Differential Prognosis of Isolated Cortical Swelling and Hypoattenuation on CT in Acute Stroke

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Background and Purpose—The Alberta Stroke Program Early CT Score (ASPECTS) is a validated method of assessing parenchymal ischemic changes, including focal swelling and hypoattenuation. The hypothesis that these signs result from different pathophysiological processes was tested by comparing CT with diffusion and perfusion-weighted MRI.

Methods—MRI and CT were performed, within 2 hours of each other, in 30 ischemic stroke patients 17 hours after symptom onset. Relative apparent diffusion coefficient, relative cerebral blood flow, and relative cerebral blood volume were calculated for individual cortical ASPECTS regions. Regional infarction was assessed on days 3 to 5.

Results—Isolated focal swelling was seen in 25 ASPECTS cortical regions from 6 patients. Cortical hypoattenuation was observed in 25 regions from 11 patients. Median relative apparent diffusion coefficient was significantly lower in hypoattenuated regions (0.84; interquartile range, 0.66 to 0.91) relative to those with focal swelling (0.97; interquartile range, 0.91 to 1.01; \( P < 0.001 \)). Median relative cerebral blood flow in focal swelling regions (70.4 to 93.0) was similar to that of tissue that appeared normal on CT (71.8%; interquartile range, 47.1 to 94.5). In hypoattenuated regions, relative cerebral blood flow was significantly decreased (37.0%; interquartile range, 25.6 to 70.2; \( P = 0.002 \)). Median relative cerebral blood volume was increased (121.1%; interquartile range, 112.0 to 130.3) in focal swelling regions, relative to normal-appearing tissue (94.7%; interquartile range, 62.0 to 114.6; \( P < 0.001 \)), but decreased in hypoattenuated regions (58.9%; interquartile range, 47.5 to 92.7; \( P = 0.012 \)). Infarction occurred in all hypoattenuated regions, but only in 32% of those with focal swelling.

Conclusions—Elevated relative cerebral blood volume and normal relative apparent diffusion coefficient in ASPECTS regions with focal swelling on CT is consistent with penumbral tissue. Isolated focal swelling is not always associated with infarction. These results support removal of focal swelling from the ASPECTS system. (Stroke. 2007;38:941-947.)

Key Words: computerized tomography • diffusion-weighted imaging • perfusion-weighted imaging

Early ischemic CT changes in acute stroke have been found to be predictive of outcome.1,2 Although controversial, there is also some evidence that ischemic changes influence the response to reperfusion therapies, including the probability of hemorrhagic transformation.2–4

The Alberta Stroke Program Early CT Score (ASPECTS) is a validated semi-quantitative scale useful for assessing the extent of ischemic changes within the middle cerebral artery territory.5,6 This is a negative ordinal scale, in which normal-appearing brains are scored as 10 and those with ischemic changes involving the entire middle cerebral artery territory are rated 0. It has previously been demonstrated that ASPECTS scores >7 predict a better outcome in patients treated with thrombolysis.3 Parenchymal changes seen in acute ischemia include focal swelling/sulcal effacement and hypoattenuation. ASPECTS currently does not differentiate between these early signs and both are included in the final scores. This has been recognized as a potential source of inaccuracy in an investigation utilizing ASPECTS.7 Indeed, another recent study suggests that hypoattenuation and focal swelling are not actually equivalent in terms of predicting the extent of final infarction.8 Specifically, it appears that hypoattenuation represents irreversible infarction, but focal swelling does not. We tested the hypothesis that ASPECTS regions with these 2 signs have different underlying pathophysiology and prognostic significance by comparing CT with diffusion-weighted imaging and perfusion-weighted imaging (PWI) changes.
Patients and Methods

Patients
Thirty patients were selected retrospectively from the imaging database at 2 tertiary care hospitals. A total of 212 patients were imaged between August 2001 and December 2004. All patients were originally included in other completed or ongoing observational and interventional stroke imaging research projects. Criteria for inclusion were cortical stroke symptoms, imaged within 24 hours of symptom onset. To be included in this study, CT and MRI must have been completed within 2 hours of each other. A follow-up MRI 3 to 5 days after onset was required to assess tissue outcome.

Image Protocol
Unenhanced CT scans were obtained at baseline with helical scanners (Lightspeed [GE Medical] or Philips Mx8000). Scanning parameters were 120 kV and 240 mA (GE)/170 mA (Philips), matrix size 512×512, and field of view 24×24 cm. MRI scans were obtained with 1.5-Tesla EPI-equipped scanners (GE Signa/Philips Intera) at baseline and 3 to 5 days after onset to assess outcome and reperfusion. Diffusion-weighted images were obtained with single-shot spin-echo EPI sequences. Sixteen to 20 slices 6-mm +1-mm gap were obtained. Matrix size was 256×256, field of view =40×40 cm, and TR/TE 6000/107 ms. Diffusion gradient strength was varied between 0 and 22 mT/m, resulting in b values of 0, 500, and 1000 s/mm. Perfusion-weighted images were obtained using a bolus of gadolinium di-ethylentetriamine penta-acetic acid (0.2 mmol/kg), injected at 5 mL/s, followed by 15-mL saline. Thirteen to 16 slices (32 to 40 time points) were obtained. Slice thickness was 6 mm + 1 mm gap, matrix sizes were 256×256, and field of view =40×40 cm.

Data Analysis
Cortical ASPECT scores of the CT scans were assessed by the 3 lead authors. Two slices were used to assess ASPECT scores. These slices were at the level of the basal ganglia and immediately superior to this, as outlined in the original ASPECTS descriptions. Three investigators assessed each patient independently. In cases when all 3 investigators were not in agreement, scans were assessed in a single session and final scores were defined by consensus. In addition to the raw scores, this same approach was used to rate individual cortical regions as “normal,” “hypodense,” “hypertensive,” or affected by “focal swelling.” Because of the fact that it is not possible to identify focal swelling in the insula or subcortical areas, these regions were not included in this analysis. CT scoring was performed before and independent of MRI analysis.

Postprocessing of all raw perfusion images was performed by a software program StrokeTool (DIS).9 This software was used to plot the change in MRI transverse relaxivity, which is linearly related to gadolinium di-ethylentetriamine penta-acetic acid concentration, on a per-voxel basis over time. Semi-quantitative perfusion maps were calculated from this tissue response curve. Relative cerebral blood flow (rCBF), volume (rCBV), and Tmax maps (impulse response time to peak) were calculated using simple value decomposition. This technique allows the impulse response curve to be calculated as a deconvolution of the raw perfusion images using an arterial input function. The arterial input function was selected from the middle cerebral artery contralateral to the affected hemisphere. Tmax was measured as the time domain PWI parameter in this study, based on our previous observation that it is less prone to calculation errors compared with the more often used mean transit time. In addition, the change in Tmax deficit volume (defined as voxels +2 s, relative to the contralateral hemisphere) between the acute and subacute scans was used to assess reperfusion as previously described. Isotropic diffusion-weighted imaging images were obtained by averaging the signal from all orthogonal directions with the highest diffusion weighting (b=1000). Apparent diffusion coefficient (ADC) values were calculated using the Stejskal-Tanner equation, as described previously.12 Regional MRI analysis was performed using the software package Analyze (Biomedical Imaging Resource). Two slices were used to assess ASPECT scores on MRI images. These slices were at the same anterior-posterior level as those used to assign the CT scores. ASPECTS slices and cortical regions were first identified on T2-weighted images (b=0) and then transferred to isotropic diffusion-weighted imaging images and ADC maps. ASPECTS regions were similarly identified on T2* images and then transferred to perfusion maps based on these images. The cortical boundary of each ASPECTS region was outlined visually, with the assistance of an algorithm that searches for large gradients in signal intensity within a 7-voxel radius. Gradients in signal intensity are found between cortical gray and subcortical white matter. A more objective definition of the cortical gray-white junction was therefore achieved using this technique. ASPECTS regions were identified on these T2-weighted images first, as the post-processed ADC and PWI maps lack the anatomical resolution required to reliably differentiate gray and white matter. Cerebrospinal fluid within the cortical sulci was excluded from regional ADC analysis with the use of an upper threshold of 120×10^{-3} mm^3/s, as described previously.13

Statistical Analysis
PWI and ADC measures were calculated as ratios (rCBF, rCBV, and relative ADC [rADC]) or delays (rTmax) relative to contralateral ASPECTS regions. Analysis was performed using statistical software (Stata Corporation). The Kolmogorov-Smirnov test confirmed that the majority of data were non-normally distributed. Regional rADC, rCBF, rCBV, and rADC differences were tested using ANOVA on ranks, followed by post-hoc Mann-Whitney rank sum comparisons. Differences in regional infarction rates were tested with Yates corrected chi^2 tests and post-hoc comparisons, between regions with different initial CT characteristics, were made with Bonferroni corrections.

Results

Demographic Data
Thirty patients met the predefined inclusion criteria and were included in the analysis. With the exception of 3 patients, the initial imaging modality was CT, followed by MRI. The median time to the initial scan was 4.0 hours (range, 1.5 to 16.8) after symptom onset. Twenty-three patients (77%) were imaged within 6 hours of onset. The second scan was performed at a median time of 1.1 hours (range, 0.2 to 2 hours) later. Twenty patients were included in placebo-controlled thrombolysis trials (Echoplanar Imaging Thrombolysis Evaluation Trial, n=19, and Desmoteplase in Acute Stroke, n=1). Two patients were treated with open label intravenous tissue plasminogen activator and a third with intra-arterial urokinase. The remaining seven patients were managed conservatively. All patients had moderate to large clinical deficits, including cortical signs and symptoms. The median NIHSS score was 15.5 (range, 4 to 25).

Cortical ASPECTS Changes: CT
A total of 180 cortical regions were analyzed in the 30 patients. Isolated focal swelling was present in 25 cortical regions. Hypoattenuation was observed in another 25 regions and the remaining 130 had no early ischemic changes. The median NIHSS (15) time to initial scan (5.9 hours) and time between scans (1.1 hours) in those with cortical swelling was not significantly different from the remaining patients.

Apparent Diffusion Coefficient Values and CT Signs of Ischemia
ADC values were decreased in hypoattenuated ASPECTS cortical regions (median rADC, 0.84; interquartile range...
The decrease in ADC in these regions was significantly lower than the mean ADC of ASPECTS regions that appeared normal on CT ($P < 0.001$). In contrast, ADC values were normal in ASPECTS regions with isolated focal swelling (0.97; IQR, 0.91 to 1.01) and not significantly different from those regions with no ischemic changes (0.98; IQR, 0.91 to 1.04; $P = 0.40$).

**Perfusion Changes and CT Signs of Ischemia**

Hypoattenuated ASPECTS regions had significantly decreased rCBF (median, 37.0%; IQR, 25.6 to 70.2), relative to those regions that appeared normal on CT (71.8%; IQR, 47.1 to 94.5; $P = 0.002$). Although rCBF was moderately decreased in the focal swelling regions (81.0%; IQR, 70.4 to 93.0), this was not significantly different from that in normal-appearing tissue in the ipsilateral hemisphere ($P = 0.11$; Figure 2). Acute time domain PWI measurements (rTmax) were consistent with the rCBF values, indicating greater prolongation of contrast transit in the hypoattenuated regions (median, 3.2 s; IQR, 2.0 to 5.3) than those areas with focal swelling (1.5 s; IQR, 0.6 to 3.3; $P = 0.006$).

Hypoattenuated ASPECTS regions were always associated with decreased rCBV (median, 58.9%; IQR, 47.5 to 92.7; IQR, 0.66 to 0.91; Figure 1). The decrease in ADC in these regions was significantly lower than the mean ADC of ASPECTS regions that appeared normal on CT ($P < 0.001$).

**Tissue Outcome**

Repeat diffusion-weighted imaging at 3 to 5 days demonstrated infarction in all 25 acutely hypoattenuated tissue regions. Infarction was observed in 65/130 (50%) of normal regions (Figure 4). The frequency of regional infarction in the areas with focal swelling was 8/25 (32%). A $\chi^2$ test indicated an overall significant difference in the rate of regional infarction ($P < 0.001$). Post-hoc comparisons, with a Bonferroni correction, confirmed significant differences between hypoattenuated cortical and focal swelling regions ($P < 0.001$). Outcome was not significantly different between normal-appearing and focal swelling regions ($P = 0.152$).

Major reperfusion, defined as resolution of $>90\%$ of acute Tmax deficit volumes, was observed in 17 patients on the
subacute scan. In 17/25 (68%) of the isolated focal swelling regions, no infarction was evident irrespective of reperfusion. All 6 patients with focal swelling had at least one ASPECTS cortical region that went on to subacute infarction, including the 4 with successful recanalization. In those patients with major reperfusion, 100% of hypoattenuated regions and 25% of those with focal swelling experienced infarct.

Discussion
This study confirms the previous finding that hypoattenuation and focal swelling are associated with very different underlying blood flow and bioenergetic changes. Specifically, hypoattenuated tissue is always associated with decreased rADC as well as rCBV, and consistently progresses to infarction, irrespective of subsequent reperfusion. We have further demonstrated that ASPECTS regions that exhibit isolated focal swelling or sulcal effacement are associated with preservation of cellular ionic transport function, as demonstrated by normal rADC, and elevation of rCBV, consistent with maintained tissue viability.

Mechanism of Ischemic Changes
Hypoattenuation of cortical tissue represents a decrease in tissue density. This has been shown experimentally to be related to additional fluid within the brain resulting from cytotoxic edema. The term cytotoxic edema is most certainly an oversimplification, because fluid shifts from the vascular to interstitial compartments must take place for a change in tissue density to occur. Thus, there is an element of vasogenic edema that accompanies the cytotoxic edema in ischemic tissue. It is also possible that very early hypoattenuation may result from a decrease in blood volume, particularly in the capillary and venous circulation. A previous PWI study demonstrated that tissue density is strongly correlated to rCBV. Conversely, isolated focal swelling has been suggested to result from compensatory hyperemia. Our results and those of a similar investigation support the hypothesis that focal swelling is a consequence of elevated rCBV, secondary to shunting within the cerebral microcirculation under ischemic conditions. Elevation of rCBV has been shown to be a characteristic of penumbral tissue, with variable outcome, in previous acute stroke MRI and positron emission tomography studies. This is most likely a homeostatic response to ischemia, which can serve to protect tissue from ischemic injury.

Prognostic Significance of Ischemic Changes
Hypoattenuation has been demonstrated in several large analyses to represent irreversible ischemic injury. Our results were entirely consistent with these previous studies. In a number of patients, infarction occurred only in the hypoattenuated tissue associated with low rADC and low rCBV, and not the focal swelling regions, despite a persisting arterial occlusion (Figure 3). This might lead one to conclude that the focal swelling is benign. However, this is clearly not always the case as in other patients with marked focal swelling and
no hypoattenuation, cortical infarction occurred despite successfull reperfusion therapy (Figure 4). This variable outcome associated with early parenchymal ischemic CT changes has been reported previously. A study design similar to our own revealed that sulcal effacement was sometimes followed by diffusion-weighted imaging lesion growth, but could also be associated with resolution of symptoms and lack of infarction.19

It appears that elevated rCBV can maintain tissue viability for varying lengths of time in different patients. In some patients, blood flow shunting appears to be sufficient to prevent infarction. In others, this homeostatic response is insufficient to maintain tissue viability indefinitely. In these patients, rADC eventually falls and infarction occurs. Focal swelling is therefore best viewed as a marker of tissue at risk for infarction. This is actually a sign of penumbral tissue that can be observed on an unenhanced CT scan, although the relative infrequency of this type of change probably limits its clinical usefulness.

Methodological Limitations
In this investigation we did not coregister the CT and MRI images. As we planned a regional analysis, based on the ASPECTS system, we did not feel this was necessary and would lead to inaccuracies in assessment because of the distortion that can accompany coregistration. It has already been demonstrated that ASPECTS regional analysis can be applied to MR images.20 Determination of the medial limits of the ASPECTS cortical regions, which in a semi-quantitative analysis normally include the subcortical white matter as well, is a somewhat arbitrary process. To make this a more objective process, we used the change in signal intensity to demarcate the boundary between gray and white matter at the cortical junction. Although most patients had MRI immediately after CT and the median time between studies was relatively short (1.1 hours), we cannot exclude errors introduced by the passage of time between scans. Finally, the treatment of 19 patients is unknown because of the fact that they were included in ongoing blinded randomized controlled thrombolysis trials. We would submit, however, that treatment allocation is less important than reperfusion status, which has been shown to be highly predictive of outcome.11

Implications for ASPECTS
ASPECTS is a useful and validated tool that has been shown in several large studies to be highly predictive of outcome and the response to thrombolytic therapy.3,4,7,21 None of these studies, however, has differentiated isolated focal swelling and hypoattenuation when determining ASPECT scores. The results of the present investigation support modification of the ASPECTS tool, specifically by removing regions with

**Figure 3.** Example of rCBV maps from the same patient shown in Figures 1 to 2 indicate that blood volume is extremely low in the hypoattenuated regions (M2 and M5) and actually increased in those with focal swelling. The whisker box plot indicates the median rCBV values were significantly elevated from normal in the focal swelling regions (*P*<0.001) and significantly decreased in hypoattenuated regions (**P*=0.002). Infarction (day 3 diffusion-weighted imaging) occurred only in the hypoattenuated regions M2 and M5, associated with decreased rADC and rCBV, and not the focal swelling regions, despite a persisting arterial occlusion.
isolated focal swelling from the final score. The chief utility of ASPECTS is the prognostic information provided. It has been repeatedly shown that lower ASPECT scores are associated with worse clinical outcome. Although most stroke clinicians would not advocate selection of thrombolysis patients on the basis of ASPECT scores within 3 hours of symptom onset, efforts to incorporate this tool into treatment selection algorithms for patients presenting beyond 3 hours are ongoing. We suggest that isolated focal swelling be excluded from ASPECT scores used for either of these purposes. Focal swelling is not a negative prognostic sign and in fact should be viewed as a reason to initiate thrombolytic therapy in otherwise suitable ischemic stroke patients.

The true frequency of focal swelling in acute stroke remains unknown. This sign is often very subtle, relative to hypodensation, which most stroke clinicians are now adept at finding. Isolated focal swelling with no hypodensation has been reported to be uncommon (2% to 13.5%) but is more often seen with concomitant “small” hypodense areas (35%). Focal swelling in hyperacute stroke actually may be more common than we and others have reported. In patients with a degree of cerebral atrophy, these acute changes are proportionally so small, relative to the previously enlarged cortical sulci, that they may be impossible to observe. At this point, no diagnostic criteria for focal swelling exist. We have defined it simply as any effacement of the cortical sulci, relative to the contralateral hemisphere, that cannot be explained by rotation of the patient within the scanner or asymmetry secondary to atrophy and/or previous strokes. Demarcating areas of isolated focal swelling from those associated with hypodensation is difficult, because the former is a regional phenomenon, without precise borders. We suggest that this is another advantage of using ASPECTS, because focal swelling can be defined as occurring only in those regions with no hypodensation.

Conclusions
ASPECTS regions demonstrating isolated focal swelling in acute ischemic stroke patients are not irreversibly infarcted. This CT sign represents potentially viable tissue and should therefore be considered a penumbral marker. A modification of the ASPECTS and other early ischemic change rating systems is suggested.

Sources of Funding
Data for this study were obtained from ongoing acute stroke studies funded by the National Health & Medical Research Council of Australia (project grant 351155 and program grant 70195).

Disclosures
None.

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Stroke. 2007;38:941-947; originally published online February 1, 2007;
doi: 10.1161/01.STR.0000258099.69995.b6
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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