The Cortical Ischemic Core and Not the Consistently Present Penumbra Is a Determinant of Clinical Outcome in Acute Middle Cerebral Artery Occlusion

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Background and Purpose—Patient selection for acute stroke therapy based on physiology rather than on time may lead to expansion of the therapeutic window, improved outcomes, and fewer side effects than currently achieved. This approach requires early determination of both irreversible (core) and reversible (penumbra) ischemia in acute stroke.

Methods—Using established perfusion thresholds, we characterized the relationship among core, penumbra, and brain tissue perfused above penumbral thresholds (non-core/non-penumbra [NC/NP]) in 36 patients with middle cerebral artery (MCA) stem occlusion who underwent quantitative cerebral blood flow (CBF) assessment with xenon-enhanced CT within 6 hours of symptom onset. Results were expressed as percentage of core, percentage of penumbra, or percentage of NC/NP relative to the ipsilateral cortical MCA territory and were correlated with clinical and radiological variables and with clinical outcomes.

Results—While great variability in the mean±SD percentage of core (37.6±18.7) and NC/NP (30.3±16.6) was observed, the percentage of penumbra was relatively constant from individual to individual, constituting approximately one third of the cortical MCA territory (32.1±7). In univariable and multivariable analyses, percent core and not percent penumbra was significantly associated with outcome.

Conclusions—in acute MCA occlusion, penumbra is consistently present within a relatively narrow range, despite great variability in the size of core. This may explain why the core and not the penumbra is the main determinant of outcome in our group of patients. Recanalization therapy in acute MCA occlusion should ideally be guided by diagnostic methods capable of rapidly and reliably identifying irreversible ischemia. (Stroke. 2003;34:2426-2435.)

Key Words: brain ischemia ■ cerebral blood flow ■ computed tomography, x-ray computed ■ middle cerebral artery occlusion ■ penumbra ■ xenon
and heterogeneous vascular occlusion sites. The objective of this study was to assess the extent of core and penumbra in acute MCA stem occlusion and to determine their relationship with clinical outcome.

Subjects and Methods
This study was conducted with institutional review board approval (institutional review board No. 020178).

Patients
Thirty-six patients with acute ischemic stroke were included according to the following criteria: onset of symptoms within 6 hours of undergoing a Xe-CT CBF study, MCA stem occlusion determined by conventional angiogram or CT angiogram at the time of the CBF study, and lack of significant motion artifact on the CBF study.

We retrospectively selected our patients from a prospective registry of 378 consecutive individuals admitted to the University of Pittsburgh Stroke Service between January 1997 and April 2001 who underwent a Xe-CT CBF study, of which 160 patients were studied within 6 hours of symptoms onset. Fifty patients had MCA occlusion. Fourteen of these 50 patients were excluded from further analysis because of excessive motion artifact. Clinical and demographic data were obtained from either a prospectively acquired clinical database or from medical records. All patients screened had a documented time of symptom onset and a documented time at which the CBF study was performed. Outcome data at 3 to 6 months were available from medical records or through telephone interview. To obtain a binary outcome, outcomes were classified as favorable, representing no or minimal disability and able to perform all prior activities (modified Rankin Scale [mRS] score 0 to 1) or unfavorable, representing death or disability (mRS score 2 to 6).

Xe-CT CBF Data Analysis
Details of the stable Xe-CT CBF technique have been published previously. Four CT images of 1-cm slice thickness were obtained along the orbitomeatal line (Figure 1A). Although the duration of each study was not recorded, a standard head CT followed by a Xe-CT CBF study typically requires approximately 20 minutes for acquisition and 5 additional minutes for CBF calculation and display. Our analysis included the ipsilateral and contralateral outer 2 cm of cortical MCA territory of all 4 levels, which, for standardization purposes, was defined by anatomic templates that are part of the Xe-CT computer software (Diversified Diagnostic Products Inc) (Figure 1B). A computer-generated division of the entire cortex into 20 regions of interest (ROIs) was also obtained (Figure 1B). A computer-generated division of the entire (ie, not separated by flow thresholds) ipsilateral cortical MCA territory on each side is 24.

Voxels (1×1×10 mm) corresponding to a CBF range of 0 to 8 mL/100 g per minute were separated out of each level and counted by the computer software in the ipsilateral and contralateral MCA cortex (Figure 1D). Areas of lack of flow due to prominent cortical sulci were not excluded from analysis. For each side, voxels corresponding to this flow range in all 4 levels were summed, and the number obtained was divided by the sum of voxels corresponding to the entire (ie, not separated by flow thresholds) ipsilateral cortical MCA territory in the same 4 levels and expressed as percentage of ischemic core to the cortical MCA territory. In a similar fashion, the number of voxels in the cortical MCA territory corresponding to a CBF range of 8 to 20 mL/100 g per minute (Figure 1E) and ≥20 mL/100 g per minute (Figure 1F) were summed and divided by the total number of voxels for the MCA cortex to yield percentage of penumbra and non-core/non-penumbra (NC/NP) values, respectively. To include the deep structures supplied by the MCA in our analysis, mean CBF values for the entire ipsilateral and contralateral MCA territory (cortex and deep structures) were obtained with the use of previously established anatomic templates, according to which the MCA territory was manually tracked. In these tracked areas, regional CBF values were computed by the Xe-CT software package, yielding mean total MCA CBF values for each of the 4 levels. These values were then averaged into 1 value representing mean total MCA CBF.

ROI-based analysis of percent core, penumbra, and NC/NP for ipsilateral and contralateral cortical MCA territory was performed to compensate for potential errors induced by a voxel-based analysis.

The number of cortical ROIs (mean, 314 voxels per ROI) with a mean CBF of <8, 8 to 20, and ≥20 mL/100 g per minute, respectively, was divided by 24. These values were correlated with the percentages of core, penumbra, and NC/NP obtained through voxel-based analysis.

Other Imaging Data Analysis
Noncontrasted baseline CT scans were reviewed by a blinded neuroradiologist (S.G.) and assessed for early CT changes involving greater or less than one third of MCA territory. Follow-up imaging studies (CT or MRI) were reviewed by a blinded coinvestigator (H.Y.), and levels in the brain similar to the levels used by the Xe-CT CBF software were analyzed and divided into the same ROIs. Each cortical MCA ROI was deemed infarcted or noninfarcted, and percent ipsilateral cortical MCA infarction on follow-up imaging was determined by dividing the number of infarcted ipsilateral cortical ROIs by 24.

In the 23 patients who underwent intra-arterial thrombolytic therapy, MCA recanalization status at 2 hours after angiogram was categorized as absent (Thrombolysis in Myocardial Infarction [TIMI] grades 0 and 1) or present (TIMI grades 2 and 3).

Statistical Analyses
Statistical analyses were performed with the Intercooled Stata 7.0 (Stata Inc) statistical software package. Pearson and Spearman correlation coefficients were used for correlations involving normally distributed and nonnormally distributed variables, respectively. The r test was used to compare means of normally distributed variables, and the Wilcoxon matched-pairs signed rank test was performed to assess the equality of rank distributions between normally distributed variables. ANOVA was used to compare means of normally distributed variables across several categorical variables of interest. Multivariate analysis of the relation between several variables of interest was performed in a stepwise logistic regression model in which entry was set at a univariate association with a probability value of ≤0.1.

Results
Median age was 69 years (range, 24 to 89 years), with a female-to-male ratio of 2:1. The median National Institutes of Health Stroke Scale (NIHSS) score was 18 (range, 2 to 25). Twenty-six patients received thrombolytic therapy; 3 patients received intravenous thrombolyis, 12 patients received intra-arterial thrombolysis, and 11 patients received combined intravenous/intraarterial thrombolysis. The median time from onset of symptoms to the CBF study was 240 minutes (range, 120 to 360 minutes). For thrombolysis-treated patients, the mean time interval between symptom onset and thrombolysis was 218 minutes (range, 120 to 360). Eleven of 36 patients (30.56%) were intubated and mechanically ventilated. Three of 36 patients (8.33%) received deep sedation with propofol, and 24 patients (66.67%) received sedation with lorazepam, midazolam, or fentanyl.

Great variability in the mean±SD percentage of core (37.6±18.7%; range, 7.6% to 70.5%) and NC/NP (30.3±16.6%; range, 4.7% to 66%) was observed. However, the percentage of penumbra was relatively constant (32.1±7%; range, 16.2% to 46.9%) (Figure 2).
Figure 1. Xe-CT CBF assessment with confidence maps (A). Anatomic templates that are part of the Xe-CT computer software divided the outer 2 cm of the cortex into arterial territories (B) and 20 standard ROIs per slice (C). CBF voxels from ipsilateral and contralateral cortical MCA territories, corresponding to a range of 0 to 8 (core), 8 to 20 (penumbra), and >20 mL/100 g per minute (NC/NP) (F) were separated out of level 3.
Figure 1 (continued).
Ipsilateral percentage of core and mean ipsilateral MCA CBF did not correlate with the time after symptom onset at which the CBF study was performed, with the admission serum glucose level, or with mean arterial pressure. These values did not significantly differ between sedated and nonsedated patients. Ipsilateral percentage of core was strongly inversely correlated with ipsilateral percent NC/ NP and with ipsilateral mean MCA CBF and was moderately inversely correlated with percent penumbra and with NIHSS score (Table 1). There was a high correlation between ipsilateral and contralateral percentages of core, penumbra, and NC/NP obtained through voxel-based analysis and those

**Figure 2.** Percentages of core, penumbra, and NC/NP in the ipsilateral cortical MCA territory of 36 patients with acute MCA occlusion.

**TABLE 1. Predictors of Favorable Outcome by Univariate Analysis and Correlations Involving Percentage of Ipsilateral Core**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
<th>ρ (Spearman)</th>
<th>P (Spearman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core, %*</td>
<td>0.93</td>
<td>0.87–0.98</td>
<td>0.018</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Penumbra, %*</td>
<td>1.03</td>
<td>0.92–1.16</td>
<td>0.5</td>
<td>−0.48</td>
<td>0.003</td>
</tr>
<tr>
<td>NC/NP, %</td>
<td>1.07</td>
<td>1.01–1.13</td>
<td>0.017</td>
<td>−0.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Final infarct, %</td>
<td>0.96</td>
<td>0.93–0.99</td>
<td>0.018</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean ipsilateral MCA CBF, mL/100 g/min</td>
<td>1.27</td>
<td>1.03–1.4</td>
<td>0.021</td>
<td>−0.95</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, y*</td>
<td>0.89</td>
<td>0.82–0.97</td>
<td>0.009</td>
<td>0.09</td>
<td>0.6</td>
</tr>
<tr>
<td>NIHSS score*</td>
<td>0.67</td>
<td>0.50–0.91</td>
<td>0.010</td>
<td>0.38</td>
<td>0.02</td>
</tr>
<tr>
<td>MAP, mm Hg*</td>
<td>0.94</td>
<td>0.90–0.99</td>
<td>0.031</td>
<td>0.28</td>
<td>0.09</td>
</tr>
<tr>
<td>Glucose, mg/dL*</td>
<td>0.97</td>
<td>0.94–1.0</td>
<td>0.117</td>
<td>0.25</td>
<td>0.14</td>
</tr>
<tr>
<td>Time to CBF, min</td>
<td>1.008</td>
<td>0.99–1.02</td>
<td>0.134</td>
<td>−0.03</td>
<td>0.8</td>
</tr>
<tr>
<td>Thrombolytic therapy</td>
<td>0.97</td>
<td>0.51–1.87</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel recanalization†</td>
<td>7.5</td>
<td>0.69–1.24</td>
<td>0.097</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal CT</td>
<td>2.88</td>
<td>0.55–4.94</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1/3 MCA territory CT changes</td>
<td>0.65</td>
<td>0.12–3.26</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Per increase in unit.
†Data available in 23 patients only.
‡Spearman correlation coefficient and §significance, between variables of interest and percent ipsilateral core.
obtained through ROI-based analysis (Spearman \( r = 0.93 \), \( P < 0.0001 \) for percent core; \( r = 0.75 \), \( P < 0.0001 \) for percent penumbra; and \( r = 0.95 \), \( P < 0.0001 \) for percent NC/NP) (Table 2).

We observed significant differences in mean CBF values between ipsilateral and contralateral total MCA CBF (17.6 versus 37.5 mL/100 g per minute, respectively; \( P < 0.000001 \)) and a high correlation between mean ipsilateral total MCA CBF and mean ipsilateral cortical MCA CBF (Spearman \( r = 0.94 \), \( P < 0.0001 \)). Patients with favorable outcomes had significantly lower percent core than patients with unfavorable outcomes (mean \( \pm \) SD, 26 \( \pm \) 14.1%; range, 9.5% to 50.4% versus mean \( \pm \) SD, 45 \( \pm \) 17.6%; range, 7.6% to 70.5%; \( P = 0.0073 \)). This difference remained significant (\( P = 0.04 \)) after we controlled for other variables (age, NIHSS score, mean arterial pressure) that were found to be significantly associated with favorable outcome. There was no significant difference in percent penumbra in the favorable outcome group compared with the unfavorable outcome group (32.6% versus 31%; \( P = 0.5 \)). In a stepwise logistic regression model that included core, penumbra, age, NIHSS score, and mean arterial pressure, variables that were found to be significantly associated with favorable outcomes in univariate analyses (Table 1), only percent core (odds ratio [OR], 0.85; 95% CI, 0.74 to 0.98; \( P = 0.025 \)) and age (OR, 0.85; 95% CI, 0.73 to 0.97; \( P = 0.020 \)) remained significantly associated with favorable outcome. When percent core and percent penumbra were substituted with ipsilateral mean MCA CBF, age (OR, 0.84; 95% CI, 0.73 to 0.98; \( P = 0.025 \)) and mean MCA CBF (OR, 1.39; 95% CI, 1.05 to 1.84; \( P = 0.02 \)) were significantly associated with favorable outcome. Substituting total ipsilateral MCA CBF for cortical MCA CBF in the logistic regression model yielded similar results; age (OR, 0.86; 95% CI, 0.76 to 0.98; \( P = 0.0026 \)) and ipsilateral total MCA CBF (OR, 1.33; 95% CI, 1.05 to 1.69; \( P = 0.016 \)) were the only factors found to be significantly associated with favorable outcome.

In 35 patients, follow-up brain imaging scans (CT, \( n = 21 \); MRI, \( n = 14 \)) at a median number of 2.5 (range, 1 to 350) days for CT and 2 (range, 1 to 238) days for MRI were available for review. One patient, who had large areas of hypodensity on admission CT, died shortly after admission, such that no follow-up scans were performed. In this patient, areas of hypodensity on baseline CT were considered infarcted. Median percent final infarct relative to ipsilateral cortical MCA territory was 50% (range, 0% to 100%). A strong and statistically significant correlation was found between percent core and percent final infarct (\( p = 0.63, \ P < 0.0001 \)) in contrast to a weak and nonsignificant negative correlation found

### Table 2. Percent Core, Penumbra, and NC/NP in the Ipsilateral Versus Contralateral Cortical MCA Territory in 36 Patients With Acute MCA Occlusion and Correlation Between Voxel-Based and ROI-Based Analyses for the Ipsilateral Hemisphere

<table>
<thead>
<tr>
<th></th>
<th>Voxel based</th>
<th></th>
<th>ROI based</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>% core</td>
<td>37.6</td>
<td>18.7</td>
<td>Core, %</td>
<td>6†</td>
</tr>
<tr>
<td>% penumbra</td>
<td>32.1</td>
<td>7</td>
<td>Penumbra, %</td>
<td>21.3</td>
</tr>
<tr>
<td>% NC/NP</td>
<td>30.3</td>
<td>16.6</td>
<td>NC/NP, %</td>
<td>72.6</td>
</tr>
</tbody>
</table>

**P** and † Spearman correlation coefficient and significance respectively for data obtained through voxel-based and ROI-based analysis in the ipsilateral hemisphere.

‡Likely represents sulcal artifact and is virtually eliminated in the ROI-based analysis.

### Table 3. Mean \( \pm \) SD for Percent Core, Percent Penumbra, and Mean MCA CBF by Vessel Recanalization and Outcomes

<table>
<thead>
<tr>
<th>Outcome (mRS)</th>
<th>Recanalized (TIMI 2–3)</th>
<th>Not Recanalized (TIMI 0–1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable (mRS 0–1)</td>
<td>n=5</td>
<td>n=1</td>
</tr>
<tr>
<td>% core*</td>
<td>25±13%</td>
<td>% core*</td>
</tr>
<tr>
<td>% penumbra†</td>
<td>34±4%</td>
<td>% penumbra†</td>
</tr>
<tr>
<td>MCA CBF‡</td>
<td>22±5 mL/100 g/min</td>
<td>MCA CBF‡</td>
</tr>
<tr>
<td>Unfavorable (mRS 2–6)</td>
<td>n=6</td>
<td>n=9</td>
</tr>
<tr>
<td>% core*</td>
<td>35±20%</td>
<td>% core*</td>
</tr>
<tr>
<td>% penumbra†</td>
<td>30±7%</td>
<td>% penumbra†</td>
</tr>
<tr>
<td>MCA CBF‡</td>
<td>18±8 mL/100 g/min</td>
<td>MCA CBF‡</td>
</tr>
</tbody>
</table>

\* \( P = 0.05 \), † \( P = 0.7 \), ‡ \( P = 0.056 \) by ANOVA.
between percent penumbra and percent final infarct ($p = -0.29$, $P = 0.077$).

A subgroup analysis was conducted on the 21 patients in whom both recanalization data at 2 hours after angiography and outcome data were available. In this group of patients, favorable outcomes were observed in 1 of 10 patients (10%) who did not recanalize (TIMI grade 0 to 1) versus 5 of 11 patients (45%) who recanalized (TIMI grade 2 to 3) ($P = 0.14$, Fisher exact test). In both patients who did recanalize and those who did not recanalize, mean percent core was higher and mean MCA CBF was lower in patients with unfavorable outcome than in patients with favorable outcome (Table 3). These differences were significant across the 4 categories of patients both for percent core and for mean MCA CBF. By contrast, no significant differences could be detected between these 4 categories when percent penumbra was substituted for percent core (Table 3).

**Discussion**

In patients with acute MCA occlusion, the ischemic penumbra in the cortical MCA territory is consistently present and relatively constant within 6 hours of symptom onset. We observed high individual variability in the amount of core, which is not explained by the different time intervals between symptom onset and CBF study. Rather, it likely reflects interindividual differences in the collateral blood supply, a major determinant of regional CBF in large-vessel occlusion.

The observation that, contrary to the highly variable core, penumbra is relatively constant may explain why the volume of core and not that of penumbra is a determinant of clinical outcome in acute MCA occlusion. Our subanalysis performed on patients with known vessel recanalization status suggests that this may apply to both patients who do and patients who do not recanalize. When a large core volume is present, any benefit of penumbral salvage through vessel recanalization may be obscured by the extensive deficit and propensity to complications attributable to the core. Therefore, recanalization therapy may preferentially be guided by diagnostic methods capable of rapidly and reliably identifying irreversible ischemia.

The importance of the core as a predictor of outcome in patients undergoing intravenous thrombolysis is underscored by studies using pretreatment MRI in patients with large-vessel occlusion, showing that clinical outcome correlated significantly with lesion volume on diffusion-weighted imaging (thought to approximate core) but not with the volume on perfusion/diffusion imaging mismatch (thought to approximate penumbra). Other authors have found that in patients studied acutely with CT perfusion in whom vessel recanalization was determined at 3 days, the ratio of penumbra to penumbra plus core (but not core or penumbra alone) was predictive of clinical outcome in patients who recanalized. In general, data regarding the importance of core versus penumbra in patients undergoing thrombolysis are limited because of different methodologies used and small sample sizes involved, such that further prospective studies are needed to clarify this issue.

Penumbral tissue of an extent similar to that reported in this study, present even beyond 6 hours, was reported by investigators using PET or MRI in acute stroke. When penumbra was estimated on the basis of perfusion/diffusion imaging mismatch on brain MRI, its presence was found to be highly correlated with the presence of large-vessel occlusion. We analyzed only patients with same vascular occlusion site to eliminate an important confounding factor in the assessment of penumbral extent. As such, our results may apply only to a selected group of patients. The high degree of correlation between the presence of penumbra and the presence of large-vessel occlusion may explain why other studies, which do not include data regarding vessel patency, failed to confirm the existence of significant penumbral areas in acute stroke.

Kaufmann et al. using quantitative CBF assessment with Xe-CT, reported that in 20 patients with large-vessel occlusion studied within 6 hours, ipsilateral penumbra was negligible. Several methodological differences between the analysis of Kaufmann et al and ours may account for these discrepant conclusions. (1) Kaufmann et al inferred that the “real” penumbra represents the difference between mean percentages of brain perfused at penumbral flow levels in the ipsilateral versus the contralateral hemisphere. Since this difference was small, Kaufmann et al concluded that penumbra was small. However, several PET, Xe-CT, and Xe-133 studies as well as the data presented in this report (Table 2) have shown that the contralateral cortical regional CBF is in fact commonly significantly reduced in large hemispheric strokes. Therefore, ipsilateral cortical CBF should be analyzed independent of contralateral CBF. (2) The analysis of Kaufmann et al included nonischemic territories (anterior and posterior cerebral arteries) as well as subcortical structures, resulting in a significant increase in the proportion of white matter, for which the perfusion thresholds that define core and penumbra are unknown. (3) Finally, the extent of penumbra may have been underestimated by restricting the analysis to only 1 axial level, that passing through the basal ganglia, and excluding areas of the cortical MCA territory that are more prone to receiving pial collaterals.

Analysis of Xe-CT data at voxel level may be prone to measurement errors due to system noise and filtering. We believe, however, that the results of our voxel-based analysis are valid. While the measurement error of a single voxel may be 100%, the error in measuring 100 contiguous voxels is approximately 10%. Because in all of our 36 patients the voxels falling within each defined flow range were clustered (Figure 1D, 1E, and 1F) rather than randomly scattered, the degree of measurement error is closer to 10%. The validity of our voxel-based analysis is supported by the high degree of correlation between percent core, percent penumbra, and percent NC/NP obtained through voxel-based analysis and those values obtained through measurement of mean CBF in cortical ROIs (Table 2). The latter has been validated as a reliable quantitative CBF measurement tool.

This study has several limitations, mainly derived from its retrospective design. Patients were included in our study according to criteria that were meant to select a patient population with the same vascular occlusion site who underwent reliable quantitative CBF assessment within a time frame relevant for thrombolytic therapy. The lack of patient complications attributable to the core. Therefore, recanalization therapy may preferentially be guided by diagnostic methods capable of rapidly and reliably identifying irreversible ischemia.

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This study has several limitations, mainly derived from its retrospective design. Patients were included in our study according to criteria that were meant to select a patient population with the same vascular occlusion site who underwent reliable quantitative CBF assessment within a time frame relevant for thrombolytic therapy. The lack of patient complications attributable to the core. Therefore, recanalization therapy may preferentially be guided by diagnostic methods capable of rapidly and reliably identifying irreversible ischemia.

The observation that, contrary to the highly variable core, penumbra is relatively constant may explain why the volume of core and not that of penumbra is a determinant of clinical outcome in acute MCA occlusion. Our subanalysis performed on patients with known vessel recanalization status suggests that this may apply to both patients who do and patients who do not recanalize. When a large core volume is present, any benefit of penumbral salvage through vessel recanalization may be obscured by the extensive deficit and propensity to complications attributable to the core. Therefore, recanalization therapy may preferentially be guided by diagnostic methods capable of rapidly and reliably identifying irreversible ischemia.

The importance of the core as a predictor of outcome in patients undergoing intravenous thrombolysis is underscored by studies using pretreatment MRI in patients with large-vessel occlusion, showing that clinical outcome correlated significantly with lesion volume on diffusion-weighted imaging (thought to approximate core) but not with the volume on perfusion/diffusion imaging mismatch (thought to approximate penumbra). Other authors have found that in patients studied acutely with CT perfusion in whom vessel recanalization was determined at 3 days, the ratio of penumbra to penumbra plus core (but not core or penumbra alone) was predictive of clinical outcome in patients who recanalized. In general, data regarding the importance of core versus penumbra in patients undergoing thrombolysis are limited because of different methodologies used and small sample sizes involved, such that further prospective studies are needed to clarify this issue.

Penumbral tissue of an extent similar to that reported in this study, present even beyond 6 hours, was reported by
inclusion according to a prospectively established protocol introduces the possibility of selection bias. Xe-CT CBF studies were ordered during the specified study dates by all physicians involved as the standard of care for acute stroke. It is therefore unlikely that a significant number of patients were omitted from our study because of different Xe-CT CBF ordering patterns. The outcome assessment may be confounded by several factors. Outcome was assessed in a retrospective fashion, at different times, and not in a blinded manner. Different treatment modalities were used, and some patients were lost to follow-up. However, the results of our clinical-based outcome analysis are paralleled by the imaging-based outcome analysis in which percent core and not percent penumbra was strongly correlated with percent final infarct.

Another limitation is that the flow thresholds chosen to define core and penumbra have not been validated as true indicators of tissue viability by follow-up imaging or (ideally) histological studies. Nevertheless, numerous animal and human studies, including studies performed with Xe-CT CBF assessment, PET, and H2 clearance, have confirmed the existence of perfusion thresholds in cerebral ischemia.3, 27, 28 The exact CBF thresholds that define core or penumbra are not known, and, given their presumed dependence on time from stroke onset and on other variables (eg, body temperature, blood glucose levels, genetic factors), it is unlikely that they are defined by a fixed CBF value. Our values chosen for these thresholds correspond to those of 8 mg/100 mL per minute for core and 20 mg/100 mL per minute for penumbra, which were recently established by human PET studies.3, 10, 18, 29

References
Challenging the Concept of a Dynamic Penumbra in Acute Ischemic Stroke

Ever since the concept of an ischemic penumbra began receiving wider acceptance in the early 1980s, much attention and endeavors has been focused on the demonstration of this “salvageable rim” in order to define the usefulness of acute stroke therapy. Several techniques have been applied to demonstrate the extent of the penumbra in acute stroke in humans. Besides that these techniques are mostly very complex and therefore far from being accessible to a considerable proportion of acute stroke patients, the interpretation and generalization of their results in human stroke are complicated by several factors. First, the ischemic penumbra is considered an unstable, dynamic, and transient condition. Moreover, aside from time since onset, several factors like residual/collateral blood flow, metabolic parameters (e.g., glucose), temperature, and the anatomical resolution of the technique applied further contribute to a patient’s “individual” penumbra. This is reflected by the fact that, second, flow thresholds for various states of tissue perfusion differ considerably among studies and techniques. Third, given the complexity and effort associated with the majority of methods capable of measuring penumbral tissue, most of our current knowledge derives from rather small cohorts and may not be applicable to subgroups of ischemic stroke, like lacunar infarction.

On first gaze, the retrospective study by Jovin et al is not much different from former studies, as it applies a very sophisticated technique (xenon-enhanced CT cerebral blood flow [Xe-CT CBF]) to a small cohort (n=36) of severely affected patients (median NIHSS score, 18) with occlusion of the middle cerebral artery (MCA) stem as determined by conventional or CT angiography. Patients were investigated with a median of 4 hours after symptom onset and treatment strategies comprised intravenous/intra-arterial thrombolysis either combined or alone in 72% of subjects. Primary aims of the study were to determine the relative proportions of tissue CBF conditions stratified into core, penumbra, and non-core/non-penumbra (NC/NP) within the cortical MCA territory and whether these proportions predict clinical outcome. In addition, clinical outcome was unblindedly determined by nonstandardized data retrieval from medical records or by telephone interview at 3 to 6 months.

So, this is just another attempt to determine crucial parameters of CBF in a small subgroup of stroke patients, hampered by methodological limitations. While this somewhat provocative resume might be appropriate in several aspects, the article by Jovin et al is of interest not only because it is the first Xe-CT CBF study associating the proportion of ischemic core with clinical outcome; more importantly and perhaps unexpectedly, its results regarding the relation and dynamics of penumbra, core, and NC/NP proportions are rather startling. Regions with CBF values indicating core (0 to 8 mL/100 g per minute) or NC/NP (>20 mL/100 g per minute) were found to be highly variable among individuals, with proportions ranging from 7.6% to 70.5% and 4.7% to 66% of the MCA cortical territory, respectively. This might be due to the many anatomical variants of collateral pathways to the cortex and concurs with recent MRI studies indicating a high variability of areas with specific flow characteristics in MCA stem occlusion. The core’s extension, however, was inversely correlated with percentage NC/NP tissue, but was neither associated with the time elapsed since symptom onset nor with the percentage of penumbral tissue, which in fact found to be rather constant (range, 16.2% to 46.9%). In addition, in a subgroup analysis of thrombolized patients (n=21), only the mean percentage core but not the status of recanalization or percentage penumbra was associated with patient outcome. Finally, the final infarct size on follow-up imaging was strongly correlated with the percentage of core, while a favorable clinical outcome was associated with lower percentages of core, but was independent from the penumbral proportion.

Currently, the penumbra is conceived as a tissue condition spreading from the center of an ischemic area, thereby shrinking and leaving behind an enlarging ischemic core region when adjacent, formerly penumbral areas undergo irreversible ischemic damage. Tissue characteristics compatible with penumbra have been demonstrated up to 48 hours after onset of ischemia, although recent studies using benzodiazepine receptor ligands as markers for neuronal integrity indicate that major cell damage occurs during the very early phase of ischemic stroke. Nevertheless, substantial changes of the penumbra have been demonstrated even several hours after onset by various techniques applying serial imaging. Thus, besides the aforementioned difficulties and variations in determining CBF and cerebral metabolic states in humans, the paradigm of a dynamic penumbral-core interdependence with expansion of the core at the cost of the penumbra over time is still an integral part of our understanding of early ischemic stroke pathophysiology. Furthermore, recanalizing treatment strategies based on this concept have been proven to be effective both in PET studies demonstrating the reversibility of penumbral tissue characteristics by early reperfusion and in larger cohorts of patients treated with thrombolysis. Thus, Jovin et al’s findings of a rather stable penumbra together with the inverse relation between core and NC/NP tissue (and not penumbral tissue) contradict the assumption of a dynamic and interdependent relation between penumbra and core. Therefore, the results presented by Jovin et al have to be viewed with skepticism.
The independence of CBF parameters from time after onset in the presented study may be explained by the merely one-time examination of patients, while serial investigations might have revealed the relation of core and NC/NP as changing over time. Even under this assumption, however, according to the results by Jovin et al, an increase of the core area would occur at the cost of NC/NP area and not the penumbra. Provided NC/NP represents functioning tissue, this should be accompanied by clinical deterioration (or improvement in case of core shrinkage). Unfortunately, neither Jovin et al nor other studies measuring CBF have correlated their findings realtime with clinical changes, since all these studies were focused on long-term clinical outcome.

The results of Jovin et al further suggest that final infarct size and clinical outcome are likely to be determined very early in the course. Other studies applying different methods but with similar mean time intervals between onset and investigation (4 to 5 hours) have also shown an association of early infarct volume with clinical outcome.14,19,20 Transferred to clinical experience, this assumption of a very early defined core even concurs with the results of large-scale trials on systemic thrombolytic therapy, where particularly patients treated within 90 minutes profited from treatment.21 To date, only 3 other Xe-CT CBF studies investigating acute stroke patients were published,22–24 partly with clearly differing results (present study,23). Nevertheless, Xe-CT CBF, despite its methodological limitations and possible side effects of xenon gas inhalation,25 is already considered a reliable tool to measure human CBF with sufficient spatial resolution.3 Thus, more studies applying Xe-CT CBF in early acute ischemic stroke are worthwhile. While not all of the results presented by Jovin et al are compatible with current knowledge and concepts, some of their findings deserve further investigation in order to confirm or refute the hypothesis of a stable penumbra.

References
The Cortical Ischemic Core and Not the Consistently Present Penumbra Is a Determinant of Clinical Outcome in Acute Middle Cerebral Artery Occlusion

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