Distal hyperintense vessels on FLAIR

An MRI marker for collateral circulation in acute stroke?

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ABSTRACT

Background: Hyperintense vessels (HV) on fluid-attenuated inversion recovery imaging are frequently observed in acute ischemic stroke patients. However, the exact mechanism and clinical implications of this sign have not yet been clearly defined. The features of HV and its relevance to other imaging factors are presented here.

Methods: Prominence and location of HV were documented in 52 consecutive patients with middle cerebral artery (MCA) territory infarction, before treatment with IV recombinant tissue plasminogen activator. Pretreatment ischemic lesion volume, perfusion lesion volume, and vessel occlusion were determined in addition to recanalization status and ischemic lesion volume on follow-up imaging. NIH Stroke Scale (NIHSS) was used as a measure of clinical severity.

Results: HV distal to arterial occlusion was observed in 73% of patients; more frequent in proximal than distal MCA occlusion patients. Among the 38 patients with proximal MCA occlusion, initial perfusion lesion volume was comparable among patients with different grade distal HV. However, patients with more prominent distal HV had smaller initial, 24-hour, and subacute ischemic lesion volumes and lower initial NIHSS scores.

Conclusions: The presence of distal hyperintense vessels before thrombolytic treatment is associated with large diffusion–perfusion mismatch and smaller subacute ischemic lesion volumes in patients with proximal middle cerebral artery occlusion. *Neurology*® 2009;72:1134–1139

GLOSSARY

DWI = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient recalled echo; **HV** = hyperintense vessels; **MCA** = middle cerebral artery; **MRA** = magnetic resonance angiography; **MTT** = mean transit time; **NIHSS** = NIH Stroke Scale; **PWI** = perfusion-weighted imaging; **rt-PA** = recombinant tissue plasminogen activator; **TE** = echo time; **TI** = inversion time; **TIMI** = thrombolysis in myocardial infarction; **TR** = repetition time.

Hyperintense vessels (HV) on fluid-attenuated inversion recovery (FLAIR) images can be observed in the hemisphere affected by an arterial occlusion in some patients, but not all.[1-6] Although HV is thought to be similar to the hyperdense artery sign on CT scan or the susceptibility vessel sign on gradient recalled echo (GRE) MRI, it has been shown to be superior to both for the detection of arterial occlusion.[4,7-9] HV usually has longer course than the other two signs and this suggests that different mechanisms other than intraluminal thrombus cause HV. While the mechanism of HV remains to be established, stationary blood and slow antegrade or retrograde collateral circulation have been suggested as possible explanations for HV.[1,5,10-12]

There are only a few reports suggesting that HV is related to poor prognosis, or has no specific prognostic meaning other than the knowledge of an arterial occlusion.[4,13] However, the stroke populations in previous studies were heterogeneous; patients with proximal and distal as well as anterior and posterior circulation occlusions were considered together, potentially confounding tests for significance. In order to verify the clinical implication of HV on FLAIR, it

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should be compared between similar groups of patients, such as those having similar sites of arterial occlusion or similar perfusion lesion volumes.

We speculate that HV may be the result of beneficial collateral arterial flow beyond the site of arterial occlusion, and those patients with HV will have a better prognosis and smaller infarction size than those patients without HV.

METHODS

Subjects. For this analysis, we considered consecutive acute stroke patients enrolled in a natural history of stroke study approved by the Institutional Review Board at the National Institute of Neurological Disorders and Stroke and Suburban Hospital in Bethesda, MD, and at Washington Hospital Center in Washington, DC. We included patients who presented with acute middle cerebral artery (MCA) territory ischemic stroke within 3 hours after onset and were treated with IV recombinant tissue plasminogen activator (rt-PA). We excluded patients with no prethrombolysis brain MRI, no follow-up MRI after treatment, or lacunar infarction. Neurologic deficit was evaluated with the NIH Stroke Scale (NIHSS) on admission and 5 days after admission. All patients, or their legally authorized representative, signed informed consent.

MRI protocol. Patients were imaged with either a 1.5 T (GE Medical Systems, Milwaukee, WI) or 3.0 T (Philips Medical Systems, Best, the Netherlands) clinical MRI system using commercially available hardware and software. The baseline and follow-up imaging protocols were standardized and included co-localized diffusion-weighted imaging (DWI), T2-FLAIR, GRE, bolus tracking perfusion-weighted imaging (PWI), as well as intracranial and extracranial contrast enhanced magnetic resonance angiography (MRA), and intracranial time-of-flight MRA. FLAIR images were acquired with commercially available 2D sequences, balanced (roughly) across field strength for conspicuity of chronic ischemic parenchyma, with the following relevant parameters at 1.5 T: repetition time (TR)/echo time (TE) = 9,000/145 msec, inversion time (TI) = 2,200 msec, 20 contiguous slices with 0.9 × 0.9 × 7 mm resolution (zero filled) for a total acquisition of 2 minutes 25 seconds; at 3T: TR/TE = 9,000/120 msec, TI = 2,600 msec, 20 contiguous slices with 1 × 1 × 4 mm resolution (SENSE R = 1.75), for a total acquisition of 2 minutes 15 seconds.

Imaging analysis. HV was defined as a linear or serpentine appearing hyperintensity on FLAIR imaging corresponding to a typical arterial course. Presence of HV was categorized as proximal or distal in relation to arterial branching of the MCA. HV was described as proximal when it was present to or within the Sylvian fissure, i.e., corresponding to the MCA M1 or M2 segments, and it was graded as either absent or present. HV was described as distal when it was present distal to the Sylvian fissure, i.e., corresponding to MCA M3 or distal segments, and was graded as 1) absent, 2) subtle, or 3) prominent (figure 1). Subtle distal HV was defined as presence of HV less than 1/3 of the perfusion lesion and prominent distal HV was defined as presence of HV more than 1/3 of the perfusion lesion. Two readers graded the FLAIR imaging independently with discordance settled by a separate consensus reading. Initial ischemic lesion volume and perfusion lesion volume were measured on initial pretreatment DWI and mean transit time (MTT) maps calculated from PWI, 24-hour lesion volume measured on DWI, and subacute ischemic lesion volume measured on 3- to 7-day follow-up FLAIR imaging. All volumes were measured by a third experienced reader, blinded to the HV grading. Initial diffusion–perfusion mismatch was calculated by the equation [(initial perfusion lesion volume on MTT − initial ischemic lesion volume on DWI)/initial perfusion lesion volume on MTT] × 100. Arterial occlusion site and recanalization status was read independently from the other readings. Arterial occlusion site was determined using MRA and PWI. We defined proximal MCA occlusion as M1 or M2 segment occlusion solely based on the MRA. M1 occlusion was defined as a main MCA trunk occlusion before the bifurcation and M2 occlusion was defined as a branch occlusion after the bifurcation. M3 distal occlusion was defined as distal branch occlusion without a perfusion lesion in the insular area on PWI. If there was no definite occlusion site visible on MRA but a perfusion lesion was visible on PWI, the patient was considered to have a M3 distal occlusion. Recanalization status was categorized by a modified grading system based on thrombolysis in myocardial infarction (TIMI) grade using both MRA and PWI.[14] TIMI 0 and 1 was regarded as poor recanalization and TIMI 2 and 3 as successful recanalization.

Statistical analysis. Statistical analysis was performed with SPSS 14.0 software for Windows. Mann–Whitney *U* test and Kruskal-Wallis H test was used to compare acute DWI ischemic lesion volume, acute perfusion lesion volume on MTT, diffusion–perfusion mismatch, 24-hour and subacute ischemic lesion volumes, and NIHSS score. Correlation between HV grade and recanalization status was analyzed by χ^2 test. Regression analysis was performed using 5-day NIHSS score as an outcome variable. Interobserver variability of HV grading was analyzed by k statistics. A two-tailed value of $p < 0.05$ was considered significant.

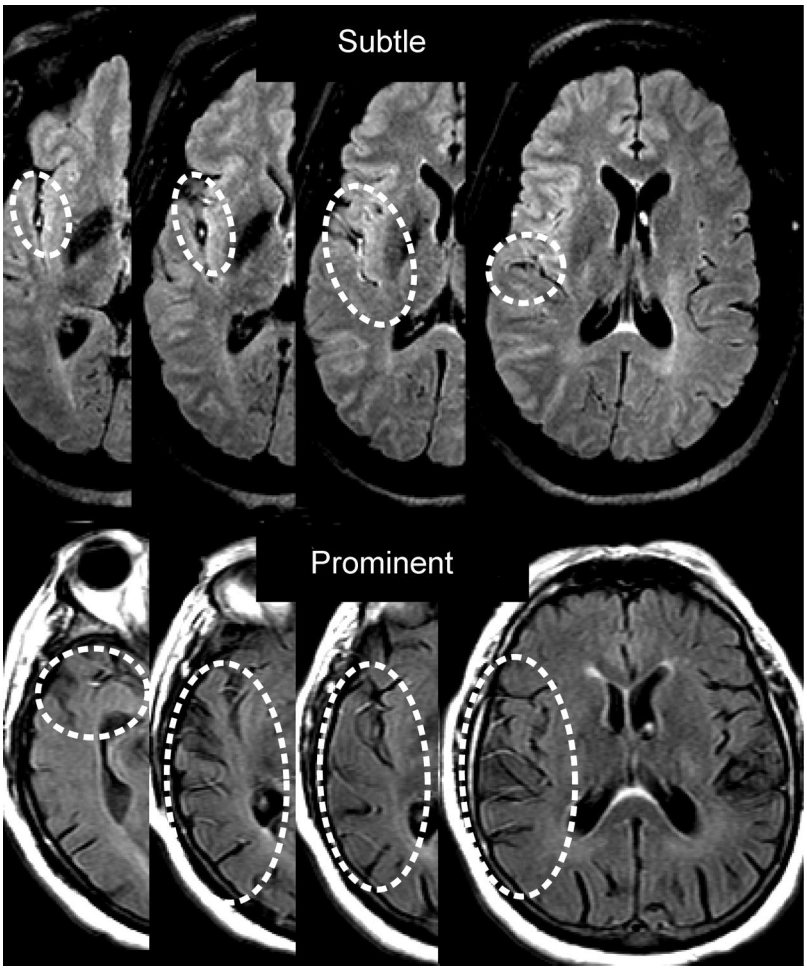
RESULTS

From 111 patients who were treated with IV rt-PA and consented to natural history study, 59 patients were excluded because of no pre rt-PA MRI (21), no follow-up MRI (10), unreadable FLAIR (5), and lacunar infarction or vertebrobasilar artery territory infarction (23). Among the 52 patients who met the inclusion criteria, 62% of patients were women, mean age was 68.9 ± 15.4 years, and the median initial NIHSS score was 8 (range 1–28). Twenty-two patients were determined to have MCA M1 occlusion (including 6 patients with an internal carotid artery T occlusion), 16 patients with MCA M2 occlusion, and 11 patients with MCA M3 distal occlusion. The remaining three patients did not have any MRA or PWI abnormalities.

All 52 patients had interpretable prethrombolysis FLAIR images; 19 of those patients were imaged at 3.0 T. Proximal HV was seen in 77% of patients ($k = 0.833$). Prominent distal HV was seen in 46% of patients and subtle distal HV was seen in 27% ($k = 0.661$) (table 1).

In the group of 38 patients having MCA M1 or M2 occlusion, ischemic lesion volume could be determined on initial DWI in all patients and on 24-

Figure 1 Example of distal hyperintense vessels (HV) grading



Both patients have middle cerebral artery M1 occlusion and demonstrate different levels of HV on fluid-attenuated inversion recovery imaging.

hour DWI in 36 patients; initial perfusion lesion volume on MTT was available in 32 and subacute lesion volume on FLAIR in 27. Patients with distal HV had smaller initial, 24-hour and subacute lesion volumes, and had larger diffusion–perfusion mismatch at baseline than did patients without distal HV. The initial perfusion lesion volume on MTT was comparable among the three groups (figure 2, table 2). DWI-positive lesions were usually distributed in the area without HV in patients with large diffusion–perfusion mismatch.

Table 1 Frequency of HV based on middle cerebral artery occlusion site

	M1 (n = 22)	M2 (n = 16)	M3 distal or none (n = 14)
Proximal HV	22 (100)	13 (81)	5 (36)
Distal HV			
Prominent	15 (68)	8 (50)	1 (7)
Subtle	4 (18)	5 (31)	5 (36)
None	3 (14)	3 (19)	8 (57)

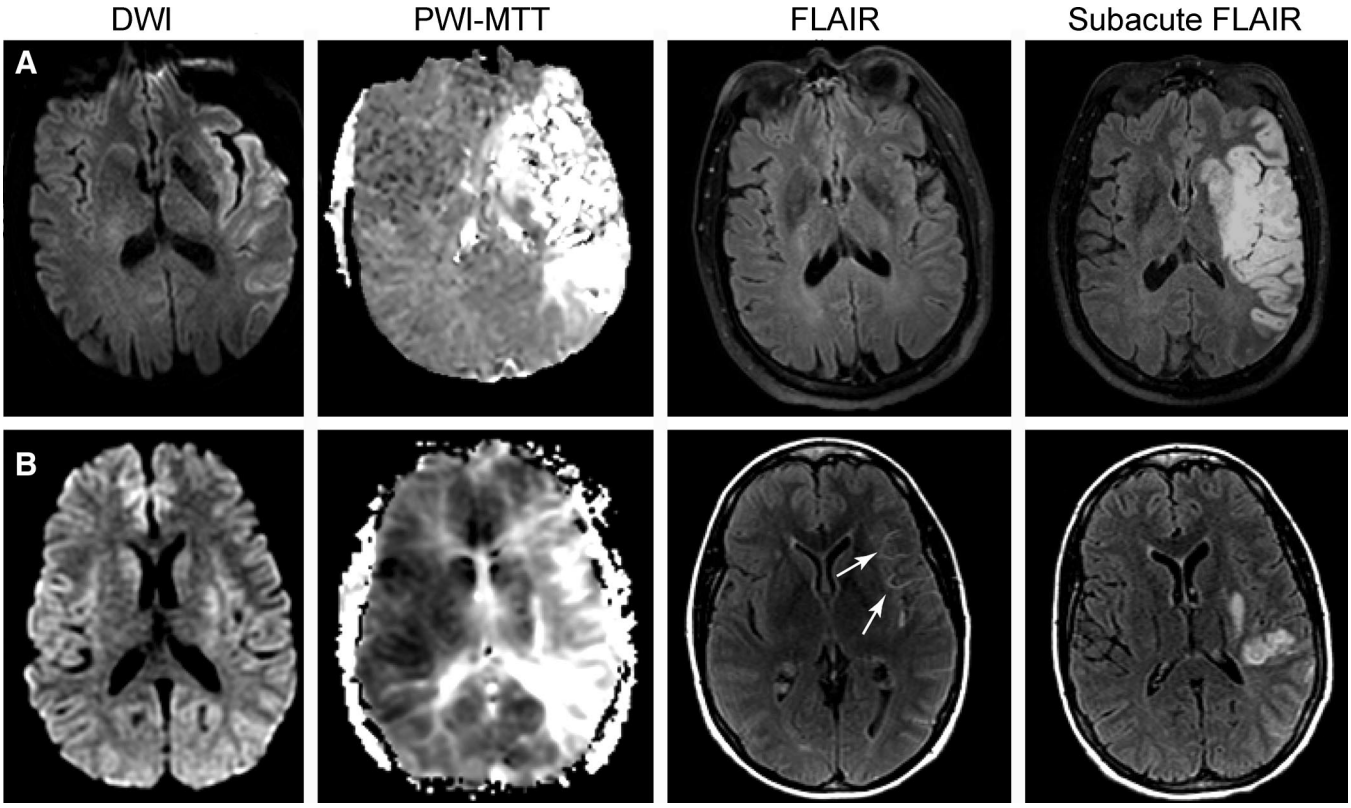
Values are n (%).
HV = hyperintense vessels; M1 = middle cerebral artery M1 portion; M2 = middle cerebral artery M2 portion; M3 distal = middle cerebral artery M3 and distal portion.

Successful recanalization was achieved in 48% (15 out of the 31 with available MRA) at 2 hours after thrombolysis and 74% (25 out of the 34 with available MRA) at 24 hours after thrombolysis in patients with M1 or M2 occlusion. There was no difference in recanalization rate among patients with different grade distal HV. Also, 24-hour and subacute infarction volume and 5-day NIHSS score did not show significant differences based on 2-hour recanalization status (table 3). However, patients with prominent distal HV who recanalized at 2 hours had smaller subacute ischemic lesion volumes on FLAIR compared with patients who did not recanalize (21.3 vs 53.0 mL; $p = 0.108$). NIHSS score was obtained in all patients with M1 or M2 occlusion at the time of initial imaging, but only in 29 of 38 patients at 5 days. Initial and 5-day NIHSS scores were lower in patients with high grade distal HV on initial imaging than in patients without, though only initial NIHSS score reached significance. Regression analysis using age, recanalization status, HV grade, and initial NIHSS score as independent variables demonstrated that only initial NIHSS score was a predictor of 5-day NIHSS score ($B = 0.666$, $p = 0.025$).

DISCUSSION This study demonstrates that the presence of distal HV on initial FLAIR imaging is associated with smaller ischemic lesion volume on MRI and milder clinical severity as measured by the NIHSS. While all patients with proximal MCA occlusion had similar perfusion lesion volumes and some degree of diffusion–perfusion mismatch on initial MRI, patients with prominent distal HV had smaller initial ischemic lesion volumes, larger diffusion–perfusion mismatch, relatively smaller lesion growth, and smaller subacute ischemic lesion volumes than did patients without it. The mechanism and causality cannot be definitively established in this study, but it is reasonable to speculate that prominent distal HV may be reflective of good collateral blood flow distal to the site of arterial occlusion and less ischemic injury to tissue supplied by occluded artery.

We categorized the HV in MCA occlusion as occurring proximally and distally. Contrary to proximal HV, which frequently appears as a single, linear structure with limited curvature and with proximity to the M1–M2 segments of the MCA, distal HV appears as a varying number of serpentine vessel-like structures distal to the M2 segment and covers an area variable in size. Therefore, we implemented a

Figure 2 Representative cases of different grade distal hyperintense vessels (HV)



(A) Initial diffusion- and perfusion-weighted MRI shows large left middle cerebral artery ischemic and perfusion lesions. No distal HV is seen on initial fluid-attenuated inversion recovery (FLAIR) imaging. Five-day follow-up FLAIR imaging shows a large cerebral infarction. (B) Initial diffusion- and perfusion-weighted MRI shows a small ischemic lesion with a large perfusion lesion. Prominent distal HV is noted on initial FLAIR imaging (arrows). Three-day follow-up FLAIR shows a small cerebral infarction. DWI = diffusion-weighted imaging; PWI = perfusion-weighted imaging; MTT = mean transit time.

grading system for distal HV based on the size of the area involved. Distal HV is frequently observed at the MCA M3 branch level, originating from an MCA M2 segment coursing anterior to posterior in the Sylvian fissure. The M3 branches in this area are still of relatively large vessel caliber and track pre-

Table 2 Comparison of ischemic lesion volume, perfusion lesion volume, clinical outcome, and recanalization rate by distal hyperintense vessels (HV) grade in patients with middle cerebral artery M1 or M2 occlusion

	Distal HV			
	None (n = 6)	Subtle (n = 9)	Prominent (n = 23)	*p* Value
Initial ischemic DWI lesion volume (mL)	127.5 ± 77.0	61.7 ± 37.1	22.1 ± 21.8	0.001
Initial perfusion lesion volume (mL)	266.8 ± 146.9	166.9 ± 112.8	185.1 ± 63.7	0.259
Initial DWI–PWI mismatch (%)*	50.7 ± 16.0	61.4 ± 26.3	84.6 ± 16.9	0.009
24-Hour ischemic DWI lesion volume (mL)	144.8 ± 78.2	95.4 ± 59.3	33.0 ± 40.5	0.001
Subacute FLAIR lesion volume (mL)	129.1 ± 169.6	137.8 ± 98.4	34.7 ± 36.6	0.025
Initial NIHSS score	18.3 ± 7.5	12.7 ± 5.6	9.4 ± 6.2	0.024
5-Day NIHSS score	15.3 ± 14.4	12.2 ± 16.0	5.2 ± 5.8	0.357
Successful recanalization at 2 hours†	3 (50)	4 (57.1)	8 (44.4)	0.718
Successful recanalization at 24 hours‡	3 (60)	7 (77.8)	15 (75)	0.613

Data are mean ± SD or n (%).
*Calculated by [(initial perfusion lesion volume on MTT − initial ischemic lesion volume on DWI)/initial perfusion lesion volume on MTT] x 100.
†Recanalization rate was evaluated in 7 subtle and 18 prominent distal HV patients.
‡Recanalization rate was evaluated in 5 none and 20 prominent distal HV patients.
DWI = diffusion-weighted imaging; PWI = perfusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; NIHSS = NIH Stroke Scale.

Table 3 Comparison of ischemic lesion volume, perfusion lesion volume, and clinical outcome by recanalization status in patients with middle cerebral artery M1 or M2 occlusion

	Recanalization at 2 hours		
	Successful (n = 15)	Poor (n = 16)	*p* Value
Initial perfusion lesion volume (mL)	202.5 ± 107.5	198.3 ± 88.0	0.919
24-Hour ischemic DWI lesion volume (mL)	66.4 ± 68.1	71.8 ± 68.9	0.812
Subacute FLAIR lesion volume (mL)	75.4 ± 98.0	71.6 ± 65.3	0.57
Initial NIHSS score	11.3 ± 8.1	12.4 ± 6.6	0.47
5-Day NIHSS score	6.5 ± 12.0	9.4 ± 9.9	0.19

DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery; NIHSS = NIH Stroke Scale.

dominantly in the plane of the axial FLAIR MRI slice, allowing for easy detection. More distal MCA branches are smaller and have an inferior–superior orientation that appear as bright dots in the transverse imaging and are therefore more difficult to detect.

Proximal HV, which is frequently observed proximal to or within the Sylvian fissure, may have different implications in comparison to distal HV. In contrast to distal HV, 92% of patients with proximal MCA occlusion had proximal HV, regardless of the initial ischemic lesion volume, lesion volume progression, and clinical severity. Proximal HV was not a useful prognostic indicator in this study. Proximal HV may be used as a marker for arterial occlusion, presumably the result of the thrombus inside the arterial lumen.[4,7] Distal HV is more likely related to either slow, anterograde flow at the site of the occlusion or retrograde collateral flow from arteries unaffected by occlusion, both having a relative delay in transit time with the latter owing to a more circuitous route of delivery. In patients with similar perfusion lesion volumes, prominent distal HV may provide a mechanism for discriminating tissue kept viable for extended periods by way of a well-developed collateral network from tissue rapidly evolving as the result of marginalized flow distal to the site of the occlusion.

We did not find any association between distal HV and successful recanalization at 2 and 24 hours after IV thrombolysis. A previous study using cerebral angiography suggested that both good collateral flow and complete recanalization were independently related to good clinical outcome and small infarction volume.[15] However, we could not find a significant difference in infarction volume and 5-day NIHSS score based on the 2-hour recanalization status. We speculated that the small sample size of our study and different outcome evaluation methods (discharge modified Rankin Scale vs 5-day NIHSS) explain these apparently discrepant findings. Subgroup analysis using the patient with prominent distal HV showed that successful recanalization at 2 hours showed trend of smaller subacute ischemic lesion volumes on FLAIR than patients with poor recanalization. This may suggest that successful recanalization, independent of collateral blood flow, remains an important prognostic factor in rt-PA–treated patients.

Multivariate regression analysis demonstrated that only initial NIHSS score was a significant predictor of 5-day NIHSS score. We speculated that the clinical significance of HV to predict good clinical outcome was already reflected to low initial NIHSS score as shown in table 2. Therefore, HV grading showed no significance in predicting 5-day NIHSS score.

Good collateral blood flow in acute ischemic stroke is known to influence prognosis and infarct volume.[15-17] The pial collaterals assessed by cerebral angiography have been reported to have prognostic significance, including an association with smaller infarct volumes and good clinical outcomes in acute ischemic stroke.[15] Collateral flow can prolong tissue viability and maximize the volume of salvageable tissue. Thus the information of collateral blood flow has potential clinical applications for making treatment decisions and predicting outcome after acute ischemic stroke. Cerebral angiography is the gold standard used to evaluate collateral blood flow, but has the limitation of invasiveness, relatively long acquisition and procedural times, and low accessibility for general use in acute ischemic stroke.[18,19] Other imaging modalities like MRI, CT, and transcranial Doppler can be used to evaluate collateral blood flow.[20-22] Based on our findings and reported cases,[1,12] we suggest that distal HV in patients with MCA occlusion results from collateral blood flow originating in neighboring arterial territories, especially via pial collaterals.

A limitation of this study is the inability to establish a direct association between distal HV on FLAIR imaging and an independent measure of collateral blood flow. We hope that direct comparison of HV on FLAIR and collateral blood flow on conventional angiography may help to define the mechanism of HV in future studies. In addition, we could not establish the relationship between presence of HV and outcome, although there was a trend of lower 5-day NIHSS score in patients with prominent distal HV than without. A larger number of patients and another outcome measurement, such as 90-day modified Rankin Scale score, are needed to prove the clinical significance of HV.

In our cohort, patients with prominent distal HV presented with small acute ischemic lesions and sub-

acute infarct volumes despite proximal MCA occlusion and large perfusion lesions. If prominent distal HV on acute evaluation is predictive of prolonged tissue viability, it can be used to identify patients who will benefit from treatment beyond the current 3-hour thrombolysis time window. Further study is needed to confirm our findings and prove this hypothesis.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by K.Y. Lee, MD, PhD.

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