Endovascular therapy has emerged as a principal approach to blood flow restoration in acute ischemic stroke. MRI evaluation of patients for diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) mismatch has been suggested as a noninvasive imaging study to help select patients for reperfusion therapy, particularly in a later time window.1–3 Good angiographic collaterals have been associated with improved recanalization and a lower incidence of hemorrhagic transformation after endovascular therapy.4–6 We undertook this study to determine the relationship between angiographic collaterals and MR-based diffusion/perfusion imaging, angiographic reperfusion, subsequent infarct growth, and clinical outcome in patients undergoing endovascular therapy for acute ischemic stroke.

**Methods**—Sixty patients with a thrombolysis in cerebral infarction (TICI) score of 0 or 1 and internal carotid artery/M1 occlusion at baseline were evaluated. A blinded reader assigned a collateral score using a previous 5-point scale, from 0 (no collateral flow) to 4 (complete/rapid collaterals to the entire ischemic territory). The analysis was dichotomized to poor flow (0–2) versus good flow (3–4). Collateral score was correlated with baseline National Institutes of Health Stroke Scale, diffusion-weighted imaging volume, perfusion-weighted imaging volume (Tmax ≥6 seconds), TICI reperfusion, infarct growth, and modified Rankin Scale score at day 90.

**Results**—Collateral score correlated with baseline National Institutes of Health Stroke Scale (P=0.002) and median volume of tissue at Tmax ≥6 seconds (P=0.009). Twenty-nine percent of patients with poor collateral flow had TICI 2B–3 reperfusion versus 65.5% with good flow (P=0.009). Patients with poor collaterals who reperfused (TICI 2B–3) were more likely to have a good functional outcome (modified Rankin Scale score 0–2 at 90 days) compared with patients who did not reperfuse (odds ratio, 12; 95% confidence interval, 1.6–98). There was no difference in the rate of good functional outcome after reperfusion in patients with poor collaterals versus good collaterals (P=1.0). Patients with poor reperfusion (TICI 0–2a) showed a trend toward greater infarct growth if they had poor collaterals versus good collaterals (P=0.06).

**Conclusions**—Collaterals correlate with baseline National Institutes of Health Stroke Scale, perfusion-weighted imaging volume, and good reperfusion. However, target mismatch patients who reperfuse seem to have favorable outcomes at a similar rate, irrespective of the collateral score.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01349946.

**Key Words:** angiography ▪ collateral circulation ▪ magnetic resonance imaging ▪ stroke

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diffusion coefficient of $<600 \times 10^{-6}$ mm²/s. The automated maps also included a measure of hypoperfused tissue, which was derived from PWI maps as the region with time to maximum (Tmax) of the tissue residue function of $\geq$6 seconds. These values for estimated ischemic core and critically hypoperfused tissue were previously validated. The target mismatch profile was predefined as a ratio between hypoperfused tissue and ischemic core of $\leq$1.5, with an absolute difference $\geq$15 mL. In addition, patients with a target mismatch profile also had ischemic core volumes $\leq$70 mL and volume of tissue with more severe hypoperfusion (Tmax $>10$ seconds) $\leq$100 mL.

Endovascular Treatment

Patients started endovascular treatment <12 hours of ictus and 1.5 hours of baseline MRI. The use of US Food and Drug Administration–approved devices for thrombectomy, including the concentric MERCI retriever and the penumbra suction thrombectomy catheter, was encouraged; however, no device or procedural method was required. Investigators were encouraged to minimize intra-arterial tissue-type plasminogen activator (tPA) use. If patients had been treated with intravenous tPA, a maximum dose of $\leq$5 mg of intra-arterial tPA was recommended. If no systemic tPA had been administered, investigators were asked to consider using $\leq$25 mg intra-arterially.

Imaging Evaluation

Infarct growth was determined based on the change between baseline DWI lesion volume and volume determined from fluid-attenuated inversion recovery image at 5 days. Hemorrhagic transformation for parenchymal hematoma formation (PH1 and PH2) was evaluated from any follow-up CT or MRI done $<7$ days of stroke onset. A single reader, blinded to angiographic and clinical outcome, evaluated the baseline angiogram before treatment. The primary arterial occlusive lesion was assigned, and a thrombolysis in cerebral infarction (TICI) score was also assigned using previously published definitions.

Intravenous tPA pretreatment, no. (%) 33 (55) 18 (58) 15 (52) 0.796

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Entire Group</th>
<th>Poor Collaterals (0–2)</th>
<th>Good Collaterals (3–4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>60</td>
<td>31</td>
<td>29</td>
<td>-</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>64 (17)</td>
<td>63 (16)</td>
<td>64 (17)</td>
<td>0.874</td>
</tr>
<tr>
<td>Women, no. (%)</td>
<td>29 (48)</td>
<td>17 (55)</td>
<td>12 (41)</td>
<td>0.316</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>35 (59)*</td>
<td>18 (60)*</td>
<td>17 (59)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>11 (19)*</td>
<td>3 (10)*</td>
<td>8 (28)</td>
<td>0.104</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>27 (46)*</td>
<td>13 (43)*</td>
<td>14 (48)</td>
<td>0.796</td>
</tr>
<tr>
<td>Atrial fibrillation, no. (%)</td>
<td>20 (34)*</td>
<td>8 (27)*</td>
<td>12 (41)</td>
<td>0.279</td>
</tr>
<tr>
<td>Previous stroke/TIA, no. (%)</td>
<td>12 (20)*</td>
<td>9 (30)*</td>
<td>3 (10)</td>
<td>0.104</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>16 (12–20)</td>
<td>18 (13.5–21.5)</td>
<td>14 (10–17)</td>
<td>0.025</td>
</tr>
<tr>
<td>Intravenous tPA pretreatment, no. (%)</td>
<td>33 (55)</td>
<td>18 (58)</td>
<td>15 (52)</td>
<td>0.796</td>
</tr>
<tr>
<td>Time from symptom onset to start of MRI, hours, median (IQR)</td>
<td>4.5 (3.4–5.9)</td>
<td>4.5 (3.2–5.7)</td>
<td>4.7 (3.7–7.3)</td>
<td>0.318</td>
</tr>
<tr>
<td>Time from symptom onset to femoral puncture, hours, median (IQR)</td>
<td>6.0 (4.7–7.7)</td>
<td>5.7 (4.7–7.0)</td>
<td>6.2 (4.7–8.3)</td>
<td>0.437</td>
</tr>
<tr>
<td>Vessel occlusion on angiogram, no. (%)</td>
<td>17 (28)</td>
<td>15 (48)</td>
<td>2 (7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICA</td>
<td>43 (72)</td>
<td>16 (52)</td>
<td>27 (93)</td>
<td>-</td>
</tr>
</tbody>
</table>

IKA indicates internal carotid artery; IQR, interquartile range; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and tPA, tissue-type plasminogen activator.

Statistics

We compared rates of good outcome between groups using Fisher exact test. We used the Cohran–Armitage test to evaluate trends in the rates of good outcome with increasing reperfusion scores; we used Jonckheere–Terpstra test to evaluate similar trends for continuous variables. Comparisons were made across the entire group of collateral scores, and we also dichotomized collateral scores into good (score of 3 and 4) versus poor collateral group (score of 0–2). Lesion growth between dichotomized groups was analyzed with the Mann–Whitney U test. We also conducted logistic regression analysis (for TICI 2B–3 reperfusion) and median regression analysis (for baseline National Institutes of Health Stroke Scale [NIHSS], lesion size at Tmax $>6$ seconds, and lesion growth) with collateral status and site of occluded artery entered as predicting factors. All tests were 2-tailed and considered significant at $\alpha = 0.05$ level. Statistical analysis was done using SAS version 9.3 (SAS Institute Inc, Cary, NC).

Results

Table 1 shows the demographic values for the study group. There was a significant difference in the incidence of good collaterals based on the location of occlusion ($P<0.001$). There was also significant differences in baseline NIHSS scores between patients with poor collaterals and those with good collaterals ($P=0.025$). Figure 1 shows the mean NIHSS score for each collateral score. There was a significant decline in NIHSS across the range of collateral scores from lower to higher ($P=0.002$).

The collateral score from baseline angiogram was correlated with Tmax perfusion delay volume on baseline MR
scan (obtained before endovascular therapy). Specifically, the lesion size defined by time to maximum (Tmax) of the tissue residue function of ≥6 seconds was correlated with collateral scores as shown in Figure 2. Across the full range of collateral scores, there was a correlation between higher collateral scores and lower PWI lesion volumes (P<0.009). The median volume of tissue at Tmax ≥6 seconds for good collaterals was 82 (interquartile range, 51–109) mL versus 115 (74–136) mL for patients with poor collaterals (P<0.012). A similar analysis comparing collateral scores with baseline DWI lesion volume did not show a correlation between collateral scores and DWI lesion volume across the range of collateral scores or by stratifying collateral scores dichotomously. We also examined the relationship between collateral score and the ratio of lesion volume at Tmax ≥6 seconds to DWI lesion volume and found that collateral scores did not correlate with this ratio.

Table 2 shows TICI reperfusion scores for patients stratified by good or poor collateral scores. There was a shift to higher rates of reperfusion with good collaterals (P=0.010). Patients with good collateral scores had significantly higher rates of TICI 2B to 3 reperfusion (65.5%) versus those with poor collateral scores (29%; P=0.009).

The relationship between volume of infarct growth seen on 5-day follow-up imaging study and collateral scores for target mismatch patients is shown in Figure 3. Patients with poor collaterals (0–2) and good reperfusion (TICI 2B–3) had significantly less infarct growth compared with those with poor reperfusion (TICI 0–2A; P=0.009). Patients with good collateral scores (3–4) had less infarct growth with good reperfusion compared with those with poor reperfusion, but the difference was not significantly different (P=0.25). There was also a strong trend for the amount of infarct growth being greater in patients with poor collaterals who did not reperfuse well versus those with good collaterals who did not reperfuse well (P=0.06). However, there was no difference in the amount of infarct growth comparing those with poor and good collaterals who reperfused (P=0.73).

Table 3 shows 90-day good functional outcome rates in target mismatch patients with good and poor collaterals stratified by whether they had good or poor reperfusion. Significantly, more patients with poor collaterals who reperfused well (TICI 2B–3) had good outcomes compared with those who had poor reperfusion (TICI 0–2A; P=0.017). Patients with good collateral scores showed a trend for higher rates of good functional outcome with good reperfusion compared with those with poor reperfusion (P=0.11). In addition, there was no difference in the rate of good functional outcome with good reperfusion in patients with poor collaterals versus those with good collaterals (P=1.0). The odds ratio for a 90-day good functional outcome with good reperfusion in those patients with poor collaterals was 12.0 (95% confidence interval, 1.6–98). In patients with good collaterals, the odds ratio for good functional outcome at 90 days with good reperfusion was 4.7 (95% confidence interval, 0.8–26), the difference between odds ratios being not significant (P=0.47).

The time from end of baseline MRI to reperfusion was correlated with the collateral score, and there was no association across the range of collateral scores (P=0.477). In a dichotomous analysis, there was no difference between the time from end of MRI to reperfusion for patients with poor collateral scores (median time, 2.6 hours; interquartile range, 1.8–3.3) versus those with good collateral scores (median time, 2.5 hours; interquartile range, 1.9–3.0; P=0.856). The interaction of time from end of MRI to reperfusion with collateral status was also not associated with lesion growth (P=0.952) or good functional outcome (P=0.211).

Table 2. Collateral Score Versus Thrombolysis in Cerebral Infarction (TICI) Reperfusion

<table>
<thead>
<tr>
<th>TICI Reperfusion</th>
<th>0</th>
<th>1</th>
<th>2A</th>
<th>2B</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor collateral score (0–2)</td>
<td>7 (23)*</td>
<td>5 (16)</td>
<td>10 (32)</td>
<td>5 (16)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Good collateral score (3–4)</td>
<td>3 (10)</td>
<td>0 (0)</td>
<td>7 (24)</td>
<td>12 (41)</td>
<td>7 (24)</td>
</tr>
</tbody>
</table>

*Number of patients (percentile).
Target mismatch patients with poor reperfusion (TICI 0–2A) and good reperfusion (TICI 2B–3) were evaluated for hemorrhagic conversion (PH1 and PH2) on the basis of collateral scores. Patients with good reperfusion and poor collateral scores (0–2) had higher rates of parenchymal hematoma development compared with those with good reperfusion and good collateral scores (44% [4/9] versus 26% [5/19]). Similarly, patients with poor reperfusion and poor collateral scores (0–2) had higher rates of parenchymal hematoma development compared with those with poor reperfusion and good collateral scores (41% [9/21] versus 20% [2/10]). However, in both cases the differences were not significant (P = 0.407 and 0.425, respectively).

Regression analysis was also performed to understand how the site of occlusion and the collateral status influenced baseline NIHSS and perfusion lesion size, as well as reperfusion status and infarct growth. The rate of TICI 2B to 3 reperfusion and lesion size at Tmax ≥6 seconds were significantly associated with collaterals adjusted for occlusion location (P = 0.043 and 0.047, respectively). In addition, there was a strong trend for baseline NIHSS (P = 0.088) and some trend for infarct growth (P = 0.120) to be associated with collateral status adjusted for occlusion site. At the same time, there was no association between these variables and occlusion location adjusted for collateral status. There was no interaction between collateral status and site of occlusion for association with above outcomes.

**Discussion**

This study demonstrated that there was a relationship between collateral status and NIHSS score at the time of presentation. This is consistent with the finding that the volume of critically hypoperfused tissue (Tmax ≥6 seconds) from baseline MR perfusion also correlated with collateral status. A previous study by Bang et al. correlating MR perfusion status and angiographic collateral scores also showed a relationship between collateral status and severity of perfusion deficit. In that study, the severity of perfusion deficit was measured as a ratio between the volume of penumbral tissue (measured as Tmax ≥4 seconds) and benign oligemic tissue (Tmax >2 and <4 seconds). However, that study was not able to show a relationship between collateral status and penumbral tissue volume using Tmax ≥4 seconds. More recent studies suggested that Tmax >6 seconds may better represent critically hypoperfused tissue, and this may explain the discrepancy in findings between the 2 studies.

When we evaluated infarct growth in patients with poor versus good collaterals, we found that patients with poor collaterals who did not reperfuse (TICI 0–2A) had more infarct growth compared with those with good collaterals who did not reperfuse. Conversely, infarct growth was not significantly different between those with good and poor collaterals when there was good reperfusion (TICI 2B–3). Bang et al. also evaluated infarct growth relative to revascularization in patients with good and poor collaterals. Unlike our results, they found that patients with poor collaterals and good revascularization had the greatest infarct growth and that it was greater than the growth seen in patients with poor collaterals who did not achieve revascularization. They also reported that in the group with poor collaterals and revascularization there was a higher rate of symptomatic hemorrhagic transformation and suggested that the higher rate of infarct growth may be because of reperfusion injury. Our study did show a higher incidence of hemorrhagic transformation (PH1 and PH2) in those patients with poor collaterals versus good collaterals, but the difference was not significant. Differences in the study population may explain these different results for infarct growth and hemorrhagic transformation. If, for example, core infarcts were larger in the Bang study, they may have been more prone to reperfusion injury. In addition, our inability to show that hemorrhagic transformation was significantly greater in patients with poor collaterals may be because of the study size being underpowered to show a difference. Campbell et al. recently used Tmax delay as a surrogate for angiographic collateral grading. Their results suggest that the collateral score may be dynamic. Using the Tmax delay for collateral grading allowed them to make repeated measures of collateral flow, and they were able to show that infarct growth was associated with collateral failure.

**Table 3. Target Mismatch Profile of Patients with Good Functional Outcome at 90 Days**

<table>
<thead>
<tr>
<th>Poor Collateral Score (0–2)</th>
<th>Good Collateral Score (3–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor reperfusion (TICI 0–2A)</td>
<td>3/18 (17%)† 3/10 (30%)  P = 0.63</td>
</tr>
<tr>
<td>Good reperfusion (TICI 2B–3)</td>
<td>5/7 (71%) 10/15 (67%)  P = 0.1</td>
</tr>
</tbody>
</table>

TICI indicates thrombolysis in cerebral infarction.

*Good functional outcome is modified Rankin Scale (mRS) score 0 to 2.

†Number of patients with mRS 0 to 2 over total number of patients in group with equivalent collateral and reperfusion scores.
Our finding that reperfusion success is related to the collateral score is in keeping with the results reported by previous studies.1,4 Bang et al1 suggested that this may be because of enhanced delivery of both intrinsic and extrinsic thrombolytics to the occlusion site. All of these studies were performed with first-generation thrombectomy devices, and it will be of interest to see how newer techniques using devices such as stentriever, which have much higher rates of revascularization, may influence these results.

We were concerned that the site of occlusion could be a confounding variable, which would influence the rate of reperfusion as we saw differences between the rates of good collaterals based on location. However, regression analysis demonstrated that TIIC 2B–3 reperfusion was associated with collateral score even after adjustment for site of occlusion, and there was no association between the rate of reperfusion and occlusion location after adjusting for collateral score.

The 90-day clinical outcome results are similar to infarct growth results seen for patients with good versus poor collaterals. Patients with poor collaterals who have TIIC 2B–3 reperfusion did significantly better than those who did not reperfuse, and the odds ratio for good outcome in this group (12.0; 95% confidence interval, 1.6–98) suggests that there is a strong association between reperfusion and good outcome in this group. Patients with good collaterals showed a trend for better outcomes with good reperfusion versus poor reperfusion (odds ratio, 4.7; 95% confidence interval, 0.8–26). The smaller odds ratio in this group could imply that patients with good collaterals are more likely to have favorable outcomes even if reperfusion does not occur; however, a larger data set is needed to explore this possibility in more detail. The data also suggest that if there is a target mismatch, patients should be offered endovascular therapy regardless of the collateral score. Although the data showed that patients with poorer collaterals were not as likely to reperfuse using the techniques available to endovascular therapists for this study, it is also clear that these patients had better outcomes if reperfused.

In conclusion, we found that angiographic collateral score correlated with baseline NIHSS score and the volume of hypoperfused tissue (Tmax ≥6 seconds) before endovascular treatment. In addition, collateral score also correlated with the rate of TIIC 2B–3 reperfusion seen in our patients. Patients with poor collaterals and poor reperfusion had the most infarct growth and were less likely to have good outcome at 90 days. However, we found a strong association between good reperfusion (TIIC 2B–3) and good outcome in target mismatch patients with poor collaterals. This suggests that reperfusion therapy may be beneficial for target mismatch patients, irrespective of collateral score.

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References
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