Diffusion- and Perfusion-Weighted MRI
The DWI/PWI Mismatch Region in Acute Stroke

Tobias Neumann-Haefelin, MD; Hans-Jörg Wittsack, PhD; Frank Wenserski, MD; Mario Siebler, MD;
Rüdiger J. Seitz, MD; Ulrich Mödder, MD; Hans-Joachim Freund, MD

Background and Purpose—Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are relatively new MR techniques increasingly used in acute stroke. During the first hours of stroke evolution, the regions with abnormal perfusion are typically larger than the DWI lesions, and this mismatch region has been suggested to be "tissue at risk." The aim of this study was to evaluate the PWI/DWI mismatch region in acute stroke patients and find parameters indicative of both infarct progression and functional impairment.

Methods—Twenty patients with nonlacunar ischemic stroke were imaged with DWI, PWI, and conventional MRI within 24 hours of symptom onset and after 1 week; in addition, the European Stroke Scale (ESS) score was recorded. With PWI, the volumes of regions with "time-to-peak" (TTP) delays of ≥ 2, 4, 6, 8, and 10 seconds were measured; these volumes were compared with the acute DWI lesion volumes, final infarct size, and ESS score.

Results—In 80% of patients the acute DWI lesion was surrounded by regions with abnormal TTP delays (PWI>DWI lesion). A TTP delay of ≥ 6 s in the mismatch region was found to be associated with lesion enlargement between the initial and follow-up MRI scans. Lesions increased in 9 of 12 patients (75%) in whom the area with TTP delay ≥ 6 s was larger than the DWI lesion, but they increased in only 1 of 8 (12.5%) of the remaining patients, in whom the area with a TTP delay ≥ 6 s was smaller than the DWI lesion. The volume of the regions with TTP delays of ≥ 4 s correlated better with ESS ($r = -0.88$, $P < 0.001$) than other PWI (or DWI) volumes, which indicated that a TTP delay of ≈ 4 s might be the threshold for functional impairment of brain tissue.

Conclusions—Only patients with severe perfusion deficits in the PWI/DWI mismatch (TTP delays of ≥ 6 s) are at high risk of lesion enlargement. Functionally, more moderate perfusion deficits (TTP delays ≥ 4 and < 6 s) appear to also contribute to the acute clinical deficit. (*Stroke*. 1999;30:1591-1597.)

Key Words: diffusion ∎ magnetic resonance imaging ∎ penumbra ∎ perfusion ∎ stroke, acute

The new MR techniques of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are rapidly becoming integral parts of the diagnostic workup in the acute stroke setting. With DWI it is possible to identify severely ischemic brain regions within minutes to hours after stroke onset.[1–3] A decrease in the apparent diffusion coefficient of water (ADC), apparent as hyperintensity on DW images, indicates a restriction in the diffusional movement of water and is believed to result from energy failure and subsequent cytotoxic edema.[1,4] DWI abnormalities typically evolve into infarction in humans, and it has been suggested that the DWI abnormality corresponds to the ischemic core.[5] PWI, on the other hand, provides information on the hemodynamic status of the tissue and can detect impaired perfusion in both the ischemic core and the surrounding brain regions, thereby complementing the information derived from DWI.[3,6,7]

During the first hours of stroke evolution, regions with abnormal perfusion (as assessed with PWI) are typically larger than the DWI lesions.[8–12] It has been postulated that this mismatch region reflects the ischemic penumbra, ie, the functionally impaired "tissue at risk" surrounding the irreversibly damaged ischemic core. Typically, the ischemic penumbra is partially recruited into the ischemic core during the first hours after symptom onset.[13–16] This process might be prevented pharmacologically and has therefore become the focus of intense interest.

In support of the hypothesis that the PWI/DWI mismatch reflects tissue at risk is the observation that a PWI>DWI lesion is associated with subsequent infarct enlargement.[8,10] However, because PWI is very sensitive in detecting perfusion deficits, the PWI/DWI mismatch region may comprise not only tissue at risk but also hypoperfused tissue with cerebral blood flow (CBF) values above the critical viability thresholds.[3] From both animal experiments and human PET studies, it is well known that the flow thresholds are ≈ 10 and 15 to 20 mL/100 g per minute for structural injury and

functional impairment, respectively (average normal CBF $\approx$50 mL/100 g per minute).[13,17–19] PWI, however, has been shown to be sensitive enough to detect perfusion deficits in patients with occlusive internal carotid artery (ICA) disease[20] but without symptoms at the time of the scan, which indicates that PWI can detect even relatively mild hypoperfusion states.

Thus, to determine the functional relevance and the risk for subsequent structural injury, it would be necessary to know the severity of the perfusion deficit within the PWI/DWI mismatch region. PWI—as it is performed in most centers—is, however, only semiquantitative. Calculating absolute CBF values, although theoretically possible, is not yet widely applied, in part because it requires time-consuming postprocessing as well as operator intervention to determine the arterial input function. In most previous stroke studies only relative measurements of various hemodynamic parameters (bolus arrival time or time to peak [TTP], mean transit time, and relative CBV and CBF) were analyzed; in fact, the perfusion deficits were mostly assessed qualitatively,[8] ie, the volume of the total PWI lesion was measured without differentiating between different degrees of ischemia.

In this prospective study we used a simple and rapid semiquantitative method of analyzing PWI abnormalities to assess both the extent of the PWI lesion and the severity of the perfusion deficits in the PWI/DWI mismatch region. The method requires minimal operator intervention and can be easily applied in the acute stroke setting.

Subjects and Methods

Patients

Between January and November 1998, we consecutively enrolled 20 patients at our stroke center. The inclusion criteria were focal neurological deficit of sudden onset with persisting symptoms at the time of the acute MR study, acute MRI study within 24 hours after symptom onset, and stable general medical status. The exclusion criteria were history of major stroke or other disabling neurological disease prior to the index event, subcortical lacunar stroke, and nonischemic conditions. Patients receiving rtPA (4 patients) or anticoagulation were eligible for the study; however, none of the patients received investigational drugs. Informed consent was obtained from all patients included in the study or from their close family members. The study was approved by the local ethics committee.

All patients enrolled in the study were imaged within 24 hours of symptom onset. Follow-up scans were obtained at 6 to 10 days (and in 1 patient at 14 days). Three clinical scores (European Stroke Scale, Rankin scale, and Barthel Index) were recorded at the time of the acute imaging study and at follow-up by a neurologist experienced in stroke management. Although similar results were obtained for all correlations between these 3 clinical scores and MR lesion volumes, only the results obtained with the ESS are presented due to the obviously nonlinear relationship between the other scores and lesion volumes. All strokes were classified by vascular territory and stroke mechanism according to the Trial of Org 10172 in Acute Ischemic Stroke (TOAST) study criteria.[21]

Imaging Protocol

The MR measurements were performed on a 1.5-T clinical whole-body MR scanner (Siemens Magnetom Vision) equipped with a gradient overdrive, using the standard head coil. The acute study included a conventional T2-weighted axial turbo spin-echo sequence (T2WI), an axial diffusion-weighted single-shot echo planar sequence (DWI), and an axial echo planar perfusion-weighted sequence (PWI). Total scan time for the acute protocol (including scout

and MRA) was $\approx$20 minutes. The follow-up study consisted of the T2 sequence and DWI.

The T2 sequence contained 20 slices (thickness 5 mm) with an interslice gap of 1.5 mm and a field of view (FOV) of 240 mm with a matrix of 345×512 pixels. Each of the 20 axial slices obtained with spin-echo DWI (slice thickness 5 mm, interslice gap 1.5 mm, TE 103 ms, FOV 240 mm, and matrix 96×128) was acquired with b values of 0 and 1000 s/mm^2; the high b value DWI measurements were performed with diffusion gradients in the 3 orthogonal *(x, y, z)* directions in space. The perfusion study (gradient echo, 12 slices, slice thickness 5 mm, interslice gap 1.5 mm, TE 54 ms, FOV 240 mm, and matrix 128×128) consisted of 40 T2*-weighted measurements obtained at intervals of 2 s. The contrast agent (15 mL Gd-DTPA) was injected at the time of the fourth scan at a rate of 5 mL/s.

Postprocessing and Image Analysis

For postprocessing the data were transferred to a Sun UltraSparc1 workstation. With DWI a trace diffusion-weighted image was calculated by averaging the images obtained with diffusion weighting in the *x*, *y*, and *z* directions using inhouse software; in addition, ADC maps were calculated from the DWI data. PWI data were computed pixel by pixel to create TTP) maps. (TTP refers here to the time between the first T2*-weighted measurement and the bolus peak.) Other parameter maps (relative regional CBV [rCBV] and bolus amplitude) were also routinely calculated but not used in this analysis, because the volume of the perfusion deficits was usually considerably more difficult to delineate on these maps than on the TTP maps.

The DWI and PWI lesion volumes were measured by 2 independent observers. The average of the lesion volumes determined by the 2 observers was used for further analysis. DWI lesion volumes were determined by manually tracing the edge of the hyperintense signal on each slice of the trace DWI scans obtained at b=1000 s/mm^2. The areas of hyperintensity were summed and multiplied with the slice thickness plus interslice gap to calculate the volume of the DWI abnormality.

For the calculation of the perfusion deficit volumes, the TTP maps were modified with use of the contralateral MCA territory as reference tissue (see Figure 1); the average TTP value obtained for this reference region was subtracted from the unmodified TTP map. Using this simple method, we were able to generate maps that depicted areas of pathological bolus delay, ie, bolus delay beyond the normal delay in unaffected tissue. To calculate the reference TTP value we always defined an area of the size depicted in Figure 1 using a slice at approximately the same high ventricular level. The mean difference between the TTP values determined for the reference regions by the 2 observers was 0.3 s (range 0.0 to 1.2 s), indicating that the interobserver error introduced by selecting the reference regions is minimal. In addition, to get an estimate of how much selecting different slice levels would influence the reference TTP value, we measured the average TTP of contralateral regions at different slice levels. When selecting regions similar in size to our reference region, the TTP delays were found to not differ by >1 s in individual patients.

We then determined the PWI lesion volumes by systematically measuring the volumes of the regions with TTP delays of >0, $\geq$2, $\geq$4, $\geq$6, $\geq$8, and $\geq$10 s in all patients. The interobserver reliability (*r*) values for measuring these volumes were 0.89 (TTP delays >0 s), 0.87 (TTP delays $\geq$2 s), 0.90 ($\geq$4 s), 0.96 ($\geq$6 s), 0.99 ($\geq$8 s), and 0.99 ($\geq$10 s), compared with 0.99 for DWI and 0.97 for T2WI lesion measurements. The volumes of the regions with abnormal perfusion determined with this method were compared with the volumes of the acute DWI lesion, the final infarct size (T2WI at follow-up), and the acute neurological scores (ESS).

Statistical Analysis

Results are presented as mean±SD unless stated otherwise. When analyzing the change in infarct size we considered (T2WI lesion at follow-up >1.05×acute DWI lesion) as indication of infarct growth. The mean acute PWI volumes were compared with the mean DWI
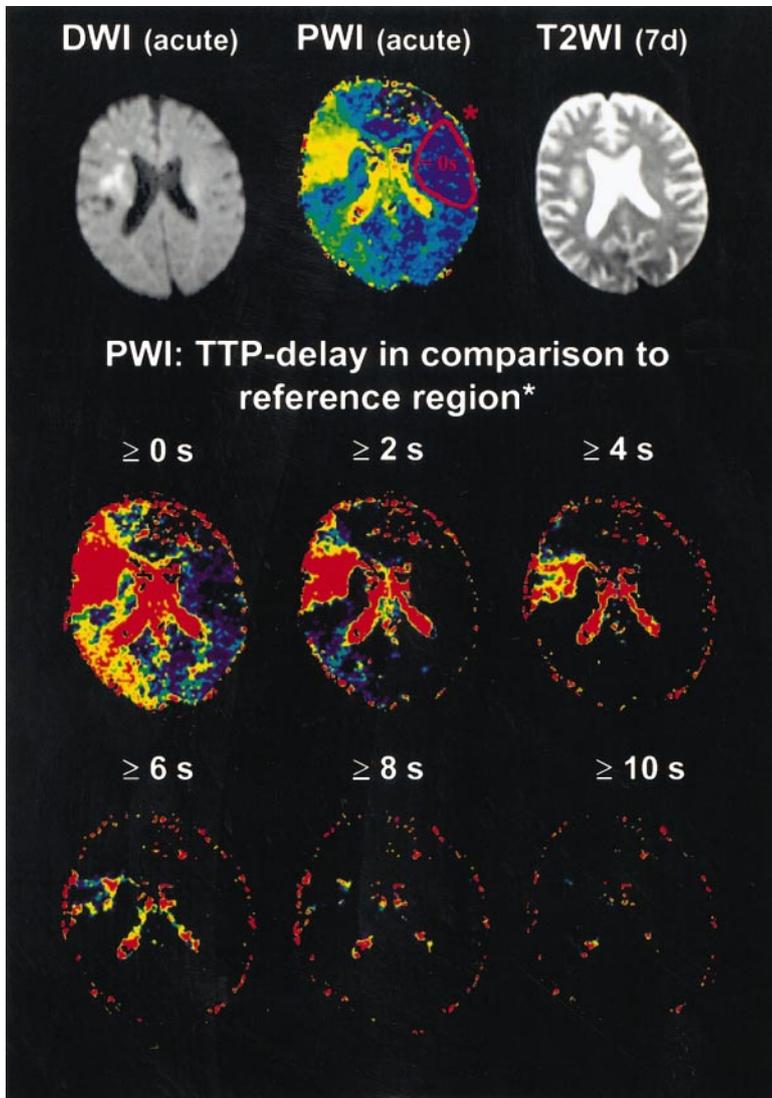
Figure 1. Acute DWI and PWI (TTP map, arbitrarily adjusted contrast) as well as follow-up T2WI (at day 7) of a single patient. The acute study revealed a large PWI/DWI mismatch in the right MCA territory. Analysis of the TTP delays in this region, however, showed that the area with a TTP delay of ≥6 s was not substantially larger than the DWI lesion, indicating a relatively small risk of lesion enlargement after the acute scan, which was confirmed by the follow-up scan. The TTP delay maps were generated by subtracting the TTP value of unaffected contralateral reference tissue (asterisk) from the original TTP map.

volume with use of ANOVA and subsequently Dunnett's procedure for multiple comparisons against a single "control" group (DWI lesion volume). For correlations between the PWI/DWI lesion volumes and ESS scores, Pearson's product moment correlation coefficient was used with Bonferroni correction for multiple comparisons.

Results

Thirty patients fulfilled our primary inclusion criteria, but 10 of these were retrospectively excluded due to the following exclusion criteria: subcortical lacunar stroke (n=3), other nonischemic neurological diseases (n=5), and insufficient PWI quality due to severe patient motion during data acquisition (n=2). We therefore analyzed the results of 20 patients with nonlacunar ischemic stroke (for demographic data see Table 1); all of these 20 patients had received our complete MR stroke protocol within 24 hours after symptom onset (mean 8.8 hours, range 1 to 23 hours) as well as the follow-up study.

Acute DWI revealed at least 1 lesion in all 20 patients included in the study; the mean±SD DWI lesion volume was 32.7±33.7 mL for all patients investigated in the study. With acute PWI we were able to identify regions with an abnormal TTP delay in 18 of 20 patients when using the contralateral MCA territory as reference tissue. In 4 of 20 patients (including the 2 patients without a perfusion deficit) the region with a TTP delay was smaller than the DWI lesion, indicating that partial or complete reperfusion had occurred before the acute MR study. In the other 16 of 20 patients the PWI lesion was larger than the DWI lesion, ie, these patients had an area with a positive PWI/DWI mismatch when the TTP maps were used to calculate the PWI lesion volumes.

The severity of ischemia was not homogenous within the PWI/DWI mismatch area of the 16 patients with a positive mismatch. The DWI lesion (ischemic core) was typically surrounded by regions with progressively less pronounced TTP delays (see Figures 1 and 2). The average size of this PWI/DWI mismatch region was 132.8±69.4 mL (in comparison, mean DWI lesion volume was 33.0±32.7 mL). The fractions of the total mismatch volume (100%) with TTP delays of ≥2 s, ≥4 s, ≥6 s, and ≥8 s were 63±42%, 31±30%, 15±23%, and 3±19%, respectively, whereas the area with a TTP delay of ≥10 s was smaller than the mean DWI lesion volume.

TABLE 1.   Summary of Demographic Data and Imaging Results

	Demographic Data					Imaging Results						
							PWI (Acute), mL:Volume With TTP Delay ≥x Seconds					
Patient	Age, y/Sex	Time of First Scan, h	Arterial Territory	DWI Volume (Acute), mL	T2W Volume (Follow-up), mL	≥0 s	≥2 s	≥4 s	≥6 s	≥8 s	≥10 s
1*	37/M	1	MCA r	17	29	253	158	70	31	10	5
2	67/M	23	MCA l	78	90	246	168	109	83	56	37
3	55/M	1.5	MCA l	11	26	114	54	31	20	14	11
4	57 /F	5	MCA l	106	136	227	211	164	157	129	112
5	55 /F	6	MCA l	87	98	165	139	119	110	96	82
6	61/M	11.5	MCA l	72	66	253	199	121	65	37	26
7	49/M	3.5	ACA l	30	35	87	71	43	33	25	18
8	71/M	12	MCA l	6	0	167	139	101	76	57	45
9	77 /F	20	MCA l	10	9	74	36	9	0	0	0
10	65/M	4	MCA l	12	2	253	221	152	95	61	42
11	77/M	11	MCA r	26	17	68	52	32	24	14	10
12	75/M	2	MCA r	17	39	59	54	44	36	27	21
13	63/M	5	PCA r	12	18	84	64	37	15	4	0
14	60/M	15.5	MCA r	8	6	221	120	50	23	4	0
15*	69/M	3	MCA r	17	22	210	158	109	85	55	34
16‡	64 /F	4	MCA r	1	23	0	0	0	0	0	0
17†	67 /F	13	MCA r	6	4	6	4	2	2	1	1
18	57/M	9.5	MCA l	23	3	0	0	0	0	0	0
19	56/M	7	MCA l	19	19	174	30	5	0	0	0
20†	63/M	18	MCA r	94	76	18	7	4	3	0	0
Mean	62	8.8		32.6	35.9	133.9	94.2	60.1	42.9	29.6	22.2
SD	9	6.5		33.7	37.5	93.2	74.9	54.0	44.8	36.2	30.3

DWI (T2W, PWI) volume indicates volume of the DWI (T2W, PWI) lesion. MCA, middle cerebral artery; ACA, anterior cerebral artery; and PCA, posterior cerebral artery.
*Treated with rtPA after initial MR study.
†Treated with rtPA before initial MR study.
‡Possible secondary ischemic event before follow-up scan.

The risk of infarct growth was clearly related to the degree of the TTP delay in the PWI/DWI mismatch region (Figure 3). When evaluating all patients with a positive PWI/DWI mismatch (n=16), infarct size increased in 9 of 16 (56%) compared with 10 of 20 (50%) for the total study population. Infarct size increased in 9 of 12 patients (75%) with a severe perfusion deficit in the PWI/DWI mismatch region (TTP delay ≥6 s). On the other hand, none of the patients with TTP delays of ≤4 s in the mismatch region showed an increase in infarct size (n=4). Lesion size increased, however, in 1 patient without a detectable perfusion deficit at acute PWI. In total, lesion size increased, therefore, in 1 of 8 patients (12.5%) with 1 of the following 3 patterns: PWI>DWI lesion (but TTP delays of ≤4 s in the mismatch), PWI<DWI lesion, and no perfusion deficit. The difference between the patients with TTP delays ≥6 s in the mismatch region and those without was also obvious when comparing the changes in lesion size between the acute DWI study and follow-up T2WI (Figure 4). Lesion size increased on average 25% (absolute change, mean 8.3±11.1 mL; percentage given is percent change of the mean) in the former group (P<0.05) but decreased (nonsignificantly) in the latter group by −13% (absolute change, mean −4.1±13 mL), with the difference between the 2 groups statistically significant at P<0.05.
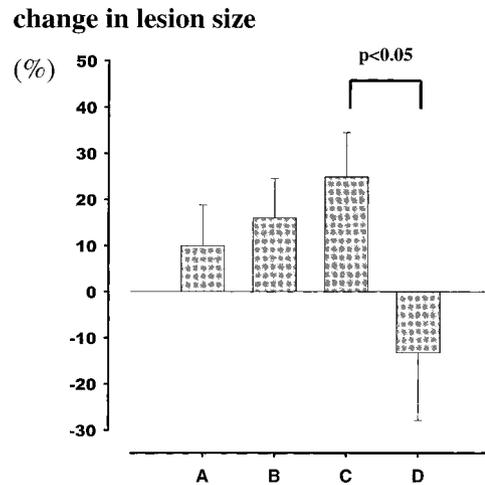
Finally, to assess the functional relevance of the different TTP delays in the PWI/DWI mismatch region, we correlated the PWI lesion volumes obtained with the different TTP thresholds with the acute neurological deficit as assessed with the ESS (see Table 2). Overall, acute PWI lesion volumes correlated better with ESS score than DWI lesion volumes. When analyzing the correlations between the TTP volumes and acute ESS score, the volume of the region with a TTP delay of ≥4 s correlated best with acute ESS, particularly when the patients with a positive mismatch were analyzed independently. In patients with PWI<DWI lesions, the functional impairment was probably mainly due to the DWI lesion. With TTP delays of ≥6 s, the correlations with ESS became weaker again, indicating that some functionally affected areas were no longer included in the PWI measurements.

Discussion

In this study we analyzed the PWI/DWI mismatch region in acute stroke with a relatively simple semiquantitative method for assessing the perfusion deficits. The currently most widely used form of PWI in acute stroke patients is "bolus-tracking" of the first pass of a paramagnetic contrast agent,

PWI (DWI) lesion volume (cm³)
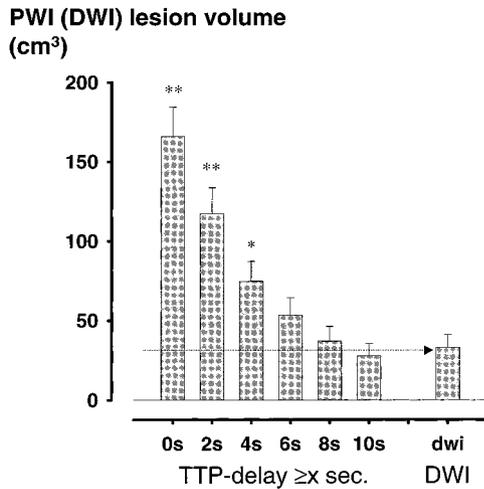
Figure 2. Average size of the regions with TTP delays of >0, ≥2, ≥4, ≥6, ≥8, and ≥10 seconds as well as the DWI lesion volume. Mean±SEM values for the group of patients with PWI>DWI lesion (16/20) are shown. As also seen in Figure 1, regions with more pronounced time delays are always included in the regions obtained with lower TTP delay thresholds. Statistical comparisons were made against the DWI volume after performing ANOVA. *$P<0.05$, **$P<0.01$.

which was also used here. Different functional maps (TTP, mean transit time [MTT], peak amplitude, and relative rCBV and rCBF) can be generated on a pixel-by-pixel basis from the raw data. The TTP maps (or the MTT maps), where a bolus delay indicates abnormal perfusion, are often used for volumetric analyses because the perfusion deficits tend to be most distinct on these maps. The absolute TTP values, however, are difficult to compare between individuals, because the time between the intravenous injection and the arrival of the bolus in the cerebral arteries varies between different patients. Our approach to circumvent this problem was to generate "bolus delay" maps; this is simply achieved by subtracting the bolus arrival time of unaffected contralateral tissue. If done in a standardized fashion, the interobserver

percentage of patients with lesion enlargement

Figure 3. Percentage of patients with lesion enlargement after the initial scan. Patient subgroups were as follows A, all patients (n=20); B, PWI>DWI lesion (n=16/20); C, only patients with areas of severe perfusion deficits in the mismatch region (TTP delay ≥6 s; n=12/20); and D, only patients without severe perfusion deficits in the mismatch region (TTP delay ≤4 s; n=8/20).

change in lesion size
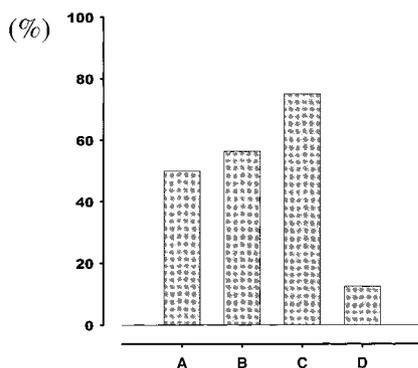

Figure 4. Relative change in lesion size (±SEM) between the initial DWI and the follow-up T2WI. A positive value translates into lesion enlargement; negative values indicate that the initial DWI lesion was larger than the final infarct measured on T2WI at ≈1 week. Patient subgroups are as in Figure 3. Statistical testing was performed only to compare changes in lesion size between subgroups C and D (because there is an overlap between all other potential group pairs).

agreement of this method is good, requires minimal postprocessing, and is feasible in the acute stroke setting.

With this approach we were able to separate areas within the PWI/DWI mismatch region with mild (TTP delay of <4 s), moderate (TTP delay ≥4 s and <6 s), and severe (TTP delay ≥6 s) perfusion deficits. Our classification (mild, moderate, severe) is based on the following findings: severe perfusion deficits (TTP delays of ≥6 s) in the mismatch region were associated with subsequent lesion enlargement, and TTP delays of ≥4 s (including severe and moderate perfusion deficits) were found to correlate highly significantly with functional impairment (ESS). The latter finding indirectly indicates that areas with TTP delays of <4 s (mild perfusion deficit) did not contribute to the clinical deficit. On average, only 31% of the total mismatch region had TTP delays of ≥4 s, which indicates that—in contrast to the ischemic penumbra—large parts of the PWI/DWI mismatch are not "at risk" on hemodynamic grounds.

TABLE 2. Correlation of PWI Lesion Volume and Acute Neurological Deficit (ESS)

	Correlation, r	
	All Patients (n=20)	PWI>DWI (n=16)
TTP ≥0 s volume vs ESS	−0.69†	−0.75†
TTP ≥2 s volume vs ESS	−0.77‡	−0.86‡
TTP ≥4 s volume vs ESS	−0.81‡	−0.88‡
TTP ≥6 s volume vs ESS	−0.77‡	−0.80†
TTP ≥8 s volume vs ESS	−0.71†	−0.72*
TTP ≥10 s volume vs ESS	−0.66*	−0.66
DWI volume vs ESS	−0.59	−0.58

TTP ≥x s volume indicates volume of regions with time-to-peak delay of at least x seconds; ESS, European Stroke Scale score; and r, Pearson correlation coefficient.

*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

The ischemic penumbra was initially defined in animal studies as the region surrounding the irreversibly damaged ischemic core with flow rates between 2 critical thresholds, those of electrical and membrane failure, which translates into functional impairment but not structural injury.[17] More recently, it has been suggested that the penumbra be defined as the region of constrained blood flow in which energy metabolism is preserved (in contrast to the ischemic core)[13] or as tissue with transiently disturbed metabolism and recurrent anoxic depolarizations.[22] Often, however, the term is used in a broader sense to characterize ischemically affected but still viable tissue surrounding the irreversibly damaged ischemic core with "uncertain chances for recovery or infarction."[14,16]

As in previous DWI/PWI studies, we operationally defined the DWI lesion as the ischemic core. Although acute DWI lesions are highly correlated with final infarct size in humans,[9,10,23–25] there is compelling evidence from animal studies[4] that DWI changes are potentially reversible for a limited time period. In transient focal ischemia models, regression of DWI abnormalities has been reported to occur after up to 60 minutes of ischemia. In rodents the periphery of the DWI lesion (ADC 90% of control values) was found to have preserved energy metabolism (normal ATP levels but increased lactate levels) even at 2 hours of middle cerebral artery (MCA) occlusion, which indicates that a small outer rim of the DWI lesion was still viable at that time.[26] In humans, on the other hand, reversal of DWI abnormalities has not been shown convincingly. However, it was previously noted (as also observed in our study) that acute DWI lesions can be larger than the final infarct.[6,8,10] This phenomenon may be due to a true reversal of the DWI abnormality at the periphery of the lesion, but other factors, such as vasogenic edema at the acute time point (and later resolution) or tissue atrophy prior to the follow-up scan, are difficult to exclude. In summary, it is likely that DWI slightly overestimates the ischemic core region and that a minor fraction of the DWI lesion extends into the ischemic penumbra.

Our study adds to previous PWI/DWI studies[8–12] in acute stroke by emphasizing the importance of quantifying the severity of the perfusion deficits within the mismatch region. With our semiquantitative approach, we were able to identify a high-risk group with TTP delays of ≥6 s in the PWI/DWI mismatch region. In this subgroup of patients (TTP delay ≥6 s in mismatch region), 75% of lesions increased in size, compared with 12.5% in the subgroup without a TTP delay of ≥6 s. Infarct size increased only in 1 patient in the latter group (n=8); because this patient (patient 16 in Table 1) deteriorated clinically before the follow-up scan and had no PWI lesion on the initial scan, we believe that lesion enlargement was due to a secondary ischemic event. With respect to the high-risk group, it is important to mention that we were unable to predict infarct growth with certainty. Even in some patients (n=2) with TTP delays of ≥10 s in the mismatch region, final infarct size did not exceed the initial DWI lesion. The most likely explanation for this phenomenon is that spontaneous thrombolysis occurred shortly after the acute scan and "rescued" the severely ischemic tissue in these patients.

Schlaug et al[5] used a different approach to define tissue at risk for infarct progression. They operationally defined the ischemic penumbra as tissue with reduced perfusion surrounding the DWI lesion, which became infarcted between the initial and the follow-up scan. With this definition they restricted their analysis a priori to a region with a very high risk. They found that the MTT was increased by a mean of 73% and that rCBV was increased by 29% in this region, while in the core both rCBF and rCBV were decreased and MTT extremely prolonged. Others found that the rCBV lesions exceeded the DWI lesions in size but were substantially smaller than the MTT lesions.[3,27] When TTP maps are used (as in this study), the total mismatch is probably of a size similar to that with MTT maps, but no systematic comparison between TTP and other relative parameter maps (MTT, rCBV, rCBF, and peak bolus) has been reported for acute stroke patients; it is therefore still difficult to directly compare the results of these studies.

The main advantages of using TTP maps to visualize the perfusion deficits are that they are easy to generate, time required for postprocessing is minimal, and abnormal regions can be easily identified and delineated. With rCBV and rCBF maps, the borders of the lesions are often less distinct than on the TTP (or MTT) maps. This is partially due to the lack of differences between gray and white matter on the latter maps; these differences are, however, prominent on rCBF and rCBV maps and can potentially obscure subtle changes, particularly those at the gray matter–white matter junction.[27] However, there are also notable limitations to the TTP maps. The TTP is only an indirect measure of tissue perfusion, and TTP delays may occur in patients with high-grade ICA stenosis without acute stroke. Therefore, use of TTP maps only qualitatively (ie, differentiating between normal and abnormal tissue perfusion) can lead to a substantial overestimation of the region at risk in acute stroke patients with high-grade ICA stenosis. In our opinion this problem can be (at least partially) overcome by quantifying the degree of the TTP delay in the mismatch region as proposed here. However, this issue needs to be addressed in a future systematic study comparing the PWI exams (and TTP delays in particular) of acute stroke patients with and without ICA stenosis.

Recently, 2 groups[28–30] reported methods of measuring absolute CBF (and CBV) in both healthy volunteers and patients with carotid artery stenosis (without acute stroke). Both techniques require determination of the arterial input function and subsequent deconvolution techniques. Until now, these techniques have not been validated in a sufficient number of stroke patients; in addition, because they require a high degree of operator intervention as well as relatively time-consuming postprocessing, it is unclear whether they are feasible in acute stroke, where time is a critical factor. Possibly, other PWI techniques, such as arterial spin tagging,[31] may eventually prove to be useful in acute stroke because they are potentially quantitative, but there are still technical problems to be overcome.

Finally, our results add further evidence to the notion that functionally affected tissue surrounds the DWI lesions. PWI lesion volumes were previously found to correlate better than DWI lesion volumes with the acute neurological deficit;[10] in

our study the best correlation was found between the volume with TTP delays of ≥4 s and ESS score. This indirectly indicates that tissue with TTP delays of ≥4 s is functionally impaired, thereby contributing to the patients' clinical symptoms. Assuming that this hypothesis is correct, the functionally impaired region would be on average more than twice the size of the DWI lesion. However, only a relatively small fraction of this region becomes recruited into the final infarct. Because PWI lesions typically regress with time, it is possible that a substantial proportion of the clinical recovery typically seen within the first few days after stroke results from a shrinkage of the mismatch region, as suggested previously,[10] which would also be in line with existing PET data.[18]

In summary, our study focused on the PWI/DWI mismatch region in acute stroke patients. We have shown that it is possible to identify patients (through severe perfusion deficit in the mismatch region) at high risk of lesion enlargement. Large parts of the mismatch region, however, appear not to be at risk, even though they may contribute to functional impairment. If our data can be confirmed in a larger patient sample, it may become possible to select specific therapies for individual patients based on the hemodynamic status of their PWI/DWI mismatch region.

Acknowledgments

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