Extending the Time Window for Endovascular Procedures According to Collateral Pial Circulation

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Background and Purpose—Good collateral pial circulation (CPC) predicts a favorable outcome in patients undergoing intra-arterial procedures. We aimed to determine if CPC status may be used to decide about pursuing recanalization efforts.

Methods—Pial collateral score (0–5) was determined on initial angiogram. We considered good CPC when pial collateral score <3, defined total time of ischemia (TTI) as onset-to-recanalization time, and clinical improvement >4-point decline in admission–discharge National Institutes of Health Stroke Scale.

Results—We studied CPC in 61 patients (31 middle cerebral artery, 30 internal carotid artery). Good CPC patients (n=21 [34%]) had lower discharge National Institutes of Health Stroke Scale score (7 versus 21; P=0.02) and smaller infarcts (56 mL versus 238 mL; P<0.001). In poor CPC patients, a receiver operating characteristic curve defined a TTI cutoff point <300 minutes (sensitivity 67%, specificity 75%) that better predicted clinical improvement (TTI <300: 66.7% versus TTI >300: 25%; P=0.05). For good CPC patients, no temporal cutoff point could be defined. Although clinical improvement was similar for patients recanalizing within 300 minutes (poor CPC: 60% versus good CPC: 85.7%; P=0.35), the likelihood of clinical improvement was 3-fold higher after 300 minutes only in good CPC patients (23.1% versus 90.1%; P=0.01). Similarly, infarct volume was reduced 7-fold in good as compared with poor CPC patients only when TTI >300 minutes (TTI <300: poor CPC: 145 mL versus good CPC: 93 mL; P=0.56 and TTI >300: poor CPC: 217 mL versus good CPC: 33 mL; P<0.01). After adjusting for age and baseline National Institutes of Health Stroke Scale score, TTI <300 emerged as an independent predictor of clinical improvement in poor CPC patients (OR, 6.6; 95% CI, 1.01–44.3; P=0.05) but not in good CPC patients. In a logistic regression, good CPC independently predicted clinical improvement after adjusting for TTI, admission National Institutes of Health Stroke Scale score, and age (OR, 12.5; 95% CI, 1.6–74.8; P=0.016).

Conclusions—Good CPC predicts better clinical response to intra-arterial treatment beyond 5 hours from onset. In patients with stroke receiving endovascular treatment, identification of good CPC may help physicians when considering pursuing recanalization efforts in late time windows. (Stroke. 2011;42:3465-3469.)

Key Words: collateral flow ■ intra-arterial ■ stroke

Endovascular treatment of an acute arterial occlusion is a safe and effective option in the setting of acute stroke and represents a therapeutic alternative when systemic thrombolysis fails to induce recanalization or it is contraindicated. However, recent studies have shown that the high recanalization rates achieved are not always paralleled by the expected clinical recovery. The time window for these procedures is typically set up to 6 to 8 hours from symptom onset; however, some studies suggest that in selected patients, this time can be successfully extended. Before the procedure, multiparametric neuroimaging is being used to select those patients with salvageable persistent ischemic penumbra that will benefit from the interventional procedure. However, definitive evidence about its value for triage is still lacking. Furthermore, once the procedure is initiated if recanalization is not promptly achieved, the interventionalist does not have any source of information to make the decision about whether to continue the efforts to recanalize or stop the process. Pursuing recanalization efforts at any price may lead to futile recanalization with no corresponding clinical improvement or even worse, to symptomatic hemorrhagic transformation. On the other hand, too early termination of the procedure before recanalization is achieved may prevent

Received April 30, 2011; final revision received June 19, 2011; accepted July 13, 2011.
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.111.623827
benefits of reperfusion in some patients with not irreversibly damaged brain tissue.

Collateral pial circulation (CPC) perfusing the ischemic penumbra can be angiographically assessed and graded during endovascular procedures.5,6,7 A good collateral flow sustains the penumbra before recanalization, offsets infarct growth,8 reduces hemorrhagic transformation,9 and was even related to a higher degree of recanalization.10 We aimed to study if information about the state of collateral flow could be used to extend the therapeutic time window in patients with acute stroke undergoing urgent intra-arterial procedures.

**Methods**

Consecutive patients with acute stroke undergoing endovascular procedures were studied. At patient arrival to the emergency department, a complete evaluation was done by the neurologist on call including a complete ultrasound evaluation (carotid arteries + transcranial Doppler).11 Early ischemic signs on cranial CT scan were quantified by the Alberta Stroke Program Early CT Score (ASPECTS).12 Eligible patients were treated with intravenous tissue-type plasminogen activator before the intra-arterial procedure. Patients with a persistent arterial occlusion at the end of intravenous tissue-type plasminogen activator infusion or with contraindications to receive intravenous tissue-type plasminogen activator were treated with endovascular procedures. When clinical status allowed, a conscious sedation protocol avoiding intubation was preferred. Heparin was administered after femoral artery puncture as a 2000- to 3000-U intravenous bolus. Only patients with angiographically documented terminal internal carotid artery or middle cerebral artery occlusion were included in the study.

Collateral pial circulation was graded according to previously published criteria.6,9 Briefly, initial angiograms of all patients were reviewed for occlusion site, pial collateral formation, and reperfusion by an interventional neurologist who was blinded to all clinical information during this review. Pial collaterals were graded on a 5-point scale based on anatomic extent as defined elsewhere with good pial collaterals being Grades 1 and 2 and poor being Grades 3 to 5. Occlusions at the internal carotid bifurcation were scored performing a contralateral carotid angiogram that could show collateral filling through the anterior communicating artery. Posterior cerebral artery collaterals were not consistently evaluated. Good pial collaterals in this study were equivalent to Grades 3 and 4 described by Higashida and Furlan.13 Patients with incomplete initial collateral circulation study (too short initial angiogram, no contralateral angiogram, etc) were excluded from the analysis.

Independent of the collateral circulation status, interventionalists tried to achieve recanalization with repeated local 3 to 5 mg tissue-type plasminogen activator injections (to a maximum of 20 mg) or mechanical clot disruption with the guidewire and/or the Merci, Solitaire, or Trevo retrievers according to their preferences and patient characteristics. The predefined protocol, approved by the local ethics committee, indicates procedure termination when recanalization is achieved at 6 to 8 hours from symptom onset. Timing of all procedural steps was recorded. Recanalization was assessed with the Thrombolysis In Myocardial Infarction grading score14 at the end of procedure. For analysis purposes, we considered successful recanalization a Thrombolysis In Myocardial Infarction score ≥2. We defined total time of ischemia (TTI) as time from symptom onset to recanalization. Neurological status was assessed by a certified neurologist on the patient’s arrival at 24 hours and at 7 days or discharge using the National Institutes of Health Stroke Scale (NIHSS). We defined clinical improvement as a >4-point decline in the NIHSS score from baseline to discharge. A 24-hour CT scan determined the presence of hemorrhage and infarct volume was measured using the ABC/2 formula.16,17 Symptomatic hemorrhage was defined as a CT-documented hemorrhage that was temporally related to deterioration in the patient’s clinical condition in the judgment of the clinical investigator.18 CT readings were performed by neuroradiologists blinded to clinical and angiographic data. The modified Rankin Scale was used to assess clinical outcome at 90 days.

**Statistical Analysis**

Descriptive and frequency statistical analysis was obtained and comparisons were made using the SPSS 15.0 statistical package. Statistical significance for intergroup differences was assessed by the Pearson χ² or the Fisher exact test for categorical variables and the Student t test and analysis of variance for continuous variables. When indicated, Mann-Whitney U and Spearman tests were used. To calculate correlations between continuous variables, the Pearson correlation test was used. To calculate the sensitivity and specificity of time cutoff points to predict clinical improvement, a receiver operator characteristic curve was configured. A logistic regression analysis was performed to determine factors that could be considered independent predictors of favorable outcome. P < 0.05 was considered statistically significant.

**Results**

From 122 patients undergoing urgent intra-arterial procedures, a complete anterior CPC evaluation was done in 61 (middle cerebral artery: 31, internal carotid artery: 30). Sixty-one patients were excluded from analysis due to insufficient collateral flow assessment. Median baseline NIHSS was 18 (interquartile range, 4); 67 patients (54.9%) received intravenous tissue-type plasminogen activator before the intra-arterial procedure. On initial angiograms, 21 patients (34%) had good CPC. Among all baseline variables, only ASPECTS (median ASPECTS score: 10 [0] versus 9 [2]; P = 0.004) and systolic blood pressure (134.1 ± 18 versus 149.7 ± 28 mm Hg; P = 0.05) were significantly different between good and poor CPC patients, respectively. Other variables are shown in the Table. The rates of recanalization were significantly higher among good CPC patients (90.5% versus 64.1%; P = 0.034). The duration of the procedure was not different between poor (100 ± 52 minutes) and good CPC

**Table. Patients’ Baseline Characteristics According to Collateral Pial Circulation (CPC) Status**

<table>
<thead>
<tr>
<th></th>
<th>Good CPC (n=21)</th>
<th>Poor CPC (n=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>66.4 ± 13</td>
<td>72.1 ± 12</td>
<td>0.099</td>
</tr>
<tr>
<td>Female gender</td>
<td>9 (42.9%)</td>
<td>17 (42.5%)</td>
<td>0.595</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (57.1%)</td>
<td>27 (67.5%)</td>
<td>0.300</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (9.5%)</td>
<td>6 (15%)</td>
<td>0.433</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8 (38.1%)</td>
<td>25 (62.5%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Intravenous tPA</td>
<td>13 (61.9%)</td>
<td>16 (40%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Glucose, mg/mL</td>
<td>135.5 ± 45</td>
<td>118.9 ± 39</td>
<td>0.219</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>134.1 ± 18</td>
<td>149.7 ± 28</td>
<td>0.050</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>75.7 ± 13</td>
<td>80.8 ± 12</td>
<td>0.197</td>
</tr>
<tr>
<td>Tandem extra-/intracranial occlusion</td>
<td>5 (23.8%)</td>
<td>8 (22.9%)</td>
<td>0.591</td>
</tr>
<tr>
<td>Carotid T occlusion</td>
<td>7 (23.3%)</td>
<td>23 (76.7%)</td>
<td>0.063</td>
</tr>
<tr>
<td>ASPECTS, median (IQR)</td>
<td>10 (0)</td>
<td>9 (2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline NIHSS, median (IQR)</td>
<td>18 (3.75)</td>
<td>19 (3)</td>
<td>0.061</td>
</tr>
<tr>
<td>Symptom to groin, min</td>
<td>257.9 ± 149</td>
<td>222.5 ± 96</td>
<td>0.305</td>
</tr>
</tbody>
</table>

tPA indicates tissue-type plasminogen activator; ASPECTS, Alberta Stroke Program Early CT Score; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.
patients (94±58 minutes; \(P=0.701\)). Among patients who achieved recanalization, the TTI was comparable between patients with poor (314±84 minutes) or good CPC (361±187 minutes; \(P=0.32\)).

Patients with good CPC had better clinical course at 24 hours (median NIHSS, 8 versus 18; \(P=0.01\)) and at discharge or 7 days (median NIHSS, 7 versus 21; \(P=0.02\)). For all patients, a correlation was found between TTI and clinical improvement at discharge or 7 days (\(r=-0.24; P=0.039\); Figure 1). Among patients with poor CPC, a receiver operator characteristic curve could define a cutoff point of <300 minutes of TTI (sensitivity 67%, specificity 75%) that better predicted further clinical improvement (TTI <300: 66.7% versus TTI >300: 25%; \(P=0.05\)) However, among patients with good CPC, no cutoff point could be determined. Although the rate of clinical improvement in patients recanalizing within 300 minutes was unrelated to CPC (poor CPC 60% versus good CPC 85.7%; \(P=0.35\)), the likelihood to experience clinical improvement after delayed recanalization (>300 minutes) was 3-fold higher in patients with good CPC (23.1% versus 90.1%; \(P=0.01\)). After adjusting for age, baseline NIHSS, and occlusion location, TTI <300 emerged as an independent predictor of clinical improvement in patients with poor CPC (OR, 6.6; 95% CI, 1.01–44.3; \(P=0.05\)) but not in patients with good CPC. In a logistic regression model after adjusting for total time of ischemia, admission NIHSS, and age, the presence of good CPC independently predicted clinical improvement (OR, 12.5; 95% CI, 1.6–74.8; \(P=0.016\)).

On follow-up CT scan, smaller infarct volumes were measured in patients with good CPC (56 mL versus 238 mL; \(P<0.001\)). Although the infarct volume in patients recanalizing within 300 minutes was unrelated to CPC (poor CPC 145 mL versus good CPC 93 mL; \(P=0.56\)), the infarct volume after delayed recanalization (>300 minutes) was 7-fold larger in patients with poor CPC (poor CPC 217 mL versus good CPC 33 mL; \(P<0.01\); Figure 2). The rate of symptomatic hemorrhagic transformation was 8.5% and no differences were found between good (9.5%) and poor CPC patients (7.9%; \(P=0.83\)).
At 3 months, patients with good CPC had a lower rate of disability (good CPC, modified Rankin Scale <2: 66.7% versus poor CPC 15.6%; \( P = 0.002 \)). Again, when comparing between patients with early and delayed recanalization, the rate of 3-month disability was significantly lower only in patients with poor CPC (9%; 1% versus 50%; \( P = 0.026 \); Figure 2).

Baseline NIHSS (OR, 1.57; 95% CI, 1.1–2.24; \( P = 0.011 \)) and good CPC (OR, 7.39; 95% CI, 1.36–40.2; \( P = 0.021 \)) were the only independent predictors of modified Rankin Scale <2 at 3 months.

**Discussion**

Our study demonstrates that the evaluation of the collateral flow status during endovascular procedures in patients with acute stroke is a valuable source of information that can be used to predict the chances of clinical recovery and even individualize the therapeutic time window. Angiographic identification of a good collateral flow has been associated with better clinical outcome and lower rate of hemorrhage in patients with stroke undergoing endovascular procedures.\(^6,9\)

Moreover, recent studies have shown that good CPC is also associated with a higher degree of recanalization.\(^10\) These results were replicated in our study. In addition, we aimed to investigate further the interaction between collateral flow and duration of ischemia and we observed that in acute stroke, the negative impact of time is modulated by the CPC status. The growing differences as TTI increases in terms of clinical recovery or infarct volume between patients with good or poor CPC reflect that the recruitment of the ischemic penumbra into irreversible infarct is accelerated when collateral flow is insufficient.

Patients with acute stroke are considered candidates for endovascular procedures according to a preprocedure neuroimaging confirming the presence of savable tissue at risk. However, if recanalization is not promptly achieved, the duration of the procedure may last several hours during which the ischemic lesion may grow making reperfusion futile or even counterproductive by increasing the risk of symptomatic intracerebral hemorrhage. In the angio suite, the decision about whether to continue or end recanalization efforts is usually solely based on the time from symptom onset and preprocedure neuroimaging, because no other intraprocedure source of information about the ischemic brain is usually available. This decision may deny the benefit of recanalization to some patients with still viable ischemic penumbra. Angiographic assessment of collateral pial circulation may be rapidly performed during endovascular procedures. The information about the presence or lack of good collateral flow probably reflects the degree of ischemia in the penumbral tissue and may be used to tailor the therapeutic window in each patient. In our study, we identified a cutoff point of 5 hours that better predicted lack of improvement only those patients with poor CPC. On the other hand, among those patients with good CPC, the negative impact of time was considerably blunted and a worthwhile clinical recovery was observed even when recanalization was achieved up to 8 hours from symptom onset. Moreover, good CPC seemed also to improve outcome in the absence of recanalization (Figure 1). These observations are sustained by the fact that CPC emerged as the only independent predictor of clinical improvement even after adjusting for total time of ischemia. Our observations may also encourage the development of different strategies to augment the collateral flow as a single treatment or in combination with recanalization procedures.\(^20\)

Our institutional treatment protocol did not observe treating patients with stroke with endovascular procedures beyond 8 hours from symptom onset. Therefore, these results should not be extrapolated to the very late time window. Future confirmatory studies of our hypothesis should also explore the time limit within good collateral flow remains a reliable indicator of salvageable brain tissue. Posterior circulation collaterals may also have an influence on outcome; however, their presence was not consistently determined because in the setting of acute endovascular therapy, our goal was to recanalize and not to fully study every artery before recanalization attempts.

**Conclusions**

The presence of good CPC predicts a better clinical response to intra-arterial treatment beyond 5 hours from symptom onset. In patients with stroke receiving endovascular treatment, identification of good CPC may help physicians when considering expanding the therapeutic time window.

**Source of Funding**

M.R. is the recipient of a grant by the Instituto de Salud Carlos III: PS09/01660.

**Disclosures**

M.R. is the recipient of a modest grant from the Instituto de Salud Carlos III: PS09/01660 (Spanish Ministry of Science).

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*Stroke.* 2011;42:3465-3469; originally published online September 29, 2011; doi: 10.1161/STROKEAHA.111.623827

*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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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脳乾動脈の側副血行路に応じた血管内治療適応時間の延長
Extending the Time Window for Endovascular Procedures According to Collateral Pial Circulation

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背景および目的：脳動脈瘤は、血管内治療を受けた患者の不良な転帰の予測因子である。本研究は、CPCの状態に基づいて再開通治療の実施を判断することが可能か否かを明らかにすることを目的とした。

方法：初回の血管造影にてCPCスコア(0〜5)を測定した。良好なCPCはCPCスコアが3未満、合計血流時間(TTI)は発症から再開通までの時間を、臨床的改善はNIHSSスコアの入院および再入院までの下がりが4点以下と定義とした。

結果：患者61例のCPC（中大脳動脈31例、内頸動脈30例）を調査した。CPC良好患者[21例（34%）]は、再入院時のNIHSSスコアが低く（7比21, p=0.02）、梗塞が小さかった（56mL対238mL, p<0.001）。CPC不良患者は、受信者操作特性（ROC）曲線で定義された臨床的改善を適切に予測するTTIのカットオフ値が300分未満（感受性: 67%, 特異性: 75%）であった（TTI<300: 66.7% 対TTI>300: 25%, p=0.05）。CPC良好患者については、時間的なカットオフ値は定義不能であった。300分以内に再開通した患者は、臨床的改善は同等であつたが（CPC不良: 60% 対CPC良好: 85.7%, p=0.35）、300分以後の臨床的改善率は、CPC良好患者で3倍高かった（23.1% 対 90.1%, p=0.01）。同様に、硬塞容積もTTIが300分であつた場合のみ、CPC不良患者と比較してCPC良好患者で7倍低下した（TTI<300のとき、CPC不良: 145mL 対 CPC良好: 93mL, p=0.56；TTI>300のとき、CPC不良: 217mL 対 CPC良好: 33mL, p<0.01）。

結論：良好なCPCは、発症から6時間後の動脈内治療に対する良好な臨床経過の予測因子である。血管内治療を受けた脳卒中患者において、良好なCPCの特定は重要な段階で再開通治療の実施を検討する際に役立つと考えられる。

Stroke 2011; 42: 3465-3469