Prediction of Early Reperfusion From Repeated Arterial Spin Labeling Perfusion Magnetic Resonance Imaging During Intravenous Thrombolysis

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Background and Purpose—There are few in vivo data on the pathophysiology of reperfusion during systemic thrombolysis. We monitored the time course of cerebral perfusion changes in patients during thrombolysis with repeated arterial spin labeling perfusion magnetic resonance imaging.

Methods—Ten patients with proximal arterial occlusion within 4.5 hours after symptom onset were prospectively enrolled. All patients received intravenous thrombolysis during the magnetic resonance imaging examination. Repeated arterial spin labeling perfusion images were acquired during the 60-minute therapy and at follow-up after 24 to 72 hours. Clinical data, magnetic resonance imaging features, and cerebral perfusion changes were analyzed.

Results—Before thrombolysis, arterial spin labeling hypoperfusion and fluid-attenuation inversion recovery vascular hyperintensity in the territory of the occluded arteries were observed in all patients. In 5 patients, extensive arterial transit artifacts (ATA) developed in the hypoperfused area. The ATA corresponded with fluid-attenuation inversion recovery vascular hyperintensities. All 5 patients who developed extensive ATA in the hypoperfused area had complete reperfusion after thrombolysis, whereas the 5 without extensive ATA showed no or only partial reperfusion (P<0.01). The development of ATA preceded the normalization of tissue perfusion.

Conclusions—The development of ATA during thrombolysis is associated with early reperfusion after thrombolysis. Arterial spin labeling assessment during intravenous thrombolysis has the potential to guide subsequent therapeutic strategies in patients with acute stroke. (Stroke. 2016;47:247-250. DOI: 10.1161/STROKEAHA.115.011482.)

Key Words: magnetic resonance imaging ■ perfusion imaging ■ reperfusion ■ spin labels ■ stroke

The response to systemic thrombolysis varies across individuals, and there are few in vivo data on the sequence of events during thrombolysis. Therefore, it is difficult to estimate early on who will benefit from thrombolysis. Furthermore, although recent clinical trials have demonstrated the efficacy of mechanical thrombectomy in acute stroke,1 it is not yet established how to select patients for additional mechanical thrombectomy. Arterial spin labeling (ASL) is a noninvasive magnetic resonance imaging (MRI) method for measuring cerebral perfusion without contrast agent or radiation exposure. Thus, it can be performed repeatedly in a short period of time. Using repeated ASL perfusion imaging, we examined the dynamic perfusion process of revascularization during and early after intravenous thrombolysis. In addition, we explored whether early reperfusion can be predicted by perfusion patterns of ASL images during thrombolysis.

Materials and Methods

This study was performed at UniversitätsMedizin Mannheim, Germany. The local ethics committee approved the study. All subjects gave their written informed consent. Between February 2011 and January 2013, 27 patients with acute stroke eligible for systemic thrombolysis were enrolled. The study protocol was described previously.2 In brief, the patients were transferred into the MRI scanner after clinical examination and prepared for systemic thrombolysis by applying an MR-compatible monitoring and infusion system. In patients eligible for systemic thrombolysis, the therapy was carried out inside the MRI scanner. During the 60-minute infusion, repeated ASL perfusion images using Q2TIPS-FAIR with 3D-GRASE readout3 were acquired at 5-minute intervals (acquisition time, 1 minute 36 s). Follow-up MRI scans were performed at 60 minutes and at 24 to 72 hours after the initiation of thrombolysis. All ASL images were analyzed using 3DSRT software (Fujifilm RI Pharma, Japan) as described previously4 (details are available in the Methods section in the online-only Data Supplement). Significance was assessed by Fisher exact test.

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Of the 27 patients enrolled, 10 patients with proximal arterial occlusion were analyzed. Flowchart is given in Figure I in the online-only Data Supplement. The Table shows the patients’ characteristics. Baseline MRI revealed fluid-attenuation inversion recovery vascular hyperintensities in the distal portion of the occluded arteries and ASL hypoperfusion in the corresponding territory in all patients.

Two patients showed a reperfusion during the 60-minute infusion (cases 1 and 2). Figures 1A, 1B, 2A, and 2B demonstrate cerebral perfusion changes during thrombolysis. At the beginning of thrombolysis, a marked tissue hypoperfusion was observed in the territory of occluded arteries. After ≈30 minutes, arterial transit artifacts (ATA) emerged in the hypoperfused area. ATA corresponded well with baseline fluid-attenuation inversion recovery vascular hyperintensities (Figures 1C and 2C) and extended gradually from the proximal to the distal portions of the corresponding fluid-attenuation inversion recovery vascular hyperintensities and then disappeared before reperfusion. Normalization of tissue perfusion was observed after the disappearance of ATA (Figures 1A and 2A). The follow-up MR angiography just after thrombolysis showed complete recanalization (Figures 1D and 2D). These 2 patients had neurological recovery early after thrombolysis.

**Results**

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**Table. Characteristics of Patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Occlusion Site</th>
<th>NIHSS, Pre/Post</th>
<th>ATA</th>
<th>AOL</th>
<th>TIMI</th>
<th>IC Ratio, Pre/Post*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>76</td>
<td>F</td>
<td>Lt-MCA-M1</td>
<td>9/6</td>
<td>Extensive</td>
<td>III</td>
<td>3</td>
<td>0.66/1.01</td>
</tr>
<tr>
<td>Case 2</td>
<td>46</td>
<td>M</td>
<td>Rt-ACA-A2</td>
<td>2/0</td>
<td>Extensive</td>
<td>III</td>
<td>3</td>
<td>0.68/0.98</td>
</tr>
<tr>
<td>Case 3</td>
<td>62</td>
<td>M</td>
<td>Lt-MCA-M2</td>
<td>4/0</td>
<td>Extensive</td>
<td>III</td>
<td>3</td>
<td>0.79/0.95</td>
</tr>
<tr>
<td>Case 4</td>
<td>89</td>
<td>F</td>
<td>Lt-MCA-M1</td>
<td>4/9</td>
<td>Extensive</td>
<td>II</td>
<td>3</td>
<td>0.84/1.19</td>
</tr>
<tr>
<td>Case 5</td>
<td>75</td>
<td>F</td>
<td>Rt-MCA-M2</td>
<td>3/1</td>
<td>Extensive</td>
<td>III</td>
<td>3</td>
<td>0.80/0.97</td>
</tr>
<tr>
<td>Case 6</td>
<td>73</td>
<td>M</td>
<td>Rt-ICA prox.</td>
<td>15/death</td>
<td>Partial (distal)</td>
<td>0</td>
<td>0</td>
<td>0.74/—</td>
</tr>
<tr>
<td>Case 7</td>
<td>70</td>
<td>M</td>
<td>Rt-PCA-P1</td>
<td>5/5</td>
<td>None</td>
<td>0</td>
<td>0</td>
<td>0.86/0.89</td>
</tr>
<tr>
<td>Case 8</td>
<td>78</td>
<td>M</td>
<td>Lt-MCA-M2</td>
<td>8/2</td>
<td>Partial (proximal)</td>
<td>0</td>
<td>0</td>
<td>0.75/0.76</td>
</tr>
<tr>
<td>Case 9</td>
<td>90</td>
<td>F</td>
<td>Lt-MCA-M1</td>
<td>11/5</td>
<td>None</td>
<td>III</td>
<td>2</td>
<td>0.58/0.82</td>
</tr>
<tr>
<td>Case 10</td>
<td>83</td>
<td>M</td>
<td>Rt-MCA-M2</td>
<td>10/4</td>
<td>Partial (proximal)</td>
<td>II</td>
<td>2</td>
<td>0.78/0.83</td>
</tr>
</tbody>
</table>

ATA indicates arterial transit; AOL, arterial occlusive lesion recanalization score; F, female; IC ratio, ipsilateral-to-contralateral cerebral blood flow ratio; Lt-MCA, left middle cerebral artery; M, male; NIHSS, National Institutes of Health Stroke Scale; Rt-ACA, right anterior cerebral artery; Rt-ICA, right internal carotid artery; Rt-MCA, right middle cerebral artery; Rt-PCA, posterior cerebral artery; and TIMI, thrombolysis in myocardial infarction reperfusion score.

*24–72 h after thrombolysis.

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**Figure 1.** Repeated arterial spin labeling (ASL) perfusion images during systemic thrombolysis (case 1). A, ASL perfusion images during thrombolysis. Arrow heads indicate arterial transit artifacts. B, Relative cerebral blood flow changes. C, Positional relationship between fluid-attenuation inversion recovery vascular hyperintensities and arterial transit artifacts. D, Magnetic resonance angiography before and just after thrombolysis. Arrows indicate the occluded arteries. Lt-MCA indicates left middle cerebral artery; Rt-MCA, right middle cerebral artery; and rCBF, regional cerebral blood flow.
and there was no expansion of the infarct into the hypoperfused area.

Other 3 patients (cases 3–5) showed regional tissue hypoperfusion with extensive ATA throughout the period of infusion (Figure II in the online-only Data Supplement). They exhibited no reperfusion during thrombolysis; however, complete reperfusion and recanalization was observed at 24 to 72 hours after thrombolysis. Further 5 patients (cases 6–10) showed regional tissue hypoperfusion with no or only partial ATA during thrombolysis. They showed no or only partial reperfusion in the follow-up MRI examinations. Taken together, 5 patients with extensive ATA had complete reperfusion after thrombolysis, whereas the other 5 with no or partial ATA had no or only partial reperfusion ($P < 0.01$).

**Discussion**

Our study demonstrates for the first time the dynamic process of reperfusion during thrombolysis. The presence of ATA seems to be a useful marker of the onset of the reperfusion process.

The presence of ATA suggests delayed arrival of tagged blood to the affected vascular tissue. It has been reported that ATA was observed proximal or distal to the occluded artery in patients with acute stroke and moyamoya disease and may represent the presence of leptomeningeal collateral flow or anterograde residual flow that could augment recanalization by delivering a thrombolytic agent to the distal end of the clot. In this study, 2 patients showed a transient ATA development before reperfusion. This phenomenon indicates incomplete microcirculatory reperfusion before complete tissue reperfusion. After opening of the occluded artery with thrombolysis, clots could move downstream to obstruct distal arterial branches and capillaries. This microvascular obstruction model can explain the slow extension of ATA and subsequent tissue reperfusion.

Our study has limitations. First, we could not analyze the associations between ASL perfusion patterns and clinical outcome because of the small sample size. Second, because we used the same inversion time in the pulsed ASL sequence for all patients, perfusion measurements might be biased toward arteries and arterioles in patients with reduced cardiac output. In addition, ATA also affected the perfusion measurements. Therefore, we did not perform a quantitative cerebral blood flow analysis and focused on the individual cerebral perfusion changes during and after thrombolysis.

In conclusion, our data suggest that ASL imaging is a promising strategy for early prediction of response to systemic thrombolysis. ATA could be a good marker of early recanalization by intravenous thrombolysis. ASL imaging during intravenous thrombolysis might be useful for the selection of patients for additional mechanical thrombectomy.

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**Disclosures**

Dr Kern received speaker’s honoraria and travel funding from Boehringer Ingelheim. The other authors report no conflicts.

**References**


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Supplemental Methods

Subjects
Between February 2011 and January 2013, 27 patients with acute neurological symptoms suggestive of hemispheric stroke within 4.5 hours after symptom onset, eligible for systemic thrombolytic therapy and without contraindication to perform an MRI were enrolled. Supplemental Figure I shows the flow diagram of the patient recruitment and selection.

![Supplemental Figure I](image)

Patients were enrolled if they fulfilled the following criteria:
- Acute neurological symptoms suggestive of hemispheric stroke
- Within 4.5 h after symptom onset
- No contraindications for rt-PA and MRI
- Ability to give informed consent

Inclusion and exclusion criteria for this study.

MRI protocol
All MRI investigations were performed on a 3.0-Tesla MRI scanner (MAGNETOM Trio, Siemens, Erlangen, Germany) using a 16-channel head coil. Baseline MRI included T2-weighted sequence (TR/TE, 6000/93 ms), diffusion-weighted sequence (TR/TE, 5700/134 ms; b = 0, 500, 1000 s/mm²), fluid-attenuated inversion recovery (FLAIR) sequence (TR/TE/TI, 9000/93/2500 ms), T2*-weighted sequence (TR/TE, 620/20 ms), and time-of-flight MR angiography (2 slabs; TR/TE, 20/3.59 ms; flip-angle, 18°; FOV, 200 mm; matrix, 331 × 384; 0.75 mm slice thickness) in this order. All axial MRI examinations were performed with a 5-mm slice thickness and a 10% distance factor. The total acquisition time approximated 15 minutes. During the 60-minute rt-PA infusion, repeated pulsed ASL perfusion weighted images were acquired at 5 minute intervals. These ASL measurements were obtained using saturation pulses (second version of a system for the quantitative imaging of perfusion with thin-slice TI1 periodic saturation, Q2TIPS), flow-sensitive alternating inversion recovery (FAIR) labeling scheme, background tissue signal suppression based on water suppression enhanced through T1 effects (WET), and single-shot three-dimensional gradient and spin echo (3D-GRASE) readout (TR/TE, 3000/13.2 ms; TI, 2300ms; 36 partitions; voxel dimensions, 3 × 3 × 3 mm3; matrix, 64 × 48; 4 averages; acquisition time, 1 min 36 sec). Follow-up MRI scans were performed at 60 min and 24 – 72 hours after the initiation of thrombolysis for all patients, except for one with ICA occlusion (Case 6) requiring mechanical ventilation after thrombolysis who underwent follow-up CTs and ultrasound examinations.

Post processing and data analysis
All images were brain extracted prior to registration using FSL's Brain Extraction Tool (BET). The non-labelled (control) ASL images before subtraction were registered to the baseline FLAIR images of each patient using a robust affine registration with 12 degrees of freedom on NiftyReg software (University College London, UK). The calculated transformation matrix was then applied to the corresponding ASL subtraction perfusion images. As a result of this processing, repeated ASL perfusion images were corrected for head movements, and shared an identical reference space with the baseline FLAIR images. For relative cerebral blood flow (CBF) analysis, these ASL images were further normalized into the Montreal Neurological Institute (MNI) space via registration of the FLAIR images to the MNI template, and analysed using fully automated 3-dimensional stereotactic region-of-interest (ROI) template software (3DSRT; Fujifilm RI Pharma, Tokyo, Japan), based on the previously described method. The ROIs of 3DSRT were categorized into 12 segments in each hemisphere according to the vascular territories: callosomarginal, pericallosal, precentral, central, parietal, angular, temporal, basal ganglia, posterior cerebral, thalamus, hippocampus, and cerebellum. We compared the relative CBF of the affected segments to the contralateral
segments and calculated the ipsilateral-to-contralateral CBF ratio (IC ratio) for each patient.

The site of artery occlusion was determined using the baseline MR angiography. FLAIR vascular hyperintensity was identified as tubular hyperintense signal in FLAIR relative to gray matter corresponding to an arterial course. Arterial transit artifact was identified as tubular hyperintense signal on ASL perfusion images. Recanalization was assessed on the follow-up MR angiography according to the primary arterial occlusive lesion (AOL) recanalization criteria. Reperfusion was visually assessed on the follow-up MR angiography and follow-up ASL images according to the Thrombolysis in Myocardial Infarction (TIMI) reperfusion criteria by reference to the ipsilateral-to-contralateral CBF ratio. TIMI 3 was defined as complete reperfusion (IC ratio ≥0.90). TIMI 1 and 2 were defined as partial reperfusion (IC ratio <0.90).

Two stroke-neurologists (S.O. and M.G.) separately evaluated MRI images of each patient blinded to the clinical data. If arterial transit artifacts covered more than 50% of the region of FLAIR vascular hyperintensities, they were classified as extensive arterial transit artifacts. If they covered ≤50%, they were classified as partial arterial transit artifacts. There was excellent agreement between the two observers. Discrepancies were resolved by consensus.

Supplemental References


Supplementary Figure II. Repeated ASL perfusion images during and after thrombolysis (Case 3 - 6). Follow-up MR angiographies were acquired at 24 - 72 hours after thrombolysis. White arrows indicate the occluded arteries. White arrow heads indicate FLAIR vascular hyperintensities and the corresponding arterial transit artifacts. (continued)
Supplementary Figure II. (continued) Repeated ASL perfusion images during and after systemic thrombolysis (Case 7 - 10). Follow-up MR angiographies were acquired at 24 - 72 hours after thrombolysis. White arrows indicate the occluded arteries. White arrow heads indicate FLAIR vascular hyperintensities and the corresponding arterial transit artifacts.
静脈内血栓溶解療法中の連続動脈スピン標識灌流MRIによる早期再灌流の予測

Prediction of Early Reperfusion From Repeated Arterial Spin Labeling Perfusion Magnetic Resonance Imaging During Intravenous Thrombolysis

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Abstract

背景および目的：全身性血栓溶解療法中の再灌流の病態生理に関するin vivoデータは少ない。本研究では、血栓溶解療法中の患者における脳灌流の経時的変化を連続動脈スピン標識(ASL)灌流MRIにより観察した。

方法：発症後4.5時間以内の近位動脈閉塞症患者10例を前向きに登録した。全患者でMRI検査中に脳静脈内血栓溶解療法を行った。60分間の治療中に24〜72時間後の経過観察時にASL灌流MRIを連続的に撮像した。臨床データ、MRI特性、脳灌流の変化を解析した。

結果：血栓溶解療法を行う前では、全例の閉塞動脈領域でASLによる低灌流およびFLAIR画像における血管高信号が認められた。5例では低灌流領域に広範なarterial transit artifact(ATA)が出現した。ATAはFLAIR画像における血管高信号と一致した。低灌流領域に広範なATAが出現した5例はすべて血栓溶解療法後に完全再灌流のものに対し、広範なATAが出現しなかった5例では再灌流が認められず、部分再灌流が認められるにすぎなかった(\(P < 0.01\))。ATAは組織灌流が正常化する前に出現した。

結論：血栓溶解療法中のATAの出現は、血栓溶解療法後の早期の再灌流と関連する。静脈内血栓溶解療法中のASLによる評価は、急性脳卒中患者におけるその後の治療戦略の指針となる可能性がある。

図1 全身血栓溶解療法中の連続動脈スピン標識(ASL)による灌流MRI（症例1）。
A：血栓溶解療法中のASL灌流画像、矢頭はarterial transit artifact(ATA)を示す。
B：脳灌流の相対的変化。
C：FLAIR画像における血管高信号とATAとの位置関係。
D：血栓溶解療法前の頭部動脈虚血領域（MRA）、矢印は閉塞動脈を示す。

Lt-MCA：左中大脳動脈，Rt-MCA：右中大脳動脈。

rcBF：局所脳灌流。