REGIONAL ANGIOGRAPHIC EVALUATION OF COLLATERAL CIRCULATION PREDICTS INFARCTION DURING ENDOVASCULAR PROCEDURES FOR MIDDLE CEREBRAL ARTERY STROKE

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ABSTRACT

Backgroud and purpose. We aimed to improve patient selection by developing a regional angiographic evaluation of leptomeningeal collateral flow that can be used to predict infarction during stroke endovascular procedures. Matherials and methods. We evaluated all consecutive patients treated for a middle cerebral artery occlusion between 2009 and 2013. Two readers performed a zonal collateral circulation evaluation in 5 cortical regions based on the vascular anatomy. Zonal scores were correlated with the presence of infarction in the same cortical sector on pretreatment and follow-up imaging.

Results. In 49 patients with 217 cortical zones we found good correlation between the degree of zonal collateral flow and the absence of infarction in the same zone on pretreatment imaging (receiver operator characteristic (ROC) curve of 0.74, $p < 0.0001$).

In a subgroup of 23 recanalized patients (TICI 3) with 105 cortical zones, retrograde collateral flow to the proximal M4 segment predicted the absence of infarction within the same zone on follow-up imaging (positive predictive value 89,4% , negative predictive value 80%). We found good inter-rater agreement for the presence of collateral flow to the M4 proximal segment or further – kappa 0.77 ($p = 0.05$, 95%CI 0.66-0.88).

The number of cortical regions with collateral flow to the M2 segment predicts the absence of insular infarction on follow-up imaging (ROC curve of 0,76, p = 0,001).

Conclusion. Anatomic collateral flow evaluation can provide a real-time estimation of the size and location of irreversible ischemia during stroke endovascular procedures.

Keywords: regional angiographic evaluation, leptomeningeal collateral flow, endovascular procedures, middle cerebral artery stroke

Abreviation key: LMF – leptomeningeal collateral flow; **ROC** – receiver operator characteristic curve; **AUC** – area under the curve

INTRODUCTION

The connection between leptomeningeal collateral flow (LMF) and the survival of brain parenchyma during acute ischemia has been confirmed in a large number of clinical studies (1-5). Better collateral flow is associated with smaller infarct volumes, better clinical outcome and higher recanalization rates.

Despite this growing body of evidence, in most centers the evaluation of LMF still receives relatively little attention during patient selection for revascularization procedures. While collaterals can be evaluated on virtually all imaging modalities employed in acute stroke (6), conventional angiography still remains the gold standard, given its resolution and the possibility for dynamic evaluation.

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Recent consensus recommendations state the importance of collateral flow assessment on DSA or alternatively on noninvasive imaging if DSA was not performed (7). A recent systematic review (8) identified no less than 41 methods of evaluation of collateral flow in angiography but concluded that inconsistency in imaging methods and grading scores is one of the factors that limit the emphasis that can be placed on collaterals in clinical practice.

We aimed to develop an angiographic regional collateral flow grading system that only requires basic anatomic knowledge of MCA branches segmentation and establish its accuracy in predicting zonal infarction on follow-up imaging.

MATERIALS AND METHODS

Patient selection

The patients were retrospectively identified from our database of stroke endovascular procedures between January 2009 and June 2013. All patients with an acute proximal cerebral artery occlusion presenting within 6 hours from symptom onset were considered for intra-arterial therapy. The main selection criteria consisted of small infarct volume on DWI, clinical – radiological mismatch and good collateral flow visualized as vascular hyper-intensities on FLAIR sequences. In the absence of specific contraindications, IV thrombolysis was administered before the endovascular procedure (up to 4.5 hours from symptom onset, 2/3 of the usual dose of 0,9 mg/kgc alteplase). Mechanical thrombectomy was then performed under general anesthesia using a stent retriever, an aspiration system or a combination of these methods. During the procedure, the remaining 1/3 of the dose of alteplase was administered intra-arterially by microcatheter and/or guiding catheter injections.

Patients were included in the study if they fulfilled all of the following criteria: (1) – endovascular treatment for MCA occlusion; (2) – initial angiography before revascularization demonstrating occlu-

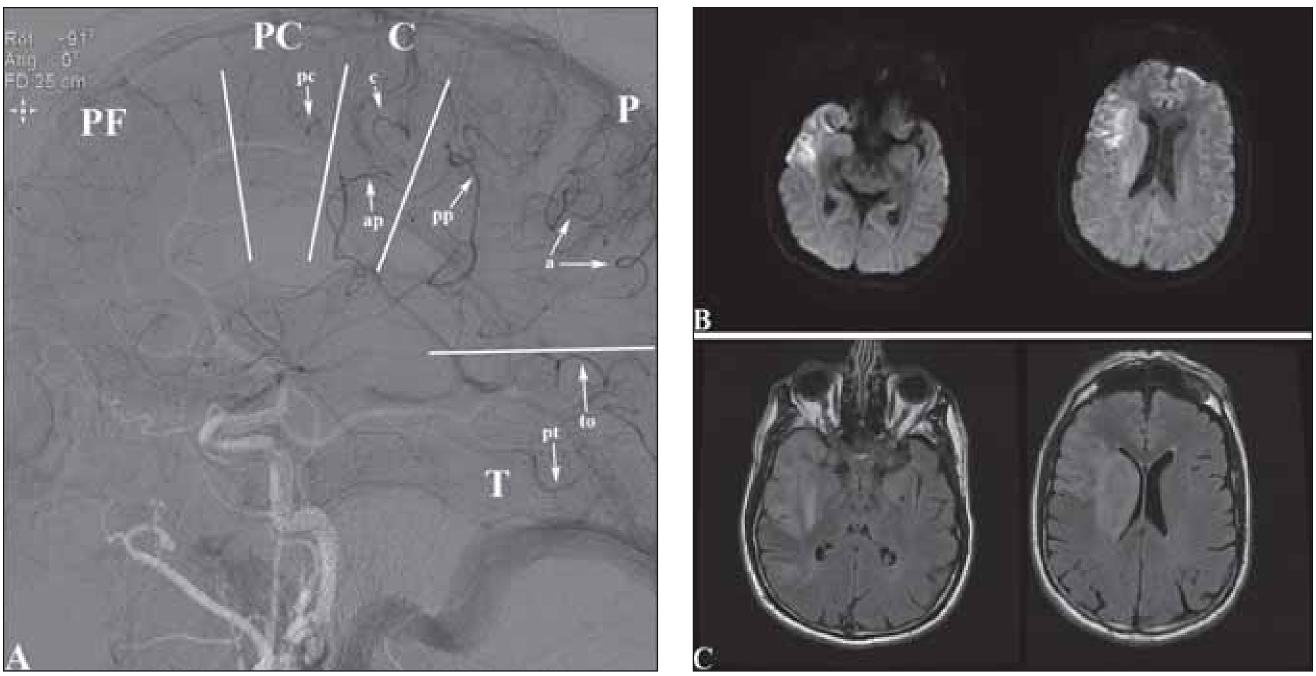

FIGURE 1. Illustrative case 1

A: *Lateral angiographic view of a patient with M1 segment occlusion. The image is re-masked in the initial arterial phase. Various levels of retrograde opacification are seen in the MCA branches:*

– No collateral flow in the prefrontal sector ***(PF)****;*

– poor collateral flow to the distal M4 segment in the precentral artery ***(pc)*** *for the precentral sector* ***(PC)****;*

– good collateral flow reaching the proximal M2 segment in the central artery ***(c)*** *and anterior parietal artery* ***(ap)*** *for the central sector* ***(C)****;*

– good collateral flow to the proximal M2 segment in the posterior parietal artery ***(pp)*** *and to the proximal M4 segment in the angular artery* **(a)** *for the parietal sector* ***(P)****;*

poor collateral flow to the distal M4 segment in the temporo-occipital artery ***(to)*** *and posterior temporal artery* ***(pt)*** *for the temporal sector* ***(T)***

B: *Pre-treatment MRI, diffusion weighted sequences (DWI) showing acute infarction in the anterior temporal lobe, prefrontal and precentral sectors, corresponding to the areas of poor collateral flow on angiography, as well as in the basal ganglia*

C: *Post-treatment MRI FLAIR sequence (after complete TICI 3 recanalization at 4 hours 18 minutes) showing infarction in the same sectors, with extension to the posterior temporal lobe. The pattern of collateral flow accurately predicted infarction areas on the follow-up scan.*

sion in the M1 segment (3) – pre-procedural MRI and follow-up imaging (either MRI or CT scan) available on PACS. The study was conducted after obtaining approval from the local ethics committee.

Angiographic evaluation

According to local protocol, all patients had a three vessel cerebral angiography with runs continued up to the late venous phase before the revascularization procedure, which allowed for a comprehensive study of the collateral circulation. Collateral flow was graded by a neuroradiologist blinded to MRI findings using antero-posterior and lateral views. A 5 point scale was assigned according to the level of retrograde opacification in five cortical areas. These areas were chosen based on the anatomy of MCA branches: prefrontal, precentral, central, parietal and temporal (Fig. 1).

Collateral flow for each area was graded on a scale inspired by the classical segmentation of MCA branches using insular landmarks: 0 – no collateral flow, 1 – flow to the distal half of M4 segment, 2 – to the proximal half of M4 segment, 3 – to the M3 segment, 4 – to the distal half of the M2 segment, 5 – to the proximal half of the M2 segment (Fig. 2).

The arteries of each region were studied from early to late phase of angiographic runs using mostly lateral views, but also antero-posterior views especially for the M3 segment. The branches were identified using angiographic particularities described in figure 3 (9-11).

Recanalization of the occluded arteries was graded by the same operator using the modified Thrombolysis in Cerebral Infarction scale (TICI) (12).

After having identified that the presence of collaterals descending to the proximal M4 segment or further is the most useful marker for infarct prediction, a second neuroradiologist blinded to MRI findings as well as to the results of the first lecture, performed a second reading of angiographic studies. These results were used to calculate the kappa coefficient for inter-rater agreement for the presence of collateral flow to the afore-mentioned segment.

For correlations with total infarct volume and clinical scores, we calculated a global collateral score for each patient, ranging from 0 to 25, by summing up the regional scores for all cortical regions (score of 0-5 in 5 areas).

MRI METHOD AND IMAGE ANALYSIS

All selected patients had pre-procedural MRI imaging and follow-up imaging (either MRI or CT scan) available on the hospital PACS system. The

FIGURE 2. Collateral flow grading system

Antero-posterior and lateral angiographic views of a patient with right M1 segment occlusion. The images are re-masked in the initial arterial phase. The grading of retrograde opacification in MCA branches is exemplified on the angular artery: 0 – no collateral flow; 1 – flow to the distal half of M4 segment; 2 – to the proximal half of M4 segment; 3 – to the M3 segment; 4 – to the distal half of the M2 segment; 5 – to the proximal half of the M2 segment. The most useful landmark is a score of 2 or higher, with 89.4% positive predictive value for the absence of infarct in the same cortical area on follow-up scans in TICI 3 recanalized patients.

majority of MRI exams were performed using 1.5 Tesla machines (Siemens Avanto and Aera, Germany), with a few exams done at 3 Tesla (Philips Achieva, Netherlands and General Electric Signa, USA). Scans were assessed for the presence or absence of infarction in the following areas: prefrontal area, precentral area, central area, parietal lobe, temporal lobe and insular cortex, using b1000 diffusion weighted sequences for pre-treatment imaging and MRI FLAIR sequences or native CT images for follow-up imaging. Total infarct volume was calculated after manual outlining of the infarcted area on all available slides, using Osirix software (Geneva, Switzerland).

STATISTICAL ANALYSIS

Angiographic collateral grade for each cortical region was compared with the presence or absence of infarct in the same region, generating a receiver operating characteristic (ROC) curve. Separate curves were generated for correlations with pre-treatment imaging and post-treatment imaging. For patients with occlusions after the M1 bifurcation, the cortical regions with normal anterograde flow were excluded from the analysis. In four patients without vertebral artery injections available for evaluation the temporal zone was also excluded from the analysis.

Global collateral scores for each patient were correlated with initial and follow-up infarct volumes and with NIHSS scores using Spearman correlation coefficients, with significance level established at $p < 0.05$.

To correlate collateral grade with the presence of insular cortex infarction, we developed an insular score representing the number of cortical sectors where collateral flow descends to the M2 segment. This score was compared with the presence or absence of insular cortex infarction by generating a ROC curve.

All statistical data was analyzed using GraphPad Prism version 6.0 software.

RESULTS

The study included 49 patients from a total of 56 patients that received endovascular treatment for a MCA occlusion. Reasons for exclusion were recanalization after intravenous thrombolytic therapy and unavailable imaging on PACS. The studied population had a mean age of 68 years (range 22-83) and a median initial NIHSS score of 16 (range 0-26). Pretreatment MRI was performed at 2.5 hours from symptom onset (range 0.4- 6.3). Collateral circulation was evaluated 1.9 hours later (range 1.3- 3.3). The final angiographic control run was performed at 5.45 hours (range 1.25-9.48) after symptom onset. TICI 2b-3 reperfusion was obtained in 73.3% of patients. PH2 hemorrhagic transformation was observed in 4 patients (8.2%). Death from all causes during the first 90 days occurred in five patients (10.2%). Good clinical outcome defined as modified Rankin score ≤ 2 was observed in 53.06% of patients.

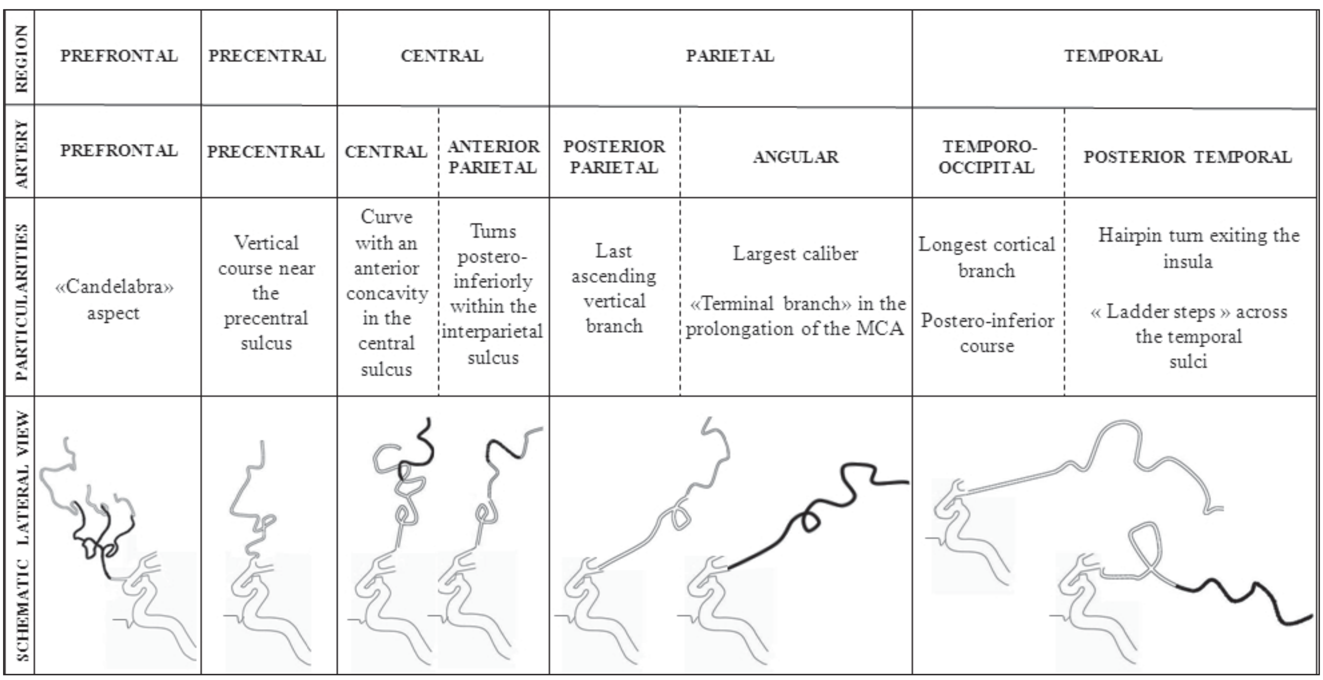

FIGURE 3. Angiographic particularities used for identifying the branches of the middle cerebral artery

Follow up imaging was analyzed on MRI in 36 patients and on CT in 13 patients, at a median interval of 7 days (range 1-45) after the qualifying event. MRI studies were preferred when available. Due to the possibility of poor visualization of infarcted areas on early post-treatment scans, 24 hours control CT images were used only in patients where no other post-treatment imaging was available (n = 4).

The regional score analyses were performed in 217 cortical zones for all 49 patients. A separate sub-analysis concerned the 23 patients with TICI 3 recanalization (105 cortical zones).

Correlations Between Regional Collateral Scores and Infarction

Regional collateral scores correlated well with the absence of infarction on pre-treatment diffusion weighted MRI sequences, with an area under the curve (AUC) of the receiver operator characteristic (ROC) curve of 0.74 ($p < 0.0001$, 95% CI 0.64-0.83). Retrograde flow to the proximal M4 segment or further (collateral score ≥ 2) demonstrated the best combination of sensitivity (92%) and specificity (51%).

We found good inter-rater agreement for the presence of collateral flow to the proximal M4 segment of further, with a kappa coefficient of 0.77 ($p = 0.05$, 95%CI 0.66-0.88).

The values were less significant when we correlated the regional collateral scores with the absence of infarction on follow-up imaging – AUC 0.67 ($p < 0.0001$, 95% CI 0.59-0.75). However, in a sub-analysis performed only on patients for which complete TICI 3 recanalization was obtained during the endovascular procedure (n = 23), the presence of collateral flow to the proximal M4 segment accurately predicted the absence of infarction on follow-up imaging with a positive predictive value 89,4% (95% CI 80,8-95,3) and a negative predictive value of 80% (95% CI 56,3-94,1) (Fig. 3).

A second sub-analysis concerned the patients with no recanalization, TICI 0-1 (n = 4). We found poor correlation coefficients between the collateral grade and the presence of infarction on follow-up scans – AUC 0.53 ($p = 0.79$, 95%CI 0.26-0.80).

Global Collateral Score versus Infarct Volume

Regardless of recanalization status, higher global collateral scores were predictive for lower total infarct volumes on follow-up imaging, as well as for less infarct growth compared to the initial pre-treatment volume.

We founda significative inverse correlation between global collateral scores and follow-up infarct volumes (Spearman correlation, $R=-0.50$, $p = 0.0003$), as well as with infarct growth ($R = -0.41$, $p = 0.0036$).

Higher correlation coefficients were found in a sub-analysis for mTICI 3 recanalized patients – correlation with follow-up infarct volume ($R = -0.57$, $p = 0.0043$) and with infarct growth ($R = -0.53$, $p = 0.008$) in comparison with mTICI 0-2b patients: $R = -0.48$, $p = 0.012$ and $R = -0.48$, $p = 0.013$ respectively.

Regional Collaterals versus Insular Cortex Infarction

We found a significant correlation between the number of cortical regions where collateral flow descends to the M2 segment (collateral score ≥ 4) and the absence of insular cortex infarction.

The correlation was significative for the absence of insular infarction on pre-treatment imaging (AUC = 0.73, $p = 0.006$), as well as on follow-up imaging (AUC 0.76, $p = 0.001$) regardless of recanalization status.

Global Collateral Score versus Clinical Scores

The correlation between global collateral scores and the initial pre-treatment NIHSS score was close to statistical significance ($R = -0.26$, $p = 0.07$).

We did not find a significant correlation between global collateral scores and follow-up NIHSS at three months. Equally, there was no significant correlation between collateral scores and the change in NIHSS score (pre-treatment to 3 months follow up).

DISCUSSION

The presented data shows that a simple regional collateral flow score correlates with the absence of infarction on pre-treatment imaging within the same cortical region and, more importantly, itcan also predict infarction on follow-up imaging for TICI 3 recanalized patients (complete recanalization without distal emboli). Although other papers have concordant results (3-5), we have not identified other studies that compared zonal collateral status both with pre and post-treatment imaging.

Our results suggest that this zonal score represents an anatomical map of collateral circulation that can quantify the amount of irreversible ischemia just like other non-invasive imaging modalities do. Thus, it becomes possible to obtain a real-time estimation of the core infarct by using normal angiographic runs obtained during stroke endovascular procedures.

One of the advantages of our evaluation lies in its simplicity – cortical regions respect the normal sectors of angiographic anatomy and grading only requires knowledge of MCA branches segmentation. Although we initially graded collaterals using a five point system, the results suggest that we can retain only two useful delimitation points: the proximal M4 segment that correlates with regional cortical infarction and the M2 segment that correlates with insular infarction. The most useful cut-off point that can allow prediction of cortical infarction (proximal half of the M4 segment) had good inter-rater agreement, demonstrating its potential for reproducibility in current clinical practice during endovascular procedures.

We found notable differences in correlations with follow-up imaging when the patients were divided in two groups depending on recanalization status. Compared to patients with partial/no recanalization, TICI 3 patients had more significant coefficients both for zonal infarct prediction on follow up-imaging and for total infarct volumes correlations. The loss of brain parenchyma is a dynamic non-linear process with great individual variability (13). Thisvariability is at least partlyexplained by differences in the presence, functionality and persistence of the leptomeningeal collateral flow. All imaging modalities are only single points on this patient-specific evolution curve. Our results suggest that collateral circulation scores can be regarded as a real-time snapshot of this dynamic process – a good score and the implied absence of infarction within the same cortical area can anticipate parenchymal outcome if the MCA is recanalized. However, in the absence of complete recanalization, the volume of infarct can grow if the collateral vascular supply becomes inefficient in maintaining an adequate cerebral blood flow. Moreover, the local hemodynamic status can be influenced by numerous factors like distal embolization, systemic hypotension and even head position (14).

In practice, collateral evaluation could be considered as a second imaging point of the cerebral parenchyma. At the moment of mechanical thrombectomy, all patients have already had initial CT or MRI imaging, which supported the treatment decision. In some patients, however, significant progression of the infarct volume can occur between the initial imaging and the start of the endovascular procedure, as exemplified in Fig. 4. Despite complete recanalization in less than three hours from symptom onset, this patient progressed to malignant middle cerebral artery infarction, although the initial imaging only showed a small anterior temporal lesion. The lack of adequate collateral flow in all cortical sectors at the initial angiography probably indicates that the volume of irreversible ischemia had already progressed before the start of the procedure, and thus the recanalization was futile.

This example is a good illustration for one of the possible uses of our results in clinical practice. The good predictive value of collateral grading for the absence of infarction on follow-up scans could allow the operator to establish if significant infarct growth has occurred since the initial imaging and eventually avoid performing futile revascularization procedures in this particular group of patients.

Moreover, if the accuracy of our score is validated in larger series of patients, it would become possible to design a prospective trial to test the safety and efficacy of patient selection directly in

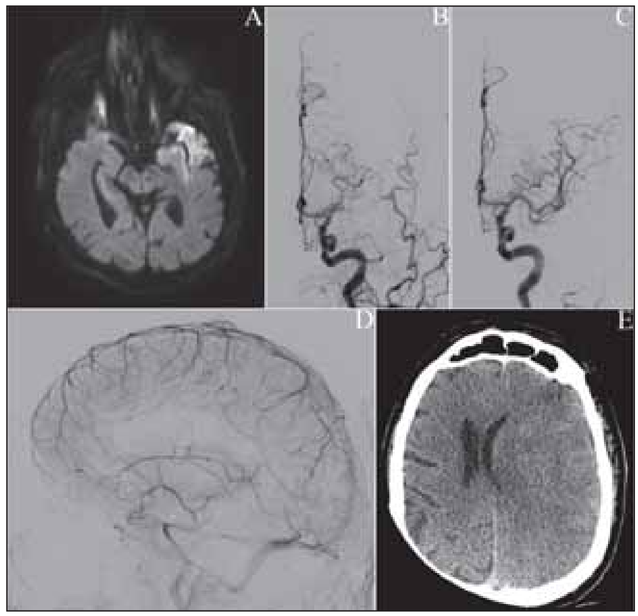

FIGURE 4. Illustrative case 2
Patient in his late 70s, NIHSS 25, left M1 segment occlusion; ***A:*** *initial MRI at 1 hour 30 minutes after symptom onset (diffusion sequence) showing only a small area of acute infarction in the anterior temporal lobe. There was a significant clinical-radiological mismatch and a good indication for combined IV thrombolysis and mechanical thrombectomy.* ***B:*** *Left common carotid artery (CCA) angiographic run at the beginning of the revascularization procedure confirming M1 segment occlusion;* ***C:*** *Early and complete TICI 3 recanalization was obtained at 2 hours 53 minutes after symptom onset. However, on* ***D:*** *Late venous phase of the initial pre-treatment left CCA run there was no collateral flow in any of the cortical sectors.* ***E:*** *CT scan at 24 hours showing malignant left MCA infarction. The patient died at day 3. The lack of adequate collateral flow in all cortical sectors at the initial angiography correlates well with final infarct size and location, and probably indicates that the lesion had already progressed between the MRI and the start of the procedure, and thus the recanalization was futile.*

the angiography suite, eliminating the need for pre-treatment non-invasive imaging.Performing an initial cone beam CT using the flat panel detector of the angiography machine can exclude intracranial hemorrhage. A diagnostic cerebral angiography, which could be done under local anesthesia,can provide a detailed diagnostic of arterial occlusions and, at the same time, evaluation of collateral circulation using our score can estimate the extent of core infarction. Potentially, this method could significantly reduce door to revascularization times, which has been shown to improve clinical outcome.

A recently published study identified insular cortex infarction as a predictive factor for total infarct volume growth in MCA occlusions (15). In our series, both the presence of insular infarction and growth in total infarct volume were linked to the degree of collateral flow. Consequently, we can hypothesize that both variables are the expression of the same pathophysiological process – less collateral flow is associated with insular infarction but also with larger follow-up infarct volumes and increased infarct growth.

The lack of significant correlations between collateral grades and clinical scores is probably partly explained by the small sample size. Notably, the correlation with the initial pre-treatment NIHSS score was close to significance (p=0.07), suggesting that better collateral grades were associated with less severe clinical presentations. Recent studies in larger patient populations have established the link between good collateral status and better clinical outcome after revascularization (1, 16).

A limitation of our study consists of its retrospective nature. The evaluation was performed on a patient population that had already been selected for thrombectomy. This process introduced a selection bias, because the main criteria consisted of small infarct volume on DWI, clinical – radiological mismatch and good collateral flow visualized as vascular hyper-intensities on FLAIR sequences. Consequently, there was relatively little representation of patients with absent/little collateral circulation, and this probably translated in lower values of specificity for the collateral evaluation scores.

Another limitation worth mentioning is the inability of the described collateral score to predict infarction within the basal ganglia. We did not visualize a quantifiable collateral flow to this territory, which is generally considered to be vascularized by end-arteries, although in rare cases the lenticulostriate arteries are vascularized by retrograde flow descending to a permeable distal M1 segment in proximal occlusions.

CONCLUSIONS

Our analysis on a series of 49 patients with acute MCA occlusion shows that a simple anatomic regional evaluation of collateral flow on usual angiographic runs before revascularization correlates well with the areas of infarction on follow-up im-*aging in patients with complete recanalization. In these patients, for each cortical area, retrograde opacification to the proximal half of the M4 segment or further has high positive predictive value-for the absence of infarction in the same area on follow-up imaging.*

Although these results need to be confirmed in larger series of patients, this method has the potential to offer real time information on the size of irreversible ischemia during stroke endovascular procedures.

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