Comparison of Computed Tomography Perfusion and Magnetic Resonance Imaging Perfusion-Diffusion Mismatch in Ischemic Stroke

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Background and Purpose—Perfusion imaging has the potential to select patients most likely to respond to thrombolysis. We tested the correspondence of computed tomography perfusion (CTP)-derived mismatch with contemporaneous perfusion-diffusion magnetic resonance imaging (MRI).

Methods—Acute ischemic stroke patients 3 to 6 hours after onset had CTP and perfusion-diffusion MRI within 1 hour, before thrombolysis. Relative cerebral blood flow (relCBF) and time to peak of the deconvolved tissue residue function (Tmax) were calculated. The diffusion lesion (diffusion-weighted imaging) was registered to the CTP slabs and manually outlined to its maximal visual extent. Volumetric accuracy of CT-relCBF infarct core (compared with diffusion-weighted imaging) was tested. To reduce false-positive low CBF regions, relCBF core was restricted to voxels within a relative time-to-peak (relTTP) >4 seconds for lesion region of interest. The MR-Tmax >6 seconds perfusion lesion was automatically segmented and registered to CTP. Receiver-operating characteristic analysis determined the optimal CT-Tmax threshold to match MR-Tmax >6 seconds. Agreement of these CT parameters with MR perfusion-diffusion mismatch in coregistered slabs was assessed (mismatch ratio >1.2, absolute mismatch >10 mL, infarct core <70 mL).

Results—In analysis of 49 patients (mean onset to CT, 213 minutes; mean CT to MR, 31 minutes), constraining relCBF <31% within the automated relTTP perfusion lesion region of interest reduced the median magnitude of volumetric error (vs diffusion-weighted imaging) from 47.5 mL to 15.8 mL (P<0.001). The optimal CT-Tmax threshold to match MR-Tmax >6 seconds was 6.2 seconds (95% confidence interval, 5.6–7.3 seconds; sensitivity, 91%; specificity, 70%; area under the curve, 0.87). Using CT-Tmax >6 seconds “penumbra” and relTTP-constrained relCBF “core,” CT-based and MRI-based mismatch status was concordant in 90% (kappa=0.80).

Conclusions—Quantitative CTP mismatch classification using relCBF and Tmax is similar to perfusion-diffusion MRI. The greater accessibility of CTP may facilitate generalizability of mismatch-based selection in clinical practice and trials. (Stroke. 2012;43:2648-2653.)

Key Words: acute stroke ■ computed tomography imaging ■ ischemia ■ magnetic resonance imaging ■ perfusion

A mismatch between the irreversibly damaged infarct core and the extent of hypoperfused tissue at risk for infarction is an attractive paradigm with which to select ischemic stroke patients for reperfusion therapies.1,2 There has been intense investigation into magnetic resonance imaging (MRI) perfusion-diffusion mismatch over the past decade with refined criteria now being tested in large clinical trials. Diffusion imaging has been established as an accurate representation of irreversible infarction,3–5 and Tmax >5 to 6 seconds has been demonstrated as the best predictor of tissue destined for infarction in the absence of reperfusion.6–8 A meta-analysis of randomized trials that used mismatch selection has demonstrated that reperfusion was associated with favorable clinical outcome in patients with mismatch.9 Computed tomography perfusion (CTP) also has the potential to identify “mismatch” indicating salvageable brain tissue and has advantages over MRI in accessibility and speed in the emergency department setting. However, there has been
limited validation of CTP parameters against the more extensively studied MRI perfusion-diffusion mismatch paradigm.\textsuperscript{10} Recent evidence has emerged that relative cerebral blood flow (relCBF) performs better than other parameters, including cerebral blood volume (CBV), in predicting the infarct core indicated by concurrent diffusion imaging.\textsuperscript{11-13} However, “false-positive” low CBF regions in white matter, particularly in regions of leukoaraiosis, were noted to be problematic. We tested the effect of restricting the core to voxels with both low relCBF and delayed time to peak (TTP) to reduce these white matter false-positive lesions. We then assessed the correspondence of CTP Tmap hypoperfusion to the threshold of MR Tmax >6 seconds. Using these optimized CTP core and penumbra definitions, we proceeded to analyze the diagnostic accuracy of CTP mismatch classification with contemporaneous perfusion-diffusion MRI mismatch.

Patients and Methods

Patients

Consecutive acute ischemic stroke patients presenting within 6 hours of stroke onset at a single center had diffusion and perfusion MRI (1.5-T Siemens Magnetom Vision) obtained <1 hour after CTP as part of a prospective observational study and as previously published.\textsuperscript{11,12} The patients were all participants in trials requiring perfusion-diffusion MRI for entry at a time when the accepted time window for thrombolysis was 0 to 3 hours. CT perfusion therefore could be obtained while awaiting MRI without delaying treatment. Eligibility criteria were symptoms of acute hemispheric stroke, absence of hemorrhage, or established infarction of more than one-third of the middle cerebral artery territory on noncontrast CT and absence of contraindication to CT or magnetic resonance (MR) contrast agents. Both imaging modalities were acquired before any thrombolysis. The study was approved by the institutional ethics committee. All patients gave written informed consent. Patients were included in this analysis if at least 1 CT perfusion slab contained abnormal CT or coregistered MR perfusion and/or a component of the coregistered diffusion lesion. Patients were excluded if the contrast bolus arrived before the commencement of the acquisition or did not give rise to a detectable arterial input function. CT and MR angiography data were reviewed by 2 independent stroke neurologists (B.C. with >5 years of experience and M.P. with >10 years of experience) to identify any cases of spontaneous recanalization between CT and MR imaging.

CT Acquisition

Two separate CTP slabs, each 24 mm thick, were acquired consecutively (16-slice Phillips Mx8000 scanner) and positioned to maximize supratentorial coverage. Iodinated contrast (40 mL) was injected at 5 mL/s and 35 images were acquired every 1.3 seconds (total acquisition time, 45 seconds). Each slab was formatted as 2×12-mm slices.

CTP Analysis

Because commercial image processing software packages use a variety of postprocessing techniques that are often incompletely specified and usually not customizable, we developed our own image processing pipeline using open-source MINC tools (Montreal Neurological Institute) and in-house developed Matlab scripts (R2009b; Mathworks, Natick, MA). Automated motion correction (in-plane) was performed and the raw CTP data were down-sampled (bicubic without antialiasing) from 512×512 to 256×256. Gaussian smoothing was applied to the raw data (kernel width from 6 pixels [5.5-mm radius]). All nonbrain tissue voxels were excluded from the kernel weighting to avoid edge smearing. An arterial input function was selected from the anterior cerebral artery and venous outflow function from the superior sagittal sinus by a user-supervised (B.C.) arterial input function detection algorithm.\textsuperscript{14} Singular value decomposition deconvolution was performed with a standard (sSVD, delay-sensitive) algorithm to create maps of CBF and TTP of the tissue residue function (Tmax). Our previous work suggested that block circulant (delay-insensitive) deconvolution did not improve accuracy.\textsuperscript{12} CBV and TTP were calculated from the concentration-time curve. CBV and CBF were calculated relative (by ratio) to the mean of the entire contralateral hemisphere. TTP was expressed relative (by offset) to the mean of the entire contralateral hemisphere.

MRI Reference Standard

The perfusion and diffusion MRI were registered to each CTP slab using the noncontrast CT as an intermediary (MINC tools) and visually verified for accuracy using interactive image blending (B.C.). The maximal visual extent of the coregistered diffusion lesion was manually outlined (B.C.) and formed the reference standard for infarct core.\textsuperscript{4} These manual regions of interest (ROI) were drawn without reference to other imaging over a 1-week period and independently verified by a second stroke neurologist (M.P.), with disagreements resolved by consensus. The B1000 image was used as the primary template because quantitative ADC thresholds tend to not accurately outline the visually evident lesion and they have been shown to vary with time after stroke onset and perfusion status.\textsuperscript{16} The MRI perfusion maps were generated using the same methodology as CTP.

Infarct Core Optimization

This analysis was performed using the summed volumes from 2 separate CT slabs for each patient. A relCBF <31% of the contralateral mean was identified as the optimal threshold to define irreversible infarction in our previous work using this software.\textsuperscript{12} Note that although relCBF was the most accurate CTP measure of infarct core, different processing pipelines may require a different threshold. In our previous work, we noted some inaccuracies because of “false-positive” low CBF in white matter, especially in regions of leukoaraiosis. To reduce the false-positive contribution from white matter, we explored the effect of restricting relCBF core to regions of significant perfusion delay indicated by relTTP >4 seconds, which visually achieved exclusion of the white matter regions with no significant influence on the ROI over the actual lesion. Furthermore, relTTP <−4 seconds (ie, nonphysiological “early” bolus arrival) was included to encompass regions of very low CBV (essentially undetectable flow), where the concentration-time curve comprises only noise and TTP therefore becomes randomly distributed throughout the acquisition duration. The relTTP ROI was automatically thresholded and then postprocessed to remove small, isolated regions of false-positive voxels caused by noise. First, isolated regions with <5 mL volume were removed. Morphological opening and closure were then performed to remove edge artifacts and to fill-in residual small regions of low TTP within the perfusion lesion in areas of very low CBV. This relTTP-based ROI provided a more accurate outline of the perfusion lesion than a Tmax-based method because more of the low CBV regions tended to have Tmax of 0 and therefore were indistinguishable from normal brain.

Comparison of CT and MR Tmax

Receiver-operating characteristic analysis was performed to determine the optimal threshold (by Youden index\textsuperscript{17}) of CT-Tmax to match the coregistered concurrent MR-Tmax >6-second lesion as the reference standard following previously published methods\textsuperscript{12,18} within an ipsilateral hemisphere reference region. Confidence intervals for the global area under the curve statistics were derived by patient-level bootstrapping (10,000 random samples with replacement). Volumetric agreement with MR-Tmax >6 seconds was then assessed (Bland-Altman) at the receiver-operating characteristic–derived optimal threshold using the summed volumes from 2 separate CT slabs for each patient.
Mismatch Analysis
Mismatch was defined using the MR criteria used for the EXTEND trial,19 ie, a perfusion lesion-to-infarct core ratio /H11022 1.2, a perfusion lesion–infarct core volume /H11022 10 mL, and an infarct core volume /H11021 70 mL. These criteria were based on subgroup analysis of tissue plasminogen activator response in the EPITHET trial20 and data indicating poor response to reperfusion in patients with large infarct core.21,22 A more stringent mismatch definition using mismatch ratio /H11022 1.823 as used in the DEFUSE-2 trial (NCT01349946) also was tested. The volumes of Tmax >6 seconds on MR and CT, the diffusion lesion on MR, and the TTP-constrained relCBF lesion on CT were calculated from the sum of 2 coregistered slabs per patient. Mismatch status using the original whole-brain perfusion and diffusion MR images was also calculated. Concordance between MR and CT mismatch was assessed using raw agreement and kappa.

Results
The study enrolled 64 patients between 2003 and 2007. Sequentially acquired CTP and diffusion MRI were available for analysis of 49 of 64 patients. Exclusions are detailed in the STAndards for the Reporting of Diagnostic accuracy studies (STARD) diagram (Figure 1). The mean age of patients was 70.4 years (standard deviation, 12.4) and 45% were male. Median baseline National Institutes of Health Stroke Scale score was 16.5 (interquartile range, 12–19). The mean time from stroke onset to CT was 213 minutes (standard deviation, 44.7; 12/49 imaged 0–3 hours, 26/49 imaged 3–4.5 hours, 11/49 imaged 4.5–6 hours) and mean time between completion of CT and commencement of MR was 31 minutes (standard deviation, 15.6).

Optimization of relCBF Infarct Core Identification
Volumetric agreement with the diffusion lesion was substantially improved by constraining relCBF <31% within the automated TTP perfusion lesion ROI (median magnitude of volume difference 15.8 mL vs unconstrained 47.5 mL; \( P<0.001 \)). The magnitude of volume difference as a proportion of DWI volume reduced from a median 219% to 38% \( (P<0.001) \). The bias (average difference DWI–CT-CBF) was reduced from −50 mL to −11.3 mL; in other words, with TTP-restriction, on average, CT-CBF core was still 11 mL larger than the corresponding diffusion lesion. Visual inspection demonstrated reduction of false-positive regions in white matter (Figure 2). The Bland-Altman 95% limits of agreement were −46.9 and 24.2 mL (Figure 3A, B).

CT vs MR Tmax
Receiver-operating characteristic analysis demonstrated the best CT-Tmax threshold to match MR-Tmax of >6 seconds was 6.2 seconds (95% confidence interval, 5.6–7.3 seconds; sensitivity, 91%; specificity, 70%; area under the curve, 0.87). Because 6.2 seconds was not significantly different to 6.0 seconds, and because Tmax is generally calculated in 1- or 2-second increments because of the timing between each image acquisition, 6.0 seconds was used as the threshold for further analyses. The median magnitude of volume difference between the 2 coregistered CT and MR slabs using a Tmax threshold of >6 seconds was 18.4 mL (28%). The Bland-Altman 95% limits of agreement were −41.1 and 56.9 mL (Figure 3C).

Mismatch Agreement
Mismatch agreement was initially tested using CT slabs and coregistered MRI diffusion and perfusion imaging to remove any effect of reduced brain coverage with CT. Using a CT-Tmax of >6 seconds “penumbra” and a relCBF of <31% (restricted to TTP >4 seconds “core”) CT-based and MRI-based mismatch status was concordant in 44 of 49 (90%) of patients. Kappa was 0.80, indicating excellent agreement. There were 2 false-positive results and 3 false-negative

Exclusions:
- No diffusion or CT/MR perfusion lesion within slab coverage, n=7
- Only one slab available, n=2
- Spontaneous partial reperfusion between CT and MR, n=2
- Inadequate contrast bolus, n=2
- Excessive motion, n=1
- Missing MR perfusion data, n=1

Figure 1. STAndards for the Reporting of Diagnostic accuracy studies (STARD) flow diagram.
results. Sensitivity for mismatch was 88% and specificity was 92%. Positive predictive value was 91% and negative predictive value was 88%. With an alternative definition of mismatch using a mismatch ratio $H_1/H_2 \geq 1.8$, agreement was similar (45/49; 92%; kappa = 0.83). Because of the reduced brain coverage with 16-slice CTP, mismatch agreement between CTP and the whole-brain MRI was reduced to 39 of 49 (80%; kappa = 0.59) or 40 of 49 (82%; kappa = 0.63) using mismatch ratio $H_1/H_2 > 1.8$. The discrepancies attributable to brain coverage were a combination of false-negative CT mismatch in 6 patients (because of unrecognized peripheral Tmax $> 6$ seconds) and false-positive CT mismatch in 4 patients (infarct core was $> 70$ mL when whole brain was assessed).

Discussion
This study has demonstrated that quantitative CTP mismatch classification using relCBF and Tmax is similar to perfusion-diffusion MRI. The identification of infarct core using relCBF can be significantly improved by simply restricting core to voxels with both low relCBF and delayed TTP. The MR-Tmax threshold of $>6$ seconds for salvageable hyperperfusion translates directly to CTP. The lower agreement of CTP with whole-brain MRI indicates the potential value of newer CT scanners with whole-brain coverage.

The problem of false-positive low CBF in white matter arises for 2 main reasons. The first is the well-recognized reduction in CBF in regions of leukoaraiosis. The second is the relatively low contrast-to-noise ratio of CTP compared with MRI and the physiological gradient in CBF between gray and white matter. This makes a good-quality acquisition, with adequate contrast bolus and slice thickness, essential to distinguish normal and abnormal white matter. To reduce the impact of low CBF in normal white matter and leukoaraiosis on mismatch classification, we restricted relCBF core to a relTTP lesion ROI to exclude regions outside the hyperperfused infarct. The TTP also may be delayed in leukoaraiosis, but the postprocessing to remove small isolated regions accounted for much of this. Despite good mismatch agreement, more sophisticated postprocessing should be actively investigated to improve the modest volumetric accuracy in this study, particularly for infarct core delineation. This is particularly relevant if measures such as infarct growth between baseline CTP and follow-up MRI are to be used.

A limitation of the CT data utilized in this study was the restricted brain coverage (5 cm), which lead to reduced mismatch agreement with whole-brain MRI compared with the within-slab CT–MR comparison. However, given the increasing use of modern CT scanners with whole-brain coverage, this limitation of CT is rapidly receding. The acquisition duration also was relatively brief, which may have led to bolus truncation in some patients. Although this did not affect the optimal relCBF threshold for core in our previous work, our current practice is to use a longer acquisition. We
chose a volumetric rather than voxel-based analysis. Coregistration of MRI data to the limited coverage CTP slabs introduces potential for error in volumetric calculations, but this effect would be magnified in a voxel-based analysis. Additionally, some variation in perfusion maps would be expected between 2 MRI perfusion acquisitions taken after separate contrast injections 30 minutes apart. Therefore, the magnitude of difference between CT and MR is probably not entirely attributable to technical variation between the 2 techniques. We believe agreement of \( \geq 90\% \) at the mismatch decision-making level is acceptable in this context. Although randomized order of CT and MRI would have been ideal, this would not have been possible without incurring treatment delay. Because the optimal threshold for infarct core utilized in this analysis was derived from within the same dataset, further studies in independent datasets are warranted to confirm the wider applicability of this threshold.

The precision of MRI perfusion-diffusion imaging, particularly in accurately identifying infarct core, may remain superior to CTP. However, there is often restricted access to urgent MRI and contraindications (eg, uncharacterized metallic foreign bodies) create difficulties in the emergency setting. We have demonstrated that CTP can provide information similar to MRI at the level of treatment decision-making. Although there may be individual cases in which uncertainty about treatment benefit persists after CTP and in which addition of MRI would be justified, we believe a treatment decision could be made for the majority of patients on the basis of CTP alone. Therefore, CTP may allow more widespread application of the “mismatch” paradigm in clinical practice and trials.

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Disclosures
None.

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