Prediction of Blood–Brain Barrier Disruption and Intracerebral Hemorrhagic Infarction Using Arterial Spin-Labeling Magnetic Resonance Imaging

Takeya Niibo, MD; Hajime Ohta, PhD; Shirou Miyata, PhD; Ichiro Ikushima, PhD; Kazuchika Yonenaga, MD; Hideo Takeshima, PhD

Background and Purpose—Arterial spin-labeling magnetic resonance imaging is sensitive for detecting hyperemic lesions (HLs) in patients with acute ischemic stroke. We evaluated whether HLs could predict blood–brain barrier (BBB) disruption and hemorrhagic transformation (HT) in acute ischemic stroke patients.

Methods—In a retrospective study, arterial spin-labeling was performed within 6 hours of symptom onset before revascularization treatment in 25 patients with anterior circulation large vessel occlusion on baseline magnetic resonance angiography. All patients underwent angiographic procedures intended for endovascular therapy and a noncontrast computed tomography scan immediately after treatment. BBB disruption was defined as a hyperdense lesion present on the posttreatment computed tomography scan. A subacute magnetic resonance imaging or computed tomography scan was performed during the subacute phase to assess HTs. The relationship between HLs and BBB disruption and HT was examined using the Alberta Stroke Program Early Computed Tomography Score locations in the symptomatic hemispheres.

Results—A HL was defined as a region where $C_{BBB}^{relative} \geq 1.4 \times \left( \frac{C_{BBB}^{relative, HT}}{C_{BBB}^{relative, contralateral}} \right)$. HLs, BBB disruption, and HT were found in 9, 15, and 15 patients, respectively. Compared with the patients without HLs, the patients with HLs had a higher incidence of both BBB disruption (100% versus 37.5%; $P=0.003$) and HT (100% versus 37.5%; $P=0.003$). Based on the Alberta Stroke Program Early Computed Tomography Score locations, 21 regions of interests displayed HLs. Compared with the regions of interests without HLs, the regions of interests with HLs had a higher incidence of both BBB disruption (42.8% versus 3.9%; $P<0.001$) and HT (85.7% versus 7.8%; $P<0.001$).

Conclusions—HLs detected on pretreatment arterial spin-labeling maps may enable the prediction and localization of subsequent BBB disruption and HT. (Stroke. 2017;48:117-122. DOI: 10.1161/STROKEAHA.116.013923.)

Key Words: blood–brain barrier ■ hemorrhage ■ infarction ■ ischemic stroke ■ perfusion imaging

Vessel recanalization with intravenous thrombolytic therapy improves functional outcomes in patients who present within 3 to 4.5 hours of ischemic stroke onset.1 However, the benefits of thrombolytic therapy are coupled with the potential risk of intracerebral hemorrhage, which is a life-threatening complication.2 Among the studies that have focused on patients who were eligible for endovascular recanalization therapy,3-5 a significant association between acute blood–brain barrier (BBB) disruption and subsequent hemorrhagic transformation (HT) has been shown. A central mechanism underlying HT is thought to be the reperfusion of brain tissues, where prolonged and severe hypoperfusion damages the BBB.6

Several imaging modalities have been proposed for the identification of BBB disruption, including contrast-enhanced head computed tomography (CT)7-8 and magnetic resonance imaging (MRI).9-12 MRI with postcontrast T1 parenchymal enhancement has been described as a predictor of HT after thrombolysis.10,11 Another recent MRI study used pretreatment MRI permeability images derived from perfusion source data to identify BBB disruption.12 These methodologies may permit the evaluation of BBB disruption and be helpful for predicting HT, but they require the use of exogenous contrast agents. Because of the current concerns regarding the use of ionizing radiation and morbidity after contrast-enhanced studies in patients with renal insufficiency,13 a truly noninvasive, noncontrast tomographic approach is desirable.

Arterial spin-labeling (ASL) techniques enable cerebral blood flow (CBF) measurements without the use of a contrast agent. ASL is sensitive in detecting hyperemic lesions (HLs) in several conditions related to ischemic stroke, tumor,
seizures, and Moyamoya disease. Previous ASL studies have reported that the HLs detected in ischemic stroke patients can be produced by true hyperperfusion after reperfusion or by artifacts, such as the sluggish transit of intravascular spin labels. The biophysical mechanism underlying this phenomenon is still unclear and may be related to differing effects of changes in BBB permeability. The aim of this study was to evaluate the relationship between HLs detected via pretreatment ASL MRI and BBB disruption detected via posttreatment nonenhanced CT scans in acute ischemic stroke (AIS) patients undergoing endovascular therapy. We hypothesized that if HLs were predictive of BBB disruption, HLs would have predictive power for determining future HT.

**Methods**

**Patient Selection**

Patients who presented with AIS from April 2011 to March 2014 were retrospectively selected from a prospectively collected database at Miyakonojo Medical Association Hospital. As part of our imaging protocol, all patients initially underwent multimodal MRI, including ASL scans, before treatment. The inclusion criteria were as follows: (1) acute stroke with proximal middle cerebral artery (MCA) or carotid artery T occlusion detected during baseline magnetic resonance angiography; (2) ASL imaging performed within 6 hours of symptom onset and before treatment; (3) angiographic procedure intended for endovascular therapy performed immediately after the first MRI; (4) a noncontrast CT scan performed immediately after treatment; and (5) repeat MRI performed during the subacute phase. Patients who met our eligibility criteria and who were seen within 4.5 hours of symptom onset received an intravenous (IV) injection of recombinant tissue-type plasminogen activator (r-tPA). In the absence of recanalization on IV therapy, additional intra-arterial (IA) injection of r-tPA or mechanical endovascular therapy (MET) was performed if the arterial occlusion persisted. Patients who were not eligible for IV r-tPA therapy and had a documented arterial occlusion were treated using a MET or an IA approach. Informed consent was obtained in all cases, and the protocol was approved by our local ethics committee.

**Data Acquisition**

The MRI protocol (3-T Signa; GE Medical Systems, Menlo Park, CA) included diffusion-weighted imaging (TR/TE 6000/7 ms, b=1000 s/mm² isotropic, 5-mm section thickness, and 1.5-mm interval), fluid attenuation inversion recovery, ASL–perfusion-weighted image (PWI) sequences, and magnetic resonance angiography (3D time of flight, TR/TE 30/2 ms, 1.5 mm section thickness, and 0 mm interval). ASL images were obtained with a pseudocontinuous ASL pulse sequence with the following parameters: TR/label time/post-label delay/TE 5500/1500/1525/2.5 ms, 3D background-suppressed fast-spin echo stack-of-spirals readout, 4-mm in-plane and 6-mm through-plane resolution, and 4-minute acquisition time. Vessel suppression was not performed.

Digital subtraction angiography (DSA) was performed using a dedicated biplane cerebral angiographic system (DIGITEX Safire HC; Shimadzu Corporation, Japan). Images of the bilateral internal and external carotid arteries and dominant vertebral artery injection were acquired and stored before endovascular therapy. Imaging through the entire arterial and venous phases was performed to carefully evaluate collateral vessels.

**Image and Data Analysis**

HT was assessed by subacute MRI or CT scans. HT grading was performed by consensus using the European Cooperative Acute Stroke Study classification of hemorrhagic infarct (petechial HT) or parenchymal hematoma (PH; HT with mass effect). Symptomatic HT was defined as a hemorrhage in association with an increase of ≥4 points in the National Institutes of Health Stroke Scale score. The recanalization status of the occluded artery was assessed with DSA and graded using the Thrombolysis in Cerebral Infarction score.

Successful recanalization was defined as an increase in flow of ≥2a Thrombolysis in Cerebral Infarction score grades. Disagreements were resolved by discussion until a consensus was reached.

Two stroke neurologists (T. Niibo and S. Miyata) who were blinded to the treatment and clinical data independently and separately reviewed the ASL images, DSA studies, and follow-up images. HLs were evaluated in the symptomatic hemisphere based on 2 slices that corresponded to the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) locations on baseline ASL images, as described in Figure 1. These slices were scored using a 3-point scale (0, no HL; 1, possible diagnosis of HL; and 2, HL can definitively be identified) to rate the lesion conspicuity. A HL was defined as a visually perceivable increase in the CBF on ASL maps either within or around the hyperperfused lesion. HLs had to be clearly distinct from vascular structures. Several slices immediately above and below the ASPECTS slice were summed to improve the robustness of this score.

DSA studies were evaluated using a 3-point collateral grading scale that describes the intensity of collateral flow. This scale was as follows: 0, no collaterals to the ischemic site visible; 1, collaterals to the periphery of the ischemic site visible; 2, complete irrigation of the ischemic bed via collateral flow; and 3, normal antegrade flow. This grading scale incorporates specific comparison of the locations between regions identified on DSA and tomographic images based on 2 slices that correspond to the ASPECTS locations. We chose to focus on cortical regions and basal ganglia because of the difficulties associated with visualizing collaterals on DSA and signals on ASL images in the white matter. Additionally, BBH disruption and HT were evaluated in the same ASPECTS regions of interests (ROIs). BBH disruption was defined as an intraparenchymal hyperdense area on noncontrast CT scans observed after angiographic procedures intended for endovascular therapy. These images represent the extravasation of contrast medium given during the procedure into the extracellular spaces as a result of increased permeability of the BBB.

A free-form ROI of the HL was hand-drawn on ASL maps independently by 2 raters to calculate the quantitative CBF values in HLs. The average CBF was acquired in both the HL ROI and its mirror

![Figure 1. Vascular territories on cerebral angiograms](http://stroke.ahajournals.org/)[A and B] and axial arterial spin-labeling (ASL) images (C and D). The regions on digital subtraction angiography are compared with the corresponding regions in cross-sectional images (C and D).
counterpart in the contralateral hemisphere. The relative CBF (rCBF) was defined as the ratio between the CBF values in the HL ROI and in its contralateral counterpart (\(\text{rCBF}_{\text{HL}} = \frac{\text{CBF}_{\text{HL}}}{\text{CBF}_{\text{contralateral}}}\)).

**Statistical Analysis**

The \(\kappa\) value was calculated for the individual inter-rater scores of HLs. In addition, after the dichotomization of the consensus DSA scores into the absence of collaterals (score=0) and the presence of collaterals (score=1–2), the agreement between the DSA collateral and the HL was compared using \(\kappa\) statistics. An interclass correlation coefficient was applied to evaluate the reliability between the 2 raters in terms of the rCBF values of HLs. We examined the association of HLs with BBB disruption and HT using the \(\chi^2\) test (Fisher exact test was used when the expected cell frequency was <5). The significance level was defined as \(P<0.05\) (2-sided). Statistical analysis was performed using SPSS (Statistical Package for the Social Science version 21.0; IBM Corp, Somers, NY) 18.0 for Windows (SPSS, Inc, Chicago, IL).

**Results**

A total of 25 patients (13 males and 12 females; median age 75 years; range 42–86 years) fulfilled the inclusion criteria. Demographic and clinical information on the 25 patients are provided in Table in the online-only Data Supplement. The median (interquartile range) lengths of the times from stroke onset to the first MRI scan and from the first MRI scan to groin puncture for the DSA study were 3.0 hours (2.0–5.0 hours) and 52 minutes (41–60 minutes), respectively. All patients had lesions in the symptomatic hemisphere in the baseline magnetic resonance angiography: 3 carotid artery occlusions and 22 proximal MCA occlusions. Nineteen patients were treated with the following thrombolytic therapies: IV r-tPA alone (n=4), IA therapy alone (n=9), and combined IV and IA therapy (n=6). Seventeen patients were treated with MET as follows: MET alone (n=6), MET combined with IA r-tPA (n=7), and MET combined with IV r-tPA (n=4). The median (interquartile range) time from stroke onset to the subacute MRI (n=24) was 7 days (range 7–9 days), and 1 patient who died of PH was assessed by CT scan 3 days after symptom onset. HTs were found in 15 (60%) patients: 2 had symptomatic PH, 2 had asymptomatic PH, and 11 had asymptomatic hemorrhagic infarct. The recanalization status was known for all 25 patients, 22 of whom underwent recanalization. Recanalization was not associated with HT (\(P=1.0\)).

The \(\kappa\) value was 0.80 (95% confidence interval 0.66–0.94) for the presence of a HL between the 2 raters. The interclass correlation coefficient between the rCBF values determined by the 2 raters was 0.91, which indicates excellent reliability. Based on the consensus reached by the raters, HLs judged to have scores of 1 and 2 were observed in 11 and 12 ROIs, respectively. The rCBF values were acquired in the ROIs, and the median rCBF in HLs with a score of 1 and 2 was 1.44 (range 1.22–1.60) and 1.70 (range 1.61–2.52), respectively. After a consensus was reached by the raters, we adopted a definition of a HL as an area with rCBF\(\geq\)1.4, which was used in the subsequent analyses.

HLs were found in 9 patients (Figure 2). HT (hemorrhagic infarct or PH) occurred in all 9 of these patients compared with 6 of the 16 patients without HLs (100% versus 37.5%; \(P=0.003\)). PH occurred in 4 of the 9 patients with HLs, compared with none of the 16 patients without HLs (\(P=0.010\)). BBB disruption was found in 15 patients. HT occurred in 14 of the 15 patients with BBB disruption, compared with 1 of the 10 patients without BBB disruption (93.3% versus 10%; \(P<0.001\)), and PH occurred in 4 of the 15 patients with BBB disruption, compared with none of the 10 patients without BBB disruption (26.7% versus 0%; \(P=0.125\)). Regarding the association between HLs and BBB disruption, BBB disruption occurred in all 9 patients with HLs, compared with 6 of the 16 patients without HLs (100% versus 37.5%; \(P=0.003\)).

Regarding the analysis using ASPECTS locations, 21 ROIs exhibited HLs. Infarctions occurred in 19 of the 21 ROIs with HLs (90.5%), and all HLs were located in areas of infarction. Regarding the relationship between HLs and HT, HT occurred in 18 of the 21 ROIs with HLs, compared with 12 of 154 ROIs without HLs (85.7% versus 7.8%; \(P<0.001\)).
both HLs and HT, the sites of HT systematically corresponded to the areas of HLs. Figures 3 and 4 show representative cases. Fifteen ROIs displayed BBB disruption. Regarding the relationship between BBB disruption and HT, HT was confirmed in 14 of 15 ROIs with BBB disruption, compared with 16 of 160 ROIs without BBB disruption (93.3% versus 10.0%; \( P < 0.001 \)). Regarding the relationship between HLs and BBB disruption, BBB disruption was found in 9 of 21 ROIs with HLs, compared with 6 of 154 ROIs without HLs (42.8% versus 3.9%; \( P < 0.001 \)). When both BBB disruption and HLs occurred, they were documented at the same site. Figure 4 shows a representative case with a right proximal MCA occlusion detected on the baseline magnetic resonance angiography. Note the clear depiction of HLs on the ASL images of the right basal ganglia, which also demonstrates BBB disruption in the noncontrast CT scan after endovascular therapy and hemorrhagic complications in the CT scan performed 3 days after treatment.

There was good agreement between the presence of HLs and collaterals \( (\kappa=0.67; 95\% \text{ confidence interval} 0.53–0.81) \). Figure 5 shows a representative case with a right proximal MCA occlusion. Note the clear depiction of HLs on the ASL images in the right MCA territory with delayed collateral flow in the DSA study, whereas HLs were not observed in the territory with poor collateral flow.

**Discussion**

In this series, ASL maps were sensitive in depicting HLs, with good inter-reader agreement. Our research showed that there was a broad range in the rCBF values in HLs. We adopted 1.4 as the cutoff point of rCBF and set this as the definition of a HL. Although the HLs with an rCBF value close to 1.4 may not be very conspicuous compared with the contralateral hemisphere, these lesions were accentuated by hypoperfusion around the lesion and were visually conspicuous. We assessed the HLs using the threshold-based approach, which can reduce inter-rater variability and enhance the accuracy in the detection of HLs. Based on the definition of a HL as an area with rCBF \( \geq 1.4 \), HLs were found in 36% of AIS patients. HLs were predictive of subsequent BBB disruption and HT development. In patients with HLs with subsequent BBB disruption and HT, BBB disruptions and HTs were systematically located at the same sites as HLs.

BBB disruption was associated with subsequent HT, which was in agreement with the results reported in previous studies.\(^4\) It is well known that contrast enhancement of ischemic brain tissue on noncontrast CT after angiographic procedures during endovascular therapy is caused by the leakage of contrast medium from the vessels into the extracellular space as a result of increased permeability of the BBB.\(^6\) We found that there was a significant association between BBB disruption and HLs. This finding suggests that HLs may be related to differing effects of changes in BBB permeability.

In the present study, HLs were associated with the subsequent development of HTs. Several mechanisms have been suggested to underlie HT after brain infarction, including
of labeled spins that are supplied not via proximal routes but via collateral routes to the ischemic tissues. An ASL study that examined a population of patients with Moyamoya disease reported that HLs could be produced by the sluggish transit of labeled spins arising from collateral flows.35

As suggested by previous positron emission tomography studies, hyperperfusion may indicate metabolic failures, such as a low oxygen extraction fraction, and should, therefore, be included in the concept of penumbra.24 In the present study, infarctions primarily developed in HLs, which is similar to the results reported in a previous ASL study of acute stroke.16 This finding implies that HLs are associated with a greater bioenergetic compromise in pretreatment imaging measures. We observed that without the subsequent development of infarction, BBB disruption, and HT, HLs appeared as serpiginous high ASL signals (Figure 3), reflecting the presence of stagnant intravascular labeled spins, which are termed arterial transit artifacts.14,15 Such HLs may be produced by the restoration of flow to ischemic areas via collaterals in combination with vasodilation. An ASL study of acute stroke suggested that arterial transit artifact was associated with tissue survival and improved clinical outcomes.25 Another ASL study of Moyamoya disease reported that arterial transit artifact in affected territories reflected the presence and intensity of collateral flow.35 By contrast, HLs with subsequent BBB disruption and HT corresponded primarily to anatomic structures, such as the basal ganglia and the cortical gyrus, which can be distinguished from arterial transit artifact. Considering our findings that HLs were associated with BBB disruption, indicating that HLs may be related to differing effects of changes in BBB permeability, such HLs may be caused by the leakage of labeled spins from the vessels into the extracellular space as a result of increased permeability of the BBB. If this theory is accurate, it is anticipated that HLs with BBB disruption would have higher CBF values than those without BBB disruption, which may permit the distinction between HLs with and without BBB disruption. In the present study, the median rCBF values in HL ROIs with and without BBB disruption were 1.65 (interquartile range, 1.58–1.81) and 1.45 (interquartile range, 1.45–1.67), respectively. Although there was no significant difference in the rCBF values between HL ROIs with and without BBB disruption in the present study (P=0.067), there was a tendency for the HL ROIs with BBB disruption to have higher rCBF values than those without BBB disruption.

ASL images are sensitive to the exact parameters used to acquire the image. In particular, the postlabeling delay (PLD) time, which is defined as the time required for spins to travel from the labeling plane to the imaged slice, is critical for image acquisition. The delineation of HLs can be affected by the PLD because HLs are indicative of arterial transit times that are equivalent to or longer than the PLD time.28 As the PLD increases, the recognition of HLs is improved. However, longer PLD times are associated with lower signal-to-noise ratios.27 In practice, most clinical ASL images adopt PLDs between 1.5 and 2 s.28 There is some evidence that this PLD time is highly sensitive to delay and can be helpful for identifying HLs.15,16

This study has several limitations. The assessment of BBB permeability based on the presence of intraparenchymal extravasation of contrast medium is an imperfect evaluation of a dynamic and complex mechanism.29 It was difficult abnormal permeability of the BBB, dysfunction of the vascular basal lamina, and reperfusion of infarcted brain tissue.6 A pathological study suggested that the reperfusion of ischemic tissue via collateral flow was an important factor involved in HT development.3 In the present study, there was a significant relationship between HLs and collateral flow, which suggests that HLs may reflect the reperfusion of ischemic tissue via collaterals. Based on our findings, HLs are likely to be associated with BBB permeability changes and the presence of collateral flows. Consequently, these types of pathologies that underlie HLs may indicate that HLs have predictive power for HT. HL assessment may allow for the identification of patients who are at risk for BBB disruption and HT. If further validated, the pretreatment recognition of HLs may enable timely intervention to counteract hemorrhagic complications. One promising approach seems to be blood pressure modification.

Previous ASL studies reported that HLs were linked to the luxury perfusion observed in positron emission tomography CBF imaging studies.22,23 However, the HLs observed in this study can be distinguished from luxury perfusion because HLs are delineated in ischemic territories attributable to persistent vessel occlusion. In addition, the delineation of HLs was associated with the presence of collateral flow, as judged by the DSA study performed before endovascular therapy. These findings indicate that the HLs were caused by the late arrival

**Figure 5.** Comparison between angiograms and magnetic resonance imaging (MRI) findings in an 83-year-old man with a right M1 middle cerebral artery (MCA) occlusion. Anterior projections from right internal carotid artery injections during the (A) early and (B) late arterial phases demonstrate delayed collateral flows in the MCA territory, which correspond to the MCA regions on Alberta Stroke Program Early Computed Tomography Score (ASPECTS). Arterial spin-labeling (ASL; C) images demonstrate hyperemic lesions (HLs) in the M5–M6 regions, in which rich collateral flow was present on angiograms; however, no HLs were present in the M1–M3 regions (D), in which poor collateral flow was present on angiograms. These HLs reflect flow arriving via collateral routes.

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to determine whether blood was present within the contrast medium because blood may be masked by the more dense contrast material, and we did not assess the disappearance of contrast medium in follow-up CT scans. Additionally, the evaluation of BBB disruption was performed in post-therapeutic CT scan. Evaluation of BBB disruption was performed in post-therapeutic contrast medium in follow-up CT scans. Additionally, the evaluation of BBB disruption should be taken into account in future studies. The presence of collaterals could have been underestimated if recanalization occurred between a baseline MRI and a DSA study. However, our study showed that an association exists between HLs and the DSA collateral score.

In conclusion, our results indicated that HLs detected on pretreatment ASL maps were associated with subsequent BBB disruption and HT in AIS patients. The identification of HLs may allow for the prediction and localization of BBB disruption and HT in AIS patients eligible for endovascular therapy.

Disclosures

None.

References

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<td>Proximal MCA</td>
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<td>15</td>
<td>MET alone</td>
<td>+</td>
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<td>PH</td>
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</table>

BBB, blood-brain barrier; HI, hemorrhagic infarction; HL, hyperemic lesion; MCA, middle cerebral artery; MET, mechanical endovascular therapy; PH, parenchymal hematoma; rt-PA, recombinant tissue plasminogen activator.