How Reliable Is Perfusion MR in Acute Stroke?
Validation and Determination of the Penumbra Threshold
Against Quantitative PET

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Background and Purpose—Perfusion magnetic resonance imaging (pMR) is increasingly used in acute stroke, but its physiologic significance is still debated. A reasonably good correlation between pMR and positron emission tomography (PET) has been reported in normal subjects and chronic cerebrovascular disease, but corresponding validation in acute stroke is still lacking.

Methods—We compared the cerebral blood flow (CBF), cerebral blood volume, and mean transit time (MTT) maps generated by pMR (deconvolution method) and PET (¹⁵O steady-state method) in 5 patients studied back-to-back with the 2 modalities at a mean of 16 hours (range, 7 to 21 hours) after stroke onset. We also determined the penumbra thresholds for pMR-derived MTT, time to peak (TTP), and Tmax against the previously validated probabilistic PET penumbra thresholds.

Results—In all patients, the PET and pMR relative distribution images were remarkably similar, especially for CBF and MTT. Within-patient correlations between pMR and PET were strong for absolute CBF ($r^2 = 0.45$) and good for MTT ($r^2 = 0.35$) but less robust for cerebral blood volume ($r^2 = 0.24$). However, pMR overestimated absolute CBF and underestimated MTT, with substantial variability in individual slopes. Removing individual differences by normalization to the mean resulted in much stronger between-patient correlations. Penumbra thresholds of $\approx 6, 4.8,$ and 5.5 seconds were obtained for MTT delay, TTP delay, and Tmax, respectively.

Conclusions—Although derived from a small sample studied relatively late after stroke onset, our data show that pMR tends to overestimate absolute CBF and underestimate MTT, but the relative distribution of the perfusion variables was remarkably similar between pMR and PET. pMR appears sufficiently reliable for clinical purposes and affords reliable detection of the penumbra from normalized time-based thresholds. (Stroke. 2008;39:870-877.)

Key Words: acute stroke ■ cerebral blood flow ■ imaging ■ magnetic resonance ■ positron emission tomography ■ penumbra ■ perfusion

Perfusion magnetic resonance imaging (pMR) is increasingly used in the acute stroke setting. In its quantitative version, maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) can be derived noninvasively by dynamic imaging of a bolus injection of gadolinium contrast agent and subsequent data analysis from the time course of the tracer in both tissue and middle cerebral artery and deconvolution. Because the method is inherently sensitive to vascular delays and dispersion effects, its validity in stroke has been questioned.

To detect ischemic but salvageable tissue, ie, the penumbra, pMR is combined with diffusion-weighted imaging (DWI), and time-based mapping, such as MTT or the semiquantitative time-to-peak (TTP) delay relative to the contralateral hemisphere, is used in preference to CBF because of the more conspicuous changes and better correlation with final outcomes. However, the MTT and TTP delays that define the penumbra with pMR still remain uncertain.

pMR-based measurement of CBF, CBV, and MTT has been previously validated against “gold standard” positron
emission tomography (PET) in normal subjects and chronic cerebrovascular disease but not yet in acute stroke. Regarding the penumbra threshold, a pMR-PET comparison study of 11 patients with minor acute stroke reported that a TTP delay threshold of 4 seconds best matched the PET-derived penumbra. In a subsequent study of 6 acute minor strokes and 7 subacute minor hemodynamic strokes, TTP delays of 4 and 6 seconds grossly overestimated the PET-defined penumbra volume. However, as shown by the Bland-Altman plots, sSVD tended to overestimate CBF, particularly for high values, as well as MTT and MTT delay, also for high (ie, ischemic-range) values.

Methods

Patients
Five acute anterior circulation stroke patients (left/right hemisphere, 3/2) with thrombolytic therapy as an exclusion criterion were studied (3 women; mean age, 69.3 years). The mean National Institutes of Health Stroke Scale score on admission was 12.2 (range, 6 to 17). The mean time to pMR was 16.3 hours (range, 7 to 21 hours) after stroke onset, and the interval between the start of pMR and that of PET was 46 minutes (range, 30 to 60 minutes). All patients had hemiparesis/hemiplegia, 2 patients had aphasia, 4 patients had hemianopia, and 2 patients had hemineglect. The cause of stroke was cardioembolic in 3 (No. 2, 3, and 4) and atherothrombotic in 2 (No. 1 and 5, both with severe ipsilateral carotid stenosis). The study was approved by the Cambridge research ethics committee. This patient population has been the basis of previous publications.

Perfusion Magnetic Resonance Imaging
pMR was performed on a 3-T magnet (Med-spec s300, Bruker, Germany) with single-shot gradient echoplanar imaging with a repetition time of 1390 to 1500 ms, an echo time of 23 to 36 ms, number of slices 11 to 15, slice thickness of 5 mm, field of view of 190 mm, and matrices of 64×128 or 128×128. The contrast agent (0.1 mmol/kg gadolinium-DTPA) was injected as a bolus through an antecubital vein at a rate of 3 to 4 mL/s followed by rapid infusion of 20 mL saline with use of a power injector. DWI, T2-weighted fast spin-echo, and T1-weighted spoiled gradient echo were also acquired, followed by PET scanning.

Positron Emission Tomography
PET was performed on a GE Advance scanner (General Electrics, Milwaukee, Wis). Emission data were acquired in 3D mode during steady-state infusion of H215O, in 2D mode during steady-state inhalation of 15O2, and in 3D mode after 60-second inhalation of C15O. Image reconstruction included corrections for attenuation, scatter, randoms, and dead time. In all patients, transcranial
Doppler was performed before imaging commenced and in between MR and PET scanning and documented no change over time.

**Image Processing**

With the use of dedicated deconvolution software, CBF, CBV, and MTT maps were generated with both standard singular value decomposition (sSVD)\(^\text{14}\) and circular SVD (oSVD).\(^\text{15}\) The latter is in principle preferable in stroke because it is less sensitive to tracer delay (see Introduction), but the former was also included here to allow comparison with published clinical studies. We also derived maps of TTP by using standard software, and of Tmax, by using the sSVD software; Tmax reflects how much the tissue response lags behind the arterial input and inherently corrects for the length of the gadolinium bolus.\(^\text{16}\) The TTP and Tmax maps were used only for the penumbra threshold substudy.

PET-generated maps of CBF, CBV, cerebral metabolic rate for oxygen (CMRO\(_2\)), and oxygen extraction fraction (OEF), including correction for CBV, were obtained.\(^\text{11,12}\) An MTT map (in seconds) was also generated by voxel-wise division of CBV by CBF. pMR maps were coregistered to the T2-weighted scan by using the normalized mutual information algorithm in the vtk-CISG software package (www.image-registration.com). First, the prebolus images were coregistered to the structural T2 images. Then the registration parameters were applied to all of the pMR maps and PET parametric maps to place them in the same T2 space.

**Regions of Interest**

Using Analyze 7.0 (AnalyzeDirect Inc, Lenexa, Kan), we symmetrically created 16-mm-diameter circular regions of interest (ROIs) on each patient’s T2 images based on gyral anatomy, after eliminating cerebrospinal fluid voxels by segmentation of the T1-weighted scans in SPM2 and previously published thresholds.\(^\text{17}\) ROIs were placed over the cortex, insula, basal ganglia, and white matter areas in both the affected and unaffected hemispheres across the whole range of axial cuts (~150 ROIs per subject and side; total number of ROIs across patients=1194). ROIs having a mean PET CBV value >8.0 mL/100 g were excluded as artifactual. For each ROI, the pMR- and PET-derived CBF, CBV, and MTT values were obtained, as well as the PET-derived OEF and CMRO\(_2\) data. Finally, the MTT delay for each pair of ROIs was determined as affected-side MTT minus unaffected-side MTT.

**Data Analysis**

We first compared the ROI data for CBF, MTT, and MTT delays obtained with the sSVD and oSVD methods by linear correlation and Bland-Altman plots to characterize the similarities and differences between the 2 methods. We then validated the absolute values of CBF, MTT, and CBV obtained with sSVD pMR against their PET counterparts by assessing the strength and slope of the linear correlations.

To determine the sSVD pMR MTT delay penumbra threshold, we used 2 independent methods, which allowed us to assess consistency. In a preliminary analysis, we plotted the PET-derived OEF versus CBF data for the affected-hemisphere ROIs to determine whether the data set included ongoing ischemia, ie, low CBF and high OEF.\(^\text{3}\) However, to avoid “contamination” by areas with established reperfusion or necrosis, all ROIs with an OEF <0.32, ie, the 95% lower confidence limit for similar ROIs from 10 normal control subjects in...
our institute, were excluded beforehand. Consistency across both modalities was verified by comparing the pMR- and PET-derived MTT delay values. In the first method, we plotted the pMR MTT delay values versus the PET-based CBF values, determined the best fit across the data set by linear or nonlinear functions, and obtained the pMR MTT delay corresponding to the PET CBF penumbra threshold directly from the equation of fit. To account for the fact that our ROIs had variable fractions of gray and white matter (which have slightly different MTT delays\(^{18}\)), affected-side CBF values were normalized by their mirror ROIs to yield CBF ratios. By using the classic PET threshold of 20 mL/100 g per minute,\(^{1,9}\) a CBF ratio of 0.496 for the penumbra was calculated on the basis of the mean CBF across ROIs of 40.3 mL/100 g per minute in normal subjects. For completeness, we also analyzed the relation between pMR MTT delay and OEF with a similar approach. In the second method, we first identified the subpopulation of ROIs that fulfilled the following 3 probabilistic criteria for the penumbra\(^{13}\): (1) PET-CBF /H_1^{-20} \text{mL/100 g per minute}; (2) OEF >0.55 (P<0.01 relative to the control group); and (3) CMRO_2 >63 \text{mmol/100 g per minute}. A probabilistic pMR MTT delay penumbra threshold was then determined as the mean MTT delay for this subpopulation of ROIs. The penumbra thresholds for the oSVD-derived MTT delay, for TTP delay, and for Tmax were then obtained by using the same procedures.

**Results**

There was an excellent linear relation between sSVD and oSVD data for CBF and MTT (Figure 1), but, as shown by Bland-Altman plots, the sSVD-derived values tended to overestimate the oSVD-derived values for high CBF and MTT values. However, the 2 methods were very close for CBF values in the ischemic range. The sSVD method also overestimated MTT delays >3 seconds. Of note, this overestimation was not more marked in the 2 patients with proximal severe internal cerebral artery stenoses than in the other 3 cases (data not shown). As explained earlier, we first present the results for sSVD, which currently has greater clinical relevance.

As illustrated in Figure 2, the relative distribution patterns of CBF, CBV, and MTT were remarkably similar with both modalities for all patients, especially for CBF and MTT, and less so for CBV. In 3 patients (No. 1 and 5 with severe proximal internal cerebral artery stenoses, and No. 3), hypoperfusion was substantially larger than the DWI lesion ("mismatch"), whereas in the remaining 2 patients, this was more limited.

The within-subject correlations, illustrated in Figure 3, exhibited marked between-subject variation in the regression slopes for CBF and CBV, with much more consistency for MTT. Within-subject correlations were however consistently high for all variables except CBV (particularly in patient No. 3), but across subjects there was a clear overestimation of absolute CBF and CBV and a slight underestimation of MTT by pMR. When all ROIs were merged across all subjects, the correlation between pMR values and PET was strong for CBF (\(r^2=0.35\), slope=1.92) and MTT (\(r^2=0.42\), slope=0.56) but less substantial for CBV (\(r^2=0.19\), slope=1.31).

To reduce this intersubject variability, we normalized the pMR and PET data, with each ROI value being expressed as

**Figure 3.** Correlation between pMR and PET for absolute CBF (a), CBV (b), and MTT (c). Slopes of the regression lines were 1.24, 0.76, 1.35, 2.30, and 2.52 for CBF in patients 1 through 5, respectively (\(r^2=0.48, 0.24, 0.44, 0.60, \) and 0.49, respectively). Corresponding slopes for CBV were 0.86, 0.77, 0.35, 1.42, and 1.51, respectively (\(r^2=0.34, 0.28, 0.06, 0.30, \) and 0.20, respectively), and for MTT they were 0.56, 0.31, 0.61, 0.49, and 0.49, respectively (\(r^2=0.41, 0.11, 0.54, 0.51, \) and 0.19, respectively). Number of ROIs in patients 1 through 5 were 243, 234, 217, 216, and 284, respectively.
a percentage of the mean across all ROIs for each patient. This normalization greatly improved the strength of the correlation (Figure 4), suggesting that a large part of the intersubject variance was due to method-related individual global scaling.

Figure 5a shows the relation between PET-CBF and PET-OEF in the affected hemisphere across subjects. The OEF increased gradually as CBF decreased to <40 mL/100 g per minute and dramatically as CBF decreased to <20 mL/100 g per minute. This confirmed that our data spanned the whole range of CBF decreases, including severe ischemia. The relation between pMR- and PET-derived MTT delays is shown in Figure 5b. Although the former tended to be underestimated, especially for high values, a strong correlation was present, indicating the overall validity of MR-derived MTT delay.

Figure 6 shows the relation between PET CBF or OEF ratios and pMR MTT delays. There was a clear increase in

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**Figure 4.** Correlation between pMR and PET for CBF and CBV, expressed in percent of the mean, across all ROIs (N=1194) and all 5 patients, constrained to 0, 0. The dotted line shows the line of identity. For CBF, $r^2=0.44$, $y=0.88x$; for CBV, $r^2=0.26$, $y=0.51x$.

**Figure 5.** a, PET CBF vs OEF for the affected hemisphere across all patients (n=501 ROIs). As CBF decreased, OEF increased first gradually, then steeply for CBF <20 mL/100 g per minute. b, Relation between pMR MTT delays and PET MTT delays for the affected hemisphere (n=501 ROIs). The dotted line shows the 95% CIs for the regression line. Good linearity was found between both modalities ($r^2=0.45$, $y=0.53x + 1.56$).
was a very good linear correlation between the 2 methods for MTT delay as PET CBF decreased (Figure 6a), with a cubic function providing the best fit. The pMR MTT delay corresponding to the CBF penumbra threshold of 0.496 was 6.07 seconds. Under the condition of an OEF ratio >0.55 (Figure 6b), the same relation as in Figure 6a was observed, with the best fit again being cubic. Similarly, a cubic curve best fitted the pMR MTT delay versus OEF ratio (Figure 6c). For the 42 ROIs that fulfilled all 3 probabilistic PET criteria for the penumbra, the mean MTT delay was 6.97 seconds. The penumbra thresholds calculated by the same 2 procedures as applied to sSVD MTT delay, TTP delay, and TMax were 4.58 and 5.05 seconds, 4.79 and 4.74 seconds, and 5.40 and 5.46 seconds, respectively.

The sensitivity, specificity and accuracy of the four pMR penumbra thresholds (MTT delay calculated with sSVD and oSVD, TTP delay and TMax), as determined using Method 1 and Method 2, are reported in Supplemental Table I, available online at http://stroke.ahajournals.org.

**Discussion**

In this study, we found good linearity between pMR and PET for all variables when expressed as relative distributions, but there were clear trends for pMR to overestimate absolute CBF and CBV in an individually unpredictable way. With the sSVD method, a pMR MTT delay penumbra threshold of 6 to 7 seconds was determined against PET. However, the standard deconvolution method clearly overestimated MTT delays relative to oSVD, especially for prolonged MTT delays, and accordingly, the derived penumbra threshold was shorter with the latter method. Finally, penumbra thresholds of ~4.8 and 5.4 seconds were derived for TTP delay and Tmax, respectively.

In patients with arterial occlusion, sSVD tends to overestimate MTT delays owing to delay of the contrast agent in ischemic areas, which motivated our choice to also implement oSVD. Consistent with a previous simulation, there was a very good linear correlation between the 2 methods for CBF, MTT, and MTT delay (Figure 1), but as expected, the sSVD method substantially overestimated long MTT and MMT delays, ie, in the ischemic range, consistent with previous reports. Thus, methods to control for delay should be recommended in acute stroke to avoid overestimating the area with hemodynamic compromise. Nevertheless, to allow meaningful comparison with current clinical literature, we opted to present and discuss mainly the results obtained with sSVD. Note that the overestimation of MTT delay by sSVD was not particularly marked in the 2 patients with severe proximal internal carotid artery stenosis compared with the remaining 3 patients, but the latter also had cerebral hypoperfusion, denoting persistent arterial obstruction intracranially.

As shown in Figure 2, an overall very good similarity between the parametric maps derived from the 2 imaging modalities was present for CBF and MTT across patients but less so for CBV. In confirmation of this visual assessment, good linearity was found in the inrasubject correlation analysis for all 3 variables, although pMR clearly overestimated CBF and CBV compared with PET (Figure 3). In addition, there was marked intersubject variability in the CBF and CBV slopes, consistent with a previous study of chronic cerebrovascular disease and an experimental study in pigs. This intersubject variability reflects the inherent difficulty of obtaining true arterial tracer concentrations in pMR, given partial-volume effects of the selected artery and complex susceptibility effects, with resultant unpredictable global scaling effects. However, this may be partly circumvented by normalization (see next section). MTT, being largely insensitive to these effects, partly explains the much better consistency of MTT slopes across patients.

To reduce intersubject variability in pMR CBF and CBV, we normalized each ROI value by the individual mean, which resulted in much improved across-subject correlation (Figure 4), consistent with earlier studies. This effect underlies the very good similarity between the pMR and PET maps in...
terms of relative distribution and patterns, illustrated in Figure 2. Thus, even though the absolute CBF and CBV values from pMR have poor reliability, their relative distribution adequately represents the real perfusion changes in acute stroke patients, which has clinical relevance. More work is needed to derive more accurate absolute pMR variables.

In all patients, there was some degree of mismatch, substantial in 3 and less pronounced in 2 (Figure 2). The presence of an MR-based mismatch is consistent with the scatterplot of the relation between PET-CBF and PET-OEF in the affected hemisphere (Figure 5a), showing OEF values gradually increasing as CBF decreased to <40 mL/100 g per minute and dramatically increasing as CBF decreased to <20 mL/100 g per minute. Our dataset therefore included the penumbral range, as well as the whole range of CBF from normal to severe ongoing ischemia of <10 mL/100 g per minute.

To determine the pMR penumbra threshold, we analyzed the relation between pMR MTT delay and PET CBF and OEF (Figure 6). As physiologically expected, pMR MTT values increased as CBF decreased. This behavior was clearly maintained for the subgroup of ROIs with high OEF, confirming that pMR MTT has the potential to detect the penumbra. As also expected, the MTT delay increased as OEF increased. A similar relation has been previously reported in chronic stroke\(^{22}\) or mixed chronic and acute stroke\(^{10}\) patients. Based on the best fit of the MTT delay–CBF relation, a pMR MTT delay of 6 seconds was finally determined as the penumbral threshold. In the second independent analysis, under the stricter probabilistic criteria, a threshold of 7 seconds was found. The consistency between these 2 values supports their validity, further strengthening both TTP delays as the most accurate pMR-DWI mismatch areas, defined with TTP delays >4 and >6 seconds and PET-based areas with OEF >150% of the contralateral hemisphere, was assessed. It was found that both mismatch areas grossly overestimated the high OEF area, suggesting that even >6 seconds was inadequate. However, an elevated OEF alone is insufficient to define the penumbra,\(^{24}\) which, with additional methodological differences from our study such as the PET method to determine the OEF and the method to determine the TTP penumbra thresholds, together probably account for the discrepancy. Using pMR only, Neumann-Haefelin et al\(^{25}\) reported that a TTP delay >6 seconds best predicted DWI growth, whereas a TTP delay >4 seconds was correlated best with acute-stage neurologic deficit; the latter would be closer to the true penumbra threshold, whereas the former would be overestimated, as it is biased toward the portion of the penumbra that proceeds to infarction.\(^{24,26}\) Our findings are broadly consistent with this report.

No previous pMR-PET comparison study has assessed MTT as the variable of interest. However, several MR-based studies have attempted to determine MTT or Tmax thresholds for tissue outcome. Grandin et al\(^ {27,28}\) reported that an MTT delay of 8.1 seconds best predicted “infarct growth,” ie, final infarct minus acute DWI lesion, whereas an MTT delay of 5.3 seconds defined the hypoperfused area that did not progress to infarction, so-called “benign hypoperfusion.” As already mentioned, this difference is expected because perfusion in the portion of the penumbra that eventually proceeds to infarction is lower than that in the portion that escapes infarction.\(^ {24,26}\) In addition, the benign hypoperfusion so defined is expected to include oligemic tissue not at risk of infarction.\(^ {24}\) Thus, the true penumbra threshold is expected to lie between the “infarct growth” and “benign hypoperfusion” thresholds. The MTT delay threshold of 6 to 7 seconds found herein is therefore entirely consistent with that report. Two studies that determined MTT threshold for final infarction\(^ {29}\) or DWI growth\(^ {30}\) reported >6 seconds as the most accurate predictor, whereas Bristow et al\(^ {18}\) reported a >7-second threshold. Despite the different methods used, our findings are broadly consistent with these pMR studies.

In the single study that determined the Tmax threshold for final infarct,\(^ {16}\) a >6-second threshold was reported to be the best predictor. In the present study, we found a Tmax penumbra threshold of ~5.4 seconds, again rather close to that earlier determination. Finally, the MTT delay threshold for the oSVD method was, as expected, lower than with standard deconvolution, ~4.5 seconds. There is no previous estimation of the MTT penumbra threshold derived from circular deconvolution to compare with our result.

Although derived from a small patient sample studied beyond 6 hours after stroke onset, our data are the first to provide formal validation of pMR against PET in the acute setting, as well as probabilistic penumbra thresholds for all pMR variables currently in use.

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Disclosures

None.

References

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In the article “How Reliable Is Perfusion MR in Acute Stroke? Validation and Determination of the Penumbra Threshold Against Quantitative PET”, by Takasawa et al., the authors have requested that a supplemental Table and accompanying Addendum be included in their online article. The Table and text include the sensitivity/specificity data for the 8 MR penumbra thresholds reported.

The corrected version can be viewed online at http://stroke.ahajournals.org.