Perfusion Thresholds in Acute Stroke Thrombolysis

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Background and Purpose—Perfusion-weighted MRI has been shown to be useful in the early identification of cerebral tissue at risk of infarction during acute ischemia. Identification of threshold perfusion measures that predict infarction may assist in the selection of patients for thrombolysis.

Methods—Mean transit time (MTT), regional cerebral blood flow (rCBF), and regional cerebral blood volume (rCBV) maps were generated in 35 acute stroke patients (17 treated with tissue plasminogen activator and 18 control patients) imaged within 6 hours from symptom onset. Day 90 outcome infarcts (T2-weighted MRI) were superimposed on acute MTT, rCBF, and rCBV maps. Perfusion-weighted MRI measures were then calculated for 2 regions: infarcted and salvaged tissue.

Results—MTT was prolonged by 22% in infarcted regions relative to salvaged tissue ($P<0.001$). rCBF was 10% lower in infarcted tissue than in salvaged regions ($P<0.01$). rCBV did not differ significantly between infarcted and salvaged regions. When reperfusion occurred, tissue with more severely prolonged MTT was salvaged from infarction relative to patients with persistent hypoperfusion ($P<0.05$). In contrast, rCBF in salvaged regions did not differ between patients with and without reperfusion. In reperfused patients, an inverse correlation ($R=0.93, P<0.001$) was found between time of initial MRI scan and MTT delay in salvaged tissue.

Conclusions—Both increases in MTT and decreases in rCBF predict infarction. Differences in MTT also predict salvage in more severely hypoperfused tissue after reperfusion, suggesting that it is the most clinically useful quantitative perfusion measure. Perfusion thresholds for infarction need to be assessed in the context of symptom duration. (Stroke. 2003;34:2159-2164.)

Key Words: magnetic resonance imaging ■ perfusion ■ thrombolysis

Thrombolysis is the only proven pharmacological treatment for acute ischemic stroke.1 Meta-analyses have indicated that tissue plasminogen activator (tPA) may be effective in a smaller portion of patients beyond the current 3-hour treatment window.2,3 To identify potential responders to thrombolysis, more rational selection criteria are required. Newer MRI techniques may allow selection of patients for thrombolysis on the basis of tissue pathophysiology rather than a rigid time frame.4

Diffusion-weighted MRI (DWI) demonstrates regions of restricted water movement that are associated with bioenergetic failure.5 Dynamic susceptibility perfusion-weighted MRI (PWI) allows the visualization of areas of altered blood flow.6 Used together, DWI and PWI may allow identification of tissue that is at risk for infarction but also potentially amenable to salvage with reperfusion and/or neuroprotective strategies, that is, the ischemic penumbra.7–10

PWI abnormalities have been shown to qualitatively predict cerebral infarction with high sensitivity.11 The final extent of infarction, however, is quite variable. In most cases, the final infarct region is intermediate between the acute PWI and DWI abnormalities. This likely represents differences in the severity of hypoperfusion within the visible abnormality identified with PWI.12–14 Attempts to more accurately predict tissue fate in ischemia with the use of quantitative DWI have been made with only moderate success.15,16 Quantitative PWI has also been assessed for its potential in determining threshold perfusion levels for infarction or recovery.10,13,14,17,18 These studies have assessed the correlation between PWI indices and infarction in natural history populations and have not taken into consideration the effect of reperfusion.

In this quantitative PWI analysis in acute stroke patients treated with tPA or conservatively, we hypothesized that hypoperfusion would be most severe in tissue that ultimately infarcts. In addition, we hypothesized that restoration of cerebral blood flow (CBF) would be associated with an elevated perfusion threshold for infarction. We tested these
Subjects and Methods

Patients

The cohort consisted of 35 patients who presented with acute cortical stroke within 6 hours of symptom onset. Patients were recruited from the stroke units at the Royal Melbourne and Princess Alexandria hospitals between January 1999 and December 2000. The imaging protocol and use of tPA were in accordance with the guidelines of the Human Research and Ethics Committee at each institution. Written informed consent was obtained from the patient or next of kin. All patients were imaged acutely with cerebral CT, followed by DWI and PWI echo-planar scans.

In 17 patients, thrombolysis was performed with 0.9 mg/kg body wt tPA according to the National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study protocol, with the exception that treatment was extended to 6 hours. Patients were also deemed ineligible for thrombolysis if stroke severity was mild (defined as National Institutes of Health Stroke Scale [NIHSS] score ≤4) or severe (defined as NIHSS score ≥22). In addition, the pretreatment CT scan was used to exclude patients with hemorrhage or parenchymal ischemic changes exceeding one third of the middle cerebral artery territory. Treatment commenced immediately after MRI in all patients.

Before the approval for use of tPA in acute stroke in January 2000, DWI and PWI were performed but were not followed by thrombolysis (n=18). Patients from this historical control group were not included in this study if they met clinical or CT exclusion criteria for thrombolysis. A single patient who was eligible for tPA treatment but refused to consent to thrombolysis was also included in the control group. Four of the control patients were enrolled in trials of the putative neuroprotective agents GV150526 (glycine agonist; n=2) and BMS-204352 (potassium channel agonist; n=2).

MRI Protocol

MRI scans were obtained with 1.5-T echo-planar imaging–equipped whole-body scanners (Signa Horizon SR 120; General Electric). The baseline and subacute (days 3 to 5) sequences included a T1-weighted sagittal localizer, DWI, PWI, and MR angiography (MRA). Repeated MRI at day 90 included a T1-weighted sagittal localizer and T2-weighted fast-spin double-echo sequence (repetition time [TR]/echo time [TE], 3500/10/60 ms).

Perfusion-weighted images were obtained with the use of a bolus of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA 0.2 mmol/kg) via a large-bore cannula in the antecubital fossa. The injection was performed at a speed of 5 mL/s with a power injector (Spectris, Medrad) and followed by a 15-mL bolus of saline. Ten to 13 slices were obtained, centered on the DWI lesion. Slice thickness was 6 mm +1-mm gap, matrix 256×256, and field of view (FOV) 40×20 cm. Images were obtained at 40 time points per slice.

Diffusion-weighted images were obtained with the use of a multislice, single-shot, spin-echo echo-planar imaging sequence. Sixteen 6-mm +1-mm gap slices were obtained. Matrix size was 128×128, FOV 24×24 cm, and TR/TE 6000/107 ms. Diffusion gradient strength varied between 0 and 22 mT/m, resulting in 3 b values of increasing magnitude from 0 to 1000 s/mm.

MRA was obtained with the use of a 2-dimensional 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 3 directions, with TR/TE 257.5 ms, flip angle 30°, matrix 256×128, FOV 20×20 cm, and number of excitations =2.

Data Analysis

Postprocessing of raw perfusion images was performed with the use of customized software developed in the commercial Interactive Data Language package (Research Systems). This software was used to plot the change in MRI transverse relaxivity (DR2*), which is linearly related to Gd-DTPA concentration, on a per-voxel basis over time. A gamma variate function was then fitted to the intensity-time curve on a per-voxel basis. Quantitative perfusion indices including mean transit time (MTT), relative CBF (rCBF), and relative blood volume (rCBV) were calculated with the single-value decomposition method. This technique allows the tissue concentration-time curve to be calculated, on an individual pixel basis, as a deconvolution of the raw contrast-enhanced perfusion images with an arterial input function. In all cases, the arterial input function was selected from a branch of the middle cerebral artery contralateral to the ischemic hemisphere.

Regional quantitative PWI map analysis was performed with the commercial software Medx (Sensor Systems). The region of viable MTT abnormality was outlined initially and then reflected to the contralateral hemisphere. The MTT of this homologous region was then recorded. On the basis of previous PWI studies, hypoperfusion was defined a priori as a MTT delay of >2 seconds beyond that of the unaffected hemisphere. Hypoperfused regions were outlined with the use of a semiautomated threshold technique on all slices. Final outcome infarct size was determined from the day 90 T2-weighted sequence. Infarct and salvage regions were determined by superimposing corresponding T2-weighted imaging outcome slices. This procedure was repeated for rCBF and rCBV maps. The infarct and salvage perfusion parameters were calculated in every slice where an abnormality (MTT delay >2 seconds) was seen. Evidence of reperfusion was assessed with the use of either visible recanalization on the subacute MRA or resolution of >80% of the acute PWI deficit, as seen on the subacute MTT maps. The time from symptom onset to initial MRI was used as an estimate of the duration of hypoperfusion because most cases of reperfusion occurred after thrombolysis, which was initiated immediately after completion of the first imaging studies.

Statistical Analysis

Analysis was performed with a statistical software package (STATA Corporation, 1999). The Student t test was used to compare initial quantitative PWI measures in infarcted and salvaged regions. The Spearman rank test was used to test the significance of correlations between quantitative PWI measures and time to initial MRI. The Pearson χ2 test was used to assess the relative frequency of reperfusion in tPA-treated and conservatively treated patients. All data are presented as mean±SEM.

Results

Baseline Clinical Data

Clinical characteristics of the tPA-treated patients (aged 71.4±1.8 years; 9 male) and historical control patients (aged 68.6±2.6 years; 10 male) were similar. Mean time to acute MRI was 3.9±0.3 hours in tPA-treated patients and 4.1±0.3 hours after stroke onset in conservatively treated patients. Mean times to subacute and outcome MRI were 3.3±0.1 and 78.8±2.9 days, respectively. There were no significant differences in age, acute NIHSS score, time to MRI, or baseline DWI and PWI volume between treatment and control patients.

MTT Maps

Acutely, MTT was prolonged within the affected hemisphere of all patients. MTT delay was consistently greater in tissue that was infarcted at 90 days relative to regions that did not progress to infarction (Figure 1). The average delay in MTT in all patients, relative to homologous regions in the unaffected hemisphere, was 8.3±0.4 seconds (range, 2.3 to 13.7 seconds) in infarcted tissue and 6.5±0.4 seconds (range, 2.2 to 11.7 seconds) in salvaged tissue. Thus, MTT delay was 22% greater in infarcted regions relative to salvaged regions.
In 3 tPA-treated patients, no infarct was visible on MRI at 90 days, consistent with complete salvage of the acutely hypoperfused tissue. In 1 control patient, the entire acute MTT abnormality progressed to infarction at 90 days, and no salvaged regions were present.

Evidence of reperfusion was seen at the time of the subacute MRI/MRA in 18 of 35 patients. Reperfusion was more frequent in tPA-treated patients (13 of 17) than in those managed conservatively (5 of 18; \( \chi^2=8.3, P<0.005 \)). In patients with acute-subacute reperfusion, tissue salvage occurred in regions with greater MTT delay compared with patients without reperfusion (7.5±0.1 versus 5.4±0.1 seconds; \( P<0.05 \)). In reperfused patients, MTT delay within infarcted regions was also greater than in those without reperfusion (9.4±0.2 versus 7.3±0.1 seconds; \( P<0.05 \)). Reperfusion therefore elevated the MTT threshold for infarction.

In patients with acute-subacute reperfusion, an inverse correlation \( (R=0.93, P<0.001) \) was found between time of initial MRI scan and MTT delay in salvaged tissue (Figure 2). An inverse correlation also existed between time to initial MRI and MTT delay in tPA-treated patients only, reflecting the high proportion of patients with reperfusion in this group \( (R=0.86, P<0.01) \). Tissue salvage occurred in regions with markedly prolonged MTT if tPA was given earlier. Thrombolyis after approximately 4.5 hours also resulted in tissue salvage, but in more moderately affected regions. Earlier tPA administration was therefore associated with salvage of tissue with more severely delayed MTT.

**rCBF Maps**

Overall, acute rCBF was 10% lower in infarcted (56±4% of contralateral; range, 29% to 125%) relative to salvaged (66±3% of contralateral; range, 38% to 94%) regions (Figure 1; \( P<0.01 \)). In 1 patient rCBF was elevated in the infarcted region, consistent with partial reperfusion before the acute MRI study. In contrast to MTT, rCBF values in salvaged regions were not significantly different between patients with and without reperfusion. This reflected the relatively smaller difference between rCBF in infarcted and salvaged regions. Thus, tissue with lower rCBF was at higher risk of infarction, but rCBF alone did not predict the response to reperfusion.
patients in whom reperfusion occurred, however, there was a direct relationship between time to initial MRI and rCBF in salvaged regions (Figure 2; $R=0.51, P<0.05$). Although this correlation was not as strong as that seen with MTT, it confirms that earlier reperfusion is associated with salvage of more severely hypoperfused tissue.

rCBV Maps
Acutely, rCBV was increased in the affected hemisphere of all patients. The increase in rCBV did not differ between infarcted (135±10%; range, 68% to 345%) and salvaged (135±6%; range, 53% to 270%) regions (Figure 1). In patients with acute-subacute reperfusion, tissue salvage occurred in regions of significantly higher rCBV. In contrast to MTT and rCBF, rCBV in salvaged regions was not correlated with time to initial MRI scan (Figure 2).

Discussion
This study confirms that tissue fate in acute ischemia is related to the severity of hypoperfusion. Both prolonged MTT and reduced rCBF increase the probability of infarction. There is significant overlap of relative MTT and rCBF values in infarcted and salvaged regions, making identification of absolute thresholds difficult. In addition, reperfusion is associated with salvage of more severely hypoperfused tissue. MTT appears to be the most sensitive PWI measure for predicting infarction or salvage. Finally, earlier reperfusion allows salvage of more severely hypoperfused tissue. Therefore, the PWI threshold for infarction is not absolute but is time dependent.

Perfusion Thresholds for Infarction
Perfusion thresholds for infarction and recovery have been demonstrated previously with positron emission studies. Outcome has also been shown to be related not only to severity of blood flow decreases but also to the duration of these changes. The relationship between severity of hypoperfusion, with the use of PWI techniques, and duration of ischemia has been demonstrated for the first time in this study.

There are several previous reports of MRI perfusion thresholds in acute stroke. None of these studies controlled for reperfusion or duration of hypoperfusion. A recent report indicated that an increase in the MTT ratio of contralateral side progressed to infarction. Similarly, rCBF ratios of 0.59 progressed to infarction, but rCBV had no predictive value. As in the present study, however, there was significant overlap between MTT and rCBF values that progressed to infarction. This inability to demonstrate absolute thresholds likely reflects that the time to reperfusion is the most critical factor in determining tissue fate.

Response to Reperfusion
The present cohort contains 18 patients with reperfusion between the acute and subacute MRI studies. Tissue salvage in these patients occurred in regions of more severe hypoperfusion, as demonstrated by prolonged MTT, relative to patients without restoration of blood flow. Thus, the threshold for infarction is elevated in the setting of tissue reperfusion. The majority of these patients (13 of 18) received tPA, confirming the ability of thrombolysis to enhance reperfusion and subsequent tissue salvage. The response to reperfusion is also time dependent. Salvage in severely hypoperfused tissue is possible if these patients are treated with tPA within 4.5 hours of ischemic symptom onset. Importantly, the response to tPA is not limited to 3 hours. Tissue salvage can be seen in patients treated up to 6 hours after symptom onset. Rescue of more severely hypoperfused tissue occurs when reperfusion occurs earlier after symptom onset. This is consistent with the diminishing clinical response to tPA with increasing time to treatment. Analysis of patients treated with thrombolysis in the present study indicates that the most significant drop in tissue salvage, relative to prolonged MTT, occurs at approximately 4.5 hours after symptom onset. A recent meta-anal-
ysis of the clinical efficacy of intravenous tPA indicates that unity is also reached at 4.5 hours. Thus, the perfusion thresholds of this study appear to correlate well with the clinical response to thrombolysis.

Relative Predictive Value of MTT, rCBF, and rCBV Maps

We have found that MTT maps are most predictive of the fate of acutely ischemic tissue. rCBF maps also demonstrate thresholds, but the magnitude of the differences between infarcted and salvaged regions is not as great as that seen with MTT maps. The relationship between rCBF and tissue salvage appears to be more variable than that observed with MTT. Furthermore, the response to reperfusion demonstrated with MTT maps is not evident on rCBF analysis.

Our results indicate that rCBV is the least useful PWI measure in predicting thresholds for infarction. Increased rCBV in ischemic tissue represents sluggish blood flow and may also be affected by vasodilatation as a compensatory response to decreased cerebral perfusion. In the present study increased rCBV accompanied prolonged contrast transit time, but this did not discriminate between infarcted and salvaged regions. Some previous PWI studies have reported that rCBV increases in cerebral ischemia, while others have indicated that rCBV decreases in cerebral ischemia. Differences may be related to the time at which the MRI studies are completed. It may be that compensatory vasodilatory responses have failed by the time of subacute studies, and this is reflected in a decrease in rCBV. Alternatively, differences may be related to the variety of methods used to estimate the concentration-time curve. In contrast to rCBV, we found a consistent relationship between rCBF and tissue outcome. Changes in rCBF are related to arterial responses, presumably via autoregulatory changes in collateral vessels. MTT prolongation had the strongest correlation with tissue fate in this study. This likely reflects the fact that MTT is proportional to both rCBF and rCBV.

MTT changes have the additional advantage of being readily visible on color maps (Figure 1). The maximal extent of the rCBF and rCBV abnormalities is not easily identifiable on color maps. Thus, in this study the areas of rCBF and rCBV changes were actually determined with the use of the MTT abnormality. Previously, it has been shown that the region of MTT prolongation (>2 seconds) is larger than the region of decreased rCBF. Thus, areas of relatively normal blood flow were likely included in the estimation of salvaged regions on rCBF maps. This would accentuate any relative differences between infarcted and salvaged regions on rCBF maps. Despite the fact that this methodology favored rCBF maps, MTT was shown to have greater predictive value.

Absolute quantitative PWI measures have not yet been validated in acute ischemic stroke. Thus, rCBF and rCBV changes are typically expressed as percentages of the contralateral homologous regions. Theoretically, absolute MTT values can be used because they are a true reflection of the time domain. In this study, however, we have reported MTT changes relative to the contralateral hemisphere because of the lack of consensus regarding the most accurate method of estimating true transit time. The MRI signal intensity—time curve is proportional but not equivalent to the gadolinium concentration–time curve. Thus, the true concentration–time response must be estimated by a mathematical approach. Alternatively, a surrogate measure, such as time to peak of signal intensity change, can be used. In the present study we used a single-value decomposition method. This calculates the true concentration-time curve as a deconvolution of the observed signal intensity–time curve and a selected arterial input function. The latter reflects the time taken for injection of the contrast agent. This method has recently been reported to have superior sensitivity to other estimates of true transit time. Nonetheless, other methods, including gamma variate fit or first moment techniques, are commonly used. Furthermore, groups using deconvolution methods have not agreed on the best measure of transit time. Therefore, until some consensus has been reached on a standardized approach to quantitative PWI or, alternatively, until absolute CBF can be validated, the utility of perfusion thresholds to prospectively predict tissue fate will be limited.

This study has 2 major limitations. The first is that time to initial MRI is only an estimate of the time when reperfusion actually occurred. Future studies would benefit from real-time monitoring of the affected artery, for example, with transcranial Doppler ultrasound. In addition, this study was based on the outcome of large regions of interest rather than a coregistered voxel approach. Although the latter would possibly be more accurate, the authors do not believe that this approach would alter the conclusions of this study. All patients studied had large cortically based perfusion deficits. From a pragmatic viewpoint, it is the fate of these large regions as a whole that is of interest to the treating physician rather than individual voxels.

Conclusions

This study confirms that severity of hypoperfusion is proportional to probability of infarction or salvage and that this can be detected reliably with PWI techniques. MTT appears to be the perfusion measure most predictive of outcome. In addition, earlier reperfusion allows salvage of more severely hypoperfused tissue from infarction. The very strong correlation between time to reperfusion and tissue salvage makes the definition of absolute perfusion thresholds problematic. Although this study confirms that time really is brain, significant tissue salvage beyond the current 3-hour thrombolysis treatment window still occurs.

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