Impact of Initial Diffusion-Weighted Imaging Lesion Growth Rate on the Success of Endovascular Reperfusion Therapy

Jean-Marc Olivot, MD, PhD; Leila Sissani, BST; Elena Meseguer, MD; Manabu Inoue, MD; Julien Labreuche, BST; Michael Mlynash, MD, MS; Pierre Amarenco, MD; Mikael Mazighi, MD, PhD

Background and Purpose—Initial diffusion-weighted imaging lesion growth rate (IGR) assessed by diffusion-weighted imaging lesion volume divided by the delay from onset to magnetic resonance imaging offers an estimate of early brain infarction progression. We investigated the impact of IGR on the rate of favorable outcome according to the occurrence of a successful endovascular revascularization within 6 hours after onset in patients experiencing an acute brain infarction complicating internal carotid artery terminus/middle cerebral artery M1 occlusion.

Methods—The primary study end point was a favorable outcome defined by a modified Rankin Scale score of ≤2, 90 days after onset. A Thrombolysis in Cerebral Infarction score 2b/3 defined a successful recanalization.

Results—A total of 166 patients were included. Median IGR was 7 mL/h (interquartile range, 2–26). Sixty-eight patients (41%) experienced a favorable outcome. After adjustment on age, systolic blood pressure, vessel site occlusion, National Institutes of Health Stroke Scale, and antithrombotic medication, increase in IGR was associated with a decreased occurrence of favorable outcome with an odds ratio per SD increase of 0.60 (95% confidence interval, 0.38–0.94; P = 0.03). A successful recanalization was achieved among 56% of the patients after a median delay of 251 minutes (interquartile range, 211–291 minutes). Increasing IGR was associated with a decreased favorable outcome only when a successful recanalization was not achieved (adjusted odds ratio, 0.32; 95% confidence interval, 0.12–0.85; P = 0.02).

Conclusions—Proximal internal carotid artery/M1 occlusion did result into a wide range of IGR within 6 hours after onset. Increasing IGR was associated with a lower rate of favorable outcome after endovascular treatment overall and when a successful recanalization was not achieved. (Stroke. 2016;47:2305-2310. DOI: 10.1161/STROKEAHA.116.013916.)

Key Words: diffusion magnetic resonance imaging ■ magnetic resonance imaging ■ thrombectomy

The neurological deficit consecutive to a large-vessel occlusion results from the progression of the irreversible brain infarction (BI). Projection have suggested that BI progression could be as high as 5.5 mL/h translating into 2 millions neurons/h downstream of a proximal cerebral artery occlusion.1 The acute recanalization of the internal carotid artery (ICA) or proximal middle cerebral artery (MCA M1) occlusion using stentrieviers combined whenever feasible with intravenous thrombolysis within 6 hours after onset is now the approved treatment to prevent infarct progression and improve functional outcome.2 Diffusion-weighted imaging (DWI) is still considered as the most accurate available clinical imaging sequence for assessing the extension of acute BI during the first hours after onset.3 Assuming the absence of necrosis at the time of stroke onset, DWI lesion volume divided by the delay from symptom onset to magnetic resonance imaging (MRI), called initial DWI lesion growth rate (IGR) has been proposed to estimate acute BI progression.4-6 IGR assessed during the first day after stroke onset is highly variable. We did with others showed that IGR was associated with hypoperfusion severity and poor collaterals.4-6 A low IGR was associated with the presence of a target mismatch on MRI suggestive of the presence of a large salvageable penumbra.6 Those patients are sometimes called slow progressors and may benefit from an endovascular revascularization outside of the approved 6-hour therapeutic window.7 Conversely, a high IGR was associated with the rapid development of a malignant profile for which an acute reperfusion might be futile. Those patients were, therefore, excluded from some

Received May 14, 2016; final revision received June 30, 2016; accepted July 11, 2016.

From the Acute Stroke Unit, Toulouse University Hospital, Toulouse Neuro Imaging Center (UMR 1214), Toulouse University Hospital, France (J.-M.O.); UMR 1148 et Centre d’Accueil et de Traitement de l’Attaque Cérébrale, CHU Bichat, Paris, France (L.S., E.M., P.A., M.M.); NCVC Stroke Center, National Cerebral and Cardiovascular Center, Fujishirodai 5-7-1, Suita, Osaka 565-8565, Japan (M.I.); and Department of Biostatistics, Université de Lille, CHU Lille, EA 2694 - Santé Publique Épidémiologie et Qualité des Soins, France (J.L.); Stanford Stroke Center, Stanford University, CA (M.M.).

Statistical analyses were conducted by Leila Sissani and Julien Labreuche.

Guest Editor for this article was Seemant Chaturvedi, MD.


The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.116.013916//DC1.

Correspondence to Jean-Marc Olivot, MD, PhD, Acute Stroke Unit, Toulouse University Hospital, Toulouse Neuro Imaging Center (UMR 1214), Toulouse University Hospital, France. E-mail jmolivot@gmail.com

© 2016 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.116.013916

2305
acute stentriever trials. However, we did demonstrate with others that some patients with large infarction defining a malignant profile with a DWI lesion volume of >70 mL may still benefit from an emergent revascularization within 6 hours.8-10

With this as a background, we aim to investigate first the characteristics of IGR in a cohort of consecutive patients experiencing an acute BI downstream of a proximal ICA term/M1 occlusion treated by endovascular treatment within 6 hours after onset and imaged by MR-DWI before treatment, and second its impact on the rate of favorable outcome according to the occurrence of a successful recanalization.

Methods

Patients

Patients experiencing an acute BI treated by endovascular treatment at Bichat University Hospital from April 2007 to March 2013 were recruited in a prospective clinical registry. Detailed Materials and Methods have been previously reported.9

Sample Selection

Patients with a complete M1 or ICA occlusion and a measurable DWI lesion, treated within 6 hours after stroke onset, by endovascular therapy were enrolled in the study. The research protocol was approved by the Comité de Protection des Personnes (Ethics Committee from Ambroise Pare Hospital), and patients or their representatives (ie, a family member) gave written consent.

DWI Measurement and Infarct Growth Velocity

DWI volumes were obtained retrospectively after processing of DWI maps using the research version of the Rapid processing of Perfusion and Diffusion software developed by Stanford Stroke Center, as previously described.7 The infarct growth velocity was defined as the ratio between the acute DWI lesion volume on baseline MRI divided by the delay from symptom onset to MRI in hours.

Clinical Outcome Definition

A favorable outcome was defined by a modified Rankin Scale score of ≤2 at 90 days. Recanalization rate was measured using the Thrombolysis In Cerebral Infarction at the end of the endovascular procedure. Successful recanalization was defined by a modified Thrombolysis in Cerebral Infarction score of 2B or 3.11

Statistical Analysis

Data are presented as means±SD or median (interquartile range [IQR]) for continuous variables and count (percentage) for categorical variables. IGR was divided into tertiles to describe the association with baseline characteristics and favorable outcome. Association between IGR (treated as continuous variables after log-transformation to reduce the skewness; see Figure in the online-only Data Supplement) and its association with baseline characteristics was assessed using Pearson correlation coefficients for association with continuous characteristics and Student t-test for association with qualitative characteristics (all binary). The association between IGR and the occurrence of a favorable outcome was assessed using univariable logistic regression model, after categorization of IGR according to tertiles. Because we found a gradual increase in odds ratio (OR) with IGR tertiles, OR per 1 SD increase in Ln IGR was calculated. We used receiver operating characteristics curve analysis to determine the optimal IGR cutoff value for discriminating favorable outcome. Association between IGR and favorable outcome was further investigated in multivariable logistic regression model adjusted for potential confounding factors selected on the basis of their association with IGR in univariate analyses (P<0.20).

Finally, we assessed the interaction between IGR and successful recanalization on favorable outcome by including the corresponding multiplicative term into logistic regression model. We also compared favorable outcome between the recanalization status (Thrombolysis in Cerebral Infarction score 0-2a versus 2b-3) according to IGR tertiles and by calculating the OR of favorable outcome per 1 SD increase in Ln IGR in patients with and without successful recanalization separately. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC).

Baseline Characteristics

A total of 166 patients with an acute BI complicating an ICA term (33%) or MCA (67%) occlusion met the inclusion criteria (Figure 1). Five of them did experience a relative hypotension (<120 mmHg) during the first 24 hours. Median DWI lesion volume was 13 mL (IQR, 4–47 mL), and median delay from onset to MRI was 105 minutes (IQR, 75–150 min). As shown in Figure 2, there was a large dispersion of DWI lesion volumes over delay from onset to MRI overall and after stratification for vessel site occlusion. The median IGR was 7 mL/h (IQR, 2–26 mL/h) overall and was lower in patients with MCA M1 occlusion than in those with ICA occlusion (median

---

Figure 1. Flow chart. CT scan indicates computed tomographic scan; DWI, diffusion-weighted imaging; IA, intra-arterial; ICA, internal carotid artery; IGR, initial DWI lesion growth rate; IV, intravenous; MCA, middle cerebral artery; and MRI, magnetic resonance imaging.
Infarct Growth Rate and Clinical Outcome

The rate of favorable outcome decreased gradually with IGR tertiles, from 46% to 21% (P for linear trend <0.001; Table 2). The unadjusted OR of favorable outcome associated with 1-SD increase in Ln IGR was 0.54 (95% confidence interval [CI], 0.38–0.77; P<0.001). The overall accuracy of the IGR was good with an area under the curve of 0.66 (95% CI, 0.58–0.74) with an optimal threshold to predict favorable outcome of 8.7 L/h (Sensitivity: 73% [95% CI, 60–82]; Specificity: 54% [95% CI, 44–64]; OR, 0.32; 95% CI, 0.17–0.64; P=0.001). After adjustment on age, systolic blood pressure, site of occlusion, antithrombotic medication, and National Institutes of Health Stroke Scale, results were unchanged (OR per SD increase in Ln IGR, 0.60; 95% CI, 0.38–0.94; OR for IGR ≥9, 0.40; 95% CI, 0.17–0.92; P=0.03).

Infarct Growth Rate and Successful Recanalization

A successful recanalization was achieved in 92 (55%) patients after a median delay from symptom onset of 251 minutes (IQR, 211–291 minutes). Successful recanalization was associated with favorable outcome (54% versus 26%; P<0.001; OR, 3.32; 95% CI, 1.70–6.45) As shown in Table 2, effect of a successful recanalization on favorable outcome increased with IGR values. Increasing IGR was associated with decreased rate of favorable outcome in patients who did not experience a successful recanalization (OR per SD increase in Ln IGR, 0.41; 95% CI, 0.21–0.77; P=0.006) but not in those who did (OR, 0.68; 95% CI, 0.43–1.06; P=0.09). The same relationships were observed after adjustment on age, systolic blood pressure, site of occlusion, antithrombotic medication, and National Institutes of Health Stroke Scale, with an adjusted OR per SD increase in

Figure 2. Scatterplot of diffusion-weighted imaging (DWI) volume vs time between symptom onset to magnetic resonance imaging (MRI) according to middle cerebral artery M1 (A) and internal carotid artery term (B) occlusion.
Ln IGR of 0.32 (95% CI, 0.12–0.85; \(P=0.02\)) if no successful recanalization was achieved and 0.83 (95% CI, 0.45–1.52; \(P=0.55\)) if a successful recanalization was achieved.

Discussion

Our results show within 6 hours after the onset of a large-vessel occlusion acute BI the large variability of IGR and its impact on functional outcome among patients treated by endovascular recanalization. They also suggest that some fast progressors may still benefit from a successful recanalization achieved within this time window.

In our study, median IGR was 7 mL/hr. This rate was higher downstream of an ICA occlusion than that of an MCA M1 occlusion. This value is close to the projection proposed by Saver et al.,\(^1\) of 5.5 mL/h, but higher than the median value observed in DEFUSE-2 (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study; 3 mL/h). Actually, 10% of the DEFUSE-2 patients had a distal MCA occlusion and were

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=166)</th>
<th>Initial DWI Lesion Growth Rate (mL/hr) by Tertiles</th>
<th>P(^\text{Value}^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;3.3 mL/h (n=55)</td>
<td>3.3–13.8 mL/h (n=56)</td>
</tr>
<tr>
<td>Initial DWI lesion growth rate, mL/min, median (IGR)</td>
<td>7 (2–26)</td>
<td>2 (0.1–2)</td>
<td>7 (5–9)</td>
</tr>
<tr>
<td>Age, y</td>
<td>71 (16)</td>
<td>75 (15)</td>
<td>70 (19)</td>
</tr>
<tr>
<td>Male sex</td>
<td>70 (42.2)</td>
<td>22 (40)</td>
<td>25 (45)</td>
</tr>
<tr>
<td>Clinical measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood glucose, mg/dL, median (IQR)</td>
<td>122 (102–145)</td>
<td>119 (106–142)</td>
<td>116 (100–142)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>150 (22)</td>
<td>154 (23)</td>
<td>150 (20)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>80 (14)</td>
<td>82 (14)</td>
<td>79 (13)</td>
</tr>
<tr>
<td>NIHSS, median (IQR)</td>
<td>17 (13–21)</td>
<td>14 (10–19)</td>
<td>17 (13–21)</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>93 (56)</td>
<td>28 (51)</td>
<td>33 (59)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20 (12)</td>
<td>6 (11)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>51 (31)</td>
<td>18 (33)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>Current or former smoker</td>
<td>50 (30)</td>
<td>17 (33)</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Antithrombotic medication</td>
<td>63 (38)</td>
<td>19 (35)</td>
<td>22 (39)</td>
</tr>
<tr>
<td>Occlusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA M1</td>
<td>111 (67)</td>
<td>41 (74)</td>
<td>38 (68)</td>
</tr>
<tr>
<td>ICA term</td>
<td>55 (33)</td>
<td>14 (25)</td>
<td>18 (32)</td>
</tr>
<tr>
<td>Previous IV tPA</td>
<td>125 (75)</td>
<td>46 (84)</td>
<td>39 (70)</td>
</tr>
</tbody>
</table>

Data are number (%), mean (SD) unless otherwise indicated. DBP indicates diastolic blood pressure; DWI, diffusion-weighted imaging; ICA, internal carotid artery; IQR, interquartile range; IV tPA, intravenous tissue-type plasminogen activator; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

\(^*\)Calculated using initial DWI lesion growth rate as continuous variable.

### Table 2. Rate of Favorable Outcome According to Successful Recanalization Status and IGR Tertiles

<table>
<thead>
<tr>
<th></th>
<th>No Successful Recanalization (n=73)</th>
<th>Successful Recanalization (n=91)</th>
<th>P(^\text{Value}^*)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>19 (26)</td>
<td>49 (54)</td>
<td>&lt;0.001</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>IGR tertiles, mL/h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3.3 (n=55)</td>
<td>8 (44)</td>
<td>23 (66)</td>
<td>0.14</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>3.3–13.8 (n=56)</td>
<td>9 (32)</td>
<td>14 (50)</td>
<td>0.05</td>
<td>0.47 (0.22–1.02)</td>
<td>0.51 (0.20–1.28)</td>
</tr>
<tr>
<td>&gt;13.8 (n=55)</td>
<td>2 (7)</td>
<td>12 (43)</td>
<td>&lt;0.001</td>
<td>0.23 (0.10–0.53)</td>
<td>0.30 (0.11–0.84)</td>
</tr>
<tr>
<td>IGR per 1-SD (0.58†) increase</td>
<td>…</td>
<td>…</td>
<td>…</td>
<td>0.54 (0.38–0.77)</td>
<td>0.60 (0.38–0.94)</td>
</tr>
</tbody>
</table>

Data are number (percentage). CI indicates confidence interval; IGR, initial diffusion-weighted imaging lesion growth rate; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

\(^*\)Adjusted on age, systolic blood pressure, site of occlusion, antithrombotic medication, and NIHSS.

\(^†\)After log-transformation.
very slow progressors. Such patients were not enrolled in the present study, and this may explain part of the difference observed.

Previous studies have suggested the large variability of IGR within 24 hours after onset. In our study, the median delay from onset to MRI was 105 minutes. Our results confirm a high IGR variability at this early time point and after stratification on vessel occlusion site. We hypothesize that as previously demonstrated, hypoperfusion severity and collateral score contributed to this variation in addition to the site of occlusion.\(^5,^6\)

IGR was as previously demonstrated an independent predictor of poor outcome.\(^5,^6\) Interestingly and contrariwise to previous observation,\(^4\) this relationship did persist after adjustment on baseline National Institutes of Health Stroke Scale. This finding suggests that IGR is not only a biomarker of large infarction but also an assessment of the aggressiveness of the ongoing ischemic process. The median delay from onset to recanalization was 4.5 hours. This delay was in keeping with the delay observed in the pivotal thrombectomy trials. DEFUSE-2 investigators demonstrated that the occurrence of a complete recanalization was not only beneficial overall but also in the subgroup of patients who did have poor collaterals, a major contributor of IGR.\(^12\) In keeping with this observation, the impact of IGR on functional outcome did not persist after the achievement of a complete recanalization. In addition, patients experiencing the highest IGR did still benefit from a complete recanalization (Table 2). This finding suggests that a successful recanalization occurring after a median delay of 4.5 hours may dramatically alter the course of a fast progressing ischemic lesion outlined by DWI. Also, we do hypothesize based on the results of previous studies that in addition to the prevention of the infarct progression, part of the beneficial effect may also be related to the reversal of the acute DWI lesion.\(^14\)

Our study has several limitations. First, a successful recanalization was achieved only among 55% of the cases when it was reported up to 30% higher in the recent thrombectomy trials.\(^15\) This lower rate might be explained by the limited use of stentriever in our study that became available only by the end of enrollment period. We may speculate, therefore, that endovascular treatment using those devices would have had a higher benefit in the group of fast progressors. Second, none of the patients did have a perfusion imaging to help us characterizing the MRI profile to confirm the relationship previously observed between IGR and hypoperfusion severity and the prevalence of a target mismatch. Moreover, collateral score was not assessed on baseline MRA/angiography, to confirm the previously observed relationship between IGR and collateral score. Finally, the retrospective design of this study is also a major limitation and may have caused some selection biases.

Our results suggest that the patients who may benefit the more from an acute recanalization are the one experiencing the more aggressive subtype of BI. On the contrary, this rapid progression may lead to critical volumes associated with limited salvageable penumbra for which reperfusion may be futile or even deleterious. Only few patients from the recent trials were enrolled with a baseline MRI. We expect that a lower proportion did have a high IGR as large DWI volume was at baseline an exclusion criterion from the studies that did use MRI for initial evaluation. Therefore, we initiated a prospective study investigating this issue that will start by the end of this year.

### Summary

In conclusion, our results confirm the high variability of IGR within the accepted time window for endovascular treatment and its deleterious impact on functional outcome. Nonetheless, they also suggest that the occurrence of an emergent and complete recanalization may dramatically improve the prognosis of the patients experiencing a fast progressing ischemic lesion outlined by DWI.

### Sources of Funding

This study was funded by SOS-Attaque cérébrale.

### Disclosures

Dr Olivot consulting fees from Astra Zeneca, Boston scientific and Servier, lecture fees from Bristol-Myers Squibb and Boehringer Ingelheim. Dr Amarenco reports receipt of research grant support and lecture fees from Pfizer, Sanofi, Bristol-Myers Squibb, Merck, AstraZeneca, Boehringer-Ingelheim, and consultancy fees from Pfizer, BMS, Merck, Boehringer-Ingelheim, AstraZeneca, Bayer, Daiichi-Sankyo, Lundbeck, Edwards, Boston Scientific, Kowa, GSK, Fibrogen, lecture fees from Bayer, Boston Scientific, St-Jude Medical, and research grants from the French government. Dr Mazighi consulting fees from Boehringer-Ingelheim and Servier. The other authors report no conflicts.

### References


Impact of Initial Diffusion-Weighted Imaging Lesion Growth Rate on the Success of Endovascular Reperfusion Therapy
Jean-Marc Olivot, Leila Sissani, Elena Meseguer, Manabu Inoue, Julien Labreuche, Michael Mlynash, Pierre Amarenco and Mikael Mazighi

Stroke. 2016;47:2305-2310; originally published online August 9, 2016;
doi: 10.1161/STROKEAHA.116.013916

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/47/9/2305

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/08/10/STROKEAHA.116.013916.DC1
Supplemental files
Supplemental figure. Distribution of IGR after log-transformation.