Multiparametric MRI and CT Models of Infarct Core and Favorable Penumbral Imaging Patterns in Acute Ischemic Stroke

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Background and Purpose—Objective imaging methods to identify optimal candidates for late recanalization therapies are needed. The study goals were (1) to develop magnetic resonance imaging (MRI) and computed tomography (CT) multiparametric, voxel-based predictive models of infarct core and penumbra in acute ischemic stroke patients, and (2) to develop patient-level imaging criteria for favorable penumbral pattern based on good clinical outcome in response to successful recanalization.

Methods—An analysis of imaging and clinical data was performed on 2 cohorts of patients (one screened with CT, the other with MRI) who underwent successful treatment for large vessel, anterior circulation stroke. Subjects were divided 2:1 into derivation and validation cohorts. Pretreatment imaging parameters independently predicting final tissue infarct and final clinical outcome were identified.

Results—the MRI and CT models were developed and validated from 34 and 32 patients, using 943,320 and 1,236,917 voxels, respectively. The derivation MRI and 2-branch CT models had an overall accuracy of 74% and 80%, respectively, and were independently validated with an accuracy of 71% and 79%, respectively. The imaging criteria of (1) predicted infarct core ≤90 mL and (2) ratio of predicted infarct tissue within the at-risk region ≤70% identified patients as having a favorable penumbral pattern with 78% to 100% accuracy.

Conclusions—Multiparametric voxel-based MRI and CT models were developed to predict the extent of infarct core and overall penumbral pattern status in patients with acute ischemic stroke who may be candidates for late recanalization therapies. These models provide an alternative approach to mismatch in predicting ultimate tissue fate. (Stroke. 2013;44:73–79.)

Key Words: computed tomography ■ diffusion-weighted MRI ■ embolectomy ■ infarction ■ magnetic resonance imaging ■ perfusion-weighted MRI ■ stroke

Vessel recanalization with intravenous thrombolytic therapy improves functional outcomes in patients presenting within 3 to 4.5 hours of ischemic stroke onset.1,2 However, treatment is limited by risk of symptomatic intracerebral hemorrhage and the narrow therapeutic time window beyond which there is no proven benefit.3-5 There is a recognized need for advanced imaging methods to select patients most likely to benefit from recanalization therapies and exclude patients who would fare worse or not benefit, particularly in later time windows.6-8 Important goals of multimodal imaging in acute stroke have, therefore, included identification of the infarct core (irreversibly injured tissue that cannot be salvaged even with tissue reperfusion), the ischemic penumbra (tissue at risk of infarction but salvageable with early restoration of blood flow), and regions of benign oligemia (tissue with reduced blood flow but not at risk of infarction).9-11 Patients most likely to benefit from treatment, particularly in late time windows, are postulated to be those with smaller regions of infarct core, substantial regions of ischemic penumbra, and a documented vessel occlusion.

Although positron emission tomography (PET) has been considered the gold standard for defining the ischemic core,
penumbra, and benign oligemia,13 it is not a practical imaging modality in the routine, clinical, acute stroke setting. As such, attention has focused on the role of multimodal magnetic resonance imaging (MRI) and multimodal computed tomography (CT) for defining the infarct core and the penumbra. Infarct core has been estimated with MRI sequences, including diffusion-weighted imaging (DWI), and with CT measures of cerebral blood volume (CBV) or cerebral blood flow (CBF).14–19 Several approaches to identification of the ischemic penumbra with both MRI and CT have also been proposed, including MRI diffusion-perfusion mismatch, and CBV or CBF thresholds; however, these approaches have some limitations.9,26–25 Of note, there has been a growing appreciation that the extent of the infarct core rather than the penumbra is the strongest predictor of outcome in the setting of a large vessel occlusion.15–19 Because the above approaches (typically based on single parameter thresholds) for distinguishing core, penumbra, and benign oligemia have shown only modest success, multiparametric models incorporating information from various sequences have been proposed as offering the potential to improve the prediction accuracy of these compartments.26–28

The 2 primary aims of this study were as follows: (1) to create multiparametric, MRI and CT-based models for distinguishing infarct core from noncore hypoperfused tissue on a voxel-by-voxel basis by using cohorts of patients undergoing successful vessel recanalization and studied pretreatment with multimodal MRI or CT; and (2) to derive patient-level volume thresholds for predicted infarct core and infarct fraction (volume of core/volume of at-risk tissue)x100) to identify a favorable penumbral pattern (small core, large penumbra; likely to benefit from reperfusion therapy) and nonpenumbral pattern (large core, small penumbra; unlikely to benefit from reperfusion therapy). The ultimate goal was to use these categorizations to stratify enrollment in a clinical trial designed to test the imaging selection hypothesis for endovascular recanalization therapies for stroke. According to this hypothesis, patients with a favorable penumbral pattern and successful recanalization would be most likely to have a good clinical outcome, and therefore this group would be the appropriate target for treatment.29

Methods

Patients

The 2 predictive models, 1 for MRI and 1 for CT, were developed independently by analysis of 2 data sets (1 for MRI, 1 for CT) obtained from patients meeting the following criteria: (1) acute ischemic stroke involving the anterior circulation; (2) recanalization therapy (any combination of intravenous tissue plasminogen activator, intra-arterial thrombolysis, and mechanical embolectomy) initiated within 8 hours of symptom onset; (3) multimodal CT or MRI performed before treatment; (4) large vessel intracranial anterior circulation occlusion documented before treatment (distal internal carotid artery, M1 or M2 middle cerebral artery); (5) recanalization (Thrombolysis In Myocardial Infarction [TIMI] score of 2 or 3)6 achieved and documented posttreatment; and (6) follow-up imaging obtained within 7 days to document final infarct size. Functional outcome was assessed on days 30 to 90 using the modified Rankin Scale (mRS), with good functional outcome defined as an mRS score of 0 to 2. For the MRI model, subjects were identified from a prospective study of diffusion-perfusion MRI changes in patients receiving endovascular recanalization therapy at UCLA. For the CT model, subjects were provided from 2 institutions (UCSF, University of Pittsburgh) routinely performing multimodal CT before recanalization treatments for acute ischemic stroke. The study was approved by the Institutional Review Boards of all sites involved.

For both models, both patient-based (eg, National Institutes of Health Stroke Scale [NIHSS], age) and imaging voxel-based variables were considered for model development. Detailed methodology regarding MRI and CT image acquisition and processing is provided in the Supplemental Methods.

Statistical Methods: Voxel-Based Predictive Models

For each model (MRI or CT), the cohort was randomly divided into a derivation group (two third of the cohort) for model development and a validation group (one third of the cohort) for model assessment.

To develop the voxel-level predictive models, a multivariate random coefficient logistic regression analysis was performed on data from the derivation sample (SAS procedure GENMOD and custom programming in SAS, similar to SAS Macro GLIMMIX) using backward stepwise regression with a liberal P<0.15 variable retention criterion for the derivation data. This model allows infarct observations among voxels from the same person to be correlated, with observations from different subjects treated as independent. Model fit was assessed by examining 3 statistics: (1) maximum rescaled R2 statistic; (2) receiver operating characteristic (ROC) curve area (C statistic); and (3) unweighted model accuracy defined as (sensitivity+specificity)/2. For the CT cohort, a second branch to the model was derived to handle voxels that were identified as having less reliable perfusion parameter estimates as a result of the numeric instability of the deconvolution process under conditions of extremely poor signal-to-noise ratio. The logit score was obtained for each voxel from the logistic model, and a cutoff (threshold) score was found such that the unweighted accuracy above was maximized, thus simultaneously maximizing both sensitivity and specificity. The Supplemental Methods section provides greater detail on model development and the variables considered in both of the models.

Statistical Methods: Patient-Level Categorical Assignments

After the voxel-level models to predict infarct core were completed, an algorithm was developed to apply the results of the voxel model at the level of individual patients to distinguish patients with a favorable penumbral pattern (good candidate for treatment) versus nonpenumbral pattern (poor candidate for treatment). Heuristically derived thresholds were identified that best correlated with good functional outcome (mRS 0–2) based on (1) total volume of tissue at-risk that was already irreversibly infarcted (predicted infarct core volume), and (2) the proportion of tissue at-risk that was infarcted (infarct fraction). The threshold was chosen to maximize the accuracy, defined as the unweighted average of the sensitivity and specificity. Infarct fraction was defined as (predicted infarct volume)x100/at-risk volume. For this purpose, a more conservative Tmax threshold of ≥4 seconds (compared with the threshold of ≥2 seconds to develop the core prediction model) was chosen to define the tissue at-risk/penumbral region for MRI, and an MTT threshold ≥6 seconds was chosen for CT.

Results

A total of 34 patient data sets were used for the MRI cohort and 32 data sets for the CT cohort. Mean age for both groups was 72 years, and median baseline NIHSS score was 16 (range, 5–26) and 15 (range, 4–25) for the MRI and CT cohorts, respectively. Treatment categories for the MRI cohort were as follows: 12 pure intra-arterial thrombolysis, 11 bridging intravenous tissue plasminogen activator to intra-arterial thrombolysis, and 11 mechanical thrombectomy. Treatment categories for the CT cohort were as follows: 3 pure intravenous tissue plasminogen activator, 1 only mechanical thrombectomy, 12 bridging intravenous tissue plasminogen...
activator to endovascular, and 16 with combined endovascular mechanical thrombectomy and intra-arterial thrombolysis. There were no significant differences in characteristics comparing the MRI versus CT cohorts, nor were there differences between the derivation versus validation groups within each cohort (data not shown).

MRI Voxel-Level Model
A total of 943320 voxels were included in the MRI model development and validation data set. In the derivation data set, there were 636967 voxel observations; of these, 24% (152603 voxels) were identified as proceeding to infarct on the follow-up scan. The final predictive model of infarct core is provided in Supplemental Table 1. The final MRI model included the following measures: the apparent diffusion coefficient value relative to the contralateral hemisphere (rADC), the cerebral blood flow value relative to the contralateral hemisphere (rCBF), mean transit time value relative to the contralateral hemisphere (rMTT), and the $T_{\text{max}}$ value minus the mean $T_{\text{max}}$ value of the contralateral hemisphere ($sT_{\text{max}}$). This model flags a voxel as likely to proceed as infarct if the equation incorporating these variables is greater than $-0.324$. There were 389550 voxel observations in the derivation data set; of these, 42% (163512 voxels) were identified as proceeding to infarct on the follow-up scan. Accuracy of this model in the derivation dataset was 85%, sensitivity 88%, and specificity 81%, with an ROC C=0.93 and max $R^2=0.54$. In the validation data set, there were 71575 voxel observations; of these, 29% were identified as proceeding to infarct. Accuracy of the above multiparametric MRI model applied to the validation group was 71%, sensitivity 62%, and specificity 80% with an ROC C=0.76 and max $R^2=0.24$. Case examples of the MRI model are shown in Figures 1 and 2.

CT Voxel-Level Model
A total of 1236917 voxels were included in the CT model development and validation data set. A 2-branch combined model was developed. The final predictive models for each branch are provided in Supplemental Table 1. Branch 1 of the predictive model uses continuous variables derived from the deconvolution process (CBF, CBV, MTT, and $T_{\text{max}}$) along with the patient-level variable of the NIHSS score at baseline, and flags a voxel as likely to proceed to infarction if the sum of the equation is greater than $-0.324$. There were 567397 voxel observations in the derivation data set; of these, 47% (267049 voxels) were identified as proceeding to infarct on the follow-up scan. Accuracy of this model in the derivation dataset was 77%, sensitivity 77%, and specificity 77%, with an ROC C=0.84 and max $R^2=0.35$ (Table). In the validation data set, there were 208395 voxel observations; of these, 24% were identified as proceeding to infarct. Accuracy of the above model applied to this group was 79%, sensitivity 88%, and specificity 69% with an ROC C=0.85 and max $R^2=0.28$.

Branch 2 uses noncontinuous (boolean) variables derived from the fundamental signal characteristics (arrival time, area under curve) of voxels where perfusion parameters cannot be reliably determined using deconvolution. Nontinuous voxels were identified as having low signal-to-noise or nonphysiologically relevant values (eg, values out of expected range) as might occur, for example, in the region of a large vessel. The final model incorporates 12 imaging variables along with the pretreatment NIHSS score and flags a voxel as infarct if the sum of the equation is greater than $-0.324$. There were 397 voxel observations in the validation data set; of these, 42% (163512 voxels) were identified as proceeding to infarct on the follow-up scan. Accuracy of this model in the derivation dataset was 85%, sensitivity 88%, and specificity 81%, with an ROC C=0.93 and max $R^2=0.54$. In the validation data set, there were 71575 voxel observations; of these, 29% were identified as proceeding to infarct. Accuracy of the above model applied to the validation group was 71%, sensitivity 62%, and specificity 80% with an ROC C=0.76 and max $R^2=0.24$. Case examples of the MRI model are shown in Figures 1 and 2.

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Figure 1. Case example of the voxel-based model and predictive algorithm from the magnetic resonance imaging (MRI) cohort in a patient with a nonpenumbral pattern. The pretreatment color-coded $T_{\text{max}}$ perfusion image is shown in the upper left panel and the baseline diffusion image in the upper right panel. The map of predicted infarction is shown in the lower left panel, where red indicates predicted infarct despite recanalization and green indicates predicted salvageable penumbra. The lower right panel shows the region of final infarct on follow-up MRI. The large region of final infarct correlates well with that of the voxel fate predicted map. Despite recanalization, the patient developed a large infarct and had a poor outcome with a day 90 modified Rankin Scale (mRS) of 5.
model applied to this group was 78%, sensitivity 89%, and specificity 67% with an ROC C=0.86 and max $R^2=0.31$.

Accuracy of the combined CT model incorporating both branches for the derivation data set was 80%, sensitivity 82%, and specificity 78%. Accuracy of this combined model applied to the validation group was 79%, sensitivity 88%, and specificity 69%. Case examples of the CT model are shown in Figure 3.

Patient-Level Penumbral Pattern Classification

For the per-patient classification of favorable penumbral versus nonpenumbral pattern for the MRI cohort, patients were accurately predicted as having an independent final clinical outcome with reperfusion if (1) the irreversibly infarcted region identified by the MRI voxel-based predictive model was ≤90 mL, and (2) the infarct fraction (ratio of predicted infarct tissue within the at-risk region) was ≤70%. These criteria classified good final outcome with 85% (95% CI, 69%–95%) accuracy across all 34 MRI patients and with 100% (95% CI, 88%–100%) accuracy in the 29 MRI patients who did not develop a parenchymal hematoma (Figure 4). For the per-patient classification of penumbral versus nonpenumbral pattern for the CT cohort, the same volume thresholds for core and infarct fraction used in the MRI model were applied. Follow-up mRS scores were not available for 5 subjects, and therefore these cases were not included in the per-patient pattern analysis. These criteria classified good final outcome with 78% (95% CI, 58%–91%) accuracy overall and with 85% (95% CI, 62%–97%) accuracy in those patients who did not develop a parenchymal hematoma (Figure 4). The incorrect classifications in the CT cohort were attributable to motion in 1 case, causing a false prediction of large regions of infarct, and inadequate brain coverage for the 3 cases with a poor outcome but labeled as penumbral. If these latter cases had full brain coverage, they would have met the volume criteria for a nonpenumbral pattern.

Discussion

Using a similar approach, we developed multiparametric models for both MRI and CT to predict infarct core on a voxel-by-voxel basis in patients undergoing successful vessel recanalization for acute ischemic stroke. We then developed an algorithm to identify patients as having a favorable penumbral pattern (good candidate for treatment) or a nonpenumbral pattern (unlikely to benefit from treatment). The infarct core models had overall accuracies of 71% to 80% in identifying tissue fated to be infarcted despite reperfusion. Across both models, the favorable penumbral versus nonpenumbral pattern achieved 85% to 100% accuracy in predicting good outcome in response to successful recanalization therapy in patients who did not develop a subsequent hematoma.

The voxel-level models predicting infarct core were derived from tissue within the at-risk region that evolved to infarction on follow-up imaging, despite successful vessel recanalization. This approach is based on the premise that the distinction between infarct core and penumbra is optimally developed in patients who achieve successful early recanalization, whereas the distinction between penumbra and benign oligemia is optimally developed in patients who do not achieve early vessel recanalization. Reperfusion typically follows recanalization, resulting in rescue of salvageable tissue and in nonrescue of already infarcted tissue, permitting discrimination of penumbra from core. In contrast, when reperfusion does not occur, tissue injury continues, resulting in death of salvageable as well as already infarcted tissue, and survival only of nonthreatened tissue, permitting discrimination of benign oligemia from penumbra, but not penumbra from core.

To date, the most commonly used method of identifying the ischemic core and penumbra using MRI has been visual assessment of diffusion-perfusion mismatch. This approach is based on assumptions that a hyperintense diffusion lesion represents the irreversibly injured core and that the full extent
of the surrounding perfusion abnormality identifies the ischemic penumbra. However, this model has been shown to have some limitations: some of the milder diffusion abnormal tissue is salvageable with early reperfusion, and much of the milder perfusion abnormal tissue is experiencing benign oligemia, insufficient to produce tissue infarction. Moreover, single-parameter thresholds have only shown modest accuracy. Because of the recognized limitations of mismatch models and single parameter thresholds, we, as others, hypothesized that models incorporating information from multiple sequences or image-based measurements would have the potential to improve prediction accuracy. These models provide an alternative approach to predicting tissue fate with the advantage of incorporating pathophysiological information from multiple sequences and the possibility of improving model accuracy as technology improves. Future studies in larger data sets will allow comparison of our models to other approaches to predicting infarct core and penumbra, including mismatch.

There have been at least 3 other published studies on multiparametric MRI prediction of tissue outcome after stroke. In all 3, baseline imaging was performed relatively late—within 12 to 24 hours after onset—and recanalization/reperfusion was not a prerequisite. None of these studies focused purely on differentiating core from penumbra. For CT, one study reported that an interaction term including both CBV and CBF had the highest accuracy for distinguishing core from penumbra.

Comparability of the CT and MRI models is an important consideration, particularly in light of the negative Desmoteplase in Acute Ischemic Stroke 2 (DIAS 2) clinical trial results. In DIAS 2, patients could be enrolled with either multimodal MRI or CT based on visual appearance of core-perfusion mismatch. There was speculation that the 2 approaches for defining a penumbral pattern were not comparable in DIAS 2, because MR patients had subsequent growth of the core lesion, whereas the CT patients had growth attenuation. There was also further concern that visual assessment of mismatch may not be an optimal approach to identifying penumbra.

Several studies comparing MRI and CT approaches to defining core and penumbra have suggested that consistent results for predicting core and penumbra can be achieved. By using similar voxel-based model development and validation approaches in CT and MRI cohorts of patients with a confirmed proximal large vessel occlusion and subsequent recanalization, we believe our models are comparable. Although the point estimates suggest that the CT infarct core model showed greater accuracy in core identification in imaged slices, the MRI infarct core model may have had a countervailing advantage of whole brain coverage and greater accuracy in predicting patient outcome; however, these differences should be interpreted with caution because of the overlap in CIs. Both CT and MRI patient outcome algorithms used the same core and infarct fraction tissue volume thresholds to identify penumbral and nonpenumbral patterns. It is important to note some differences in the model development and results. First, the MRI model was developed before the CT model on an older data set; lessons learned from development of the MRI model improved our approach to development of the CT model, including a 2-branch approach. Second, perfusion CT provides more accurate absolute CBF and CBV measures compared with MRI. Third, the CT models predicted a greater fraction of at-risk voxels would proceed to infarction. This may reflect differences in the 2 cohorts overall or inherent differences in the models or imaging modalities themselves. An additional advantage to the voxel-based approach used here is that all calculations have been fully automated using the same approach to AIF selection and deconvolution, as well as automated lesion volume determinations of per-patient outcome status. Fully automated image analysis avoids the potential pitfalls of variability in visual assessment of penumbral-core mismatch status.

We derived an algorithm for favorable penumbral status using our predictive model which differentiated patients with good versus poor clinical outcome after successful recanalization. This approach was based on the premise that all patients had a large vessel occlusion with a disabling clinical deficit before treatment, and therefore good functional outcome reflected salvage of clinically-meaningful penumbral tissue. These voxel-based tissue fate and patient-level favorable penumbral pattern predictive models are currently being used in the National Institutes of Health–funded Mechanical Retrieval
and Recanalization of Stroke Clots Using Embolecotmy (MR RESCUE) multicenter trial.29

There are several limitations to the present study. The total number of patients available for model development was modest; even so, the patient cohorts contributed data from 2 million voxels for model development. Tissue swelling at day 7 was partially addressed by coregistration of images but likely added noise to voxel fate mapping analyses. The area of hyperperfusion we included in our analysis region when deriving the MRI infarct core model is known to include regions of benign oligemia. However, the inclusion of benign oligemia regions among candidate voxels would not be expected to alter substantially derivation of parameters that distinguish core from penumbra. We used multiparametric techniques to model tissue core but single-parameter techniques to model tissue at-risk, and excluded voxels with a $T_{max}$ <2 seconds. The single-parameter thresholds for distinguishing penumbra from benign oligemia have only performed modestly well in the literature and have not been completely validated. It is also possible that voxels without a perfusion deficit at the time of imaging could have already proceeded to infarction (eg, infarction of lenticulostriates followed by distal clot migration) or could do so ultimately. This may have led to an overestimation of model sensitivity. Although use of a random coefficient logistic regression analysis accounts for correlation among voxels from the same person, it does not take account of the 3-dimensional spatial distribution of the voxels. Pooled data from other studies allowing a larger sample size will be needed to appropriately address and understand correlation patterns. Future refinements of the models are likely to achieve greater accuracy by improved definitions of the at-risk region using multiparametric techniques (including an ADC or CBV measure), incorporating larger data sets, and using delay-insensitive deconvolution for perfusion processing. A 2-branch approach for the MRI model may also achieve improved accuracy by addressing perfusion voxels having abnormal signal characteristics due to insufficient curve fit. Of note, our model is only applicable to anterior circulation strokes and its utility in the posterior circulation needs to be independently assessed.

In summary, we have developed and validated multiparametric MRI and CT models that predict infarct core on a voxel-by-voxel basis as well as presence of favorable penumbral and nonpenumbral patterns on a per-patient basis. These models show comparable sensitivity and accuracy. These approaches are being used to stratify patients to ensure equal representation of penumbral and nonpenumbral subjects among treatment groups in the MR RESCUE clinical trial.

Acknowledgments
We thank Philips Healthcare who provided a software analysis program for processing CT perfusion imaging: Advanced Brain Perfusion (Philips Healthcare, Cleveland, OH).

Sources of Funding
This study was supported by a grant from the National Institutes of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH), P50 NS044378, and the American Heart Association Bugher Foundation Award for Stroke (to Dr Kidwell) 2001–2004.

Disclosures
Dr Wintermark has received research grants from Philips Healthcare and GE Healthcare. Dr Jahan has served on the speakers’ bureau for Concentric Medical Inc and serves as a consultant for Covidien Inc. The University of California, Regents receive funding for Dr Saver’s services as a scientific consultant regarding trial design and conduct to Covidien and Grifols. Drs Jahan, Alger, Starkman, Liebeskind, Gornbein, and Saver are employees of the University of California, which holds a patent on Merci Retriever devices for stroke.

References


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Stroke. 2013;44:73-79; originally published online December 11, 2012;
doi: 10.1161/STROKEAHA.112.670034
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

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Supplemental Methods Section: Image Acquisition and Processing

**MRI Methods**

MRIs were acquired on 1.5 Tesla scanners. Baseline MRIs included axial DWI and perfusion (PWI) pulse sequences. Follow-up MRIs included axial T2-weighted or fluid attenuated inversion recovery (FLAIR), gradient echo (GRE), DWI and PWI sequences. Diffusion imaging was acquired using 18-20 slices with 5-7 mm slice thickness and no interslice gap, field-of-view (FOV) of 240 mm. Two levels of diffusion sensitization (b values = 0 and 1000 sec/mm²), applied in each of the three principal gradient directions (x, y, z), were used to calculate the ADC map.

PWI was performed using the bolus passage of contrast method (0.1 mg/kg dose via power injector) employing gradient-echo echo-planar imaging (EPI). Images were acquired using 12-18 slices with 5-7 mm slice thickness and no interslice gap, FOV of 240 mm. Following deconvolution of an arterial input function identified from the contralateral middle cerebral artery and the tissue concentration curves, perfusion maps of relative CBF, relative CBV, mean transit time (MTT) and time to peak of the residue function (Tmax) were generated employing in-house software. MTT was calculated in two separate ways: first employing the first moment technique (MTT(fm)), and second by dividing CBV by CBF (MTT(vf)). CBF values in mL/100g/min were generated, but were considered estimates rather than absolute values.

**CT Methods**

Baseline imaging included non-contrast CT and perfusion CT studies. Perfusion CTs were acquired on either 16 or 64 slice multidetector CT scanners with 2 or 4 cm width detectors, and involved successive gantry rotations performed in cine mode during intravenous administration of one or two boluses of 40-50 mL of iodinated contrast material at an injection
rate of 4-5 mL/sec. Acquisition parameters were 80 kVp and 100-200 mAs. Perfusion images were acquired using 2-16 slices (with 5-10 mm reconstructed slice thickness) and FOV of 240-250 mm. In 7 cases, there were two separate acquisitions. Brain coverage ranged from 40-120 mm. CBV, MTT, time to peak (TTP) and CBF perfusion maps were generated via post-processing, employing prototype (unreleased) software provided by Philips Medical Systems (Cleveland, Ohio) and Philips Healthcare. This software includes motion correction and a noise reduction filter followed by a deconvolution algorithm using arterial input and venous output functions. Relative variables were created for each perfusion map by normalizing each voxel of the involved hemisphere to the mean value of the contralateral hemisphere. An estimated Tmax (eTmax) was generated for each voxel by calculating the TTP relative to the time of peak of the arterial input function (AIF).

Image Outcome Analyses

The follow-up imaging studies were coregistered to the baseline scan (pretreatment b0 image for MRI or non-contrast head CT) using Automated Image Registration (AIR) and/or a mutual information algorithm from the National Library of Medicine Insight Segmentation and Registration Toolkit. Voxel dimensions for MRI ranged from 0.9 x 0.9 x 7 mm to 1 x 1 x 7 mm; CT dimensions were 1 x 1 x 10 mm. For development of the MRI model, all voxels of the involved hemisphere with a Tmax ≥ 2 seconds on the pretreatment scan were included in the analysis, under the assumption that voxels with Tmax < 2 seconds are unlikely to be at risk of infarction. Based on results of subsequent publications, a more conservative threshold of MTT ≥ 6 seconds on the pretreatment scan was employed for the CT model. The final infarct region was visually outlined on the follow-up FLAIR (or T2-weighted image if FLAIR not available) or non-contrast CT scan by an experienced stroke neurologist with imaging expertise (CSK). Each
voxel in the at-risk region was thus classified as either proceeding to infarction or not.

**Supplemental Methods Section: Model Development**

**a. MRI**

To develop the voxel-based predictive MRI model, 4 patient-level and 13 voxel-level variables were simultaneously considered. The patient-level variables were age, serum glucose, baseline NIHSS score, and time to MRI. Of the 13 voxel-level variables, 6 were estimated absolute measures (Tmax, ADC, MTT_fm, CBF, CBV, MTT_vf), and 7 were measures relative to contralateral hemisphere (sTmax, dTmax, rcADC, rcMTT_fm, rcCBF, rcCBV, rcMTT_vf). Variable sTmax was defined as ipsilateral voxel value minus the contralateral mean value. Variable dTmax was defined as ipsilateral voxel value divided by the contralateral mean value. For the remaining perfusion variables and diffusion variable rcADC, relative values were calculated as the ipsilateral voxel value divided by the contralateral hemispheric mean value. The final derived model incorporates 4 of the 13 variables considered: rADC, rCBF, rMTT and sTmax.

**b. CT**

To develop the voxel-based predictive CT model, 3 patient-level and 10 voxel-level variables were simultaneously considered. The patient-level variables were age, baseline NIHSS score, and time to angiography (time to CT was not available for all subjects). Voxels were first categorized as meeting criteria for being continuous or non-continuous. Continuous voxels were identified as voxels having sufficient signal-to-noise and physiologically relevant signal characteristics.

For the continuous branch of the model, 7 voxel-level variables were considered including CBF, CBV, MTT, rCBF, rCBV, rMTT, eTmax. The “r” values were normalized to the
mean value for that measure in the contralateral hemisphere. The \( eT_{\text{max}} \) measure was defined as the TTP relative to the time of peak contrast level in the artery. Seven additional measures were considered relative to contralateral hemisphere: mean CBF, mean CBV, mean MTT, mean rCBF, mean rCBV, mean rMTT, and mean ET_{\text{max}}. The final model for the continuous branch incorporates all 7 of the variables considered in the regression analysis.

For the non-continuous branch of the model, the same variables were considered as described above for the continuous branch in addition to the following boolean variables: early peak (peak signal of the voxel occurred before the peak of the reference artery), MTT too low (e.g. likely due to voxel location within an artery), shortMTT incomplete TCC (MTT too short and incomplete TCC [tissue contrast curve] assumed), MTTtooHigh (the MTT was greater than 25 s), CBVoutofRange (the CBV was either <0 or >254), CBFoutofRange (the CBF was either <0.01 or >254), TTPoutofRange (the TTP was either <0 or >254), CBVvessel (CBV was >9), and LSD (low signal density defined as the count of number of voxels in the surrounding 13-pixel area that did not have sufficient signal to provide reliable data). The final model for the non-continuous branch incorporates 12 of the variables considered in the regression analysis.
Online Supplemental Table 1. Voxel-based multivariate predictive equations for MRI and CT

| MRI                  | 
|----------------------|----------------------|
| IF [-1.90312*rADC - 0.55246*rCBF + 0.26948*rMTT + 0.09*sTmax - 0.47155] is greater than -1.13007 THEN voxel is identified as infarct |

<table>
<thead>
<tr>
<th>CT</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF perfusion values for a voxel are determined to be reliable and IF [-1.813 - 0.1030<em>CBV + 0.0898</em>MTT - 0.0103<em>rCBF – 0.0082</em>rCBV + 0.0080<em>rMTT + 0.1275</em>baselineNIHSS – 0.0327*mean contralateral rMTT] is greater than -0.503 THEN voxel is identified as infarct</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT</th>
<th>Non-continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF perfusion values for a voxel are determined to be unreliable and IF [-8.76 + 1.43<em>MTT too Low + 0.84</em>shortMTT incomplete TCC + 2.40<em>MTT too High -1.18</em>CBF out of Range + 0.162<em>Low Signal Density + 0.20</em>baseline NIHSS + 0.10<em>mean contralateral CBF – 1.80</em>mean contralateral CBV + 0.72<em>mean contralateral MTT + 0.026</em>mean contralateral rCBF + 0.14<em>log( mean contralateral rCBV) - 0.85</em>mean contralateral eTmax] is greater than -0.324 THEN voxel is identified as infarct</td>
<td></td>
</tr>
</tbody>
</table>
急性虚血性脳卒中における梗塞中心部および転帰の良好なペナンブラの画像パターンを対象としたマルチパラメトリックなMRIモデルおよびCTモデル

Multiparametric MRI and CT Models of Infarct Core and Favorable Penumbral Imaging Patterns in Acute Ischemic Stroke

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Abstract

背景および目的：発症後時間を経た再開通療法のためには、最適な候補患者を特定する客観的な画像診断法が必要である。本研究の目的は、(1) 急性虚血性脳卒中患者における梗塞中心部およびペナンブラを対象としたMRIおよびCTのマルチパラメトリックなボクセルベースの予測モデルの開発、および(2) 再開通の成功による良好な臨床転帰に基づく良好なペナンブラパターンに対する患者レベルの画像基準を開発することとした。

方法：画像および臨床データの解析は、大血管性の前方循環脳卒中に対する治療が成功した2つの患者コホート（一方はCTによる、もう一方はMRIによるスクリーニング）に対して実施した。症例は、誘導コホートと検証コホートに2対1で割り付けた。最終的な組織梗塞および臨床転帰を個別に予測する治療前の画像診断のパラメータを特定した。

結果：MRIモデルは943,320ボクセルを使用した患者34例から、CTモデルは1,236,917ボクセルを使用した患者32例から開発し、検証した。全体的な精度は、誘導MRIモデルが74%、CTモデルが80%で、個別に検証した精度は、誘導MRIモデルが71%、CTモデルが79%であった。

(1) 予測した梗塞中心部が90 mL以下、および(2) リスク領域内で予測した梗塞組織の割合が70%以下という画像診断の基準により、78～100%の精度で、転帰良好なペナンブラパターンをもつ患者を特定した。

結論：マルチパラメトリックなボクセルベースのMRIモデルおよびCTモデルを開発し、発症後時間を経た再開通療法の対象となり得る急性虚血性脳卒中患者における梗塞中心部の範囲および全体的なペナンブラパターンの状態を予測した。これらのモデルは、最終的な組織の転帰予測においてミスマッチ法に代わる選択肢となる。

Stroke 2013; 44: 73-79