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ABSTRACT

BACKGROUND AND PURPOSE: Collateral flow is associated with clinical outcome after acute ischemic stroke and may serve as a parameter for patient selection for intra-arterial therapy. In clinical trials, DSA and CTA are 2 imaging modalities commonly used to assess collateral flow. We aimed to determine the agreement between collateral flow assessment on CTA and DSA and their respective associations with clinical outcome.

MATERIALS AND METHODS: Patients randomized in MR CLEAN with middle cerebral artery occlusion and both baseline CTA images and complete DSA runs were included. Collateral flow on CTA and DSA was graded 0 (absent) to 3 (good). Quadratic weighted κ statistics determined agreement between both methods. The association of both modalities with mRS at 90 days was assessed. Also, association between the dichotomized collateral score and mRS 0–2 (functional independence) was ascertained.

RESULTS: Of 45 patients with evaluable imaging data, collateral flow was graded on CTA as 0, 1, 2, 3 for 3, 10, 20, and 12 patients, respectively, and on DSA for 12, 17, 10, and 6 patients, respectively. The κ -value was 0.24 (95% CI, 0.16–0.32). The overall proportion of agreement was 24% (95% CI, 0.12–0.38). The adjusted odds ratio for favorable outcome on mRS was 2.27 and 1.29 for CTA and DSA, respectively. The relationship between the dichotomized collateral score and mRS 0–2 was significant for CTA ($P = .01$), but not for DSA ($P = .77$).

CONCLUSIONS: Commonly applied collateral flow assessment on CTA and DSA showed large differences, indicating that these techniques are not interchangeable. CTA was significantly associated with mRS at 90 days, whereas DSA was not.

ABBREVIATIONS: CS = collateral score; IAT = intra-arterial therapy; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands

Recently, the effectiveness of intra-arterial therapy (IAT) in patients with acute ischemic stroke of the anterior circulation treated within 6 hours after symptom onset was established by

multiple randomized controlled trials.^{1–5} In the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN), the largest of these trials, a substantial number of patients did not reach functional independence, despite high recanalization rates after IAT. Other trials showed higher recanalization rates, with better overall patient outcome. Contrary to MR CLEAN, these latter trials used neuroimaging for patient selection. In the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial, a CTA collateral score (CS) was used for this purpose.³

Collaterals are defined as a network of vascular channels that variably restore blood flow when the main supplying artery is blocked.⁶ A good collateral circulation is believed to be of major importance for sustaining the penumbra in patients with acute ischemic stroke, is considered predictive of final infarct volume, and is associated with improved clinical outcome after both intravenous thrombolysis and IAT.^{7–16}

The criterion standard for the assessment of collateral flow is multivessel DSA.¹⁷ This generates images with high spatial and

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temporal resolution, which allows the evaluation of contrast flow into the ischemic region via collaterals.^{18,19} However, in practice, multivessel DSA is considered impractical as a primary diagnostic procedure for acute ischemic stroke triage because speed of treatment is an important factor in these cases. In addition, the expected benefit is low relative to the resources needed. Single-vessel DSA is the pragmatic choice but has several drawbacks, including incomplete assessment of the MCA or anterior cerebral artery territory. Alternatively, CTA is currently used for assessment of collateral flow because of its 24/7 availability and short acquisition time.^{8–10} Also, good interrater agreement for this technique has been reported.^{10,20} Additionally, CTA has the advantage of allowing visualization of collateral flow from all vessels at once, both intra- and extracranial.⁹ A drawback of CTA, however, is the lack of temporal information. Multiphase CTA could solve this problem, but it is not yet widely available.

The purpose of this substudy of MR CLEAN was to assess the agreement between CTA and DSA for grading of collateral flow in patients with acute ischemic stroke due to proximal anterior circulation occlusion, analogous to current practice. In addition, we investigated the association of CTA and DSA collateral grades with clinical outcome as measured on the mRS.

MATERIALS AND METHODS

Patient Inclusion and Study Design

The design of MR CLEAN has been published previously.¹ In short, MR CLEAN was a randomized clinical trial of IAT in addition to the usual care versus usual care alone in patients with a proximal intracranial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 hours after symptom onset. The inclusion criteria for the current substudy were the availability of baseline CTA combined with a complete DSA run of the ipsilateral ICA territory showing a middle cerebral artery occlusion (M1 or M2), including a lateral projection. Exclusion criteria were occlusion of the ipsilateral cervical ICA or ICA terminus, the presence of multiple ipsilateral occlusions, an ipsilateral hypoplastic A1 segment, and occurrence of contralateral flash filling (resulting in dilution of contrast by blood from the contralateral circulation). Approval from the local institutional review board was obtained, and all patients or their legal representatives gave written informed consent to participate. The MR CLEAN study protocol was approved by a central medical ethics committee and the research board of each participating center.

Imaging Assessment

All imaging data were collected before this substudy, as part of the overall evaluation in MR CLEAN. The relevant scan protocols of CTA and DSA used in this study are shown in the On-line Table. The data were anonymized before assessment. The CS on CTA source imaging was determined in separate sessions by pairs of experienced neuroradiologists, with at least 5 years of experience. Discrepancies between the initial readers were solved by a third reader. CS on DSA was determined by 1 experienced neuroradiologist (A.J.Y., with >10 years of experience). All readers were blinded to clinical findings, and the initial readers were blinded to each other's scores. On both CTA and DSA, CS was graded on a 4-point scale, with zero representing absent collateral flow of the

Table 1: Patient characteristics^a

Baseline Characteristic	Value
Patients	45
Median age (range) (yr)	63 (44–85)
Sex ratio (M/F)	22/23
Stroke side (L/R)	22/23
DSA occlusion site	M1 (n = 35), M2 (n = 10)
Clot migration (CTA to DSA)	ICA-T to M1 (n = 1) M1 to M2 (n = 6) M2 to M1 (n = 1)
IVT (yes/no)	36/9
Median NIHSS at baseline (range)	16 (6–30)
Median time onset to CTA (range) (min)	204 (21–496)
Median time onset to DSA (range) (min)	260 (108–390)

Note:—ICA-T indicates ICA terminus; IVT, intravenous thrombolysis. R, right; L, left.
^a Range is displayed in parentheses. IVT displays if patients received IVT prior to IAT. Time to CTA and time to DSA represent the median time in minutes from symptom onset to the acquisition of CTA and DSA scans, respectively.

occluded territory, 1 representing poor collateral flow (<50% flow of the occluded territory), 2 representing intermediate collateral flow (between 50% and 100% flow of the occluded territory), and 3 representing good collateral flow (100% flow of the occluded territory).^{15,21}

Clinical Outcome Assessment

The mRS is a 7-point scale on which functional independence of the patient is measured, ranging from 0 (no symptoms) to 6 (dead). In MR CLEAN, the mRS was constructed from a follow-up interview at 90 days, which was conducted by an experienced trial investigator (blinded to the treatment-group allocation) by telephone with the patient, proxy, or health care provider.

Statistical Analysis

Analysis was performed by using SPSS software (Version 22.0 for Windows; IBM, Armonk, New York). We assessed interobserver reliability for collateral flow on CTA by estimating the agreement beyond chance with quadratic weighted κ statistics. Interobserver reliability was considered poor at a κ -value of 0, slight between 0.01 and 0.20, fair between 0.21 and 0.40, moderate between 0.41 and 0.60, substantial between 0.61 and 0.80, almost perfect between 0.81 and 0.99, and perfect at 1.0.²² Quadratic weighted κ statistics were also used to determine consistency between both modalities. Ninety-five percent confidence intervals were set to quantify uncertainty. The overall observed proportion of agreement of CS scoring between both methods was determined. Multivariable ordinal logistic regression analysis was performed to determine the adjusted odds ratio of a shift toward better clinical outcome on the mRS, adjusted for early successful recanalization, which was defined as a modified Thrombolysis in Cerebral Infarction score of 2B or higher. Additionally, for secondary analyses, CS was dichotomized into poor (absent and poor collateral flow) and good (moderate and good collateral flow), and mRS was dichotomized into a score of 0–2 (functional independence) versus 3–6. χ^2 tests were performed to determine the association between dichotomized CS and mRS 0–2 for both modalities in the entire population and for patients with early recanalization separately.

RESULTS

Of the 500 patients in MR CLEAN, 84 met the inclusion criteria on quality of CTA and DSA imaging. Of these, 39 patients were excluded due to the presence of either ICA or ICA terminus occlusion ($n = 25$), presence of multiple occlusions ($n = 7$), occurrence of contralateral flash filling ($n = 4$), a hypoplastic A1-segment ($n = 2$), or motion artifacts ($n = 1$). This exclusion left 45 patients available for comparison. Table 1 provides an overview of the relevant baseline characteristics of the included patients. Thirty-five patients had an M1, and 10, an M2 occlusion on DSA. In 8

of these patients, CTA clot location was different on DSA (in 6 patients from M1 on CTA to M2 on DSA, in 1 patient from the ICA terminus on CTA to M1 on DSA, and in 1 patient from M2 on CTA to M1 on DSA). Table 2 shows the distribution of CSs for CTA and DSA in all patients.

Interobserver agreement for collateral flow assessment on CTA had a quadratic weighted κ -value of 0.68 (95% CI, 0.40–0.96), indicating substantial agreement. Figure 1 gives examples of both methods. The quadratic weighted κ -value for the agreement between CTA and DSA was 0.24 (95% CI, 0.16–0.32). When patients in whom clot location differed between CTA and DSA were excluded from analysis, the quadratic weighted κ -value was 0.25 (95% CI, 0.13–0.38). The overall observed proportion of agreement was 24% (95% CI, 0.12–0.38).

There was a significant shift in mRS distribution toward better clinical outcome for CTA based on CS (adjusted OR, 2.27; 95% CI, 1.18–4.40; $P = .015$) (Fig 2). For the DSA-based CS, there was no significant association (adjusted OR, 1.29; 95% CI, 0.76–2.21; $P = .35$).

Of the 16 cases in which the dichotomized CS was graded as good on DSA (grades 2–3), in 13 (81%), it agreed with the CTA assessment. In contrast, of 29 cases in which dichotomized CS was graded as poor on DSA (grades 0–1), in only 10 (35%) did it agree with the CTA assessment. There was a significant relationship between dichotomized CS on CTA and mRS 0–2 in the entire population ($\chi^2 = 6.7$, $P = .010$) and for patients with early recanalization ($\chi^2 = 5.2$, $P = .023$). This was not the case for dichotomized CS on DSA in the total population ($\chi^2 = 0.1$, $P = .77$) or for patients with early recanalization ($\chi^2 = 1.1$, $P = .31$).

DISCUSSION

With a straightforward grading scale, collateral flow on CTA and DSA has poor agreement, revealing that these approaches are not interchangeable. Irrespective of early recanalization, CTA-based collateral flow is significantly associated with clinical outcome, whereas DSA-based collateral flow is not.

In a recent study, Frolich et al²³ found that early triggering of CTA image acquisition could result in diminished visibility and underestimation of collateral flow. In contrast, the same group found that delaying CTA triggering relative to contrast injection could result in overestimation of collateral flow, due to washout of contrast within normal reference arteries, resulting in a relatively weaker opacification of the unaffected

Table 2: Distribution of collateral score for CTA and DSA in all patients^a

CTA CS	DSA CS				Total
	Absent (0)	Poor (1)	Moderate (2)	Good (3)	
Absent (0)	2	1	0	0	3
Poor (1)	4	3	2	1	10
Moderate (2)	5	8	4	3	20
Good (3)	1	5	4	2	12
Total	12	17	10	6	45

^a The score corresponding with the relevant category is given in brackets.

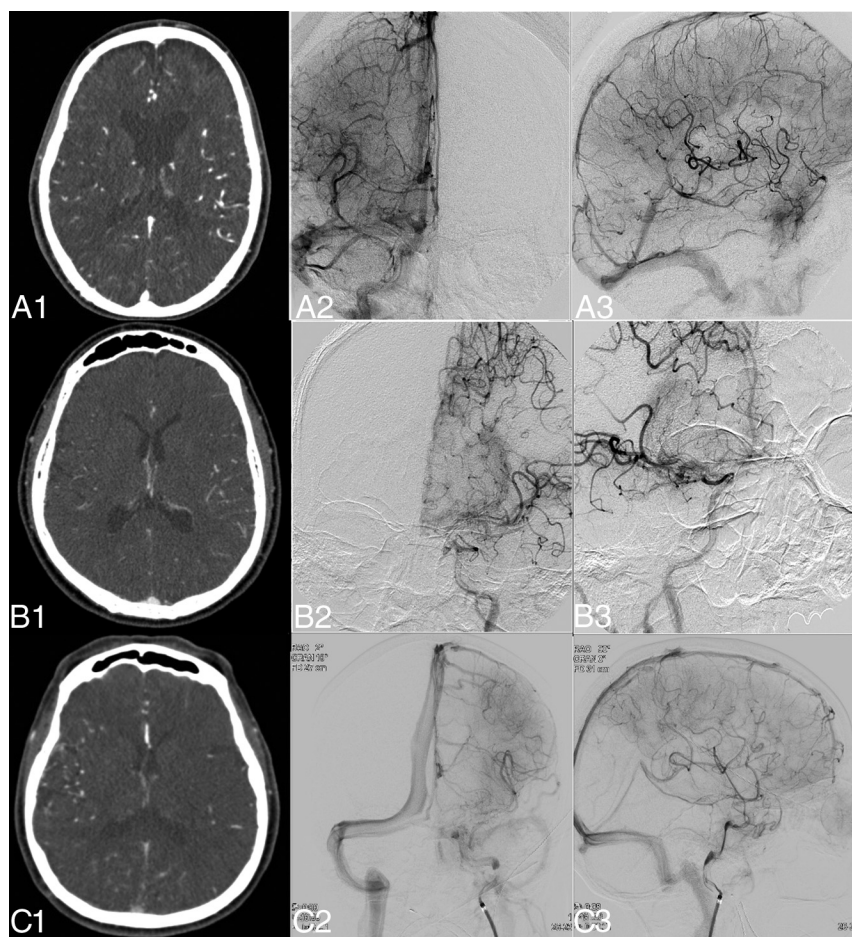


FIG 1. Examples of DSA- and CTA-based collateral scores in 3 different patients. Images were selected by a maximum amount of contrast in the middle cerebral artery for CTA and adequate opacity in the venous phase for DSA. In the left column, the CTA image is shown (A1–C1); in the middle column, the anteroposterior DSA (A2–C2); and in the right column, the lateral DSA (A3–C3). A1–A3, Patient A with a right-sided M1 occlusion, which DSA assessed as grade 3, and CTA, as grade 3. B1–B3, Patient B with a left-sided M1 occlusion, which DSA assessed as grade 1, and CTA, as grade 3. C1–C3, Patient C with a left-sided M1 occlusion, which DSA assessed as grade 3 collateral flow, and CTA, as grade 1.

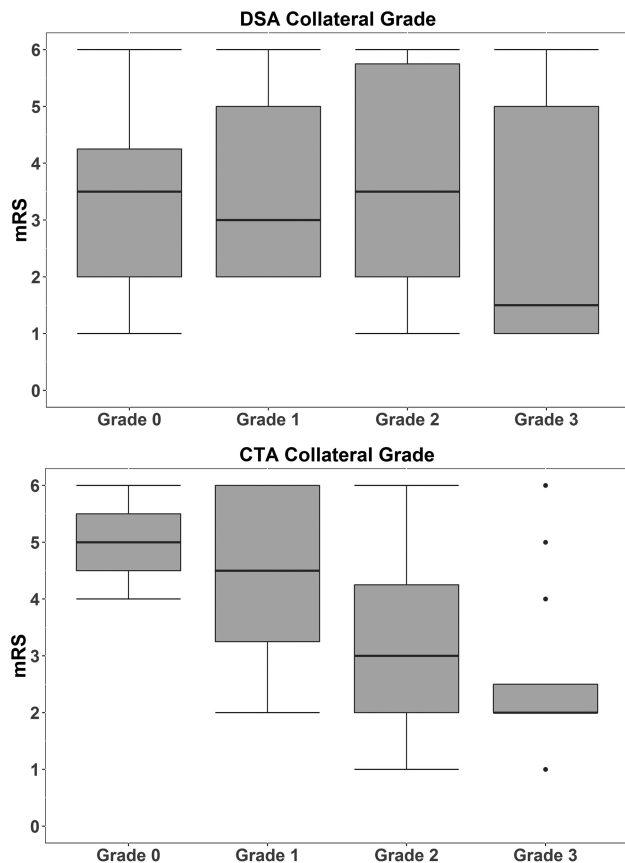


FIG 2. Distribution of CTA- and DSA-based collateral grades on the modified Rankin Scale. For CTA-based collateral grades, a clear change in distribution can be seen toward better clinical outcome for higher collateral grades. For DSA-based collateral grades, there is no change in distribution on mRS for higher collateral grades.

hemisphere. Nambiar et al¹³ also recently reported this washout effect. Both this over- and underestimation could account for the poor agreement found in our study because CTA only provides a snapshot at a set time point, whereas DSA gives information about collateral flow with time.

In the case of DSA, a complete collateral flow assessment requires imaging of both left and right carotid and 1 or both vertebral arteries.¹⁶ The delay required for diagnostic DSA and the need for a fast response in acute ischemic stroke management are seen as reasons for not performing DSA collateral imaging routinely in clinical practice, though alternative methods of IAT patient selection on DSA are currently being studied.²⁴ Given the potential of collateral flow assessment as a patient-selection tool for IAT, CTA is seen as the imaging technique of choice because it is already obtained for documenting vessel occlusion status, given its availability and low cost.²⁰ Another promising alternative is multiphase CTA, as was used for the inclusion of patients with moderate-to-good collaterals in ESCAPE. This also provides fast information on the degree of collateral flow but in a time-resolved manner, without the need for complicated postprocessing. Menon et al²⁵ reported high interrater reliability for this method. Time-invariant CTA based on CTP has also been mentioned and has so far shown good interrater agreement and agreement with DSA.²⁶ Kim et al²⁷ compared collateral flow on time-invariant CTA images with DSA and showed a high level of agreement be-

tween the 2 modalities, considerably higher than that in the current study. Time-invariant CTA, like DSA and multiphase CTA, has the advantage of giving information of blood flow across time.

There are some limitations to this study. The most important is that validation of DSA as a criterion standard for collateral flow assessment should be based on multivessel imaging. In our study, all patients underwent single-vessel DSA as part of IAT, due to the importance of rapid treatment. Therefore, collateral flow originating from the posterior circulation or the contralateral side could not be assessed, and this omission could have resulted in incomplete information on the degree of collateral flow.¹³ However, because 4-vessel diagnostic DSA is currently not being used routinely, our study is focused on a more pragmatic approach to collateral flow assessment, analogous to current clinical practice. Additionally, our study was designed to minimize this limitation, ensuring, for example, that patients with ICA terminus occlusions or hypoplastic A1 segments were excluded; this exclusion allowed assessment of collateral flow from the ipsilateral anterior and middle cerebral arteries. In addition, in about 20% of patients, differences in clot location were observed between CTA and DSA, most likely due to clot migration. However when these patients were excluded from the analysis, no difference in the level of agreement between modalities compared with the full analysis was observed. Finally, CTA was performed by using different scanner protocols, due to the large number of centers participating in MR CLEAN. These protocol differences could influence the degree of collateral flow observed. However, we believe that this heterogeneity and the incorporation of cases showing clot migration in our study population add to the generalizability of our study.

Collateral flow could be considered an important target for selection of patients for IAT because it is becoming increasingly clear that patients with poor collateral flow have marginal benefit of treatment.²⁸ It can be argued that due to the lack of interchangeability between CTA and DSA, the lack of association between DSA and clinical outcome, and the low application of multivessel DSA in current clinical practice, CTA could be sufficient for this purpose. For future studies excluding patients with poor collateral flow as in ESCAPE, the use of single-vessel DSA for collateral flow assessment could prove precarious. To uphold the role of DSA-based collateral assessment in future patient selection for IAT, further research is warranted to confirm the ability of accurately assessing poor or absent collateral flow on CTA, ideally compared with the criterion standard multivessel DSA. The findings of this study show that the direct comparison of collateral scores acquired by different modalities must be approached with caution. In the near future, it is possible that collateral flow will aid in patient selection for IAT. It is therefore important to consider the properties of the technique with which collateral assessment is performed and how these will affect collateral grading itself, as well as clinical outcome prediction.

CONCLUSIONS

Commonly applied collateral flow assessment on CTA and DSA showed large differences, indicating that these techniques are not interchangeable. CTA was significantly associated with mRS at 90 days, whereas DSA was not.

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