

Regional Angiographic Grading System for Collateral Flow Correlation With Cerebral Infarction in Patients With Middle Cerebral Artery Occlusion

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Background and Purpose—Collateral flow plays an important role in maintaining tissue viability in proximal large vessel occlusion. We developed and tested a regional angiographic collateral grading system for patients with angiographically confirmed acute symptomatic middle cerebral artery occlusion to predict regional infarction.

Methods—A subset of 42 patients was selected from 180 patients enrolled in the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial. Readers evaluated baseline cerebral angiograms in a blinded fashion for the degree of regional collateral circulation, which was graded on a 4-point scale in each of 15 anatomic regions. Regional and total collateral flow scores were compared with the presence or absence of infarction on 7- to 10-day follow-up computed tomography (CT), as well as clinical outcome as assessed by National Institute of Health Stroke Scale (NIHSS) scores.

Results—The collateral flow score on baseline angiography accurately predicted infarction, demonstrating a receiver operating characteristic curve of 0.87 (95% CI: 0.83 to 0.91) for all regions. Collateral grades on baseline angiography correlated moderately with infarct volume on follow-up CT scan at 7 to 10 days ($R=0.61$; $P=0.0001$). Collateral grades also correlated with follow-up NIHSS scores for patients who received thrombolysis ($R=0.36$ to 0.49 , $P<0.05$), but not for control patients.

Conclusions—An angiographic grading system for regional collateral flow accurately predicts the extent and location of cerebral infarction. This study corroborates the correlation between the presence of collateral flow, infarction volume, and clinical outcome, and it reinforces the need to control for collateral flow in clinical trials. (*Stroke*. 2004;35:1340-1344.)

Key Words: cerebral infarction ■ angiography

New therapies directed at acute middle cerebral artery (MCA) occlusion have increased the need to define imaging markers of tissue viability. Although it is important to detect salvageable tissue, it is equally important to recognize tissue that is destined to infarct. The angiographic correlates of brain ischemia and infarction are important to recognize, because angiography is performed at the time that endovascular treatment options are considered. Collateral flow helps to maintain cerebral perfusion in the setting of arterial occlusion.¹⁻³ Several studies have established the importance of collateral flow in predicting stroke outcome, correlating the degree of collateral circulation with infarct volume and functional status.^{2,4-9}

Roberts et al¹⁰ recently assessed imaging findings in patients with acute symptomatic MCA occlusions enrolled in the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial who underwent angiography, with or without intraarterial thrombolysis, within 6 hours of symptoms. Global hemispheric collateral flow was graded on baseline angiogram as none, partial, or full. Patients with “full” collateral supply to the ischemic hemisphere had smaller baseline

computed tomography (CT) infarct volumes and lower baseline stroke scale scores than patients with partial or no collateral supply. This study, however, did not attempt to correlate regional collateral flow to the presence or absence of regional infarction.

We developed and tested an angiographic collateral grading system to establish its accuracy in predicting regional infarction and to determine the influence of collateral flow on patient outcome after stroke, as measured by infarct volume on CT and functional status.

Materials and Methods

Subjects

Our subjects were selected from the 180 patients enrolled in the PROACT II study, the methods of which have been described extensively elsewhere.¹¹ These patients presented with symptoms of acute ischemic stroke with duration of <6 hours caused by angiographically proven occlusion of the MCA and were randomized 2:1 to receive either 9 mg intraarterial recombinant prourokinase (r-ProUK) over 120 minutes plus intravenous low-dose heparin or intravenous heparin alone. In the initial assessment of PROACT II patients, hemispheric collateral flow was graded on a 3-point scale: 1=no collateral flow, 2=partial collateral flow to the ischemic site,

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and 3=full collateral flow to the site of occlusion. Of 162 patients (108 r-ProUK patients and 54 control patients) who actually received the treatment to which they were randomized, 50 patients had no angiographic collaterals, 100 had partial collaterals, and 11 had full collaterals (1 patient could not be assessed for collaterals).

For the present study, 44 patients were selected by a statistician (Y.L.) to represent the full spectrum of collateral flow. All 11 patients in the “full” collateral subgroup in the PROACT II population were included in our study. Eleven patients with partial collaterals were then randomly selected, as were 22 patients with no evidence of global collateral flow. A sample size of 44 patients was determined to be sufficient (based on 80% power and 5% significance level) to test the null hypothesis of no association between collateral score and outcome using Spearman correlation testing, if the true correlation (R) was $>40\%$.¹² Angiograms were of poor quality in 2 patients who were eliminated from the study, leaving a total of 42 patients (11 with full collaterals, 11 with partial collaterals, and 20 with no collaterals). Twenty-nine of these patients had been randomized to treatment with intraarterial thrombolysis whereas 13 were not, reflecting the 2:1 ratio of the original PROACT II study.

Collateral Assessment on Angiography and Infarction on CT Scans

For the present study, 2 neuroradiologists blinded to patient treatment evaluated bilateral internal carotid and vertebral artery angiograms (anterior/posterior and lateral views) performed at baseline. To the extent possible, all branches of the contributing vessels were evaluated. In 5 patients, vertebral artery injections were not available; however, the potential for significant collateral flow in these patients was quite low given the lesion locations in relation to the posterior circulation. Angiograms were graded by consensus and without knowledge of CT findings or the previous readings from PROACT on a scale from 0 to 3: 0=no collaterals visible to the ischemic site (absence of any capillary blush); 1=collaterals to the periphery of the ischemic site; 2=complete irrigation of the ischemic bed via collateral flow; and 3=normal antegrade flow. Because angiograms were obtained from different hospitals and injection and filming rates varied, we could not quantify the rapidity of collateral filling.

Guided by the Alberta Stroke Programme Early CT Score (ASPECTS) study,¹³ we divided the angiogram of the affected hemisphere into 15 anatomic sites based on regional vascular territories (Figure 1). The collateral flow score was recorded for each of these 15 areas. Readers then evaluated the 7- to 10-day follow-up CT scan by consensus, classifying each of the 15 anatomic regions as infarcted or not based on the presence or absence of new or evolving hypodensity as compared with baseline CT.

Statistical Analysis

Statistical analysis was based on 42 patients with 630 anatomic sites (15 sites per patient). The collateral grade for each region of interest on baseline angiography was compared with the presence or absence of infarct within that region, generating a receiver operating characteristic (ROC) curve. The area under the curve (AUC) for the ROC curve for each anatomic site and its corresponding CI were evaluated using the approach of DeLong et al.¹⁴ ROC curves combining all anatomic sites were based on true-positive rates (sensitivity) and false-positive rates ($1 - \text{specificity}$) for different cutoff values for collateral scores estimated by the general estimation equation.¹⁵ The AUC of the combined ROC curve was calculated by the trapezoid method, and its corresponding CI by the bootstrap method.¹⁵

The overall state of collaterals for a given patient was assessed by total collateral score (the sum of collateral scores for all regions of interest in a given patient) and the total number of sites with poor collateral flow (sites with grades of 0 or 1).

Correlations between overall collateral circulation grade on baseline angiography and infarct volume on follow-up CT scan, as well as clinical outcome as assessed by National Institute of Health Stroke Scale (NIHSS) scores at 7 to 10 and 30 and 90 days were determined

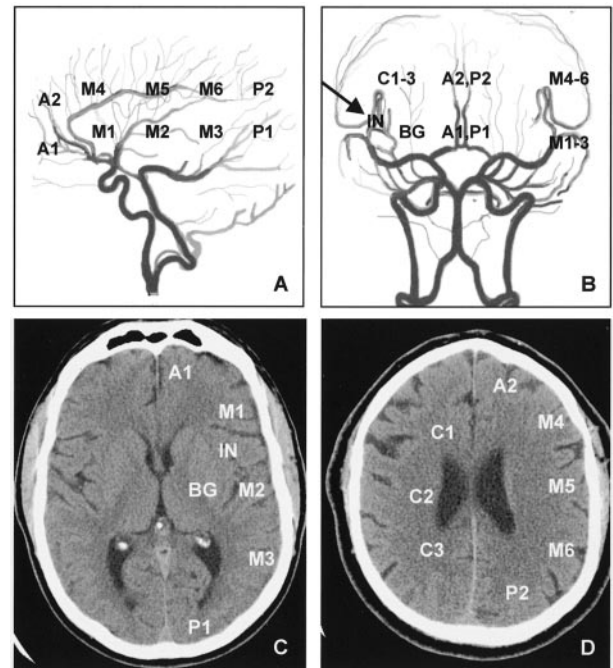


Figure 1. Vascular territories on cerebral angiograms (A, B) and axial CT scan images (C, D).

by Spearman correlation coefficients, with significance established at $P < 0.05$. Infarct volumes on baseline and follow-up CT scans were taken from the data accumulated in the initial analysis of the PROACT II study.^{10,11}

Results

The primary findings of this study were that the grade of regional collateral flow on baseline angiography predicted regional infarction with high sensitivity and specificity, and better collateral circulation was correlated with lower infarct volume and better clinical outcome.

Accuracy of Collateral Flow Grading System for Predicting Infarction

The grade of collateral flow on baseline angiography was highly predictive of regional infarction (Figures 2 and 3). The incidence of infarction increased as the collateral flow score on baseline angiography decreased. Table 1 demonstrates the incidence of infarction in anatomic sites stratified by collateral score calculated using general estimation equation methods to adjust for multiple anatomic sites from the same subject.

Collateral flow scores ≤ 1 (absent or partial collateral flow) predicted infarction with the highest combination of sensitivity (73%) and specificity (90%) (Figure 4). The AUC of the ROC curve is 0.87 (95% CI: 0.83 to 0.91), indicating high accuracy of collateral scores at baseline for predicting infarction. Comparing control ($n = 13$) to r-ProUK ($n = 29$) patients, no significant difference was found in the distribution of collateral flow grades on baseline angiography, and no significant difference in sensitivity or specificity of collateral scores for predicting infarction was found.

ROC analyses were also performed separately for each of the anatomic sites. AUC for sites in the MCA cortex (M1–6)

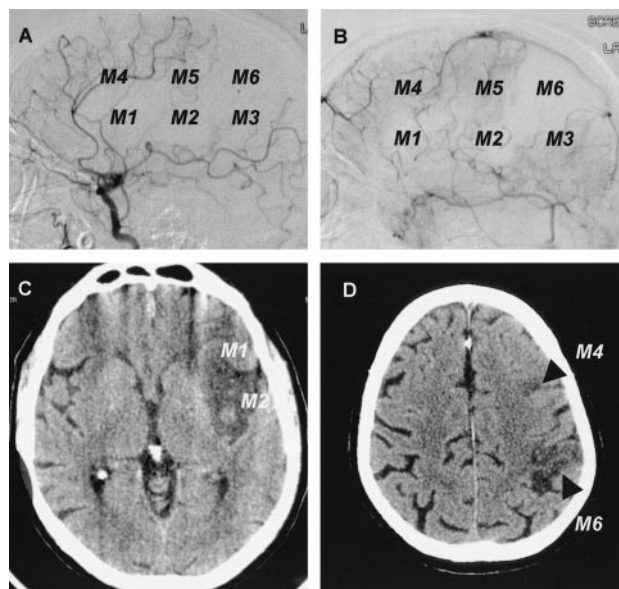


Figure 2. Example of inadequate collateral flow on angiograms (A, B) and follow-up CT (C, D).

ranged from 0.76 to 0.92; AUC was 0.73 (95% CI: 0.43 to 1.0) for the basal ganglia and 0.87 (95% CI: 0.05 to 1.0) for the insula. The accuracy of predicting infarction from collateral scores was low for the centrum semiovale, anterior cerebral artery, and posterior cerebral artery circulations.

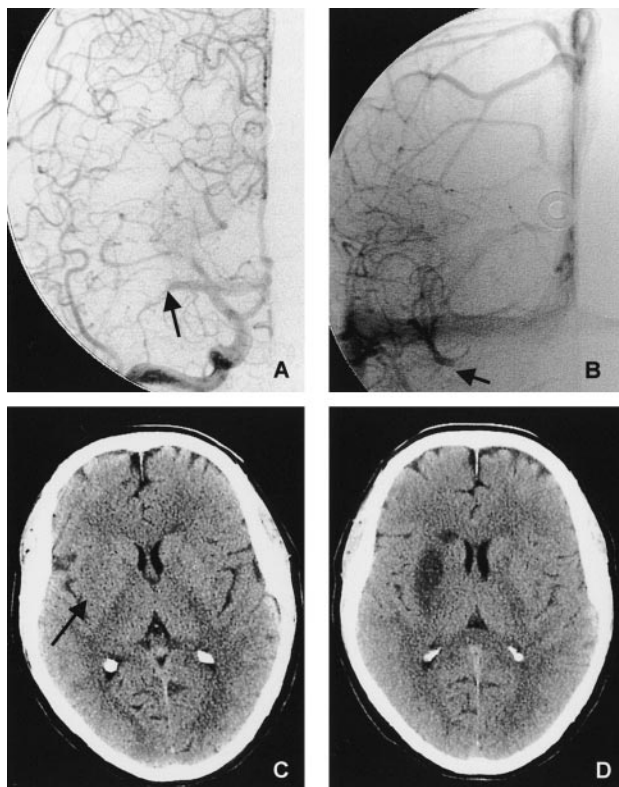


Figure 3. Example of robust collateral flow on angiograms (A, B) and follow-up CT (C, D).

TABLE 1. Incidence of Infarction in Anatomic Sites, Stratified by Collateral Score on Baseline Angiogram

Collateral Score	N of Anatomic Sites	N of Sites With Infarction (%*)
0	109	94 (85)
1	93	68 (72)
2	154	40 (31)
3	274	17 (6)
Total	630	219 (35)

*Percent of sites with infarction was estimated by general estimation equation to adjust for multiple anatomic sites from the same subject.

Correlation Between Collateral Flow Score and Final Infarction Volume

The presence of collateral flow on baseline angiography correlated with lower infarct volume on follow-up CT scan at 7 to 10 days (Figure 5). Total infarct volume significantly correlated with the total number of sites with poor collateral flow (score ≤ 1) (Spearman correlation, $R=0.61$; $P=0.0001$). Similarly, as the total collateral score increased (indicating better overall collateral circulation in a given patient), infarct volume decreased significantly ($R=-0.58$, $P=0.0002$).

Correlations between total collateral score or the number of sites with poor collateral flow and final infarct volume were also analyzed separately for control and r-ProUK patients. A higher correlation was found between the number of poor collateral sites and infarct volume in control patients ($R=0.85$, $P=0.0002$) versus r-ProUK patients ($R=0.54$, $P=0.003$). Considering total collateral score and final infarct volume, correlation was slightly higher for control ($R=-0.64$, $P=0.02$) than for r-ProUK ($R=-0.54$, $P=0.002$) patients.

Correlation Between Collateral Flow and Clinical Outcome

Collateral scores on baseline angiography showed significant correlation with neurological outcome (NIHSS scores) at 7 to

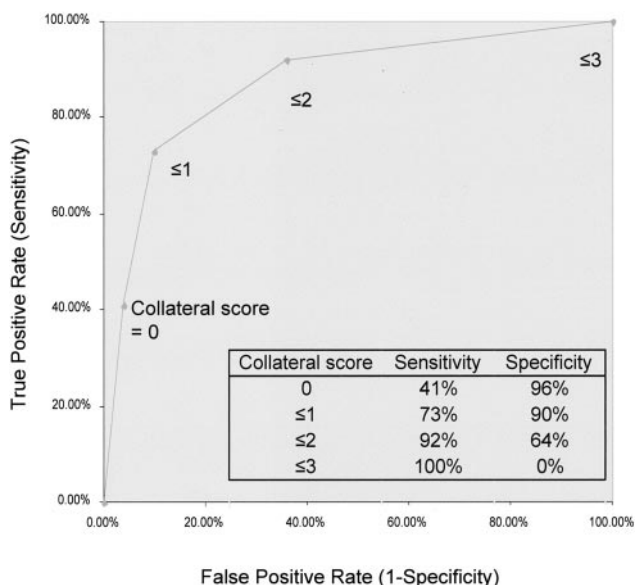


Figure 4. ROC curve for using collateral grading system to predict infarction.

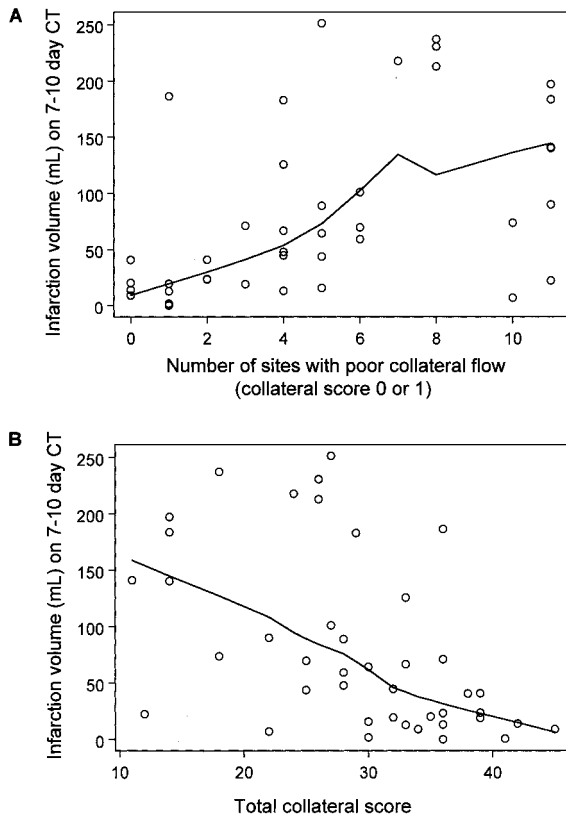


Figure 5. Correlation between collateral flow on baseline angiogram and infarct volume on follow-up CT (scatterplot).

10 and 30 and 90 days (Table 2). Analyzing all patients, as the number of sites with poor collateral flow (score ≤ 1) increased, NIHSS scores at 7 to 10 and 30 and 90 days significantly increased as well, indicating poor neurological status. As the total collateral score increased (better collateral circulation), NIHSS scores decreased significantly for all patients. In a subanalysis of patients treated with r-ProUK, significant correlations were found between NIHSS scores and total collateral score and between NIHSS scores and the number of sites with poor collateral flow scores (Table 2), except at 7 to 10 days, although P values were close to the significant level. However, no significant correlation between collateral scores and clinical outcome was found for control patients at any time point.

Discussion

Our analysis showed that the use of a regional angiographic grading system for collateral flow accurately predicts re-

gional brain infarction. Basing positive infarct predictions on collateral flow scores ≤ 1 (no or partial collateral flow) resulted in fairly high sensitivity and specificity (73% and 90%, respectively).

The accuracy of using baseline collateral flow to predict infarction was high for all sites in the MCA distribution, with AUC of the ROC curve ranging from 0.73 to 0.92. The accuracy was lowest for the basal ganglia, which are supplied by end arteries. Although the presence of a vascular “blush” or arteriovenous shunting from luxury perfusion and loss of cerebral autoregulation may indicate an ischemic insult to the basal ganglia, angiographic correlates for infarction in this region are still relatively insensitive. There was limited accuracy in interpreting collateral flow for the centrum semiovale, as well as the anterior cerebral artery and posterior cerebral artery distributions, with 95% CIs spanning 0 to 1. Because this study focused on patients with MCA occlusion, few anterior cerebral artery and posterior cerebral artery infarcts were present, limiting the accuracy of interpreting collateral flow in these regions. Hypoperfusion and subsequent infarction of the centrum semiovale are known to occur in the setting of proximal large vessel occlusions.¹⁶ The lower blood flow and small caliber of vessels supplying this region made predicting infarction difficult by angiography.

As collateral flow scores improved, infarct volumes on follow-up CT significantly decreased and clinical outcome as measured by NIHSS scores improved. Our results corroborate those published elsewhere, with Spearman correlation coefficients between collateral flow and clinical outcome very similar to those found by Wildermuth et al in a study using CT angiography to evaluate collateral flow.^{6,17} However, in a subgroup analysis of control patients, no significant correlation between baseline collateral status and follow-up neurological outcome was found. Oddly, in the case of 30-day NIHSS scores, there was a negative correlation between good collateral flow and neurological outcome, although the very small R values imply a chance result. The lack of significant correlation between collateral flow and clinical outcome in control patients is likely caused by a small sample size of 13 patients.

Although the correlations between collateral flow and (1) infarct volume and (2) clinical outcome were significant, R values were not strong. Factors besides collateral flow, such as clot location and extent of recanalization, influence infarct size and outcome.^{2,6,18} Without recanalization, leptomeningeal collateral flow may be insufficient to sustain cerebral perfusion. Patients with MCA occlusions may have autoreg-

TABLE 2. Spearman Correlation Between Collateral Circulation and Clinical Outcome Defined by NIHSS Score

NIHSS	All Patients (n=42)		Control Patients (n=13)		r-ProUK Patients (n=29)	
	N of Sites With Poor Collaterals	Total Collateral Score	N of Sites With Poor Collaterals	Total Collateral Score	N of Sites With Poor Collaterals	Total Collateral Score
7- to 10-day	0.57 ($P<0.0001$)†	-0.35 ($P=0.023$)	0.36 ($P=0.23$)	-0.36 ($P=0.22$)	0.36 ($P=0.052$)	-0.31 ($P=0.1$)
30-day	0.42 ($P=0.006$)†	-0.37 ($P=0.015$)	-0.089 ($P=0.77$)	0.012 ($P=0.97$)	0.49 ($P=0.007$)†	-0.48 ($P=0.009$)†
90-day	0.34 ($P=0.029$)*	-0.36 ($P=0.019$)*	0.083 ($P=0.79$)	-0.018 ($P=0.95$)	0.43 ($P=0.019$)*	-0.43 ($P=0.019$)*

Poor collateral flow indicates collateral score of 0 or 1; total collateral score, sum of collateral scores for all 15 anatomic sites.

* $P\leq 0.05$.

† $P\leq 0.01$.

ulatory vasodilation and increased oxygen extraction fraction, suggesting that pial collaterals fail to maintain adequate perfusion pressure.¹⁹ Given the potential importance of these other variables, it is not surprising that the relationship between collateralization and outcome is not stronger.

The intent of this study was not to assess the effect of collateral circulation in the presence or absence of thrombolysis, but rather to validate a regional grading system for collateral flow. For this reason, only a subset of patients enrolled in the study was reviewed. Saver et al²⁰ reported correlations range from 0.43 to 0.53 between CT infarct volume at days 6 to 11 and the neurological outcome at 3 months. Our study was designed to have sufficient power (>80%) to determine correlations >40% at a 5% significance level. According to these parameters, a sample size of 44 patients was deemed sufficient to accomplish our goal.²⁰ Given our sample size, we presented data for treated and control groups together (if statistical analysis did not demonstrate significant difference between the 2 groups).

A final general consideration for this study concerns the use of angiography to evaluate collateral flow and predict infarction. Although our study attempted to evaluate the perfusion status of tissue by assessing angiographic collateral flow, CT and magnetic resonance perfusion techniques can quantitatively and qualitatively describe the hemodynamic status of ischemic tissue. Many studies have investigated the use of hemodynamic parameters obtained from CT and magnetic resonance perfusion (such as cerebral blood volume, blood flow, and mean transit time) to identify penumbra and predict infarction.^{21–24} Such cross-sectional methods will no doubt be important for further advances in stroke imaging and for consideration in clinical trial design. Our study addresses the angiographic correlates of brain ischemia and infarction, which are important to recognize because angiography is performed at the time of consideration for endovascular stroke therapy.

This study demonstrates that a grading system for regional collateral flow on baseline angiography accurately predicts the presence and location of final infarction. The study also corroborates the correlation between collateral flow, infarction volume, and clinical outcome, which suggests the need to control for the status of regional collateral flow in clinical trials directed at treatment of MCA occlusion. This may be best accomplished by integrating magnetic resonance or CT perfusion studies as surrogates for assessment of collateral flow.

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