ASPECTS (Alberta Stroke Program Early CT Score)
Assessment of the Perfusion–Diffusion Mismatch

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Background and Purpose—Rapid and reliable assessment of the perfusion-weighted imaging (PWI)/diffusion-weighted imaging (DWI) mismatch is required to promote its wider application in both acute stroke clinical routine and trials. We tested whether an evaluation based on the Alberta Stroke Program Early CT Score (ASPECTS) reliably identifies the PWI/DWI mismatch.

Methods—A total of 232 consecutive patients with acute middle cerebral artery stroke who underwent pretreatment magnetic resonance imaging (PWI and DWI) were retrospectively evaluated. PWI-ASPECTS and DWI-ASPECTS were determined blind from manually segmented PWI and DWI volumes. Mismatch-ASPECTS was defined as the difference between PWI-ASPECTS and DWI-ASPECTS (a high score indicates a large mismatch). We determined the mismatch-ASPECTS cutoff that best identified the volumetric mismatch, defined as Volume\(_{\text{pwi}}\)/Volume\(_{\text{DWI}}\) ≥ 1.8, a volume difference ≥ 15 mL, and a Volume\(_{\text{DWI}}\) < 70 mL.

Results—Inter-reader agreement was almost perfect for PWI-ASPECTS (κ = 0.95 [95% confidence interval, 0.90–1]), and DWI-ASPECTS (κ = 0.96 [95% confidence interval, 0.91–1]). There were strong negative correlations between volumetric and ASPECTS-based assessments of DWI lesions (ρ = −0.84, P < 0.01) and PWI lesions (ρ = −0.90, P < 0.01). Receiver operating characteristic curve analysis showed that a mismatch-ASPECTS ≥ 2 best identified a volumetric mismatch, with a sensitivity of 0.93 (95% confidence interval, 0.89–0.98) and a specificity of 0.82 (95% confidence interval, 0.74–0.89).

Conclusions—The mismatch-ASPECTS method can detect a true mismatch in patients with acute middle cerebral artery stroke. It could be used for rapid screening of patients with eligible mismatch, in centers not equipped with ultrafast postprocessing software. (Stroke. 2016;47:2553–2558. DOI: 10.1161/STROKEAHA.116.013676.)

Key Words: magnetic resonance imaging ■ middle cerebral artery ■ perfusion imaging ■ stroke

Operationally, ischemic penumbra is defined using magnetic resonance imaging as the mismatch between the hypoperfused area on perfusion-weighted imaging (PWI) and the abnormal area on diffusion-weighted imaging (DWI). The presence of a PWI/DWI mismatch has been used as inclusion criteria in clinical trials. However, although debated, the visual assessment of PWI/DWI is insufficiently reliable to be used in trials because of limited agreement with volumetric measurements. Volumetric measurements are accurate and reproducible, but manual segmentation is time consuming, which may delay acute stroke therapy. Although software for ultrafast automated assessment of PWI/DWI mismatch such as RAPID (Rapid Processing of Perfusion and Diffusion) are commercially available, there is a need for alternative surrogates in case of software failure. Moreover, in centers not equipped with ultrafast automated software, clinicians do not have mismatch information at hand for decision making.

The semiquantitative DWI-Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) is increasingly used because it is straightforward, reproducible, and assessable at bedside. It has been proposed as a surrogate for large (70–100 mL) DWI volume cut points. ASPECT scoring could also be applied to PWI maps to rapidly estimate the extent of hypoperfusion and the PWI/DWI mismatch. In a study on a small sample, this approach reached high specificity for the detection of volumetric mismatch, with excellent between-rater agreement. In this latter study, mismatch definition was based on time-to-maximum (T\(_{\text{max}}\)) > 2 s, which overestimates the area at risk of infarction. Using state-of-the-art more stringent T\(_{\text{max}}\) threshold (> 6 s), we aimed to determine whether ASPECTS-based assessment can reliably substitute for the volumetric approach for the evaluation of the PWI/DWI mismatch, in a large series of consecutive patients with acute middle cerebral artery (MCA) stroke imaged before...
treatment. To this end, ASPECTS scoring implementation mimicked the acute clinical situation, that is, with both DWI and PWI images accessible for comparison.

Methods
Study Population
Data for this retrospective analysis were extracted from a monocentric prospective register of consecutive patients treated by intravenous thrombolysis, thrombectomy or both for acute ischemic stroke from 2001 to 2014. Patients were included if they had 1/a MCA ischemic stroke, 2/a pretreatment magnetic resonance imaging (1.5-T, GE Healthcare), including at least a DWI (3 directions; b=1000 s/mm²; 6-mm contiguous slices, 24 axial sections), and a PWI sequence (T2*-weighted echoplanar sequence, repetition time/echo time 2000/60, field of view 24×24 cm², one excitation, 64×96 matrix, 6-mm contiguous slices, 24 axial sections and repetition 50 times after a bolus [5–7 mL/s] of 20 mL of gadoteric acid). Patients with technically inadequate PWI sequences were excluded. Patients with anterior cerebral artery and posterior circulation stroke were also excluded because ASPECTS was originally designed for the assessment of stroke in the MCA territory. Part of the population (77%) was included in a former study on the relationship between DWI volume and DWI-ASPECTS. In accordance with the French legislation, Institutional or Ethics Committee approval was not required for this study because it only implied retrospective analysis of anonymized data collected as part of routine clinical care.

Volume Segmentation
PWI and DWI were processed, blind to clinical data, using an automated 3-dimensional rigid registration (FMRIB’s Linear Image Registration Tool; FLIRT, v5.5). The quality of this registration was visually checked. DWI lesions were manually segmented using interactive tools based on DWI signal intensity (MANGO software, v3.1.1, Research imaging Institute, UTHSCSA). DWI lesions were outlined according to their maximal visual extent, after careful adjustment of the window level, PWI data were postprocessed using BrainStat arterial input function (READY View) software for automated generation of Tmax maps. These were obtained by circular deconvolution of the tissue concentration time course using an arterial input function from controlateral arteries. Tmax was corrected for slice acquisition timing differences using temporal interpolation and was, thus, a continuous parameter. The following steps were then performed using the MANGO software: extracting a brain mask of apparent diffusion coefficient <1.3×10⁻⁴ mm²/s to remove cerebrospinal fluid voxels, projecting this mask onto Tmax maps for brain voxels extraction, and segmenting the hypoperfused voxels according to Tmax >6 s threshold, as recommended by others. The presence of a PWI/DWI-mismatch was derived from the DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) 2 criteria and defined as VolumeTmax VolumeDWI ≥1.8, a volume difference ≥15 mL, and a VolumeTmax VolumeDWI <70 mL. This binary variable was set as the reference and termed volumetric mismatch in what follows.

Alberta Stroke Program Early CT Score
In this pragmatic study, image assessment for ASPECTS scoring was designed to mimic the acute clinical setting where one needs to make fast decisions based on the DWI and PWI images. PWI-ASPECTS and DWI-ASPECTS were assessed by a radiologist (5 years of experience), and 50 (21.5%) cases were randomly selected for an independent assessment of reproducibility by a stroke neurologist (8 years of experience). DWI and PWI images were displayed simultaneously. DWI was scored first based only on trace images (b=1000 s/mm²). To overcome potential difficulties in identifying the anatomic landmarks necessary for ASPECTS scoring on the Tmax maps, the raters could use a cursor synchronized between PWI and DWI (Figure 1). In case of obvious misregistration because of head motion between DWI and PWI acquisitions, raters were instructed to use the first volume of the PWI, before signal stabilization, as anatomic landmark instead of DWI. The 2 ASPECTS slices (basal ganglia and immediately superrior to them) were identified on the DWI images. Investigators could vary at the intensity window level and width settings on DWI, but not on thresholded Tmax maps, which were displayed using a binary scale. Each ASPECTS region was scored 0 if abnormal and 1 if normal. These subscores were summed to compute DWI-ASPECTS and PWI-ASPECTS. Mismatch-ASPECTS was then computed as the difference between PWI-ASPECTS and DWI-ASPECTS (ranging from 0 to 10, a high score corresponding to a large mismatch).

Statistical Analysis
Statistical analysis was performed using IBM SPSS 19.0 software. A weighted κ was used to assess interobserver reproducibility separately for PWI-, DWI- and mismatch-ASPECTS total scores. Correlations between DWI-ASPECTS, PWI-ASPECTS, mismatch-ASPECTS, and volumetric measurements were determined using Spearman rank correlation coefficient. The ability of the mismatch-ASPECTS to predict the presence of a volumetric mismatch (binary variable) was assessed with receiver operating characteristic (ROC) analysis.
curve. Given the lack of established ASPECTS cut point in literature for identification of the volumetric mismatch, the optimal cut point was determined using the Youden Index. This cut point was used to measure the diagnostic performances of the mismatch-ASPECTS for determining the presence of a volumetric mismatch and for assessing interobserver agreement (κ-statistic).

Results

Study Population

During the study period, 620 patients underwent intravenous thrombolysis, thrombectomy or both for acute ischemic stroke. Excluded patients (n=388; pretreatment CT: n=68, pretreatment magnetic resonance imaging not available in DICOM format: n=50, PWI not performed or technically inadequate: n=219, posterior circulation or anterior cerebral artery stroke: n=51) did not differ from included patients for age and National Institutes of Health Stroke Scale (NIHSS). Two-hundred thirty-two patients met the eligibility criteria. Clinical and imaging characteristics of the studied population are presented in Table.

Imaging Results

The median (IQR) DWI, PWI, and mismatch volumes were 16.3 mL (6.5–47.4), 64.5 mL (24.2–125.4), and 40 mL (13.4–81.8), respectively. A volumetric mismatch was present in 118 of 232 (50.9%) patients. Median (IQR) DWI-ASPECTS, PWI-ASPECTS, and mismatch-ASPECTS were 7 (6–8), 5 (2–7), and 2 (0–4), respectively. As shown in Figure 2, the distribution of mismatch patterns in each ASPECT region (hypoperfusion with a normal DWI) was as follows: M2 (45.7%), M6 (40.5%), and M3 (37.5%), but <7% in basal ganglia and internal capsule. Interobserver reproducibility was weighted κ≥0.95 (95% confidence interval [CI], 0.90–1) for PWI-ASPECTS, and 0.96 (95% CI, 0.91–1) for DWI-ASPECTS. There were strong correlations between volumetric and ASPECTS-based assessments of DWI lesions (p=0.84, P<0.01), PWI lesions (p=0.90, P<0.01; Figure 3) and mismatch-ASPECTS (p=0.80, P<0.01).

On the basis of the receiver operating characteristic curve analysis (area under the curve=0.93 [95% CI, 0.9–0.97]) and Youden Index, a mismatch-ASPECTS≥2 best identified a volumetric mismatch (Figure 4). The associated sensitivity and specificity were 0.93 (95% CI, 0.89–0.98) and 0.82 (95% CI, 0.74–0.89) with positive and negative predictive values of 0.84 (95% CI, 0.77–0.90) and 0.92 (95% CI, 0.85–0.96), positive and negative likelihood ratios of 5.06 (95% CI, 3.43–7.47) and 0.08 (95% CI, 0.04–0.16). When focusing on the 145 patients with proximal occlusions (ICA or M1), the same mismatch-ASPECTS≥2 cut point best identified a volumetric mismatch (area under the curve=0.93 with sensitivity=0.98 (95% CI, 0.95–1) and specificity=0.71 (95% CI, 0.59–0.83).

An alternative mismatch-ASPECTS cut point ≥3 allowed to reach a specificity of 0.93 (95% CI, 0.88–0.98) and a positive predictive value of 0.91 (95% CI 0.84–0.96) but lowered the sensitivity to 0.72 (95% CI, 0.64–0.80) and negative predictive value to 0.76 (95% CI 0.68–0.83). Interobserver reproducibility of mismatch-ASPECTS≥2 was κ=0.87 (95% CI, 0.76–0.99). Using an alternative definition of the volumetric mismatch (PWI/DWI>1.2 instead of 1.8), the same mismatch-ASPECTS cut point (≥2) best identified the volumetric mismatch with sensitivity=0.90 (95% CI, 0.85–0.96), specificity=0.83 (95% CI, 0.76–0.90).

Table. Clinical and Imaging Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median [IQR] or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70 [56–79]</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>109 (47)</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>14 [7–19]</td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>29 (13.7)</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>124 (58.5)</td>
</tr>
<tr>
<td>Atrial fibrillation*</td>
<td>52 (24.5)</td>
</tr>
<tr>
<td>Smoking*</td>
<td>89 (42)</td>
</tr>
<tr>
<td>Dyslipidemia*</td>
<td>87 (41)</td>
</tr>
<tr>
<td>History of stroke*</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Onset-to-MRI time, min</td>
<td>115 [87–159.8]</td>
</tr>
<tr>
<td>Occlusion site</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>40 (17.2)</td>
</tr>
<tr>
<td>M1</td>
<td>105 (45.3)</td>
</tr>
<tr>
<td>Distal MCA</td>
<td>63 (27.2)</td>
</tr>
<tr>
<td>No visible occlusion</td>
<td>24 (10.3)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Thrombolysis alone</td>
<td>199 (86)</td>
</tr>
<tr>
<td>Thrombolysis and intra-arterial treatment</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Intra-arterial treatment alone</td>
<td>24 (10)</td>
</tr>
<tr>
<td>DWI volume, mL</td>
<td>16.3 [6.5–47.4]</td>
</tr>
<tr>
<td>DWI volume ≥70 mL</td>
<td>41 (17.7)</td>
</tr>
<tr>
<td>PWI volume, mL</td>
<td>64.5 [24.2–125.4]</td>
</tr>
<tr>
<td>Mismatch volume, mL</td>
<td>40 [13.4–81.8]</td>
</tr>
<tr>
<td>DWI-ASPECTS</td>
<td>7 [6–8]</td>
</tr>
<tr>
<td>PWI-ASPECTS</td>
<td>5 [2–7]</td>
</tr>
<tr>
<td>Mismatch-ASPECTS</td>
<td>2 [0–4]</td>
</tr>
</tbody>
</table>

ASPECTS indicates Alberta Stroke Program Early CT Score; DWI, diffusion-weighted imaging; IQR, interquartile range; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and PWI, perfusion-weighted imaging.

*Evaluated on 212 of 232 patients (91.4%).

Discussion

In this study, we found that (1) PWI-ASPECTS provided an estimate of the hypoperfusion volume, (2) interobserver reproducibilities of ASPECTS-based assessments were almost perfect, and (3) a mismatch-ASPECTS≥2 identified patients with volumetric mismatch with a high sensitivity and specificity. Given its simplicity and excellent performance, the ASPECTS-based approach may represent a convenient surrogate for mismatch assessment in future clinical trials involving multiple centers and whenever PWI is routinely used for treatment decision.
Although not initially designed to substitute for volumes, the ASPECTS-based method does provide semiquantitative estimates of them. This has been shown about DWI in large populations with stroke, with excellent correlation between this semiquantitative and the volumetric approach.\textsuperscript{10,11,20} offering the possibility of using extreme DWI-ASPECTS scores as surrogates for important volume cut points.\textsuperscript{10,21} About PWI and PWI/DWI mismatch, the correspondence between ASPECTS and volumetric measurements has received little attention so far. We found that, although each ASPECTS point corresponded to a wide range of volumes, there was a strong correlation between the 2 methods. As proposed for DWI,\textsuperscript{10,11,20} our results could be used to derive PWI-ASPECTS or mismatch-ASPECTS cut points that could serve as surrogate for volume cut points. However, to date, there is no established volume cut point based on PWI maps thresholded at $T_{\text{max}}>6$ s, as used in this study.

The inter-rater agreement was almost perfect for both DWI- and PWI-ASPECTS, and consequently for the assessment of the mismatch-ASPECTS. These results confirm those from another group in a small sample of 35 patients and using a less stringent $T_{\text{max}}$ threshold.\textsuperscript{12} This excellent reproducibility is first explained by the regional ASPECTS analysis that overlooks variability at the voxel level. This variability, which has been shown to be prominent at the periphery of the hypoperfused area,\textsuperscript{12} was avoided in our study by the use of binary-scaled $T_{\text{max}}$ maps.

The hypoperfused, but not yet compromised, regions most often involved superficial cortical ASPECTS regions. This is consistent with the known pathophysiology of the core and penumbra in proximal MCA occlusions, with the core early involving the deep territory and the penumbra the more superficial one.\textsuperscript{22,23} Importantly, we found that a mismatch-ASPECTS $\geq 2$ identified the presence of a volumetric mismatch with a high sensitivity and specificity. An alternative mismatch-ASPECTS$\geq 3$ cut point would insure a low false-positive rate, thus minimizing the risk of detecting a mismatch.

![Figure 2](image1.png)

**Figure 2.** Frequency of Alberta Stroke Program Early CT Score (ASPECTS) mismatch (ie, presence of hypoperfusion but normal diffusion-weighted imaging) in each ASPECTS region. C indicates caudate nucleus; I, insular ribbon; IC, internal capsule; L, lentiform nucleus; M1, anterior middle cerebral artery (MCA) cortex; M2, MCA cortex lateral to the insular ribbon; M3, posterior MCA cortex; and M4, M5, M6, anterior, lateral, and posterior MCA territory immediately superior to M1, M2, and M3.

![Figure 3](image2.png)

**Figure 3.** Box plot of perfusion-weighted imaging (PWI)- and mismatch-Alberta Stroke Program Early CT Score (ASPECTS) vs corresponding segmented volumes. Boxes indicate interquartile range; horizontal lines, median; points, mean; and whiskers, extreme values.
in patients without volumetric mismatch. Although a score of 2 seems a relatively small number of affected ASPECTS regions, they corresponded to sizeable volumes of mismatch given that they frequently involved cortical (ie, large) areas in our data set. Moreover, the proposed ASPECTS-mismatch method provides geographic information that are not available with simple volumetric assessment. For instance, a mismatch in 2 contiguous cortical ASPECTS regions could be due to a dominant M2 branch occlusion, which may be treatable by thrombectomy. The ≥2 optimal cut point in our study matches the one found on a smaller sample using less stringent criteria (T\text{max}>2 s). This is partly because of the fact that the choice of a different T\text{max} threshold affects both ASPECTS and volumetric PWI evaluations in the same direction. Although the cut point theoretically depends on the extent of the mismatch that one aims to detect, we found that mismatch-ASPECTS≥2 was also the best cut point to identify a smaller mismatch (PWI/DWI>1.2).

In daily practice, thresholded T\text{max} maps can be quickly generated by the radiographer and transferred to the PACS (Picture Archiving and Communication System) or any DICOM viewer. By simply looking at T\text{max} maps and DWI on a dual-screen computer, the attending stroke physician can score these images for mismatch using ASPECTS in real time, with no additional software-related costs or further postprocessing. Similar advantages are advocated for the ABC/2 method, which consists in 3 linear diameters along orthogonal axes to estimate the DWI and hypoperfused areas. This method is, however, limited in case of fragmented lesions and requires calculations. It also does not provide an accurate estimation of the mismatch area whenever PWI and DWI lesions are not colocalized.

The coregistered mismatch, which takes into account these spatial relationships, was a better selection criterion than the conventional noncoregistered mismatch in a post hoc analysis of EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) and pooled DEFUSE-EPITHET data sets. Coregistration, however, requires dedicated software and is time consuming. An estimate of the coregistered mismatch could, however, be obtained with no additional time by simply scoring ASPECTS for regions showing a coregistered mismatch pattern, that is, hypoperfused but normal DWI. According to the design of this study, the volumetric and ASPECTS mismatches were not coregistered to fit with daily clinical practice and trials. We, however, repeated post hoc analysis based on a coregistered mismatch-ASPECTS, and found again that the ≥2 cutoff accurately identifies the coregistered mismatch (sensitivity=0.90 [95% CI, 0.84–0.94] and specificity=0.79 [95% CI, 0.70–0.86]).

Our study has some limitations. First, we focused on the diagnostic performance of mismatch-ASPECTS to identify the volumetric mismatch, but did not assess its prognostic value in terms of infarct growth or clinical outcome. Second, our results were based on a single T\text{max} threshold (6 s) and cannot be generalized to more stringent thresholds. Moreover, we did not use the precise definition of target mismatch as originally defined in DEFUSE 2 (T\text{max}>10 s <100 mL). Third, the simultaneous display of DWI and PWI maps may have biased the scoring of PWI-ASPECT; and hence that of the mismatch-ASPECT. However, this approach is pragmatic because it mimics that used in clinical setting. Fourth, our results were obtained on a single-center database and might be influenced by the rate of distal occlusions. The spatial distribution of the mismatch-ASPECTS would likely be different in cohorts of patients with more proximal occlusions. However, the mismatch-ASPECTS optimal cut point is unlikely to be substantially modified by the rate of distal occlusion because results were similar when the analysis was focused on ICA and M1 occlusions. Our findings need to be confirmed with an independent data set, ideally using data from several MR manufacturers. Finally, our findings apply only to MR and hence to those centers using acute stroke MR as routine admission imaging. Further studies are needed to test the performances of mismatch-ASPECTS extracted from plain CT and CT perfusion data.

In conclusion, the mismatch-ASPECTS method can detect MR-based mismatch in acute MCA stroke patients before treatment decision. A mismatch-ASPECTS≥2 identified patients with a volumetric mismatch with a high sensitivity and specificity. This simple method, applicable at the bedside, may be of use in centers that routinely perform PWI in the clinical setting. It could also promote the use of multimodal MR inclusion/exclusion criteria in future therapeutic trials by providing a surrogate for PWI/DWI mismatch. This would help patient recruitment in case of software failure, when expertise in PWI/DWI segmentation is lacking, or in centers not equipped with dedicated software.

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**Disclosures**

None.
References


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