Among patients with acute ischemic stroke, both antegrade flow and (delayed) retrograde collateral flow maintain cerebral perfusion within ischemic regions. Previous reports have suggested that an angiographic collateral grade determines the rate of recanalization, hemorrhagic transformation, and infarct growth after revascularization therapy.1–3 Patients with poor collateral flow show a low recanalization rate, regardless of the revascularization therapy mode or occlusion site.2 Even if recanalization is achieved after revascularization therapy, these patients often experience clinical deterioration because of symptomatic hemorrhagic transformation.3 Recanalization is related to a positive clinical outcome only if adequate collateralization prevents infarction until the vessel is recanali- zed.1,4,5 Therefore, a good collateral status could feasibly extend the time window for endovascular procedures.6,7

A recent trend is to visualize collaterals using noninvasive imaging methods such as computed tomography, angiography or perfusion, dynamic susceptibility contrast-enhanced magnetic resonance (MR) perfusion (DSC-MRP), and arterial spin labeling imaging.5,8–12 Tmax (deconvoluted time to peak) and cerebral blood volume (CBV) approaches are most widely used, allowing clinicians to identify mismatch.

The present study hypothesized that differential perfusion parameters and thresholds would predict collateral status. The Background and Purpose—Good collateral flow is an important predictor for favorable responses to recanalization therapy and successful outcomes after acute ischemic stroke. Magnetic resonance perfusion–weighted imaging (MRP) is widely used in patients with stroke. However, it is unclear whether the perfusion parameters and thresholds would predict collateral status. The present study evaluated the relationship between hypoperfusion severity and collateral status to develop a predictive model for good collaterals using MRP parameters.

Methods—Patients who were eligible for recanalization therapy that underwent both serial diffusion-weighted imaging and serial MRP were enrolled into the study. A collateral flow map derived from MRP source data was generated through automatic postprocessing. Hypoperfusion severity, presented as proportions of every 2-s Tmax strata to the entire hypoperfusion volume (Tmax≥2 s), was compared between patients with good and poor collaterals. Prediction models for good collaterals were developed with each Tmax strata proportion and cerebral blood volumes.

Results—Among 66 patients, 53 showed good collaterals based on MRP-based collateral grading. Although no difference was noted in delays within 16 s, more severe Tmax delays (Tmax16–18 s, Tmax18–22 s, Tmax22–24 s, and Tmax>24 s) were associated with poor collaterals. The probability equation model using Tmax strata proportion demonstrated high predictive power in a receiver operating characteristic analysis (area under the curve=0.9303; 95% confidence interval, 0.8682–0.9924). The probability score was negatively correlated with the volume of infarct growth (P=0.030).

Conclusions—Collateral status is associated with more severe Tmax delays than previously defined. The present Tmax severity–weighted model can determine good collaterals and subsequent infarct growth. (Stroke. 2015;46:2800–2807.

DOI: 10.1161/STROKEAHA.115.009828.)

Key Words: collateral circulation • diffusion magnetic resonance imaging • magnetic resonance imaging • ROC curve • stroke
current study evaluated the relationship between hypoperfusion severity (as measured by $T_{\text{max}}^5$), CBV, and collateral status (as measured by a DSC-MRP–based collateral map), while also developing a $T_{\text{max}}$ severity–weighted predictive model for good collaterals. We also evaluated clinical outcome (as measured by infarct growth at day 7 and modified Rankin Scale at 3 months) in relation with $T_{\text{max}}$ severity–weighted predictive model.

**Patients and Methods**

**Patient Selection**

Using data from a prospectively maintained registry, patients considered eligible for recanalization therapy for acute infarction within the middle cerebral artery (MCA) territory were identified. Data were retrospectively analyzed from consecutive patients who were treated from June 2005 to December 2012 at a university medical center. Inclusion criteria for this study were as follows: (1) subjects who presented within 6 hours of symptom onset; (2) subjects who underwent pretreatment and day 7 post-treatment brain magnetic resonance imaging (MRI), including diffusion-weighted imaging (DWI), MRP, and MR angiography (MRA); (3) subjects who had a National Institutes of Health Stroke Scale score of $\geq 4$ points at admission; and (4) subjects with internal carotid artery or proximal MCA (M1 segment) occlusion associated with symptoms as determined by an admission MRA. The local institutional review board approved this study.

**Evaluations**

Patients were evaluated on demographic characteristics, medical history, vascular risk factors, routine blood tests, brain imaging, and cardiological assessments. Stroke mechanisms were subtyped using the Trial of Org10172 in Acute Stroke Treatment (TOAST) classification\(^{13}\) and were diagnosed by the consensus of 2 stroke neurologists (S.J.K. and S.R.). In patients who underwent conventional angiography, collateral grades were assessed by using the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology Collateral Flow Grading System.\(^{14}\)

**MRP Methods and Image Analysis**

MRI was performed using a 3T Philips Achieva MR scanner (Philips Medical Systems, Best, Netherlands). The identical MR scanner was used for all study subjects. Typical MRI sequences for acute stroke included at least DWI, DSC-MRP, fluid-attenuated inversion recovery, and MRA of the cervical and intracranial vessels (3-dimensional time-of-flight MRA and contrast-enhanced MRA, including the extracranial carotid and vertebral arteries). DWI was performed with 2 levels of diffusion sensitization ($b$ values of 0 and 1000 s/mm\(^2\); 5- to 7-mm slice thickness; no gap). DSC-MRP was performed using gradient-echo and echo-planar imaging techniques after administration of intravenous gadolinium (Dotarem [gadoterate meglumine]; Guerbet, Aulnay-sous-Bois, France) with a repetition time of 1718 ms for a total acquisition time of \approx 90 s with 20 to 22 slices. A contrast agent was injected at a dose of 0.1 mmol/kg body weight with a flow rate of 3 mL/s by a power injector into an antecubital vein via...
an 18-gauge intravenous cannula ≈7 s after beginning the acquisition. Other parameters for DSC-MRP were as follows: echo time=35 ms, flip angle=40°, acquisition matrix=128×128, field of view=24×24 cm², section thickness=5 mm, and intersection gap=2 mm. In total, 1000 DSC-MRP raw images, composed of 50 time points per slice, were obtained.

Perfusion delay was defined based on the perfusion parameter $T_{\text{max}}$. $T_{\text{max}}$ is the time to the peak of the residue function map generated by deconvolution of the tissue concentration over the time curve, using an arterial input function from the contralateral MCA.15 MRP postprocessing and data analysis were performed as described in our previous studies.16 MRI volume measurements were performed by an investigator (J.P.S.), who was blinded to the clinical information. $T_{\text{max}}$ volumes were stratified using a 2-s strata of $T_{\text{max}}$ thresholds, from $T_{\text{max}}$2–4 s, $T_{\text{max}}$4–6 s, …, $T_{\text{max}}$22–24 s, and $T_{\text{max}}>24$ s. Because of too small volumes, $T_{\text{max}}$12–16 s and $T_{\text{max}}$18–22 s were merged into 4-s strata to avoid the possibility of under- or overestimation. To identify hypoperfusion severity distributions, the proportion of every single $T_{\text{max}}$ strata to the entire hypoperfusion volume ($T_{\text{max}}\geq2$ s) was used in the analysis (Proportion $T_{\text{max}}$ strata=Volume $T_{\text{max}}$ strata/Volume $T_{\text{max}}\geq2$ s).

CBV values were determined in the lesion with $T_{\text{max}}\geq2$ s using a computer-assisted volumetric analysis program (Medical Image Processing, Analysis and Visualization, version 3.0; National Institutes of Health, Bethesda, MD). Regions of interest (ROIs) of the $T_{\text{max}}\geq2$ s lesion were semiautomatically defined. Mirror ROIs were manually drawn over contralateral homologous regions and also manually corrected to avoid misregistration when the mirror ROI covered an area outside of the brain parenchyma. The same ROIs were used to calculate the relative CBV values. Relative CBV (rCBV) was defined as a ratio of the mean lesional CBV to the mean contralesional CBV in the mirror ROI.

### Postprocessing Techniques to Generate an MRP-Derived Collateral Flow Map

Collateral flow maps were generated based on source data derived from DSC-MRP, as previously described.1 Collateral flow maps were automatically generated using in-house software—Fast Analysis SysTem for COLLaterals—developed using MATLAB (MathWorks, Natick, MA). All steps were typically completed within 5 minutes. Criteria for collateral flow map–based grades were chosen based on the concept of the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale14 with a classification of grade 0 (no visible collaterals), grade 1 (subtle collaterals), grade 2 (moderate collaterals), and grade 3 (marked collaterals).

<table>
<thead>
<tr>
<th>Patient Characteristics Based on MR Perfusion–Based Collateral Grading</th>
<th>Poor (n=13)</th>
<th>Good (n=53)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>3 (23.1)</td>
<td>18 (34.0)</td>
<td>0.526</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>63 (59–69)</td>
<td>65 (52–72)</td>
<td>0.699</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (53.8)</td>
<td>22 (41.5)</td>
<td>0.422</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (30.8)</td>
<td>26 (49.1)</td>
<td>0.235</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (30.8)</td>
<td>11 (20.8)</td>
<td>0.471</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (30.8)</td>
<td>14 (26.4)</td>
<td>0.739</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (7.7)</td>
<td>5 (9.4)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0 (0.0)</td>
<td>10 (18.9)</td>
<td>0.190</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>4 (30.8)</td>
<td>13 (24.5)</td>
<td>0.645</td>
</tr>
<tr>
<td>Stroke mechanism, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherosclerotic</td>
<td>3 (25.0)</td>
<td>21 (45.7)</td>
<td>0.426</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>6 (50.0)</td>
<td>19 (41.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (16.7)</td>
<td>4 (8.7)</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>1 (8.3)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Occlusion site, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>1 (7.7)</td>
<td>14 (26.4)</td>
<td>0.413</td>
</tr>
<tr>
<td>Distal ICA</td>
<td>10 (76.9)</td>
<td>30 (56.6)</td>
<td></td>
</tr>
<tr>
<td>Distal ICA+M1</td>
<td>2 (15.4)</td>
<td>9 (17.0)</td>
<td></td>
</tr>
<tr>
<td>Initial NIHSS score, median (IQR)</td>
<td>16 (13–19)</td>
<td>12 (10–16)</td>
<td>0.024</td>
</tr>
<tr>
<td>Initial DWI lesion volume, mL, median (IQR)</td>
<td>56.4 (23.2–74.1)</td>
<td>7.0 (4.3–13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recanalization therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV tPA only</td>
<td>0 (0.0%)</td>
<td>4 (7.5%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Endovascular only</td>
<td>1 (7.7%)</td>
<td>16 (30.2%)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>9 (69.2%)</td>
<td>29 (54.7%)</td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>3 (23.1%)</td>
<td>4 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Onset to MR perfusion, min, median (IQR)</td>
<td>170 (145–220)</td>
<td>165 (121–245)</td>
<td>0.468</td>
</tr>
<tr>
<td>DWI–PWI mismatch volume, mL, median (IQR)*</td>
<td>132.0 (102.0–159.7)</td>
<td>118.2 (67.3–152.7)</td>
<td>0.425</td>
</tr>
</tbody>
</table>

DPl indicates diffusion-weighted image; ICA, internal cerebral artery; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; M1, main trunk of the middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and PWI, perfusion-weighted image.

*Difference between PWI ($T_{\text{max}}\geq4$ s) volume and DWI volume.
Outcome Measurements

In patients who underwent endovascular treatment, angiographic reperfusion was determined with the Thrombolysis in Cerebral Infarction grading system. Infract growth was defined as the difference in DWI volume between day 7 and baseline. Modified Rankin scale was judged at 3 months after stroke onset.

Statistical Analysis

All data are presented as medians (25–75th percentile) or frequencies (percentages), unless otherwise specified. A Student t test or Mann–Whitney U test was used to compare continuous variables, and a Pearson χ2 test or Fisher exact test was used to compare categorical variables between groups. The Bonferroni method was used to correct P values for multiple comparisons.

Multiple Proportion values were transformed because of skewed distributions. Square root or natural log transformations were applied in each Proportion values as shown below. The value 1 was added to enable the transformation. All Proportion values were multiplied by 100, and rCBV values were multiplied by 10 to overcome their small units. Finally, transformations for each Proportion (Trans) are as follows:

\[ \text{Trans}_{\text{max strata}} = \text{Proportion}_{\text{max strata}} \times 100 \]

For predicting good (grades 3–4) collateral grades, a logistic regression analysis was performed using a stepwise method. Predictors were each Trans, whereas Trans was excluded because

### Table 2. Multivariable Logistic Regression Analysis for Good Collaterals (Grade 3–4)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>β Coefficients*</th>
<th>SE</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans</td>
<td>2.3929</td>
<td>0.9830</td>
<td>10.945</td>
<td>1.594–71.145</td>
<td>0.015</td>
</tr>
<tr>
<td>Trans</td>
<td>-2.5236</td>
<td>1.0624</td>
<td>0.080</td>
<td>0.010–0.643</td>
<td>0.018</td>
</tr>
<tr>
<td>Trans</td>
<td>-8.9566</td>
<td>3.5760</td>
<td>&lt;0.001</td>
<td>&lt;0.001–0.143</td>
<td>0.012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 2</th>
<th>β Coefficients*</th>
<th>SE</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans</td>
<td>0.4281</td>
<td>0.1712</td>
<td>0.534</td>
<td>1.097–2.146</td>
<td>0.012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model 3</th>
<th>β Coefficients*</th>
<th>SE</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trans</td>
<td>3.7583</td>
<td>1.5821</td>
<td>42.876</td>
<td>1.930–952.636</td>
<td>0.018</td>
</tr>
<tr>
<td>Trans</td>
<td>-3.7938</td>
<td>1.5828</td>
<td>0.023</td>
<td>0.001–0.501</td>
<td>0.017</td>
</tr>
<tr>
<td>Trans</td>
<td>-14.8868</td>
<td>5.8017</td>
<td>&lt;0.001</td>
<td>&lt;0.001–0.030</td>
<td>0.010</td>
</tr>
</tbody>
</table>

*Obtained from stepwise logistic regression models adjusted for each Tmax strata proportion to the entire hypoperfusion volume (Tmax >2s; model 1), relative CBV (model 2), and both (model 3).
of high multicollinearity (model 1). A univariable logistic regression with TransrCBV (model 2) was performed, and a subsequent multivariable logistic regression with the addition of TransrCBV from model 1 (model 3) was established. Receiver operating characteristic (ROC) curves were used to evaluate the prediction performance of each model. The area under the curves (AUCs) were compared using a method18,19 and an open-source package pROC (version 1.7.2) for R. Correlations between the prediction model scores and infarct growth were assessed with Spearman test.

A value of \( P<0.05 \) was considered statistically significant. Statistical analyses were executed using SAS version 9.3 (SAS Institute, Cary, NC) and R 3.1.2 (Vienna, Austria; http://www.R-project.org/).

**Results**

Among 79 patients who met inclusion criteria during the study period, 66 (83.5%) were finally enrolled. Thirteen patients were excluded because of technically suboptimal imaging data: (1) an inability to generate a collateral flow map because of poor contrast bolus (n=2), (2) large perfusion defects because of chronic tissue loss (n=7), and (3) failure of MRI postprocessing for Tmax because of excessive patient motion or the absence of an identifiable, technically adequate arterial input function (n=4). Study profile is presented in Figure I in the online-only Data Supplement.

Of the 66 patients enrolled, 53 (80.3%) showed good (3–4) collaterals, and the other 20 patients demonstrated poor (1–2) collaterals. No patient showed a collateral grade=0. Typical cases are demonstrated in Figure 1. Patient characteristics are shown in Table 1. General characteristics, including vascular risk factors, stroke mechanisms, and occlusion sites, did not differ between groups. The median baseline National Institutes of Health Stroke Scale score was lower, and the median DWI volume was smaller, in the good collateral group (\( P=0.024 \) and \( P<0.001 \), respectively).

Each Proportion \( \text{Tmax}_{\text{strata}} \) was compared between patients with good (n=53) and poor (n=13) collaterals (Figure 2). Each Proportion \( \text{Tmax}_{\text{strata}} \) within 16 s did not differ between the good and the poor collateral groups. Rather, patients with poor collaterals showed higher proportions of severely (>16 s) delayed perfusion, including Proportion \( \text{Tmax}_{16-18} \), Proportion \( \text{Tmax}_{18-22} \), and Proportion \( \text{Tmax}_{22-24} \) (adjusted \( P=0.010, P<0.0001, P<0.0001, \) and \( P<0.0001 \), respectively).

Multivariable logistic regression was performed (Table 2). Models for predicting good collaterals were made by using Tmax proportions (model 1), CBV (model 2), and both (model 3).

Model 1 (based on Tmax) Probability = \[
\frac{\exp(6.9689 + 2.3929 \text{Trans}_{\text{Tmax 12-16}} - 2.5236 \text{Trans}_{\text{Tmax 18-22}} - 8.9566 \text{Trans}_{\text{Tmax 22-24}})}{1 + \exp(-6.9689 + 2.3929 \text{Trans}_{\text{Tmax 12-16}} - 2.5236 \text{Trans}_{\text{Tmax 18-22}} - 8.9566 \text{Trans}_{\text{Tmax 22-24}})}
\]

Model 1 (based on CBV) Probability = \[
\frac{\exp(-2.6839 + 0.4281 \text{Trans}_{\text{rCBV}})}{1 + \exp(-2.6839 + 0.4281 \text{Trans}_{\text{rCBV}})}
\]

Model 3 (based on both Tmax and CBV) Probability = \[
\frac{\exp(17.3215 + 3.7583 \text{Trans}_{\text{Tmax 12-16}} - 3.7938 \text{Trans}_{\text{Tmax 18-22}} - 14.8868 \text{Trans}_{\text{rCBV}})}{1 + \exp(-17.3215 + 3.7583 \text{Trans}_{\text{Tmax 12-16}} - 3.7938 \text{Trans}_{\text{Tmax 18-22}} - 14.8868 \text{Trans}_{\text{rCBV}})}
\]

The ROC curve for the equation using Tmax (model 1) demonstrated high predictive power (\( R^2=0.625, \) AUC=0.930; 95% confidence interval, 0.8682–0.9924; Figure 3). The predictive power of CBV (model 2) was fair (AUC=0.7097; 95% confidence interval=0.5567–0.8627) but inferior to model 1 (\( P=0.001 \)). The addition of CBV into the Tmax model (model 3) showed no additional accuracy above model 1 (AUC=0.9390; 95% confidence interval=0.8804–0.9977; \( P=0.534 \) for comparing ROC curves). The multinomial logistic regression analysis and prediction models for the individual collateral grades are presented in Table I in the online-only Data Supplement. Using the prediction equation, predicted collateral grades were consistent with observed grades in 44 patients (66.7%).

Infarct growth at day 7 was negatively correlated with predicted probability scores (model 1, Spearman’s \( \rho=-0.268; P=0.030 \). In patients who underwent conventional angiography (n=57), the association between probability scores (model 1) and infarct growth was similar to that between collateral grading and infarct growth (Figure 4). When stratified to the achievement of good recanalization (Thrombolysis in Cerebral Infarction 2b-3), a trend for negative correlation was seen between collateral probability scores and modified Rankin Scale at 3 months in the recanalized group (\( \rho=-0.392; P=0.051 \)). Such correlations were not observed in nonrecanalized group.
Discussion

The main findings of the present study are as follows: (1) collateral status is more associated with the more severe hypoperfusion ($T_{\text{max}}>16 \text{ s}$) than a shorter perfusion delay; (2) a $T_{\text{max}}$ severity–weighted model predicts poor collaterals with high predictive power, whereas CBV data did not provide additional information for the prediction; and (3) a $T_{\text{max}}$-derived collateral prediction model is negatively correlated with infarct growth.

Researchers have continuously sought to determine the optimal definition of a target mismatch pattern, as well as a mismatch ratio, MRP parameters, and the threshold for each parameter.20–25 However, few studies have demonstrated MRP parameters and thresholds for predicting collateral status (ie, a hypoperfusion intensity ratio).9 Besides the development of dedicated MRI sequences for collaterals, an effort to predict collateral status using $T_{\text{max}}$ is valuable for the following reasons. First, $T_{\text{max}}$ has several attractive properties for clinical use. In fact, $T_{\text{max}}$ has already been used in a number of clinical trials, including the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET). Second, $T_{\text{max}}$ is the most widely studied MRP parameter for patients with acute ischemic stroke. $T_{\text{max}}$ has also been established as an accurate perfusion metric for discriminating both the infarct core and the penumbra. Therefore, comparing the $T_{\text{max}}$ thresholds for the penumbra versus collaterals may help our understanding of hemodynamic status. Finally, $T_{\text{max}}$ has the advantage of being able to measure the time to peak of the tracer fraction within a voxel at any given time. This is in comparison with the time the contrast bolus takes to transverse the voxel (eg, mean transit time) or the area under the deconvolved tissue curve (AUC) of the contrast bolus intensity (eg, CBV).

The present study revealed that collateral status is correlated with more severely delayed perfusion, and a $T_{\text{max}}$ severity–weighted model predicts poor collaterals with high accuracy. These results suggest that the more delayed perfusion ($T_{\text{max}}>16 \text{ s}$) was more closely correlated with collateral status than was a less delayed perfusion ($T_{\text{max}} 6–16 \text{ s}$). These findings indicate that delayed perfusion ($T_{\text{max}}>16 \text{ s}$) might be closer to the real infarct core than the $T_{\text{max}}$ threshold for the presence of a mismatch used in the EPITHET ($\geq 2 \text{ s}$),26 DEFUSE ($\geq 2 \text{ s}$),25 and DEFUSE-2 ($>6 \text{ s}$).20 The present findings are in line with results from previous studies showing that collateral status on conventional angiography was not correlated with MR perfusion-diffusion mismatches and CBV/cerebral blood flow mismatches on a perfusion computed tomography.1,27 No significant difference was found between diffusion–perfusion mismatch (defined as $T_{\text{max}} \geq 4 \text{ s}$) and pretreatment collaterals.1 The present results are also supported by previous studies revealing that a severe, but not mild, perfusion delay15 and low CBV are associated with hemorrhagic transformation, which is probably related to poor collaterals.28

It was speculated that high $T_{\text{max}}$ values seen in hyperacute stroke indicate poor delayed collateral supply. Furthermore, regions with long arrival delays, even if relatively well-perfused, are the most at risk if perfusion pressure further declines.29 However, there is increasing evidence that collateral status predicts tissue fate, regardless of the presence or absence of a target mismatch pattern and successful recanalization.1,5 The present data showed that $T_{\text{max}}$ thresholds for predicting collaterals are higher than those for the penumbra. This illustrates that collaterals and mismatches represent related, yet distinct, aspects of ischemic pathophysiology. First, most MRP studies have focused on the early phase (arterial and early capillary phase), but perfusion status at a later phase (late capillary or venous) may also influence tissue fate. It was recently reported that venous drainage identified by computed tomographic angiography was correlated with collateral status and infarct growth.30 Second, $T_{\text{max}}$ primarily
reflects macrovascular features, but a severe $T_{\text{max}}$ change may reflect microvascular integrity supplied by collateral circulations. Microvascular features, including vasodilatory compensatory mechanisms, may be important for functional collaterals. Although the diameter of the leptomeningeal collateral needed to be $>1.0$ mm to provide adequate flow, the individual diameter in cadaver studies was $=0.3$ mm. Further studies are needed to better understand the physiological differences underlying these 2 conditions.

A few study limitations should be noted. First, the present findings should be interpreted with caution because of the limited sample size and data from a single center where the prevalence of intracranial atherosclerosis is high. Our results demonstrating a high prevalence of good collaterals may be because of the high prevalence of intracranial atherosclerosis. Pretreatment collateral status differs greatly among stroke subtypes. Almost two thirds the patients with intracranial atherosclerosis, but less than one third of patients with cardioembolism, show good collaterals. Further studies with different populations and larger cohorts are warranted. In this context, a multicenter study is being planned to evaluate the impact of collateral flow on stroke outcomes using this approach. Second, $T_{\text{max}}$ is sensitive to several hemodynamic effects, and its physiological interpretation is complex. Finally, further studies are needed to validate associations between clinical outcomes, $T_{\text{max}}$-based collateral status and successful recanalization in a larger number of patients.

In conclusion, the present results indicate that collateral status is associated with a higher proportion of more severe $T_{\text{max}}$ delays than was previously defined. The $T_{\text{max}}$ severity–weighted model predicted good collaterals with high predictive power. Given that routine perfusion-weighted imaging data were used in the present study, this method could be feasible for clinical practice. However, these findings prompt larger, confirmatory studies. For instance, among clinical trials analyzing the $T_{\text{max}}$-based mismatch pattern, additional analyses of $T_{\text{max}}$-based collateral status may help elucidate possible differences regarding hemodynamic aspects and clinical impact between these 2 conditions.

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**Disclosures**

None.

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