Poor Collateral Circulation Assessed by Multiphase Computed Tomographic Angiography Predicts Malignant Middle Cerebral Artery Evolution After Reperfusion Therapies

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Background and Purpose—Collateral circulation (CC) has been associated with recanalization, infarct volume, and clinical outcome in patients undergoing acute reperfusion therapies. However, its relationship with the development to malignant middle cerebral artery infarction (mMCAi) has not been evaluated. Our aim was to determine the impact of CC using multiphase computed tomographic angiography (during the acute stroke phase in the prediction of mMCAi).

Methods—Patients with consecutive acute stroke with <4.5 hours who were evaluated for reperfusion therapies and presented with an M1-MCA or terminal internal carotid artery occlusion by CTA were included. CC was evaluated on 6 grades by multiphase CTA according to the University of Calgary CC Scale; CC status was defined as poor (grades, 0–3) or good (grades, 4–5). The mMCAi was defined according to clinical and radiological criteria. Recanalization was assessed with transcranial Doppler at 24 hours and final Thrombolysis in Brain Ischemia score ≥2b in patients undergoing endovascular reperfusion treatment.

Results—Eighty-two patients were included. Mean age was 65.1±13.83 years, median baseline National Institutes of Health Stroke Scale score was 18 (interquartile range, 13–20), and 67.9% M1 and 32.1% terminal internal carotid artery occlusions. Fifty-three patients received endovascular reperfusion treatment. Fifteen patients developed mMCAi. In the univariate analysis, patients with mMCAi had lower CC scores (2.29 versus 3.71; \( P = 0.001 \)). Endovascular reperfusion treatment was associated with lower rate of mMCAi development than only intravenous reperfusion treatment (9.4% versus 29.6%; \( P = 0.028 \)). Patients with poor CC had higher risk of developing mMCAi (13% versus 2%; \( P = 0.001 \)). On the multivariate analysis adjusted by age, vessel occlusion, baseline National Institutes of Health Stroke Scale, and recanalization, the presence of poor CC by multiphase CTA was the only independent predictor of mMCAi (\( P = 0.048; \text{ odds ratio}, 9.72; 95\% \text{ confidence interval}, 1.387–92.53 \)).

Conclusions—CC assessment by multiphase CTA independently predicts malignant MCA infarction progression. In patients with persistent occlusion after reperfusion therapies, the presence of poor CC may improve the early mMCAi detection and management. (Stroke. 2015;46:3149-3153. DOI: 10.1161/STROKEAHA.115.010608.)

Key Words: cerebral infarction ■ collateral circulation ■ infarction, middle cerebral artery ■ reperfusion ■ stroke

One of the most devastating complications of ischemic stroke is evolving to malignant middle cerebral artery infarction (mMCAi). The mMCAi evolution occurs in ≤10% of the patients with acute ischemic stroke, especially affecting young people. The mortality rate of mMCAi arises ≤80% in nonsurgery cases, with a high proportion of severe disability in the rest of cases.1

Early detection and management with præcox decompressive surgery within 48 hours may improve the vital and functional outcome of these patients.²,³ Therefore, early indicators of mMCAi evolution during the first hours after ischemic stroke symptoms onset are of high relevance.

Several predictors of mMCAi had been evaluated in the acute phase. Neuroimaging parameters as baseline

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diffusion-weighted imaging lesion volume has been shown to be a strong and accurate predictor of mMCAi. A diffusion-weighted imaging lesion volume >82 mL below 6 hours of stroke onset predicts, with low sensitivity, mMCAi evolution. This threshold of diffusion-weighted imaging volume raises 144 mL for patients imaged at 6 to 14 hours time-window.2,4 In noncontrast computed tomography (CT), ischemia that affects more than two thirds of the MCA territory predicts the development of mMCAi with a sensitivity of 91% and specificity of 94%.5 Recent studies have shown that some CT perfusion sequences (cerebral blood volume, cerebral blood flow, and cerebral blood volume/cerebrospinal fluid reserve volume) have shown positive correlation with mMCAi prediction.6,7 On the contrary, the degree of leptomeningeal or pial collateral circulation (CC) in acute stroke has been associated with clinical outcome, infarct volume, hemorrhage transformation risk, and recanalization rates.8–11 Single-phase CT angiography (CTA) is more widely used for CC status evaluation on acute stroke, but it lacks of temporal resolution and may mislabel CC status. In this perspective, a new time-resolved technique, multiphase CTA (mCTA) may improve CC evaluation, showing a better inter-rater reliability and clinical outcome prediction comparing with single CTA on patients with acute stroke.12–14 Moreover, a recent trial has proven the use of endovascular reperfusion treatment in patients selected by CC status determined by mCTA.15 However, the relationship with CC status and the development of mMCAi is less known.

We postulate that poor CC status may represent an early predictor of mMCAi evolution. Therefore, we aimed to determine their relationship in the setting of patients with acute stroke evaluated by multiphase CTA (mCTA).

**Methods**

This was an observational, prospective, single-center study. Between March 2013 and July 2014, patients with consecutive acute stroke with <4.5 hours from symptoms onset who were evaluated for

### Table. Baseline Characteristics

|                     | Total          | mMCAi Patients (n=15) | Non-mMCAi Patients (n=66) | P Value |
|---------------------|----------------|-----------------------|---------------------------|---------|
| Age, y, mean (SD)   | 66 (±13.8)     | 60.9 (±114.550)       | 6212 (±14210)             | 0.191   |
| Baseline NIHSS, median (IQR) | 18 (14–21)     | 19 (17–23)            | 15 (11–18)                | 0.015   |
| ASPECTS score, median (IQR) | 8 (8–10)       | 8 (7–10)              | 9 (7–10)                  | 0.134   |
| ET, n (%)           | 53 (64.6%)     | 5 (33%)               | 48 (71.6%)                | 0.028   |
| Infarct volume, mL (mean) | 82.8 (±111.2)  | 23042 (±78689)        | 5558 (±93765)             | <0.001  |
| Pial collateral score, median (IQR) | 4 (3–4)       | 2 (1–3)               | 4 (3–4)                   | 0.001   |
| Good collateral, n (%) | 43 (52.4)      | 2 (13.3)              | 41 (50.6)                 | 0.001   |
| Recanalization, n (%) | 34 (52.3)      | 3 (20)                | 31 (46.2)                 | 0.193   |
| TICA occlusion, n (%) | 12             | 7 (46.6)              | 5 (7.4)                   | 0.033   |

ASPECTS indicates Alberta Stroke Program Early Computed Tomography; ET, endovascular reperfusion treatment; IQR, interquartile range; mMCAi, malignant middle cerebral artery infarction; NIHSS, National Institutes of Health Stroke Scale; and TICA, terminal internal carotid artery.
reperfusion therapies and presented with proximal anterior circulation occlusion were included.

According to our radiological acute stroke protocol, approved by the local ethics committee, all patients received a noncontrast CT to rule out hemorrhage and an mCTA to determine large-vessel occlusion and CC status. All scans were obtained with the patient in supine position by using a 128-slice CT scanner (Definition AS; Siemens, Erlangen, Germany). Collaterals were measured with a multiphase CTA and the following parameters, collimator of 128x0.6 mm, 120 kVp, and 250 mAs, covering the first phase from the carina until the vertex and the second and third phases from the foramen magnum to the vertex. Acquisition was triggered using a bolus tracking (100 HU) in the aortic arch after 60 mL of intravenous injection contrast, then the second a third phases started 4 second after the previous phase.\(^{14}\) Collaterals were measured comparing backfilling arteries beyond the occluded artery to similar arteries in the opposite unaffected hemisphere in three different phases. MCA vascular enhancement distal to occlusion was rated by using Calgary Scoring on mCTA.\(^{12}\) Scores 0 to 3 were categorized as poor CC status, in contrast with scores 4 and 5, which were considered as good CC. When endovascular reperfusion treatment (ET) was performed, CC was also evaluated by digital subtraction angiography using a previous published scale.\(^{16}\)

Neurological status was assessed by a certified neurologist on patient’s arrival, at 24 hours, and at discharge using the National Institutes of Health Stroke Scale (NIHSS).

Recanalization was defined by transcranial Doppler (TCD) when Thrombolysis in Brain Ischemia 4 or 5 was detected on a 24-hour TCD. In patients treated with ET, Thrombolysis in Brain Ischemia score \(\geq 2b\) was considered as recanalization too. At 24 to 48 hours, a noncontrast CT scan was performed to evaluate infarct volume and presence of hemorrhagic transformation.

The modified Rankin Scale score was used to assess functional outcome at 3 months. Good outcome was defined as modified Rankin Scale 0 to 2. Malignant MCA infarction was defined according to previously published clinical and radiological criteria.\(^{1,2,5}\)

The primary outcome was the presence of mMCAi. CC score was analyzed as a dichotomic variable (poor and good CC status) for analysis. Univariate comparisons were performed by Fisher exact test or Pearson \(\chi^2\) as appropriate. Univariate correlations between the CC score and baseline NIHSS, age, and infarct volume were determined by Spearman correlation coefficients. Logistic regression models with backward elimination of nonsignificant variables \((P=0.05)\) were used to identify variables independently associated with mMCAi. Statistical analyses were conducted by using SPSS version 17.0 statistical package. All tests were 2 tailed, and conventional levels of statistical significance were used \((P=0.05)\).

**Results**

Eighty-one patients with acute stroke with large-vessel anterior circulation occlusion were included in the study. The mean age of the series was \(65.1\pm13.8\) years, and the median baseline NIHSS was 18 (interquartile range, 13–20). On mCTA, 81.7% of patients had a M1 middle cerebral artery (MCA) occlusion and 19.2% an intracranial distal or terminal carotid occlusion. Fifty-seven (69.5%) patients received intravenous tissue-type plasminogen activator and 53 (46.4%) ET (primary intra-arterial therapy, 9.7%). Seventeen patients did not receive reperfusion therapies because extensive early ischemic signs on baseline CT (Alberta Stroke Program Early CT [ASPECTS] score <5) or either contraindication according to protocol. Fifteen patients (18.2%) developed mMCAi, and 5 underwent decompressive hemicranectomy according to local protocols.

Baseline characteristics of all, non-mMCAi, and mMCAi patients are shown in the Table. mMCAi patients presented more often with internal carotid artery occlusion than with M1 occlusion (71% versus 11.9%; \(P=0.033\)), and had higher baseline median NIHSS (19.86 versus 15.70; \(P=0.016\), but similar ASPECTS score in the baseline CT scan.

In the univariate analysis, patients with mMCAi had significantly higher infarct volume (230.42 versus 55.58 mL; \(P<0.001\)) in the 24-hour CT control.

In patients who received reperfusion therapies \((n=64)\), no significant association was detected between recanalization evaluated after 24 hours by TCD and mMCAi evolution (52.3% mMCAi patients recanalized versus 47.7% who did not; \(P=0.22\)). However, in patients treated with ET, we could find a significant correlation between lower Thrombolysis in Brain Ischemia scores and mMCAi evolution \((P=0.005)\). Furthermore, treatment with endovascular reperfusion

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**Figure 2.** Graphic bars that shows the number of patients with good and bad collaterals according to malignant middle cerebral artery infarction (mMCAi) and non-mMCAi patients in the no-recanalization group.
therapies when compared with intravenous thrombolysis was significantly associated with absence of mMCAi development (9.4% versus 29.6%; \( P = 0.021 \)). No significant differences were found on ASPECTS score and proximal site occlusion between these groups, being baseline median NIHSS higher in the ET group than in only intravenous thrombolysis group (median, 17 versus 13; \( P = 0.032 \)).

From the global series, 43 (52.4%) patients presented with good CC score by mCTA. In those patients treated with ET, CC evaluation by mCTA was significantly correlated with the digital sustraction angiography pial CC score (\( r = 0.437; \ P = 0.004 \)). The presence of poor CC status evaluated by mCTA was significantly associated with mMCAi evolution \( n = 13 \) (86.6%). A receiver operating characteristic curve shows a cutoff point \( \geq 2 \) CC score for malignant progression with a specificity of 85% and a sensitivity of 65% with a positive predictive value of 35% and negative predictive value of 63%. Moreover, patients with poor CC \( n = 13 \) (34.2%) evolved to mMCAi versus patients with good CC \( n = 2 \) (3.03%; \( P = 0.001 \); Figure 1). Neither patient with good CC developed mMCAi in no-recanalization patients (0 versus 6; \( P = 0.68 \); Figure 2).

In the multivariate analysis adjusted by age, vessel occlusion, baseline NIHSS and recanalization, the presence of poor CC status by mCTA emerged as the only independent predictor of mMCAi (odds ratio, 9.72; 95% confidence interval, 1.387–92.53; \( P = 0.048 \)).

Discussion

Malignant MCA infarction evolution is a devastating disease, and our study has shown that a poor CC status is an independent predictor of developing mMCAi that can be detected in the baseline mCTA, even before 4.5 hours from symptoms onset.

CC through leptomeningeal or pial collaterals is a highly relevant factor in the acute stroke setting. The use of mCTA for CC assessment in our series was correlated with CC evaluation by digital sustraction angiography, giving support to mCTA for CC evaluation as was demonstrated in previous studies.\(^{11,16}\) Rationally, the clear association between CC status and final infarct volume\(^{9,17}\) induces to presume the same association with the risk to develop mMCAi seen in experimental animal models.\(^{18}\) Our study has also detected this significant association of CC status and infarct volume.

On the contrary, unexpectedly, absence of recanalization was not associated with mMCAi evolution in our cohort. However, this may be caused by the way recanalization was evaluated in our study; that is, by TCD at 24 hours. It is possible that at that time-frame, recanalization have lost relevance on ischemic tissue outcome. On the contrary, in patients treated with ET, lower final Thrombolysis in Brain Ischemia scores were associated with mMCAi evolution. Furthermore, ET therapy by itself when compared with intravenous thrombolysis was associated with lower risk of mMCAi, suggesting a protective effect of early recanalization. Therefore, even if complete recanalization by TCD was not associated with lack of mMCAi evolution, it is possible that the higher probability of ET to achieve any degree of early recanalization\(^{19}\) would be enough to avoid a malignant infarct process. This should be taken into account when the real benefit of ET is estimated.

Moreover, the presence of baseline parenchymal lesion defined by ASPECTS score was not related to mMCAi evolution; the precocity of acquisition parenchymal imaging (<4.5 hours) and the relative small sample could explain this finding.

CC status has emerged as the only independent predictor of mMCAi evolution. Especially in patients who did not achieved recanalization, CC status was strongly associated with malignant outcome. This finding could be useful to the early assessment of patients with risk of mMCAi, especially in those patients undergoing reperfusion therapies when recanalization is not achieved. Therefore, predictive models adding CC assessment could improve the accuracy of predictors as volume lesion (ie, diffusion-weighted imaging lesion).\(^{2–14}\) If our results could be confirmed by further research, CC score would emerge as an early predictor of mMCAi evolution. On this way, early identification of candidates for neuro-intensive care unit admission and early hemicranectomy could be performed, which could potentially improve the prognosis of these patients.

Our study has some limitations. The short number of patients of the series precludes conclusions. In relation with baseline findings, our percentage of mMCAi (18%) is higher than the usual reported in the literature.\(^{12}\) However, our series is focused on severe stroke (median NIHSS, 18) with proximal anterior circulation occlusions.\(^{6–21}\)

Another limitations are the lack of information on early recanalization in those patients who did not received reperfusion therapies and our time frame for determine recanalization. However, on the analysis of the influence of recanalization on mMCAi evolution, these patients were excluded.

In conclusion, CC assessment by mCTA is feasible and predicts malignant MCA progression. In patients with persistent occlusion after reperfusion therapies, the presence of poor CC may help in the early malignant MCA detection and management.

Disclosures

None.

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