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.1,2 However, recent studies have shown that the high recanalization rates achieved are not always paralleled by the expected clinical recovery.3 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.4 Before the procedure, multiparametric neuroimaging is being used to select those patients with salvageable persistent ischemic penumbra that will benefit from the interventional procedure.5 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...
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. A good collateral flow sustains the penumbra before recanalization, offsets infarct growth, reduces hemorrhagic transformation, and was even related to a higher degree of recanalization. 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). Early ischemic signs on cranial CT scan were quantified by the Alberta Stroke Program Early CT Score (ASPECTS). 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. 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. 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 or 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 score 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 ≥10-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 ABC2 formula. 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. 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±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 patients.
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%; \(P=0.83\)).

Figure 1. Degree of clinical improvement at discharge according to total time of ischemia among patients with poor or good collateral flow. NIHSS indicates National Institutes of Health Stroke Scale.

Figure 2. Differences in clinical improvement and final infarct grow according to total time of ischemia in patients with good and poor collateral flow (mRS indicates modified Rankin Scale; *\(P<0.005\)).
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, 1.5; 95% CI, 1.1–2.2; \(P=0.011\)) 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

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脳軟膜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: 良好な脳軟膜動脈の側副血行路 (CPC) は、血管内治療を受けた患者の臨床的改善に関与すると示唆されている。これにより、CPC の状態に基づいて再開通治療の適応時間を決定することが可能であると予想される。

方法: 初回の血管造影にて CPC スコア (0 〜 5) を測定した。CPC スコアは 3 未満、合計虚血時間 (TTI) は発症から再開通までの時間、臨床的改善は NIHSS スコアの入院時から退院までの低下が 4 点で評価した。

結果: 患者 61 例の CPC (中脳動脈 31 例、頭蓋動脈 30 例) を調査した。CPC 良好患者 [21 例 (34 %)] は、退院時の NIHSS スコアが低く (7 対 21, p = 0.02)、脳梗塞が小さかった (56 mL 対 238 mL, p < 0.001)。CPC 良好患者は、受診者操作特性 (ROC) 曲線で定義された臨床的改善を分類するための TTI のカットオフ値が 300 分未満 (感度: 67 %, 特異度: 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可能であった。300 分以内に再開通した患者は、臨床的改善は同等であったが (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、反応時間も TTI が 300 分を超えた場合のみ、CPC 良好患者と比較して CPC 良好患者で 7 倍低下した (TTI < 300 のとき、CPC 不良: 145 mL 対 CPC 良好: 93 mL, p = 0.56; TTI > 300 のとき、CPC 不良: 217 mL 対 CPC 良好: 33 mL, p < 0.001)。年齢およびベースライン時の NIHSS スコアについて補正後、TTI が 300 分未満は CPC 不良患者における臨床的改善の独立した予測因子として示された (OR = 6.6, 95 % CI: 1.01 〜 44.3, p = 0.05)。CPC 良好患者では示されなかった。ロジスティック回帰分析で、良好な CPC は、TTI, 入院時 NIHSS スコア, および年齢で補正した後に、臨床的改善の独立した予測因子であった (OR: 12.5, 95 % CI: 1.6 〜 74.8, p = 0.016)。

結論: 良好な CPC は、発症から 5 時間以後の動脈内治療に対する臨床的改善の予測因子である。血管内治療を受けた脳卒中患者において、良好な CPC のの定義は、再開通治療の適応時間を検討する際に役立つと考えられる。

Stroke 2011; 42: 3465-3469

図2 側副血行路が良好および不良な患者における合計虚血時間別の臨床的改善および最終的な硬塞容積の差（mRS：改变 Rankin 尺度, *p < 0.005）