Better Collaterals Are Independently Associated With Post-Thrombolysis Recanalization Before Thrombectomy

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Background and Purpose—In acute stroke patients with large vessel occlusion, the goal of intravenous thrombolysis (IVT) is to achieve early recanalization (ER). Apart from occlusion site and thrombus length, predictors of early post-IVT recanalization are poorly known. Better collaterals might also facilitate ER, for instance, by improving delivery of the thrombolytic agent to both ends of the thrombus. In this proof-of-concept study, we tested the hypothesis that good collaterals independently predict post-IVT recanalization before thrombectomy.

Methods—Patients from the registries of 6 French stroke centers with the following criteria were included: (1) acute stroke with large vessel occlusion treated with IVT and referred for thrombectomy between May 2015 and March 2017; (2) pre-IVT brain magnetic resonance imaging, including diffusion-weighted imaging, T2*, MR angiography, and dynamic susceptibility contrast perfusion-weighted imaging; and (3) ER evaluated ≤3 hours from IVT start on either first angiographic run or noninvasive imaging. A collateral flow map derived from perfusion-weighted imaging source data was automatically generated, replicating a previously validated method. Thrombus length was measured on T2*-based susceptibility vessel sign.

Results—Of 224 eligible patients, 37 (16%) experienced ER. ER occurred in 10 of 83 (12%), 17 of 116 (15%), and 10 of 25 (40%) patients with poor/moderate, good, and excellent collaterals, respectively. In multivariable analysis, better collaterals were independently associated with ER (P=0.029), together with shorter thrombus (P<0.001) and more distal occlusion site (P=0.010).

Conclusions—In our sample of patients with stroke imaged with perfusion-weighted imaging before IVT and intended for thrombectomy, better collaterals were independently associated with post-IVT recanalization, supporting our hypothesis. These findings strengthen the idea that advanced imaging may play a key role for personalized medicine in identifying patients with large vessel occlusion most likely to benefit from IVT in the thrombectomy era. **(*Stroke*. 2019;50:867-872. DOI: 10.1161/STROKEAHA.118.022815.)**

Key Words: collateral circulation ■ magnetic resonance imaging ■ perfusion imaging ■ stroke ■ thrombectomy

In acute stroke patients with large vessel occlusion (LVO), early recanalization (ER) is the mainstay of therapy because it strongly predicts clinical outcome.[1] Whenever indicated, intravenous thrombolysis (IVT) with alteplase followed by mechanical thrombectomy, that is, bridging therapy, is currently recommended to achieve recanalization as early as possible.[2] Although it has the distinct advantage of being widely and quickly available, IVT on the contrary results in a limited (10%–20%) rate of ER before thrombectomy[3,4] and furthermore exposes to the risk of intracranial hemorrhage. Its utility before thrombectomy has, therefore, been recently questioned, and randomized trials testing bridging therapy versus thrombectomy alone are underway.[5] With the aim to select patients for individualized therapy, namely IVT alone, bridging therapy, or thrombectomy alone, some advocate imaging-guided personalized therapy.[5,6] Along this line, identifying

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predictors of post-IVT ER may ultimately help to select those patients most likely to benefit from IVT before thrombectomy.

The strongest predictors of post-IVT ER reported to date are distal occlusion site (ie, second segment of the middle cerebral artery [MCA]), lower admission National Institutes of Health Stroke Scale (NIHSS), and short and nontotally occlusive thrombi.[4,7–12] It has been suggested that collateral circulation, that is, the alternative vascular network that provides residual blood flow to ischemic areas downstream of an arterial occlusion,[13] is also associated with ER.[14,15] However, support to this hypothesis is limited. Although a classic angiographic study showed higher rates of IVT-induced ER with better collaterals,[16] it was limited by the small sample size and an unusual alteplase dose. Three recent studies reported a similar association, but recanalization was assessed at 24 hours, which is not relevant in the thrombectomy era.[17–19] Thus, the association between collateral grade and post-IVT ER in patients with LVO has not been established thus far.

In the present proof-of-concept, mechanistic study, we tested the hypothesis that post-IVT ER occurring before thrombectomy is independently associated with better collaterals.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design, Data Sources, and Inclusion Criteria

From a large French multicenter registry (PREDICT-RECANAL; Predict Recanalization) of consecutive LVO stroke patients referred for thrombectomy after IVT,[11] we analyzed for the present study the data of the 6 centers that perform perfusion-weighted imaging (PWI) as part of routine admission imaging (Sainte-Anne [Paris], Hospices Civils [Lyon], Orléans, Tours, Montpellier, and Nancy University hospitals). Among these 6 centers, the data were collected prospectively or retrospectively for 3 centers each. All centers had on-site endovascular capabilities except one, whose eligible patients were transferred to the nearest thrombectomy-capable center (ie, drip-and-ship, as opposed to mothership, paradigm). In line with French recommendations,[20] magnetic resonance imaging (MRI) was implemented as first-line imaging in candidates for reperfusion therapy in all centers of the present study. Computed tomography (CT) and CT angiography were performed in case of contraindication to MRI. The stroke MRI protocol in the participating centers included diffusion-weighted imaging (DWI), T2*, intracranial MR angiography, and dynamic susceptibility contrast PWI, whenever feasible with no delay. The PWI acquisition parameters used in each participating center are presented in Table I in the online-only Data Supplement. The PWI data were not a basis for decision-making in routine except in borderline cases.

Inclusion criteria for the present study were, therefore, (1) patient admitted for acute stroke with LVO of the anterior circulation between May 2015 (when thrombectomy became routine care in these centers) and March 2017; (2) pre-IVT imaging with MRI, including DWI, T2*, MR angiography, and PWI; (3) IVT with alteplase of 0.9 mg/kg; and (4) evaluation of ER before thrombectomy (see below).

In accordance with French legislation, each patient was informed of his/her participation in this study and was offered the possibility to withdraw. However, because this study only implied retrospective analysis of anonymized data collected as part of routine care, formal approval by an ethics committee was not required.

Clinical Data

The following variables were extracted from the registries: age, sex, vascular risk factors, medical history, prestroke medication, NIHSS score on admission, time between symptom onset and start of IVT (onset-to-IVT time), and time between start of IVT and evaluation of ER (IVT-to-ER_{eval} time; see below).

Imaging Data

A stroke neurologist (P.S.) reviewed the pre-IVT imaging of all included patients, blinded to recanalization status. The following variables were collected: (1) occlusion site, according to 4 categories: intracranial internal carotid artery occlusion T or L, M1 proximal, M1 distal, and M2, where the M1 segment was defined as the first portion of the MCA up to the main bifurcation and dichotomized as proximal or distal based on the MCA origin-to-thrombus distance (<10 and ≥10 mm, respectively)[7,21]; (2) length of the susceptibility vessel sign (SVS), a marker of thrombus on T2*, based on previously published methodology[22]; and (3) DWI lesion volume, semiautomatically segmented by means of Olea Sphere (Olea Medical SAS, La Ciotat, France) after applying a threshold of 0.620×10^{-6} mm^2/s on apparent diffusion coefficient maps,[23] with manual correction when necessary.

PWI Collateral Flow Map Generation and Grading

In the present study, we used the method previously published and validated against formal angiography—the gold standard collateral grading technique—by Kim et al.[24] This method uses the PWI raw dataset to automatically generate 3 sets of maps covering the MCA territory, namely 1 early-phase map, 1 mid-phase map, and 1 late-phase map—corresponding to the arterial, capillary, and venous phase of angiography, respectively—from which collaterals are visually graded from 1 to 4 based on the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology angiographic classification.[21,24] To replicate the method by Kim et al[24] for the present study, postprocessing of the PWI dataset was performed using an in-house Nipype workflow in Python, implementing the following steps: (1) interframe rigid registration to correct for patient motion; (2) subtraction of the first frame from all consecutive frames to enhance the visualization of the contrast agent; (3) for 6 axial slices covering the MCA territory, summing the R2* values across all voxels of each slice and each time point; (4) automatic determination of the reference time point, defined as the average of the time points with the maximal summated R2* value for each slice, and assumed to be the mid-point of the mid-phase; and (5) generation of collateral flow maps by summing up adjacent time frames, divided into an early, mid, and late phase with a duration of 7, 11, and 14 seconds, respectively.[24]

One reader (P.S.) reviewed all collateral flow maps, blinded to clinical and imaging data, including recanalization status, except for the symptomatic side and site of occlusion. To assess reproducibility, an experienced neuroradiologist (L.L.) independently reviewed a random subset (n=100) of the sample. Discrepancies were resolved by consensus. For each patient, the raters visually assessed the affected MCA territory save for the striatocapsular region. As per the method by Kim et al,[24] grade 1 was defined as no collaterals or slow collaterals (visible only in the late phase) with persistence of some of the parenchymal contrast defect, grade 2 as collaterals visible from the mid-to-late phase but with persistence of some defect, grade 3 as slow but eventually complete collateral flow, and grade 4 as rapid and complete collateral flow (see the Figure for an illustration).

ER Evaluation

In all participating centers, eligible patients were referred for thrombectomy as soon as possible after the start of IVT. ER was defined as recanalization occurring within 3 hours after initiation of IVT. This delay reflects well day-to-day practice, where many patients reach the angiosuite 2 to 3 hours after IVT start, particularly in the drip-and-ship setting.[11,25,26] Recanalization was evaluated on first angiographic run for intended thrombectomy. However, in some patients with significant change in neurological status before reaching the angiosuite, recanalization was evaluated using noninvasive vascular imaging (MR angiography or CT angiography). For the purpose of this

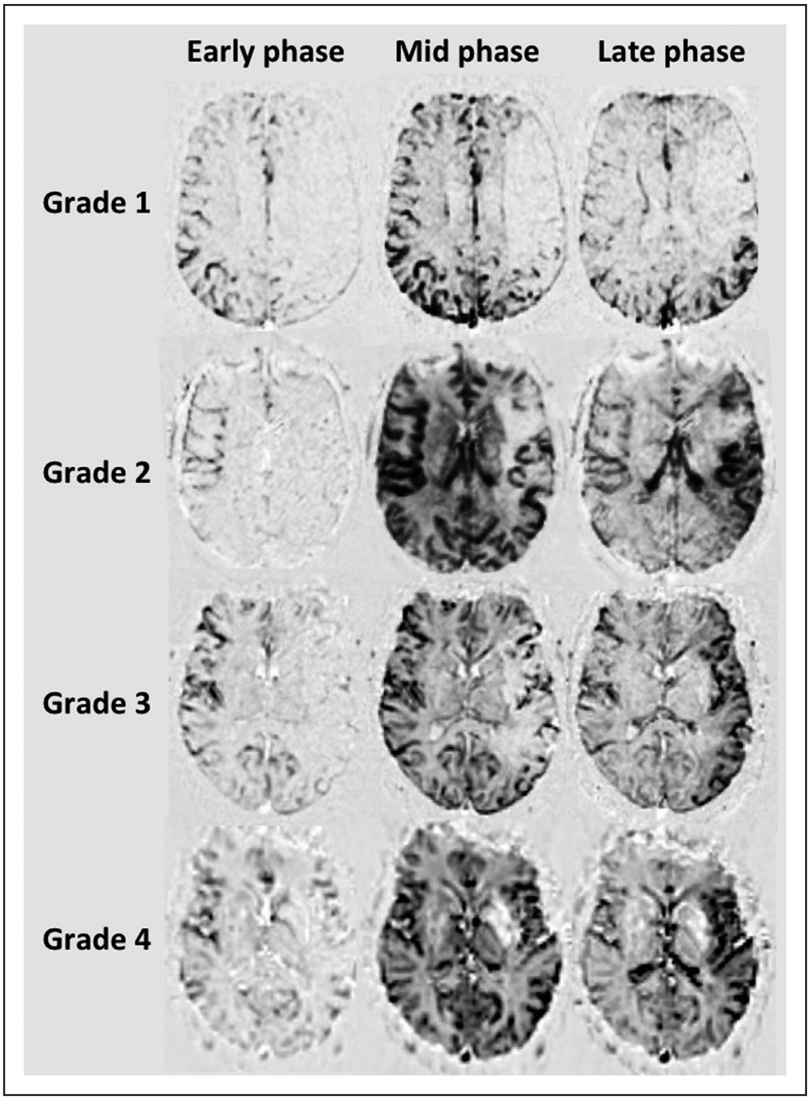

Figure. Grading of collaterals on subtracted dynamic susceptibility contrast perfusion imaging maps, illustrated in 4 different patients with left M1 occlusion (see Methods for details). For each patient, the territory of the affected middle cerebral artery was assessed, save for the striatocapsular region. Grade 1: no collaterals or slow collaterals (visible only in the late phase) with persistence of some of the parenchymal defect; grade 2: collaterals visible from the mid-to-late phase but with persistence of some defect; grade 3: slow but eventually complete collateral flow; and grade 4: rapid and complete collateral flow.

specific study, 2 readers (P.S. for the whole dataset and 1 interventional neuroradiologist from each participating center) independently evaluated recanalization by reviewing the raw angiographic images, blinded to clinical and other imaging data. Discrepancies were resolved by consensus. On conventional angiography, ER was defined as 2b-3 on the modified Thrombolysis in Cerebral Infarction scale for internal carotid artery occlusion T or L or M1 occlusions, and 3 on the Arterial Occlusive Lesion scale for M2 occlusions.[21] Otherwise, ER was defined as 3 on the Arterial Occlusive Lesion scale on CT angiography or MR angiography.

Statistical Analysis

Continuous variables were described as mean±SD or median (interquartile range), as appropriate. Interobserver agreement of collateral grade was measured using weighted Kappa. Correlation between collateral grade and prespecified variables of interest (namely, baseline NIHSS, DWI volume, SVS length, and occlusion site) was assessed using Spearman (Rho) coefficient. Univariable comparison of ER and no-ER patients was performed using Student *t* test or Mann-Whitney *U* test for continuous variables and χ^2 or Fisher exact test for categorical variables, as appropriate. Baseline variables associated with ER in univariable analysis at a level of $P<0.20$ were candidates for inclusion into a multivariable binary logistic regression model, with ER as the dependent variable. Variable selection was performed stepwise, whereby candidate variables entered the model at $P<0.20$ and were retained only if they remained associated at $P<0.05$ with the dependent variable. Covariates were assessed for collinearity and interaction effects. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, NC) and SPSS 16.0 (SPSS, Inc). Two-tailed $P<0.05$ was considered statistically significant.

Results

Patient Characteristics

During the study period, 386 patients eligible for thrombectomy with ACI-T/L, M1, or M2 occlusion received IVT in the 6 participating centers. Among them, 162 patients were excluded for the following reasons: no MRI (ie, CT and CT angiography, n=46), PWI not performed (n=84) or of poor quality (n=19), ER assessed beyond 3 hours after IVT start (n=10), or no ER assessment (n=3), leaving 224 patients for the final analysis. Patients with baseline MRI but without or with inadequate-quality PWI had similar age (P=0.53), sex (P=0.13), NIHSS (P=0.06), occlusion site (P=0.47), and ER rate (P=0.83) than included patients (Table II in the online-only Data Supplement).

The baseline characteristics of included patients are presented in Table 1. ER was evaluated on first angiographic run in 213 of 224 (95%) patients. ER occurred in 37 of 224 (16%)

patients. Grade 1 collaterals were present in 6 of 224 (3%) patients, grade 2 in 77 of 224 (34%), grade 3 in 116 of 224 (52%), and grade 4 in 25 of 224 (11%). The weighted Kappa value for interrater agreement in grading PWI collateral flow maps was 0.85 (95% CI, 0.76–0.93). Given the small number of patients with grade 1 collaterals, grades 1 and 2, both of which represent inadequate collaterals, were merged for subsequent analyses.

Correlation Between Collateral Grade and Other Variables

As expected, collateral grade was negatively correlated with admission NIHSS (Rho=−0.29; *P*<0.01) and DWI lesion volume (Rho=−0.64; *P*<0.01), that is, the better the collaterals, the lower the NIHSS and DWI lesion volume. Collateral grade was not correlated with SVS length (Rho=−0.07; *P*=0.35) or occlusion site (Rho=0.10; *P*=0.13).

Variables Associated With ER in Univariable Analysis

The univariable analysis with ER as the dependent variable is presented in Table 1. The following variables were significantly associated with ER: use of statins before stroke, lower baseline NIHSS, more distal occlusions, shorter SVS, smaller DWI lesion volume, and higher collateral grade. ER occurred in 1 of 41 (2%), 7 of 93 (8%), 12 of 40 (30%), and 17 of 50 (34%) patients with ICA-T/L, proximal M1, and distal M1 and M2 occlusions, respectively, and in 10 of 83 (12%), 17 of 116 (15%), and 10 of 25 (40%) patients with collateral grades 1–2, 3, and 4, respectively.

Table 1. Baseline Characteristics of the Population and Univariate Relationships With ER*

	Whole Cohort (n=224)	ER (n=37)	No ER (n=187)	*P* Value
Patient history				
Age, y	71 (61–80)	74 (61–83)	71 (61–80)	0.49
Men	125 (56)	21 (57)	104 (56)	0.90
Hypertension	124 (55)	21 (57)	103 (55)	0.85
Diabetes mellitus	36 (16)	9 (24)	27 (14)	0.14
Current smoking	28 (13)	6 (16)	22 (12)	0.45
Antiplatelet use	75 (34)	15 (41)	60 (32)	0.32
Statin use	70 (31)	17 (46)	53 (28)	0.04
Pre-IVT characteristics				
NIHSS	16 (9.5–19.5)	12 (7–17)	16 (10–20)	0.02
Onset-to-IVT time, min	160 (129–194)	165 (145–200)	155 (126–192)	0.25
Pre-IVT MRI				
Occlusion site				<0.01
ICA-T/L	41 (18)	1 (3)	40 (21)	
Proximal M1	93 (42)	7 (19)	86 (46)	
Distal M1	40 (18)	12 (32)	28 (15)	
M2	50 (22)	17 (46)	33 (18)	
DWI volume, mL	12 (5–24)	11 (2–18)	12 (6–29)	0.05
SVS visible	203 (91)	33 (89)	170 (91)	0.75
SVS length,† mm	12.6 (9.2–17.6)	7.3 (5.8–8.9)	14.0 (10.2–19.2)	<0.01
Collateral grade				<0.01
Grades 1 and 2	83 (37)	10 (27)	73 (39)	
Grade 3	116 (52)	17 (46)	99 (53)	
Grade 4	25 (11)	10 (27)	15 (8)	
ER evaluation				
IVT-to-ER_{eval} time, min	62 (37–97)	61 (45–118)	61 (35–94)	0.28

DWI indicates diffusion-weighted imaging; ER, early recanalization; ER_{eval}, evaluation of early recanalization; ICA-T/L, intracranial internal carotid artery occlusion; IQR, interquartile range; IVT, intravenous thrombolysis; M1, first segment of the middle cerebral artery; M2, second segment of the cerebral artery; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; and SVS, susceptibility vessel sign.

*Categorical variables are expressed as numbers (%) and continuous variables as median (IQR).

†Missing values: 21 patients without visible SVS.

Table 2. Variables Independently Associated With ER in Multivariable Logistic Regression*

	Adjusted OR (95% CI)	*P* Value
SVS length, per 1 mm increase	0.67 (0.56–0.80)	<0.001
Occlusion site		0.010
ICA-T/L	Reference	
M1 proximal	1.20 (0.40–3.55)	
M1 distal or M2	7.45 (1.57–35.32)	
Collateral grade		0.029
Grades 1 and 2	Reference	
Grade 3	1.06 (0.10–11.49)	
Grade 4	5.39 (0.56–51.47)	

Statin use, diabetes mellitus, NIHSS, and DWI volume were candidate variables because their *P* value was <0.20 in univariable analysis (Table 1) but were not retained in the multivariable model. DWI indicates diffusion-weighted imaging; ER, early recanalization; ICA-T/L, intracranial internal carotid artery occlusion; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and SVS, susceptibility vessel sign.

*Twenty-one patients without visible SVS were excluded from the model, which, therefore, included 203 patients (33 with ER and 170 without).

Multivariable Analysis With Early Recanalization as the Dependent Variable

The multivariable model (n=203 patients, excluding 21 patients without visible SVS) is presented in Table 2. Variables independently associated with ER were SVS length (*P*<0.001), occlusion site (*P*=0.010), and collateral grade (*P*=0.029).

Discussion

Based on a large multicentric population of patients with stroke referred for thrombectomy who underwent MRI with PWI before IVT, the present proof-of-concept study showed that a better collateral grade was independently associated with ER occurrence. As expected, smaller thrombus and more distal occlusion sites were also independently associated with ER.

Consistent with our observation, in a seminal study from 1992 on 32 patients with LVO in whom conventional angiography was performed before and 90 minutes after IVT, good collaterals were associated with higher ER rate at the end of IVT infusion.[16] However, this result was not adjusted on other key variables now known to be associated with ER and cannot be transposed to current practice because the dose of alteplase in this study was higher than currently recommended (100 mg for all patients versus 0.9 mg/kg with a maximum of 90 mg, respectively). Also in line with our results, 3 recent studies reported an association between post-IVT recanalization in patients with LVO and (1) lower normalized index derived from Tmax maps of PWI[17]—a surrogate marker of good collateral circulation; (2) good collaterals evaluated on CT perfusion source images[19]; and (3) rapid collateral filling evaluated on PWI, respectively.[18] These studies, however, had 2 major limitations. First, in all studies, recanalization was evaluated at 24 hours after IVT, which includes futile recanalization and is not anymore relevant in the era of bridging therapy. Second, they all used small samples, precluding adjustment on 2 key confounders of post-IVT recanalization, namely occlusion site (except in the study by Zhang et al[18]) and thrombus length.

Regarding mechanisms, 1 attractive hypothesis to explain the relationship between collaterals and ER is that good collaterals may improve delivery of (endogenous and exogenous) thrombolytics to both ends of the thrombus.[14,15] However, association does not prove causality, and some as yet unidentified factors might account for both ER and high collateral grade. Interestingly, using a PWI-based approach different from ours, Zhang et al[18] found that the velocity, but not the extent, of collateral filling was associated with 24-hour post-IVT recanalization. In the present study, using a method that grades collaterals based on both timing and extent of collateral flow, the 2.5-fold higher ER rate found for grade 4 as compared with grade 3 would be consistent with Zhang et al.[18] Indeed, although both grades entail collaterals eventually covering the entire MCA territory, this occurs more rapidly in grade 4 versus grade 3 (Figure). As a mechanistic interpretation of this somewhat puzzling observation, Zhang et al[18] hypothesized that "rapid collateral flow, as opposed to slow ones, may apply higher shear stress to the thrombus to cause the disruption of the clot," which, however, remains entirely speculative.

The 16% incidence rate of post-thrombolysis ER before thrombectomy present in our cohort is in line with the available literature.[3,4] Considering both these relatively limited rates of post-IVT ER and the potential harm from IVT in thrombectomy candidates, the utility of IVT before thrombectomy has been recently questioned.[5] However, the option of skipping IVT should be formally tested in randomized trials, which should ideally recruit patients with low ER probability only. More generally, our results highlight the potential utility of advanced imaging for personalized medicine and suggest that collateral imaging, together with thrombus imaging, may help to select patients most likely to benefit from IVT in the thrombectomy era.

Our study has several strengths. First, it is based on a large multicentric sample of patients with LVO treated with IVT and referred for thrombectomy since bridging therapy has become standard of care. Also, patients with early neurological improvement, in whom ER was evaluated using noninvasive vascular imaging, were included, thereby limiting selection bias. Second, the method used for collateral flow grading has been previously validated with angiography-based collateral grading.[24] Last, ER was assessed by 2 independent raters, reducing the risk of classification errors, and interrater agreement for collateral grading was good.

This study also has limitations. First, the decision to refer patients for thrombectomy was under the treating physician, which might have induced selection bias. For instance, the presence of a large DWI lesion may have reduced patient's eligibility for thrombectomy, which in turn may explain why only few patients in our sample had grade 1 collaterals. That said, the median DWI volume in our population (Table 1) was similar to both CT perfusion[27] and DWI[28] median core volumes reported in recent thrombectomy trials. Second, 31% (103 of 327) of patients from our MR-assessed population were excluded because PWI was not performed or was of poor quality, which might have induced selection bias. Note, however, that the included and excluded MRI populations were similar in terms of age, NIHSS, occlusion site, and ER rate.

Third, the MR-based method used to grade collaterals does not have the temporal resolution necessary to distinguish truly excellent retrograde collateral flow (ie, grade 4) from anterograde trickle flow through the thrombus.[7,9,10,12] Fourth, the sample of patients with grade 4 collaterals was small, and our findings should be confirmed in larger populations. Last, despite the relatively large sample size and the substantial ER rate, the absolute number of patients who recanalized within 3 hours of IVT was relatively low, precluding subgroup analysis.

Conclusions

This mechanistic study in patients eligible for thrombectomy revealed an independent association between better collaterals and early post-IVT recanalization, supporting the idea that delivery of thrombolytic agents to both ends of the thrombus may enhance early recanalization. Collateral imaging may play a role in identifying patients with LVO who are most likely to benefit from IVT in the thrombectomy era.

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Disclosures

None.

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