MEP amplitude with decreasing muscle length ($F=8.47$, $df=6$, $P<0.001$; power of performed test, 1.0), which showed the highest amplitude at 120° (the Figure, A). Accordingly, MEP amplitudes rose in parallel with the decreasing muscle length in the triceps muscle ($F=6.04$, $df=6$, $P<0.001$; power of performed test, 0.994; the Figure, B).

Stroke Patients

The scores on the arm section of the Rivermead Motor Assessment were 9.0 ± 3.9 for the cortical stroke group and 9.5 ± 3.8 for the subcortical stroke group; they did not differ significantly. The mean latency between stroke and enrollment into the study was 41 days for the cortical group and 39 days for the subcortical group; they did not differ significantly. The resting motor threshold was 67.4 ± 13.5% for subcortical stroke and 76.3 ± 14.0% for cortical stroke; they did not differ significantly.

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**TABLE 1. Characteristics of the Stroke Group, Subdivided Into Cortical (C; n=12) and Subcortical (SC; n=19) Stroke Patients**

<table>
<thead>
<tr>
<th></th>
<th>M:C</th>
<th>Age, y</th>
<th>Handedness, R:L</th>
<th>Time Since Stroke, d</th>
<th>Side of Hemiparesis, R:L</th>
<th>Function: Arm Section of RMA, 0–15</th>
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RMA indicates Rivermead Motor Assessment.
In a comparison of subcortical stroke with cortical stroke patients regarding the effect of muscle length on MEP amplitudes of the biceps (the Figure, A), there was a statistically significant difference for the factor group (\(F^2/11=0.050, df^1=11, P=0.003\)), with no effect of elbow angle on MEP amplitude in cortical strokes and a statistically significant linear contrast for the group\(\times\)angle interaction (\(F^2/11=0.050, df^1=11, P=0.006\)). Contrary to the biceps muscle, the MEP amplitudes of the triceps muscle at different lengths revealed no statistically significant difference between cortical and subcortical stroke groups for the factor group (\(F^2/11=0.050, df^1=11, P=0.827\)) or for the group\(\times\)angle interaction (\(F^2/11=0.050, df^1=1, P=0.264\)). In the biceps muscle, the MEP–elbow angle curve of the cortical stroke group was statistically significantly different from the MEP–elbow angle curve of the control group (\(F=10.936, df^1=1, P=0.008\)), whereas the MEP–elbow angle curve of the subcortical stroke group did not differ from that of the control group (\(F=1.341, df^1=1, P=0.263\); the Figure, A and B). In the triceps muscle, the MEP–elbow angle curve of the cortical stroke group (\(F=6.770, df^1=1, P=0.025\)) was statistically different from the MEP–elbow angle curve of the control group without any change in MEP-amplitude, whereas in the subcortical group, the MEP–elbow angle curve did not show a statistically significant linear contrast to the control curve (\(F=3.898, df^1=1, P=0.064\)).

**Discussion**

The aim of the present study was to find an explanation at the level of the central nervous system for the selective weakness at short muscle length,\(^2\) reported by Ada and colleagues. The major findings of this study are as follows: (1) There seems to be a distinct MEP–elbow angle relation with increasing excitability at short muscle lengths of the biceps and triceps muscles in healthy subjects; (2) this relation seems to be preserved for the biceps and to a lesser degree for the triceps muscle after subcortical stroke; and (3) this relation is lost for both the biceps and triceps muscles after cortical stroke.

In controls, the corticospinal excitability increased at shortened range for both muscles, as revealed by an increase of MEP amplitude. This could reflect a mechanism compensating for the nonoptimal force-producing length of the muscle. It corresponds to the finding that in neurologically normal subjects, twitch duration at short muscle lengths is decreased whereas motor unit firing rates are increased to achieve fusion of twitches of the involved motor unit during maximal voluntary contraction.\(^3,4\) Other investigators have also found increased neural activation during isometric contractions at short muscle length compared with a longer muscle length, but the M-wave amplitude after peripherally delivered electrical twitches remained unaffected by different muscle lengths.\(^16–19\) Therefore, a supraspinal mechanism may be activated at shortened muscle range during isometric contraction.

The subcortical stroke group was not significantly different from the control group regarding the increased corticospinal excitability at short muscle length of the biceps and triceps, whereas the cortical stroke group did not show any MEP increase at shortened range. Previous reports found reduced motor unit firing rates after stroke,\(^6,20,21\) indicating a generally reduced corticospinal excitability after stroke. Considering an intact MEP–muscle length relation after subcortical stroke but not after cortical stroke suggests cortical control of this MEP–muscle length relation. Bearing in mind that motor cortex excitability is modulated by afferent input from the periphery and that sensory-motor interactions are essential for physiological motor performance,\(^22,23\) it is conceivable that the muscular afferents are integrated by cortical interneurons. They cannot be integrated after cortical lesions, although they still can be integrated after subcortical lesions, yielding the
facilitatory effect at short muscle range. Muscle afferents are reported to provide a net facilitation to the motoneuron pool.\(^{23}\) The small sample size of the cortical stroke group (n = 12) seems unlikely to account for the lack of increase in corticospinal excitability, as there was a statistically significant difference for the linear contrast of group \(\times\) angle interaction between the controls and the cortical stroke group (biceps, \(P = 0.008\); triceps, \(P = 0.025\)).

It remains unclear why the biceps after subcortical stroke preserves the excitability muscle-length relation more than does the triceps. The MEP–elbow angle curve of the subcortical group showed a trend of increasing MEP amplitude with decreasing length of the triceps, yet it reached a statistically significant linear contrast neither to the curve of the controls (\(P = 0.264\)) nor to the curve of the controls (\(P = 0.064\)). The failure to reach significance compared with the control curve may be related to the small sample size. However, in the control group, the effect of increased corticospinal excitability at short muscle length appeared less pronounced in the triceps than in the biceps muscle as well. It has been proposed that the motor units of the triceps muscle record fewer excitatory postsynaptic potentials after magnetic stimulation, owing to disynaptic projections with inhibitory spinal interneurons, than the biceps motor units that receive fast monosynaptic corticospinal projections.\(^{24}\)

Although the stroke group was significantly older than the healthy subjects, age does not seem to be a reasonable cause for the lack of facilitation at short triceps muscle range. First, the facilitatory effect persisted in the biceps muscle after subcortical stroke despite age, and second, there is solid evidence that age has no effect on resting threshold or peak slope of the stimulus–response curve.\(^{14–16}\)

In conclusion, we found an excitability muscle-length relation for both the biceps and triceps muscles in healthy subjects. This relation was abolished after cortical strokes but preserved, especially for the biceps muscle, after subcortical strokes. This differentially affected excitability muscle-length relation after stroke may account for the disproportionate reduction of muscle strength at shortened range.\(^{2}\) If one assumes this excitability muscle-length relation to be controlled cortically, there may be different mechanisms of motor recovery after cortical stroke versus subcortical stroke. With respect to motor plasticity, these findings emphasize the necessity to practice upper limb muscles at short lengths to counterbalance the impaired excitability muscle-length relation, especially after cortical stroke. Whether this particular approach in physiotherapy can improve functional outcome after stroke remains to be proven in prospective clinical trials.

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We thank PD Dr Ernst Schuster from the Institute of Medical Informatics, Statistics and Epidemiology of the University of Leipzig, Germany, for expert statistical advice.

### Disclosures

None.

### References

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