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ORIGINAL COMMUNICATION

Small vessel disease and collaterals in ischemic stroke patients treated with thrombectomy

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Abstract

Background and purpose To determine the influence of the cerebral small vessel disease (SVD) burden on collateral recruitment in patients treated with mechanical thrombectomy (MT) for anterior circulation acute ischemic stroke (AIS).

Methods Patients with AIS due to large vessel occlusion (LVO) from the Thrombectomie des Artères Cérébrales (THRACE) trial and prospective cohorts from 2 academic comprehensive stroke centers treated with MT were pooled and retrospectively analyzed. Collaterals' adequacy was assessed using the American Society of Interventional and Therapeutic Radiology/Society of Interventional Radiology (ASITN/SIR) score on initial digital subtraction angiography and dichotomized as good (3,4) versus poor (0–2) collaterals. The SVD burden was rated with the global SVD score on MRI. Multivariable logistic regression analyses were used to determine relationships between SVD and ASITN/SIR scores.

Results A total of 312 participants were included (53.2% males, mean age 67.8 ± 14.9 years). Two hundred and seven patients had poor collaterals (66.4%), and 133 (42.6%) presented with any SVD signature. In multivariable analysis, patients demonstrated worse leptomeningeal collaterality with increasing SVD burden before and after adjustment for SVD risk factors (adjusted odds ratio [aOR] 0.69; 95%CI [0.52–0.89] and aOR 0.66; 95%CI [0.5–0.88], respectively). Using individual SVD markers, poor collaterals were significantly associated with the presence of lacunes (aOR 0.40, 95% CI [0.20–0.79]).

Conclusion Our study provides evidence that in patients with AIS due to LVO treated with MT, the burden of SVD assessed by pre-treatment MRI is associated with poorer recruitment of leptomeningeal collaterals.

Keywords Thrombectomy · Stroke · Cerebral small vessel disease · Collateral circulation · Magnetic resonance imaging

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Introduction

Cerebral small vessel disease (SVD) is a common feature of brain aging [1], associated with less favorable functional outcomes in patients with acute ischemic stroke (AIS) including those with large vessel occlusion (LVO) treated with mechanical thrombectomy (MT) [2–4]. In AIS-LVO patients, leptomeningeal collaterals play a key role in maintaining substantial blood perfusion to at-risk brain tissue until revascularization occurs; and in turn, their adequacy is amongst the strongest determinant of favorable functional outcome after MT [5–7].

The factors associated with adequate recruitment of collaterals at the time of LVO remain poorly understood, but emerging evidence suggests the role of the cortical microvascular environment in establishing an adequate retrograde flow to the affected territory in the presence of an occlusion [8]. In murine models, hypertension and aging, both important risk factors for SVD have been associated with impaired vasodilatory responses of collaterals [8], and there is a strong rationale to study the impact of SVD on the adequacy of collateral circulation because of their intricate functional and anatomical relation, suggesting that the pathophysiological processes chronically affecting brain microvessels may alter their response to acute ischemic insult. To date, few reports have assessed the association between the severity of SVD burden and the collateral status in AIS-LVO patients yielding conflicting results [9–13]. In these works, heterogeneity in patient populations studied as well as in means for SVD and collaterals measurements posed limitations. To further understand the relationship between SVD and collateral blood flow recruitment during AIS due to LVO, we performed a post hoc analysis of the MT arm of the THRombectomie des Artères CErébrales (THRACE) study [14] associated with a multicenter cohort and aimed to examine the relationship between collateral arterial network and SVD in patients with anterior AIS treated by MT. In this population, we tested the hypothesis that collaterals recruitment would be impaired with increasing burden of SVD.

Methods

Standard protocol approvals, registrations, and patient consent

THRACE (THRombectomie des Artères CErébrales, ClinicalTrials.gov, number NCT01062698) was a randomized controlled trial performed at 26 centers in France. Study design and protocol have been detailed elsewhere [14]. In brief, patients with anterior AIS-LVO were randomly assigned 1:1 to receive either intravenous thrombolysis (IVT) alone or IVT plus MT (IVTMT arm). IVT and MT had to be started within 4 and 5 h of symptom onset, respectively. Before randomization, written informed consent was obtained from all patients or their legal representatives. The study protocol was approved by the CPP (Comité de Protection des Personnes) III Nord Est Ethics Committee and the research boards of the participating centers.

Patients from the IVTMT arm of THRACE, and retrospective cohorts of consecutive patients from two additional large volume academic comprehensive stroke centers using pre-treatment MRI as routine imaging in suspected stroke patients between 2015 and 2020 (Centre Hospitalier Régional, Lille—Center 1—and Centre Hospitalier Sainte-Anne, Paris—Center 2; France) were pooled and retrospectively analyzed, as previously described [2].

In both centers, MT indication was at the discretion of the treating team. In accordance with French legislation, written informed consent was waived for the retrospective analysis of data collected as part of routine clinical care in these cohorts, but patients were informed that according to French legislation they could oppose the use of their data for research purposes.

Study design, setting, patient population and variables

The preliminary pooled sample was retrospectively queried to identify adult patients meeting the following criteria: (1) Baseline clinical MRI, routinely obtained before MT, with available T2-weighted FLAIR (fluid-attenuated inversion recovery), diffusion-weighted imaging and T2* or susceptibility-weighted imaging sequences of adequate quality for SVD assessment; (2) initial images of adequate quality from digital subtraction angiography (DSA) during MT for collateral assessment; (3) AIS with anterior LVO including M1 segment of middle cerebral artery and/or intracranial internal carotid artery ICA (anterior cerebral artery occlusions were not included); (4) 90-day-modified Rankin Scale score (mRS) assessed through in person or telephone interview; and (4) for both retrospective cohorts, patients treated between January 1st 2015 as MT became standard of care and January 1st 2020.

Baseline clinical characteristics and laboratory values were collected prospectively at each center, and retrospectively queried. Patients with incomplete or artifacted MRI precluding SVD burden assessment were excluded. Patients with no DSA acquisition, kinetic artifact, insufficient acquisition time for collateral assessment, or recanalization at the time of first acquisition were also excluded.

Clinical and treatment-related variables

Age, sex, and past medical history [including diabetes mellitus (DM), dyslipidemia, hypertension (HTN), and tobacco use] were determined from medical records or patient/surrogate interview. All patients were evaluated by a neurologist in the acute setting, at which point stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Stroke imaging severity was assessed using the Alberta Stroke Program Early CT Score (ASPECTS) on the initial Diffusion weighted Imaging (DWI-ASPECTs) [15]. Treatment with intravenous tissue plasminogen activator (IV tPA), and procedural endovascular variables (onset-to-groin puncture time, site of occlusion, revascularization as assessed with the mTICI score) were prospectively collected. Symptomatic intracerebral hemorrhage was defined according to the European Cooperative Acute Stroke Study 2 criteria, as a NIHSS score higher of 4 points than the value at baseline or the lowest value in the first 7 days, or that led to death or was identified as the predominant cause of the neurological deterioration [16].

Favorable outcome was defined as mRS of 2 or less.

Small vessel disease

Imaging biomarkers of SVD were independently assessed by 2 radiologists (GF and RA) blinded to functional outcomes, collaterals status and clinical information according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) [1].

Images at both participating academic centers with echo-planar capabilities, and stroke protocol included DWI, FLAIR, T2* GRE, and 3D time-of-flight MRA as part of routine clinical care. The Fazekas scale [17] was used to quantify the severity of deep and periventricular white matter intensities (WMH). Cerebral microbleeds (CMB) are small (> 2 and < 10 mm diameter) round or ovoid brain tissue lesions with of low signal intensity on gradient-recalled echo image or susceptibility-weighted image [18], and were quantified as lobar (cortico-subcortical) or deep. Cerebral atrophy was assessed according to Pasquier's global cortical atrophy scale [19], and lacunes were defined as round or ovoid, fluid-filled (similar signal as cerebrospinal fluid) cavity, of between (> 3 mm < 15 mm diameter) in the territory of one perforating arteriole [1] on fluid-attenuated inversion recovery without restricted diffusion. To avoid confounding from the ischemic lesion, Fazekas scale was rated in the non-affected hemisphere, as per current standards [2].

The SVD burden score was then calculated according to previous literature [20] by summing the presence of each of the 3 MRI features of SVD described above: 1 point for the presence of ≥ 1 lacune(s), 1 point for the presence of ≥ 1 CMB, 1 point for the presence of periventricular WMH Fazekas 3 (extending into the deep white matter) and/or deep WMH Fazekas 2–3 (confluent or early confluent). The presence and severity of enlarged perivascular spaces was not integrated due to the unavailability of T2 sequences, yielding a 0–3 truncated total SVD burden score, as has been done in previous works [21].

For sensitivity analyses, we used the WMH volume. WMH volumes were obtained by semi-automated planimetric segmentation of axial T2-FLAIR sequences with MRICron (nitrc.org/projects/mricron/), as reported in details in a previous work [2].

Collateral grading

Collateral cerebral blood flow was independently assessed by two readers (GF and RA) blinded to each other and functional outcomes on DSA according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) collateral scale: grade 0 (no collaterals visible to the ischemic site); grade 1 (slow collaterals to the periphery of the ischemic site with persistence of some of the defect); grade 2 (rapid collaterals to the periphery of the ischemic site with persistence of some of the defect and to only a portion of the ischemic territory); grade 3 (collaterals with slow but complete angiographic blood flow of the ischemic bed by the late venous phase); and grade 4 (Complete and rapid collateral blood flow to the vascular bed in the entire ischemic territory by retrograde perfusion) [22]. For each discrepancy, a pragmatic consensus was established in a third joint reading session. Then, we dichotomized in poor, and good collateral flow for grades 0–2 and 3–4, respectively. Further, ASITN/SIR scores were performed blinded to SVD readings and functional outcomes in distinct reading sessions.

Statistics

Descriptive statistics are presented as absolute number (percentage) for discrete variables and mean (SD) or median [25th–75th percentiles] for continuous variables as appropriate. Chi-square, Fisher exact test, Student's *t*-test, and Mann–Whitney tests were used as appropriate for the univariable analyses, with a p value < 0.05 as the threshold for statistical significance. Variables associated with the collateral cerebral blood flow in univariable analysis ($p \leq 0.1$) were entered into multivariable logistic regression models and then backward elimination was used to remove non-significant variables ($p \geq 0.05$).

Multivariable logistic models were used to determine factors that were independently associated with the dichotomized ASITN/SIR scores, with a prespecified adjustment for SVD score (Model 1). To prevent confounding and moderating from variables associated with SVD burden in

the analysis of the determinants of ASITN/SIR scores, we constructed a second multivariable model that incorporated the determinants of SVD (Model 2). Variables explained by poor collaterals as per current knowledge (NIHSS, Infarct volume) were not included in the multivariable models investigating the determinants of collateral status, so as not to create a circular argument. In the multivariable models, SVD score was analyzed both as an ordinal 0–3 variable, and as a continuous variable.

In sensitivity analyses, we tested the association between each score element, as well as crude SVD markers (lacunes, microbleeds, and Fazekas score of WMH) and the ASITN/SIR score. All analyses were done using JMP Pro 14 (SAS Institute Inc. 2015. JMP® Pro 14. Cary, NC: SAS Institute Inc) software. The inter-rater agreement for ASITN/SIR and SVD ratings was evaluated using the Cohen-Kappa [23].

This report was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [24].

Data availability statement

Data from this cohort shall be made available upon reasonable request by a qualified investigator to the corresponding author and after clearance by the local ethics committee.

Results

Patients selection and study population

Amongst 559 patients treated with MT in the preliminary pooled sample with pre-treatment MRI available for review, 312 (79 in the THRACE trial, 96 in center 1, and 137 in center 2) were included (mean age 67.8 ± SD 14.9; 53.2% males). See flowchart in Fig. 1 for detailed patients' sampling. When compared with included subjects, excluded patients had higher DWI-ASPECTs (7.1 ± 2 vs, 6.6 ± 2; $p < 0.001$), lower NIHSS scores (15.1 ± 4 vs 16.0 ± 6; $p < 0.001$) and higher blood glucose levels ($p = 0.006$). They did not differ otherwise for baseline characteristics (See Supplemental Table I for details).

Clinical and imaging characteristics as well as procedural and outcome data of included patients are stratified by collateral status and detailed in Table 1.

In the study sample, 105 patients (33.6%) showed good collaterals and 149 (47.8%) achieved a favorable functional outcome. Patients with poor collaterals ($n = 207$, 66.4%) were more often male (57.5% vs 44.8%; $p = 0.041$), had higher NIHSS scores (16.7 ± 7.7 vs 14.6 ± 6.3; $p < 0.001$) and lower ASPECT scores (7 [5–8] vs 8 [6–9]; $p < 0.001$) and did not differ otherwise.

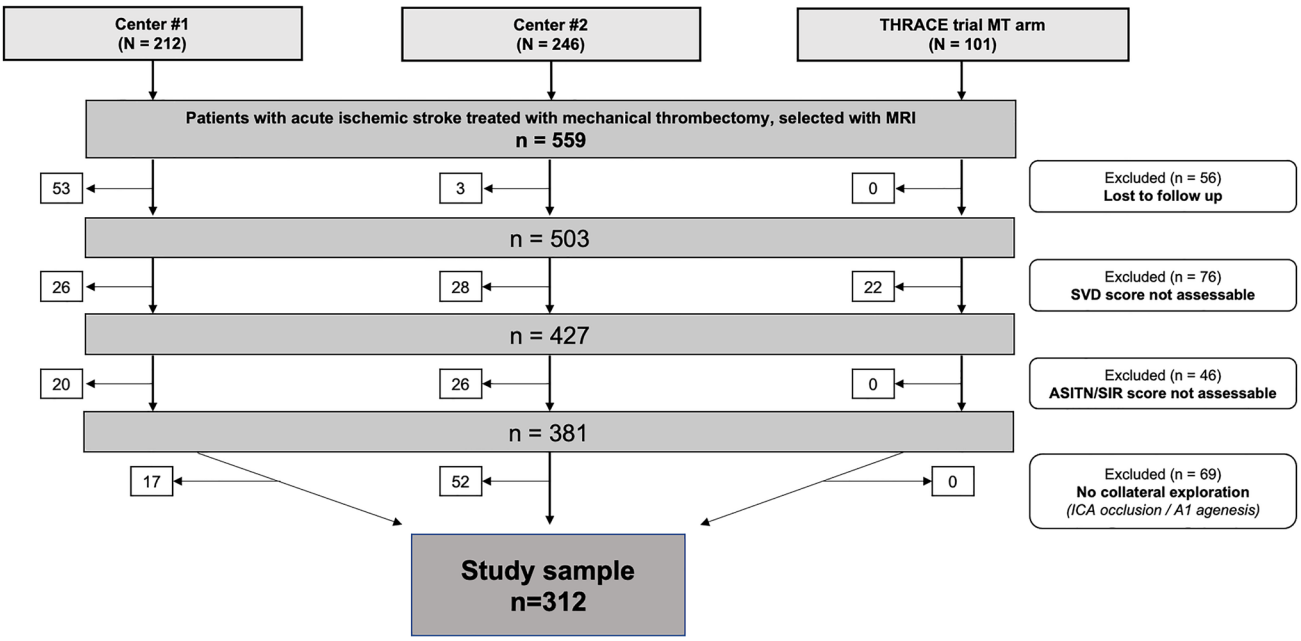

Fig. 1 Flowchart of patient selection. *ICA* Internal carotid artery

Table 1 Baseline and outcome characteristics of included patients

Variables	All patients ($n=312$)	Poor collaterals ($n=207$)	Good collaterals ($n=105$)	p value
Age (years)	67.8 ± 14.92	67.8 ± 14.44	67.9 ± 15.9	0.53
Male sex	166 (53.2%)	119 (57.5%)	47 (44.8%)	0.041
NIHSS	16.0 ± 6.0	16.68 ± 5.7	14.63 ± 6.3	< 0.001
Hypertension	169 (54.2%)	116 (56.0%)	53 (50.5%)	0.35
Diabetes mellitus	36 (11.5%)	22 (10.6%)	14 (13.3%)	0.60
Current smoking	89 (28.5%)	56 (27.05%)	33 (31.4%)	0.69
Dyslipidemia	117 (37.5%)	77 (37.2%)	40 (38.1%)	0.96
Blood glucose level, g/L	1.27 ± 0.43	1.27 ± 0.45	1.27 ± 0.4	0.46
DWI-ASPECT score	7 [5–8]	7 [5–8]	8 [6–9]	< 0.001
M1 Location	270 (86.5%)	175 (84.5%)	95 (90.5%)	0.34
ICA Location	37 (11.9%)	28 (13.5%)	9 (8.6%)	0.34
Total SVD score	0 [0–1]	0 [0–1]	0 [0–1]	0.53
Onset to groin (hours)	3.74 ± 1.15	3.68 ± 1.14	3.87 ± 1.16	0.92
IV tPA prior to MT	234 (75%)	154 (74.0%)	80 (76.2%)	0.78
Onset to groin (hours)	3.74 ± 1.15	3.68 ± 1.14	3.87 ± 1.16	0.92
Revascularization*	250 (80.1%)	171 (82.6%)	79 (75.2%)	0.135
Symptomatic ICH	16/305 (5.25%)	13/204 (6.4%)	3/101 (3.0%)	0.30
Unfavorable outcome	163 (52.2%)	107 (51.7%)	56 (53.3%)	0.81

Variables are displayed as absolute number (percentage of column total), mean ± SD or median [25th–75th percentiles] as appropriate

ASPECT Alberta Stroke Program Early CT, *DWI* diffusion-weighted imaging, *ECASS II* European Cooperative Acute Stroke Study 2, *ICA* Internal carotid artery, *IV* intravenous, *M1* first segment of the middle cerebral artery, *NIHSS* NIH Stroke Scale, *ICH* intracerebral hemorrhage, *tPA* tissue plasminogen activator

*Revascularization, defined as TICI2B/3 after mechanical thrombectomy

Factors associated with SVD burden

A total of 133 patients (42.6%) in the study sample demonstrated any degree of SVD burden. When comparing with patients with no SVD, those with any SVD were older (73.7 years old ± 12.5 vs 63.6 ± 15.1; $p<0.001$), more frequently females ($p=0.029$), with more frequent hypertension ($p<0.001$) and received less frequently tPA before MT ($p=0.001$). See Supplemental Table II for details.

In univariable analysis, a higher SVD score was associated with increasing age (Estimate − 0.052; Std Error 0.009, $p<0.001$), hypertension ($p<0.001$), lower ASITN-SIR score (Estimate − 0.100; $p=0.01$), but not with current smoking ($p=0.579$), Male sex ($p=0.144$), Dyslipidemia ($p=0.747$), or Diabetes ($p=0.980$).

Factors associated with collaterals adequacy

The inter-rater agreement for ASITN/SIR dichotomized (Poor versus Good) score was 0.56, corresponding to a moderate agreement, as in previous agreement studies [25]. In univariable analyses, a lower ASITN/SIR score was associated with the presence of lacune(s) ($p=0.002$), female sex ($p=0.034$); higher SVD scores (β estimate − 0.36; $p<0.007$), shorter delays between symptoms and groin puncture (β estimate 0.23; $p=0.01$), and a higher NIHSS (β estimate − 0.06; $p<0.001$).

In multivariable analysis, the total SVD score remained associated independently with lower ASITN/SIR scores (aOR 0.69; 95%CI [0.52–0.89]; see model 1 in Table 2)

Table 2 Multivariable model for ASITN/SIR scores

Variable	aOR [95% CI]	p value
Model 1		
Total SVD Score	0.69 [0.52–0.89]	0.005
Male sex	0.87 [0.71–1.07]	0.145
Model 2		
Total SVD Score	0.66 [0.5–0.88]	0.004
Male sex	0.77 [0.65–0.99]	0.043
Age (years)	1.01 [0.99–1.03]	0.30
Hypertension	*1.29 [0.55–3.14]*	*0.60*
Diabetes Mellitus	*3.47 [0.84–14.64]*	*0.11*
Dyslipidemia	*1.56 [0.93–2.64]*	*0.09*
Current smoke	*1.36 [0.75–2.52]*	*0.28*

Ordinal regression of ASITN/SIR Scores. All variables in the model are displayed

SVD cerebral small vessel disease

and remained so after adjustment for SVD risk factors (See model 2 in Table 2, aOR 0.66; 95%CI [0.5–0.88]).

Figure 2 is a visual representation of the predicted ASITN/SIR score plotted against increasing SVD scores.

Exploratory analyses of individual SVD markers and collateral status

In multivariable analysis, with each feature of the SVD score analyzed as a separate independent variable, the presence of lacunes was the only variable independently associated with poor collateral status (aOR 0.40, 95% CI 0.20–0.79, $p=0.007$; AIC: 877; Supplemental Table III).Further, when using crude SVD markers, the number of lacunes was associated with poorer collaterals (aOR 0.56; 95%CI [0.38–0.80], $p=0.002$), see supplemental Tables IV and V.

When considering WMH volumes, instead of Fazekas scale, we found greater WMH volumes to be associated with lower ASITN/SIR Scores ($p=0.01$), with a stable association after adjustment for sex, and hypertension (aOR 0.40 95%CI, [0.23–0.70], $p=0.020$).

Discussion

In this multicenter study, we found that SVD assessed on the baseline MRI obtained during emergency evaluation in patient undergoing MT for AIS due to LVO was associated with poor leptomeningeal collaterals recruitment. These data add to the evidence of a relationship between chronic cerebral microvascular impairment and altered acute macrovascular response to cerebral ischemia in patients with emergent LVO eligible for MT and may suggest a widespread alteration across the cerebral arterial supply with potential implications in prognostication.

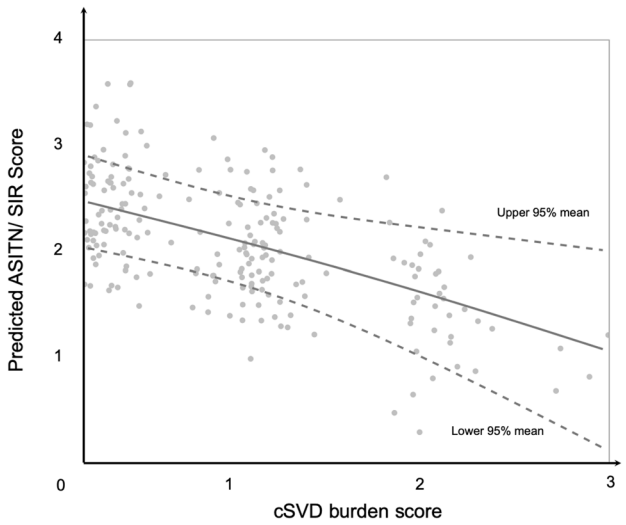

Fig. 2 ASITN/SIR score predicted values per increasing SVD in the study sample. *p* values are derived from a log-linear model

The baseline clinical imaging determinants of robust collateral response in the context of emergent LVO have been studied extensively [9, 10, 26, 27], yet with still many aspects to be clarified. Among these biomarkers, the presence of a deep infarct pattern (versus large cortical patterns) [28], a lower diastolic blood pressure, both male [29] and female [9, 10] sex, and higher baseline glucose levels [28, 29] have been shown to be associated with poorer collateral flow. The assessment of the relationship between SVD and leptomeningeal collaterals has recently been made possible in larger and more homogenous patients pools with the advent of MT for AIS-LVO and the possibility to visualize collateral circulation during the initial angiographic runs of the intervention. As more data become available, the impact of pre-existing SVD on the vasodilatory potential of collaterals to effectively ensure retrograde flow to the hypoperfused brain tissue becomes more robustly described. The question of the pathophysiological processes underlying the association though remain unclearly solved. Previous work in animals models [8, 30], demonstrated the considerable impact of hypertension in decreasing the ability of pial anastomoses to maintain adequate blood flow to ischemic brain tissue. This association has been hypothesized to derive mostly from a structural decrease in leptomeningeal anastomoses lumens in hypertensive subjects, but also to an increased vasoreactivity to elevated pressure in chronically hypertensive rats contributing to the increased perfusion deficit in the at-risk tissue [31]. This may suggest that there is a shift in the autoregulatory curve to higher blood pressure in hypertension, with a shift in the lower threshold which is detrimental in acute hypoperfusion This is supported by the demonstration of the reduction in longitudinal development of leptomeningeal collaterals in murine models with chronic hypertension after common carotid occlusion [32], an effect that was not observed under antihypertensive treatment, suggesting complex pathophysiological pathways linking SVD due to hypertension and reduced collaterals observed in human patients.

Of important note, we found WMH volumes to be associated with lower ASITN/SIR scores, further reinforcing the above assertions. While this sensitivity analysis was not preplanned, and should be considered hypothesis-generating, there have been previous reports showing the association between SVD-related white matter damage and reduced collaterals in ischemic conditions in humans [10, 11, 27]. Giurgiutiu and colleagues, in a preliminary analysis in 73 subjects [11], found WMH volumes to be associated with poorer collaterals, and Lin et al. [10] demonstrated a dose-dependent relation between Fazekas scale scores and collaterals' adequacy. Our results, although hypothesis generating, corroborate these results found in distinct settings. A recent

report by Derraz and colleagues did not show such an association in a sample of 302 patients that demonstrated a very low mean WMH volume, potentially limiting the statistical power to detect an existing association [13].

There has not been to our knowledge a previous description of an association between lacunes and decreased collateral adequacy in the context of AIS-LVO, as was found in our sample in explanatory analyses. Yet, the role of lacunes as a biomarker for cerebral microvascular pathology in the presence of vascular risk factors has been extensively studied [1]. Lacunes are indeed a common feature of hypertensive SVD, along with CMB and white matter lesions, and their presence has been indirectly linked to greater infarct volumes in rat models [33]. The association found in our sample substantiates further the potential role of pre-existing SVD burden in impairing the leptomeningeal anastomoses' response to ischemia. Pathophysiologically, this distinct association may be explained by the fact that lacunes are a marker of advanced occlusive lypohyalinosis in perforating arterioles as well as endothelial dysfunction, more advanced than in patients with only WMH [34]. Yet this argument remains speculative, and the nature of this association should be confirmed and further studied in pre-clinical as well as larger samples.

Our findings add to the body of evidence that SVD biomarkers as assessed on pretherapeutic MRI in ischemic stroke patients could act as a non-invasive biomarker of poor collateral blood flow recruitment. However to date, the association between collaterals and SVD in patients with AIS treated with MT has been reported with conflicting results [9–11, 27, 35]. Recently, both Eker et al. [9] and Lin et al. [10] studied whether the severity of SVD burden, assessed on MRI, may be associated with inadequate recruitment of the collateral supply in patients treated by MT, and reported different results despite similar inclusion criteria. In the study by Eker et al. the collaterals status was not affected by the SVD burden whereas observed in the work by Lin et al. SVD appeared to double the likelihood of observing poor collaterals. The discrepancy in the authors' findings triggered additional debate [36, 37], in which the authors agreed that the main biases may have emerged from the use of single center data, with possible selection, ethnic and risk factor prevalence specificities. Our study does not share this limitation, as the analyzed data derive from a largely multicentric randomized controlled trial, as well as two additional large volume academic centers' cohorts. Several other factors may explain the differences between the present report and previous works. First, the methods for leptomeningeal collaterals' assessment diverged between studies. Lin et al., [10] as well as Mark et al. [35], evaluated the collateral flow on single phase computed tomographic angiography, while Eker et al., [9] and our group used the ASITN/SIR score. Second, the majority of our patients were assessed as having poor collaterals (66.4%) unlike previous works (in which poor collaterals ranged from 43 to 46%) [9–11, 35].

Third, the methods for SVD assessment diverged in that we did not include the rating of perivascular spaces enlargement due to the unavailability of T2-weighted image, recommended in the STRIVE criteria [38]. As Eker et al. acknowledged, rating enlarged perivascular spaces on a FLAIR sequence, likely led to an underestimation of this element of the SVD score, at the risk of negating or creating a spurious association, even if we acknowledge that the truncated total SVD burden without rating perivascular spaces enlargement is one of the major limits of our study. Fourth, our patients were included between January 1st 2015 and January 1st 2020, after the publication of MT related guidelines. This may in turn have homogenized our study sample to better reflect real-world patients' population treated with MT, unlike previous reports where inclusion period spanned several years before 2015, at a time when MT indications were not standardized, with an increased risk of selection biases. Finally, we made every effort to prevent confounding in our multivariable models, by conducting sensitivity analyses, and analytically controlling for the determinants of SVD in the models investigating the determinants of ASITN/SIR. As collateral recruitment is known to be a dynamic process, it should be emphasized that its association with SVD burden remained after adjustment for delay since onset.

We acknowledge the following limitations. First, our results derive from multiple cohorts, including the MT arm of the THRACE trial and was designed retrospectively, with an inherent yet undemonstrated cohort effect. Procedural and follow-up imaging as well as treatment delays were prospectively recorded at each center, but no core lab reviewed imaging data, beyond baseline MR findings and collaterals scores. Further, there was a low agreement for ASITN/SIR scores, a known limitation of this scale [25]. Last, we acknowledge an uncontrolled potential selection bias in that a non-negligible proportion of the initial sample was not included for analysis, and therefore limits the generalizability of our study since the excluded patients were less severely affected by stroke at admission.

Strengths include a large sample of well phenotyped patients with homogenous and current indication for MT, converging and stable statistical analyses and novelty in this subset of AIS patients. Another key strength of this cohort is that it is derived from centers using MRI as first line imaging selection tool for MT, limiting selection biases for this study.

Conclusion

Our study provides some evidence that increased SVD burden is associated with poor leptomeningeal collaterals in patients with AIS due to LVO treated with MT, providing

further insight into the pathophysiology of collaterals recruitment, on the way to collaterals-targeted therapeutic approaches.

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Declarations

Conflicts of interest The authors declare that they have no conflict of interest/competing interests.

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