INTRODUCTION

In human cerebral ischemia, the temporal evolution of signal intensity on magnetic resonance imaging (MRI), especially on diffusion weighted imaging (DWI), has been documented in the literature (1-5). Apparent diffusion coefficient (ADC) values typically decrease sharply shortly after stroke onset, remain low for at least 72 to 96 hours, and then gradually increase, reaching and surpassing normal levels. Many animal studies, especially in rodent models, have shown imaging and pathologic changes after ischemic injury with or without subsequent reperfusion (6-11). Such studies provide information on the mechanism of tissue injury in ischemic stroke and implications on clinical treatment of ischemic stroke patients.

Over the past decades, the development of endovascular procedures to achieve recanalization aims at salvage of ischemic penumbra and better clinical outcome in patients (12). Signal evolution on MRI after recanalization of ischemic stroke lesions...
may reflect tissue change from reperfusion, and helps to clarify critical pathophysiology of acute ischemic stroke.

Though post-procedural MR imaging is not performed routinely, information on changes in MR imaging findings in the early reperfusion state may attribute to our understanding of pathophysiology of ischemic stroke and reperfusion injury after recanalization of occluded intracranial arteries.

There are only a few studies with human subjects probably due to the impracticality of serial imaging follow up in humans; however, changes on DWI finding after reperfusion or recanalization are reported (13, 14). The purpose of this study was to evaluate ADC changes immediately after interventional full-recanalization in patients with acute cerebral ischemia.

MATERIALS AND METHODS

Study Population

Study population was selected among the patients who received intra-arterial revascularization therapy (IART) in our institution for hyperacute to acute ischemic stroke, from January 2010 to December 2013. Institutional Review Board approval was obtained for this retrospective study, and informed consent was waived. Only a small number of patients underwent post-recanalization diffusion weighted MR imaging immediately after the procedure.

Inclusion criteria for this study were as follows: 1) patients who had both pre- and post-procedural DWI, 2) patients who received endovascular mechanical thrombectomy (either with stent retrieval or direct aspiration), intra-arterial thrombolysis, and/or stent insertion as treatment, 3) patients who showed successful recanalization with thrombolysis in cerebral infarction (TICI) grade 2b or more. Definition of TICI categories were according to that of Higashida et al. (15). The initial TICI grades were 0 and post-treatment TICI grades were 3 in all cases, except for a single case of TICI grade 2b; a detailed discussion of this exceptional case was provided later in the manuscript.

Exclusion criteria included: 1) hemorrhagic transformation that may attribute to signal change on DWI, seen as dark signal intensity on susceptibility weighted images acquired after the recanalization, 2) more than 4 hours of time interval between recanalization and post-recanalization DWI. Recanalization time was recorded for each case, as the time stated on images of the first angiography obtained after retrieval of Solitaire stent, aspiration of thrombus, or IA tirofiban injection demonstrating fully-recanalized artery. The average time interval between recanalization and post-recanalization DWI was 72 minutes for the overall study population.

Finally, a total of 18 patients were included in the study. Clinical characteristics of the cases, including initial National Institutes of Health Stroke Scale (NIHSS) and onset time, were collected through review of electronic medical record system of our hospital.

MR Imaging

One patient had pre-recanalization MR imaging in outside hospitals, in a 1.5T system (Genesis Signa, GE Healthcare, Milwaukee, WI, USA). The other 17 patients’ pre-recanalization MR exams and all post-recanalization MR exams were performed in our own institution, using 1.5T or 3T MR imaging systems (Avanto, Verio, or Skyra, Siemens Medical Systems, Erlangen, Germany).

Overall, 36 MR exams were reviewed, of which, 18 pre-recanalization included images from an outside hospital and 18 post-recanalization images were obtained in our hospital.

Lesion Classification

Some of the patients had multifocal infarction, and the lesions were considered separately. Lesions that were not in the territory of the recanalized vessels (i.e., acute infarction in the posterior cerebral artery territory when the interventional treatment of anterior circulation was successfully applied) were not included in the analysis. Some small cortical infarctions, in which ADC value could not be obtained, were also disregarded.

Overall, 25 lesions of 18 patients were included in the study. The lesions were divided into either territorial infarction (TI) or watershed infarction (WI) according to pathophysiologic differences. WI is an ischemic lesion that occurs at the junction between 2 non-anastamosing distal arterial distributions. Two of 18 patients showed both TI and WI lesions and 1 patient presented with WI alone. All 3 lesions of WI were located in the internal watershed zone, deep white matter.

Means of Recanalization

Three patients were given intravenous tissue plasminogen ac-
tivator (tPA) infusion in emergency room before endovascular treatment, since they satisfied indications at the time of arrival and first examination by the neurologist. Two of the 3 patients had completed tPA infusion, but did not show any clinically significant improvement i.e., NIHSS was unchanged and were referred to the angioroom for endovascular treatment. One of 3 patients had persistently high blood pressure (BP) from the beginning of the tPA infusion and the infusion was discontinued due to increased risk of hemorrhage associated with uncontrollably high BP. The other 15 patients were treated with endovascular intervention alone.

ADC Value Measurement

For each lesion, a representative image that could best demonstrate characteristics of the entire lesion was selected. Small region of interests (ROIs) that were as small as possible but large enough to generate meaningful ADC value for analysis were selected in representative images of the lesion. Another ROI of the same size was also placed on the contralateral anatomic location for comparison. The selected locations of ROIs were based on ease of sampling and to minimize interference of cerebrospinal fluid signal.

Table 1. Patient Demographics and Clinical Informations

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Occlusion Site</th>
<th>Infarction Type</th>
<th>IV tPA</th>
<th>Outside</th>
<th>NIHSS at ER</th>
<th>Interval 1</th>
<th>Interval 2</th>
<th>Recanalization Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69/F</td>
<td>T-occlusion</td>
<td>TI</td>
<td>-</td>
<td></td>
<td>5</td>
<td>373</td>
<td>77</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>2</td>
<td>77/F</td>
<td>M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>418</td>
<td>211</td>
<td>Wingspan 3.5 × 15</td>
</tr>
<tr>
<td>3</td>
<td>76/F</td>
<td>M1</td>
<td>TI</td>
<td>-</td>
<td>o</td>
<td>19</td>
<td>289</td>
<td>54</td>
<td>Solitaire 6 × 20</td>
</tr>
<tr>
<td>4</td>
<td>45/F</td>
<td>M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>300</td>
<td>57</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>5</td>
<td>67/F</td>
<td>M1</td>
<td>TI and WI</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>625</td>
<td>82</td>
<td>Wingspan 3 × 15</td>
</tr>
<tr>
<td>6</td>
<td>58/M</td>
<td>ICA</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>12</td>
<td>391</td>
<td>77</td>
<td>Wingspan 4.5 × 20</td>
</tr>
<tr>
<td>7</td>
<td>56/M</td>
<td>ICA/M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>488</td>
<td>28</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>8</td>
<td>55/F</td>
<td>M1</td>
<td>WI</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>680</td>
<td>48</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>9</td>
<td>59/M</td>
<td>M2</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>264</td>
<td>51</td>
<td>Solitaire 4 × 20</td>
</tr>
<tr>
<td>10</td>
<td>77/M</td>
<td>M1</td>
<td>TI</td>
<td>o</td>
<td>-</td>
<td>20</td>
<td>271</td>
<td>55</td>
<td>Tirofiban IA</td>
</tr>
<tr>
<td>11</td>
<td>72/M</td>
<td>M1</td>
<td>TI and WI</td>
<td>-</td>
<td>-</td>
<td>13</td>
<td>172</td>
<td>86</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>12</td>
<td>73/F</td>
<td>M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>229</td>
<td>57</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>13</td>
<td>61/M</td>
<td>ICA/M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>909</td>
<td>62</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>14</td>
<td>62/M</td>
<td>ICA/M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>279</td>
<td>55</td>
<td>Aspiration</td>
</tr>
<tr>
<td>15</td>
<td>75/F</td>
<td>BA</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>166</td>
<td>148</td>
<td>Solitaire 6 × 30</td>
</tr>
<tr>
<td>16</td>
<td>59/M</td>
<td>CCA/T/M1</td>
<td>TI</td>
<td>o</td>
<td>-</td>
<td>17</td>
<td>341</td>
<td>40</td>
<td>Aspiration/solitaire 6 × 30</td>
</tr>
<tr>
<td>17</td>
<td>67/F</td>
<td>ICA/M1</td>
<td>TI</td>
<td>-</td>
<td>-</td>
<td>22</td>
<td>353</td>
<td>67</td>
<td>Aspiration/solitaire 6 × 30</td>
</tr>
<tr>
<td>18</td>
<td>51/M</td>
<td>M2</td>
<td>TI</td>
<td>o</td>
<td>-</td>
<td>24</td>
<td>274</td>
<td>33</td>
<td>Aspiration/solitaire 4 × 20</td>
</tr>
</tbody>
</table>

BA = basilar artery, CCA = common carotid artery, ER = emergency room, ICA = internal carotid artery, Interval 1 = time interval between symptom onset and recanalization (expressed in minutes), Interval 2 = time interval between recanalization and post-recanalization imaging (expressed in minutes), IV tPA = intravenous tissue plasminogen activator, M1 = M1 segment of middle cerebral artery, M2 = M2 segment of middle cerebral artery, NIHSS = National Institutes of Health Stroke Scale, TI = territorial infarction, T-occlusion = occlusion of the carotid artery, middle and anterior cerebral artery, WI = watershed infarction.

Review of MRI images and measurement was performed by 2 authors, a radiology trainee (J.E.R) and an experienced neuroradiologist (S.K.B), in consensus. ADC values of the infarcted area and the contralateral normal structure were recorded for pre- and post-recanalization DWI in each case. Subsequently, differences between pre- and post-recanalization ADC values were calculated. Also, relative ADC (rADC) values (ADC value of the lesion divided by ADC value of the normal contralateral region) were generated, and changes in rADC values were also recorded.

Statistical Analysis

The difference between pre-recanalization and post-recanalization ADC values were compared with paired t-test. The change of ADC values in TI and WI was compared with Mann-Whitney-U test. All statistical analyses were conducted with SPSS 21.0 (IBM SPSS., Statistics, IBM Corp., Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 18 patients were analyzed in this study, including 9...
female patients and 9 male patients. The mean age of the study population was 64.39 years old (range from 45 to 77 years old), and the initial NIHSS on arrival time ranged from 1 to 28. The occlusion site of the cases and devices/method used for recanalization for each case were listed in Table 1.

The overall results were shown in Table 2. ADC values were expressed in 10 to minus 6th power of square millimeter per second (× 10⁻⁶ mm²/sec). Mean ADC values of the overall 25 lesions before IART were 415.12 × 10⁻⁶ mm²/sec, and after the IART, it was 619.08 × 10⁻⁶ mm²/sec.

Table 2. Changes in ADC Values in TI and WI

<table>
<thead>
<tr>
<th>Lesion</th>
<th>ADC_pre</th>
<th>ADC_post</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion all</td>
<td>415.12</td>
<td>619.05</td>
<td>0.000</td>
</tr>
<tr>
<td>TI</td>
<td>436.09</td>
<td>666.45</td>
<td>0.000</td>
</tr>
<tr>
<td>WI</td>
<td>261.33</td>
<td>271.67</td>
<td>0.498</td>
</tr>
<tr>
<td>Contralateral</td>
<td>743.40</td>
<td>740.80</td>
<td>0.571</td>
</tr>
</tbody>
</table>

rADC = relative apparent diffusion coefficient value (ADC value of the lesion divided by normal contralateral ADC value), TI = territorial infarction, WI = watershed (or borderzone) infarction

TI
There was a marked increase of ADC value after recanalization of TI lesions (Fig. 1). Average ADC value for 22 TI lesions before thrombectomy was 436.09 × 10⁻⁶ mm²/sec, and after the IART, it increased to 666.45 × 10⁻⁶ mm²/sec after the endovascular intervention (p < 0.000). Consequently, the relative ADC value (the ADC value measured on the infarction lesion divided by the ADC value measured at the contralateral anatomy of the infarction lesion) was also increased from 0.59 to 0.92 (p < 0.000).

One of the cases showed interesting features in the course of treatment. A 77-year-old male patient presented with dysarthria and right hemiparesis, after only 1 hour from symptom onset. Acute infarction was noted in left middle cerebral artery (MCA) territory. Intravenous tPA was indicated, but infusion could not be completed due to his uncontrollably high BP. Stenosis in distal M1 was noted on digital subtraction angiography. Recanalization of inferior division was achieved after intraarterial injection of tirofiban. However, the patient’s BP was still too unstable, so further thrombolysis was suspended after TICI 2b recanalization to prevent catastrophic hemorrhage. Follow up DWI at 50 minutes post-partial recanalization showed increased ADC in recanalized inferior division territory alone. The ADC change was well correlated with reperfusion (Fig. 2).

WI
Of the 3 WI lesions included in the study, none showed prominent increase in ADC value after IART. Mean ADC value for the 3 WI lesions was 261.33 × 10⁻⁶ mm²/sec and increased to 271.67 × 10⁻⁶ mm²/sec after the intervention (p = 0.498). WI did not show significant increase in ADC value after IART, whereas TI lesions presented marked increase in ADC values.
Fig. 2. A 77-year-old male patient with left MCA territory infarction (case no. 10). Initial DWI and ADC maps show acute infarction at the level of superior division territory of left MCA (A, B) and inferior division territory (C, D). Severe stenosis of left distal M1 is seen on pre-recanalization angiography (E). Angiography after IA injection of tirofiban (F) presents recanalization of inferior division and still occluded superior division. Post-recanalization ADC map (G) shows no remarkable change in superior division territory, but increased ADC in recanalized inferior division territory (H).

ADC = apparent diffusion coefficient, DWI = diffusion weighted imaging, MCA = middle cerebral artery

Fig. 3. Change in ADC value after full-recanalization of a WI lesion (case no. 9). Acute infarction is seen in right internal border zone (A, B). The right proximal MCA is occluded (C, left) and after successful mechanical thrombectomy (C, right), post-recanalization ADC map (D) shows no significant change in comparison with pre-recanalization image.

ADC = apparent diffusion coefficient, MCA = middle cerebral artery, WI = watershed infarction
An example case from the WI subgroup was shown in Fig. 3.

**DISCUSSION**

The key findings of our study were as follows: first, there was a substantial increase of ADC value in acute infarction lesion immediately after IART i.e., less than 4 hours after the procedure, and secondly, there was no significant change in ADC values of WI lesions, whereas TI lesions showed marked increase. The results of our study indicated changes in ADC values at the earliest stage after recanalization in human ischemic stroke; furthermore, it is the first to show different profile in changes of ADC values between TI and WI, to the best of our knowledge.

In an early study on rat MCA occlusion model, Neumann-Haefelin et al. (9) reported dynamic change of MRI characteristics of transient ischemic lesions during the reperfusion period. In the 0.5 and 1.0 hours occlusion groups, ADC value of the ischemic region increased sharply after reperfusion with secondary decline at day 1, and (pseudo) normal level at 2–3 days. However, early increase in ADC value was absent in the 2.5 hours group and started to increase at day 1 and normalized between day 2 and 7.

In another animal study of Li et al. (16), which included 16 rats with temporary MCA occlusion or sham operation, ADC values decreased significantly during occlusion, as compared with those in the contralateral regions but fully recovered after reperfusion. The ADC values remained normal thereafter in the 10-min group but declined secondarily 12 hours after reperfusion in the 30-min group. The transient or permanent resolution of DWI lesions does not necessarily indicate full tissue recovery from ischemic injury. In addition, selective neuronal necrosis was seen in the selected ROI of the rats undergoing 10 minutes of transient MCA occlusion.

Despite the relatively long time interval between onset and recanalization (average of 379 minutes, over 6 hours), the remarkable increase in ADC values after recanalization seen in our study may be comparable to those of short-term occlusion group. This discrepancy may have resulted from differences between primate and rodent, and sex and age differences of subjects included in the studies. Human ischemic strokes are usually small in volume and collateralization may affect outcome; however, rodent models may simulate malignant infarction in many cases (17). Also, molecular differences in thrombotic, inflammatory, and DNA repair cascades, as compared with primates (18) can limit direct comparison of human and rodent studies.

Secondary ADC decline could not be confirmed in our study, as in previous rodent studies (9, 16), because patients could not undergo serial MR imaging follow up as in animal studies. Subacute phase MR images might provide additional information, though it has limited use in daily practice.

DWI changes after reperfusion in ischemic stroke has been reported in human subjects. In 2000, Kidwell et al. (13) showed reversal of lesions on DWI and perfusion weighted images immediately after thrombolysis, in 7 patients treated with intravenous or intraarterial tPA.

Their study included a small number of cases treated with IA or combined IV/IA thrombolysis. Moreover, mainstream endovascular treatment for ischemic stroke is currently changed to mechanical thrombectomy. The change was described as a reversal indicating that thrombolysis could potentially normalize the ischemic lesion. Increase of ADC value after recanalization does not mean normalization of the infarcted tissue. In support, some animal studies showed that normalization of DWI lesion does not necessarily indicate tissue salvage from ischemic injury, but is associated with neuronal damage (16, 19, 20).

Recently, Inoue et al. (14) demonstrated transient reversal of DWI immediately after IART in most of the study population, using DWI Evaluation for Understanding Stroke Evolution Study-2 data. They analyzed DWI before, within 12 hours of IART and follow-up MR on day 5. In their study, early DWI reversibility was not uncommon but typically transient, and the authors suggested that early DWI reversal may result from the transient rise in ADC values after reperfusion, which is possibly related to vasogenic edema (21).

On the other hand, subjects included in our study were imaged in less than 4 hours after recanalization, so we evaluated changes in ADC values at the earlier reperfusion state. We observed a prominent ADC increase in the majority of the patients (in TI lesions); furthermore, we demonstrated different profile of ADC changes between TI and WI. However, we could not assess if the change of ADC values were transient or permanent because the small subset of patients with follow-up MR imag-
ing were not included in the analysis.

The early increase in ADC value observed in our study may reflect vasogenic edema after reperfusion. Recanalization of occluded vessels could result in reperfusion hyperemia due to the loss of autoregulation, the release of vasodilating substances, and the process of neovascularization (22). Delayed reperfusion injury may occur in the setting of reperfusion hyperemia due to oxidants or free radical damage (23).

Relationship between perfusion changes and cellular damage was investigated by Lee et al. (24), in a study using cats with 1 hour transient occlusion of MCA by clipping. They reported significant increase in TUNEL (terminal dUTP nick end labeling)-positive cells, which indicates nonspecific cellular damage including necrosis, in the groups of continuous hyperperfusion and early hyperperfusion with gradual decrease, as compared to normal perfusion and persistent hypoperfusion groups.

The second key finding of this work was that the prominent increase in ADC value seen on TI was not seen on WI lesions. Different evolution profile between WI and TI has been reported previously. Huang et al. (25) reported that ADC value increased more rapidly in the 14 TI patients, as compared to the 9 WI patients included in their study on temporal evolution of ADC values. The different pathophysiologic and hemodynamic features of the 2 infarction types are the likely cause of this difference.

In our study, the change of ADC value immediately after full recanalization in WI were not as significant as in cases of TI. While the exact pathophysiology underlying the increase of ADC value after full-recanalization remains to be determined, the change was not observed in WI as much as TI. This difference could possibly be due to the difference in pathophysiologic and hemodynamic features of the 2 types.

Our study had several limitations. The retrospective nature of the study possibly caused some degree of selection bias. Secondly, 2 patients had acquired pre-recanalization DWIs at 2 different outside hospitals, which were analyzed in the same manner as the images acquired in our own institution.

In addition, the ADC value measurement was conducted through ROI selection by the reviewer on a representative image of the case, hence the analysis was subjective. Overall average change of the ADC value of the lesion could not be assessed. Fourth, a relatively small number of WI lesions were analyzed.

Lastly, the final infarct core could not be compared with the initial lesions because only a small number of patients had follow up MR images, and thus, clinical outcome of the patients included in this study was not assessed. Further investigation with long term outcome and follow up MR imaging findings of patients who were treated with IART, as compared to untreated patients or patients treated with other methods will provide additional information.

In conclusions, ADC value was increased in acute ischemic stroke immediately after full-recanalization, on images acquired in less than 4 hours after recanalization. TI lesions showed a substantial increase in ADC values, but the increase was not seen in WI lesions.

REFERENCES


급성 허혈성 뇌경색에서 동맥내 재관류요법을 통한 재개통 직후 현성확산계수의 변화

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목적: 급성 허혈성 뇌경색에 대한 치료로 혈전 제거술은 점차 그 사용이 증가하고 있다. 그러나 재관류 직후 현성확산계수(apparent diffusion coefficient; 이하 ADC)의 변화를 주목한 연구는 많지 않았다. 본 연구의 목적은 동맥내 재관류요법(intra-arterial revascularization therapy) 직후의 현성확산계수의 변화를 연구하는 것이다.

대상과 방법: 18명의 급성 허혈성 뇌경색 환자의 25개의 병변에 대해서 동맥내 재관류요법 전과 후의 ADC값을 기록하고 비교하였다. ADC값의 측정은 대표 아미지에서 원형의 관심영역(region of interest)을 그려서 구하였다. 병변은 영역성 뇌경색(territorial infarction)과 분수령 뇌경색(watershed infarction)으로 나누어 분석하였다.

결과: 25개 병변 전체의 평균 ADC값은 동맥내 재관류요법 전 415.12 × 10⁻⁶ mm²/sec에서 619.08 × 10⁻⁶ mm²/sec로 동맥내 재관류요법 후 증가하였다. 22개의 영역성 장색 병변에서는 상대 현성확산계수(relative ADC)가 0.59에서 시술 뒤 0.92로 증가하였으나(p < 0.000), 3개의 분수령 장색 병변에서는 상대 현성확산계수의 변화가 거의 없었다.

결론: 영역성 장색에서 동맥내 재관류요법을 통한 재개통 직후에 현저한 ADC값의 증가를 볼 수 있었다. 한편, 분수령 장색의 경우 재개통 후에 ADC값에 큰 변화를 보이지 않았다.

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