Thrombus Length Estimation on Delayed Gadolinium–Enhanced T1

Shenqiang Yan, MD; Qingmeng Chen, MM; Mengjun Xu, MD; Jianzhong Sun, MB; David S. Liebeskind, MD; Min Lou, MD, PhD

Background and Purpose—Previous studies revealed a close relationship between thrombus length and recanalization rate after intravenous thrombolysis (IVT). As a novel approach, we prospectively adjusted the order of sequence acquisition to obtain delayed gadolinium–enhanced T1 (dGE-T1) and thereby assess thrombus length on dGE-T1 to evaluate its predictive value for recanalization after IVT.

Methods—We reviewed prospectively collected clinical and imaging data from acute ischemic stroke patients with middle cerebral artery occlusion who underwent multimodal magnetic resonance imaging before and 24 hours after IVT. Perfusion-weighted imaging was performed followed by conventional T1. We measured thrombus length on dGE-T1 and examined its association with middle cerebral artery recanalization.

Results—Of the included 74 patients, the median age was 66 years and 28 (37.8%) were women. Thrombus length was 8.18±4.56 mm on dGE-T1, which was an acceptable predictor for no recanalization (odds ratio, 1.196; 95% confidence interval, 1.015–1.409; P=0.033), with a receiver–operator characteristic of 0.732 (95% confidence interval, 0.619–0.845; P=0.001). The optimal cut-off point was identified at 6.77 mm, which yielded a sensitivity of 77.8%, a specificity of 57.9%, and an odds ratio of 4.81 (95% confidence interval, 1.742–13.292; P=0.002). Moreover, no one achieved recanalization after IVT when length of thrombus exceeded 14 mm on dGE-T1.

Conclusions—The dGE-T1, obtained by simply adjusting scanning order in multimodal magnetic resonance imaging protocol, is a useful tool for thrombus length estimation and middle cerebral artery recanalization prediction after IVT. (Stroke. 2016;47:756-761. DOI: 10.1161/STROKEAHA.115.011401.)

Key Words: artifact • magnetic resonance imaging • middle cerebral artery • stroke • thrombolytic therapy

See related article, p 643.

arterial recanalization is extremely important in acute ischemic stroke because of middle cerebral artery (MCA) occlusion, where the natural history carries a poor prognosis. Target clot burden, measured by thrombus length, has been shown to be an important determinant of recanalization in intravenous thrombolysis (IVT). Our previous study has already demonstrated that the morphology of susceptibility vessel sign (SVS) on susceptibility-weighted imaging (SWI) correlates well with time-of-flight magnetic resonance angiography (TOF-MRA), first-pass GE-MRA, and digital subtraction angiography. However, in clinical practice, ≥26% to 73% patients with MCA occlusion will not present the sign of SVS because the clot composition. Moreover, the sign of SVS usually overestimate the true length and volume of clot because of the blooming artifact, which may make it difficult to accurately measure the clot burden.

With multimodal magnetic resonance imaging (MRI), we observed that conventional T1, which is obtained after perfusion-weighted image (PWI; ≈90 s) can generate delayed gadolinium–enhanced T1 (dGE-T1), which can visualize the distal vessels beyond the clot within the artery. Using coregistration of dGE-T1 with TOF-MRA, which only displays the arteries devoid of occlusion, it is thus possible to estimate the length of thrombus. This method will be manageable without adding extra scan time and contrast agent, when PWI/diffusion-weighted imaging (DWI) mismatch profile was used to guide IVT for extending the time window (≤6 hours). Therefore, in this study, we assessed for the first time the thrombus length on dGE-T1 in patients with MCA occlusion by adjusting the scanning order of conventional T1 after PWI, and then evaluated its predictive value for MCA recanalization after IVT, to find a new measurement of the clot burden, which can be effectively used in all patients with MCA occlusion.
Subjects and Methods

Study Subjects
We retrospectively reviewed our prospectively collected database for consecutive patients with acute ischemic stroke received thrombolytic therapy between June 2009 and March 2015. We then enrolled patients who (1) had a diagnosis of acute ischemic stroke confirmed by DWI; (2) received IVT within 6 hours from symptom onset; (3) underwent multimodal MRI in the following sequences: DWI, SWI, TOF-MRA, fluid-attenuated inversion recovery, PWI and then conventional T1; (4) MCA occlusion without involvement of internal carotid artery demonstrated on baseline TOF-MRA; and (5) underwent follow-up TOF-MRA 24 hours after IVT. The mismatch profile was defined as a PWI lesion that was ≥10 mL and ≥120% of the DWI lesion.9,10 We excluded patients who were treated with combined endovascular and IVT, and whose image quality was poor because of motion artifacts.

We retrieved demographic, clinical, laboratory, and radiological data including age, sex; comorbid conditions such as history of hypertension, diabetes mellitus, coronary heart disease, and atrial fibrillation; previous antplatelet use; time interval from stroke onset to treatment; National Institutes of Health Stroke Scale (NIHSS) score, serum platelet and international normalized ratio level before IVT; baseline infarct volume, occlusion site, recanalization 24 hours after IVT, and modified Rankin Scale (mRS) score after 3 months.

MRI Parameters
All subjects underwent MRI on a 3.0T system (Signa Excite HD, General Electric Medical System, Milwaukee, WI) equipped with an 8 channel–phased array head coil. DWI sequence was used to measure the infarct volume (repetition time [TR]=4000 ms; echo time [TE]=69.3 ms; b value=1000 s/mm²; slice thickness=5.0 mm; and interslice gap=1.0 mm). SWI used 11 equally spaced echoes: TE=4.5 ms (first echo); interecho spacing=4.5 ms; TR=58 ms; flip angle=20°; and slice thickness=2.0 mm with no gap between slices. TOF-MRA consisted of 3 slabs with TR=20 ms; TE=3.2 ms; flip angle=15°; and slice thickness=5.0 mm. PWIs were obtained using the standard bolus passage of contrast method by injecting gadolinium (0.1 mmol/kg dose via power injector). PWI parameters were TR=1500 ms; TE=30 ms; and slice thickness=5.0 mm. Conventional T1 parameters were TR=1900 ms; TE=25 ms; and slice thickness=5.0 mm.

Imaging Analysis
Acute arterial occlusion was determined by the invisibility of the artery on MRA with corresponding symptoms compatible with the involved artery. Occluded arteries on initial MRA were identified as M1 occlusion or M2 occlusion in this study. Two neurologists, blinded to patients’ clinical information, independently assessed the thrombus length on dGE-T1 and SWI, respectively. SVS was defined as presence of hypointensity in MCA with a blooming artifact, that is, the diameter exceeded the hypointense signal in the homologous contralateral vessel diameter on GRE or SWI scans.11,12 Distal vessels beyond the clot can be visible on dGE-T1 clearly, whereas TOF-MRA only displayed the arteries without occlusions (Figure 1 in the online-only Data Supplement), so that we coregistered the source images of TOF-MRA and dGE-T1 with MRIcon (Chris Rorden, University of South Carolina, Columbia, SC) and then manually measured the distance between proximal and distal end of MCA occlusion as thrombus length by using a straight line (Image J, National Institutes of Health, Bethesda, MD; Figure 1). When the proximal and distal end of the thrombus were not shown on a single slice, maximum intensity projection images (20–30 mm thick) was used. In case of continuous M1 and M2 segment occlusions, the length was summed. When thrombus branched into ≥2 M2 vessels, the longest thrombus length was measured.

Evaluation of Outcome
We used the Arterial Occlusive Lesion scale (grade 0: complete occlusion of the target artery; grade 1: incomplete occlusion or partial local recanalization at the target artery with no distal flow; grade 2: incomplete occlusion or partial local recanalization at the target artery with any distal flow; and grade 3: complete recanalization and restoration of the target artery with any distal flow) to define recanalization or no recanalization based on the presence (grade 2 or 3) or absence (grade 0 or 1) of any downstream flow.13 Clinical outcome at 3 months was assessed with mRS and dichotomized into good outcome (0–2) and poor outcome (3–6).

Reliability and Validity of the Radiological Data
The 2 investigators who jointly evaluated the MRI findings were blinded to the patients’ clinical data. A single trained observer (S.Y.) measured thrombus length of all patients twice, at an interval of 3 months apart. Another observer (Q.C.) independently made the same evaluation.

Statistical Analysis
Fisher exact test was used to compare the dichotomous variables between groups, whereas independent samples 2-tailed t test or Mann–Whitney U test were used for the continuous variables, as appropriate. Variables with a P value of <0.1 in univariate analyses were included in the binary logistic regression model. Pearson or Spearman correlation analysis was used depending on the normality of the distribution. Receiver operating characteristics curve analysis was used to determine predictive value. Statistical significance was set at a P value of <0.05. All statistical analysis was performed with SPSS package.

Results
The interobserver and intraobserver reliabilities about the measurements of thrombus length on dGE-T1 were excellent (intraclass correlation coefficients=0.977 and 0.941, respectively). A total of 74 remaining patients were included for the final analysis. Demographic, clinical, and laboratory data were not different between included and excluded subjects. Of the included patients, the median age was 66 years (mean, 66±13 years; range, 43–94 years) and 28 (37.8%) were women. Median baseline NIHSS score was 13 (interquartile range, 6–17). Mean time from onset to treatment was 240±85 minutes.

Follow-up MRA 24 hours after IVT revealed recanalization in 38 (51.4%) patients and no recanalization in 36 (48.6%).
SVS sign on SWI existed in 78.4% (58 of 74) of the included patients. The mean length of SVS was 12.62±7.59 mm (range, 3.83–47.23 mm). Thrombus length on dGE-T1 was 8.18±4.56 mm (range, 1.63–30.26 mm). Maximum intensity projection images were used in 21 subjects, mainly because their thrombus length was longer than those measured on a single slice (12.50±5.15 mm versus 6.47±2.91 mm; \( P < 0.001 \)). The thrombus length measured by SVS was longer than that measured on dGE-T1, with the overestimation ratio ranging from 1.03 to 3.47. However, these 2 measurements had a good association (Pearson \( r = 0.805; P < 0.001 \)) in the 58 patients with SVS.

Table 1 shows the characteristics of patients with and without recanalization for comparison. Patients with recanalization had a lower rate of M1 occlusion and poor outcome. Thrombus length on dGE-T1 was significantly longer in patients without recanalization in univariate analysis. Moreover, age was marginally associated with recanalization. Thus, age, M1 occlusion, and thrombus length were included in the binary logistic regression model. Both thrombus length and M1 occlusion were independent predictors for no recanalization of MCA (Table 2). Receiver operating characteristics analysis revealed acceptable predictive value of thrombus length for recanalization (area under the curve, 0.732; 95% confidence interval, 0.619–0.845; \( P = 0.001 \)). The cut-off point of thrombus length measured on dGE-T1 for no recanalization was 7.71 mm, and this yielded a sensitivity of 59.5% and a specificity of 75.0%, and an odds ratio of 4.41 (95% confidence interval: 1.607–12.112; \( P = 0.004 \)). The relationship between thrombus lengths on dGE-T1 and probability of recanalization and good outcome were shown in Figure 2.

Discussion

In this study, we found that ≈20% patients of acute ischemic stroke with MCA occlusion will not present SVS sign on

Table 1. Univariate Comparison Between Patients With and Without Recanalization

<table>
<thead>
<tr>
<th>Variable</th>
<th>MCA Recanalization</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>No (n=36)</td>
<td>Yes (n=38)</td>
</tr>
<tr>
<td>Female</td>
<td>63.2±13.8</td>
<td>68.9±12.1</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (63.9%)</td>
<td>27 (71.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (8.3%)</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>3 (8.3%)</td>
<td>6 (15.8%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16 (44.4%)</td>
<td>22 (57.9%)</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td>14 (8–17)</td>
<td>11 (6–16)</td>
</tr>
<tr>
<td>Onset to treatment, min</td>
<td>242.3±101.3</td>
<td>236.8±66.7</td>
</tr>
<tr>
<td>Previous antiplatelet use</td>
<td>6 (16.7%)</td>
<td>5 (13.2%)</td>
</tr>
<tr>
<td>Platelet, 10^9/L</td>
<td>192.4±70.0</td>
<td>173.5±52.5</td>
</tr>
<tr>
<td>INR</td>
<td>1.030 (0.990–1.080)</td>
<td>1.035 (1.005–1.090)</td>
</tr>
<tr>
<td>Radiological data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline infarct volume, mL</td>
<td>10.8 (3.9–55.1)</td>
<td>7.5 (2.4–33.5)</td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>32 (88.9%)</td>
<td>17 (44.7%)</td>
</tr>
<tr>
<td>Thrombus length, mm</td>
<td>9.99±5.20</td>
<td>6.47±3.06</td>
</tr>
<tr>
<td>Poor clinical outcome, mRS≥3</td>
<td>28 (77.8%)</td>
<td>14 (36.8%)</td>
</tr>
</tbody>
</table>

INR indicates international normalized ratio; MCA, middle cerebral artery; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Mann–Whitney U test.

Table 2. Multivariate Regression Analysis of Independent Predictors for No Recanalization in the Patients With MCA Occlusions

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.994</td>
<td>0.952–1.037</td>
<td>0.773</td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>6.555</td>
<td>1.828–23.501</td>
<td>0.004</td>
</tr>
<tr>
<td>Thrombus length, mm</td>
<td>1.196</td>
<td>1.015–1.409</td>
<td>0.033</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI indicates confidence interval; MCA, middle cerebral artery; and OR, odds ratio.

Patients with poor outcome were older, had higher frequency of M1 occlusion, higher baseline NIHSS score, larger DWI volume, and longer thrombus length than those with good outcome. The thrombus length on dGE-T1 was an significant independent predictor for poor outcome (odds ratio, 1.253; 95% confidence interval, 1.026–1.529; \( P = 0.027 \)) after adjusting for baseline NIHSS score, age, baseline DWI volume, and M1 occlusion in the binary logistic regression model (Table 3). The cut-off point of thrombus length measured on dGE-T1 for poor outcome was 7.71 mm, and this yielded a sensitivity of 59.5% and a specificity of 75.0%, and an odds ratio of 4.41 (95% confidence interval: 1.607–12.112; \( P = 0.004 \)). The relationship between thrombus lengths on dGE-T1 and probability of recanalization and good outcome were shown in Figure 2.
We thus established a novel approach for estimation of thrombus length with dGE-T1, which can be obtained in all patients of MCA occlusion by changing the scanning order of conventional T1 after PWI. We further demonstrated that this measurement of thrombus length could independently predict MCA recanalization and clinical outcome after IVT.

The length of large vessel occlusion is considered a major influencing factor for the prognosis after IVT in patients with acute ischemic stroke.2,3 On nonenhanced computed tomography (CT), it was found that IVT had nearly no potential to recanalize the occluded vessels if the length of thrombus exceeds 8 mm, which was depicted as hyperdense middle cerebral artery sign.3 The hyperdense middle cerebral artery sign may be absent in ≈50% to 70% patients with acute MCA occlusion using standard 3-mm nonenhanced CT slice thicknesses,14,15 whereas the sensitivity would become higher by using thin slice nonenhanced CT reconstructions.3 However, Rohan et al’s2 study did not confirm the specificity of a threshold of 8 mm for recanalization,3 which may be because of the different thrombus constituents with the presence of hyperdense middle cerebral artery sign.15 Recently, Mortimer et al16 also found that delayed contrast enhanced CT can reliably be used to estimate thrombus length, which indicates that the use of contrast may improve the visualization of thrombus.

Obviously, delineating the distal end of thrombus is the key to accurately measure the length of thrombus. Considering that retrograde flow from the patent pial collaterals is the dominant source to reach the distal end of occlusion, we prefer to use the images that can fully display the retrograde flow of contrast, to determine the distal end. Usually, the maximal enhancement in a nonoccluded artery was observed around 30 s after the administration of contrast, with a plateau at around 80 s to 120 s after contrast injection.17 As we can see, a delayed phase of gadolinium-enhanced T1, which occurred when conventional T1 was obtained after PWI (usually taking 90 s after contrast injection), allows several passes of contrast, which can even visualize the slow retrograde flow of contrast, making the face of distal clot fully delineated.

This evaluation of thrombus length on dGE-T1 in our study was confirmed to be comparable with SVS on SWI. Although SVS on SWI is limited in the clinical practice because of its blooming effect and invisibility in ≈26% to 73% of patients, the application of thrombus length on dGE-T1 will be wide in all patients with MCA occlusion. It is worthwhile to note that, in contrast to SWI, dGE-T1 is an indirect technique to visualize the thrombus length. Because of partial volume effects, each bright T1-weighted structure will simulate an open vessel, even in the close surrounding area of the thrombus. A thrombus may not be detected in its full length as the high signal of gadolinium in the open vessel dominates the signal of the whole voxel. In addition, similar false results can be produced by enhancement of the vessel wall, enhancement of adjacent veins, or penetration/diffusion of gadolinium into the thrombus. Therefore, the possibility also exists that there is an underestimation of thrombus length by the indirect visualization on dGE-T1 because of the above mentioned technical factors. Furthermore, slice thickness on SWI sequences was 2.0 mm, whereas slice thickness on dGE-T1 was 5.0 mm, which might also explain some differences in thrombus length estimation.

Recently, Friedrich et al18 demonstrated an inverse correlation between distance from carotic terminus to thrombus (DT) and a poor clinical outcome, which indicated the importance of thrombus location because a long DT might represent proximal MCA occlusion along with the occlusion of lenticulostriate perforator, which would have a great impact on clinical

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.087</td>
<td>1.020–1.159</td>
<td>0.010</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.174</td>
<td>1.052–1.311</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline infarct volume, mL</td>
<td>1.007</td>
<td>0.991–1.023</td>
<td>0.450</td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>5.748</td>
<td>1.338–23.803</td>
<td>0.016</td>
</tr>
<tr>
<td>Thrombus length, mm</td>
<td>1.253</td>
<td>1.026–1.529</td>
<td>0.027</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

Figure 2. Regression curve representing an estimate of recanalization (A) and good functional outcome (B) probability by intravenous thrombolysis depending on the thrombus length measured on delayed gadolinium–enhanced T1 (dGE-T1).
outcome. However, the relationship between DT and recanalization still remains unclear. It would be interesting in future studies to investigate whether a comprehensive measurement of thrombus, including length and DT, could improve patient triage and finally improve overall patient outcomes when reperfusion therapy is needed.

Intra-arterial thrombectomy has been established as an effective treatment in patients with documented occlusion of the distal internal carotid or proximal MCA.\textsuperscript{19–23} Our results may not directly affect clinical decision making; however, it is still worth exploring whether IVT with recombinant tissue-type plasminogen activator might be omitted in patients who can be quickly moved to the endovascular suite in future investigations, if the rate of recanalization with IVT is considered low based on the thrombus length. However, the prediction of recanalization after IVT would also help the clinicians in the hospitals without endovascular suites to evaluate the cost effectiveness and the quick decision of transference to the comprehensive stroke center for endovascular treatment. Recently, Weisstanner et al\textsuperscript{17} have shown that recanalization rates are independent from the length of the thrombus, if modern endovascular recanalization techniques are applied with highly increased rate of recanalization. Certainly, it is also worth exploring the relationship between thrombus length on dGE-T1 and recanalization or clinical outcome in patients received combined IVT and endovascular treatment in the future.

Most excitingly, a recent study has showed that it was feasible and practical to achieve the benchmark of door-to-needle time ≤60 minutes, by using MRI as the routine screening modality before reperfusion therapy.\textsuperscript{24} MRI is unlikely to be faster than CT currently, not only because of the longer acquisition duration but also because of the time taken for safety screen, access to the scanner and image acquisition. However, multimodal MRI was proved to easily exclude stroke mimics, make diagnosis of small stroke even located in posterior circulation, and provide comprehensive information that is useful for clinical decision making. Further studies may need to investigate whether the benefits of multimodal MRI outweigh the harms of the time delay. However, we would like to note that our novel protocol provides more information about clot, not needing to add extra scan time and contrast agent.

Our study had several limitations. First, although we prospectively collected data using a stroke registry and MRI protocol, our study had a retrospective design and might have a retrospective bias. Second, there is a lack of information about early recanalization because the thrombus length was determined 24 hours after IVT. Third, thrombus length is hard to be accurately measured via real vascular pathways on dGE-T1. However, this is also difficult to be achieved on digital subtraction angiography. Fourth, the use of dGE-T1 could theoretically differentiate slow flow, incomplete stenosis from occlusion; however, this has not yet been confirmed by digital subtraction angiography. Fifth, we only included patients with MCA occlusion to reduce the heterogeneity. It would be clinically important to determine the specific threshold of thrombus length for both anterior cerebral artery and internal carotid artery in the future. Finally, the sample size was modest, and it was performed at a single center. Confirmation and extension in larger and multicenter cohorts is needed.

In summary, we presented a novel approach to estimate the thrombus length on dGE-T1, which can be easily obtained by adjusting scanning order in multimodal MRI protocol. The thrombus length measured on dGE-T1 was proved to independently predict MCA recanalization and clinical outcome after IVT.

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Disclosures
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References


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Supplemental Figure I:

Comparison of ipsilateral and contralateral vessels on delayed gadolinium-enhanced T1 (dGE-T1) and time-of-flight magnetic resonance angiography (TOF-MRA) of a patient with right middle cerebral artery (MCA) occlusion. (A) were source images of TOF-MRA; (B) were same slices of source images of dGE-T1, respectively.
背景および目的：これまでの研究では血栓長と静脉内血栓
溶解療法（IVT）後の再開通率は密接に関連することが明らかになった。本研究では、新しいアプローチとしてガドリニューム降圧造影T1（dGE-T1）強調画像を得るための撮
像順序を前向きに調整し、dGE-T1で測定された血栓長の
IVT後の再開通の予測因子としての有用性を評価した。

方法： IVT前および24時間後にマルチモードMRIを撮像
した中大脳動脈閉塞を有する急性虚血性脳卒中患者の臨床
データと画像データを前向きに収集して調整した。灌流
強調画像を撮像した後、従来のT1強調画像を撮像した。
DGE-T1で血栓長を測定し、中大脳動脈再開通との関連性
を検討した。

結果：患者74例を対象とし、年齢中央値は66歳、女性は
28例（37.8％）であった。dGE-T1での血栓長は8.18±4.56
mmで再開通不成功の許容しうる予測因子であり（オッズ
比=1.196,95%信頼区間（CI）: 1.015～1.409, P= 0.033），
ROC曲線下積分0.732（95% CI：0.619 ～ 0.845, P =
0.001）であった。最適なカットオフ値は6.77 mmであり、
この場合の感受性は77.8％、特異度は57.9％、オッズ比は4.81
（95% CI: 1.742 ～ 13.292, P = 0.002）であった。さらに、
dGE-T1での血栓長が14 mmを超える場合はIVT後に再
開通した患者はなかった。

結論：マルチモードMRIにおいて単純に撮像順序を調整
することによって得られたdGE-T1は、血栓長の推定と
IVT後の中大脳動脈再開通の予測において有用なツールで
ある。

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