Comparison of TMS-induced Arm Activation and Upper Limb Functional Tests in Hemiparetic Stroke

Ina M. Tarkka

Abstract—Stroke has a major impact in the total cost of healthcare in the Western world as stroke is the most common cause of long-term disability [1]. In attempts to enhance motor recovery after stroke effective treatment strategies have been developed in recent years. Appropriate evaluation of the intervention programs requires comprehensive and accurate assessment of the residual abnormal function. In the present study we compare two well-known clinical functional scoring tests developed for the assessment of hemiparetic upper limb function due to stroke and navigated transcranial magnetic stimulation (nTMS), which measures involuntary target muscle response to cortical stimulation. The aim is to investigate the equivalence of these methods and thus add objective evidence of the limb function to strengthen evidence-based practice. In addition to functional tests, four muscles of both arms were studied in twenty chronic stroke patients. Those patients without motor evoked potentials (MEP) to nTMS in the affected upper limb had significantly lower total score in Action Research Arm Test and Wolf Motor Function Test and longer performance time than those patients with MEP. Patients, in whom MEP in each of the four target muscles was elicitable, had better than average scores in clinical functional tests while patients, in whom no MEP was elicitable in any target muscle, had worse than average scores. Transcranial magnetic stimulation adds crucial information when clinical assessment based on voluntary activation by command is challenging, e.g. in patients suffering from cognitive deficits.

I. INTRODUCTION

CEREBROVASCULAR STROKE is among the three leading causes of mortality and the most common cause of long-term disability in the Western world [1]. The incidence of stroke is declining especially in the most developed countries but still the total number of strokes continues to increase because the number of people in the older age groups, where stroke is most common, increases [2]. In order to enhance motor recovery after stroke, effective treatment strategies have been developed in recent years. However, the evaluation of the treatments and intervention programs and the effective individualization of the rehabilitation need comprehensive and detailed assessment of the effects of rehabilitation. Additionally an early and valid prognosis of stroke would be very important in guiding the necessary decisions on the path to best individually obtainable recovery. A number of clinical functional tests have been introduced, some of them addressing only the deficient function [3] and some of them attempting to assess motor function of the whole person with stroke [4,5]. The tests differ in many aspects from each other and usually the degree of experience of the assessor also has a role in the reliability of the test results. And importantly, many motor function tests demand the collaboration of the subject, e.g. to follow the commands accurately, which is not always possible for stroke patients having cognitive or sensory deficits. For the above reasons, tests and assessments which do not demand collaboration, are important in clinical use.

Transcranial magnetic stimulation (TMS) is a relatively new non-invasive method for stimulation of brain in many applications of clinical neurophysiology, basic science, rehabilitation and psychiatry. It is useful in the examination of cortical excitability and functional connectivity of healthy and diseased brains and e.g. in mapping of eloquent brain areas prior to neurosurgical resections and it may be useful in determining the extent and location of brain damage and the effects of stroke to motor function [6,7,8]. In the present study, we compare two well-known clinical functional scoring systems which have been developed to assess deficits in upper limb function due to stroke and responses to TMS in same patients measured in the same day. The aim is to test the equivalence of the methods in analyzing defected upper limb function.

II. METHODS

A. Subjects

Two upper limb motor function tests and navigated TMS responses to upper limb stimulation were compared in same 20 chronic stroke patients (Table I).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Gender, male/female</td>
<td>13/7</td>
</tr>
<tr>
<td>Age of Years, m±SD (range)</td>
<td>52.6 ± 11.3 (23-64)</td>
</tr>
<tr>
<td>Time from stroke, months m±SD</td>
<td>32.0 ± 25.5 (6-100)</td>
</tr>
<tr>
<td>Ischemic/hemorrhagic stroke</td>
<td>12/8</td>
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<tr>
<td>Affected upper extremity, right/left</td>
<td>10/10</td>
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Wolf motor function test (WMFT) was originally developed to assess the impact of forced use (constraint-induced movement therapy) on upper extremity function with hemiplegic patients and it is performed only with the affected arm [9,10]. Tasks in WMFT are sequenced according to joints involved (shoulder to fingers) and level of difficulty (from gross movements to fine motor skills). The
examiner measures the performance time with a stop-watch and evaluates movements by scoring the functional ability and quality of movement. Tasks are performed as quickly as possible and the maximum time allowed to complete any one item is 120 seconds. The reliability and validity [11,12] of the WMFT have been ascertained in assessment of stroke patients.

The Action Research Arm Test (ARAT) was developed for the evaluation of the upper extremity function in hemiplegic stroke patients. It is designed for assessment of both unaffected and affected upper extremities in the same session [13]. ARAT consists of 19 items that are divided into 4 subscales: grasp, grip, pinch, and gross movement. The items are scored by the examiner on a 4-level scale ranging from 0 to 3. Scores of each subscale are summed and the total maximum (healthy) score is 57 [14]. ARAT is faster to perform than WMFT in the clinical environment. ARAT is reliable [15] and valid [12] in assessment of stroke patients.

The present subjects, 20 chronic stroke patients signed an informed consent prior to participation and the study was approved by the local ethical committee. The patients were consecutive consented patients who fulfilled the inclusion criteria among patients entering one rehabilitation centre.

The inclusion criteria were: first ever stroke resulting in hemiparesis, no contraindications for TMS (such as metal in head), residual voluntary function in the affected hand to make its functional testing feasible, no acute infections or other acute diseases, ability to give an informed consent. All three tests were performed during the same day for each patient, MRI and TMS during the morning and the functional tests in the afternoon. TMS was performed using MRI-based individual navigation. Brain MRI was performed with a 1.5T Siemens Magnetom Avanto (Erlangen, Germany) using a T1-weighted sequence. The MR-images were rendered to a subject-specific 3D image of the head, which was transferred into the navigation software.

The setup consisted of navigation system combined with a stimulator (Magstim 2000, London, England) using a figure-of-eight TMS coil (wing diameter of 50 mm). Responses to stimulation were recorded with EMG and monitored continuously on-line (ME 6000, Mega Electronics Ltd, Kuopio, Finland). The electrodes were placed on the skin overlying thenar, hypothenar, wrist flexor and wrist extensor muscles. The 3D image of the individual cortical surface was guiding the mapping. The 3D image was peeled to the depth of 2 cm to reveal the cortical surface. The anatomical location at which TMS evoked the highest peak-to-peak EMG response (MEP = motor evoked potential) in the thenar muscle was defined as the optimal cortical stimulus site. The M1 area was mapped to obtain the optimal stimulus site for the thenar. After finding the site, the coil was rotated to different directions to make sure of the optimal orientation evoking the largest MEP. Stimulating the exact point-like anatomical location to elicit MEP may still show amplitude variability with small orientation changes (in the order of 5-15°). Care with orientation of the coil is especially important with stroke patients who have brain lesions with various locations and sizes.

For each patient, the unaffected motor cortex was stimulated first and then the affected motor cortex. The resting Motor Threshold (MT) was defined from thenar muscles by determining a minimum TMS intensity that induced five responses (MEP amplitude =50µV) of 10 consecutive stimuli delivered 10 s apart. The MEP onset latency was calculated from the TMS trigger signal obtained in ME6000 to where the waveform deflection crossed 5 µV from baseline. Five MEPs were collected in each location at the intensity of 130 % of MT to determine onset latency and peak-to-peak amplitude of thenar, hypothenar, wrist flexors and wrist extensors. All four muscles of both hands were recorded in every patient. The stimulus intensity was set to 130% MT for all hand and forearm muscles. Latency and amplitude of the MEP in each recorded muscle were calculated as a mean value of five consecutive responses. In case no large enough MEPs (=50µV) were obtained, most likely due to the extent of the lesion, no response was marked as a result for the muscle in question.

For the statistical testing Wilcoxon signed rank test was used to compare same patient’s unaffected and affected upper limbs and Mann Whitney U-test was used to compare clinical scores and nTMS results for assessing motor function in the affected upper extremity. Significance level was set at p<0.05. Furthermore, the concurrent validity between ARAT and WMFT was determined by using Spearman’s correlation coefficient, and the floor and ceiling effects (percentages of the minimum and maximum scores) of the tests were investigated.

III. RESULTS

Upper limb functional tests and nTMS recordings were performed in all patients. Affected arm WMFT total time (including all tasks) was 895.3±593.1 s (100.4-1920.0) and total functionality score was 37.3±22.3 (0-69) for 20 patients. This gives a mean time of 56.0±37.1 s to perform the requested movements and a mean functionality score of 2.3±1.4. ARAT mean total score for the unaffected arm was 56.9±0.2 (56-57) and for the affected arm 12.5±13.7 (0-42.0) directly demonstrating the level of hemiparesis in these patients.

Figure 1: WMFT, ARAT and MEP manifestation are plotted for each patient. WMFT is shown as the mean functionality score of the 16 movements (max 5) and ARAT as the affected arm total score. Each patient’s MEP manifestation is plotted. Patients who had MEP in all muscles groups are shown as red triangles, patients with MEP in some muscle group are shown as red squares and patients with no MEP in any muscle group are shown as open squares.

Spearman’s correlation coefficient, and the floor and ceiling effects (percentages of the minimum and maximum scores) of the tests were investigated.
Motor function tests showed very little floor effect, only 5% of patients needed maximum time and got a minimum score from WMFT and 20% of the patients got a minimum score from ARAT. This indicates that the floor effect did not effectively bias the total results of both tests. There was no obvious ceiling effect in either test.

The percentage of patients who got maximum values varied 0%-15% between tasks in WMFT and 0%-20% between ARAT test sections. WMFT may appear to be more able to separate small differences the upper limb function in patients with poor motor function. Furthermore, ARAT may have shown better sensitivity to distinction of good motor function among patients who got higher scores (see Fig. 1). All in all, all these patients had rather poor hand function in the affected side and there was a very strong correlation between the two functional tests (Spearman's rank correlation coefficient, r=0.96, p<0.001). MEPs were obtained in all target muscles of the unaffected upper limb and in the affected upper limb MEP was obtained in 10 patients’ thenar muscles and in 10 patients’ hypothenar muscles and in four cases also in wrist flexor and wrist extensor muscles (Table II).

### Table II. MEP latencies in stroke patients (n=20)

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Non-affected hand</th>
<th>Affected hand</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>MEP mean±SD</td>
<td>MEP mean±SD</td>
<td></td>
</tr>
<tr>
<td>Thenar</td>
<td>20</td>
<td>10</td>
<td>0.064</td>
</tr>
<tr>
<td>Hypothenar</td>
<td>20</td>
<td>10</td>
<td>0.002**</td>
</tr>
<tr>
<td>Flexors</td>
<td>20</td>
<td>4</td>
<td>0.375</td>
</tr>
<tr>
<td>Extensors</td>
<td>20</td>
<td>4</td>
<td>0.125</td>
</tr>
</tbody>
</table>

The complete data on the unaffected side shows that the stimulus locations and stimulus intensities were appropriate for the unaffected or less affected hemisphere to elicit responses in the target muscles. Thus the same intensities to start stimulation of the affected side were appropriate. The motor threshold differed between unaffected and affected arms, 51.4±13.1% (range 34-73) and 82.7±20.5% (55-99), (p=0.001), respectively. MEP latencies of hypothenar muscles were longer in the affected arm than in the unaffected arm (p=0.002). The difference between MEP latencies of the unaffected and affected arm in thenar muscles were almost significant (p=0.064). The thenar muscle MEP amplitudes were smaller in the affected arm than in the unaffected arm, 270.9±338.0 µV and 1361.1±1570.5 µV (p=0.027), respectively. The relationship between WMFT and ARAT are shown in Fig.1, where each patient is depicted according to the manifestation of MEPs in his/her affected side.

The MT was obtained in thirteen patients in the thenar muscles however, in ten patients the required 130% stimulus intensity was possible to perform and obtain a MEP with the required amplitude. It means that the stimulus intensity for MT was already close to the maximum output of the stimulator. Additionally, WMFT total time was shorter in those patients with MEP in wrist flexors (p=0.021) and wrist extensors (p=0.028) than those patients without MEP in wrist muscles.

Patients without MEP in any target muscle had lower than average scores in both ARAT and WMFT functionality score. The WMFT total time of the 16 tasks is shown separately in patients with MEP and without MEP in Fig. 2, where it can be seen that those with faster movements also had MEPs.

Figure 2: WMFT time in patients with MEP (light gray) and without MEP (dark gray). All recorded muscles are shown separately.

Also the WMFT functionality score demonstrates a similar phenomenon, i.e. those patients with MEP had higher functionality scores than those without MEP (see Fig. 3).

Figure 3: WMFT movement functionality shown as a functional capacity mean score in patients with MEP (light gray) and without MEP (dark gray). All recorded muscles are shown separately.
When analyzing the ARAT score, a corresponding feature can be observed; those patients, who had MEP also had higher scores in ARAT test of their affected hand (see Fig. 4).

![Figure 4: ARAT score in patients with MEP (light gray) and without MEP (dark gray). All recorded muscles are shown separately.](image)

**IV. DISCUSSION**

The aim of the study was to investigate clinical motor function tests commonly used for testing the upper limb affected by stroke and the relationship of these tests to involuntary function test performed with nTMS. The main question was how the presence or absence of elicitable MEP response was related to the level of motor ability of the upper limb. In addition to comparison of voluntary movements and involuntary responses in hemiparetic hands, the study was also motivated by doubts that clinical functional tests which demand patient actions by command may not always be useful. When the patient presents with borderline healthy motor abilities or borderline complete paralysis in the affected side or have poor cognitive abilities (e.g. early signs of dementia or for instance afatic paralysis in the affected side or have poor cognitive abilities (e.g. early signs of dementia or for instance afatic syndrome) the clinical functional motor test is insufficient.

The present patients had upper limb paralysis on one side and no motor deficits in the unaffected limb. All these patients had in general rather poor affected hand function and thus it was important to scrutinize the involuntary response in the paralyzed limb. Even though WMFT and ARAT correlate with each other, WMFT appeared to be more sensitive in assessing motor function of subjects with poor upper limb whereas ARAT seemed to have better sensitivity to variation in subjects with better upper limb motor function.

Those patients without MEP to nTMS in the affected upper limb had lower total score in ARAT and WMFT and longer performance time in WMFT than those patients with MEP response in one or more upper limb muscles. Patients with MEP in all target muscles had noticeable better than average scores from the clinical functional tests while patients without MEP in any target muscle had worse than average scores. When the results of ARAT and WMFT of each individual were evaluated according to in how many of the recorded muscles MEP was obtained, it was evident that the more muscles MEP was obtainable the better were the scores of clinical functional tests. The present high concurrent validity between ARAT and WMFT adds to the reliability of clinical tests and also strengthens the value of comparison between the clinical tests and nTMS.

Stimulating the unaffected hemisphere produced normal MEP amplitudes with typical latencies in all four recorded arm and hand muscles in the unaffected limb. This clearly indicated that the nTMS strategy (location, intensity, etc.) chosen was able to produce appropriate MEPs in healthy brain. Thus the lack of MEP in one or more muscles in the affected side in these patients definitely pointed out their functionally meaningful lesion in the descending pathway from the primary motor cortex, M1, to the ventral horn in the spinal cord. Thus nTMS can be a useful tool in understanding lesions caused by stroke and in clinical assessment of stroke patients. It could be combined with the clinical tests to increase the validity and reliability of assessment of stroke patients at one time point or it could be used in the follow-up of patients’ recovery or response to rehabilitation efforts. Especially it would add crucial information when clinical assessment is challenging in patients suffering from various cognitive deficits.

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**REFERENCES**


