Temporal Relationship Between Apparent Diffusion Coefficient and Absolute Measurements of Cerebral Blood Flow in Acute Stroke Patients

Weili Lin, PhD; Jin-Moo Lee, MD, PhD; Yueh Z. Lee, MS; Katie D. Vo, MD; Thomas Pilgram, PhD; Chung Y. Hsu, MD, PhD

Background and Purpose—Diffusion-weighted imaging (DWI) has been established as a marker of acute ischemic brain injury. We sought to determine the relationship between cerebral blood flow (CBF) and apparent diffusion coefficient (ADC) and to explore whether the elapsed time between MRI acquisition and symptom onset alters this relation in acute stroke patients.

Methods—Sixteen acute stroke patients were studied with DWI and perfusion-weighted imaging, from which ADC and CBF were calculated. ADC values were normalized (nADC) to the contralateral, nonischemic hemisphere and then correlated pixel by pixel with CBF within a region of interest defined by abnormal transit time. To explore potential temporal effects on the relationship between CBF and nADC, patients were divided into 2 groups based on the duration between symptom onset and MR imaging for data analysis: group A, 2 to 4 hours (n=8), and group B, 4.5 to 6.5 hours (n=8).

Results—nADC was plotted against CBF for each pixel in all 16 subjects, and a composite relationship was derived. After a gradual decline, an abrupt drop in nADC occurred below a CBF threshold value of 21 mL · min⁻¹ · 100 g⁻¹. When subjects were divided into early and late imaging groups, the group of patients imaged earlier (group A) had a lower threshold (15 mL · min⁻¹ · 100 g⁻¹) than the group imaged later (group B, 24 mL · min⁻¹ · 100 g⁻¹).

Conclusions—Our results demonstrate that a relationship between nADC and CBF exists in the ischemic brain and that ADC values alone may provide useful information in predicting perfusion status. However, this relationship may change with elapsing time between stroke onset and imaging. (Stroke. 2003;34:64-70.)

Key Words: cerebral blood flow ■ diagnostic imaging ■ magnetic resonance imaging ■ magnetic resonance imaging, diffusion-weighted

Diffusion-weighted imaging (DWI) has been shown capable of depicting cerebral ischemic lesions earlier than other conventional MRI sequences and imaging modalities in both animal and human studies.¹⁻³ Using a middle cerebral artery occlusion animal model, Moseley et al² observed a substantial reduction in the apparent diffusion coefficients (ADCs) within 10 to 45 minutes after occlusion. In contrast, no signal alterations were observed in the conventional T1- and T2-weighted images, indicating that DWI was able to reveal regions of ischemic insults during the hyperacute stage. Many investigators have since used DWI as a means to noninvasively depict the extent of ischemic lesions during the acute state.³⁻¹²

Given the early sensitivity of DWI for acute ischemia, there is little doubt that DWI is one of the most attractive noninvasive methods for imaging acute stroke patients. However, the lack of conclusive evidence for the biophysical mechanisms that result in signal changes on DWI in acute stroke patients has hampered the potential clinical utility of DWI. Therefore, the ability to establish a direct link between DWI and physiological parameters may prove to be of critical importance. Recently, it has been suggested that the observed reduction in ADC in acute stroke patients is indicative of a decline in CBF.¹⁻³,⁹⁻¹³⁻¹⁶ Many investigators have examined the relationship between brain perfusion status and the reduction of ADC in both acute stroke patients and animal models.⁵⁻⁸,¹³⁻¹⁶

A rather consistent observation has been reported in the literature: a drop in CBF is accompanied by a reduction in ADC.¹³⁻¹⁶ However, most studies have used a region-of-interest (ROI) approach incorporating relative measurements of cerebral blood flow (CBF), making it difficult to determine the direct and continuous relationship between ADC and CBF. Therefore, in this study, a pixel-by-pixel analysis was
used in an attempt to better depict the relationship between the absolute measurements of CBF and ADC in patients with hyperacute cerebral ischemia. Subsequently, the influence of timing of MR imaging after symptom onset on this relationship was also explored.

Materials and Methods

Patients

Patients with the following inclusion criteria were enrolled in the study: age >18 years, first acute ischemic stroke, and ability to perform MRI within 8 hours of stroke onset. Patients were excluded for the following reasons: prior stroke, bilateral strokes, baseline CT scan with evidence of hemorrhage, and contraindication for MRI. The National Institutes of Health Stroke Scale (NIHSS) score at presentation was obtained for all patients. Sixteen patients were studied after written, informed consent was obtained. All imaging experiments were approved by the Institutional Review Board at Washington University.

Magnetic Resonance Imaging

All images were acquired on a SIEMENS 1.5-T whole-body Vision scanner (Siemens AG Medical Systems Inc) with a gradient strength of 25 mT/m and a ramp time of 600 microseconds to the maximum gradient. In addition to the conventional spin-echo T1- and T2-weighted imaging sequences, an echo-planar imaging (EPI) diffusion-weighted sequence was used. Five images were obtained for each slice: 1 was for $b=0 \text{ s} \cdot \text{mm}^{-2}$, 3 were for $b=1000 \text{ s} \cdot \text{mm}^{-2}$ with the diffusion gradient along each main axis separately, and the remaining image was the average of the 3 DWI images (the trace image). The trace and the b = 0 mm²·s⁻¹ images were subsequently used to obtain ADC maps. The imaging parameters for the DWI sequence were as follows: repetition time (TR), 2 seconds; echo time (TE), 100 milliseconds; slice thickness, 6 mm with 20 slices to cover the entire brain; and field of view, 220 mm². Furthermore, a dynamic imaging approach was used to obtain perfusion-weighted images (PWIs). A 2-dimensional T2*-weighted EPI sequence was repeated 40 times with the contrast agent (0.1 mmol/kg Gd-DTPA) administered intravenously at the completion of the fifth scan. The imaging parameters for the 2-dimensional T2*-weighted EPI sequence were as follows: TR, 2 seconds; TE, 54 milliseconds; slice thickness, 6 mm with 12 slices; field of view, 220 mm²; and matrix size, 128×128. The slice positions were kept identical between the DWI and PWI so that a pixel-by-pixel comparison between the 2 data sets could be made.

ADC and CBF Estimates

All images were transferred to a Sun Workstation for postprocessing. ADC values were derived from the following equation: 

$$\text{ADC} = \ln(b_0) - \text{S}_{\text{mean}}(b=1000)/b_0,$$

where $b_0 = 0$ s mm²⁻¹ and the trace images acquired with $b=1000$ s mm⁻², respectively. CBF maps were obtained via the following equation: 

$$\text{CBF} = \ln(b_0) - \text{S}_{\text{mean}}(b=1000)/b_0.$$

ADC and CBF estimates could be obtained among all patients. More detailed descriptions delineating the correction scheme have been given elsewhere.17–20

ROI Analysis

Three contiguous mean transit time (MTT) maps at the center of the lesion were used to determine the ROIs for measurement of both ADC and CBF. For each MTT map, an ROI encompassing the entire hemisphere contralateral to the ischemic lesion was selected to obtain the mean and SD of the MTT. Pixels in the ipsilateral hemisphere with MTT values greater than the mean+2 SD were classified as MTT-defined lesions. Similar approaches were also used to determine ADC-defined lesions. An ROI on the contralateral side encompassing the mirror image of the MTT-defined lesion was also defined to obtain a measure of normal mean ADC values (ADCnormal). ADC-defined lesions were derived as pixels that have ADC values less than ADCnormal – 2 SD and within the MTT-defined lesion were classified as cerebrospinal fluid and were excluded from the data analysis. Subsequently, ADC and CBF values within the ADC- and MTT-defined lesions were measured. Furthermore, the ADC values obtained in the MTT-defined lesion were normalized to ADCnormal.

A pixel-by-pixel correlation between the normalized ADC (nADC) and CBF in the MTT-defined abnormal tissue was performed to determine the relationship between nADC and CBF. However, because of the enormous numbers of pixels within the predefined ROI, the nADC values for each CBF value were averaged first and used for the correlation between nADC and CBF.

Results

Sixteen patients with hemispheric strokes were enrolled in the study: 8 in group A (imaged ≤4 hours of symptom onset) and 8 in group B (imaged >4 but <6.5 hours after symptom onset) (see Table 1). The mean±SD age for patients was 71±8.8 years in group A and 64.5±10.0 years in group B. There were no statistically significant differences between groups, nor was the mean NIHSS different between groups (15.5±5.0 for group A and 14.9±4.7 for group B). The sex mix was also similar. All DWI lesions were within the territory of the middle cerebral artery. In addition, carotid duplex examinations, when available (12 of 16), were also

Lesion Volume Measurements

To determine whether the extent of MTT- and ADC-defined lesion volumes differs between the 2 groups, approaches identical to those mentioned previously for identifying ADC and MTT lesions were used for all ADC and MTT maps obtained so that the entire MTT- and ADC-defined lesion volumes could be obtained from each patient.

Statistical Analysis

To determine the threshold CBF value below which all nADC values were significantly lower than the normal nADC (between 50 and 60 mL · min⁻¹ · 100 g⁻¹), 95% confidence intervals for the normal nADC obtained from all patients were calculated. The CBF value corresponding to the first nADC that was below the 95% confidence interval of the normal nADC was defined as the threshold CBF. This same 95% confidence interval was also used for analysis of the 2 subgroups of patients to determine whether there was a difference in CBF threshold between groups. To explore further whether the timing of MRI after symptom onset alters the relationship between CBF and nADC, a 2-tailed t test was used to compare the nADC at each CBF value between the 2 groups so that the CBF values for which the corresponding nADC values diverged significantly between the 2 groups could be determined. The 2-tailed t test was also used for comparisons of ADC and CBF values within the MTT- and ADC-defined lesions, lesion volumes, and demographic data between the 2 groups. A value of P<0.05 was considered statistically significant.
There were 2 patients with significant carotid stenosis (1 patient in each group) and 3 patients with carotid occlusion (2 in group A, 1 in group B).

ADC- and MTT-defined lesion volumes are given in Table 2 for groups A and B. A significantly larger lesion volume was observed for MTT-defined lesion compared with that for ADC-defined lesions for both groups. However, no significant differences were observed between the 2 groups for both ADC- and MTT-defined lesion volumes.

Quantitative measures of ADC and CBF values in MTT- and ADC-defined lesions are shown in Table 3 for groups A and B, respectively. No significant differences are observed for both ADC and CBF between the 2 groups regardless of how lesion regions are defined. In contrast, when CBF values between MTT- and ADC-defined lesions are compared, a significantly lower CBF is observed for the ADC-defined lesions in group B. However, ADC values for the ADC-defined lesions for both groups A and B were significantly lower than the ADC values in the MTT-defined lesions.

Images obtained from 1 representative patient from groups A and B are shown in Figures 1 and 2, respectively. Figure 1 shows the MTT, CBF, ADC, lesion mask, and relationship between nADC and CBF from 1 patient imaged 2 hours after symptom onset. Elevated MTT and diminished CBF are observed in the left hemisphere, whereas the area of reduced ADC appears to be smaller than that of the abnormal CBF and MTT. A gradual reduction in nADC is observed for CBF $\geq 18 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ and below which a marked reduction in nADC is seen. In contrast, Figure 2 shows the same parameters as those in Figure 1 from 1 patient imaged 6 hours after symptom onset. Similar to the patient shown in Figure 1, an increase in MTT and a decrease in CBF and ADC are observed. A gradual reduction in nADC is also seen with decreasing CBF. However, the CBF threshold at which an abrupt decline in nADC is noted appears to be higher ($\geq 26 \text{ mL} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$) in this patient (scanned 6 hours after stroke onset) compared with that observed in Figure 1.

The relationship between CBF and nADC when all patients were analyzed as a group is shown in Figure 3. Error bars indicate the intersubject variability, and the lines represent 95% confidence intervals of the normal nADC (CBF between 50 to 60 mL $\cdot \text{min}^{-1} \cdot 100$ g$^{-1}$). Consistent with the results shown in Figures 1 and 2, a gradual reduction in nADC is seen with reducing CBF in the mild ischemic range. A marked decline in nADC occurs when CBF falls below 21

<table>
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<th>Table 1. Results of Study Groups</th>
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<tr>
<td>Patient</td>
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<tr>
<td><strong>Group A</strong></td>
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<td>1</td>
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<td>2</td>
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<td>3</td>
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<tr>
<td><strong>Group B</strong></td>
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<tr>
<td>8</td>
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<tr>
<td><strong>Mean±SD</strong></td>
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| ND indicates nonsignificant disease; ICA, internal carotid artery; NP, not performed; SD, standard deviation. |

<table>
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<tr>
<th>Table 2. Lesion Volumes</th>
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<tr>
<td>ADC-Defined Lesion, cm$^3$</td>
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<tr>
<td><strong>Group A</strong></td>
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<td><strong>Group B</strong></td>
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ADC indicates apparent diffusion coefficient; MTT, mean transit time.

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<th>Table 3. Quantitative Values</th>
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<td>CBF, mL/min/100 g</td>
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<td>-------------------</td>
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<tr>
<td><strong>Group A</strong></td>
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<tr>
<td>ADC lesion</td>
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<td>MTT lesion</td>
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*P<0.043 between ADC- and MTT-defined lesions.
†P<0.0001 between ADC- and MTT-defined lesions.
mL · min⁻¹ · 100 g⁻¹, corresponding to the first nADC value (89% of the normal nADC) that is below the 95% confidence level. The patients were then divided into 2 groups based on the duration between stroke onset and MR imaging for data analysis. The relationships between nADC and CBF for both groups are shown in Figure 4. The general pattern of the 2 curves is similar to that shown in Figure 3 for all subjects: a gradual reduction in nADC with diminished CBF in the mild ischemia range followed by a marked reduction in nADC with a further decline in CBF beyond a threshold. The CBF threshold at which a steep drop in nADC occurs is 15 mL · min⁻¹ · 100 g⁻¹ for group A (imaged earlier) compared with 24 mL · min⁻¹ · 100 g⁻¹ for group B. The solid box in Figure 4 indicates the CBF range (P<0.05) at which a significant divergence occurred between the 2 groups.

Discussion
The major finding of this study is that nADC values change with respect to CBF in a predictable manner during human cerebral ischemia. Normalized ADC values declined gradually with reducing CBF in the mild ischemic range but fell much more sharply at a CBF threshold of 21 mL · min⁻¹ · 100 g⁻¹ when all patients were analyzed as group. In contrast, when patients were divided into 2 groups based on the duration between symptom onset and imaging, this CBF threshold differs between the 2 groups: 15 mL · min⁻¹ · 100 g⁻¹ for patients imaged earlier (group A) and 24 mL · min⁻¹ · 100 g⁻¹ for patients imaged later (group B). Thus, the relationship between CBF and nADC appears to be time dependent, with the threshold noted at a higher CBF level if imaging was conducted longer after ischemic onset.

The CBF threshold for nADC change found in our study is in agreement with that in other reports in the literature. Busza et alⁿ found a sharp increase in DWI signal intensity at CBF values <20 mL · min⁻¹ · 100 g⁻¹ in gerbils using a hydrogen clearance polarized technique for measuring CBF, consistent with our findings when all patients were analyzed as a group. Others⁷,⁸ have reported a more gradual, linear relationship between brain perfusion reduction and nADC decline in animal models. It is conceivable that differences between species may account for the observed discrepancies; however, the study by Pierce et al⁸ reported a linear relationship only between a perfusion index of 0.28 and 0.6, whereas no relationship was observed beyond this preselected range. Assuming that normal CBF in humans is 50 mL · min⁻¹ · 100 g⁻¹, the range of CBF investigated by Pierce et al⁸ would reflect values between 14 and 30 mL · min⁻¹ · 100 g⁻¹, consistent with the linear range found in our study. In contrast, Roberts et al⁹ found a linear relationship between ADC and perfusion index at 1 and 6 hours after ischemic onset in cats. However, most of the data points were obtained within 90% to 100% of the normal ADC values, making it difficult to compare those results directly with our results. Moreover, their results also indicated that a 10% reduction in ADC values could be associated with a reduction in perfusion index between 40% and 100%. Therefore, despite the fact that the authors reported a linear relationship, ADC values remained relatively stable across a wide perfusion index (100% to 40%), in good agreement with our findings.
ischemia animal model, reported that a 30% depletion of ATP occurred at a CBF value of 20 mL \( \cdot \) min\(^{-1} \) \( \cdot \) 100 g\(^{-1}\) and 50% at a CBF of 10 mL \( \cdot \) min\(^{-1} \) \( \cdot \) 100 g\(^{-1}\). Using similar approaches, Hoehn-Berlage\(^{28}\) also reported that a 32% depletion of ATP took place at a CBF of 18 mL \( \cdot \) min\(^{-1} \) \( \cdot \) 100 g\(^{-1}\). Moreover, the CBF threshold for electrical failure lies in close approximation to the large-scale release of excitatory amino acids into the extracellular fluid space (estimated at 20 mL \( \cdot \) min\(^{-1} \) \( \cdot \) 100 g\(^{-1}\))\(^{26}\) and early tissue edema formation (astrocytes swelling as a consequence of their removal of lactate and excitatory amino acids from the extracellular space).\(^{30–32}\) Therefore, our results appear to support the generally held view that diffusion abnormality observed in acute stroke patients is indicative of the cellular dysfunction in response to diminished CBF.

**Temporal Effects on the Relationship Between nADC and CBF**

The temporal effect on the relationship between CBF and nADC is reflected by the observed difference between the early and late imaging in CBF thresholds at which a steep drop in nADC begins. As shown in Figure 4, although the shape of the curves representing this relationship is similar between the groups, the overall curve of group A is shifted to the left compared with that of group B. When a 2-tailed \( t \) test is used, significant differences in nADC reduction are also observed between the groups in the CBF range of 10 to 16 mL \( \cdot \) min\(^{-1} \) \( \cdot \) 100 g\(^{-1}\). Thus, the inflection point, ie, the CBF value at which the association between nADC and CBF changes from linear to constant, was lower in the early imaging than in the late imaging group, suggesting a temporal dependence of the relationship between nADC and CBF.

**Technical Considerations**

Several caveats in our study need to be addressed. First, coregistration was not performed between the ADC and CBF maps. However, anatomic landmarks (ventricles and sulci) were carefully examined between the DWI and PWI during data analysis. Although some misregistration between ADC and CBF maps was observed in some patients (2 of 16), it was minimal and should not result in substantial errors in our study. In addition, because a large number of pixels were included in the data analysis, errors that may have been induced by misregistration would be minimal. Second, temperature, well known to affect ADC values especially under conditions of severe ischemia,\(^{33–35}\) was not factored into our ADC map calculations. Nevertheless, brain temperature changes induce minimal alterations in ADC during cerebral ischemia and therefore should not alter the conclusions of our study.\(^{33}\) Third, the pixel-by-pixel analysis used in this study is likely to affect the experimentally derived relationship between nADC and CBF. When ischemic lesions are large, averaging nADC values that have the same CBF substantially minimizes variability for the relationship between CBF and nADC. In contrast, when lesion volume is small, a large variability may be observed. Nevertheless, as shown in Table 2, no significant differences were observed for both the MTT- and ADC-defined lesion volumes between the 2 groups.
Therefore, the potential variability of lesion volumes should not affect the conclusions of this study. Fourth, blood gas information was not available in our study, which could potentially alter the relationships between nADC and CBF. More studies are needed to further consider the potential effects of blood gases. Finally, it is well known that CBF values are different between gray matter and white matter. Therefore, a more appropriate approach of determining the relations between CBF and nADC is to analyze gray matter and white matter separately. Unfortunately, the limited spatial resolution of the EPI images has made it difficult to accurately separate gray matter from white matter. Given the improved technology of gradient coils, it is likely that higher-resolution EPI images can be obtained in the near future while a sufficient signal-to-noise ratio is maintained. More studies are required to determine whether the relationship between CBF and nADC differs for gray and white matter.

Although quantitative estimates of CBF through dynamic imaging approaches have been demonstrated, little attention has been focused on the accuracy of CBF estimates under pathophysiological conditions. To this end, we have recently reported results from the comparison of MRI-measured CBF (through dynamic imaging approaches and postprocessed via SVD) with that obtained through PET (using $H_2O^{15}$) in patients with unilateral carotid artery occlusion. With a correction algorithm based on the area of the concentration-time curves obtained from the superior sagittal sinus, a highly linear relationship between MRI- and PET-measured CBF was obtained (slope, 1.02; $r=0.8$ for the linear regression line). In the present study, the previously proposed correction scheme was used to obtain quantitative estimates of CBF in stroke patients, allowing a direct comparison of CBF and nADC.

To explore the potential effects of timing of MRI and symptom onset on the relationship between nADC and CBF, we have arbitrarily divided patients into 2 distinct groups for data analysis. Clearly, with the observed temporal effects, the best approach is to analyze the data in a continuous fashion rather than with the discrete approach used here. However, this will require a much larger sample size than the current studies with patients having different intervals between MRI and symptom onset. Therefore, interpreting the observed critical CBF values below which a significant reduction in nADC occurred should take into account the time intervals evaluated in our studies. A more extensive study with a larger sample size is required to further determine the temporal dependence of nADC reduction in relation to CBF decline.

Finally, PWI provides an estimate of CBF, and DWI has been widely used in the setting of acute stroke. However, a major limitation associated with this approach is the long postprocessing times required to calculate CBF measures, making it difficult to provide an immediate assessment of CBF in acute stroke patients. In contrast, obtaining ADC maps is relatively quick and simple; thus, establishing a relationship between ADC and CBF in acute stroke patients can potentially be of clinical importance. In this study, a pixel-by-pixel analysis was used to investigate the temporal relationship between the absolute measurements of CBF and ADC in patients with hyperacute cerebral ischemia.

Acknowledgment

This work was supported in part by NIH grant NS37312. We would like to thank Dr Leif Ostergaard for providing us the source code for CBF calculation.

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Stroke. 2003;34:64-70; originally published online December 12, 2002;
doi: 10.1161/01.STR.0000048151.28173.0D
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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