Effect of low-frequency rTMS on motor neuron excitability after stroke


Objectives – The purpose of this study was to test the effects of low-frequency repetitive transcranial magnetic stimulation (rTMS) over the non-lesional hemisphere on motor neuron excitability of the paretic upper limb in post-stroke patients by electrophysiological examination. Materials and methods – Thirteen post-stroke patients with spastic upper limb hemiparesis were studied (age, 57.5 ± 11.1 years; time after stroke, 55.2 ± 51.4 months). Low-frequency rTMS of 1 Hz was applied for 20 min to the motor cortex of the non-lesional hemisphere. The M-response amplitude and F-wave parameters were recorded in the abductor pollicis brevis muscle following stimulation of the median nerve in both the affected and unaffected upper limbs. The F-wave frequency, F-max/M ratio (ratio of maximum F-wave amplitude to M-response amplitude), and F-mean/M ratio (the ratio of mean F-wave amplitude to the M-response amplitude) were measured before and after the 20-min rTMS, analyzed for both limbs. Results – Application of low-frequency rTMS did not result in significant changes in the frequency of F-wave and F-max/M ratio in both upper limbs, but significantly decreased F-mean/M ratio in the affected upper limb (P < 0.005), but not in the unaffected limb. Conclusions – Low-frequency rTMS applied to the non-lesional hemisphere might be potentially useful therapeutically for post-stroke patients with spastic upper limb hemiparesis.

Introduction

Spasticity is defined as velocity-dependent increase in the tonic stretch reflex accompanied by increased tendon reflexes (1). Spasticity is considered the hallmark of upper motor neuron lesions, because it develops with increased excitability of motor neuron (2). In patients with chronic stroke, the reported prevalence of spasticity is around 20% (3, 4), and its presence can result in motor weakness and clumsiness of the affected limb, pain, and various other complications. Consequently, spasticity inhibits activities of daily living and quality of life in such patients (4). For the evaluation of spasticity, modified Ashworth scale (MAS) and modified Tardieu scale have been developed and applied in the clinical settings (5, 6). The F-wave parameters, which evaluate long-pathway nerve conduction and motor neuron excitability, have been recommended for the evaluation of the severity of spasticity in post-stroke patients (7, 8). The frequency and amplitude of the F-wave increase with the increase in motor neuron excitability, suggesting the deterioration of spasticity of the examined limbs (9, 10).

Repetitive transcranial magnetic stimulation (rTMS) was introduced recently as a therapeutic tool for upper limb hemiparesis after stroke. Several groups have already reported the beneficial effect of low-frequency rTMS applied over the non-lesional hemisphere in post-stroke patients (11–13). In addition, other reports indicated that rTMS also has anti-spastic properties in post-stroke patients with spastic hemiparesis (14, 15). In other words, it is considered that rTMS can reduce pathologically increased excitability of motor neuron. To our knowledge, there are no
studies that investigated the effects of low-frequency rTMS on motor neuron excitability in the paretic upper limb using electrophysiological tests such as the F-wave parameters. The purpose of this study was to elucidate the effects of low-frequency rTMS over the non-lesional hemisphere on motor neuron excitability of the affected upper limb using F-wave parameters, in post-stroke patients.

Materials and methods

Materials

This study protocol was approved by the ethics committees of both Jikei University School of Medicine and Shimizu Hospital, and informed consent was obtained from all the patients. The study subjects were 13 consecutive post-stroke patients with spastic upper limb hemiparesis. The study subjects met the following inclusion criteria: (i) spastic upper limb hemiparesis categorized as Brunnstrom stage for hand–fingers of 4–6; (ii) age at study entry between 18 and 80 years; (iii) the period between onset of stroke and the study of >12 months; (iv) history of a single stroke only; (v) no cognitive impairment; (vi) good general condition without physical and mental illness requiring medical management; (vii) no previous history of seizure; and (viii) no pathological conditions referred as contraindications for rTMS in the guidelines suggested by Wasserrmann (e.g., cardiac pacemaker, intracranial implants) (16). In addition, we excluded patients who had received local injections of pharmacological compounds as treatment for spasticity, such as botulinum toxin type A. The clinical characteristics of the studied patients are shown in Table 1. The mean age at admission was 57.5 ± 11.1 years, and the mean period after onset of stroke was 55.2 ± 51.4 months. The patients consisted of eight patients with intracerebral hemorrhage and five patients with cerebral infarction. The baseline severity of upper limb hemiparesis was categorized as Brunnstrom stage 4 for hand–fingers in seven patients, stage 5 in three patients, and stage 6 in three patients. The mean MAS for the group was 0.62 ± 0.62 points for finger flexors and 0.73 ± 0.63 points for wrist flexors (MAS of +1 was analyzed as 1.5 point). There were three patients with the disturbance of both superficial and deep sensation.

In all patients, 20-min low-frequency rTMS was applied to the motor cortex of the non-lesional hemisphere. The F-wave parameters were evaluated immediately before and after rTMS administration.

| Table 1 Clinical characteristics of the patients (n = 13) |
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| Age at admission, years* | 57.5 ± 11.1 |
| Time after onset of stroke, months* | 55.2 ± 51.4 |
| Female, n (%) | 2 (15) |
| Subtype of stroke, n (%) | Intracerebral hemorrhage 5 (38) Cerebral infarction 8 (62) |
| Side of hemiparesis, n (%) | Dominant hand 11 (85) Non-dominant hand 2 (15) |
| BRS for hand–fingers at admission, n (%) | Stage 4 7 (54) Stage 5 3 (23) Stage 6 3 (23) |
| MAS of finger and wrist flexors, point* | Finger flexors 0.54 ± 0.58 Wrist flexors 0.67 ± 0.62 |
| Sensory disturbance | Absent 10 (77) Present 3 (23) |

BRS, Brunnstrom recovery stage; MAS, modified Ashworth scale.

*Data are mean ± SD.

Application of low-frequency rTMS

Low-frequency rTMS was performed with a 70-mm figure-8 coil attached to MagPro R30 stimulator (MagVenture Company, Farum, Denmark). According to the current safety recommendations, focal 1 Hz rTMS was applied to the non-lesional hemisphere over the primary motor area for 20 min (1200 pulses) (13). The optimal site of stimulation on the skull was defined as the location where the largest motor evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle of the unaffected upper limb was elicited on surface electromyography. The motor threshold (MT) of the FDI muscle of the upper limb was defined as the lowest intensity of stimulation that could activate MEPs of the muscle. Based on the MT level, the intensity of stimulation was set at 90% of MT of the FDI muscle on the unaffected upper limb. All patients were monitored carefully throughout the rTMS session by the physician applying rTMS.

F-wave evaluation

The F-wave parameters were measured by the occupational therapist (T. K), using Neuropack Σ MEB-5504 (Nihon Kohden, Tokyo, Japan), with the band-pass filter set at 50–3 kHz and sensitivity at 5 mV and 200 μV/division. During the measurement, the patient was seated with the eyes closed in a full reclining wheelchair tilted to 45°. The F-waves and M-responses were recorded from the abductor pollicis brevis muscles of the affected and unaffected upper limbs. The explor-
Surface electrodes were taped to the belly of the muscles after disinfecting the skin with alcohol and lowering skin resistance with Elefix EEG Paste (Nihon Kohden). After the measurements of the amplitude of the M-response, 16 consecutive F-waves were recorded antidromically with stimulation of the median nerve in the affected and unaffected upper limbs. The intensity of the stimulation was adjusted to 20% higher than the intensity that elicited the largest M-response. The rate and duration of stimulation were 0.5 Hz and 0.5 ms, respectively. The F-wave frequency was defined as the ratio of the number of stimulation which evoked F-wave of >20 μV to 16 (total number of stimulation) (If the amplitude of evoked F-wave was <20 μV, the F-wave response was considered absent). The maximum F-wave amplitude (F-max) among the 16 recorded stimulations and their mean F-wave amplitude (F-mean) were determined as the peak-to-peak amplitude. Based on these measurements, the ‘F-max/M ratio’ (the ratio of F-max to the M-response amplitude) and ‘F-mean/M ratio’ (the ratio of F-mean to the M-response amplitude) were computed. The F-wave parameters were measured in both the affected and unaffected upper limbs within 5 min before and immediately after the 20-min application of low-frequency rTMS over the non-lesional hemisphere.

Statistical analysis
The signed Wilcoxon’s rank sum test for paired samples was used to analyze the difference in the frequency of F-wave, the F-max/M ratio, and F-mean/M ratio measured before and after rTMS application, for both the affected and unaffected upper limb. All statistical analyses were performed with the use of SPSS version 19.0 (SPSS Inc, Chicago, IL, USA). A P value less than 0.05 was considered statistically significant.

Results
The application of low-frequency rTMS for 20 min was safely completed in all patients without any adverse effects, and the recording of F and M waves was successfully performed. Before rTMS application, the F-wave frequency in the affected upper limb (87.0 ± 17.6%) was significantly higher than in the unaffected upper limb (69.7 ± 24.5%, P < 0.01). After rTMS application, the F-wave frequency decreased to 80.3 ± 25.2% in the affected upper limb and to 61.5 ± 24.2% in the unaffected upper limb. The change in the F-wave frequency after rTMS application was not significant for both sides (P = 0.176 for the affected upper limb, P = 0.183 for the unaffected upper limb) (Fig. 1).

Before rTMS application, the F-max/M ratio and the F-mean/M ratio were significantly higher in the affected upper limb than the unaffected upper limb (P < 0.05 for both ratios). After rTMS application (Fig. 2), the F-max/M ratio decreased from 6.51 ± 5.07% to 4.90 ± 3.64% in the affected upper limb and from 3.07 ± 1.68% to 2.64 ± 2.38% in the unaffected upper limb. The change in F-max/M ratio after rTMS application was not significant in both upper limbs (P = 0.196 for the affected upper limb, P = 0.388 for the unaffected upper limb).

Application of rTMS tended to decrease the F-mean/M ratio in the unaffected upper limb, but the change was not significant (from 1.37 ± 0.65% to 1.28 ± 1.10%, P = 0.650, Fig. 3). In contrast, the F-mean/M ratio decreased significantly in the affected upper limb from 4.24 ± 3.69% at baseline to 2.60 ± 2.39% after rTMS application (P < 0.005).

![Figure 1](image1.png)
**Figure 1.** F-wave frequency in the affected and unaffected upper limb before and after low-frequency rTMS. Data are mean ± SD.

![Figure 2](image2.png)
**Figure 2.** F-max/M ratio in the affected and unaffected upper limb before and after low-frequency rTMS. Data are mean ± SD.
Discussion

There is little or no information on the effect of rTMS on motor neuron excitability in the affected upper limb after stroke, although the beneficial effects of rTMS in improving motor function in post-stroke patients have been reported in several clinical studies (14, 17, 18). Mally and Dinya (14) reported that the repeated consecutive application of 1-Hz rTMS to the non-lesional hemisphere for 1 week significantly reduced the spasticity on the affected limbs in post-stroke patients. In the report of Centonze et al. (18), 5-Hz rTMS applied to the lesional hemisphere for 2 weeks resulted in a significant improvement of spasticity of the affected limbs in patients with multiple sclerosis. Furthermore, Kakuda et al. (15) showed that a 15-day protocol of 1-Hz rTMS over the non-lesional hemisphere applied with intensive occupational therapy improved the motor function as well as significantly reduced the spasticity on the affected limbs in post-stroke patients. On the other hand, several authors have demonstrated the possibility that F-wave parameters can be useful for evaluating motor neuron excitability as well as the severity of spasticity. Udby et al. (19) reported that the F-wave frequency was significantly higher in post-stroke than in control patients. Tsai et al. (20) demonstrated a significant correlation between the severity of spasticity in post-stroke patients and F-wave amplitude. Thus, the measurement of F-wave parameters represents a non-invasive and quantitative neurophysiological test for the assessment of motor neuron excitability. To our knowledge, however, the effect of low-frequency rTMS on motor neuron excitability in post-stroke patients has not been evaluated using F-wave parameters. The results showed that low-frequency rTMS over the non-lesional hemisphere significantly decreased the F-mean/M ratio in the affected upper limb after stroke, suggesting that this modality of rTMS has effects to reduce motor neuron excitability in paretic upper limbs of post-stroke patients. This is the first study to show the effects of low-frequency rTMS over the non-lesional hemisphere on motor neuron excitability in post-stroke patients using F-wave parameters.

We speculate that the outcome was owing to neural activation in the lesional hemisphere. This is based on the finding that low-frequency rTMS over the non-lesional hemisphere and high-frequency rTMS over the lesional hemisphere, both of which have been reported to exhibit anti-spastic effects, increase the neural activity in the lesional hemisphere (18, 21, 22). Any increase in neural activity in the motor cortex of the lesional hemisphere results in an increase in descending inhibitory input through the corticospinal tracts (23, 24). This reduces the excitability of motor neurons, which can lead to a reduction in peripheral muscle spasticity.

In this study, we did not find any significant change in the F-wave frequency and F-max/M ratio, although these two parameters tended to decrease in the affected upper limb after rTMS application. It can be speculated that the 20-min duration of rTMS application may be too short to reduce motor neuron excitability in some patients, although the relationship between the duration of rTMS and extent of the effect of rTMS on motor neuron excitability remains unclear. In this regard, the decrease in the F-wave frequency following rTMS application could have been amplified with a larger number of test stimulations (16 times in the present study), as there seems to be a tendency toward a frequency decrease with rTMS application.

This study has certain limitations. First, the study involved only a small number of patients and lacked a control group, and thus the findings should be confirmed in another study of a larger number of patients involving a randomized controlled trial. Second, whether the reduced excitability of motor neurons in the affected upper limb with rTMS application is maintained after the cessation of rTMS application remains to be investigated. The long-term effect of the 20-min rTMS application on motor neuron excitability should be studied, as this issue is important in clinical settings. Third, we were not able to statistically investigate the relationship between the baseline severity of spasticity and baseline F-wave parameters, because of the small number of patients. There may also be a significant relationship between the baseline severity of spasticity.
and extent of changes in F-wave parameters with rTMS application. Furthermore, no data on the influence of rTMS on motor neuron excitability in the legs are available.

In conclusion, low-frequency rTMS applied to the non-lesional hemisphere in post-stroke patients significantly decreased the F-wave frequency and amplitude in the affected upper limb, suggesting that this modality has an anti-spastic effect in post-stroke patients. The results highlight the potential of low-frequency rTMS as a therapeutic option for patients with post-stroke spasticity of the upper limb.

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Conflicts of interest

The authors declare no conflict of interest.

References

6. Singh P, Joshua AM, Ganesan S, Suresh S. Intra-rater reliability of the modified Tardieu scale to quantify spasticity in elbow flexors and ankle plantar flexors in adult stroke subjects. Ann Indian Acad Neurol 2011;14:23–6.

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