Clinical and Imaging Determinants of Collateral Status in Patients With Acute Ischemic Stroke in MR CLEAN Trial and Registry

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Background and Purpose—Collateral circulation status at baseline is associated with functional outcome after ischemic stroke and effect of endovascular treatment. We aimed to identify clinical and imaging determinants that are associated with collateral grade on baseline computed tomography angiography in patients with acute ischemic stroke due to an anterior circulation large vessel occlusion.

Methods—Patients included in the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; n=500) and MR CLEAN Registry (n=1488) were studied. Collateral status on baseline computed tomography angiography was scored from 0 (absent) to 3 (good). Multivariable ordinal logistic regression analyses were used to test the association of selected determinants with collateral status.

Results—In total, 1988 patients were analyzed. Distribution of the collateral status was as follows: absent (7%, n=123), poor (32%, n=596), moderate (39%, n=735), and good (23%, n=422). Associations for a poor collateral status in a multivariable model existed for age (adjusted common odds ratio, 0.92 per 10 years [95% CI, 0.886–0.98]), male (adjusted common odds ratio, 0.64 [95% CI, 0.53–0.76]), blood glucose level (adjusted common odds ratio, 0.97 [95% CI, 0.95–1.00]), and occlusion of the intracranial segment of the internal carotid artery with occlusion of the terminus (adjusted common odds ratio 0.50 [95% CI, 0.41–0.61]). In contrast to previous studies, we did not find an association between cardiovascular risk factors and collateral status.

Conclusions—Older age, male sex, high glucose levels, and intracranial internal carotid artery with occlusion of the terminus occlusions are associated with poor computed tomography angiography collateral grades in patients with acute ischemic stroke eligible for endovascular treatment. **(*Stroke*. 2020;51:1493-1502. DOI: 10.1161/STROKEAHA.119.027483.)**

Key Words: collateral circulation ■ computed tomography angiography ■ odds ratio ■ stroke ■ thrombosis

Leptomeningeal collateral flow has been considered an important determinant of clinical outcome in patients with acute ischemic stroke. Poor collateral status has been associated with larger follow-up infarct volumes, increased mortality, and poor functional outcome.[1–5] Collateral circulation may prevent the penumbra, at least temporarily, to become infarcted by maintaining a certain level of cerebral blood flow. It has been shown that patients with absent collateral flow benefit less from endovascular treatment (EVT).[6–9] As a result, several guidelines already recommend collateral status as a method to select patients for EVT.[10,11]

Little is known about the biological mechanisms that leads to the variability in filling pattern of leptomeningeal collaterals. Genetic factors have been suggested to be the strongest determinants of collateral strength.[12] Previous studies demonstrated that higher age, diabetes mellitus, history of hypertension,

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high systolic blood pressure, location of the occlusion, presence of extracranial internal carotid artery (ICA) stenosis and poor hydration status are related to worse collateral status.[13–18] Further research on potential determinants for poor collateral status could improve our understanding of the collateral system. Possibly, this might help to find ways to improve collateral status during acute ischemic stroke and thus increase chances of a better clinical outcome.

In this study, we aim to identify clinical and imaging determinants that are associated with collateral status on baseline computed tomography angiography in patients with acute ischemic stroke due to a proximal intracranial occlusion in the anterior circulation.

Methods

The data of the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) have been made publicly available at the Virtual International Stroke Trials Archive and can be accessed at http://www.virtualtrialsarchives.org/vista/. Individual patient data of the MR CLEAN Registry cannot be made available under Dutch law, as we did not obtain patient approval for sharing individual patient data, even in coded form. However, all syntax files and output of statistical analyses will be made available upon reasonable request.

We used data from the MR CLEAN and the MR CLEAN Registry. Patient selection criteria and methods of the MR CLEAN trial have been reported previously.[19] In short, MR CLEAN was a randomized clinical trial of EVT with usual care (intervention group) versus usual care alone (control group) in patients (n=500) with a proximal intracranial arterial occlusion in the anterior circulation demonstrated on vessel imaging, treatable within 6 hours after symptom onset. Study-specific inclusion criteria were the presence of an occlusion of the ICA, intracranial carotid artery terminus (ICA-T), middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2), as confirmed on computed tomography angiography (CTA).[19,20]

The MR CLEAN Registry is an ongoing, prospective, multicenter, observational monitoring study, including all consecutive patients treated with EVT in the Netherlands since the final inclusion in the MR CLEAN trial. The aim of the MR CLEAN Registry is to monitor the safety and clinical practice of EVT in a well-defined set of patients, who are comparable to the patients in the MR CLEAN trial.[21] Overall, 1628 patients were registered in the MR CLEAN Registry between March 16, 2014 and June 15, 2016. For the current analysis, we applied the same inclusion criteria as in the MR CLEAN trial and therefore we excluded 140 patients, mostly because of occlusion in the posterior circulation or treatment starting after 6.5 hours from the onset of symptoms (Figure I in the Data Supplement). A total of 1488 patients from the MR CLEAN Registry were available for final analysis.

Assessment of Collateral Status

Collateral assessment was performed by 10 observers (each assessed 100–200 different CTAs) from the MR CLEAN Registry imaging core laboratory, who were blinded to the clinical findings. All observers were provided with a training set including relevant definitions. Collateral status was graded on single-phase CTA source images on a 4-point scale according to the visual collateral score using the method of Tan et al, with grade 0 for absent collaterals (0% filling of the occluded vascular territory), grade 1 for poor collaterals (>0% and ≤50% filling of the occluded vascular territory), grade 2 for moderate (>50% and <100% filling of the occluded vascular territory), and grade 3 for good collaterals (100% filling of the occluded vascular territory; Figure 1). This score has shown to be a prognostic marker for outcome.

Clinical and Imaging Parameters

We analyzed patient and imaging characteristics that are expected to influence collateral status, based on expert opinion and recent literature. These included age, sex, level of glucose at baseline, history of atrial fibrillation, previous ischemic stroke, diabetes mellitus, hypercholesterolemia, hypertension, peripheral arterial disease, myocardial infarction, smoking, systolic and diastolic blood pressures, the current use of statins, antihypertensive drugs and antiplatelets, extracranial carotid stenosis, location of occlusion, and time from symptom onset to CTA. We distinguished 2 subgroups for occlusion location: one subgroup included ICA or ICA-T occlusions, and the other included a segment of the middle cerebral artery and/or anterior cerebral artery.

Acquisition Phase

In an earlier study, CTA acquisition phase appeared to be significantly associated with collateral status.[22] The CTA acquisition phase is evaluated by comparing peak arterial opacification with peak venous opacification. An observer measured the opacification of the contralateral internal carotid artery and the transverse sinus and classified all CTA studies into one of the 5 acquisitions: early arterial (arterial Hounsfield units [HU] higher than venous structure, and venous structure ≤200 HU), peak arterial (arterial HU ≥100 higher than venous structure and venous structure >200 HU), equilibrium (arterial HU <100 higher or equal to venous structure and venous structure >200 HU), peak venous (arterial HU >200 and venous structure higher than artery), or late venous (arterial HU ≤200 and venous vessel higher than artery).[23]

Statistical Analysis

To assess potential nonlinearity of the relation between continuous variables and outcome, we used restricted cubic splines. Ordinal logistic regression analyses were used to test the effect of the selected determinants on the collateral status. The following analyses were performed:

- Step 1: univariable analysis with adjustment for CTA acquisition phase[24]
- Step 2: univariable analysis of all determinants with a *P* value <0.15 in Step 1, adjusted for age, sex, and CTA acquisition phase
- Step 3: multivariable analysis of all determinants with a *P* Value of *P*<0.05 in Step 2, adjusted for study (MR CLEAN trial or MR CLEAN Registry) and CTA acquisition phase.

We performed sensitivity analyses by repeating the analyses in all patients with a M1 or M2 occlusion, after dichotimization of the collateral score into good (grade 2+3) and poor (grade 0+1), in patients who were scanned in acquisition phases 3 or 4, and in women and men separately.

All reported *P* values are 2-sided. Missing values were imputed with multiple imputation on the combined dataset, using the AregImpute function in R statistical software. The imputations (also for missing collateral status) were performed per study (MR CLEAN trial or -Registry) based on relevant covariates and outcome (Table II in the Data Supplement). Statistical analyses were performed in the R software environment (Version 3.2.2 or higher, the R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

All 500 patients from the MR CLEAN trial (December 2010 to March 2014) and 1488 patients from the MR CLEAN Registry database (March 2014 to June 2016), in total 1988 patients, were included in this analysis. Distribution of the collateral status was as follows: grade 0 (7%, n=123), grade 1 (31.8%, n=596), grade 2 (39.1%, n=734), grade 3 (22.5%, n=422).

Baseline characteristics are reported in Table 1. The median age of the total population was 69 years (interquartile range, 58–79) and 1086 patients (55%) were men. In 113 patients (5.7%), the collateral status was not assessed (Table I in the Data

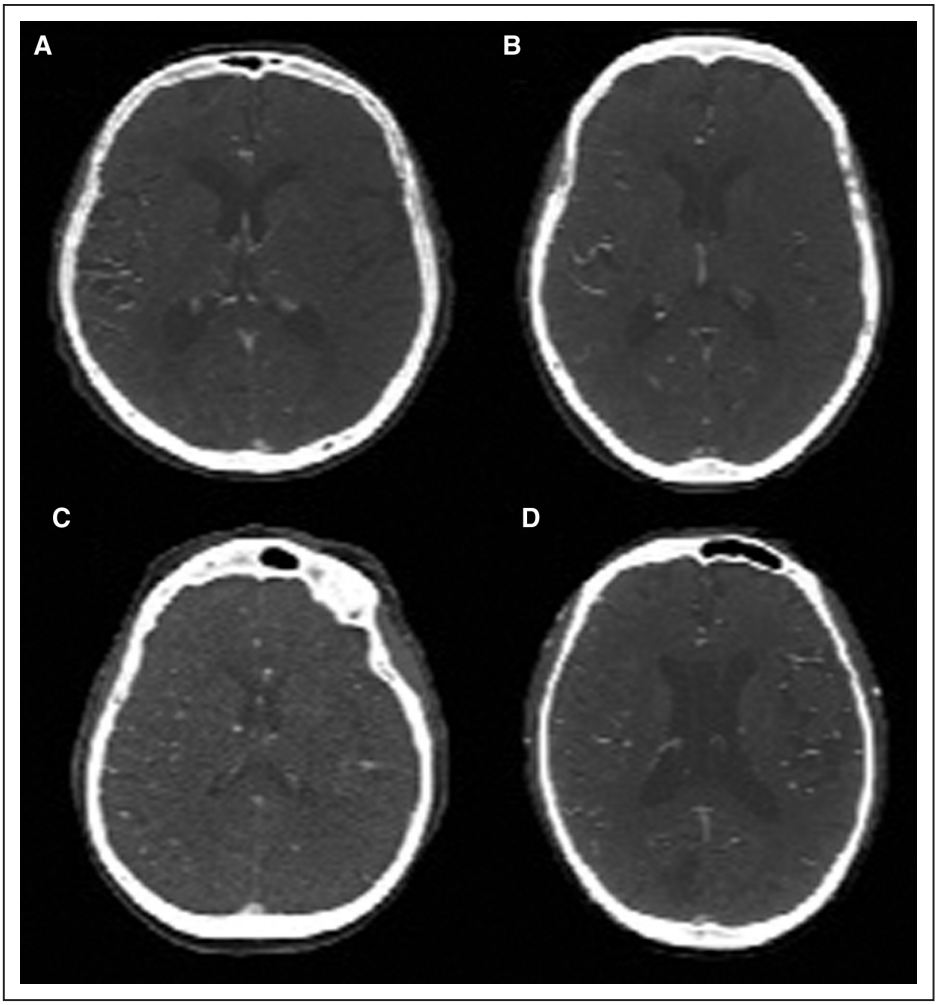

Figure 1. Collateral score grading for each category of the 4-point scale. Left hemisphere was affected in all examples above. **A**, Grade 0, representing absent collaterals (0% filling of the occluded territory). **B**, Grade 1, representing poor collaterals (>0% and ≤50% filling of the occluded territory). **C**, Grade 2, representing moderate (>50% and <100% filling of the occluded territory). **D**, Grade 3, representing good collaterals (100% filling of the occluded territory).

Supplement), and therefore 1875 patients were eligible for analysis. In total, 1639 values (3.9%) were missing at baseline and subsequently imputed. Except for time to CTA (n=1351, 68%) and smoking status (n=1645, 83%), all other determinants were in >95% complete (Table II in the Data Supplement).

Acquisition Phase

Distribution of the acquisition phase was as follows: phase 1 (25.7%, n=483), phase 2 (16.4%, n=308), phase 3 (27.2%, n=510), phase 4 (20.2%, n=380), and phase 5 (10.5%, n=197). In phase 1, more patients had a collateral grade of 1 compared with other phases. Most patients whom were scanned during phase 3 or phase 4 had a collateral grade of 2 (Figure 2).

Associations With Collateral Status

The following determinants had a *P* value <0.15 in Step 1 and were therefore considered in Step 2: age, sex, diastolic and systolic blood pressures, glucose level, a history of hypercholesterolemia, hypertension, myocardial infarction, peripheral arterial disease and ischemic stroke, the use of statins, antiplatelets and antihypertensives, ICA-T occlusion, and time to CTA (Table 2). None of the continuous variables appeared to be nonlinear.

After adjustment for, age, sex, and CTA acquisition phase in Step 2, diastolic blood pressure, glucose, history of peripheral arterial disease, and occlusion in the ICA-(T) were significantly associated with collateral status (Table 2).

An independent association with worse collateral status in Step 3 was observed for higher age (adjusted common odds ratio, 0.92 [95% CI, 0.86–0.98] per 10 years, *P*=0.01), men (adjusted common odds ratio, 0.64 [95% CI, 0.53–0.83], *P*=0.76), higher glucose levels (adjusted common odds ratio, 0.97 [95% CI 0.95–1.00] per mmol/L, *P*=0.02), and an occlusion of the ICA-T segment (adjusted common odds ratio, 0.50 [95% CI, 0.41–0.61], *P*<0.001) in the multivariable model (Table 2; Figure II in the Data Supplement).

No additional determinants could be identified in sensitivity analysis in patients with an M1 or M2 occlusion, after dichotimization of the collateral score, or patients who were scanned in acquisition phase 3 or 4. Reanalysis in men and women separately revealed that in men, age and glucose were no longer associated with collateral status, but the use of antiplatelets was associated with worse collateral status. In

Table 1. Clinical and Imaging Characteristics at Baseline per Collateral Status

	Total (n=1988)	Grade 0 (n=123)	Grade 1 (n=596)	Grade 2 (n=734)	Grade 3 (n=422)	*P* Value
Clinical						
Age, y; median (IQR)	69 (58–79)	72 (60–79)	71 (61–80)	68 (58–78)	67 (56–77)	<0.001
Men, no. (%)	1086 (55)	81 (66)	355 (60)	392 (53)	199 (47)	<0.001
NIHSS; median (IQR)	16 (12–20)	19 (15–23)	18 (14–22)	16 (12–19)	14 (10–18)	<0.001
SBP, mm Hg; mean (SD)	149 (25)	154 (25)	149 (25)	148 (25)	148 (24)	0.04
DBP, mm Hg; mean (SD)	82 (15)	85 (15)	82 (16)	81 (15)	81 (16)	0.01
Glucose at baseline, mmol/L; median (IQR)	6.7 (5.9–8.0)	7.1 (6.0–8.5)	6.8 (6.0– 8.1)	6.7 (5.8– 7.9)	6.5 (5.8–7.8)	0.01
Atrial fibrillation, n (%)	462 (24)	34 (28)	134 (23)	180 (25)	87 (21)	0.24
Hypercholesterolemia, n (%)	560 (29)	35 (29)	185 (32)	192 (27)	111 (27)	0.19
Hypertension, n (%)	973 (49)	59 (48)	315 (53)	334 (46)	199 (48)	0.06
Diabetes mellitus, n (%)	323 (16)	26 (21)	91 (15)	120 (16)	61 (15)	0.33
Myocardial infarction, n (%)	302 (15)	19 (16)	100 (17)	107 (15)	54 (13)	0.34
Peripheral artery disease, n (%)	159 (8.1)	8 (6.6)	66 (11)	58 (8.0)	22 (5.3)	0.01
Ischemic stroke, n (%)	304 (15)	21 (17)	108 (18)	104 (14)	54 (13)	0.08
Prestroke modified Rankin Scale score, n (%)						0.10
0	1395 (71)	81 (68)	409 (69)	524 (72)	302 (73)	
1	240 (12)	19 (16)	64 (11)	90 (12)	51 (12)	
2	135 (6.9)	10 (8)	47 (8)	46 (6)	24 (6)	
>2	190 (10)	10 (8)	69 (12)	65 (9)	39 (9)	
Current smoking, n (%)	481 (29)	27 (22)	146 (25)	180 (25)	113 (27)	0.50
Statin use, n (%)	666 (34)	44 (36)	232 (40)	221 (30)	128 (31)	<0.01
Antiplatelet use, n (%)	638 (32)	37 (30)	235 (40)	209 (29)	121 (29)	<0.001
Antihypertensive medication use, n (%)	1004 (51)	59 (50)	338 (57)	353 (49)	194 (47)	<0.01
Intravenous alteplase treatment, n (%)	1607 (81)	95 (77)	485 (81)	598 (81)	338 (80)	0.52
Imaging						
Level of occlusion on noninvasive vessel imaging, n (%)						<0.001
ICA	86 (4.5)	2 (1.6)	21 (3.5)	31 (4.3)	27 (6.4)	
ICA-T	447 (23)	46 (37)	176 (30)	157 (22)	64 (15)	
M1	1144 (60)	63 (51)	333 (56)	452 (61)	271 (64)	
M2	214 (11)	12 (10)	60 (10)	88 (12)	52 (12)	
ASPECTS on NCCT—median (IQR)	9 (7–10)	8 (6–10)	8 (7–10)	9 (7–10)	9 (8–10)	<0.001
Other						
Time from onset to CTA—median (IQR)	105 (72–171)	106 (66–183)	99 (72–160)	104 (72–174)	115 (80–189)	0.23

Collateral status was missing in 113 patients. We performed χ^2 test for categorical variables and ANOVA and Kruskal-Wallis testing for continuous variables. CTA indicates computed tomography angiography; DBP, diastolic blood pressure; ICA, intracranial carotid artery; ICA-T, intracranial carotid artery terminus; IQR, interquartile range; NCCT, noncontract computerized tomography; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.

women, age was no longer associated with collateral status, but a history of peripheral arterial disease was associated with worse collateral status (Table III in the Data Supplement).

Discussion

In this analysis, we found that worse collateral status in patients with acute ischemic stroke with a large vessel occlusion was associated with the following clinical and imaging determinants: higher age, male, glucose level at baseline, and ICA-T occlusion segment.

The results of our multivariable analysis suggest that a higher age has a direct negative effect on collateral status. A possible explanation has been described as pruning of collaterals with increasing age, involving a decline in vessel diameter and increase in vessel tortuosity.[25] Previous studies suggested that the association of age and collateral status is mediated through other age-related factors such as hyperlipidemia or systolic blood pressure.[12,21] However, we did not find an effect of systolic blood pressure or a history of hypercholesterolemia on collateral status.

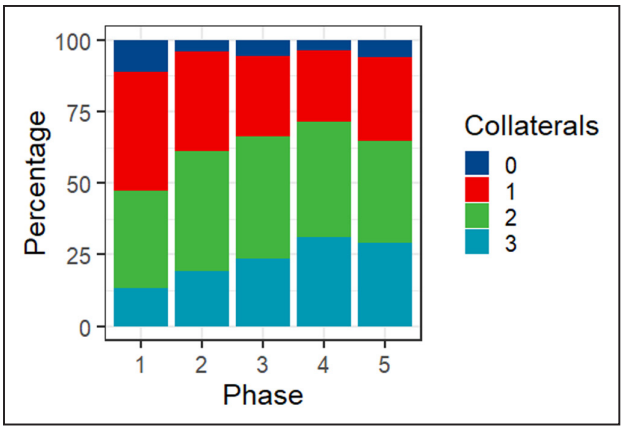

Figure 2. Distribution of collateral grades per computed tomography angiography (CTA) acquisition phase. The contrast density in Hounsfield units in the unaffected hemisphere of the M1 segment of the MCA territory (arterial structure) and the confluence of sinuses (venous structure) was measured to determine the CTA acquisition phase. On the basis of these contrast measurements, all CTA studies were classified into 1 of the 5 acquisition phases: 1 (early arterial), 2 (peak arterial), 3 (equilibrium), 4 (peak venous), and 5 late venous).

We found poorer collateral status in men then in women, although it is reported that women have worse stroke outcomes than men. The main explanation for these sex differences are said to be attributable to a difference in sex hormones.[26–28] Sex differences in the collateral circulation in mice have been investigated by a recent study. However, the authors concluded that the cerebral collateral circulation was not different between male and female mice.[29] Further research is needed to investigate possible anatomic differences related to cerebral collaterals between men and women.

We found an association of a higher level of glucose at baseline and worse collateral status. Among patients without a history of diabetes mellitus, admission hyperglycemia may be resulting from previously undiagnosed diabetes mellitus or glucose intolerance, stress response mediated by cortisol and noradrenaline, or combination of these.[30,31] Earlier studies showed that hyperglycemia, whether acute or chronic, impairs nitrogen oxide availability and endothelium-dependent vasodilation and enhances the production of endothelial-derived vasoconstrictor prostanoids.[32,33] In a recent pooled-data meta-analysis, it was found that treatment effects of thrombectomy were larger at lower glucose levels.[34] Together with our finding, this implicates that appropriate testing whether tight glucose control is needed to further improve outcomes after EVT.

Finally, ICA-T occlusions have worse collaterals compared with ICA occlusions, M1 and M2 occlusion because an ICA-T occlusion leads to an occlusion of both the A1 segment

Table 2. Univariable and Multivariable Effects of the Studied Determinants on Collateral Status

	Univariable		Univariable+Age and Sex		Multivariable Model	
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age, y*	0.92 (0.87–0.97)	0.01	0.90 (0.85–0.96)	<0.01	0.92 (0.86–0.98)	0.01
Male sex	0.67 (0.56–0.79)	<0.001	0.65 (0.55–0.77)	–	0.64 (0.53–0.76)	<0.001
Systolic blood pressure	0.97 (0.94–1.01)	0.11	0.99 (0.95–1.02)	–		
Diastolic blood pressure†‡	0.94 (0.89–0.99)	0.03	0.95 (0.89–1.00)	0.07		
Glucose at baseline‡	0.97 (0.94–0.99)	0.02	0.97 (0.94–1.00)	0.02	0.97 (0.95–1.00)	0.02
Atrial fibrillation	0.95 (0.77–1.16)	0.59				
History of hypercholesterolemia	0.90 (0.75–1.09)	0.28				
History of hypertension	0.91 (0.78–1.08)	0.29				
History of diabetes mellitus	0.84 (0.66–1.07)	0.21				
History of myocardial infarction	0.83 (0.66–1.04)	0.10	0.92 (0.73–1.16)	0.47		
History of peripheral arterial disease	0.66 (0.50–0.89)	0.01	0.71 (0.53–0.96)	0.02	0.76 (0.56–1.04)	0.09
History of ischemic stroke	0.9 (0.62–1.01)	0.06	0.82 (0.65–1.05)	0.11		
Current smoking	0.93 (0.83–1.05)	0.25				
Current statin use	0.79 (0.66–0.95)	0.01	0.86 (0.71–1.03)	0.11		
Current antiplatelet use	0.78 (0.66–0.93)	0.01	0.84 (0.70–1.00)	0.06		
Current antihypertensive use	0.84 (0.71–1.00)	0.05	0.86 (0.71–1.03)	0.09		
Extracranial carotid stenosis	1.19 (0.85–1.68)	0.32				
ICA-T occlusion	0.50 (0.41–0.61)	<0.001	0.50 (0.41–0.61)	<0.001	0.50 (0.41–0.61)	<0.001
Time from onset to CTA§	1.04 (0.98–1.11)	0.23				

All determinants with an association with $P<0.15$ in Step 1 were included in Step 2. All determinants with a significant association ($P<0.05$) in Step 2 were included in the multivariable analysis (Step 3). All models were adjusted for acquisition phase. CTA indicates computed tomography angiography; and ICA-T, intracranial carotid artery terminus.

*Per 10 y.

†Per 10 mm Hg.

‡Per 1 mmol/L.

§Per 60 min.

of the anterior cerebral artery and the M1 segment of the middle cerebral artery and collateral flow may occur via the AComA and the cortical branches of the anterior cerebral artery to the middle cerebral artery branches. However, in this situation, collateral flow is dependent on a patent AComA. This dependency also exists in case of an ICA occlusion, but collateral flow may directly occur via the AComA, to the A1 segment and subsequently to the M1 segment. In a middle cerebral artery occlusion, collateral flow is independent of a patent AComA.

In single-phase CTA, collateral assessment is influenced by the time of the CTA snapshot. Acquiring CTA too early after contrast bolus administration runs the risk of underestimating collateral capacity, while a delayed venous phase scan may hamper detection of the primary occlusion. Also, delayed venous phase cannot discriminate between fast and slow collaterals.[35] Previous studies suggest single-phase CTA might underestimate collateral status in some patients.[36,37] As collateral status is used as a predictor in various prediction models for patients with acute ischemic stroke, this further supports the need to implement newer techniques like multiphase CTA, time-invariant CTA, or 4D-CTA.[37–39]

Furthermore, several factors were associated with collateral status in univariable analysis but not in the multivariable analysis in which we adjusted for age and sex. These included history of myocardial infarction, history of ischemic stroke, the current use of antihypertensive medication, and time to CTA. In the final multivariable analysis, the association with collaterals disappeared for diastolic blood pressure, history of peripheral arterial disease, the use of statins, and the use of antiplatelets. For all these variables, this could suggest that cardiovascular-related factors as age and history of peripheral arterial disease moderate the association.[15,40–42]

The role of pathophysiological factors in augmenting or diminishing collateral status is still mostly unclear. In the literature, several factors have been studied. The presence and luminal diameter of both primary collaterals (arterial segments of the circle of Willis) and secondary collaterals (ophthalmic artery and leptomeningeal vessels), formed during prenatal period, are considered the most important determinants.[14,18,43–45] This was however beyond the scope of our current study.

Limitations

Collateral status assessment is prone to interobserver variability, although all images were assessed by highly experienced and trained assessors.[46] A range of different scanner protocols was used, which could have added to the variability. However, we think this heterogeneity adds to the generalizability of our study. Furthermore, all our patients underwent single phase CTA, which could have led to underestimation of collateral status in the case of delayed filling in combination with an early acquisition phase. However, the sensitivity analysis in which we restricted the analysis to scans acquired with optimal timing revealed the same results. Selection bias might have appeared, since we were unable to assess the collateral status in 113 patients. Since multiple imputation was used to handle this missing data, we assume that our results could be safely interpreted. The golden standard for assessing collateral status is digital subtraction angiography. However, we aimed to represent the acute clinical setting, in which multivessel digital subtraction angiography is not performed. Furthermore, we did not have any information on ethnicity. It is known that ethnicity groups show differences in prevalence in acute ischemic stroke, and some studies also indicate possible differences in rates of collateralization.[47,48]

Finally, important to note is that the associations with collateral status do not necessarily imply a causal relationship. For example, the association we found with higher glucose level could be the cause of poor collateral status but may also be the result of poor collateral status. Further studies to investigate the causality of associations with collateral status are pivotal.

Conclusions

In conclusion, this study shows that higher age, male sex, higher glucose levels, and occlusion of the ICA-T are associated with poor CTA collateral grades in patients with acute ischemic stroke eligible for EVT. No clear modifiable determinants of collateral status could be identified.

Appendix

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