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Original Article

Assessment of collateral blood flow in patients with distal branch occlusion of the middle cerebral artery

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ABSTRACT

Purpose. – Aim of this study was to evaluate the collateral blood flow between more distal branches of the middle cerebral artery (MCA) in the case of peripheral MCA branch occlusion on dynamic 4D angiograms. We sought to individually predict the finally resulting infarction volume with regard to the extent of collateral blood flow.
Methods. – Overall, 35 acute ischemic stroke patients with peripheral MCA branch occlusion were included. Volumes of the ischemic infarctions and perfusion deficits were measured on diffusion-weighted images DWI and time-to-peak TTP (> 4 s). Collateral flow on 4D MR angiograms were classified as previously specified.
Results. – On DWI, the ischemic lesions had a mean volume of 3.4 ± 15.1 mL while the mean volume on TTP (> 4 s) was significantly larger 22.0 ± 18.1 mL ($P < 0.001$). On dynamic 4D angiograms we observed grade 1 in 8 (22.9%), grade 2 in 4 (11.4%), grade 3 in 10 (28.6%), and grade 4 in 13 (37.1%) patients. In comparison to patients with better collateralization (grade 3–4) patients with less sufficient collateralization (grade 0–2) demonstrated larger infarction volumes on initial (11.1 mL (IQR 2.9–35.5) vs. 2.1 mL (IQR 0.5–4.5), $P = 0.03$) and follow-up DWI (15.5 mL (IQR 12.6–23.3) vs. 1.9 mL (IQR 0.5–4.5), $P = 0.03$) with prominent infarction growth (7.4 mL (IQR 2.6–10.1) vs. 0.9 mL (IQR 0.2–2.6), $P = 0.08$).
Conclusions. – In the majority of cases with distal MCA branch occlusion a good collateral blood flow has been observed. Nevertheless, in approximately one quarter of patients an insufficient collateral blood flow has been detected that was associated with substantial infarction growth.

Introduction

In more than half of all cerebral infarctions the middle cerebral artery (MCA) territory is affected [1]. Clinical outcome of patients with acute ischemic stroke is highly dependent on the location of the vessel occlusion, the volume of ischemic core and penumbra as well as the grade of collateral blood flow. Invasive digital subtraction angiography (DSA) is still regarded as the gold standard diagnostic procedure to assess collateral blood flow in these patients. However, while DSA is feasible for collateral blood flow estimation in patients with proximal MCA occlusion undergoing endovascular recanalization therapy, it is not routinely performed in smaller and more distal MCA branch occlusion usually still treated with intravenous thrombolysis. Nowadays, due to advances in imaging techniques and analysis methods, it is possible to estimate non-invasively collateral blood flow by computed tomography (CT) or magnetic resonance imaging (MRI) [2] based approaches. In this context, the recently presented dynamic 4D angiograms derived from dynamic susceptibility contrast (DSC) perfusion MRI raw images [3] seem most promising to assess collateral blood flow as prior studies showed a good correlation with conventional DSA [4]. Up to now, this MRI-based method has shown convincing results in patients with anterior cerebral artery occlusion [5], MCA occlusion [3,4], posterior cerebral artery and basilar artery occlusion [6,7] as well as lacunar infarction [8]. However, so far no study investigated the extent of collateralisation in more peripheral MCA branch occlusions. These are known to have a more favourable clinical course in comparison to proximal MCA occlusions [9] and as a consequence the necessity of intravenous thrombolysis [10] as well as endovascular treatment [11] in these patients is a matter of debate. Nevertheless, severe clinical presentations with worse clinical outcome also have been reported [9]. Besides different intra-individual factors that can influence prog-

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nosis and functional outcome, the grade of blood flow through leptomeningeal anastomoses is regarded as an essential condition enabling the survival of potentially salvageable brain tissue [12]. Moreover, it would be of high clinical interest to non-invasively identify patients with poor collateralisation that are at highest risk of clinical deterioration by early stage standard MRI as these might benefit from interventional mechanical thrombectomy of more distal MCA branches.

Therefore, the aim of this study was to evaluate the collateral blood flow between more distal branches of the MCA on dynamic 4D angiograms in a patient cohort with peripheral MCA branch occlusion (occlusions of the M2-Segment or more distal branches). Furthermore, we sought to individually predict the finally resulting infarction volume with regard to the extent of collateral blood flow on dynamic 4D angiograms.

Methods

Patients

From a prospectively maintained MRI report database, we identified patients with acute ischemic stroke due to peripheral branch occlusion of the MCA who underwent a standardized stroke MRI protocol including PWI (2005–2016). Of these, only those patients were included who had:

- the first MRI within 12 hours after stroke onset;
- good diagnostic quality of MRI;
- no occlusion prior to the M2-Segment in the TOF-MRA, and;
- a perfusion deficit in the MCA territory.

A good quality of MRI was defined as no or minimal head motion artifacts and a good arterial contrast bolus in the DSC perfusion. Peripheral branch occlusion was defined as an occlusion of the M2-Segment or more distal MCA branches. Since TOF-MRA does usually not allow evaluation of more distal branches due to its limited spatial resolution as well as anatomical coverage, assessment of PWI was used as the best noninvasive technical approach to detect distal occlusions as described previously by Lemmens [9]. Another non-invasive approach to detect vessel occlusions is the susceptibility vessel sign (SVS) on $T2^*$-weighted gradient echo magnetic resonance (GRE) images which is frequently present in the hyperacute phase of acute ischemic stroke due to large vessel occlusion in the first hours of an occlusion [13,14].

Demographic details, clinical presentation, and acute treatment were abstracted from the case records. This study has been approved by the local institutional review board (Medizinische Ethikkommission II der Medizinischen Fakultät Mannheim) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Patient consent was waived for this analysis by the local institutional review board due to its retrospective nature.

MRI studies

Magnetic resonance imaging was performed on a 1.5-T MR system (Magnetom Sonata or Avanto, Siemens Medical Systems, Erlangen, Germany) or a 3-T MR system (Magnetom Trio, Siemens Medical Systems, Erlangen, Germany). A standardized protocol was used in all patients including:

- transverse, coronal and sagittal localizing sequences followed by transverse oblique images aligned with the inferior borders of the corpus callosum;
- T1-weighted images;
- T2-weighted images;
- diffusion-weighted images (DWI);
- fluid attenuation inversion recovery (FLAIR) images;
- perfusion-weighted imaging (PWI) following the first pass of contrast bolus through the brain; and;
- a 3D time-of-flight MR angiography (MRA).

Table 1
Sequence parameters of DWI and PWI at the department's MRI scanners.

Sequence	Parameters	MRI scanner 1.5-T Siemens Sonata	1.5-T Siemens Avanto	3-T Siemens Trio
DWI	FOV	230 × 230	230 × 230	230 × 230
	Matrix	128 × 128	192 × 192	192 × 192
	Number of slices	24	24	24
	ST	5	5	5
	TR	4400	4000	4000
	TE	101	96	91
PWI	FOV	230 × 230	230 × 230	230 × 230
	Matrix	128 × 128	128 × 128	128 × 128
	Number of slices	12	19	24
	ST	6	5	5
	TR	1500	1430	1770
	TE	46	30	32

FOV: field of view (mm × mm), ST: slice thickness (mm), TR: repetition time (ms), TE: echo time (ms).

Perfusion-weighted imaging was acquired using a gradient-echo planar imaging sequence. The contrast agent gadoteric acid (Dotarem, Guerbet, Aulnay-sous-Bois, France) was bolus injected by a power injector (Spectris MR injection system, Medrad, Volkach, Germany) with a dose of 0.1 mmol/kg of body weight at a rate of 4 mL/s. Parameters of DWI and PWI are displayed in Table 1. Follow-up MRI was available in 17 (48.6%) patients.

Post-processing

Perfusion maps

The post-processing of the perfusion-weighted raw images was performed by a specific software, Signal Processing In NMR (SPIN, The MRI Institute for Biomedical Research, Detroit, USA) [13]. Deconvolution with singular value decomposition (SVD) was used to create quantitative maps of mean transit time (MTT), cerebral blood flow (CBF), and cerebral blood volume (CBV). The position of the arterial input function was automatically determined by using the maximum concentration (Cmax), TTP and first moment MTT (fMTT). The concentration-time curve for arteries has short first moment MTT, short TTP and high maximum concentration. Twenty voxels, which best fitted these properties were selected. Then the concentration-time curves of these voxels were averaged, smoothed and truncated to avoid the second pass of the tracer.

Dynamic 4D angiograms

Furthermore, perfusion-weighted raw images were used to create a dynamic angiographic representation of blood flow as described recently L. For this purpose, the baseline pre-bolus image was subtracted from each frame of the raw perfusion data as in digital subtraction angiography by use of the subtract series function in SPIN.

MRI analysis

Diffusion-weighted images and dynamic 4D angiograms were analyzed by two independent raters (J.B. and A.F.) blinded to the other MRI sequences and clinical information. Cases with discrep-

ancies were re-reviewed by both readers and discussed until a consensus was reached.

DWI findings

Acute ischemic lesions in the MCA territory were noted on axial DWI. The topography was determined according to the maps by Tatu et al. and categorized in:

- frontal lobe;
- temporal lobe;
- parietal lobe;
- insular lobe;
- internal capsule, and;
- basal ganglia.

Ischemic lesion size was measured on DWI by manually delineated ROI, summation of these areas in cm^2 on each section and multiplication with the slice thickness (plus interslice gap), to determine the volume in cm^3 by use of OsiriX.

Perfusion maps

For the calculation of the perfusion deficit volumes, we used a modification of an established method for perfusion deficit volume estimation [15,16]. First, the mean TTP value for a reference region in the contralateral PCA territory was obtained. In a second step, these mean values were applied for automatic PWI lesion definition by using an automatic threshold method. Using this simple method, we were able to generate maps that depicted areas of pathological bolus delay (TTP delay $\geq$4 s). Finally, these generated maps were placed on the calculated CBF and CBV maps, mirrored to the contralateral unaffected hemisphere, and ratios between the physiological estimates (CBF, CBV) of the lesion and of the contralateral mirror ROI were determined. All image-processing steps were performed by using a semiautomatic image display program (MRIcron, www.mccauslandcenter.sc.edu/mricro/mricron) [17].

Dynamic 4D angiograms

The quality of the collateral circulation was assessed using a modification of the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) Collateral Flow Grading System as established recently [11]. According to this modification a rapid collateral blood flow is defined as a signal drop in the respective vascular territory within the arterial phase on the subtracted perfusion study, while a slow collateral blood flow is defined as a signal drop in the respective vascular territory in the venous phase on the subtracted perfusion study:

- grade 0 (no collateral vessels visible);
- grade 1 (slow collateral blood flow to the periphery of the ischemic site with persistence of some of the defect);
- grade 2 (rapid collateral blood flow to the periphery of ischemic site with persistence of some of the defect);
- grade 3 (collateral blood flow with slow but complete angiographic blood flow of the ischemic bed by the late venous phase), and;
- grade 4 (complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion).

Statistical analysis

All statistical analyses were performed using Statistical Product and Service Solutions (SPSS) statistics for Windows (Release 17.0; SPSS, Chicago, IL, USA). Comparison of lesion size on DWI and PWI was performed using the student's *t*-test. Correlations of collateralization grade on 4D angiograms and CBF and CBV ratios were assessed using the Spearman correlation. Correlations of lesion localization and collateralization grade on 4D angiograms as well as time between onset and MRI were assessed using the Spearman correlation. The interrater reliability was assessed using a simple kappa test. All statistics was performed with a 0.05 level of significance.

Table 2
Demographic characteristics and clinical presentation.

Mean age (years)	77±10.2 (51–94)
Female gender (%)	25 (62.9%)
Clinical presentation	
Aphasia (%)	22 (62.9%)
Hemiparesis (%)	26 (65%)
Dysarthria (%)	14 (40.0%)
Hemihypaesthesia (%)	6 (17.1%)
Hemianopia (%)	2 (5.7%)
Neglect (%)	2 (5.7%)
Dysphagia (%)	2 (5.7%)
Ataxia (%)	2 (5.7%)

Results

Baseline characteristics and clinical presentation

Overall, we identified 48 patients with peripheral branch occlusion of the MCA. In the final analysis, 35 (72.9%) patients were included who met the pre-specified inclusion criteria. Mean patient age was 77 ± 10.2 (51–94) years; 25 patients were female (62.9%). Clinical symptoms included aphasia in 22 (62.9%), hemiparesis in 26 (65%), dysarthria in 14 (40.0%), hemihypaesthesia in 6 (17.1%), hemianopia in 2 (5.7%), neglect in 2 (5.7%), dysphagia in 2 (5.7%), ataxia in 2 (5.7%). Intravenous thrombolysis with rtPA was performed in 7 (20.0%) patients. The details of demographic data are presented in Table 2.

MRI findings

On initial DWI, ischemic lesions were found in 33 (94.3%) patients. Ischaemic lesions were located in the frontal lobe in 12 (34.3%), in the temporal lobe in 4 (11.4%), in the parietal lobe in 19 (54.3%), in the insular lobe in 24 (68.6%), in the internal capsule in 2 (5.7%) and in the basal ganglia in 6 (17.1%). In general, mean DWI lesion volume was 3.4 ± 15.1 mL. In the patients with follow-up MRI the initial mean DWI lesion volume was 1.72 ± 5.9 mL; on follow-up DWI the ischemic lesions had larger mean DWI lesion volume of 3.18 ± 7.9 mL. Growth of DWI lesions was observed in 12 (70.6%) patients.

In all patients, PWI showed an area of hypoperfusion that extended beyond the observed DWI lesion. The hypoperfused areas had a mean volume of 22.0 ± 18.1 mL while the corresponding mean DWI lesion size 3.41 ± 15.1 mL was significantly smaller ($P < 0.001$). The mean CBF and CBV ratios were 0.88 ± 0.24 and 0.92 ± 0.22 respectively.

On dynamic 4D angiograms, all patients demonstrated to some extent collateral blood flow from adjacent vascular territories:

- grade 1 in 8 (22.9%) patients.
- grade 2 in 4 (11.4%) patients.
- grade 3 in 10 (28.6%) patients, and;
- grade 4 in 13 (37.1%) patients.

For examples see Fig. 1. Interrater reliability for collateral blood flow patterns prior to consensus was substantial ($\kappa = 0.79$, $P < 0.01$).

The collateralization grade on dynamic 4D angiograms correlated well with the relative CBF (rS = 0.63, $P < 0.001$) and CBV (rS = 0.43 $P = 0.01$). In comparison to patients with better collater-

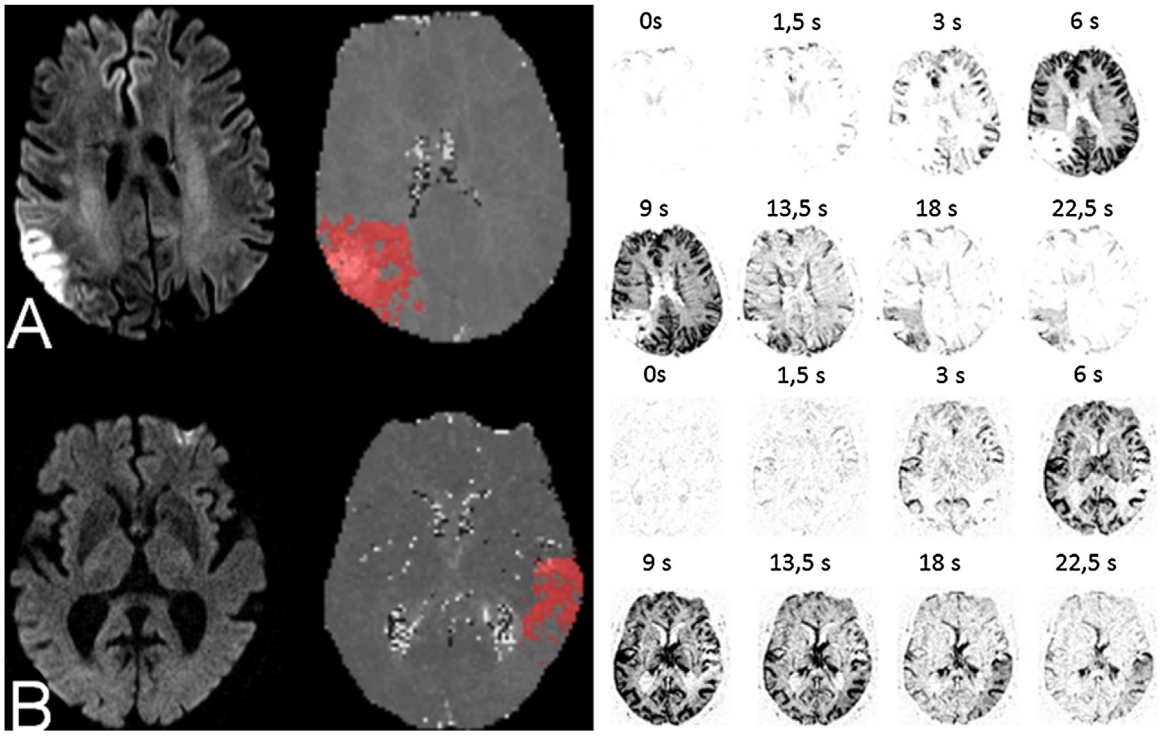

Fig. 1. Examples of different collateralization grades in MCA branch occlusion. Diffusion-weighted images (DWI, left column), time-to-peak (TTP) maps (middle column), and collateralization grades on dynamic 4D angiograms (right column). A. Grade 1 (slow collateral blood flow to the periphery of the ischemic site during the venous phase with persistence of some of the defect) with large ischemic lesion on DWI and corresponding perfusion deficit on TTP map (red coloured). B. Grade 4 (complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion during the arterial phase) without ischemic lesion on DWI and perfusion deficit on TTP maps (red coloured).

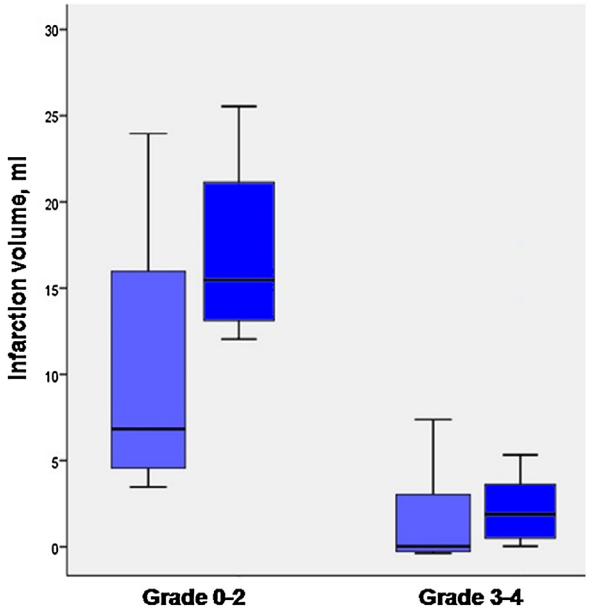

Fig. 2. Infarct volumes on initial (light blue) and follow-up MRI (dark blue) in cases with low (grade 0–2) and high (grade 3–4) collateralisation grade on dynamic 4D angiograms.

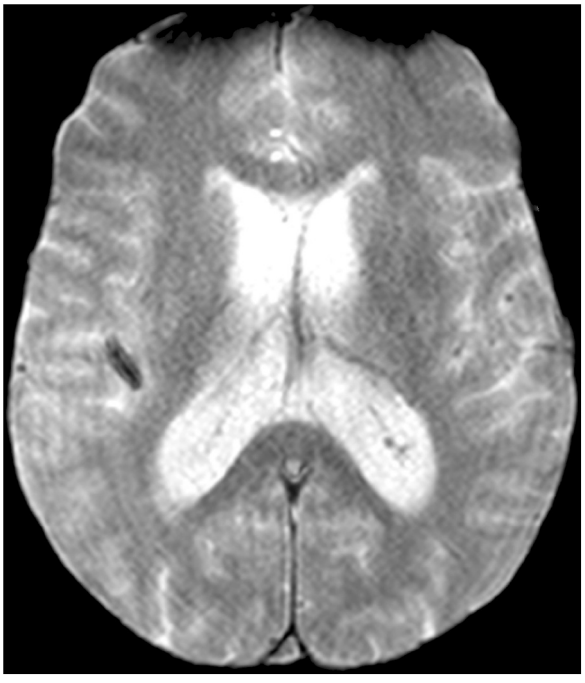

Fig. 3. Susceptibility vessel sign in the M2 segment on the T2*-weighted gradient echo magnetic resonance images representing intra-arterial thrombus.

alization (grade 3–4), patients with less sufficient collateralization (grade 0–2) had larger infarction volumes on initial (11.1 mL (IQR 2.9–35.5) vs. 2.1 mL (IQR 0.5–4.5), $P = 0.03$) (see Fig. 2) and follow-up DWI (15.5 mL (IQR 12.6–23.3) vs. 1.9 mL (IQR 0.5–4.5), $P = 0.03$) as well as larger infarction growth (7.4 mL (IQR 2.6–10.1) vs. 0.9 mL (IQR 0.2–2.6), $P = 0.08$) in the clinical course.

Overall, MR angiography demonstrated an occlusion of the MCA in the M2-segment in 13 (32.5%), and in the M3-segment in 2 (5.0%) patients. On follow-up MRA, recanalization was observed in 5 (12.5%) patients.

On T2*-weighted GRE, an SVS in more peripheral MCA branches could be demonstrated in 27 (77.1%) patients.

Discussion

In acute ischemic stroke due to large vessel occlusions, sufficient collateral blood flow is associated with improved clinical status on presentation and increased likelihood of recanalization after endovascular therapy [18]. Moreover, a good collateralization predicts a better functional patient outcome at follow-up after 3 months [19]. While DSA is the gold standard for the assessment of collateral blood flow via leptomeningeal anastomoses, different non-invasive approaches for the assessment of collateral blood flow have been evaluated and used in the last years such as several variants of CT angiography [15], FLAIR images [16], T2* images [17], SWI [20], dynamic susceptibility contrast (DSC) perfusion-weighted imaging (PWI) [3], and arterial spin labeling perfusion-weighted imaging [19].

Dynamic 4D angiograms derived from DSC perfusion raw images were proposed as a novel imaging biomarker of collateral blood flow in 2013[3]. This method has been established in a post-hoc analysis of the EPITHET patient sample, mainly consisting of subjects with occlusions of the internal carotid artery (ICA) and the proximal MCA [3,21]. In the present study, dynamic 4D angiograms derived from perfusion raw data of routinely performed standard MRI examinations enabled us to evaluate and categorize leptomeningeal collateral blood flow in patients with peripheral MCA branch occlusion for the first time. In combination with further parameters of DWI, TTP > 4 s, CBF and CBV maps the presented data give novel insights into the pathophysiologic process of cerebral perfusion in the presence of a distal MCA branch occlusion. We found significant correlations of collateralization grades and infarction size and growth in the clinical course. Although the majority (> 65%) of distal MCA branch occlusions were associated with high grade collateral blood flow of neighbored vascular territories, more than a quarter of patients showed only minor grade of collateralization which was associated with infarct growth. These observations reflect the well-known clinical presentation and course of patients with distal MCA occlusion.

An SVS on T2*-weigted GRE images as indirect sign of vessel occlusion was present in 77.1% of patients, confirming the study results described by Soize [14] et al. In contrast to this only a minor proportion of occlusions were seen on TOF-MRA, probably due to limited spatial resolution[22] and anatomic coverage, so that a DSC-PWI should be used to detect distal MCA occlusions [9].

While some patients with stroke due to distal MCA occlusion have been shown to have a better clinical outcome compared to patients with proximal MCA occlusions, also less favourable outcomes in the clinical course have been reported [9]. Moreover, we were able to predict infarction growth based on the initial MRI scan. Hence, the presented imaging approach with dynamic 4D angiograms derived from the perfusion raw data could help to identify patients with an M2 segment MCA occlusion, who possibly might benefit from intravenous thrombolysis and/or endovascular therapy [23]. In our cohort 13 patients (32.5%) had an M2 occlusion, where mechanical thrombectomy might have been possible. However, during the study period acute management of these patients included intravenous thrombolysis only. Nevertheless, mechanical thrombectomy has been demonstrated to be feasible in patients with an MCA occlusion in the M2 segment [24]. This could be of major interest, in particular since the necessity of intravenous thrombolysis [10] as well as endovascular treatment [11] in these patients is a matter of debate, while the management of proximal MCA occlusion [25] is well established. The present study has some limitations. First, this is a retrospective clinical study of moderate size. However, to our knowledge this is the largest series of patients investigating collateral blood flow in distal MCA occlusion in detail with an MRI-based approach. Second, we could not perform a direct comparison of dynamic 4D angiograms with collateral blood flow on conventional angiography as gold standard. Third, we did not perform a multivariate data analysis assessing the influence of clinical risk factors (e.g. age, sex, comorbidities) or baseline parameters (e.g. temperature, laboratory test results) on collateralization grade because of the moderate study size. Fourth, the hospital-based retrospective study design might cause several types of bias and statistical errors such as selection bias, sample bias, or image-based selection bias. Finally, follow-up PWI was only available in a subset of patients and consequently, no information about the evolution of perfusion abnormalities could be obtained. Fifth, we focused on the analysis of more distal MCA occlusions (i.e., vessels with quite small diameter) that limited in most cases the direct visualization of the occlusion itself. However, the combination of a typical clinical presentation and a defined perfusion deficit in a corresponding vascular territory seem to present a good surrogate for the existence of a distal vessel occlusion. However, although we did not observe MRI findings supporting different underlying etiologies of a perfusion deficit (such as vasodysregulation or local edema), we cannot completely exclude such alternative causes.

In conclusion, the present study focused on a non-invasive method for the estimation of cerebral collateral blood flow – dynamic 4D angiograms – and demonstrated that previous evidence, derived mainly from patients with distal ICA and proximal MCA occlusion is transferrable to patients with an acute ischemic stroke due to more distal MCA branch occlusion. In the majority of cases with distal MCA branch occlusion a good collateral blood flow through anastomoses has been observed. Nevertheless, in approximately one quarter of patients an insufficient collateral blood flow has been detected that was associated with substantial infarction growth. Future research is needed to address the question whether the estimation of collateral blood flow with this specific technical approach could be used to improve patient selection for recanalization therapies or to extend the therapeutic time window in acute ischemic stroke due to more distal MCA branch occlusion.

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