Functional Role of the Corticoreticular Pathway in Chronic Stroke Patients

Sung Ho Jang, MD; Chul Hoon Chang, MD; Jun Lee, MD; Chung Sun Kim, PhD; Jeong Pyo Seo, MS; Sang Seok Yeo, PhD

Background and Purpose—The corticoreticular pathway (CRP) is known to be an important extrapyramidal tract for walking ability. However, little is known about the functional role of the CRP in recovery of walking ability. We investigated the relation between the CRP and walking ability in chronic hemiparetic stroke patients.

Methods—Among 209 consecutive patients, 54 patients, who showed complete injury of the corticospinal tract (CST) in the affected hemisphere on diffusion tensor tractography, and 20 normal subjects were recruited. Functional ambulation category was used in measurement of walking ability. The fractional anisotropy value, apparent diffusion coefficient value, and fiber volume of the CRP and CST were used for the diffusion tensor imaging parameters.

Results—In the affected hemisphere, no significant difference in diffusion tensor imaging parameters of the CRP was observed between patient subgroups. In the unaffected hemisphere, patients who were able to walk showed significantly increased fiber volume of the CRP, compared with patients who could not walk and normal control subjects (P<0.05), without significant difference in fractional anisotropy and apparent diffusion coefficient values. In addition, the fiber volume of the CRP in the unaffected hemisphere showed positive correlation with functional ambulation category (P<0.05). In contrast, diffusion tensor imaging parameters of the CST in the unaffected hemisphere showed no correlation with functional ambulation category (P>0.05).

Conclusions—The increased fiber volume of the CRP in the unaffected hemisphere seems to be related to walking ability in patients with chronic stroke. Therefore, the compensation of the CRP in the unaffected hemisphere seems to be one of the mechanisms for recovery of walking ability after stroke. (Stroke. 2013;44:1099-1104.)

Key Words: corticoreticular pathway ■ corticoreticulospinal tract ■ diffusion tensor imaging ■ stroke ■ walking ability

Stroke is a leading cause of major disability in adults; ≈20% to 30% of stroke patients have suffered walking dysfunction as a disabling sequela.1–3 The descending motor pathways are classified according to the corticospinal tract (CST, pyramidal tract) and non-CST (extrapyramidal tract).6,7 A number of studies have reported on stroke patients who were unable to perform fine motor activities of the hands after complete injury of the lateral CST;8–12 in contrast, recent studies have demonstrated that stroke patients were able to walk even after complete injury of the lateral CST, suggesting that walking is not as strongly associated with the lateral CST as hand function.9,13–15 Greater involvement of non-CSTs in walking ability has been suggested.9,14–15 In particular, the corticoreticulospinal tract, consisting of the corticoreticular pathway (CRP) and the reticulospinal tract, is known to be an important neural tract for walking ability14–16 because it mainly mediates proximal and axial muscles; consequently, it is known to have a major role in relation to walking ability.16,17

Several previous studies using conventional brain MRI, single photon emission computed tomography, and functional near infrared spectroscopy have reported on the relation between walking dysfunction and injury of the premotor cortex (PMC).18–22 However, these studies could not clearly elucidate definitive relation between specific neural tracts and walking ability. The PMC is the main origin site of the corticoreticulospinal tract; therefore, the corticoreticulospinal tract has been suggested as one of the plausible neural tracts.16 Recent development in diffusion tensor imaging (DTI) has enabled investigators to estimate the state of the neural tracts at the subcortical level in 3 dimensions.23 A study using DTI reported on a method for identification of the CRP in the live human brain.24 Few studies have reported on injury of the CRP in patients with stroke and traumatic brain injury.25,26 However, little is known about the relation between the CRP and walking ability.
In this study, using DTI, we attempted to investigate the relation between the CRP and walking ability in chronic hemiparetic stroke patients.

**Materials and Methods**

**Subjects**
Fifty-four stroke patients (39 men, 15 women; mean age, 54.4 years; range, 32–75) and 20 age- and sex-matched control subjects (10 men, 10 women; mean age, 53.1 years; range, 33–72) with no history of neurological or psychiatric disease were recruited for this study.

Stroke patients were recruited consecutively among 209 stroke patients according to the following inclusion criteria: (1) first-ever stroke, (2) age: 30 to 75 years, (3) >3 months after stroke onset, (4) hemorrhage or infarction confined to the subcortical supratentorial level (the corona radiata, basal ganglia, and internal capsule), (5) patients who could not walk within 24 hours after stroke onset, and (5) patients who showed complete CST injury (discontinuation of the CST around or below the lesion) in the affected hemisphere on diffusion tensor tractography (DTT). Patients with apraxia, somatosensory problems, severe cognitive problems (mini-mental state examination <25), or intracerebral hemorrhage because of vascular anomaly or hemorrhagic transformation after cerebral infarct were excluded. This study was conducted retrospectively, and the local ethics committee of a university hospital approved the study protocol.

**Clinical Evaluation**
Motor function was evaluated at the time of DTI scanning. The functional ambulation category (FAC) scale was used for determination of walking ability. The FAC was designed for examination of the levels of assistance required during a 15-m walk. Six categories are included in the FAC: 0 (nonambulatory), 1 (needs continuous support from 1 person), 2 (needs intermittent support from 1 person), 3 (needs only verbal supervision), 4 (help is required on stairs and uneven surfaces), and 5 (can walk independently anywhere). We classified patients into 2 subgroups according to the ability to walk independently; subgroup A: patients who could not walk independently (FAC: 0 to 2) and subgroup B: patients who could walk independently (FAC: 3 to 5). Motricity index (MI) was used for measurement of motor function of the affected upper and lower extremities (maximum score: 100). The reliabilities and validities of FAC and MI have been well established. Evaluators of clinical data were blinded to DTT data, and analyzers of DTT were also blinded to the clinical data.

**Diffusion Tensor Imaging**
DTI data were acquired at an average of 22 months (range, 3–125) after stroke onset, using a 1.5-T Philips Gyroscan Intera system equipped with a synergy-L Sensitivity Encoding head coil using a single-shot, spin-echo planar imaging pulse sequence. For each of the 32 noncollinear and noncoplanar diffusion sensitizing gradients, we acquired 60 contiguous slices parallel to the anterior commissure-posterior commissure line. The imaging parameters were a matrix =128×128 matrix, field of view =221×221 mm², repetition time=76 ms, time to echo=10,726 ms, sensitivity encoding factor =2; echo-planar imaging factor=67 and b=600 mm² s⁻¹; NEX =1; and a slice thickness of 2.3 mm. We scanned T₁-weighted, T₂-weighted, fluid attenuated inversion recovery, and T₂-weighted gradient echo images to confirm the stroke lesion.

Affine multiscale 2-dimensional registration was used for reduction of eddy current-induced image distortions and motion artifacts. Preprocessing of DTI data sets was performed using the Oxford Center for Functional MRI of Brain Software Library, DTI-Studio software (CMRM, Johns Hopkins Medical Institute, MD) was used for reconstruction of the CRP and CST. For analysis of the CRP, the seed region of interest (ROI) was placed on the reticular formation of the midbrain and the target ROI on the pontomesencephalic junction (Figure 1C). For analysis of the CST, the seed ROI was placed on the CST portion of the pontomesencephalic junction and the target ROI on the CST portion of the anterior midpons. The CRP and CST were determined by selection of fibers passing through seed and target ROI. Fiber tracking was performed using a fractional anisotropy (FA) threshold of >0.2 and direction threshold <70°. We measured the FA value, apparent diffusion coefficient (ADC) value, and fiber volume of the CRP in both hemispheres and the CST in the unaffected hemisphere.

**Statistical Analysis**
The $\chi^2$ test was used for determination of the difference in incidence of CRP injury in the affected hemisphere between patient subgroups. The independent $t$ test was performed for comparison of motor functions between hemorrhagic and infarct patients. The Mann-Whitney $U$ test was performed for determination of difference in motor function according to the CRP injury in the affected hemisphere. One-way ANOVA with Scheffe post hoc test was performed for determination of the statistical difference of DTI parameters of the CRP and CST between the patient and control groups. Spearman correlation test was used for determination of correlation between DTI parameters of constructed neural tracts and motor functions. For evaluating interobserver and intraobserver reliability, we used intraclass correlation coefficient (ICC). Software (v.15.0; SPSS, Chicago, IL) was used in performance of statistical analyses, and statistical significance was set at $P<0.05$.

**Results**
Thirty-nine (72.2%) of the 54 patients had experienced an intracerebral hemorrhage and the remaining 15 had experienced a cerebral infarct. In terms of all motor functions, significant difference was not observed between hemorrhagic and infarct patients ($P>0.05$). In classification according to walking ability, 20 (37.0%) of 54 patients belonged to subgroup A (FAC: 0–2) and 34 to subgroup B (FA: 3–5).

All patients in subgroup A and 30 of 34 patients in subgroup B showed a discontinuation of the CRP in the affected hemisphere; however, no significant difference in incidence of CRP injury was observed between subgroups A and B ($P>0.05$). In addition, in subgroup B, patients with intact CRP in the affected hemisphere showed significantly higher motor function in terms of FAC and all MIs compared with patients with injured CRP ($P<0.05$). In terms of FA, ADC and fiber volume of the CRP in the affected hemisphere did not show significant difference between patient subgroups ($P>0.05$). In addition, no significant differences in FA and ADC values of the CRP in the unaffected hemisphere were observed between patient and control groups and between patient subgroups A and B ($p>0.05$). By contrast, fiber volume of the CRP in the unaffected hemisphere of subgroup B was significantly higher than that of subgroup A and the control group ($P<0.05$) (Table 1). Regarding the CST in the unaffected hemisphere, the FA value of subgroup A was significantly lower than that of the control group ($P<0.05$). In contrast, there were no differences in ADC values and fiber volume of all patient subgroups and the control group ($P<0.05$) (Table 1). In the result of reliability, we observed strong intraobserver and interobserver reliability of DTI parameters in the CST (intra-ICC =0.883–0.993, inter-ICC =0.872–0.996) and CRP (intra-ICC =0.874–0.957, inter-ICC =0.860–0.976). A summary of the correlations between DTI parameters of constructed neural tracts and motor functions is shown in Table 2. Fiber volume of the CRP in the affected hemisphere
did not show any correlation with FAC and all MIs (P>0.05). By contrast, fiber volume of the CRP in the unaffected hemisphere showed moderate positive correlation with FAC (r=0.425, P=0.006), and mild positive correlation with upper MI (r=0.307, P=0.038), lower MI (r=0.340, P=0.021), and total MI (r=0.308, P=0.037). However, the FA and ADC values did not show correlation with FAC and all MIs (P>0.05). On the contrary, the ADC value of the CST in the unaffected hemisphere showed negative correlation with upper MI (r=−0.408, P=0.005), lower MI (r=−0.357, P=0.015), and total MI (r=−0.401, P=0.006), without correlation with FAC. In addition, the FA value and fiber volume of the CST in the unaffected hemisphere did not show correlation with FAC and all MIs (P>0.05) (Figure 2).

Table 1. Comparisons of Diffusion Tensor Image Parameters of the Corticoreticular Pathway and Corticospinal Tract Between Patient Subgroups and Control Group

<table>
<thead>
<tr>
<th></th>
<th>Corticoreticular Pathway</th>
<th>Corticospinal Tract</th>
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<tbody>
<tr>
<td></td>
<td>Unaffected Hemisphere</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>FA 0.49 (0.03) ADC 0.83 (0.05) FV 658.50 (298.50)</td>
<td>FA 0.55 (0.02) ADC 0.83 (0.05) FV 1074.15 (341.10)</td>
</tr>
<tr>
<td></td>
<td>Subgroup A (FAC &lt;3)</td>
<td>Subgroup B (FAC ≥3)</td>
</tr>
<tr>
<td>TH</td>
<td>FA 0.50 (0.03) ADC 0.84 (0.04) FV 1047.00 (323.38)</td>
<td>FA 0.57 (0.02) ADC 0.81 (0.08) FV 1205.32 (385.81)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>FA 0.50 (0.02) ADC 0.83 (0.05) FV 758.93 (282.52)</td>
<td>FA 0.58 (0.03) ADC 0.83 (0.06) FV 924.48 (305.59)</td>
</tr>
<tr>
<td></td>
<td>Subgroup A vs B</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>0.870 0.713 0.000*</td>
<td>0.207 0.497 0.404</td>
</tr>
<tr>
<td></td>
<td>Subgroup A vs Control</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>0.323 0.996 0.835*</td>
<td>0.000* 0.900 0.280</td>
</tr>
<tr>
<td></td>
<td>Subgroup B vs Control</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>0.526 0.551 0.000*</td>
<td>0.063 0.671 0.380</td>
</tr>
</tbody>
</table>

Values represent mean (SD).

ADC indicates apparent diffusion coefficient; FAC, functional ambulation categories; FA, fractional anisotropy; and FV, fiber volume. One-way ANOVA with Scheffe post hoc test was used for comparison of diffusion tensor parameters between patient groups and normal control.

*P<0.05.
Discussion

In the current study, among 209 consecutive chronic stroke patients, we recruited 54 stroke patients who showed complete injury of the CST in the affected hemisphere on DTT. We found that, in the unaffected hemisphere, the fiber volume of the CRP was higher in patients who were able to walk independently (subgroup B), compared with patients who could not walk (subgroup A) and normal control subjects, without change of FA and ADC values. In addition, in terms of the CST in the unaffected hemisphere, the FA value was lower in patients who could not walk (subgroup A), compared with normal control subjects, without change of ADC values and fiber volume. The fiber volume is determined by the number of voxels contained within a neural tract.\textsuperscript{31,32} In contrast, the FA value indicates the degree of directionality of water diffusion.\textsuperscript{33,34} It represents the white matter organization; in detail, the degree of directionality and integrity of white matter microstructures, such as axon, myelin, and microtubule, and the ADC value indicates the magnitude of water diffusion.\textsuperscript{33,34} Therefore, increased fiber volume and reduced FA value without change of the ADC value seems to indicate increased numbers of neural fibers and disintegration of neural fibers, respectively.\textsuperscript{23,31–34} In the correlation analysis, the fiber volume of the CRP in the unaffected hemisphere showed moderate

| Unaffected | FAC Upper MI | Lower MI | Total MI |
| Hemisphere | P Value | P Value | P Value | P Value |
| CRP | 0.153 | 0.311 | 0.071 | 0.638 | 0.069 | 0.647 | 0.056 | 0.712 |
| ADC | 0.007 | 0.961 | 0.039 | 0.796 | 0.034 | 0.821 | 0.037 | 0.808 |
| FV | 0.455 | 0.001* | 0.307 | 0.038* | 0.340 | 0.021* | 0.308 | 0.037* |
| CST | 0.233 | 0.120 | 0.118 | 0.436 | 0.124 | 0.413 | 0.111 | 0.464 |
| ADC | −0.282 | 0.057 | −0.408 | 0.005* | −0.357 | 0.015* | −0.401 | 0.006* |
| FV | 0.062 | 0.683 | −0.182 | 0.226 | −0.183 | 0.224 | −0.178 | 0.237 |

ADC indicates apparent diffusion coefficient; CRP, corticoreticular pathway; CST, corticospinal tract; FA, fractional anisotropy; FAC, functional ambulation categories; FV, fiber volume; and MI, motricity index.

*\(P<0.05\).
and mild positive correlation with walking ability and motor functions, respectively; however, that of the CST showed no correlation. Consequently, increased fiber volumes of the CRP in the unaffected hemisphere seem to be related to recovery of walking ability and some motor functions in hemiparetic stroke patients. By contrast, decreased FA of the CST in the unaffected hemisphere might be related to long-term immobility after stroke.35,36

Several previous studies have reported on stroke patients who were able to walk even after complete injury of the CST; however, these studies could not elucidate the alternative neural tract of the injured CST associated with walking ability.3,9,13 On the contrary, even without exact estimation of the CRP, several studies have demonstrated the predominant role of the PMC in control of walking ability. In 1999, Miyai et al19 reported on 12 stroke patients with a lesion in the PMC who showed delayed recovery of walking ability. During the same year, using single photon emission computed tomography, Hanakawa et al18 reported on decreased activation in the PMC in patients affected by Parkinson’s disease with gait disturbance. In 2002, using functional near infrared spectroscopy, Miyai et al20 evaluated cortical activation patterns in stroke patients with severe walking dysfunction during passive treadmill walking. They demonstrated that passive treadmill walking could activate the PMC in the affected hemisphere. Subsequently, using functional near infrared spectroscopy, Miyai et al21 reported that the enhanced PMC activation in the affected hemisphere showed significant correlation with improvement of walking ability in stroke patients. In 2006, using functional near infrared spectroscopy, they also reported on 6 patients with subcortical stroke, who showed improvement of walking ability with enhanced PMC activation in the unaffected hemisphere.22 These results seem to be compatible with the results of the current study, which showed increased fiber volume of the CRP in the unaffected hemisphere. Therefore, the compensation of the CRP in the unaffected hemisphere seems to be one of the mechanisms for recovery of walking ability after stroke.22

Conclusions

In conclusion, we investigated the role of the CRP in relation to walking ability for patients with chronic stroke. It was found that the increased fiber volume of the CRP in the unaffected hemisphere seems to be related to walking ability in patients with chronic stroke. This result demonstrates the importance of the CRP for walking ability in stroke patients. Therefore, we suggest that evaluations of the CRP using DTT would be useful for stroke patients with walking dysfunction. However, limitations of this study should be considered. First, because most recruited patients (92.6%) showed severe injury of the CRP in the affected hemisphere, we were unable to fully elucidate the functional role of the CRP in the affected hemisphere. This seems to be ascribed to the fact that we recruited stroke patients with severely affected motor function who showed complete injury of the CST in the affected hemisphere. The CRP descends through the corona radiata and posterior limb of the internal capsule just anterior to the CST; patients with complete injury of the CST are vulnerable to severe injuries in the CRP pathway.24 Second, further prospective studies involving follow-up clinical and DTT data from acute to chronic stage of stroke are warranted because this study was performed retrospectively. Third, DTI analysis is operator-dependent, and because of fiber complexity and crossing fiber effect, it may underestimate the fiber tracts.37,38 Another limitation is that we could not consider the other neural tracts that have been suggested as playing a role in walking, including the vestibulospinal tract and anterior CST.8 Therefore, conduct of further studies, including more neural tracts that are related to walking ability, would be necessary. In addition, the role of the CRP in the affected hemisphere should be clarified by conduct of further studies involving larger number of patients with mild CRP injury.

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Disclosures

None.

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慢性期脳卒中患者における皮質網様体路の機能的役割

Functional Role of the Corticoreticular Pathway in Chronic Stroke Patients

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Abstract

背景および目的: 皮質網様体路 (CRP) は歩行能力に重要な椎体外路である。しかし、歩行能力回復時の CRP の機能的役割についてはほとんど知られていない。我々は、慢性期脳卒中片麻痺患者の CRP と歩行能力の関係を調べた。

方法: 連続登録症例 209 例のうち拡散テンソルトラクトグラフィ上で患側半球の皮質脊髄路 (CST) が完全に損傷している 54 例、および正常被験者 20 例を対象に、functional ambulation category を使用して歩行能力を測定した。CRP および CST の異方性比率、みかけの拡散係数、および線維量を拡散テンソル画像パラメーターとした。

結果: 患側半球では、患者のサブグループ間において CRP の拡散テンソル画像パラメーターに有意差はなかった。非患側半球では、歩行可能群の方が歩行不可能群と正常対照群と比較して CRP の線維量が有意に増加した (p < 0.05) ただし、異方性比率およびみかけの拡散係数には有意差はなかった。また、非患側半球の CRP の線維量と functional ambulation category に正の相関が認められた (p < 0.05)。対照的に、非患側半球の CST の拡散テンソル画像パラメーターは functional ambulation category に相関していなかった (p > 0.05)。

結論: 慢性期脳卒中患者では非患側半球の CRP における線維量増加が歩行能力と関連しているようである。したがって、非患側半球の CRP の補償作用は、脳卒中後の歩行能力回復のメカニズムの一つと考えられる。

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