Pathophysiological Topography of Acute Ischemia by Combined Diffusion-Weighted and Perfusion MRI

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Background and Purpose—Combined echoplanar MRI diffusion-weighted imaging (DWI), perfusion imaging (PI), and magnetic resonance angiography (MRA) can be used to visualize acute brain ischemia and predict lesion evolution and functional outcome. The appearance of a larger lesion by PI than by DWI quantitatively defines a mismatch of potential clinical importance. Qualitative lesion variations exist in the topographic concordance of this mismatch. We examined both the topographic heterogeneity and relative frequency of mismatched patterns in acute stroke using these MRI techniques.

Methods—Acute DWI, PI, and MRA studies of 34 prospectively recruited patients with supratentorial ischemic lesions scanned within 24 hours of stroke onset (range 2.5 to 23.3 hours, 12 patients <6 hours) were analyzed.

Results—Ischemic lesions were predominantly in the middle cerebral artery (MCA) territory (94%), with DWI lesions most commonly affecting the insular region. Mismatched patterns with PI lesion larger than DWI lesion occurred in 21 patients (62% overall), in all 4 patients imaged within 3 hours, and in 44% of patients imaged after 18 hours. A patient with a large PI but no DWI lesion and severe clinical deficit at 2.5 hours after stroke onset recovered completely. Regional variations in DWI and PI lesion loci were found, inferring site of proximal MCA occlusion, embolic pathogenesis, and regional arterial reperfusion.

Conclusions—Analysis of the topographic concordance of PI and DWI lesions in acute stroke reveals regional PI lesions without concomitant DWI lesions, which do not necessarily progress to infarction but may suggest stroke pathogenesis and site of current arterial occlusion. Location of DWI lesions may suggest an earlier site of arterial occlusion and regions of maximal perfusion deficit. (Stroke. 1999;30:2043-2052.)

Key Words: cerebral ischemia ■ echo-planar imaging ■ diffusion ■ perfusion

Earlies thrombolytic treatment of acute ischemic stroke may significantly improve prognosis by reestablishing arterial flow in a region of hypoperfusion.1 Thrombolytic therapy is currently recommended only in patients who present within 3 hours of stroke onset and without significant CT abnormalities indicative of hemorrhage or major infarction. Unfortunately, benefit is not universal even within this time window,1 and there is experimental and clinical evidence to suggest that in some cases, treatment after longer delays might be beneficial.2,3 There is therefore a need for techniques that refine current patient selection criteria to identify those with clinically significant regions of potentially salvageable ischemic tissue at any time after infarction onset.

Perfusion (PI) and diffusion-weighted (DWI) MRI techniques can detect both tissue hypoperfusion and usually irreversible injury in acute infarction.4–8 A single imaging session can therefore rapidly visualize and quantify the presence, extent, and evolution of acute ischemia-associated changes. These measures correlate quantitatively with short- and long-term functional deficits,7 which indicates their utility for predicting clinical course. They can also depict regions around the infarction core (as defined by areas of impaired diffusion on DWI images) where perfusion is reduced on PI but tissue diffusion is near normal.7 Such regions may be a surrogate marker of the true ischemic penumbra, as originally defined physiologically.7,9,10 Reperfusion, including reperfusion after thrombolysis, into these areas may prevent transition to infarction.11 In addition, magnetic resonance angiography (MRA) allows rapid visualization of proximal large cerebral arterial patency and predicts the presence of lesions that appear larger on PI than on DWI.12

There are 6 possible regional concordance combinations of acute PI and DWI, which have been divided into putative “penumbral” and “nonpenumbral” patterns on the basis of the mismatch between PI and DWI lesion volume.7 Evolution is reported only in those cases with mismatch patterns in which PI lesion volume is larger than DWI lesion volume.7,13,14
Hence, the presence of a PI>DWI mismatch is likely to be an independent predictor of benefit from thrombolysis. One small trial using tissue plasminogen activator supports this contention,11 although larger-scale trials are required.15,16 In combination, PI, DWI, and MRA techniques allow accurate specification of the state of the hemodynamic perturbations in an individual patient’s infarction and may lead to more rational targeting of therapy, so that benefit is maximized and adverse events are avoided.15,16

Our previous work has described quantitative correlations of these MRI methods and clinical deficits acutely and serially,7,12,17 but qualitative aspects of lesion concordance may also be relevant to therapy. In the present study, we therefore examined the concordance of DWI, PI, and MRA lesions and their clinical consequences in patients scanned within 24 hours of infarction onset with serial studies included in cases in which pathophysiology could be further elucidated. We aimed to identify patterns that might be clinically useful in the examination and treatment of an acute stroke patient. We were particularly interested in determining whether PI and DWI lesions were usually concentric, as suggested by the quantitative core–penumbra model described above, and whether the likely stroke mechanism could be inferred by imaging alone (eg, embolism or border-zone or deep-perforator occlusion).

Subjects and Methods

Patients

Patients were prospectively recruited from the Stroke Service of the Royal Melbourne Hospital as previously described.7,12 They were included if they presented within 24 hours of sudden onset of a focal neurological deficit consistent with hemispheric ischemic stroke. Stroke onset was defined as the last time the patient was known to be without neurological deficit.

Exclusion criteria were the presence of cerebral hemorrhage, preexisting significant nonischemic neurological deficits (including dementia or extrapyramidal disease), or a history of prior stroke that would hamper interpretation of clinical and radiological data. There were no age, sex, handedness, or prior therapy exclusions. The study was performed with the approval of our institution’s Ethics Committee, and written informed consent was obtained from all patients or their next of kin.

Imaging Protocol

MRI scans were obtained with a 1.5-T echoplanar imaging (EPI)–equipped whole-body scanner (Signa Horizon SR 120, General Electric) according to a protocol optimized to obtain high-quality images as rapidly as possible in ill and potentially uncooperative patients. Sequences were always performed in the same order, with an initial T1-weighted sagittal localizer (T1-W), the diffusion-weighted sequence, then the perfusion sequence, a proton-density (PD) and T2-weighted (T2-W) fast-spin double-echo sequence (TR/TE/TE 3500/10/60 ms), and other studies as previously described.7 Similar slice positions were used to facilitate comparisons. The acute DWI, PI, and MRA studies are reported here, although later studies are mentioned if relevant.

Diffusion Imaging

DWI was performed with a multislice, single-shot, spin-echo EPI sequence with imaging time of either 1 minute 23 seconds or 2 minutes 10 seconds. The rapid acquisition times made cardiac or respiratory gating and special head restraint unnecessary. Slice thickness was 6 mm with a 1-mm gap. The number of slices was set to include the entire brain (average of 15 slices). Matrix size was 256 × 128, and field of view was 40 × 20 cm. The remainder of the protocol for the first 27 patients was as described previously.7 In the final 7 patients recruited for the study, DWI sequences used TR/TE of 10 000/100 ms. The diffusion gradient strength was varied between 0 and 22 mT/m, resulting in 3 b values from 0 to 1000 s/mm2.18 The diffusion gradient was applied in 3 orthogonal directions (x, y, and z), and an average of these measurements was calculated that yielded isotropic images19 and a trace of the diffusion tensor, which may minimize the effects of diffusion anisotropy.20

Perfusion Imaging

The initial 18 patients were imaged according to the protocol described previously.7 Perfusion images were obtained in subsequent patients by dynamic first-pass bolus tracking of gadolinium diethyl-enediamine penta-acetic acid (Gd-DTPA) with an EPI gradient echo sequence (TR/TE 2000/70 ms). The Gd-DTPA bolus (0.1 to 0.2 mmol/kg) was administered by a power injector (Spectris MR Injector, MEDRAD) over 3 to 5 seconds via an 18-gauge antecubital fossa cannula. The concentration time curve obtained was processed on a voxel-by-voxel basis to determine an observed or relative mean transit time (rMTT) map, where the rMTT is related to the sum of the true mean transit time plus injection time.21 No arterial input function was used, which made the rMTT maps equivalent to time-to-peak maps. We found that in addition to giving the most visually distinct perfusion-deficit border, as previously reported,7,13 the rMTT map also resulted in perfusion deficits of greater volume than other hemodynamic parameters, which suggests it was more representative of the maximum anatomic extent of perfusion impairment. In addition, rMTT maps give individual voxels scalar values, which allows delineation of regional variations in perfusion within each image. Imaging time was 1 minute 21 seconds.

Magnetic Resonance Angiography

Magnetic resonance angiograms were obtained by use of a 2D phase-contrast sequence in the region of the Circle of Willis with slab thickness of 10 mm (1-mm gap) and velocity encoding speeds of 70 cm/s. Gradients were applied in all 3 orthogonal directions: TR/TE of 25/7.5 ms; flip angle of 30°; matrix of 256 × 128; field of view 20 × 20 cm; and the 2 excitations. Imaging time was 1 minute 50 seconds.12

Data Analysis

Postprocessing of MR images was performed with customized commercial software based on AVS (Advanced Visualization Systems) and an Indigo 2 workstation (Silicon Graphics Inc). Quantitative analysis methods used in our institution have been reported previously.7 The present study used DWI and PI images at the same levels for qualitative comparisons. Isotropic DWI images at the maximum diffusion sensitivity were used to differentiate hypertensive lesions from surrounding normal tissue. We compared the spatial extent and conformation of DWI with rMTT lesions. MRA studies were examined independently by 2 neuroradiologists blinded to other imaging and clinical data and were evaluated for presence and site of vessel occlusion. Statistical analyses were descriptive, with mean and SD for demographic data, and correlations were tested by use of Pearson product moment correlation coefficients.

Results

A total of 41 patients were studied between September 1996 and June 1998. Seven patients were excluded; 3 had cerebral venous sinus thrombosis; 1 each had lobar hemorrhage, pontine infarct, or postseizure paresis; and an additional patient was excluded because of technical difficulties. Paired DWI and PI studies were available for the remaining 34 patients (21 men and 13 women aged 69.1 ± 12.7 years [range 37 to 90 years]).7 MRA was performed in 27 of these patients; results of examinations of 26 of these patients have been reported previously with respect to correlations with lesion...
volumes in cases in which the lesion was in the middle cerebral artery (MCA) territory, and 1 additional patient with an anterior cerebral artery territory lesion is reported here.

MRI studies were performed in the 34 patients at a mean of 11.8 ± 7.2 hours (range 2.5 to 23.3 hours, 12 < 6 hours, and 4 < 3 hours). There were 32 patients with MCA territory lesions (94%), of whom 1 had additional anterior cerebral artery (ACA) territory involvement. The remaining 2 patients had either isolated ACA or posterior cerebral artery (PCA) territory lesions.

Abnormalities of DWI and/or PI were seen in all subjects (Table). Conventional MRI sequences (T1-W, T2-W, and PD sequences), however, showed either no lesion or underestimation of lesion extent compared with DWI and PI lesions. Patients scanned later in the 24-hour time window were more likely to show abnormalities on conventional scans. Lesions were present on MRA examinations in 12 patients (44%), with major vessel occlusions in 8 patients (MCA in 7 patients, ACA in 1 patient).

Clinicoradiological Correlations
The arterial territories depicted by DWI and PI lesions showed good correspondence with acute clinical deficits. Motor abnormalities were always contralateral to the MRI lesions. Isolated left facial weakness was associated with DWI and PI lesions in the right insular region in 1 patient. Of 4 patients with hemiparesis and dysarthria (but without aphasia or neglect), all had lesions only on DWI (2 each with subcortical or small cortical lesions). One patient with isolated right distal arm paresis had a small DWI lesion involving the left motor cortex.

Of 16 patients with aphasia, DWI and PI lesions were seen in the left MCA (15) or PCA (1) territory. One patient with adynamic mute state showed bilateral ACA territory lesions (Figure 1). The right ACA territory was hypoperfused, but the left side showed hyperperfusion, as evidenced by reduced rMTT values; together, this suggested earlier ACA stem occlusion and partial reperfusion by the time of scanning. Unilateral spatial neglect or inattention was associated with right-sided DWI and PI lesions.

Frequency of Lesions
The frequency of the 6 possible combined DWI and PI lesion variations (patterns 1 through 6) is shown in the Table. The mismatch patterns in which the perfusion lesion was of larger volume than the diffusion lesion (PI>DWI patterns 1 and 5)
were the commonest subtype overall (61.7%). Only 1 patient showed a large perfusion and no diffusion lesion (pattern 5). This patient, designated N.A., showed dramatic resolution of all clinical deficits within 2 hours and concomitant resolution of perfusion deficit when scanned at 3 days (Figure 2).

Patterns in which the perfusion deficit was smaller than the diffusion lesion or absent were seen less commonly (38.3%). In patients with patterns 3 or 4 (all but 1 of whom were scanned after 10 hours), some reperfusion was presumed to have occurred by the time of scanning.

Mismatch PI-DWI patterns were seen at all scan times up to 23 hours from onset. All 4 patients scanned within 3 hours had this type of mismatch (3 with pattern 1 and 1 patient [N.A.] with pattern 5). Of the 12 patients scanned within 6 hours, 9 showed PI-DWI patterns, 2 showed equal diffusion and perfusion deficits (pattern 2), and 1 had DWI without PI lesion (pattern 4). The proportion of PI-DWI patterns decreased with scan delay, constituting 75.0% before 6 hours, which in the following 6-hour periods decreased to 71.4%, 50.0%, and 44.4% (Figure 3). Hence, although PI-DWI patterns were more common at an earlier time of scanning, the time to scan alone could not be used to exclude them. Significant reperfusion (pattern 3 or 4) was unusual in patients scanned before 10 hours.

**Topography of PI-DWI lesions**

The anatomic extent and magnitude of DWI and PI lesions were compared in the 20 patients with PI-DWI mismatch pattern 1. In 17 patients, the PI lesion contained most or all of the DWI lesion or lesions, which conforms to the expected model in which DWI lesions develop within the region of hypoperfusion. Of these, 14 had PI lesions within tributaries of the main or distal branches of the MCA territory (hereafter called MCA DWI within PI lesion patients), including 1 with an additional ipsilateral distal ACA territory lesion. In 1 patient, the lesion was solely in ACA territory, and 2 others involved border-zone regions.

Ten of the 14 MCA DWI within PI lesion patients had MRA studies. All but 2 had either occlusion of the MCA stem or of more distal branches. The 2 patients with normal MRA examinations were not distinguishable from the others on the basis of any discernible diffusion or perfusion lesion characteristics. It remains possible that better-quality MRA examinations might have delineated additional abnormalities.

In the MCA DWI within PI lesion patients, the size of the DWI lesion varied markedly relative to the PI lesion. However, there was no significant relationship between time of...
scan after onset and either size of DWI lesion (Pearson product moment correlation $r=0.17$, $P=0.56$) or ratio of DWI to PI lesion volume ($r=0.08$, $P=0.78$). Thus, DWI lesions were not significantly smaller if the MRI study was performed earlier after stroke onset, which implies that time alone was not the major determinant of transition to DWI lesion.

Specific anatomic regions appeared preferentially susceptible to DWI lesions. Twelve MCA DWI within PI lesion patients had DWI lesions involving the insula (eg, Figures 4 and 5). In these cases, there was extension of the DWI abnormality beyond the MCA insular arteries into distal MCA arterial tributaries in 6 patients. In 10 of these 12 cases, MRA studies had been performed, of which 8 were abnormal (6 MCA occlusions, 2 more-distal branch occlusions). Another patient, scanned at 4 hours, showed a curvilinear external capsule DWI lesion medial to the insula and lateral to the lenticulostriate territory (Figure 6A). The lenticulostriate territory was affected by DWI abnormality in 2 patients, either in continuity with insular region lesion (Figure 5) or as the sole territory with DWI abnormality (Figure 7).

None of the 14 patients with insular, capsular, or lenticulostriate DWI abnormalities showed PI lesions proximal to their DWI lesions, which suggests the DWI lesion developed at the site of MCA occlusion. Two patients showed normal perfusion in the proximal abnormal DWI region (eg, Figure 7) suggestive of reperfusion, despite more lateral PI abnormalities in regions consistent with distal MCA tributaries. Both of these were clinically considered of embolic pathogenesis due to atrial fibrillation. At follow-up scanning, neither showed infarction beyond the initial DWI lesions, which indicates the distal PI lesions had reperfused without evolution to infarction.

In the majority of patients, the regional severity of rMTT abnormality at the time of scanning did not appear to directly correlate with the site of DWI lesion. Ten patients showed relatively uniform PI lesions, including those within the region of the DWI lesion. However, 2 patients showed inhomogeneity of rMTT abnormality within the PI lesion, with slowest transit times colocalizing with the DWI lesions (Figure 4A and Figure 8). These core rMTT lesions were surrounded by regions of lesser but still abnormal perfusion without DWI lesions. Patency of the MCA on MRA was shown in 1 patient (Figure 4A), but in the other patient (Figure 8), reduced MCA flow and distal occlusions were
found. Hence, in these 2 patients, the DWI lesion appeared to be developing only where hypoperfusion was maximal, which suggests a quantitative regional correlation.

Two PI>DWI pattern patients showed regional hyperperfusion as evidenced by hypointense regions on the rMTT maps (Figures 1 and 5). In 1 patient, the hyperperfused area was within the MCA territory between 2 areas of hypoperfusion and was colocalized with this patient’s DWI abnormality (Figure 5), which had not enlarged when reimaged 3 days later. Cardioembolic pathogenesis was suspected in the setting of atrial fibrillation. The other patient showed hypoperfusion in the right ACA territory and hyperperfusion in the left ACA territory with occlusion of the right ACA on MRA (Figure 1). A DWI lesion was present only in the right ACA territory, even at follow-up imaging, but pathogenesis was not determined. Anatomic observations suggested these were not artifactual in nature. Their locations were limited to recognized arterial territories and were contiguous with vascular territories affected by regional hypoperfusion, ie, distal branches of the MCA or the common trunk of the ACA, which suggests a common pathogenesis.

Mismatch between DWI and PI lesions at their margins was common. There were 2 MCA DWI within PI lesion patients who had DWI lesions on inferior slices without corresponding PI abnormalities at these levels. On the other hand, DWI lesions were not present on all imaged levels at which PI lesions were observed. Six of the MCA DWI within PI lesion patients had at least 2 imaged levels with PI lesion...
but no DWI lesion. These were seen both above and below the DWI lesion and at any scan time (range 4 to 21.7 hours from stroke onset), so that this was not just an early phenomenon (eg, Figure 7). Scanning at just these levels would have missed the DWI lesions.

The 2 patients with presumed border-zone lesions showed small, patchy, deep-white-matter DWI lesions within the border-zone region of MCA, ACA, and PCA territories. In 1 of these patients, the DWI lesions lay within wedge-shaped cortically based PI lesions with apices toward the lateral ventricles.22 The second patient had poor-quality perfusion images related to low cardiac output, which markedly delayed and attenuated the signal intensity–time curve so that conclusions about PI lesion extent were not possible.

**Topography of Other Lesions**

In the 13 patients with non-PI>DWI patterns, 5 had DWI lesions in the deep white matter with minimal or no concomitant PI lesions. Four of these patients showed multiple lesions consistent with partial internal border-zone infarction and clinical histories consistent with systemic hypoperfusion.23,24 The fifth nonpenumbral patient was presumed to have single lenticulostriate territory deep-perforator occlusion.

Small, superiorly situated, peripheral cortical MCA territory DWI lesions with no perfusion deficit were seen in 4 patients. These were all left sided and had minor or circumscribed functional impairments, such as an isolated contralateral brachial paresis, consistent with occlusions of a single small MCA branch.

The remaining 4 patients had patterns consistent with cortical arterial territory ischemia. Two showed insula involvement (eg, Figure 6B) and variable branches of MCA territory DWI lesions, and 1 had PCA territory involvement.

**Discussion**

Concordance analysis of combined diffusion and perfusion MRI in acute stroke has revealed several novel findings of clinical interest. Clinico-radiological correlations confirm that in addition to quantitative correlations with clinical scale scores,7 individual MRI lesion loci relate appropriately to clinical syndromes. These techniques can therefore augment other modalities in correlative studies elucidating brain-behavior relationships acutely.

Patterns with PI>DWI are likely to be found in the early hours after stroke onset but may also be seen up to 24 hours. The greater efficacy of thrombolytic treatment with earlier administration1,2,25–27 is likely to be influenced by the frequency of significant volumes of salvageable hypoperfused tissue, for which we believe PI>DWI patterns are markers. Although our study supports the vast majority of patients having PI>DWI patterns throughout the first 24 hours of stroke,28-29 the fact that benefit from early thrombolysis is no more than 30%-31 suggests other factors must interact (eg, apoptosis, DWI lesion size or site, and rapidity of reperfusion).15,30,31

Individual deviations from the theoretical topography of an infarct-core DWI lesion wholly within a larger perfusion lesion were commonly seen. MRI images are but a snapshot of a complex dynamic state with evolution based on the individual’s unique anatomic and vascular constraints, as well as the responsible pathophysiological cause. Thus, there was a spectrum of lesions, from perfusion without diffusion abnormality (N.A., Figure 2)32 through diffusion lesion cores mostly contained within perfusion abnormalities, perfused diffusion lesions in the distributions of proximal arterial branches but with distal cortical-branch perfusion deficits (eg, Figure 7), and other patterns in which diffusion lesions were larger than concomitant perfusion deficits. Each of these patterns may have implications for clinical decision making.

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**Figure 7.** Nonconcordance of isotropic DWI (A) and rMTT (B) lesions. Patient presented with sudden aphasia and right hemiparesis at 23 hours. A, Dense DWI lesion limited to left lenticulostriate territory. B, Noncontiguous patchy hypoperfusion on rMTT maps in branches of the left inferior division of the MCA. Infarction on T2-weighted images matched DWI lesion at 3 months. Pathogenesis was not determined.
Recognition of pattern 5, in which there is PI deficit only (Figure 2), is particularly instructive. Although uncommon, this likely represents a pure perfusion deficit (ie, tissue at risk but not committed to infarction) at the time of scanning. Our single patient showed spontaneous resolution of clinical and perfusion deficits within hours of imaging, consistent with a spectacular shrinking deficit syndrome. Another patient, with similar isolated perfusion deficit only, subsequently failed to improve clinically or radiologically, and transition to infarction in 3 other patients has been described recently. In contrast, our 2 patients with proximal DWI lesion and distal PI lesions in MCA tributaries did not evolve to distal infarction. We believe these 2 clinical courses lie at the extremes of a spectrum of possible outcomes in such patients that probably is influenced by the intensity and persistence of hypoperfusion, as well as by other factors. Transition to eventual infarction (as represented by early DWI lesions) is not made inevitable by the presence of a PI lesion. Thus, the absence of a DWI lesion is not a “false-negative” finding, even in profound ischemia, but an important marker of persisting viability. The presence of this pattern at any time after onset of ischemia may argue for revascularization therapy.

The main findings in the present study relate to the topographic lesion deviations from the prototypic central core and hypoperfused periphery, which suggests the likely site of arterial occlusion, prior or current locus of maximal hypoperfusion, and pathogenesis. The clearest demonstration of the likely site of arterial occlusion was seen in patients with DWI lesions in the territories of the perforating branches of the horizontal segment of the MCA (Figures 4 through 7). These involved the arteries that sequentially arise from the MCA to supply the lenticulostriate, external capsular, and insular regions. Such lesions suggested arterial obstruction at their origin sufficient to cause probable transition to infarction at some time before scanning. Some of these regions with DWI lesions but not contained within PI lesions indicated proximal reperfusion. In support of this contention were the few patients with additional PI lesions in more-distal cortical branches of the MCA (eg, Figure 7) and clinical evidence of sources of emboli that implied dissolution and dislodgement of clot. However, the situation in this patient (Figure 7) was complex, because MRA showed MCA occlusion, which implies that collateral flow was supplying much of the overlying cortical mantle. Although a PI>DWI mismatch existed (with overall volume of PI greater than DWI lesion), there was no overlap in these lesions, with additional reperfusion only possible within the PI lesion. This patient’s final infarct did not include these cortical branches, unlike other similar acute patients, which again emphasizes the parlous but not committed state of tissue with PI but no DWI deficit. In such patients, prediction of net benefit from thrombolysis may be complex.

The insular region was frequently involved by DWI or PI lesions or both (Figure 4). Where no MCA arterial territory
proximal to insular branches was involved, the site of arterial occlusion could be inferred and was frequently confirmed on MRA (80% of cases). The fact that 2 patients had no occlusions on MRA despite insular PI lesions suggested occlusions in branches beyond the resolution of MRA sequences used in the present study. Abnormalities of the “insular ribbon” on CT scans have been reported previously to predict contiguous MCA infarction. Similar logic would apply to DWI abnormalities seen in the lenticulostriate territory (Figure 7), consistent with prior proximal occlusion theories of the mechanism of striatocapsular infarction.37,38

The high frequency of DWI lesions in the proximal MCA territories may relate to the severity of perfusion deficits. In 2 patients, there was direct evidence for colocalization of the most severe hyperperfusion and the development of diffusion lesions (Figure 4A and Figure 8). In 1 of these patients, the appropriate MRA occlusions were consistent with the expected maximal hyperperfusion furthest from collateral supplies. However, in the majority of patients with PI>DWI mismatch, DWI lesions occurred within regions of homogeneous hyperperfusion, which suggests that perfusion abnormalities had been more severe or were present longer in these regions before scanning, or perhaps that the DWI lesions were emerging in selectively vulnerable tissue. Additional research is required to investigate these alternatives.

Topographic appearance also suggested likely stroke pathophysiology in selected patients. In 2 patients, we were able to identify border-zone mechanisms.22 Lacunar infarction was recognized as a pattern with matching PI and DWI lesions in central white matter. Embolic pathogenesis was suggested where multiple sites of occlusion occurred with the presence of PI lesions in regions supplied by cortical arterial branches and separate proximal DWI lesions (eg, Figure 7). The reperfusion inferred by the presence of isolated proximal DWI lesions strongly suggests that the initial proximal occlusion had lysed or fragmented, perhaps lodging downstream in the regions represented by the multiple divisional-branch PI lesions. Embolic pathogenesis was also suggested by the single case with both MCA and distal ipsilateral ACA territory perfusion lesions, consistent with origin from a cardiac valvular lesion. Moreover, the uncommon finding of focal hyperperfusion, as observed in 2 patients, in arterial territories contiguous or within those affected by other PI or DWI lesions also suggested fragmentation of prior occlusions. The mechanism of such focal hyperperfusion is unknown but did not appear to be nonnutritional or “luxury” perfusion, because later DWI lesions did not develop.39 Future prospective trials should clarify the predictive value of patterns suggestive of embolic fragmentation for subsequent reperfusion.

Imaging at the periphery of PI>DWI mismatched lesions showed variability, which might confound limited radiological assessments. Perfusion abnormalities without concomitant DWI lesions were seen at the margins of lesions in 43% of patients with the most common PI>DWI pattern. This combination of lesions resembled pattern 5. In addition, 2 patients showed the opposite pattern, with DWI lesion but no PI abnormality in slice levels at the inferior lesion margin. This pattern may relate to focal reperfusion as discussed above, with early, more-proximal occlusion, or other mechanisms.40–42 In both cases, less than complete infarct imaging might lead to erroneous inferences about the pattern of perfusion-to-diffusion mismatch.40

We conclude that consideration of the qualitative features of DWI and PI studies is an important area of future study, particularly where revascularization therapies are being considered. Variations in the patterns of abnormalities, which are present within minutes of infarction onset, may refine clinical decisions regarding pathophysiology, including decisions for patients who present beyond currently accepted therapeutic time windows.

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