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Abbreviations:

ADC = apparent diffusion coefficient
DW = diffusion weighted
TI = thromboembolic infarction
WI = watershed infarction
rT2 = T2 ratio

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Time Course of Cerebral Infarction in the Middle Cerebral Arterial Territory: Deep Watershed versus Territorial Subtypes on Diffusion-weighted MR Images¹

PURPOSE: To examine possible differences between the evolution of cerebral watershed infarction (WI) and that of territorial thromboembolic infarction (TI) by using diffusion-weighted (DW) and T2-weighted magnetic resonance (MR) images and apparent diffusion coefficient (ADC) maps.

MATERIALS AND METHODS: Fourteen patients with TI and nine with WI underwent MR imaging from the acute to chronic infarction stages. ADC maps were derived from DW images. Lesion-to-normal tissue signal intensity ratios on ADC maps (rADC), echo-planar T2-weighted images, and DW images were calculated. Lesion volumes at acute or early subacute infarction stages were measured on DW images, and final lesion volumes were estimated on fluid-attenuated inversion-recovery images.

RESULTS: Analysis of variance revealed a significant difference in temporal evolution patterns of rADC between WI and TI ($P < .001$). rADC pseudonormalization following TI began about 10 days after symptom onset, but that following WI did not occur until about 1 month after symptom onset. The Pearson correlation coefficient between final and initial infarct volumes was 0.9899 for both infarction subtypes, indicating that the initial ischemic injury volume measured at the acute or early subacute stage predicted the final lesion volume fairly well.

CONCLUSION: The evolution time of ADC is faster for TI than for WI. This difference, which likely originates from the different pathophysiologic and hemodynamic features of the two infarction types, might account for the relatively large range of ADC values reported for the time course of ischemic strokes.

The time course of signal intensity changes on diffusion-weighted (DW) images reported for strokes occurring in humans varies greatly (1–5). For example, Warach et al (1) examined 40 patients with cerebral ischemia and reported pseudonormalization of diffusion abnormality at 5–10 days following ischemic attack. With a larger patient group, Burdette et al (2) found no signal intensity abnormality on DW images of stroke lesions until 2 or more weeks after the initial onset of symptoms. In a study performed by Schwamm et al (3) involving 14 patients, apparent diffusion coefficients (ADCs) did not return to normal until 42 days after stroke symptom onset. Although evolutions of infarction may differ according to the cerebral territories involved, to our knowledge they have not been studied before. It is perhaps more important that alterations in the underlying hemodynamics also might influence the temporal profiles of ADC evolution, as has been reported with animal models of cerebral ischemia (6,7).

Deep watershed infarction (WI) typically occurs in the supraganglionic periventricular

white matter within the border zones of a single territory of one major artery (8–10). In contrast to patients with territorial thromboembolic infarction (TI), patients with WI often have a history of transient ischemic attack (8,11), generally have better outcomes (11), and, most important, do not benefit from acute stroke interventions such as intravenous administration of recombinant tissue-type plasminogen activator (12). Because the hemodynamic evolution of WI is pathogenetically different from that of the thromboembolic territorial subtype (9,11,13), the time course of signal intensity changes on DW magnetic resonance (MR) images of these infarction subtypes also may vary. If this difference in signal intensity time courses can be explained, the information may help us better understand the pathogenetic mechanisms of these infarctions and help us establish the best therapeutic strategies for the different subtypes of cerebral infarctions.

The purpose of this study was to examine the possible differences between the evolution of cerebral WI and the evolution of TI in the middle cerebral arterial territories by using DW MR images, T2-weighted MR images, and ADC maps. The ischemic evolutions of these infarction subtypes were compared by following up patients from the acute to chronic stages of infarction.

MATERIALS AND METHODS

Patients

A cohort of 23 consecutive patients with acute ischemic strokes were prospectively examined for 18 months. Four patients were examined within 6 hours; seven, within 6–48 hours; 11, within 3–4 days; and one, within 7–8 days after the onset of ischemic symptoms. Patients were selected according to the following criteria: definite clinical diagnosis of stroke, time of stroke symptom onset determinable by using medical history, persistent neurologic deficits, and unilateral infarction.

Patients who had negative MR imaging results, symptoms of recurrent stroke, or ischemic stroke in a territory other than the middle cerebral artery or who showed evidence of acute cerebral hemorrhage were excluded from the study. One patient with cortical WI between the territories of the left middle and posterior cerebral arteries also was excluded. Because any acute stroke intervention may affect the evolution of the ischemic brain tissue, only those patients who did not

receive thrombolytic treatment or medications that contained neuroprotective agents were included. All the patients who underwent MR examinations in this study received only conservative treatments.

Three to five sequential MR images were obtained in each patient at predetermined intervals after study enrollment: Three patients with TI and one with WI underwent imaging at the hyperacute stage—6 or fewer hours after stroke symptom onset; four patients with TI and three with WI, at the acute stage—more than 6 hours and 2 or fewer days after onset; 11 patients with TI and seven with WI, at the early subacute stage—3–4 days after onset; 10 patients with TI and six with WI, at the late subacute stage—7–9 days after onset; 12 patients with TI and eight with WI, at the early chronic stage—10–15 days after onset; and 12 patients with TI and nine with WI, at the late chronic stage—30–31 days after onset. The total number of MR examinations was 86 (Table 1).

We determined the TI or WI subtype by using DW imaging according to the templates of Bogousslavsky and Regli (10) and the atlas of Damasio (14). TI was defined as the presence of an ischemic lesion that involved both the cortical and subcortical areas and was restricted to the unilateral middle cerebral arterial territory. WI was defined as the presence of an ischemic lesion in the subcortical white matter within the border zones between the superficial branches and the deep perforators of the same middle cerebral artery. Informed consent for participation in the study was obtained from patients or their families. The MR imaging protocols for this ischemic cerebral stroke study were approved by the institutional review board of Tri-Service General Hospital, Taipei, Taiwan, Republic of China. MR imaging was performed in all subjects by using a 1.5-T unit (Magnetom Vision+; Siemens, Erlangen, Germany).

Imaging Parameters

Whole-brain DW images were obtained by using a multisection single-shot echo-planar DW sequence. The imaging parameters were 4,700/120 (repetition time msec/echo time msec), 256×256 matrix, 230-mm field of view, 5-mm section thickness, 1.5-mm inter-section gap, and 20 sections obtained in one acquisition. To avoid the anisotropy phenomenon that occurs in cerebral white matter (15), DW factors b of 0 and 1,000 sec/mm² were applied at the three

orthogonal gradient axes (section selection, phase encoding, and readout) to acquire four images. The images were then transferred to a workstation for the calculation of ADC maps. The total imaging time was about 23 seconds. T2-weighted images with cerebrospinal fluid suppression also were obtained by using a fluid-attenuated inversion-recovery technique (9,000/110; inversion time, 2,500 msec) to assess the final infarct volume.

Data Analysis

The calculation of ADC was based on the equation used by Stejskal and Tanner (16): $ADC = -\{[\ln(S_1 - S_2)]/(b_1 - b_2)\}$, where $\ln$ is the natural logarithm function and S_1 and S_2 are the signal intensities on DW images applied with DW factors 1 (b_1) and 2 (b_2), respectively. The ADC maps were computed on a pixel-by-pixel basis by averaging the ADCs obtained from the three orthogonal directions (section selection, phase encoding, and readout), that is, as the trace of the diffusion tensor. To avoid intersubject differences in ADCs caused by factors that might affect the absolute ADC values (such as brain topography, temperature, and iron concentration), ADC changes in ischemic regions were evaluated as the relative ADC, or ADC ratio (rADC)—that is, the mean ADC of the ischemic lesion as a percentage of the ADC of the normal contralateral homologous region (ie, lesion-to-normal tissue signal intensity ratio) (17,18) (Table 2).

Similarly, the contrast between the ischemic lesion and the normal brain parenchyma measured on DW images was expressed as a ratio of lesion-to-normal tissue signal intensity (rDW) (Table 3). A doctoral student (I.J.H.) manually drew regions of interest to encircle the entire lesion encompassing the ischemic core and the peripheral area; these regions were confirmed by one of the neuroradiologists (C.Y.C. or C.C.L.). The regions of interest determined at the acute stage of stroke were based on findings on DW images with a b of 1,000 sec/mm² that revealed the most conspicuous contrast between ischemic lesions and normal areas. The region-of-interest measurements obtained at later stroke stages were based on findings on DW images with a b of 0 sec/mm² (intrinsically T2 weighted). In our experience, this procedure enables robust measurements that substantially reduce the variances in intra- and inter-operator definitions of the infarction core that result from the intrinsic heterogeneity of signal intensities of ischemic

TABLE 1
Clinical and Longitudinal MR Data in 23 Patients with Middle Cerebral Artery Infarction

Patient No./ Sex/Age (y)*	Stroke Stages when MR Imaging Performed†	Total No. of MR Examinations	Progression of Stroke
1/M/20	AC, ES, EC, LC	4	Yes
2/M/80	AC, LS, EC, LC	4	No
3/M/67	ES, LS, EC, LC	4	No
4/M/51	AC, LS, EC, LC	4	No
5/M/61	ES, EC, LC	3	No
6/M/51	ES, LS, EC, LC	4	Yes
7/F/34	LS, EC, LC	3	No
8/F/52	HA, ES, LS, EC, LC	5	No
9/M/67	HA, ES, EC	3	Yes
10/M/85	HA, ES, LS	3	No
11/F/71	ES, LS, LC	3	No
12/F/41	ES, LS, EC, LC	4	No
13/F/35	AC, ES, LS, EC, LC	5	No
14/M/54	ES, EC, LC	3	Yes
15/M/69	ES, LS, EC, LC	4	Yes
16/F/48	AC, EC, LC	3	No
17/F/66	ES, EC, LC	3	No
18/F/81	ES, LS, EC, LC	4	No
19/M/81	HA, ES, LS, EC, LC	5	Yes
20/F/69	ES, LS, EC, LC	4	Yes
21/F/57	AC, LS, EC, LC	4	No
22/M/71	ES, EC, LC	3	No
23/F/59	AC, ES, LS, LC	4	Yes

* Patients 1–14 had TIs, and patients 15–23 had deep WIs.

† AC = acute, EC = early chronic, ES = early subacute, HA = hyperacute, LC = late chronic, LS = late subacute.

TABLE 2
rADC Values Obtained at Hyperacute to Late Chronic Stroke Stages

Patient No.	Hyperacute	Acute	Early Subacute	Late Subacute	Early Chronic	Late Chronic
1	NA	0.592	0.694	NA	1.036	2.084
2	NA	0.490	NA	0.920	1.859	2.599
3	NA	NA	0.558	0.725	1.013	2.127
4	NA	0.520	NA	0.661	1.547	2.599
5	NA	NA	0.599	NA	0.655	2.142
6	NA	NA	0.590	0.848	1.263	1.637
7	NA	NA	NA	0.937	1.549	1.958
8	0.664	NA	0.540	0.763	1.506	2.310
9	0.325	NA	0.679	NA	1.231	NA
10	0.841	NA	0.850	1.230	NA	NA
11	NA	NA	0.734	0.859	NA	1.023
12	NA	NA	0.533	0.667	0.882	1.483
13	NA	0.430	0.536	0.655	0.601	1.022
14	NA	NA	0.602	NA	1.376	1.920
15	NA	NA	0.581	0.585	1.054	1.313
16	NA	0.650	NA	NA	0.936	1.388
17	NA	NA	0.647	NA	0.779	1.007
18	NA	NA	0.485	0.536	0.761	0.802
19	1.033	NA	0.348	0.578	0.918	1.097
20	NA	NA	0.383	0.496	0.542	0.445
21	NA	0.678	NA	0.552	0.637	0.73
22	NA	NA	0.802	NA	0.859	1.377
23	NA	0.552	0.644	0.777	NA	1.284

Note.—NA = not applicable because MR imaging was not performed at the given stroke stage.

contralateral normal area, a region of the same size that was homologous to the ischemic region was selected. In unusual cases in which the contralateral normal area contained substances that might affect ADC calculations (eg, cerebrospinal fluid), a neighboring area that comprised both white matter and gray matter was used instead.

The effect of T2 (17,19) on images and its time course were evaluated by using DW images with a b of 0 sec/mm²—that is, the intrinsically T2-weighted echo-planar images with minimal diffusion weighting. Echo-planar T2-weighted images were chosen to avoid image registration when the evolution times of ADC and T2 were compared, because the echo-planar images with a b of 0 sec/mm² and a b of 1,000 sec/mm² showed the same degree of geometric distortion. Regions of interest that represented the ischemic and normal regions were then derived from regions of interest that were defined previously on the DW images. The relative T2, or T2 ratio (rT2), defined as the ratio of ischemic lesion signal intensity to contralateral homologous region signal intensity at T2-weighted imaging, was subsequently derived as a measure of the effects of T2 on DW images (17,19) (Table 4).

The infarct volumes at the acute or early subacute stage of stroke were measured manually on the DW images with a b of 1,000 sec/mm² by the doctoral student (I.J.H.), whereas the final infarct volumes were estimated on the T2-weighted fluid-attenuated inversion-recovery images to take advantage of the conspicuous distinction between ischemic infarctions and cerebrospinal fluid demonstrated by using this method. MR imaging volume measurements were performed by using a previously described (20) planimetric method. A comparison of the initial and final infarct volumes between the two subtypes of infarction was then performed. The MR imaging data obtained at the hyperacute stroke stage in four patients were analyzed separately, because ischemic penumbral regions may have normal diffusion during the hyperacute stroke stage (20,21).

Repeated-measures analysis of variance was performed to examine the significant differences between the two infarction subtypes and between the stages of MR examination as measured by using rDW, rT2, and rADC values. The findings of post hoc comparisons between stages within each subtype group were analyzed by using the Tukey wholly significant difference tests (22), which are known to give more accurate experiment-wise type

lesions. The defined regions of interest were then copied and transferred to ADC maps to obtain mean ADC values.

Hemorrhagic foci, if present in the infarctions at the time of follow-up imag-

ing, were not included in the regions of interest, because their presence resulted in susceptibility-related signal loss that could invalidate the computation of ADC values. To measure the ADC value of the

I error rates, as compared with other tests. (Note: experiment-wise type I error rates measure the significance level associated with multiple tests using the same data set.) Finally, the relationship between lesion volumes measured at the acute stroke stage and those measured at the late chronic stage was examined by using the Pearson correlation coefficient.

RESULTS

When the signal intensity on DW images was compared as a single parameter, the TI and WI subtypes both showed markedly hyperintense tissue relative to the normal brain tissue at the acute and early subacute stroke stages (Figs 1, 2)—with mean rDW values of 2.53–2.60 and 2.05–2.65, respectively—and less hyperintense tissue relative to the normal brain tissue at the early chronic to late chronic stroke stages—with decreasing mean rDW values of 1.64–1.31 and 1.79–1.82, respectively (Fig 3). Raw rDW, rADC, and rT2 data for each patient are listed in Tables 2–4. The rDW values for the two infarction subtypes were only marginally different at the late subacute and late chronic stages ($P < .05$).

The ADC time courses revealed on ADC maps for the two infarction subtypes, however, were significantly different. Compared with TIs, WIs had a longer ADC decline duration, spanning from the acute to early chronic stages, and had only a mild increase in ADC value at the late chronic stage (Fig 4). Two-way analysis of variance results showed that the two types of infarction interacted significantly ($P < .001$) with the stages at which MR examinations were performed; these findings indicated that the evolution time of rADC between TI and WI was significantly different. Particularly, the ADC pseudonormalization for TI commenced during the period between the late subacute and early chronic stages, which corresponded roughly to about 10 days after stroke symptom onset. On the other hand, pseudonormalization of ADC in the patients with WI did not occur until about 1 month after stroke symptom onset.

The findings of post hoc comparisons performed by using Tukey wholly significant difference tests showed that differences in rADC between the two subtypes were statistically significant ($P < .01$) at the late subacute to chronic stages. Statistical test results further showed that rADCs for the two infarction subtypes were different at the hyperacute stage

TABLE 3
rDW Values Obtained at Hyperacute to Late Chronic Stroke Stages

Patient No.	Hyperacute	Acute	Early Subacute	Late Subacute	Early Chronic	Late Chronic
1	NA	2.381	2.513	NA	1.542	1.354
2	NA	2.574	NA	1.970	1.233	0.930
3	NA	NA	2.868	2.746	1.472	1.192
4	NA	2.882	NA	2.550	1.602	0.831
5	NA	NA	2.584	NA	2.700	1.328
6	NA	NA	2.978	2.576	1.246	1.330
7	NA	NA	NA	2.132	1.746	1.334
8	1.879	NA	3.057	1.900	1.187	0.864
9	1.962	NA	2.272	NA	1.419	NA
10	1.112	NA	2.249	1.803	NA	NA
11	NA	NA	2.652	1.868	NA	2.029
12	NA	NA	2.184	1.614	1.408	2.030
13	NA	2.277	2.601	2.240	2.638	1.837
14	NA	NA	2.577	NA	1.572	1.301
15	NA	NA	2.655	2.784	1.644	1.648
16	NA	2.242	NA	NA	2.100	1.674
17	NA	NA	2.861	NA	1.709	2.091
18	NA	NA	2.670	2.801	1.789	1.717
19	1.028	NA	2.566	2.766	1.673	2.304
20	NA	NA	2.482	2.490	2.288	2.496
21	NA	1.406	NA	2.109	1.683	1.633
22	NA	NA	1.896	NA	1.288	1.496
23	NA	2.495	3.392	3.017	NA	1.326

Note.—NA = not applicable because MR imaging was not performed at the given stroke stage.

TABLE 4
rT2 Values Obtained at Hyperacute to Late Chronic Stroke Stages

Patient No.	Hyperacute	Acute	Early Subacute	Late Subacute	Early Chronic	Late Chronic
1	NA	1.809	2.027	NA	1.583	2.860
2	NA	1.701	NA	1.855	2.281	2.840
3	NA	NA	2.052	2.217	1.485	2.633
4	NA	2.043	NA	2.000	2.308	2.490
5	NA	NA	1.910	NA	2.137	2.918
6	NA	NA	2.197	2.239	1.600	2.451
7	NA	NA	NA	1.785	1.785	2.695
8	1.461	NA	2.105	1.542	1.733	2.484
9	1.189	NA	1.775	NA	1.681	NA
10	0.993	NA	2.035	2.137	NA	NA
11	NA	NA	2.139	1.670	NA	2.069
12	NA	NA	1.573	1.298	1.296	1.908
13	NA	1.556	1.868	1.783	2.051	1.870
14	NA	NA	2.952	NA	1.796	2.957
15	NA	NA	2.111	2.050	1.707	2.043
16	NA	1.724	NA	NA	1.999	2.193
17	NA	NA	2.342	NA	1.468	2.101
18	NA	NA	1.689	1.891	1.478	1.457
19	1.052	NA	1.617	2.035	1.572	2.483
20	NA	NA	1.423	1.602	1.500	1.429
21	NA	1.134	NA	1.536	1.319	1.352
22	NA	NA	1.648	NA	1.172	1.938
23	NA	1.839	2.698	2.583	NA	1.620

Note.—NA = not applicable because MR imaging was not performed at the given stroke stage.

($P < .05$). This finding at this level of significance is weak, because it is based on only one WI case at the hyperacute stage: This single case does not suggest that all WI lesions should show a normal ADC at the hyperacute stage.

The T2 shine-through effects on DW images were present from the acute to

chronic stages with both WI and TI (Fig 5). This T2 contribution to the signal intensity enhancement on DW images reached a maximum level (mean rT2 value, 2.51) at the chronic stage with TI, but it remained steady from the early subacute to chronic stages with WI (mean rT2 value, 1.81). The difference in

Figure 1. Time course of TI of the right middle cerebral artery, as demonstrated on T2-weighted (4,700/120) (top row) and DW (middle row) MR images and on ADC maps (bottom row) at 5 hours (first image from the left), 3 days (second image from the left), 7 days (third image from the left), and 30 days (fourth image from the left) after stroke symptom onset in a 52-year-old patient. On the DW images, the infarction lesion shows a similar degree of hyperintensity (arrows) on days 3 and 7. The corresponding ADC maps, however, show markedly different diffusion abnormalities (arrowheads), as characterized by a substantial decline in ADC on day 3 and seemingly normal diffusion on day 7. This difference in appearance between DW images and ADC maps is due to the T2 shine-through effect on the DW images, as evident on the T2-weighted image obtained on day 7. On day 30, the normalized signal intensity on the DW image is due to an increased ADC and the T2 effect of the lesions.

intrinsic T2 (rT2) between the two infarction subtypes was significant only at the late chronic stage ($P < .01$).

With both types of infarction, the final infarct volumes measured at the late chronic stage were slightly decreased compared with the initial infarct volumes measured at the acute or early subacute stage. The Pearson correlation coefficient between initial and final infarct volumes was 0.9899. The bivariate plot in Figure 6 shows such a linear relationship, which implies that the initial size of the ischemic injury measured at the acute or early subacute stage predicted the final lesion volume fairly well. However, this was not the case when the final infarct volumes were compared with the infarct volumes measured at the hyperacute stage. In four patients (three with TI and one with WI) who underwent initial MR imaging at the hyperacute stage (<6 hours after stroke symptom onset), a sig-

nificant increase in final infarct volume ($\geq 40\%$) was noted between the hyperacute and late chronic stages. One patient who underwent MR imaging 6 hours after symptom onset had a final infarct volume increase of 83% relative to the size of the initial abnormality at DW imaging.

DISCUSSION

Hemodynamically induced WIs, which account for 5%–10% of all ischemic cerebral strokes diagnosed by using computed tomography (CT) (11,13), may occur between the territories of two major arteries or within a single territory in the supraganglionic white matter, a border zone of the superficial and deep penetrating arterioles. WI is distinct from territorial cortical infarction owing to its unique pathogenesis and topographic and epidemiologic features.

The differentiation and characterization of these two infarction subtypes are important for clinical treatment strategies. For instance, TI can be effectively treated within the first 3 hours after symptom onset by using thrombolytic therapy (23,24). In WI, because the basic pathogenesis is a critical reduction in brain perfusion in response to stenosis or occlusion of major brain-supplying arteries distant from the infarction, acute thrombolytic therapies are not considered to be effective and may even lead to life-threatening hemorrhages (12). Moreover, in early multicenter trials, the failure of external carotid-internal carotid bypass surgery for treatment of patients with hemodynamically caused transient ischemic attacks suggests that more studies on WI are needed to determine better treatment strategies (25). Our study data demonstrate the distinct dynamic course of progressive ischemic brain injury in WI, which is different from that of TI. This difference suggests that all neuroprotective measures should be individualized for ischemic brain injuries according to the different pathophysiologic features.

Ischemia-sensitive DW MR imaging has been performed extensively in research to characterize the evolution of cerebral ischemia as new treatments for acute stroke have become available (1,3,26). Previously published data regarding the time course of cerebral infarction have shown typical sequential signal-intensity changes in ischemic brain tissue on DW images obtained at different stroke stages (2–4). When the signal-intensity changes on DW images were studied as a single parameter, abnormally high signal intensity was constantly observed at the acute and subacute stages of cerebral infarction (2,17). This abnormal signal intensity increased with time and then declined 2 weeks after symptom onset (2,27).

However, imaging factors other than the time of the infarction, such as the ADC value and the intrinsic T2 effect, also may substantially affect the signal intensity on DW images. Previously reported ADC values, although consistently decreased at acute cerebral infarction, have been quite variable at the subacute stage, with values from low or normal to elevated, as compared with the ADC values of the normal brain parenchyma (1–5,18). This difference in ADC values for strokes occurring in humans was once explained as being related to the use of different measurement and analysis techniques, such

as the directions and strengths of diffusion-sensitizing gradients (2).

The data from the present study show a trend in ADC evolution: an initial decline in values and subsequent pseudo-normalization with both subtypes of infarction; this finding is consistent with previously published results (1,18,26). Such a trend, however, occurred earlier in the time course of TI than in that of WI in the present study. The ADC decline persisted until the late chronic stage of WI (≥ 30 days after symptom onset); this finding is qualitatively consistent with the report by Schwamm et al (3). However, the ADC normalized at the early chronic stage of TI (10–15 days after symptom onset); this finding is in agreement with that in the previous investigation by Warach et al (1).

Our study results indicate that the time courses of ischemic strokes are different among subtypes. The inconsistency in ADC changes reported in previous studies could therefore be the consequence of enrolling subjects with different subtypes of infarction. Moreover, variations among subjects with the same subtype of infarction can exist if longitudinal follow-up studies are not used (2). In our study, data were obtained from longitudinal MR imaging examinations performed in patients who had the same subtypes of infarction. Therefore, the time courses of changes in ADC were more accurately determined.

To our knowledge, the mutual effects of T2 and ADC value on the final signal intensity on DW images of each subtype of acute cerebral infarction have not been reported before. In our study, the subtype-dependent time course of cerebral infarction was observed on the ADC maps rather than on the DW images themselves. The similarity in rDW time courses with TI and WI shown in Figure 3 indicates that the specificity of DW images in depicting ADC evolution is substantially lower due to the T2 shine-through effect (17). Therefore, although DW imaging alone has been demonstrated to be accurate in the identification of early cerebral infarctions (where ADC decreases and T2 increases) (28,29), our study data again support the conclusion that a calculation of ADC maps is crucial in this regard. The T2 shine-through effect on DW images, as evident in Figure 5, may mask important clinical information to different extents, depending on the time progression of ischemic injury. Due to variations in ADC evolution (4), careful quantification is especially important in acute stroke treatment when the duration of ischemic

Figure 2. Time course of WI of the left middle cerebral arterial territory, as depicted on T2-weighted (4,700/120) (top row) and DW (middle row) MR images and on ADC maps (bottom row) at 3 (first image from the left), 7 (second image from the left), 14 (third image from the left), and 30 (fourth image from the left) days after stroke symptom onset in an 81-year-old patient. The evolution of WI lesions (arrows) is different from that of TI lesions (Fig 1), as shown by the slower normalization of the signal intensity on the ADC maps and DW images. The evolution of T2 effect is similar to that with TI.

stroke cannot be determined by using the clinical history and when DW imaging is to be used to screen patients and thus develop therapeutic strategies.

The difference in ADC evolution time between WI and TI suggests that infarction type may play an important role in determining the speed of infarction progression. We believe that the difference in ADC values reflects a slower metabolic and perfusion change with WI that is mostly hemodynamic in nature (9,11). As reported in animal studies (6,7), the progression of ischemic infarction appears to evolve at a speed that depends on tissue perfusion. Consequently, in humans, strokes with different pathogenetic and/or hemodynamic mechanisms may have different ADC evolution profiles as well. To our knowledge, this is the first study in which sequential ADC changes are reported with respect to infarction types in humans. Previously reported results of animal studies (6,30) suggest that longitudinal changes in ADC might reveal important diagnostic information regarding cerebral ischemia, such as tissue salvageability. The slower evolution time of WI therefore suggests

that ischemic injury in WIs might have a prolonged evolution of ischemic changes.

In our study, despite the significant differences in ADC evolution, the lesion size changes from the early subacute to late chronic stages were similar to those in previous reports (3) in which the subtypes of infarction were not determined. Only a mild decrease in final infarct volume relative to the infarct volume at the acute stage was found with both subtypes of infarction. In contrast, a substantial increase in the area of diffusion abnormality was found when DW images or ADC maps obtained at the hyperacute versus late chronic stage of stroke were compared. Such discrepancy is due to a delay in cell death in the peripheral regions of the ischemic penumbra that is still viable and hence exhibits no DW image hyperintensity or ADC decrease during the hyperacute stage (21).

Our study data suggest that the size of diffusion abnormality stabilizes at about 20 hours following symptom onset. This observation is consistent with that in a previous study, in which an increased infarct volume of 20% or more was observed in 12 of 28 patients who under-

Figure 3. Plot illustrates mean ratios of lesion-to-normal tissue signal intensity on DW images (*rDWI*) obtained at MR imaging performed at six defined stages of stroke: the hyperacute stage—that is, 6 or fewer hours after stroke symptom onset; the acute stage—that is, more than 6 hours and 2 or fewer days after symptom onset; the early subacute stage—that is, 3–4 days after symptom onset; the late subacute stage—that is, 7–9 days after symptom onset; the early chronic stage—that is, 10–15 days after symptom onset; and the late chronic stage—that is, 30–31 days after symptom onset. There were only marginal differences in *rDWI* between the two infarction subtypes at the late subacute and late chronic stages ($P < .05$).

Figure 4. Plot illustrates mean *rADC* values at six defined stages of TI and WI. The interaction between subtypes and stages was statistically significant ($P < .001$; analysis of variance) and indicated that evolution time strongly depended on infarction subtype. Also, the mean differences between subtypes were significant at the hyperacute stage ($P < .05$) and late subacute, early chronic, and late chronic stages ($P < .01$). The asterisks indicate the stages that reached statistically significant differences.

Figure 5. Plot illustrates mean *rT2* values at six defined stages of TI and WI. The mean difference in *rT2* between infarction subtypes was significant ($P < .01$) during only the late chronic stage. The asterisk indicates the stage that reached a statistically significant difference.

went DW imaging 2–53 hours after stroke symptom onset (31). The duration of the value of ADC maps for predicting final ischemic infarct volume therefore may be limited to about 1 day after symptom onset.

In conclusion, the evolution time of the ADC in TI is faster than that in deep WI. This difference, which we believe originates from the different pathophysiologic features and cerebral perfusion rates of the two stroke types, might ac-

count for the relatively large range of ADC values that have been reported for the time course of ischemic stroke (1–5). Understanding the subtype-dependent ADC evolution of cerebral infarctions might aid in stroke image interpretation

and in determining implications for the investigation and management of strokes.

References

1. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-

Figure 6. Plot illustrates initial versus final infarct volumes. The plotted values indicate that for both the TI and WI patient groups, the final infarct volumes were well predicted from the initial infarct volumes on the DW images ($r = 0.9899$). However, all cases of infarction at the hyperacute stage deviated from the regression line; the final lesion volumes were much greater than the initial lesion volumes (difference of $\geq 40\%$) estimated at the hyperacute stage, at which DW images may lead to an underestimation of infarct volumes.

- weighted magnetic resonance imaging. *Ann Neurol* 1995; 37:231–241.
2. Burdette H, Ricci PE, Pettiti N, Elster AD. Cerebral infarction: time course of signal intensity changes on diffusion-weighted MR images. *AJR Am J Roentgenol* 1998; 171:791–795.
3. Schwamm LH, Koroshetz WJ, Sorensen AG, et al. Time course of lesion development in patients with acute stroke: serial diffusion- and hemodynamic-weighted magnetic resonance imaging. *Stroke* 1998; 29:2268–2276.
4. Welch KM, Windham J, Knight RA, et al. A model to predict the histopathology of human stroke using diffusion and T2-weighted magnetic resonance imaging. *Stroke* 1995; 26:1983–1989.
5. Chien D, Kwong KK, Gress DR, Buonanno FS, Buxton RB, Rosen BR. MR diffusion imaging of cerebral infarction in humans. *AJNR Am J Neuroradiol* 1992; 13:1097–1102.
6. Rother J, de Crespigny AJ, D'Arceuil H, Iwai K, Moseley ME. Recovery of apparent diffusion coefficient after ischemia-induced spreading depression relates to cerebral perfusion gradient. *Stroke* 1996; 27:980–987.
7. Dijkhuizen RM, Berkelbach van der Sprenkel JW, Tulleken KA, Nicolay K. Regional assessment of tissue oxygenation and the temporal evolution of hemodynamic parameters and water diffusion during acute focal ischemia in rat brain. *Brain Res* 1997; 750:161–170.
8. Ringelstein EB, Zeumer H, Angelou D. The pathogenesis of strokes from internal carotid artery occlusion: diagnostic and therapeutic implications. *Stroke* 1983; 14:867–875.
9. Moriwaki H, Matsumoto M, Hashikawa K, et al. Hemodynamic aspect of cerebral watershed infarction: assessment of perfusion reserve using iodine-123-iodoamphetamine SPECT. *J Nucl Med* 1997; 38:1556–1562.
10. Bogousslavsky J, Regli F. Unilateral watershed cerebral infarcts. *Neurology* 1986; 36:373–377.
11. Weiller C, Ringelstein EB, Reiche W, Buell U. Clinical and hemodynamic aspects of low-flow infarcts. *Stroke* 1991; 22:1117–1123.
12. Caplan LR, Mohr PJ, Kistler JP, Koroshetz W. Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? *N Engl J Med* 1997; 337:1309–1310.
13. Bladin CF, Chambers B. Frequency and pathogenesis of hemodynamic stroke. *Stroke* 1994; 25:2179–2182.
14. Damasio H. A computed tomographic guide to the identification of cerebral vascular territories. *Arch Neurol* 1983; 40:138–142.
15. Chenevert TL, Brunberg JA, Pipe JG. Anisotropic diffusion in human white matter: demonstration with MR techniques in vivo. *Radiology* 1990; 177:401–405.
16. Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J Chem Phys* 1965; 42:288–292.
17. Burdette JH, Elster AD, Ricci PE. Acute cerebral infarction: quantification of spin-density and T2 shine-through phenomena on diffusion-weighted MR images. *Radiology* 1999; 212:333–339.
18. Schlaug G, Siewert B, Benfield A, Edelman RR, Warach S. Time course of the apparent diffusion coefficient (ADC) abnormality in human stroke. *Neurology* 1997; 49:113–119.
19. Provenzale JM, Engelter ST, Petrella JR, Smith JS, MacFall JR. Use of MR exponential diffusion-weighted images to eradicate T2 “shine-through” effect. *AJR Am J Roentgenol* 1999; 172:537–539.
20. Sorensen AG, Buonanno FS, Gonzalez RG, et al. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. *Radiology* 1996; 199:391–401.
21. Wang PYK, Barker PB, Wityk RJ, et al. Diffusion-negative strokes: a report of two cases. *AJNR Am J Neuroradiol* 1999; 20:1876–1880.
22. Games PA. Alternative analyses of repeated-measure designs by ANOVA and MANOVA. In: Alexander VE, ed. *Statistical methods in longitudinal research*. Vol 2, Principles and structuring change. New York, NY: Academic Press, 1990.
23. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study. *JAMA* 1995; 274:1017–1025.
24. Tissue plasminogen activator for acute ischemic stroke: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* 1995; 333:1581–1587.
25. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial—the EC/IC Bypass Study Group. *N Engl J Med* 1985; 313:1191–1200.
26. Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. *Ann Neurol* 1997; 41:574–580.
27. Baird AE, Warach S. Magnetic resonance imaging of acute stroke. *J Cereb Blood Flow Metab* 1998; 18:583–609.
28. Chong J, Lu D, Aragao F, et al. Diffusion-weighted MR of acute cerebral infarction: comparison of data processing methods. *AJNR Am J Neuroradiol* 1998; 19:1733–1739.
29. Singer MB, Chong J, Lu D, Schonewille WJ, Tuhim S, Atlas SW. Diffusion-weighted MRI in acute subcortical infarction. *Stroke* 1998; 29:133–136.
30. Reith W, Hasegawa Y, Latour LL, Dardzinski BJ, Sotak CH, Fisher M. Multislice diffusion mapping for 3-D evolution of cerebral ischemia in a rat stroke model. *Neurology* 1995; 45:172–177.
31. Baird AE, Benfield A, Schlaug G, et al. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. *Ann Neurol* 1997; 41:581–589.