Reperfusion Within 6 Hours Outperforms Recanalization in Predicting Penumbra Salvage, Lesion Growth, Final Infarct, and Clinical Outcome

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**Background and Purpose**—The relative merits of reperfusion versus recanalization to predict tissue and clinical outcomes in anterior circulation stroke have been previously assessed using data acquired >12 hours postonset. To avoid late-occurring confounders such as non-nutritional reperfusion, futile recanalization and no-reflow phenomenon, we performed ultraearly assessment of reperfusion and recanalization.

**Methods**—From a multicenter prospective database, 46 patients with acute magnetic resonance angiography–visible occlusion and in whom both reperfusion and recanalization were assessed on follow-up magnetic resonance imaging ≤6 hours of symptom onset were identified. Multiple linear regressions modeled salvaged penumbra, diffusion-weighted imaging lesion growth, and final infarct at 1 month using baseline clinical and imaging parameters and acute reperfusion or recanalization. Best predictors were determined with the Akaike information criterion. Univariate and multivariate logistic regressions identified the clinical and imaging predictors of clinical outcome.

**Results**—Admission magnetic resonance imaging showed M1 occlusion in 15 (33%) patients; median penumbra volume was 13.4 mL. Acute reperfusion was observed in 27 (59%) patients; 42% of nonrecanalized patients demonstrated reperfusion. The dichotomized classification of reperfusion and recanalization was discordant (P=0.0002). Reperfusion ≤6 hours was a significant (P<0.05) predictor of increased penumbra salvage, reduced lesion growth, and final infarct size. Recanalization did not improve model accuracy. Reperfusion, but not recanalization, was significantly associated with good clinical outcome in logistic regressions.

**Conclusions**—Reperfusion ≤6 hours was consistently superior to recanalization in predicting tissue and clinical outcome. Reperfusion without recanalization was frequent and probably related to retrograde reperfusion through leptomeningeal collaterals. Acute reperfusion was the strongest predictor of, and may therefore, represent a reliable surrogate for, clinical outcome. (Stroke. 2015;46:600-600. DOI: 10.1161/STROKEAHA.114.007964.)

**Key Words:** magnetic resonance imaging ■ reperfusion

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Early restoration of perfusion within the ischemic tissue is the only therapy of proven benefit in reducing infarct growth and promoting clinical improvement in ischemic stroke. The effectiveness of intravenous tissue-type plasminogen activator (tPA) in clinical trials is probably driven by early reperfusion, with decreasing benefit for more delayed treatment.1,2 Magnetic resonance imaging (MRI)–based studies suggest that reperfusion might be a surrogate marker for clinical outcome, and this concept is being introduced in phase 2 trials.3

Although reperfusion indicates restoration of blood flow at the distal, capillary level, recanalization specifies the patency of the primary arterial occlusive lesion. Although both the events are closely related, one does not necessarily entail the other. Complete recanalization may fail to induce reperfusion because of distal microemboli or extensive damage to the microvascular circulation (no-reflow phenomenon).4 Conversely, significant reperfusion can be observed, despite incomplete recanalization, presumably from collateral
sources. A partial recanalization may also promote reocclusion and clinical deterioration. Notwithstanding these conceptual differences, recanalization and reperfusion have often been used interchangeably in previous publications. Multiple methods of assessing and reporting revascularization endpoints have further compounded this confusion. To date, only 3 magnetic resonance (MR)- or computed tomography (CT)-based studies have directly compared the accuracy of reperfusion versus recanalization to predict imaging or clinical outcomes. In a substudy of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET), recanalization was correlated with the presence and extent of MR-based reperfusion, but only reperfusion was independently associated with clinical outcome. A study including 22 patients found that CT-based reperfusion was a more accurate predictor of final infarct volume than recanalization. Still, neither reperfusion nor recanalization was associated with clinical or functional outcomes, as assessed by the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale. Eilaghi et al confirmed that CT-based reperfusion, but not recanalization, was predictive of functional independence at 90 days. However, in the above studies reperfusion and recanalization were assessed at late time points, namely days 3 to 5, mean 25 hours, and ≤24 hours after stroke onset, respectively. In this late time frame, non-nutritional reperfusion of established infarct or futile recanalization, from, for example, no-reflow phenomenon could have affected previous assessments. In addition, the occurrence of reperfusion without recanalization may also be time-dependent and influence the findings, however, its incidence and clinical role are unknown.

In this study of acute stroke patients with serial MRI examinations, our objectives were to (1) compare the value of acute (≤6 hours) reperfusion and recanalization for predicting both tissue (penumbra salvage, lesion growth, and final infarct) and clinical (NIHSS and modified Rankin Scale) outcomes; and (2) assess, in this early time frame, the occurrence of discrepancies between reperfusion and recanalization, specifically reperfusion without recanalization.

Methods

Patients and Clinical Outcome Measures

We analyzed a multicenter, prospective database (I-KNOW) of patients who underwent both admission and serial follow-up MRI. Several previous published reports are based on this cohort. Inclusion criteria for I-KNOW were (1) NIHSS ≤2 ≤6 s was used to define the perfusion lesion at H0 and H3. The initial at-risk tissue (ie, penumbra) was defined as voxels with a score of T_\text{max} ≥2 ≤6 s not included in the H0 DWI lesion. Reperfusion was assessed at H3, and defined as voxels with T_\text{max} ≥2 ≤6 s at H0 and T_\text{max} ≥2 ≤6 s at H3. Acute reperfusion was defined by a reperfusion ratio (volume of reperfused voxels at H3/perfusion lesion volume at H0) of ≥50%. Acute reperfusion was defined on H3 MRA using the arterial occlusive lesion classification: 0=no recanalization of the primary occlusive lesion; 1=complete or partial recanalization of the primary occlusive lesion with no distal flow; 2=complete or partial recanalization of the primary occlusive lesion with any distal flow; and 3=complete recanalization of the primary occlusive lesion with any distal flow. A score ≥2 indicated acute recanalization. The volume of salvaged penumbra (voxels included in the initial tissue at risk but not in the final FLAIR lesion), lesion growth (voxels included in the final FLAIR lesion but not in the baseline DWI lesion), and final infarct, as well as the baseline DWI lesion, were measured. DWI lesion reversal was defined as those voxels included in the initial DWI lesion mask but not in the final FLAIR and, expressed both in absolute volume and in percentage of baseline DWI lesion. Finally, we assessed the hypoperfusion intensity ratio (HIR), defined as the proportion of voxels with T_\text{max} ≥2 ≤6 s within the T_\text{max} ≥2 ≤6 s lesion. Similar HIRs were found to be related to angiographic and PWI-based collateral circulation grade in previous reports. We compared the HIR in patients without early recanalization according to their acute reperfusion status.

Statistical Analysis

Clinical and imaging variables were described as median and interquartile range (IQR) or proportions as appropriate. The dichotomized classification of acute reperfusion and recanalization was compared with McNemar test. Statistical significance for intergroup differences was assessed with the Wilcoxon rank-sum test for continuous variables, and Fisher exact test for categorical variables.

Multiple linear regressions were performed to model the volume of salvaged penumbra, lesion growth, and final infarct with the following variables: age, glycemia at admission, time from symptoms onset to first MRI, baseline NIHSS score, DWI lesion volume, volume of tissue at risk, intravenous thrombolysis, acute reperfusion, and recanalization. A stepwise variable selection using the Akaike information criterion (AIC) was used to select the most accurate predictive model for each imaging end point (ie, the model with the lowest AIC and R^2 closest to 1).

Univariate logistic regression was used to evaluate the association between favorable clinical response or good functional outcome and the same explicative variables that were tested in the multiple linear regressions. Significant variables (P<0.05) in univariate analyses were subsequently tested in a stepwise multiple logistic regression to identify independent predictors of a favorable clinical response or good functional outcome. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org/) and SPSS (IBM SPSS Statistics, Armonk, NY).
Results

Of the 168 patients included in I-KNOW, 46 were eligible for this study. Causes for exclusion were missing H3 MRI (n=83), no visible occlusion on H0 MRA (n=23), and incomplete clinical data (n=16). No significant difference in baseline clinical parameters was observed between included and excluded patients. The median delay between the admission and acute follow-up MRI was 170 minutes (IQR, 147–190). Reperfusion and recanalization were thus assessed within 6 hours of symptoms onset in all eligible patients (median delay, 302 minutes; IQR, 282–337).

The initial characteristics of the included patients are presented in Table 1. Stroke pathogeneses were as follows: cardioembolic, n=19 (41%); large artery atherosclerosis, n=16 (35%); other determined causes, n=5 (11%); and undetermined, n=6 (13%). Occlusion levels on MRA were internal carotid artery with M1 (7 patients); M1 (8 patients); internal carotid artery with M2 (5 patients); M2 (16 patients); M3 (9 patients); and A1 (1 patient).

Acute reperfusion was present in 27 (59%) patients. No patient had the no-reflow pattern (recanalization without reperfusion). Conversely, 14 (31%) patients showed acute reperfusion without evidence of recanalization (Figure 1); 13 (28%) patients had both early reperfusion and recanalization. A McNemar test on the dichotomized classification of acute reperfusion and recanalization confirmed a significant discrepancy between these 2 parameters (P=0.0002). Among patients without recanalization, those with acute reperfusion had a significantly lower HIR than patients without reperfusion: 0.08 (IQR, 0–0.27) versus 0.43 (IQR, 0.24–0.51), respectively (P=0.005).

Thirty-four patients (74%) received intravenous tPA (median delay from symptoms onset, 157 minutes; IQR, 135–192). Patients treated with tPA were older (70.5 versus 64.5; P=0.04), had higher NIHSS score (15 versus 8; P=0.003) and were admitted earlier (124 versus 189 minutes; P=0.0007) than those managed conservatively (n=12). There was no significant difference between patients treated and those not treated for baseline volumes of DWI lesion and penumbra, rates of reperfusion (62% versus 50%, respectively; P=0.51) and recanalization (29% versus 25%; P=1.0), and clinical outcomes. Likewise, reperfusion without recanalization was present in 11 of 24 (46%) versus 3 of 9 (33%), respectively (P=0.70).

Compared with those without reperfusion, patients with acute reperfusion had a larger proportion of eventually salvaged penumbra (P<0.0001), smaller lesion growth (P=0.0003), and smaller final infarct size (P=0.0001). A lesser, albeit significant, benefit from recanalization was also observed for the same 3 imaging variables (Figure 2). Patients with acute reperfusion more often experienced favorable clinical response (74% versus 32%; P=0.007) and good functional outcome (56% versus 16%; P=0.01) than those who did not reperfuse. Conversely, the recanalization status had no significant impact on the rate of favorable clinical response (recanalization versus no recanalization: 62% versus 55%; P=0.75) or good functional outcome (46% versus 36%; P=0.74). During the entire cohort, median and percentage DWI lesion reversal volume were 5.4 mL (2.7–11.8) and 43% (22–72), respectively. Reperfused patients had a higher percentage of DWI lesion reversal than those without reperfusion: 68% (33–89) versus 24% (13–31), respectively (P=0.002). No significant difference in volume of DWI lesion reversal was found between patients with or without reperfusion (P=0.14). Imaging and clinical parameters on follow-up are summarized in Table 1.

Table 1. Patients’ Characteristics at Admission and Follow-Up*

<table>
<thead>
<tr>
<th>Baseline parameters</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>69 (64.3–74.0)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>18 (39)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>12 (7–17)</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>6.5 (5.9–7.6)</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI, min</td>
<td>129.5 (94.0–171.2)</td>
</tr>
<tr>
<td>Intravenous tPA, n (%)</td>
<td>34 (74)</td>
</tr>
<tr>
<td>DWI lesion, mL</td>
<td>18.9 (5.5–44.7)</td>
</tr>
<tr>
<td>Tissue at risk, mL</td>
<td>13.4 (4.8–29.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reperfusion, n (%)</td>
<td>27 (59)</td>
</tr>
<tr>
<td>Recanalization, n (%)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Salvaged penumbra, mL</td>
<td>8.6 (2.5–18.6)</td>
</tr>
<tr>
<td>Final infarct, mL</td>
<td>22.8 (4.9–60.4)</td>
</tr>
<tr>
<td>Favorable clinical response, n (%)</td>
<td>26 (57)</td>
</tr>
<tr>
<td>Good functional outcome, n (%)</td>
<td>18 (39)</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Values are given as median and interquartile range or proportions.
The volume of salvaged penumbra was modeled using multiple linear regression, including as explicative variables age, admission glycemia, time from symptom onset to first MRI, baseline NIHSS score, DWI lesion volume, initial at-risk tissue volume, intravenous thrombolysis, acute reperfusion, and recanalization. This full model achieved an adjusted $R^2$ of 0.79 and AIC of 160.97, and was significantly predictive of the volume of salvaged penumbra ($P<0.0001$). Among the tested variables, at-risk tissue volume and acute reperfusion were the only independent predictors of salvaged penumbra volume ($P<0.0001$ and $P=0.018$, respectively; Table 2). Stepwise variable selection using the AIC showed that the most predictive model incorporated only at-risk tissue volume and acute reperfusion, with an AIC=150.46 and $R^2=0.81$ ($P<0.0001$). The other variables, including recanalization, did not significantly improve model accuracy. As baseline NIHSS score and DWI lesion volume showed only a weak, albeit significant, relationship ($R^2=0.20; P=0.001$), models excluding either the former or the latter were tested, and yielded the same results.

The volumes of lesion growth and final infarct were modeled with the same variables as with penumbra salvage (Table 2). Stepwise variable selection showed that a combination of glycemia, initial DWI lesion size, volume of penumbra, and reperfusion produced the best model for both lesion growth (AIC=308.58, $R^2=0.61; P<0.0001$) and final infarct size (AIC=327.91, $R^2=0.75; P<0.0001$). Again, the addition of recanalization did not increase the predictive value of these models.

Univariate logistic regression for predicting good functional outcome showed a significant impact of age, baseline NIHSS score, initial DWI lesion volume, initial at-risk tissue volume, and acute reperfusion (Table 3). Acute recanalization, glycemia, time from symptom onset to MRI, and thrombolysis were not significantly associated with functional outcome in the univariate analysis, and were not considered in the multiple logistic regression. Given the weak relationship between baseline NIHSS score and DWI lesion volume, we tested several multivariate logistic regressions, including either the NIHSS score, DWI lesion size or both, in addition to age, volume of penumbra, and reperfusion. Results differed for each model, and no definite hierarchization was possible among these 5 variables. Acute reperfusion was the only parameter significantly predictive of a favorable clinical response in univariate logistic regression (Table 4).
Discussion

In this study, reperfusion within 6 hours of stroke onset was consistently superior to recanalization in predicting tissue-based and clinical measures of outcome. Reperfusion, but not recanalization, was a significant variable in predictive models of penumbra salvage, lesion growth, and final infarct size. Accordingly, reperfusion was significantly associated with favorable clinical outcome, whereas recanalization was not. Finally, there was a marked discordance between reperfusion and recanalization, as the former occurred, despite persistence of the initial occlusion in nearly a third of our sample. Thus, acute tissue reperfusion without arterial recanalization is not just a frequent, but also a clinically relevant phenomenon. Conversely, no instance of recanalization without reperfusion was identified, suggesting that futile recanalization is infrequent at ultraearly time points.

In this study, we uniquely cross-classified and compared reperfusion and recanalization with multimodal MRI acquired

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**Table 2. Multiple Linear Regression for Predicting the Volume of Salvaged Penumbra, Lesion Growth, and Final Infarct**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized Coefficients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of Salvaged Penumbra ($R^2=0.79$, AIC=160.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>...</td>
<td>0.987</td>
</tr>
<tr>
<td>Age</td>
<td>0.021</td>
<td>0.810</td>
</tr>
<tr>
<td>Glycemia</td>
<td>−0.073</td>
<td>0.326</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI</td>
<td>−0.001</td>
<td>0.991</td>
</tr>
<tr>
<td>Intravenous tPA treatment</td>
<td>−0.013</td>
<td>0.892</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.082</td>
<td>0.391</td>
</tr>
<tr>
<td>Baseline DWI lesion volume</td>
<td>−0.104</td>
<td>0.250</td>
</tr>
<tr>
<td>Baseline at risk tissue volume</td>
<td>0.896</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Early reperfusion</td>
<td>0.261</td>
<td>0.018*</td>
</tr>
<tr>
<td>Early recanalization</td>
<td>−0.034</td>
<td>0.703</td>
</tr>
</tbody>
</table>

Volume of lesion growth ($R^2=0.60$, AIC=314.13)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized Coefficients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>...</td>
<td>0.902</td>
</tr>
<tr>
<td>Age</td>
<td>−0.170</td>
<td>0.174</td>
</tr>
<tr>
<td>Glycemia</td>
<td>0.260</td>
<td>0.015*</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI</td>
<td>−0.048</td>
<td>0.695</td>
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<tr>
<td>Intravenous tPA treatment</td>
<td>0.078</td>
<td>0.550</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.095</td>
<td>0.480</td>
</tr>
<tr>
<td>Baseline DWI lesion volume</td>
<td>0.348</td>
<td>0.001*</td>
</tr>
<tr>
<td>Baseline at risk tissue volume</td>
<td>0.393</td>
<td>0.001*</td>
</tr>
<tr>
<td>Early reperfusion</td>
<td>−0.333</td>
<td>0.029*</td>
</tr>
<tr>
<td>Early recanalization</td>
<td>0.186</td>
<td>0.146</td>
</tr>
</tbody>
</table>

Volume of final infarct ($R^2=0.74$, AIC=333.90)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized Coefficients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>0.758</td>
</tr>
<tr>
<td>Age</td>
<td>−0.144</td>
<td>0.151</td>
</tr>
<tr>
<td>Glycemia</td>
<td>0.179</td>
<td>0.034*</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI</td>
<td>−0.016</td>
<td>0.873</td>
</tr>
<tr>
<td>Intravenous tPA treatment</td>
<td>0.073</td>
<td>0.482</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.088</td>
<td>0.412</td>
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<tr>
<td>Baseline DWI lesion volume</td>
<td>0.671</td>
<td>&lt;0.0001*</td>
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<tr>
<td>Baseline at risk tissue volume</td>
<td>0.136</td>
<td>0.121</td>
</tr>
<tr>
<td>Early reperfusion</td>
<td>−0.253</td>
<td>0.037*</td>
</tr>
<tr>
<td>Early recanalization</td>
<td>0.109</td>
<td>0.283</td>
</tr>
</tbody>
</table>

The $R^2$ and AIC for each full model are given. AIC indicates Akaike Information Criterion; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

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**Table 3. Univariate Logistic Regressions for Predicting a Good Functional Outcome (Modified Rankin Scale, 0–1)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.92</td>
<td>0.85–0.98</td>
<td>0.017*</td>
</tr>
<tr>
<td>Glycemia</td>
<td>0.75</td>
<td>0.46–1.07</td>
<td>0.167</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI</td>
<td>1.00</td>
<td>0.99–1.00</td>
<td>0.443</td>
</tr>
<tr>
<td>Intravenous tPA treatment</td>
<td>0.87</td>
<td>0.23–3.47</td>
<td>0.834</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.79</td>
<td>0.67–0.90</td>
<td>0.002*</td>
</tr>
<tr>
<td>Baseline DWI lesion volume</td>
<td>0.94</td>
<td>0.88–0.98</td>
<td>0.014*</td>
</tr>
<tr>
<td>Baseline at risk tissue volume</td>
<td>0.94</td>
<td>0.88–0.98</td>
<td>0.021*</td>
</tr>
<tr>
<td>Early reperfusion</td>
<td>6.67</td>
<td>1.73–33.74</td>
<td>0.010*</td>
</tr>
<tr>
<td>Early recanalization</td>
<td>1.50</td>
<td>0.40–5.58</td>
<td>0.541</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Significant variables for each model.

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**Table 4. Univariate Logistic Regression for Predicting a Favorable Clinical Response (Reduction of $\geq 8$ Points on the NIHSS Score Between Admission and 1 Mo, or a NIHSS Score of 0–1 at 1 Mo)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.91–1.02</td>
<td>0.274</td>
</tr>
<tr>
<td>Glycemia</td>
<td>0.82</td>
<td>0.56–1.12</td>
<td>0.232</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI</td>
<td>0.99</td>
<td>0.98–1.00</td>
<td>0.116</td>
</tr>
<tr>
<td>Intravenous tPA treatment</td>
<td>2.26</td>
<td>0.60–9.12</td>
<td>0.233</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.98</td>
<td>0.89–1.08</td>
<td>0.713</td>
</tr>
<tr>
<td>Baseline DWI lesion volume</td>
<td>0.99</td>
<td>0.97–1.00</td>
<td>0.168</td>
</tr>
<tr>
<td>Baseline at risk tissue volume</td>
<td>0.97</td>
<td>0.93–1.00</td>
<td>0.107</td>
</tr>
<tr>
<td>Early reperfusion</td>
<td>6.19</td>
<td>1.78–24.27</td>
<td>0.006*</td>
</tr>
<tr>
<td>Early recanalization</td>
<td>1.33</td>
<td>0.36–5.23</td>
<td>0.667</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Significant variables for each model.
≤6 hours of stroke onset (median delay, 5 hours). Our results showing greater accuracy of reperfusion over recanalization in predicting outcome are overall consistent with previous similar data acquired at later time points. In a previous MR-based study, reperfusion assessed at days 3 to 5 predicted good clinical outcome independently of recanalization, but tissue end points were not reported.\(^6\) In a smaller CT-based study, reperfusion assessed at mean 25 hours was a stronger predictor of final infarct volume than recanalization but had no significant impact on clinical end points.\(^8\) Another recent CT-based study also reported superiority of reperfusion during recanalization assessed ≤24 hours after onset in predicting clinical outcome. However, although the data suggested smaller infarct volumes with reperfusion than recanalization, no direct comparison was presented.\(^9\) Thus, our data obtained in the ultraearly stage point to the superior predictive value of reperfusion for both imaging and clinical end points.

Our findings are also consistent with 2 additional recent reports that explored the acute phase but did not cross-classify reperfusion and recanalization. In Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution-2 (DEFUSE-2), angiographic reperfusion (modified treatment in cerebral ischemia ≥2b) improved clinical outcome, whereas no significant amelioration was observed with recanalization (arterial occlusive lesion ≥3). Both the angiographic end points were associated with reduced lesion growth on MRI.\(^22\)

Angiographic reperfusion relies on a qualitative visual assessment probably less accurate and reproducible than voxel-based measurements on MRI or CT. DEFUSE-2 also included perfusion MRI to assess reperfusion at a median delay of 10 hours, but the direct comparison of reperfusion versus recanalization as outcome predictors is still unpublished. Another recent study showed that DWI lesion reversal at 24 hours together with younger age, lower admission NIHSS score and early MR-based reperfusion, but not recanalization, predicted good clinical outcome.\(^23\) Again, neither cross-classification of reperfusion and recanalization nor analysis of their respective predictive value for imaging end points were presented.

Our results show that within 6 hours from stroke onset reperfusion not uncommonly represents an event distinct from recanalization. Indeed, 31% of the whole sample had reperfusion without recanalization, which accounted for ≈40% of the nonrecanalizers, a markedly larger proportion than previously reported (7%–9%).\(^8,9,16\) This difference may be explained by our ultraearly time frame, and previous studies may have been confounded by futile recanalization. Conversely, our acute assessment may also explain the lack of no-reflow pattern, which probably develops at a later interval. Indeed, no-reflow was observed in 9% of patients assessed ≤10 hours after stroke onset,\(^16\) a proportion that increased to 12% to 23% after 24 hours.\(^7,9\)

Reperfusion without recanalization is probably related to retrograde reperfusion through leptomeningeal collaterals, possibly thanks to reduced resistance of arteriolar channels or improved systemic perfusion pressure and blood rheology. Previous studies have shown that good collaterals reduce penumbral loss and enhance the likelihood of reperfusion and favorable clinical outcome.\(^24\) In support of this interpretation, the lower HIR observed in this patient subset suggests that they had better collaterals at baseline than those without subsequent reperfusion. The rare occurrence of arterial occlusive lesion=1 score in this subgroup (14%) further supports the idea that anterograde reperfusion was not a significant contributor. Dynamic mapping of collateral flow using endovascular angiography or PWI source images would help clarify this phenomenon.\(^26,28\)

The results from linear regressions were otherwise consistent with current knowledge on DWI lesion progression. We confirmed that baseline DWI lesion volume is a strong predictor of lesion growth and final infarct size. Similarly, the initial extent of at-risk tissue was, as expected, a significant predictor of both penumbral salvage and lesion growth. Although baseline penumbra volume was not independently associated with final infarct size, variable selection with the AIC kept this parameter in the final optimal model. Glycemia was positively associated with lesion growth and final infarct size, even though the majority of our patients had normal to mildly elevated glucose levels (Table 1). This is in line with the known negative impact of hyperglycemia on clinical outcome in acute ischemic stroke.\(^29,30\)

Acute DWI lesion size was not confirmed as an independent predictor of clinical evolution when admission NIHSS and acute reperfusion were included in the logistic regressions. In our sample, voxel-based analyses revealed DWI lesion reversal ≥10 mL and ≥10% at 1 month in 16 (35%) patients, as compared with a recently reported rate of 17% at 24 hours.\(^31\) This substantial lesion reversal may have reduced the prognostic value of acute DWI lesion volume in our ultraearly study.

Limitations of our study mainly relate to the retrospective nature of the analysis in a limited sample size. Specifically, larger prospective cohorts are required to confirm the frequency of reperfusion without recanalization and no-reflow patterns at ultraearly time points. Reperfusion and recanalization were analyzed within 6 hours, that is, during the period when revascularization is expected to have the greatest impact.\(^32\) However, some patients may also benefit from delayed recanalization. MRA is probably less sensitive than perfusion imaging for identifying distal branch occlusions in acute stroke. Comparing MR-based reperfusion and recanalization could, therefore, be biased against the latter. We included patients with mainly distal (>M1) occlusions, and accordingly the penumbra volume was small (median, 13.4 mL), which is smaller than previously reported even considering the use of a stringent \(T_{\text{max}}\) penumbra threshold.\(^16\) Our results, therefore, apply only to this population and will need confirmation in cohorts with more prevalent proximal occlusions. In our sample, intravenous thrombolysis was not associated with increased reperfusion or recanalization, or favorable clinical evolution.

I-KNOW was not designed to assess the efficacy of tPA or the merits of MRI to guide therapy. Treatment decisions were not randomized or otherwise controlled. The inclusion criteria and sample size probably explain the imbalance of baseline characteristics between patients treated with tPA or not, and the apparent lack of benefit of thrombolysis. Nevertheless, this negative finding does suggest that tPA may not be a significant facilitator of collateral reperfusion. Finally, as in previous studies, reperfusion was defined according to a prespecified perfusion cutoff (\(T_{\text{max}} \geq 6\) s) and relative volume difference
from baseline (eg, 50%).17,26 The former has been validated against positron emission tomography33,34 and is widely used in randomized trials, whereas the latter has been validated against clinical end points.17 This dichotomized approach is consistent with the validated penumbra model,35 but does not capture the heterogeneity of the perfusion deficit and subsequent reperfusion, and may partly underlie the frequent occurrence of beneficial reperfusion, despite actual recanalization. Future studies should quantify voxel-wise the degree of reperfusion in addition to its anatomic extent.

In conclusion, in our population reperfusion within 6 hours was superior to recanalization in predicting imaging and clinical outcomes, and occurred, despite lack of MR-based recanalization in 30% of patients. In addition, recanalization was always associated with tissue reperfusion, suggesting that no-reflow and futile recanalization are not prevalent in this early time frame. Ultraearly reperfusion, therefore, may be the strongest predictor of, and consequently a reliable surrogate for, clinical outcome. It should, therefore, be considered part of the systematic evaluation of novel therapeutic approaches in ischemic stroke.

Sources of Funding
This work was supported by the European Commission’s Sixth Framework Program (grant 027924).

Disclosures
None.

References


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Stroke, published online April 23, 2015;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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MRI protocol
At admission, all patients underwent DWI (with 3 or 12 directions; repetition time >6000s, field of view 24cm, matrix 128 x 128, slice thickness 3 or 5mm), Fluid-Attenuated-Inversion-Recovery (repetition time, 8690ms; echo time, 109ms; inversion time 2500ms; flip angle, 150°; field of view, 21cm; matrix, 224x256; 24 sections; section thickness, 5mm; slice gap, 1mm), T2-weighted gradient echo, time of flight MRA and PWI (echo time 30-50ms, repetition time 1500ms, field of view 24cm, matrix 128x128, 18 slices, thickness 5mm with gap=1mm ; gadolinium contrast at 0.1mmol/kg). The same protocol was repeated 3hrs after the first scan to assess acute reperfusion and recanalization (H3). A final MRI was performed at 1 month to map the final infarct on FLAIR.

Image analysis
Lesion segmentation and PWI processing
Baseline DWI lesions (b=1000 images) and final FLAIR infarcts were semi-automatically outlined using an in-house developed software. After motion correction, maps of the time-to-maximum of the residue function ($T_{\text{max}}$) were computed by circular singular value decomposition of the tissue concentration curves with an arterial input function from the contralateral middle cerebral artery (Penguin software, MATLAB 2010b; MathWorks Inc., Natick, MA, USA). All images were coregistered within subjects to the baseline MRI using Statistical Parametric Mapping 8 (SPM; http://www.fil.ion.ucl.ac.uk/spm).
Reference

6시간 이내 재판류가 재판형성에 비해 반응영 희박, 병변 증가, 최종 경색 및 임상적 예후 예측에 더 우월하다

Reperfusion Within 6 Hours Outperforms Recanalization in Predicting Penumbra Salvage, Lesion Growth, Final Infarct, and Clinical Outcome

Tae-Hee Cho, PhD; Norbert Nighoghossian, PhD; Irene Klerke Mikkelsen, PhD; Laurent Derex, PhD; Marc Hermier, PhD; Salvador Pedraza, MD; Jens Fiehler, MD; Leif Östergaard, PhD; Yves Berthozène, PhD; Jean-Claude Baron, ScD

(Stroke. 2015;46:1582-1589.)

Key Words: magnetic resonance imaging ■ reperfusion

배경과 목적
전신향 난중 환자의 조직 및 임상 예후를 예측하는 데 있어 재판형성에 대한 재판류의 상대적 장점이 증상 발생 12시간 이상 경과한 환자를 대상으로 하여 보고된 바 있다. 비양양성(non-nutritional) 재판류, 헛된(futile) 재판형성 및 재혈류 부재현상 (no-reflow)과 같은 뒤늦게 나타날 수 있는 교란요인을 피하기 위해 연구자들은 재판류와 재판형성에 대한 초-초기(ultraearly) 평가를 시행하였다.

방법
다기관 전합적 데이터베이스에서, 난자가공명영상을 촬영에서 보이는 급성 패혈이 있으며 6시간 이내에 추적 난 자기공명영상 촬영으로 혈류 재공급 및 혈관 재관형성이 평가된 83명의 환자를 확인하였다. 반응영의 회복, 합성강조영상 병변의 증가, 1개월 시점의 최종 경색 등을, 기저 임상 및 영상지표와 급성기 재판류 또는 재판형성을 포함한 다중적선형회귀분석으로 모델링하였다. 가장 적합한 예측 인자를 아카이케 정보 침소(Akaike information criterion)로 선택하였다. 단변량 및 다변량로지스틱회귀분석으로 임상 예후를 예측하는 임상-영상 지표를 선정하였다.

결과
입원 당시 MRI에 나타난 M1 패혈이 15명(33%)의 환자에서 확인되었고, 반응영 부피의 증가값은 13.4 mL이었다. 급성 재판류는 27명(59%)의 환자에서 관찰되었고, 재판형성이 이루어지지 않은 환자 중 42%에서 재판류가 확인되었다. 재판류 여부와 재판형성 여부는 상호간의 일치성이 없었다(P=0.0002). 6시간 이내의 재판류는 반응영 회복 증가, 병변 증가 약제, 최종 경색 크기에 유의한 예측 인자(P<0.05)였다. 재판형성은 모델의 예측력을 증가시키지 않았다. 재판형성이 아닌 재판류가 로지스틱회귀분석에서 양호한 임상 예후와 연관되어 있었다.

결론
6시간 이내의 재판류는 조직 및 임상적 예후 예측에 있어 혈관 재관형성에 비하여 우월하였다. 재판형성을 동반하지 않는 재판류는 빈번하였고, 이는 연속감절이론을 통한 혈청학적 체류공급과 관련 있을 것이다. 급성 재판류는 임상 예후에 있어 중요한 예측 인자이며, 아마도 믿을 수 있는 대표자자가 될 것이다.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.91-1.02</td>
<td>0.274</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.82</td>
<td>0.56-1.12</td>
<td>0.232</td>
</tr>
<tr>
<td>Time from symptoms onset to MRI</td>
<td>0.99</td>
<td>0.98-1.00</td>
<td>0.116</td>
</tr>
<tr>
<td>Intravenous tPA treatment</td>
<td>2.26</td>
<td>1.60-9.12</td>
<td>0.233</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
<td>0.98</td>
<td>0.89-1.08</td>
<td>0.713</td>
</tr>
<tr>
<td>Baseline DWI lesion volume</td>
<td>0.99</td>
<td>0.97-1.00</td>
<td>0.168</td>
</tr>
<tr>
<td>Baseline at risk tissue volume</td>
<td>0.97</td>
<td>0.93-1.00</td>
<td>0.107</td>
</tr>
<tr>
<td>Early reperfusion</td>
<td>6.19</td>
<td>1.78-24.27</td>
<td>0.006*</td>
</tr>
<tr>
<td>Early recanalization</td>
<td>1.33</td>
<td>0.36-5.23</td>
<td>0.667</td>
</tr>
</tbody>
</table>

DWI indicates diffusion-weighted imaging; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

*Significant variables for each model.

Figure 1. Patient with acute reperfusion without recanalization (baseline National Institutes of Health Stroke Scale [NIHSS]; 12). A. Admission magnetic resonance imaging (MRI) showing, from left to right, right internal carotid artery and M1 occlusion (arrowhead) with a corresponding perfusion deficit on the T_max map (red overlay indicates T_max<6 s) and limited lesions on diffusion-weighted imaging (arrow). B, Follow-up MRI at 3 hours disclosed significant reperfusion (no voxel >6 s on the presented T_max slice), despite persistent arterial occlusion (arrowhead). C, Final Infarct on Fluid-Attenuated-Inversion-Recovery images at 1 month (arrow). One-month outcome was favorable (NIHSS, 0; modified Rankin Scale, 0).

Table 4. Univariate Logistic Regression for Predicting a Favorable Clinical Response (Reduction of ≥8 Points on the NIHSS Score Between Admission and 1 Mo, or a NIHSS Score of 0–1 at 1 Mo)