Collateral Vessels on CT Angiography Predict Outcome in Acute Ischemic Stroke

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Background and Purpose—Despite the abundance of emerging multimodal imaging techniques in the field of stroke, there is a paucity of data demonstrating a strong correlation between imaging findings and clinical outcome. This study explored how proximal arterial occlusions alter flow in collateral vessels and whether occlusion or extent of collaterals correlates with prehospital symptoms of fluctuation and worsening since onset or predict in-hospital worsening.

Methods—Among 741 patients enrolled in a prospective cohort study involving CT angiographic imaging in acute stroke, 134 cases with proximal middle cerebral artery occlusion and 235 control subjects with no occlusions were identified. CT angiography was used to identify occlusions and grade the extent of collateral vessels in the sylvian fissure and leptomeningeal convexity. History of symptom fluctuation or progressive worsening was obtained on admission.

Results—Prehospital symptoms were unrelated to occlusion or collateral status. In cases, 37.5% imaged within 1 hour were found to have diminished collaterals versus 12.1% imaged at 12 to 24 hours ($P=0.047$). No difference in worsening was seen between cases and control subjects with adequate collaterals, but cases with diminished sylvian and leptomeningeal collaterals experienced greater risk of worsening compared with control subjects measured either by admission to discharge National Institutes of Health Stroke Scale increase ≥ 1 (55.6% versus 16.6%, $P=0.001$) or ≥ 4 (44.4% versus 6.4%, $P<0.001$).

Conclusion—Most patients with proximal middle cerebral artery occlusion rapidly recruit sufficient collaterals and follow a clinical course similar to patients with no occlusions, but a subset with diminished collaterals is at high risk for worsening. **(*Stroke*. 2009;40:3001-3005.)**

Key Words: acute stroke ■ angiography ■ collateral ■ outcomes

Collateral circulation is an important consideration in the acute management of ischemic stroke. In cases of proximal artery occlusion, collateral vessels may provide blood flow to preserve remaining viable tissue.[1] Although CT angiography (CTA) source images and diffusion-weighted MRI are useful in delineating infarct volume,[2–4] the ability to predict the stability of the infarct using clinical and imaging characteristics is limited. MR and CT perfusion parameters to predict the outcome of the ischemic penumbra have not been accurately established,[5,6] although a small study of 29 patients has identified a relationship between perfusion images and clinical outcome in a pattern that suggests a protective effect of leptomeningeal collaterals.[7]

Certain attributes of collateral vessels remain hypothetical. A phenomenon of arterial collateral recruitment is frequently described[8] but with limited empirical evidence. Knowledge of whether collateral arterial channels are recruited or change in a time-dependent manner in the acute phase of ischemic stroke as a compensatory mechanism due to vessel occlusion would be useful in guiding treatments goals for volume expansion and blood pressure. Finally, it is unknown whether the absence of collateral vessels predicts evolution of symptoms. The purpose of this study is to explore whether (1) proximal arterial occlusions alter flow in collateral vessels; (2) a time-dependent collateral vessel recruitment phenomenon exists; (3) symptom fluctuation or worsening since initial onset correlates with the presence of a proximal arterial occlusion or the extent of active collaterals; and (4) whether extent of collaterals predicts further in-hospital worsening.

Materials and Methods

Patient Selection and Clinical Data

We analyzed data from 741 consecutive patients enrolled between March 2003 and January 2006 in a prospective cohort study at 2 university-based hospitals, part of the Screening Technology and Outcomes Project in Stroke (STOPStroke). All patients presenting with symptoms consistent with acute cerebral ischemia were considered eligible. Admission nonenhanced CT scans were obtained

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followed by CTAs. Patients were excluded from enrollment for contraindication to iodinated contrast agent administration (history of contrast agent allergy, pregnancy, congestive heart failure, renal insufficiency) or if the nonenhanced CT scan showed evidence of intracranial hemorrhage. The study received Institutional Review Board approval at both participating institutions and was Health Insurance Portability and Accountability Act-compliant. At enrollment, all subjects gave informed consent for participation.

Subjects with middle cerebral artery (MCA) M1 and/or M2 segment occlusion without evidence for occlusion in the contralateral MCA or internal carotid artery were selected as study cases. Subjects with symptoms consistent with anterior circulation ischemia but no angiographic occlusions in the territory of either internal carotid artery or MCA were selected as control subjects. Time-to-imaging was calculated as the amount of time elapsed between the onset of symptoms and the acquisition of the CTA segment of the neuroimaging protocol. Patients without time of onset data were excluded. Time of onset was defined as time of symptom onset for witnessed events and time the subject was last known normal for unwitnessed events. For patients with unwitnessed events in whom the time last known normal could only be estimated as "AM" or "PM," a conservative estimate of midnight for AM and noon for PM were used. Patients for whom time-to-imaging was >24 hours were excluded.

Information was collected on the trajectory of subjects' symptoms. At the time of initial evaluation, it was determined by interview of the patient and/or accompanying family or friends whether the subject's neurological symptoms had definitely fluctuated, improved, worsened, or remained unchanged since the time of initial onset. National Institutes of Health Stroke Scale (NIHSS) was measured at the time of initial presentation, at various time intervals during the course of hospitalization, and at the time of discharge. In-hospital worsening is defined as a discharge NIHSS greater than admission NIHSS and severe worsening as an increase ≥4 between admission and discharge, including death.

Neuroimaging Protocol

Nonenhanced CT and CTA acquisitions were performed according to standard departmental protocols with 8- or 16-section multidetector CT scanners (LightSpeed; GE Healthcare, Milwaukee, Wis).[7,8] Nonenhanced CT was performed with the patient in a head holder in the transverse plane. Representative sample parameters, with minimal variations between scanners and sites shown as ranges, were as follows: 120 to 140 kVp, 170 mA, 2-second scan time, and 5-mm section thickness. Imaging with these parameters was immediately followed by biphasic helical scanning performed at the same head tilt as was nonenhanced CT. CTA was performed after a 25-second delay (40 seconds for patients in atrial fibrillation) and administration of 100 to 140 mL of a nonionic contrast agent (Isovue; Bracco Diagnostics, Princeton, NJ) at an injection rate of 3 mL/s by using a power injector (Medrad Power Injector; Medrad, Indianola, Pa) through an 18-gauge intravenous catheter. Parameters were 140 kVp, 220 to 250 mA, 0.8- to 1.0-second rotation time, 2.5-mm section thickness, 1.25-mm reconstruction interval, 3.75 mm per rotation table speed, and 0.75:1 pitch. Images were obtained from the C6 vertebral body level through the circle of Willis. Immediately afterward, a second set of images was obtained from the aortic arch to the skull base. Afterward, source images were reconstructed into standardized maximum intensity projection views of the intracranial and extracranial vasculature.

Image Review

Image review was independently performed on a picture archiving and communication system workstation (Impax; Agfa Technical Imaging Systems, Richfield Park, NJ) by a board-certified neuroradiologist and a clinical neurologist experienced in stroke imaging (M.H.L. and W.J.K., 15 and 25 years of neuroimaging review experience, respectively). Reviewers were blinded to follow-up clinical and imaging findings but had information in regard to the patients' age, sex, and presenting clinical symptoms. Neither of the reviewers had participated in the selection of the patients.

Table 1. Patient Characteristics

	Cases	Control Subjects	*P* Value
No. of subjects	134	235	
Age, years	68.2	65.4	0.102
Sex, male	44.0%	54.9%	0.051
Initial NIHSS	9.8	4.2	<0.001
Final NIHSS	9.9	3.3	<0.001
Died in hospital	10.4%	0.9%	<0.001
Time-to-imaging, hours	8.1	8.2	0.874
History of worsening or fluctuation since onset	17.2%	18.3%	0.888
Worsened	23.1%	16.6%	0.131
Severely worsened	13.4%	6.4%	0.035

Analysis

For the primary analysis, patients who receive intravenous thrombolysis or intra-arterial therapy were excluded. Angiographic occlusions, with a 1 to 5 level of certainty rating, were recorded for 27 defined vessel segments. Lesions identified as subtotal or total occlusion of Level 4 and 5 certainty (probably or definite) were defined as an occlusion. CTA source images (CTA-SI) were used to assess for the presence of collateral vessels in the region of the sylvian fissure and the leptomeningeal convexity and to assign separate grades for each. Collateral vessels were graded in a comparison manner for the symptomatic hemisphere against the contralateral hemisphere as follows: 1, absent; 2, less than the contralateral normal side; 3, equal to the contralateral normal side; 4, greater than the contralateral normal side; and 5, exuberant. Diminished is defined as Grades 1 to 2, adequate as Grades 3 to 5, and augmented as Grades 4 to 5. The anterior communicating artery (ACom) and posterior communicating arteries (PCom) were graded as follows: 1, absent; 2, probably present; 3, hairline; 4, definitely present; and 5, robust. Adequate ACom and PCom are defined as Grades 4 to 5.

To explore the question of a time-dependent collateral vessel recruitment phenomenon, case subjects were divided into the following time-to-imaging groups: 0 to 1 hour, 1 to 2 hours, 2 to 3 hours, 3 to 6 hours, 6 to 9 hours, 9 to 12 hours, and 12 to 24 hours and the Mantel-Haenszel trend test was used to evaluate for a time-variant relationship between extent of collaterals and time of imaging. The relationship between collaterals and clinical outcomes (prehospital symptom fluctuation and worsening and in-hospital worsening and severe worsening) was performed by evaluating outcome of subjects dichotomized into groups with diminished or adequate collaterals using Fisher exact test. The relationship between anterior and ipsilateral PCom and in-hospital worsening and severe worsening was assessed by Fisher exact test. Student *t* test was used for continuous data.

In a secondary analysis, patients who received intravenous thrombolysis and/or intra-arterial therapy were included and all analyses repeated.

Results

Of the 741 subjects enrolled in the study, 134 met criteria as cases and 235 as control subjects. An additional 59 cases and 27 control subjects who received thrombolytic therapy were included for secondary analysis. The characteristics of the subjects included in the primary analyses are summarized in Table 1. There were no significant differences in age or sex between groups. Case subjects had significantly higher initial and discharge NIHSS scores (9.8 versus 4.2 and 9.9 versus 3.3, both $P<0.0001$). There was no difference in time-to-imaging between groups (8.1 versus 8.2 hours, $P=0.87$). Nearly one in 6 case and control subjects had a reported

history of fluctuation of symptoms or had evolved worsening of symptoms since the time of initial symptom onset, and there was no difference between the groups. With respect to in-hospital worsening, there was no significant difference in the rate of all in-hospital worsening, although cases experienced a significantly greater rate of severe worsening compared with control subjects (13.4% versus 6.4%, $P=0.035$).

Based on the 1 to 5 rating scale, no difference in the average extent of visualized collaterals was found between the case and control groups in the region of the sylvian fissure (2.93 versus 2.93, $P=1.0$) or leptomeningeal convexity (3.04 versus 2.95, $P=0.09$). Nearly all control subjects were found to have equal (Grade 3) extent of arterial tree filling, whereas half of case subjects showed either augmented or diminished flow in the symptomatic hemisphere.

In the time-to-imaging analysis, 50% of case subjects imaged within 1 hour had diminished collaterals compared with 14.5% imaged between 12 and 24 hours ($P=0.12$ for trend). The same apparent trend was present for both the sylvian (50% to 19.4%, $P=0.21$) and leptomeningeal collaterals (50% to 9.7%, $P=0.31$). Inclusion of subjects who had received thrombolysis showed the same trend, which achieved significance with the increased number of subjects (37.5% to 12.1%, $P=0.047$). No time-dependent changes were seen in the extent of collaterals of control subjects.

The key results of the clinical outcomes analysis are summarized in Table 2. No relationship could be demonstrated between reports of prehospital symptom fluctuation or worsening since onset and the extent of collaterals in the sylvian fissure or leptomeningeal convexity (symptoms present in 16.1% with adequate versus 27.8% with diminished collaterals, $P=0.31$). The relationship between reduced collaterals and in-hospital worsening was marked. There was no difference in the rate of worsening or severe worsening between cases with adequate sylvian and leptomeningeal collaterals and control subjects. Diminished sylvian and leptomeningeal collaterals nearly quadrupled the rate of worsening when studied separately (34.1% and 45.8% versus 16.6% in control subjects; $P=0.019$ and $P=0.002$, respectively) or in patients in whom both sylvian and leptomeningeal collaterals were diminished compared with control subjects (55.6% versus 16.6%, $P=0.001$). The effect was nearly identical for severe worsening (diminished sylvian 24.4%, diminished leptomeningeal 33.3%, and both diminished 44.4% versus 6.4% for control subjects; $P=0.002$, 0.001, and <0.001, respectively). Likewise, the protective effect of collaterals was magnified in subjects with absent (Grade 1) collaterals. When compared with control subjects, 66.7% of subjects with either absent sylvian and leptomeningeal collaterals experienced severe worsening (versus 6.4% control subjects, $P=0.017$ for both). The rates of in-hospital worsening and severe worsening for cases in which both the ACom and PCom were adequate versus cases in which neither was adequate were not significantly different (worsening 23.3% versus 23.0%, $P=1.0$ and severe worsening 10.0% versus 16.2%, $P=0.32$).

Table 2. Worsening and Collaterals

Collateral Grade	Cases	Control Subjects	*P* Value
Worsening		16.6%	
Adequate sylvian	18.3%		0.873
Diminished sylvian	34.1%		0.019
Adequate leptomeningeal collaterals	18.2%		0.880
Diminished leptomeningeal collaterals	45.8%		0.002
Adequate sylvian and leptomeningeal collaterals	18.4%		0.870
Diminished sylvian and leptomeningeal collaterals	55.6%		0.001
Adequate ACom and PCom	23.3%		1.000
Neither ACom nor PCom adequate	23.0%		
Prehospital fluctuation or worsening		22.7%	0.390
No prehospital fluctuation/worsening		18.2%	
Severe worsening		6.4%	
Adequate sylvian	8.6%		0.650
Diminished sylvian	24.4%		0.002
Adequate leptomeningeal collaterals	9.1%		0.527
Diminished leptomeningeal collaterals	33.3%		0.001
Adequate sylvian and leptomeningeal collaterals	9.2%		0.639
Diminished sylvian and leptomeningeal collaterals	44.4%		<0.001
Adequate ACom and PCom	10.0%		0.322
Neither ACom nor PCom adequate	16.2%		
Prehospital fluctuation or worsening		12.1%	0.341
No prehospital fluctuation/worsening		8.3%	

Discussion

The importance of this study is the objective demonstration of time-dependent collateral recruitment and the correlation of collateral status with clinical outcome measures. A history of symptom fluctuation or progressive worsening since initial onset of stroke has traditionally been viewed as indicating that an at-risk area of brain is receiving diminished perfusion near the threshold for normal function.[9] Despite conventional wisdom, no correlation could be demonstrated between a history of prehospital fluctuation or worsening and either the finding of diminished collaterals or as a predictor of greater risk for in-hospital worsening. Although the clinical history of prehospital symptom change was not predictive of clinical status, the extent of collaterals was. Despite the presence of a proximal MCA occlusion, the risk for in-hospital worsening for patients with adequate collaterals was not significantly greater compared with subjects who had no occlusions regardless of whether an inclusive or strict definition was used for worsening. In contrast, the rate of worsening was nearly 4 times greater in subjects with proximal MCA occlusion but diminished collaterals.

Table 3. Angiographic Grading of Cerebral Collaterals in Prior Studies of Patients With Ischemic Stroke

Study	Subjects	Imaging Sequence	Method	Scale
Schramm, 2002[3]	Ischemic stroke within 6 hours; 20 patients	CTA-SI 2 mm slice	Degree of perilesional vessel enhancement	Poor or good
Kim, 2004[12]	Ischemic stroke from MCA occlusion within 6 hours; 42 patients	DSA	Collateral vessels in each of 15 anatomic sites (per ASPECTS study) in the affected hemisphere	0=no collaterals visible to ischemic site (absence of capillary blush); 1=collaterals to the periphery of the ischemic site; 2=complete irrigation of the ischemic bed through collateral flow; 3=normal antegrade flow
Tan, 2007[11]	Ischemic stroke within 48 hours; 55 patients	CTA-SI axial with sagittal and coronal MPR 1.25- or 1.5-mm slice	Degree of perilesional vessel enhancement	Poor or good
		CTA-MIPs axial, sagittal, and coronal 20 mm	Degree of collateral vessel enhancement (enhancing vessels within the total vascular territory supplied by the occluded arterial segment)	0=absent collaterals; 1=collaterals filling ≤50% of the occluded territory; 2=collaterals filling >50%, but <100% of the occluded territory; 3=collaterals filling 100% of the occluded territory
Rosenthal, 2008[13]	Ischemic stroke within 6 hours with symptoms consistent with proximal MCA ischemia; 44 patients	CTA-SI 3-mm slice	Degree of leptomeningeal and Sylvian vessel enhancement	1=absent; 2=less than the contralateral normal side; 3=equal to the contralateral normal side; 4=greater than contralateral normal side; 5=exuberant

CTA-SI indicates CTA source images; DSA, digital subtraction angiography; MIPs, maximal intensity projections; ASPECTS, Alberta Stroke Program Early CT Score.

Major clinical trials have used either change in NIHSS ≥1 or ≥4 to define worsening. In this study, the impact of collaterals was significant whether a broad definition of NIHSS ≥1 was used or NIHSS ≥4 to target severe worsening. Whereas the occlusion patients with normal or increased collateral flow fared no worse than patients with stroke with no visible occlusions, the fraction with diminished flow experienced a significantly greater risk of in-hospital progression of stroke deficits to the point that patients with absent collaterals had a 10-fold increased risk of severe worsening or death. Diminished or absent collaterals, although only affecting only one fourth of subjects with proximal MCA occlusion, was a clear harbinger of further worsening of stroke severity. Thus, the disparity in outcomes between case subjects and control subjects reported in Table 1 is accounted for by the minority of cases with diminished collaterals.

Patients presenting with proximal MCA occlusions showed a time-dependent recruitment of flow to the symptomatic hemisphere through collateral vessels. Overall, half of such patients showed a symmetrical extent of collaterals between hemispheres, and the remaining half was evenly divided between one subset that experienced augmented flow through collateral vessels (26%) and another with diminished flow in the same regions (26%). The fraction of patients with augmented flow remained constant. Although most patients appear to eventually achieve adequate collateral flow, the ability to generate augmented flow to the affected hemisphere appears to be established within the first hour. These findings suggest a possible intrinsic capacity for collateral flow that is important for clinical outcome.

This study contributes important advances in the current understanding of how collateral vessels influence outcome in acute stroke. First, data are presented to demonstrate an alteration in the extent of collaterals in the context of proximal arterial occlusion. Second, a time-dependent trend is identified implying a successful early (<1 hour) recruitment of collaterals in approximately three fourths of patients with stroke with proximal arterial occlusion as well as a slow secondary recruitment phenomenon. Finally, CTA imaging can identify a unique subset of patients with diminished or absent collateral vessels in the symptomatic hemisphere. This group of patients experiences markedly higher risk for further worsening. Despite the abundance of emerging multimodal imaging techniques in the field of stroke, there is a paucity of data demonstrating a strong correlation between an imaging finding and clinical outcome.

There are inherent limitations involved with evaluating the role of collateral vessels. Ascertaining a history of fluctuation or progression relies on the patient and family being capable of observing and correctly interpreting signs attributable to multiple domains of neurological function, which is fraught with limitations. Use of the NIHSS by properly trained staff is a more objective measure than report of prehospital symptoms. Use of CTA reveals the extent of patent arterial collaterals by observing contrast filling of vessel lumens but cannot account for any difference in volume of flow within collateral vessels that may be induced by occlusion. Furthermore, the technique of identifying collaterals depends on an approximation based on vessels visualized in the sylvian fissure and leptomeningeal convexity region.

Prior studies have used angiographic techniques to assess cerebral arterial collaterals in the context of acute to subacute ischemic stroke (Table 3). Tan et al[10] compared the techniques used to visualize collateral vessels used in earlier studies by Schramm[3] and Kim[11] and found that the less subjective ordinal scale used by Kim et al had higher interobserver agreement (κ=0.669) and correlated significantly with infarct volume both in patients with persistent

arterial occlusion and those who showed recanalization. Rosenthal et al[12] used a multivariable analysis model to study clinical and radiological predictors of patient outcomes. More recently, arterial spin-labeled MR angiography has been shown to accurately image collateral flow.[13] Although other imaging techniques have successfully visualized leptomeningeal vessels in acute stroke, no correlation was found between abnormal visualization of leptomeningeal vessels and clinical status.[14] This may have been due to small numbers of patients studied.

Given the predictive clinical implications of diminished or absent collateral vessels, CTA-based assessment of collaterals may provide a clinically useful method of selecting patients likely to benefit from intra-arterial therapies. Further research correlating extent of collateral vessels, extent of perfusion defect–infarct core mismatch, and clinical outcome may lead to advances in patient care. Other studies have found a relationship between perfusion parameters such as regional cerebral blood volume and cerebral blood flow and delayed contrast arrival on perfusion source images that suggests the role of collateral vessels.[7] Future research to explore those relationships would be useful. Likewise, future research into treatments directed at improving cerebral blood flow such as induced hypertension may use collateral vessel grading in their selection of patients. Some patients with diminished collateral vessels may not respond to such treatments despite being identified as good candidates by perfusion mismatch, or they may prove to be the ideal candidates for such treatment due to their propensity for progression of deficits.

Conclusion

In patients presenting with acute cerebral ischemia and proximal MCA occlusion, initial recruitment of collaterals occurs rapidly. A secondary, gradual recruitment effect occurs over at least 24 hours, and pathological diminution of flow diminishes over time. Although most individuals demonstrate collateral circulation sufficient to show adequate filling of the distal arterial tree after acute proximal MCA occlusion, approximately one fourth are unable to generate substantial collateral flow measured by sylvian fissure and leptomeningeal convexity vessels on CTA. Although nearly all patients with MCA occlusions and adequate collaterals experience stable deficits with in-hospital improvement similar to patients with no angiographic occlusions, the subset with diminished collaterals is at very high risk for worsening. This group may be an ideal population for blood flow-enhancing treatments such as intra-arterial therapies.

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