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Letter to the Editor

Role of Venous Delay on Stroke Outcome: Prospective Evaluation Before and After Mechanical Thrombectomy

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Dear Sir:

Endovascular treatment (EVT) has become a routine therapeutic approach for acute ischemic stroke (AIS) patients with large vessel occlusion, emphasizing the importance of successful arterial reperfusion as a predictor of positive clinical outcomes. However, a significant subset of patients experiences poor functional outcomes despite achieving complete angiographic reperfusion. Factors contributing to this disparity include age, brain atrophy, pre-EVT National Institutes of Health Stroke Scale (NIHSS), large infarct core at admission, poor arterial collaterals, and the number of passes during the EVT procedure.[1]

While the majority of AIS studies focus on the arterial system, some recent studies have shown an association between cortical venous drainage and clinical outcomes in AIS patients.[2-4] These studies included patients who underwent different treatments and used diverse methodologies. However, it is still unclear the impact of venous drainage delay in patients who undergo EVT and whether this delay persists after the procedure. We aimed to evaluate the predictive value of cortical venous delay, measured through dynamic magnetic resonance angiography (dMRA)—a time-resolved sequence capturing arterial filling and venous emptying—before and after EVT, on infarct volume and functional outcomes in patients with large anterior artery occlusion undergoing EVT.

This project is a preplanned substudy of the FUtile Recanalization in Ischemic Acute Stroke (FURIAS) study. The study design and methodology have been published.[5] The magnetic resonance imaging (MRI) protocol has been described in Supplementary Table 1. Briefly, we prospectively enrolled patients with acute intracranial carotid artery or middle cerebral artery M1 or proximal M2 occlusion undergoing EVT that received serial brain MRI. The Research Ethics Committee of the Germans Trias Hospital approved this study (approval number PI-15-071). Written informed consent was obtained from all patients. The brain MRI scans were systematically analyzed at three distinct time points: at hospital admission (pre-EVT), within 2 hours after EVT (post-EVT), and 5 days after EVT by a trained investigator. A previous paper showed that the delay in cortical veins seems to be a stronger predictor of outcome than the delay in the deep veins.[3] Therefore, we decided to restrict our study to the cortical veins. Cortical venous delay was quantified by identifying the time point in which venous filling was maximal in the main cortical veins for both hemispheres and calculating the percentage of delay for each vein for both pre-EVT and post-EVT MRIs (Supplementary Figure 1). We considered successful reperfusion as a final modified Thrombolysis in Cerebral Infarction (mTICI) grade ≥2B. Associations between venous delay and infarct volumes post-EVT

and on day 5 were studied using multivariable linear regression. An ordinal logistic regression was performed to study the influence of venous delay on the modified Rankin Scale (mRS) at 3 months. We did these analyses for the whole cohort and for the group of patients that achieved successful reperfusion. The analyses were adjusted by relevant variables according to previous literature (Supplementary Table 2).

We enrolled 94 stroke patients (mean age: 69.9; median NIHSS: 17; final mTICI ≥2b: 86.2%) undergoing EVT (the selection flowchart and further comparison are published elsewhere). From those, we could evaluate 89 pre-EVT dMRAs and 88 post-EVT dMRAs (Supplementary Figure 2). Eighty-two of them had evaluable pre-EVT and post-EVT dMRA. An overview of the patient sample characteristics is shown in Table 1 and Supplementary Table 3. Pre-EVT and post-EVT mean venous delays were 31.9% and 13.5%, respectively. Successful reperfusion resulted in a 15.5% reduction in post-EVT venous delay with no significant change for non-reperfused patients (Supplementary Figure 3). Pre-EVT venous delay showed no significant correlation with infarct volume or clinical outcome, adjusting for reperfusion success (Table 2). However, for each 10% increment in post-EVT venous delay, there was an adjusted 0.12 mL increase (95% confidence interval [CI], 0.05–0.19) in infarct volume at 5 days and higher odds of an elevated mRS score at 3 months (adjusted crude odds ratio 1.14; 95% CI, 1.01–1.29) (Table 2).

Our key finding was that post-EVT cortical venous delay was linked to larger infarct volume at 5 days and worse functional outcomes at 3 months. However, the association between pre-EVT venous delay and clinical and radiological outcomes was not significant after adjustments by collateral grade and reperfusion status. Previous studies have yielded mixed results in this respect.[2-4,6-8] Of note, venous delay in AIS can be explained by arterial occlusion, poor collateral flow, breakdown of the blood-brain barrier causing edema and venous compression, and microthrombi formation.[9]

It is unclear whether our lack of significance is due to our small sample size or if reperfusion status and collateral grade might act as confounding variables, influencing radiological and clinical outcomes more than pre-EVT venous delay itself.

Notably, the study identified a trend for improved venous outflow post-EVT in successfully reperfused patients. Nevertheless, this group of patients still had some grade of venous delay, possibly due to tissue edema or microthrombi. While venous delay post-EVT was linked to larger infarct volumes, the association with clinical outcomes in the reperfused group was not significant, potentially due to limited statistical power.

Strengths of the study included systematic evaluation of veins using consistent radiological methods, quantitative assessment

Table 1. Comparison between patients with assessable dMRA pre-EVT and patients with assessable dMRA post-EVT

Characteristic	Assessable dMRA pre-EVT (n=89)	Assessable dMRA post-EVT (n=88)	*P* (overall)
Age (yr)	69.9±13.5	70.0±13.2	0.964
Sex			0.761
Male	51 (57.3)	48 (54.5)	
Female	38 (42.7)	40 (45.5)	
Hypertension	62 (69.6)	61 (69.3)	>0.999
Diabetes	14 (15.7)	15 (17.0)	>0.999
Dislipidemia	38 (42.6)	37 (42.0)	>0.999
Atrium fibrillation	27 (30.7)	30 (34.1)	0.747
Clinical category			0.814
Cardioembolism	32 (35.9)	36 (40.9)	
Large-artery atherosclerosis	30 (33.7)	27 (30.7)	
Stroke of undetermined etiology	27 (30.3)	25 (28.4)	
NIHSS baseline	17.0 [12.0–20.0]	17.5 [12.0–21.0]	0.598
Occluded artery			0.996
M1 MCA	46 (51.6)	46 (52.3)	
M2 MCA	10 (11.2)	12 (13.6)	
Tandem (ICA+MCA)	22 (24.7)	21 (23.9)	
TICA (ICA terminal)	11 (12.4)	9 (10.2)	
Glycemia (mg/dL)	116 [101–140]	121 [101–144]	0.661
Wake up	21 (23.5)	22 (25.0)	>0.999
rTPA	38 (42.7)	36 (40.9)	0.878
Onset-puncture (min)	314 [236–528]	322 [238–546]	0.758
Sedoanalgesia	84 (95.5)	84 (95.5)	>0.999
Final mTICI			0.999
mTICI 0	5 (5.61)	6 (6.82)	
mTICI 2a	7 (7.86)	7 (7.95)	
mTICI 2b	19 (21.3)	19 (21.6)	
mTICI 2c	24 (26.9)	24 (27.3)	
mTICI 3	34 (38.2)	32 (36.4)	
Ischemia duration (min)	366 [266–598]	376 [269–608]	0.771
First MRI to recanalization (min)	103 [77–142]	102 [78–144]	0.930
DWI volume pre-EVT (mL)	12.0 [5.5–20.0]	12.0 [6.0–21.8]	0.752
DWI volume post-EVT (mL)	17.7 [7.2–38.4]	21.3 [7.5–40.4]	0.707

Values are presented as mean±standard deviation, n (%), or median [interquartile range].
dMRA, dynamic magnetic resonance angiography; EVT, endovascular treatment (pre-EVT, at hospital admission; post-EVT, <2 hours after EVT); NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; M1, M1 segment of the MCA; M2, M2 segment of the MCA; ICA, internal cerebral artery; TICA, terminal internal cerebral artery; rtPA, recombinant tissue plasminogen activators; mTICI, modified Thrombolysis in Cerebral Infarction; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

Table 2. Associations of venous delay pre-EVT and venous delay post-EVT with outcomes on multivariable analysis

Outcome	Multivariable model	Adjustment covariates	Venous time point evaluation	Cohort	Effect size[§] [95% confidence interval]	*P*
Infarct volume post-EVT (mL)	Linear regression	Number of passes, site of occlusion, time from onset to MRI, successful reperfusion, volume of infarct pre-EVT	Venous delay pre-EVT*	Complete cohort	0.01 [-0.04–0.05]	0.672
				Reperfused patients[‡]	0.00 [-0.05–0.05]	0.991
Infarct volume at 5 days (mL)	Linear regression	Number of passes, site of occlusion, time from onset to MRI, successful reperfusion, volume of infarct pre-EVT	Venous delay pre-EVT*	Complete cohort	0.01 [-0.04–0.06]	0.631
				Reperfused patients[‡]	0.00 [-0.05–0.05]	0.997
			Venous delay post-EVT[†]	Complete cohort	0.12 [0.05–0.19]	0.007
				Reperfused patients[‡]	0.12 [0.04–0.20]	0.003
mRS 3 months	Ordinal regression	Age, sex, NIHSS at hospital arrival, site of occlusion, HIR, successful reperfusion, ischemia duration	Venous delay pre-EVT*	Complete cohort	1.04 [0.96–1.12]	0.291
				Reperfused patients[‡]	1.06 [1.00–1.01]	0.193
			Venous delay post-EVT[†]	Complete cohort	1.14 [1.01–1.29]	0.035
				Reperfused patients[‡]	1.11 [0.96–1.28]	0.138

*Venous delay pre-EVT was measured in the assessable pre-EVT dMRA group and included 89 patients; [†]Venous delay post-EVT was measured in the assessable post-EVT dMRA group and included 88 patients; [‡]In the subset of reperfused patients, no adjustment by final mTICI grade was done; [§]The effect size is calculated per each increase of a 10% venous delay. All results of the ordinal regression are expressed as crude odds ratio [95% confidence interval].
EVT, endovascular treatment (pre-EVT, at hospital admission; post-EVT, <2 hours after EVT); MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; HIR, hypoperfusion intensity ratio.

of venous delay, and dMRA allowing precise identification of maximal contrast enhancement. However, limitations included a small sample size, incomplete brain coverage in the imaging protocol, and the simplification of venous delay measures.

This study emphasized the need for further research on venous patterns in AIS, advocating for larger patient populations and using dynamic imaging techniques to better understand cerebrovascular circulation complexity. Our findings suggest that venous circulation plays a role in post-stroke recovery, highlighting the importance of comprehending venous function in ischemic stroke for identifying potential neuroprotective targets and improving outcomes.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.00150.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: LZ, JM, MHP. Study design: JM, MHP. Methodology: AV, JM, MHP. Data collection: MW, SR, LD, JS, JP, NPO, MG, AB, BFP, MM (Marina Martinez), CC, LM, AM, MM (Monica Millan), LZ, JM, MHP. Statistical analysis: AV. Writing—original draft: LZ, MHP. Writing—reveiw & editing: all authors. Funding acquisition: NPO, MM (Monica Millan), MHP. Approval of final manuscript: all authors.

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Supplementary Table 1. The MRI protocol used in the study

	Details of protocols
MRI protocol	MRI scans were performed using a 3-T Magnetom Verio (Siemens, AG, Erlangen, Germany) at pre-EVT, post-EVT, and 5 days after EVT, except for 17 patients, for whom the 5-day post-EVT MRI was conducted using a 1.5-T Philips scanner. The protocol included the acquisition of diffusion-weighted imaging, time-of-flight MRA, susceptibility-weighted imaging, perfusion-weighted imaging (PWI and dMRA after bolus injection of 0.1 mg/kg of gadolinium [TE 1.17 ms, TR 3.15 ms, flip angle 25° with 30 dynamic acquisitions and a temporal resolution of 2.28 seconds/volume for a voxel size of 1.0×0.9×2.5 mm]). dMRA and PWI sequences were not acquired on day 5.
MR contrast	In this study, we used gadoterate meglumine. We used a total of 0.2 mL/kg of gadolinium for each acquisition. The dosage was split into two administrations: patients received 0.1 mL/kg before dMRA and another 0.1 mL/kg before PWI. In total, the patients in this study received 0.4 mL/kg of gadolinium on the same day. The dosages were authorized by the Ethics Committee of the Germans Trias i Pujol Hospital, and informed consent was obtained from each patient.

EVT, endovascular treatment (pre-EVT, at hospital admission; post-EVT, <2 hours after EVT); MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; PWI, perfusion weighted imaging; dMRA, dynamic MRA; TE, echo time; TR, repetition time.

Supplementary Table 2. Statistical analyses

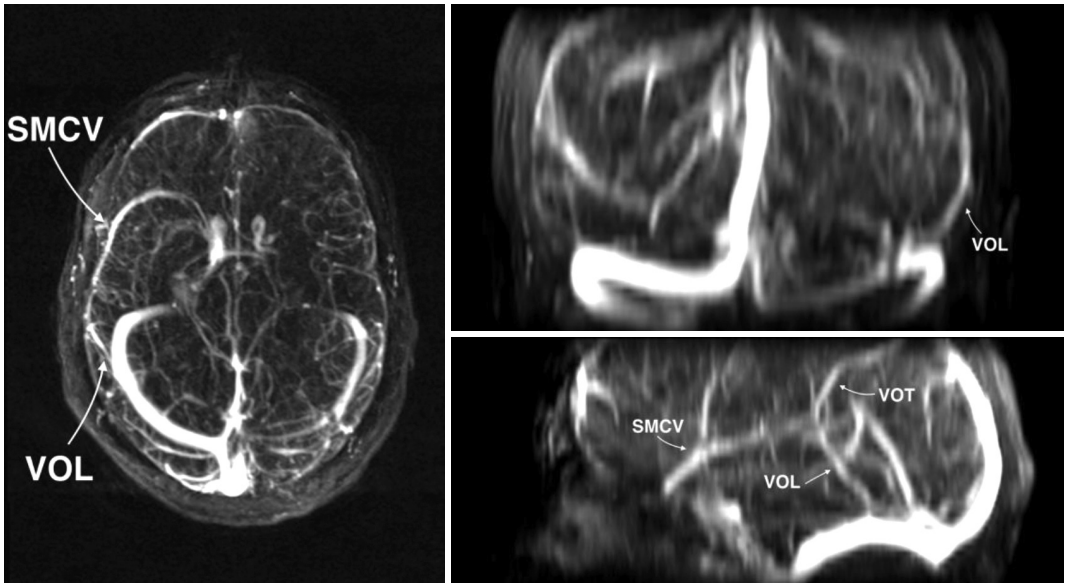
Statistical test	Variables	Adjusted by
Multivariable linear regression	Pre- and post-EVT venous delay and infarct volumes post-EVT and at day 5	Successful reperfusion, number of passes, pre-EVT infarct volume, time from onset to MRI pre-EVT, site of occlusion, and HIR
Ordinal logistic regression	Pre- and post-EVT venous delay and mRS at 3 months	Age, sex, successful reperfusion, baseline NIHSS, site of the occlusion, and HIR

EVT, endovascular treatment (pre-EVT, at hospital admission; post-EVT, <2 hours after EVT); MRI, magnetic resonance imaging; HIR, hypoperfusion intensity ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

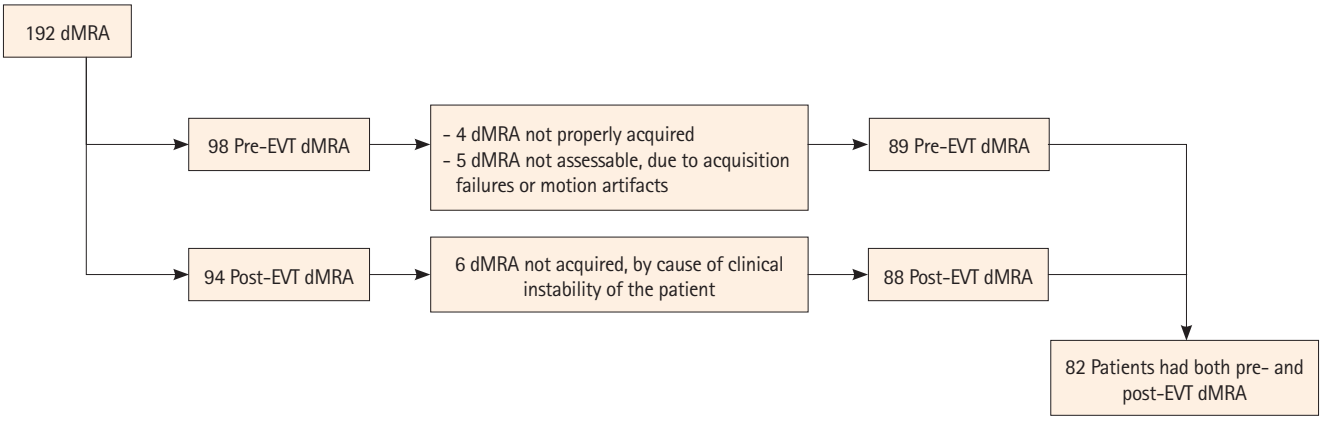
Supplementary Table 3. Characteristics of the stroke patients undergoing EVT

Characteristics	Total sample (n=94)
Age (yr)	69.9±13.2
Female sex	41 (43.6)
Smoking	24 (25.5)
Hypertension	64 (68.1)
Dyslipidemia	40 (42.6)
Diabetes	16 (17.0)
Atrial fibrillation	30 (31.9)
Stroke etiology*	
Atheroembolic	30 (31.9)
Cardioembolic	37 (39.4)
Undetermined	27 (28.7)
Onset to admission (min)	252 [135–429]
NIHSS baseline	17 [12–21]
Glycemia baseline (mg/dL)	120 [101–143]
Wake up stroke (yes)	22 (23.4)
Site of occlusion	
Intracranial carotid	9 (9.6)
Tandem	23 (24.5)
MCA M1 segment	49 (52.1)
MCA M2 segment	13 (13.8)
Previous intravenous alteplase	47 (50.0)
Onset to groin (min)	319 [235–516]
Time from MRI pre-EVT to end of procedure (min)	103 [78–140]
Conscious sedation	90 (95.7)
Final mTICI grade	
mTICI 0	6 (6.4)
mTICI 2a	7 (7.4)
mTICI 2b	19 (20.2)
mTICI 2c	27 (28.7)
mTICI 3	35 (37.2)

Values are presented as mean±standard deviation, median [interquartile range], or n (%).
NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; M1, M1 segment of the MCA; M2, M2 segment of the MCA; MRI, magnetic resonance imaging; EVT, endovascular treatment; mTICI, modified Thrombolysis in Cerebral Infarction.
*According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) etiology.



Supplementary Figure 1. Cortical veins on maximum intensity projection in the three planes of space. SMCV, superficial middle cerebral vein; VOT, vein of Trolard; VOL, vein of Labbé.



Supplementary Figure 2. Flowchart of the dMRA selection. dMRA, dynamic magnetic resonance angiography; EVT, endovascular treatment.

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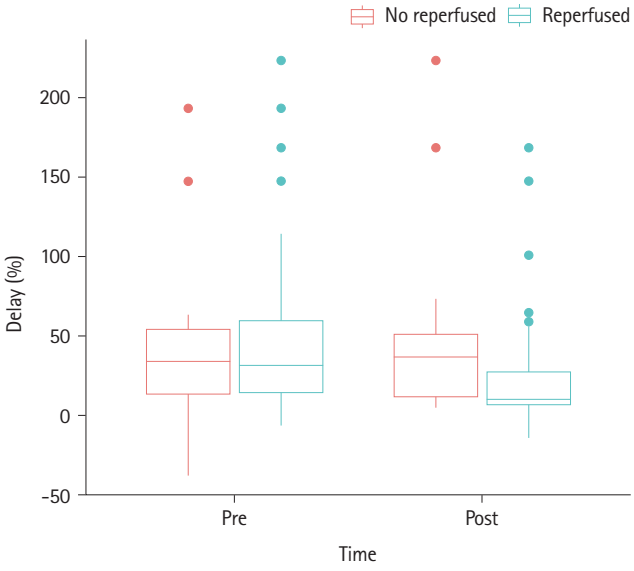

Supplementary Figure 3. Box plot representing the change in maximum delay pre- and post-EVT in reperfused and non-reperfused patients. EVT, endovascular treatement.