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Associations Between Collateral Status and Thrombus Characteristics and Their Impact in Anterior Circulation Stroke

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Background and Purpose—Thrombus characteristics and collateral score are associated with functional outcome in patients with acute ischemic stroke. It has been suggested that they affect each other. The aim of this study is to evaluate the association between clot burden score, thrombus perviousness, and collateral score and to determine whether collateral score influences the association of thrombus characteristics with functional outcome.

Methods—Patients with baseline thin-slice noncontrast computed tomography and computed tomographic angiography images from the MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) were included (n=195). Collateral score and clot burden scores were determined on baseline computed tomographic angiography. Thrombus attenuation increase was determined by comparing thrombus density on noncontrast computed tomography and computed tomographic angiography using a semiautomated method. The association of collateral score with clot burden score and thrombus attenuation increase was evaluated with linear regression. Mediation and effect modification analyses were used to assess the influence of collateral score on the association of clot burden score and thrombus attenuation increase with functional outcome.

Results—A higher clot burden score (B=0.063; 95% confidence interval, 0.008–0.118) and a higher thrombus attenuation increase (B=0.014; 95% confidence interval, 0.003–0.026) were associated with higher collateral score. Collateral score mediated the association of clot burden score with functional outcome. The association between thrombus attenuation increase and functional outcome was modified by the collateral score, and this association was stronger in patients with moderate and good collaterals.

Conclusions—Patients with lower thrombus burden and higher thrombus perviousness scores had higher collateral score. The positive effect of thrombus perviousness on clinical outcome was only present in patients with moderate and high collateral scores.

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Key Words: collateral circulation ■ computed tomography angiography ■ Netherlands ■ stroke ■ thrombosis

Recent trials demonstrated treatment benefit of endovascular treatment (EVT) in patients with acute ischemic stroke caused by a proximal intracranial large vessel occlusion of the anterior circulation.[1–5] Various imaging measures were associated with good outcome.[6,7] Among these markers, collateral filling and thrombus characteristics are strongly associated with functional outcome.[8–10]

The collateral circulation consists of a network of vascular anastomoses that potentially mitigate the effect of a blocked artery.[11] Multiple studies have suggested that good

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collateral circulation protects cortical areas and maintains penumbra, leading to improved outcome after EVT.[12–15] Further, treatment benefit of EVT in patients with absent or poor collateral filling of middle cerebral artery branches is still questionable.[8,16]

In addition to the collateral circulation, different thrombus properties may also have clinical implications.[17] Thrombus permeability may allow oxygen and nutrients to reach tissue distal to the occlusion.[18,19] It has been associated with functional outcome, final infarct volume, and recanalization rate, especially after intravenous thrombolysis.[9,20] Clot burden, length, and location were also associated with clinical outcome.[10,21] Further, thrombus attenuation (ie, the hyperdense artery sign) has been associated with poor outcome and lower recanalization rates after intravenous tPA (tissue-type plasminogen activator).[22]

It has been suggested that collateral circulation and thrombus characteristics are related.[23] For example, thrombus burden and location are thought to be associated with the extent of the collateral circulation.[24,25] However, the association between collateral circulation and thrombus characteristics is still poorly understood. This study aims to investigate whether there is an association between thrombus characteristics and collateral circulation and whether the association between thrombus characteristics and functional outcome is modified or mediated by collateral circulation.

Methods

Patient Selection

The MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) was a multicenter prospective randomized trial comparing EVT in addition to usual care (intervention group) versus usual care only (control group) in patients with acute ischemic stroke caused by a proximal intracranial large vessel occlusion of the anterior circulation. Eligible patients had distal intracranial carotid artery, middle cerebral artery (M1 or M2), or anterior cerebral artery (A1 or A2) occlusions. MR CLEAN did not use clot burden score, collateral score, or thrombus attenuation increase as imaging selection criteria.[1] Patients from the MR CLEAN database were retrospectively analyzed and included if thin-slice (≤2.5 mm) baseline noncontrast computed tomography (NCCT) and computed tomographic angiography (CTA) were available. Exclusion criteria were excessive noise, presence of motion artifacts, and incomplete visualization of the intracranial vasculature.

The MR CLEAN trial was approved by a central medical ethics committee and the research boards of all participating centers. Written informed consent was acquired from all patients or legal representatives. Because of the sensitive nature of the data collected for this study, requests to access the data set may be sent to the MR CLEAN executive committee (https://www.mrclean-trial.org/).

Collateral Score and Thrombus Characteristics Assessment

Clot burden was determined according to the clot burden score as described by Puetz et al.[26] A score of 10 on the clot burden score indicates that no occlusion is present. Two points are deducted for lack of contrast opacification in the supraclinoid internal carotid artery and both the proximal and distal M1 segment. One point is deducted for lack of opacification in the M2 branches, the A1 segment, or the infraclinoid internal carotid artery. Two experienced neuroradiologists from the MR CLEAN imaging committee evaluated the CTA data. In case of discrepancies between the 2 observers, a third observer performed a consensus reading. All readers were blinded to clinical findings, except symptom side.

Thrombus segmentation was performed using an adapted semiautomated method.[27,28] This method operated on a custom-developed Mevislab interface in which NCCT and CTA were coregistered and simultaneously displayed. Thrombus segmentation on CTA images was performed in 3 steps: (1) segmentation of the contralateral vasculature by a trained observer (E.M.M.S.); (2) segmentation of the occluded artery using mirror symmetry; (3) thrombus segmentation using intensity-based region growing. The CTA-based thrombus mask was automatically projected on NCCT. Thrombus attenuation increase was defined by the difference between the CTA and NCCT thrombus attenuation distribution.

Collaterals and clot burden were determined on baseline CTA. The collateral score grades distal arteries filling with a 4-point scale with 0 constituting absent collaterals (0% filling of the occluded territory), 1 for poor collaterals (>0% and ≤50% filling of the occluded territory), 2 for moderate collaterals (>50% and <100% filling of the occluded territory), and 3 for good collaterals (100% filling of the occluded territory).[25]

Statistical Analysis

Functional outcome was assessed using the modified Rankin Scale (mRS) score at 3 months. On this scale, a score of 0 corresponds to no symptoms and a score of 6 to death. Ordinal regression analysis was used to evaluate the associations of clot burden score, thrombus attenuation increase, and collateral score with functional outcome (mRS score). The association between thrombus characteristics (clot burden score and thrombus attenuation increase) and collateral score was assessed using linear regression. Complete recanalization was defined as a modified arterial occlusive lesion score of 3.

Mediation analyses[29,30] were used to assess whether the association between thrombus characteristics (clot burden score or thrombus attenuation increase) and functional outcome could be secondary to the influence of these thrombus characteristics on collateral circulation. Mediation analysis seeks to explain a relation between an independent variable (thrombus characteristics) and a dependent variable (mRS score) via the inclusion of a third hypothetical variable (collateral score). To assess mediation, the first step is to show that the independent variable (*X*) is associated with outcome (*Y*). The second step is to establish an association between *X* and the mediator (*M*). The third step is to demonstrate the association between *M* and *Y*, using *X* and *M* as independent variables (Figure 1). The mediation model proposes that X influences *M*, which in turn influences *Y* by an indirect

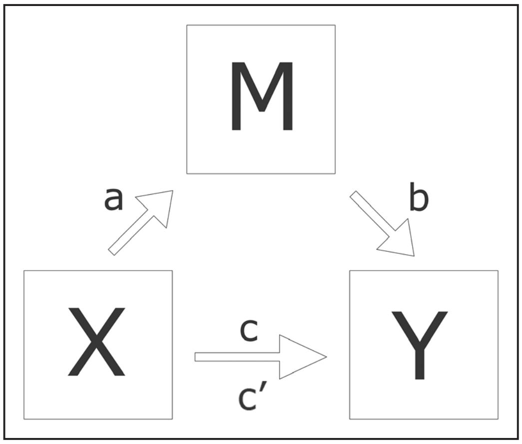

Figure 1. The steps of mediation analysis; *X*, independent variable; *M*, mediator variable; *Y*, outcome variable; a, regression coefficient of the association between *X* and *M*; b, regression coefficient of the association between *M* and *Y*, using *X* and *M* as independent variables; c, regression coefficient of the association between *X* and *Y*; c′: regression coefficient of the association between *X* and *Y*, using *X* and *M* as independent variables.

Table 1. Patients Characteristics

Patients Characteristics				
	CS 0 (n=11)	CS 1 (n=57)	CS 2 (n=74)	CS 3 (n=53)
Age, median (IQR), y	69 (57–81)	67(56–78)	66(56–77)	63(57–70)
NIHSS score, median (IQR)	21 (16–26)	16(11–21)	14(7–21)	17(8–26)
Systolic blood pressure, mean mm HG (SD)	150 (9.8)	139 (2.8)	142 (2.8)	146 (3.3)
Onset to randomization in min, median (IQR)	217 (161–273)	184(129–239)	184.5(131–237)	188(132–244)
Clot burden score, median (IQR)	5 (4–6)	5(4–7)	6(5–7)	6(4–8)
Thrombus attenuation increase, mean (SD)	1.9 (1.9)	6.9 (1.5)	8.2 (1.2)	10.1 (1.4)
Male sex, n(%)	7 (63.4)	36 (63.2)	44 (59.5)	32 (60.4)
Symptomatic hemisphere, left, n (%)	7 (63.4)	26 (45.6)	45 (60.8)	32 (60.4)
Atrial fibrillation, n (%)	4 (36.4)	16 (28.1)	21 (28.4)	12 (22.6)
History of ischemic stroke, n (%)	0 (0)	10 (17.5)	5 (6.8)	6 (11.3)
History of myocardial infarction, n (%)	1 (9.1)	10 (17.5)	16 (21.6)	6 (11.3)
History of peripheral artery disease, n (%)	0 (0.0)	4 (7.0)	5 (6.8)	4 (7.5)
History of diabetes mellitus, n (%)	2 (18.2)	8 (14.0)	10 (13.5)	6 (11.3)
History of smoking, n (%)	5 (45.5)	14 (24.6)	19 (25.7)	13 (24.5)
Current statin use, n (%)	3 (27.3)	23 (40.4)	17 (23.0)	17 (32.1)
Current anticoagulant use, n (%)	1 (9.1)	7 (12.3)	5 (6.8)	6 (11.3)
Current antiplatelet use, n (%)	4 (36.4)	18 (31.6)	26 (35.1)	12 (22.6)
Prestroke mRS score, n (%)				
0	9 (81.8)	41 (71.9)	57 (77.0)	40 (75.5)
1	2 (18.2)	9 (15.8)	11 (14.9)	8 (15.1)
≥2	0 (0.0)	7 (12.3)	6 (8.1)	4 (7.5)
Treatment with IV alteplase, n (%)	9 (81.8)	48 (84.2)	69 (93.2)	46 (86.8)
Treatment with endovascular therapy, n (%)	1 (9.1)	24 (42.1)	32 (43.2)	21 (39.6)

CS indicates collateral score; EVT, endovascular therapy; IQR, interquartile range; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

pathway, rather than a direct causal relationship between *X* and *Y*. The unstandardized regression coefficients were analyzed. To demonstrate mediation, the coefficient describing the association of *X* with *Y* (*c*) must be greater than the regression coefficient describing the association of *X* with *Y* after controlling for M (*c′*). The extent of mediation is estimated by subtracting the coefficients (*c*–*c′*). The Sobel test is used to evaluate the significance of the mediation (indirect) effect. An assumption for mediation analysis is that *X* and *M* do not interact in the association to *Y*.[31] To assess effect modification, a multiplicative interaction term (*X***M*) was included in the analysis. If there was evidence of significant interaction, the association of *X* and *Y* in subgroups of *M* (ie, collateral grade) was further explored. Statistical analyses were performed using SPSS v22.0 (IBM Corp, Armonk, NY).

Results

Of the 500 patients from the MR CLEAN trial, 227 had thin-slice (≤2.5 mm) baseline NCCT and CTA. Thirty-two patients were subsequently excluded for excessive noise (n=8), presence of motion artefacts (n=21), or incomplete visualization of the intracranial arterial tree (n=3). A total of 195 patients were included in this study. One hundred seventy-two (88%) received intravenous alteplase and 78 (40%) were treated with EVT. Evaluations with χ^2 tests indicated that there was no significant difference in frequency of EVT (*P*=0.19) and intravenous alteplase (*P*=0.36) per collateral grades. Seventy-nine (40%) patients had complete recanalization. Baseline characteristics are displayed in Table 1.

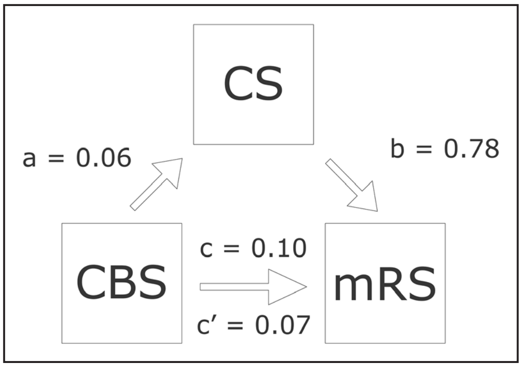

Figure 2. The mediation analysis by collateral score of the association between clot burden score and modified Rankin Scale (mRS) score; a, regression coefficient of the association between clot burden score (CBS) and collateral score (CS); b, regression coefficient of the association between CS and mRS score, using CS and CBS as independent variables; c, regression coefficient of the association between CBS and mRS score; c′, regression coefficient of the association between CBS and mRS score, using CS and CBS as independent variables.

Table 2. Mediation Analysis by Collateral Score on the Association of Clot Burden Score With Functional Outcome (mRS Score)

Effect	*B*	SD	OR	CI 95%		*P* Value
a	0.063	0.028	…	…	…	0.025
b	0.771	0.1556	2.162	1.593	2.933	0.000
c	0.104	0.0569	1.110	0.993	1.241	0.067
c′	0.069	0.0577	1.071	0.957	1.199	0.234

B is unstandardized regression coefficient; a is regression coefficient of the association between clot burden score and collateral score; b is regression coefficient of the association between collateral score and mRS score, using collateral score and clot burden score as independent variables; c is regression coefficient of the association between clot burden score and mRS score; c′ is regression coefficient of the association between clot burden score and mRS score, using collateral score and clot burden score as independent variables. CI 95% indicates 95% confidence interval; mRS, modified Rankin Scale; and OR, odds ratio.

Association Between Thrombus Characteristics and Collateral Score

Higher clot burden score was significantly associated with a higher collateral score (*B*=0.063; 95% confidence interval, 0.008–0.12), indicating that patients with smaller clot burden usually have higher collateral scores. Thrombus attenuation increase was also significantly associated with collateral score (*B*=0.014; 95% confidence interval, 0.003–0.026). This indicates that patients with a pervious thrombus more frequently have higher collateral scores.

Mediation by Collateral Score of the Association Between Clot Burden Score and mRS Score

There was no significant interaction between collateral score and clot burden score in their association with functional outcome (*P* value for the interaction=0.86). Collateral score mediated the association between clot burden score and mRS score and the significance of the indirect pathway (Sobel test) was 0.04 (Figure 2). After adding collateral score as an independent variable, the regression coefficient of clot burden score with mRS score reduced from 0.10 to 0.069 (Table 2).

Modification of the Association Between Thrombus Attenuation Increase and mRS Score by Collateral Score

Collateral score significantly modifies the relation between thrombus attenuation increase and mRS score (*P* value for the interaction of 0.021). For patients with good and moderate collaterals, increases in thrombus attenuation increase leads to higher probability of lower mRS score (Figure 3). This relation between thrombus attenuation increase and mRS score could not be established in patients with collateral score <2 (Table 3). Given the significant interaction between thrombus attenuation increase and collateral score, the mediation analysis has not been performed.

Discussion

In our population, higher collateral scores were associated with lower clot burden and greater thrombus perviousness. We have shown that the association between thrombus perviousness and functional outcome varies for different collateral scores. The relation between thrombus attenuation increase and functional outcome was only established for patients with good and moderate collaterals.

Only few studies assessed the relation between collateral score and thrombus characteristics and the mediation of collateral score on the association of thrombus characteristics with outcome. Qazi et al[23] found an association between collaterals and thrombus length in which patients with poor baseline collaterals had longer clots. Our study is in agreement with 2 previous studies in which poorer collaterals in patients with more proximal thrombus[29] and an association between collateral score and clot burden score have been described.[25]

Higher clot burden score indicates smaller thrombus. Patients with a smaller clot burden are more likely to have patent anterior cerebral arteries and posterior communicating

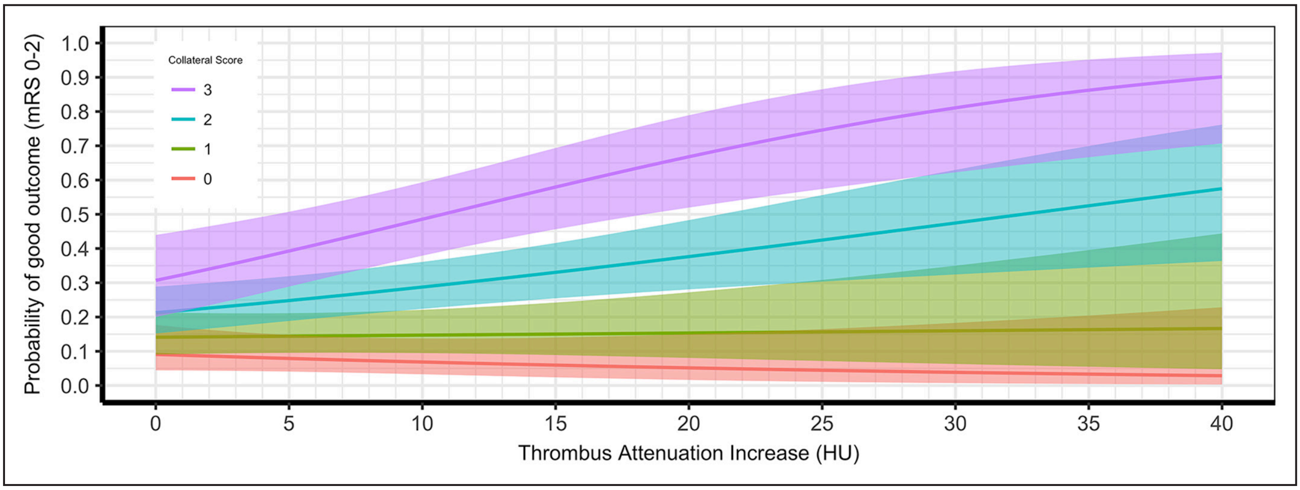

Figure 3. Linear plot demonstrating the probability of good functional outcome for different values of collateral score and thrombus attenuation increase. Effect modification (or moderation) analysis demonstrating that the association between thrombus attenuation increase and good outcome is different depending on the collateral score. The probability was calculated using the ordinal regression equation with the multiplicative interaction term. mRS indicates modified Rankin Scale.

Table 3. Effect Modification Analysis to Evaluate the Interaction of Collateral Score and Thrombus Attenuation Increase on the Association With Functional Outcome

IV	OR	CI 95%		*P* Value
CS	1.64	1.14	2.36	0.01
TAI	0.97	0.91	1.03	0.32
TAI*CS	1.04	1.01	1.07	0.02
TAI*CS0	0.84	0.69	1.00	0.06
TAI*CS1	0.98	0.95	1.02	0.42
TAI*CS2	1.06	1.03	1.10	0.01
TAI*CS3	1.10	1.06	1.14	0.01

CI 95% indicates 95% confidence interval; CS, collateral score; IV, independent variable; mRS, modified Rankin Scale; OR, odds ratio; and TAI, thrombus attenuation increase.

arteries (Willisian routes), leading to increased pial collateral flow. The enhanced pial collateral improves the collateral score and subsequently increases the odds of favorable outcome.[8] Conversely, higher collateral score also results in higher clot burden score through retrograde filling of distal branches in proximal occlusions. The significant mediation by collateral score of the association of clot burden score and mRS score found in this study supports the thesis that enhancing collateral circulation at least partially underlies the association between clot burden score and functional outcome. However, the value of the coefficient implies limited explanation of the functional outcome by the clot burden score.

Higher collateral scores are also associated with more pervious thrombi. Thrombus perviousness may allow flow through the thrombus, resulting in anterograde filling of the arteries distal to the occlusion. The presence of residual flow through the thrombus is associated with increased recanalization rate after intravenous thrombolysis.[30] This effect on treatment success might explain the strong association between thrombus attenuation increase and improved functional outcome. Only in patients with good and moderate collaterals, however, are increases in thrombus attenuation strongly associated with functional outcome. This finding corroborates the importance of good collateral circulation on anterograde flow. Other possible reason is that poor and absent collaterals are so strongly associated with poor functional outcome that variations in thrombus attenuation are not relevant.

Limitations

The automated segmentation method to measure thrombus perviousness is a strength in our study. It reduces user-dependent measurement variations and improves reproducibility. However, our study also has several limitations. First, this study has a relatively modest sample size and is an exploratory post hoc analysis. It is of great interest to study whether the mediation and effect modification differ between treatment arms. This was beyond the scope of this study. The small number of patients, in particular with collateral score of 0, seems unbalanced for prognostic factors (age, National Institutes of Health Stroke Scale score, time to randomization, and treatment allocation) and precluded independent analysis of each treatment arm of MR CLEAN. The lack of adjustment for possible confounders because of the small number of patients with collateral score 0 might also have influenced our results. Such a study could be performed in future pooled analysis. Further, single-phase CTA has a major impact on collateral grading status. Previous studies have shown that the lack of temporal information in a CTA causes an underestimation of collateral score when compared with multiphase CTA, particularly in early-phase acquisitions.[31] The presence of anterograde flow through the thrombus was implied by thrombus attenuation increase; however, directional flow information can be derived by time-density curves on dynamic imaging and by attenuation coefficient gradients on single-phase CTA.[32] The lack of backflow from collateral circulation can also underestimate clot burden score.[33,34] Single-phase CTA acquisition may also underestimate the maximum attenuation increase of the thrombus. However, a recent study demonstrated that arterial-phase CTA is stronger associated with outcome than any other phase or combination of phases.[35] Also, tube voltage can change the Hounsfield unit of the thrombus.[36] The mediation analysis harbors potential limitations by inferring causal relations to observational data. Last, to assess the association between clot burden score and collateral score, we used both variables as if they are continuous.

Conclusions

In our population, collateral scores are associated with thrombus characteristics: Patients with higher collateral scores had lower thrombus burden and more pervious thrombi. The association between clot burden score and mRS score seems to be partially explained by lower clot burden score leading to higher collateral score. There is also an important influence of the collateral score on the association of thrombus attenuation increase with functional outcome.

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