Dramatic Recovery in Acute Ischemic Stroke Is Associated With Arterial Recanalization Grade and Speed

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**Background and Purpose**—Dramatic recovery (DR) is a predictor of stroke outcome among others. However, after successful recanalization, systematic favorable outcome is not the rule. We sought to analyze the impact of recanalization on DR in patients with acute ischemic stroke eligible for any revascularization strategies (either intravenous or endovascular).

**Methods**—We analyzed data collected between April 2007 and May 2011 in our prospective clinical registry. All patients with acute ischemic stroke with National Institutes of Health Stroke Scale $\geq 10$ at admission and an identification of arterial status before treatment were included. DR was defined as National Institutes of Health Stroke Scale $\leq 3$ at 24 hours or a decrease of $\geq 10$ points within 24 hours.

**Results**—DR occurred in 75 of 255 patients with acute ischemic stroke (29.4%). Patients with persistent occlusion had a low DR rate (11.1%) than those with no documented occlusion (36.5%) and those with occlusion followed by recanalization (35.3%; both $P<0.001$). Among patients with recanalization monitored by angiography, DR was higher among patients with complete recanalization than among those with partial recanalization (46.8% versus 14.3%; $P<0.001$) and increased with tertiles of time to recanalization ($P_{\text{trend}}=0.002$). In multivariable logistic regression analysis, grade and time to recanalization appeared independently associated with DR; the adjusted ORs were 4.17 (95% CI, 1.61–10.77) for complete recanalization and 1.24 (95% CI, 1.04–1.48) for each 30-minute time decrease. Patients with versus without DR more frequently had modified Rankin Scale $\leq 1$ (67.6% versus 9.0%; $P<0.001$) and less frequently had hemorrhage (17.3% versus 33.9%; $P=0.024$).

**Conclusions**—DR is strongly associated with favorable clinical outcome and is dependent on complete recanalization and time to recanalization. 

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Key Words: acute stroke syndromes ■ dramatic recovery ■ thrombolysis ■ recanalization

In the setting of acute ischemic stroke, dramatic recovery (DR) has been reported as an early and stable excellent clinical outcome that is sustained in the long term.1 A transcranial Doppler monitoring study has suggested that DR is associated with arterial recanalization2 and that fewer patients will achieve a good long-term outcome without early recanalization. Although recanalization is a critical factor for favorable clinical outcome,3 lack of early clinical improvement is common after recanalization.4,5 Additional evidence is needed to understand the role, if any, of recanalization on DR.

We sought to analyze the effect of recanalization on DR in patients with acute ischemic stroke with National Institutes of Health Stroke Scale (NIHSS) $\geq 10$ using a control group of patients without documented occlusion. We also assessed the impact of recanalization characteristics (ie, grade and time to recanalization) on DR among patients with angiographic monitoring of arterial occlusion status.

**Methods**

**Bichat Stroke Program**

Patients were identified from a prospective clinical registry of patients with acute ischemic stroke treated between April 2007 and May 2011 at Bichat University Hospital. As described previously,6 patients eligible for intravenous (IV) treatment received conventional IV thrombolysis in case of no documented arterial occlusion or IV/intra-arterial (IA) treatment in case of documented arterial occlusion. Conventional IV thrombolysis was performed using the standard recombinant tissue-type plasminogen activator (rtPA) dose (0.9

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mg/kg) according to the National Institute of Neurological Disorders and Stroke guidelines:7,8 (time window 4.5 hours) unless the patient had early infarct signs in more than one third of the middle cerebral artery territory on CT scan and/or had severely impaired consciousness. Age was not a contraindication in our center. The systematic IV/IA approach was performed using an IV rtPA dose of 0.6 mg/kg followed by an IA rtPA dose of 0.3 mg/kg if the arterial occlusion persisted. In the absence of recanalization after IV/IA rtPA administration, additional mechanical endovascular therapy (MET) was performed.

Patients with a documented arterial occlusion who were not eligible for IV treatment were treated by the IA approach.3 The IA approach was performed using an IA rtPA dose of 0.5 mg/kg followed by adjunctive MET if the arterial occlusion persisted. In patients with a contraindication to rtPA,6 a direct MET approach was considered. No MET was performed beyond 6 hours after symptom onset.

Sample Selection
Patients were included in this study if they had a pretreatment NIHSS score ≥10 and an arterial examination before treatment (by MRI, CT scan, or transcranial Doppler). We chose a cutoff of NIHSS ≥10 points to select patients with a high rate of large-vessel occlusion. Patients without documented occlusion were used as a reference group to assess the impact of recanalization of occluded arteries on DR.

Data Collection and Definitions
Information on patients’ demographic characteristics, vascular risk factors, laboratory and imaging findings, vital signs before treatment, severity of ischemic stroke, and clinical outcomes were collected prospectively using a structured questionnaire. Hypertension and hypercholesterolemia were defined by a history of treatment. Subjects were classified as diabetic when treated for Type 1 or Type 2 diabetes. Smoking history was coded as never, past, or current.

The severity of the ischemic stroke was assessed using the NIHSS score. Subsequent NIHSS recordings were collected prospectively at 1, 3, and 24 hours after initiation of treatment. DR was defined as an NIHSS score of 0 to 3 at 24 hours or a decrease of ≥10 points in the NIHSS score at 24 hours.4 Time from symptom onset (or when the patient was last seen in a normal condition) to initiation of therapy were also recorded. All patients had a CT or MRI scan 24 hours after treatment onset to assess hemorrhagic complications. Arterial status of the occluded artery was monitored with conventional angiography during the IA approach and time to recanalization was noted. Recanalization was measured using the Thrombolysis In Myocardial Infarction (TIMI) score.9 The TIMI score was assessed by 2 members of the staff (E.M. or M.M.) certified for modified Rankin Scale scoring. A TIMI score of 0 represents complete occlusion; a TIMI score of 1 is a contrast penetration with minimal perfusion of either the M1 segment or an M2 division of the middle cerebral artery; a TIMI score of 2 is a partial flow in either middle cerebral artery segment; and a TIMI score of 3 is a complete flow in both the M1 segment and M2 divisions of the middle cerebral artery.

The modified Rankin Scale at 3 months was assessed during face-to-face interviews or by telephone calls by a senior vascular neurologist (E.M. or M.M.) certified for modified Rankin Scale scoring.

Patient Consent and Protocol Approval
Informed consent was obtained from the patient or surrogate, and the research protocol was approved by the Ethics Committee from Ambroise Pare Hospital.

Statistical Analysis
Bivariate comparisons between patients with and without DR were made using χ² tests (Fisher exact test was used when the expected cell frequency was <5) for categorical variables and Student t test for continuous variables (Mann–Whitney U test was used for the skewed distribution). Adjustments for between-group differences were done using logistic regression analysis. We assessed the effect of recanalization of the occluded arteries on DR outcome by calculating adjusted ORs using the patients with no documented occlusion as the reference group. Among the patients who achieved recanalization documented by angiography monitoring, we also studied the impact of the grade and time to recanalization on DR. Our first analyses covered the whole study group; a sensitivity analysis was also performed by excluding patients ineligible for IV therapy (ie, those with documented occlusion treated only by the IA approach). Statistical testing was done at the 2-tailed level of 0.05. Data were analyzed using the SAS software package, Release 9.2 (SAS Institute, Cary, NC).

Results
During the 4-year study period, 441 consecutive patients with acute ischemic stroke were treated with IV and/or IA therapy, of which 264 patients (59.9%) had an NIHSS score ≥10 at admission. Of these, 255 had either an angiography examination (MRI or CT scan, n = 249) or transcranial Doppler (n = 6, angiography not performed due to renal insufficiency or technical issues) before revascularization therapies and constituted the study sample (Figure 1). Among the 255 patients, 82 were treated by IV thrombolysis, 111 by an IV/IA approach (adjunctive MET, n = 44), and 62 by an IA approach (rtPA, n = 28; direct MET, n = 27; rtPA+MET, n = 7). In this study sample, DR occurred in 75 patients (29.4%) with a significant difference between patients eligible for IV treatment and those who were ineligible for IV treatment, so received IA treatment (16.1% versus 33.7%; P = 0.008). The baseline characteristics for patients with and without DR are described in Table 1. With the exception of admission NIHSS score, no significant differences were found between patients with or without DR.

DR and Vessel Occlusion Status
A complete occlusion was documented in 203 patients, 139 of whom (68.5%) had a successful recanalization (partial or
As shown in Figure 2, the rate of early DR differed according to vessel occlusion status (P<0.001). Patients with persistent occlusion had a low DR rate (11.1%) compared with patients with no documented occlusion (36.5%) and those with occlusion followed by recanalization (35.3%). Using patients with no documented occlusion as the reference, the NIHSS-adjusted OR of early DR was 1.23 (95% CI, 0.61–2.48; P=0.56) for patients with occlusion followed by recanalization and 0.26 (95% CI, 0.10–0.69; P=0.007) for patients with persistent occlusion. Similar results were found when the analysis was restricted to those patients who were eligible for IV rtPA treatment; NIHSS-adjusted ORs (95% CIs) were 1.56 (0.75–3.26) and 0.30 (0.10–0.92), respectively.

Regarding the site of occlusion, patients with internal carotid artery occlusion (isolated or in tandem with the middle cerebral artery) had DR less often (9 of 53 [17.0%]) than patients with isolated middle cerebral artery occlusion (42 of 137 [30.7%]) or with posterior circulation occlusion (5 of 13 [38.5%]; P=0.09). A similar difference was found when analysis was restricted to patients with occlusion followed by recanalization; the DR rates were 22.0% (9 of 41) in patients with internal carotid artery occlusion, 40.2% (37 of 92) in patients with isolated middle cerebral artery occlusion, and 50.0% (3 of 6) in patients with posterior circulation occlusion (P=0.10).

### DR and Recanalization Results

Of the 139 patients with occlusion followed by recanalization, 11 had no angiography monitoring during treatment due to no endovascular therapist being available (n=9), failure of catheter angiography (n=1), or acute respiratory failure (n=1); all of these patients received a full dose of IV rtPA.

As shown in Table 2, patients with complete recanalization had DR significantly more frequently than those with partial recanalization. After adjustment for admission NIHSS, the OR for DR associated with complete recanalization was 4.97 (95% CI, 1.98–12.51; P<0.001). In addition to the impact of recanalization grade, a gradual increase in DR rate was found with decreasing tertiles of time to recanalization (P_trend=0.006; Table 2). The NIHSS-adjusted OR for each 30-minute decrease in time to recanalization was 1.30 (95% CI, 1.10–1.55; P=0.002). In multivariable logistic regression analysis including both recanalization results, grade and time appeared to be independently associated with DR; the multivariable ORs were 4.17 (95% CI, 1.61–10.77; P=0.003) for complete recanalization and 1.24 (95% CI, 1.04–1.48; P=0.016) for each 30-minute decrease in time to recanalization. In the sensitivity analysis restricted to those patients eligible for IV rtPA treatment, multivariable ORs were 2.76 (95% CI, 0.98–7.79; P=0.055) for complete recanalization and 1.28 (95% CI, 1.00–1.63; P=0.049) for each 30-minute decrease in time to recanalization.

### DR and Clinical Outcomes

Functional outcome at 3 months was available in 252 of 255 (98.8%) of cases. Of the 3 patients lost to follow-up, one had DR. As shown in Figure 3, patients with DR more frequently had an excellent outcome (modified Rankin Scale 0–1) than patients without DR (67.6% versus 9.0%; P<0.0001). After adjustment for admission NIHSS, the OR for excellent outcome associated with DR was 23.83 (95% CI, 10.85–
52.35; \(P<0.001\) in all patients and 19.95 (95% CI, 8.56–46.50; \(P<0.001\) in patients eligible for IV rtPA treatment.

Concerning the safety outcome, a lower risk of hemorrhagic complications was found in patients with DR (17.3% versus 33.9%; adjusted OR, 0.45; 95% CI, 0.23–0.90; \(P=0.024\)). A similar difference was found in the sensitivity analysis with an NIHSS-adjusted OR of 0.39 (95% CI, 0.18–0.84; \(P=0.017\)).

### Discussion

We found that DR correlated strongly with favorable clinical outcome at 3 months and with a lower risk of hemorrhagic complications in patients with acute ischemic stroke and NIHSS ≥10. The absence of arterial occlusion status was a good predictor for DR, but, interestingly, patients with documented occlusion followed by recanalization had a similar rate of DR as patients with no documented occlusion. Among patients with documented occlusion followed by recanalization, a complete recanalization and shorter time to recanalization were independent predictors for DR.

DR occurred in 35.3% of our patients with recanalization, which is consistent with the results of Felberg et al., but higher than a study that reported a 20% rate of DR when recanalization was monitored on transcranial Doppler. This transcranial Doppler study found that patients with persistent occlusion were less likely to achieve DR. Similarly, our findings show an increase in DR rates for complete (versus partial) recanalization and for decreasing time to recanalization. The association of DR with time to recanalization reinforces previous evidence showing that early recanalization correlates with a favorable clinical outcome at 3 months.

Besides DR, other factors that can predict good clinical outcome include low initial NIHSS score, low diffusion-weighted imaging volume,10 leptomeningeal collaterals pattern,14 vessel recanalization,3 shorter time to recanalization,6 site of occlusion,15,16 and younger age.17 Recently, Galimaris et al.15 have shown that good collaterals and successful recanalization are the strongest predictors of good outcome, more so than initial NIHSS or younger age. In the same study,
time to treatment did not predict outcome or complications, but the average time to treatment was almost 4.5 hours. This point is critical, because previous evidence has shown that recanalization within 3.5 hours after stroke onset is associated with a favorable outcome in $>90\%$ of patients.\textsuperscript{6} The probability of a favorable outcome decreases by approximately 20\% for each 30-minute delay in recanalization of the artery.\textsuperscript{6} The absence of a beneficial effect of shorter time to treatment in the study by Galimanis et al\textsuperscript{14} is probably related to the delay in treatment initiation and, as a consequence, an increased time to recanalization. In the same study,\textsuperscript{15} collaterals were the critical factor for outcome in endovascular therapy and were associated with symptomatic intracranial hemorrhage in case of poor collaterals. In the present study, patients with DR had a 55\% lower risk of hemorrhagic complications compared with patients without DR. This element may contribute to the stable favorable clinical outcome observed in patients with DR. It is possible that the risk of hemorrhagic reperfusion is potentially reduced with early recanalization. Because fewer patients achieve good long-term outcome without early recanalization,\textsuperscript{7} future guidelines should probably include time to treatment and time to reperfusion targets as standards of care.

Among patients with DR, 11.1\% had persistent arterial occlusion, suggesting that other phenomena are taking place beyond arterial recanalization. In our study, the absence of data on collateral flow or perfusion imaging studies in the acute phase is a limitation. Although only patients with an NIHSS score $\geq 10$ were included, the admission NIHSS score remained a main confounding factor in relation to DR and arterial occlusion status, which was taken into account by multivariable analysis. The cutoff of 10 NIHSS points was used because such patients have a high rate of complete occlusion, which was a selection criterion for adjunctive IA therapy.\textsuperscript{18} Therefore, we cannot exclude the chance that the impact of complete recanalization and time to recanalization would have been modified (likely stronger) if patients with documented occlusion and admission NIHSS $< 10$ had been included. In addition, we cannot exclude a selection bias related to the absence of an arterial examination before treatment ($n=9$) or to the absence of recanalization monitoring ($n=11$).

Conclusions
The results from this study suggest that DR is positively correlated with complete arterial recanalization and time to recanalization. DR is associated with reduced hemorrhagic rates and increased 3-month excellent clinical outcome. These findings consolidate complete arterial recanalization and time to recanalization as critical aims to achieve in the management of patients with acute stroke.

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References
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