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ARTICLE

Early hemodynamic predictors of good outcome and reperfusion injury after endovascular treatment

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Abstract

Objective

To find early hemodynamic predictors of outcome and reperfusion injury in patients with acute ischemic stroke due to anterior circulation large artery occlusion (LAO) after endovascular treatment (EVT).

Methods

Serial transcranial color-coded sonography examinations assessed the vessel status and cerebral hemodynamics of 185 (109 [58.9%] men, mean age 69.5 ± 12.3 years) consecutive patients with acute anterior circulation LAO soon after, at 48 hours after, and 1 week after EVT.

Results

Successful recanalization (odds ratio [OR] 0.25, 95% confidence interval [CI] 0.11–0.61) and normal peak systolic velocity (PSV) ratio (PSV of recanalized middle cerebral artery/PSV of contralateral middle cerebral artery) at 48 hours (OR 0.22, 95% CI 0.15–0.64) and after 1 week (OR 0.11, 95% CI 0.07–0.31) from EVT were independent predictors of good outcome at 3 months. Thrombectomy failure (OR 10.22, 95% CI 1.47–45.53) and pathologic PSV ratio at 1 week from EVT (OR 15.23, 95% CI 4.54–46.72) were associated with a worse 90-day outcome. Patients who subsequently developed postinterventional intracranial hemorrhage (ICH) showed a higher mean PSV ratio (3.5 ± 0.2 vs 2.4 ± 0.1, $p < 0.0001$) soon after successful recanalization. In multivariate analysis, early PSV ratio was independently associated with postprocedural ICH (OR 8.474, 95% CI 3.066–45.122, $p < 0.01$]. At 1 week from EVT, 15 of 21 (71.4%) patients with ICH who resumed normal PSV values had a better 90-day outcome (modified Rankin Scale score 0–2: 40% vs 0%).

Conclusion

Post-EVT ultrasound monitoring of stroke patients might be an effective bedside method for assessing treatment efficacy, shedding light on outcome variability and identifying patients at increased risk of ICH.

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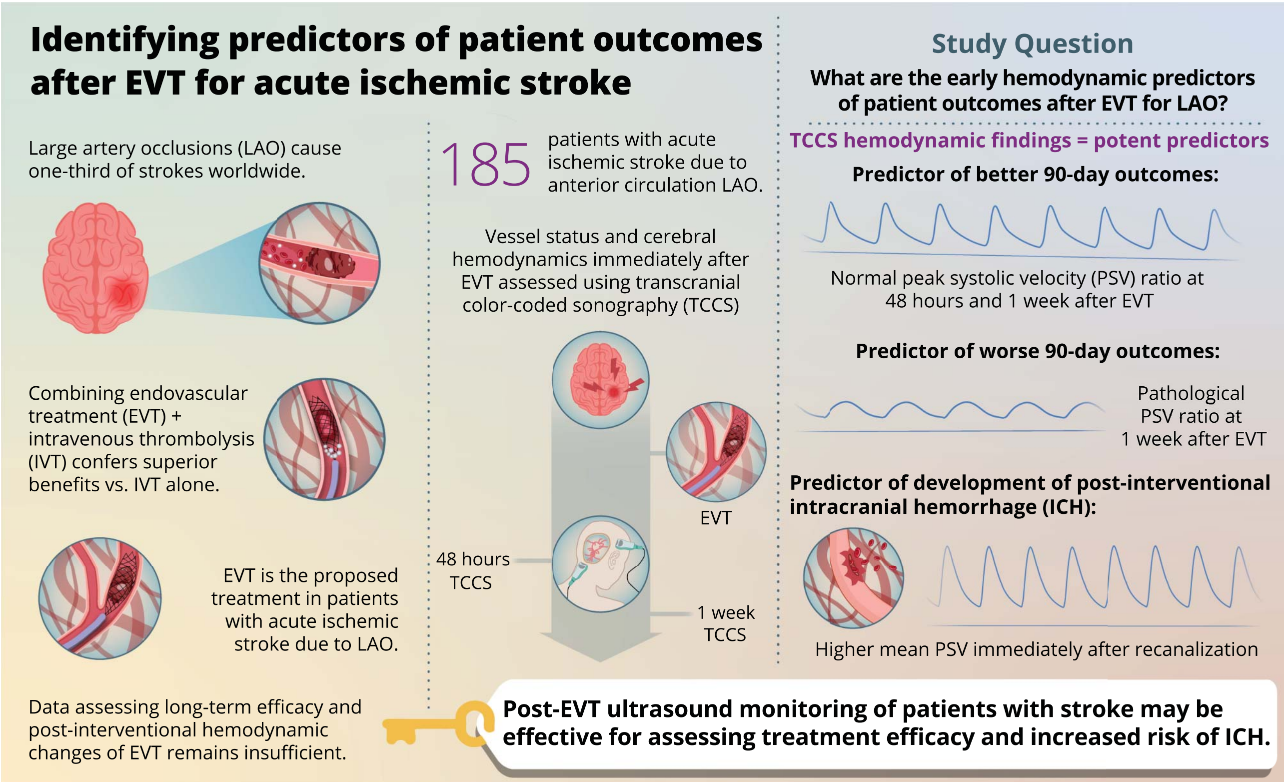
Glossary

BFV = blood flow velocity; **CI** = confidence interval; **CTA** = CT angiography; **CTTS** = transcranial color-coded sonography; **DSA** = digital subtraction angiography; **EDV** = end-diastolic velocity; **EVT** = endovascular treatment; **ICA** = internal carotid artery; **ICH** = intracranial hemorrhage; **IVT** = IV thrombolysis; **LAO** = large artery occlusion; **MCA** = middle cerebral artery; **mRS** = modified Rankin Scale; **mTICI** = modified Treatment in Cerebral Ischaemia; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PSV** = peak systolic velocity; **TCCS** = transcranial color-coded sonography; **TCD** = transcranial Doppler.



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Neurology

Nearly a third of strokes worldwide are anterior circulation acute ischemic strokes due to large artery occlusion (LAO), and they are characterized by a more severe clinical presentation and a worse outcome.[1,2] Five large interventional randomized trials[3–7] have shown a superior benefit when endovascular treatment (EVT) is combined with IV thrombolysis (IVT) vs IVT alone, and EVT has been proposed as the treatment of choice in patients with acute ischemic stroke due to LAO.[8,9] Digital subtraction angiography (DSA) remains the gold standard for the diagnosis of LAO, but because it is expensive and invasive, it is not commonly used as a follow-up method. On the other hand, transcranial color-coded sonography (TCCS) is a noninvasive bedside tool that provides real-time dynamic morphologic information, along with unique evaluation of hemodynamic changes in different clinical settings (e.g., angiographic suite, recovery room, intensive care unit, stroke unit) and treatment stages, providing complementary information to radiologic data.[10] Therefore, TCCS might be an effective method for assessing the efficacy of EVT because this procedure does not guarantee a successful recanalization (defined as modified Treatment in Cerebral Ischaemia [mTICI] score 2b–3) in all cases,[11] and some patients do not improve despite adequate treatment, while others recover even if partially recanalized. Surprisingly, insufficient research is available on postinterventional hemodynamic changes. For this reason, we conducted a TCCS study to see whether blood flow velocities (BFVs) could explain the clinical variability observed after EVT.

Methods

Between January 1, 2015, and December 31, 2017, we recruited all first-ever stroke patients undergoing EVT due to acute LAO of the anterior circulation (intracranial internal carotid artery [ICA] or middle cerebral artery [MCA; M1 segment and/or proximal M2 segment]). Patient details were entered into a computerized database, recording their demographics, vascular risk factors, medication use, and routine blood tests. On admission, neurologic syndrome was assessed with the NIH Stroke Scale (NIHSS). MRI or repeat

CT defined territorial distribution, while diagnosis was made by TCCS[12] and confirmed by CT angiography (CTA) or magnetic resonance angiography, if CTA was contraindicated, and by DSA as patients underwent EVT. Management of vital parameters, correction of modifiable risk factors, and administration of antithrombotic drugs followed current guidelines.[13]

Mechanical revascularization protocol

EVT was performed by 2 experienced neuroradiologists (G.C. and F.C.) within 6 hours from symptom onset, according to the following criteria: Alberta Stroke Program Early CT score >5, anterior circulation LAO on CTA, and NIHSS score >6 or evolution of stroke symptoms. The procedure was performed under general anesthesia or conscious sedation, depending on clinical neurologic conditions. The American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology system was used for grading collaterals.[14]

An 8F guiding catheter (Neuron Max, 2.24 mm, Penumbra, Alameda, CA; Destination 6F Terumo, Elkton, MD) was placed in the cervical ICA, and a distal aspiration catheter (Catalyst 6F, Strycker, Freemont, CA; 5Max, Penumbra; Sofia Plus Microvention 2.1 mm, Tustin, CA) was forwarded to the site of vessel occlusion A first attempt of thrombus aspiration was made, and in case of failure, a stent retriever thrombectomy was performed. Successful recanalization was defined when an mTICI score of 2b or 3[15] was documented by DSA.

To exclude intracranial bleeding, a CT was performed at the end of EVT and repeated 4 to 6 hours later. DSA was repeated 24 hours after the end of the procedure to verify the patency of the treated vessel.

Ultrasound insonation protocol

Stroke neurologists experienced in neurovascular ultrasound (F.V., F.F., C.B.) performed a clinically oriented, fast-track ultrasound assessment.[16] Cervical vessels were examined with high-resolution color-coded duplex sonography scanners with a high-frequency (5–10 MHz) linear probe. In particular, carotid plaques were rapidly recorded, and stenoses were graded according to validated criteria.[17] A low-frequency (1–3 MHz) phased-array TCCS probe, adjusted for the analysis of middle-high velocity signals, was used to examine intracranial arteries following a validated protocol with reference values of normal intracranial BFV ranges.[18] Hemodynamic data (flow direction, peak systolic velocity [PSV], end-diastolic velocity [EDV]) were recorded from the MCA and anterior cerebral artery visualized in the mesencephalic plane and from the carotid syphon and the terminal ICA visualized in the anterior coronal plane. The highest BFV value was registered without correction of the angle of insonation, except when a >1.5-cm vessel segment was detected. Then, the pulsatility index, an indicator of downstream intracranial arterial resistance, was calculated as follows: PSV − EDV/mean flow velocity. The diagnosis of cerebral artery stenosis was based on the following criteria: aliasing phenomenon visible on TCCS in a short segment of the vessel, increased flow velocities in the area of the stenosis, and flow disturbances upstream and downstream from the lesion. In particular, previously validated criteria were used to detect >50% intracranial stenosis and occlusion.[12] Whenever there was an insufficient or absent temporal bone window or a suspicion about an anterior circulation LAO, an ultrasound contrast agent (SonoVue, Bracco, Milan, Italy) was administered.[19]

All patients were re-evaluated by TCCS immediately after in the angiographic suite, stroke unit, or neurointensive care unit. The treated vessel was examined along with the contralateral homologous artery following a validated protocol.[10] A mean PSV ratio (PSV of recanalized MCA/PSV of contralateral MCA) was calculated to account for interindividual variability of absolute PSV values and to exclude factors that might affect PSV (e.g., heart rate, blood pressure, hematocrit). Moreover, to avoid any influence on intracranial velocity measurements, patients with ≥70% stenosis or occlusion of the extracranial ICA or ≥50% stenosis of the contralateral MCA were also excluded.

Follow-up

Brain MRI/CT was performed in all patients 24 hours after admission and at hospital discharge. In the event of a neurologic deterioration (NIHSS score increase of >2 points in 1 category or >4 points in total), immediate CT/MRI was obtained to exclude stroke recurrence or intracranial hemorrhage (ICH). ICH was classified as hemorrhagic transformation, parenchymal hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage.[20] Neurologic syndrome and functional status were assessed with the NIHSS and modified Rankin Scale (mRS), respectively, at discharge and at 1, 3, and 6 months. TCCS assessed vessel patency and cerebral hemodynamics at 48 hours, 1 week, and 1, 6, and 12 months; in case of restenosis, the diagnosis was confirmed by CTA/magnetic resonance angiography. With regard to the study protocol, no changes were made over the study period. In particular, MRI was not used to select patients for EVT.

Statistical analysis

SPSS statistical software (SPSS version 17.0 for Windows, SPSS Inc, Chicago, IL) was used for all statistical analyses.

Patient demographic and clinical characteristics were recorded as mean ± SD, as median and range, or as percentage. Categorization of continuous variables was performed to obtain clinically relevant groups (e.g., mRS score 0–2 or 3–6). Student t test or analysis of variance was used to compare mean values, while frequencies and categorical data were examined with the χ^2 or Fisher exact test. To identify early predictors of clinical outcome and ICH occurrence, multiple logistic regression analyses were performed, calculating the corresponding odds ratios (ORs) and 95% confidence intervals (CIs). For all analyses, values of $p < 0.05$ were considered statistically significant.

Table 1 Demographic and clinical characteristics of ischemic stroke patients with LAO of the anterior circulation before EVT

	Total (n = 185)
Mean ± SD age, y	69.5 (±12.3)
Men, n (%)	109 (58.9)
Hypertension, n (%)	136 (73.5)
Diabetes mellitus, n (%)	28 (15.1)
Hypercholesterolemia, n (%)	36 (19.4)
Smoking habit, n (%)	48 (25.9)
Coronary syndromes, n (%)	32 (17.3)
Atrial fibrillation, n (%)	56 (30.3)
Antiplatelet therapy at admission, n (%)	88 (47.6)
Anticoagulant therapy at admission, n (%)	23 (12.4)
NIHSS score, median (range)	18 (5–26)
mRS score, median (range)	0 (0–4)
MCA occlusion	150 (81.1)
ICA + MCA occlusion	19 (10.3)
ICA occlusion	16 (8.6)
Bridging thrombolysis	110 (59.5)

Abbreviations: EVT = endovascular treatment; ICA = internal carotid artery; LAO = large artery occlusion; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.

Standard protocol approval and patient consent

The study was approved by our local ethics committee, and informed consent was obtained for all patients.

Table 2 BFV changes in ischemic stroke patients with LAO of the anterior circulation after successful recanalization (mTICI 2b-3)

Time	Mean PSV, cm/s	Mean PSV ratio[a]
After EVT (same day of treatment)	278.9 ± 29.2	2.6 ± 0.2
After EVT (48 h)	212.0 ± 22.7[b]	1.9 ± 0.1[b]
After EVT (1 wk)	114.5 ± 12.4[b,c]	1.2 ± 0.1[b,c]
After EVT (1 mo)	110.7 ± 15.4	1.1 ± 0.1
After EVT (1 y)	108.6 ± 12.6	1.1 ± 0.1

Abbreviations: BFV = blood flow velocity; EVT = endovascular treatment; LAO = large artery occlusion; mTICI = modified Treatment in Cerebral Ischaemia; PSV = peak systolic velocity.
[a] Mean PSV ratio = PSV recanalized middle cerebral artery/contralateral middle cerebral artery.
[b] Compared with post-EVT same-day values, $p < 0.05$.
[c] Compared with post-EVT 48-hour values, $p < 0.05$.

Data availability

Any data not published within the article are available for sharing, and anonymized data will be shared by request from any qualified investigator.

Results

During the study period, 197 consecutive patients were hospitalized with their first-ever anterior circulation acute ischemic stroke due to LAO. Twelve (6.1%) were excluded due to a ≥50% contralateral MCA stenosis (n = 3), a severe (≥70%) extracranial ICA stenosis (n = 5), or an extracranial ICA occlusion (n = 4). Therefore, 185 patients (109 [58.9%] men, mean age 69.5 ± 12.3 years) were recruited into the study: 150 (81.1%) with an MCA occlusion, 16 (8.6%) with an intracranial ICA occlusion, and 19 (10.3%) with a combined intracranial ICA and MCA occlusion. The median NIHSS score at admission was 18 (range 5–26). Before EVT, 110 (59.5%) received IVT. A complete summary of demographic and clinical characteristics of the study population is reported in table 1.

A successful recanalization (mTICI grades 2b and 3) was obtained in 146 patients (78.9%); a partial recanalization (mTICI grade 2a) was obtained in 27 patients (14.6%); and minimal/no reperfusion (mTICI grades 1 and 0) was obtained in 12 cases (6.5%).

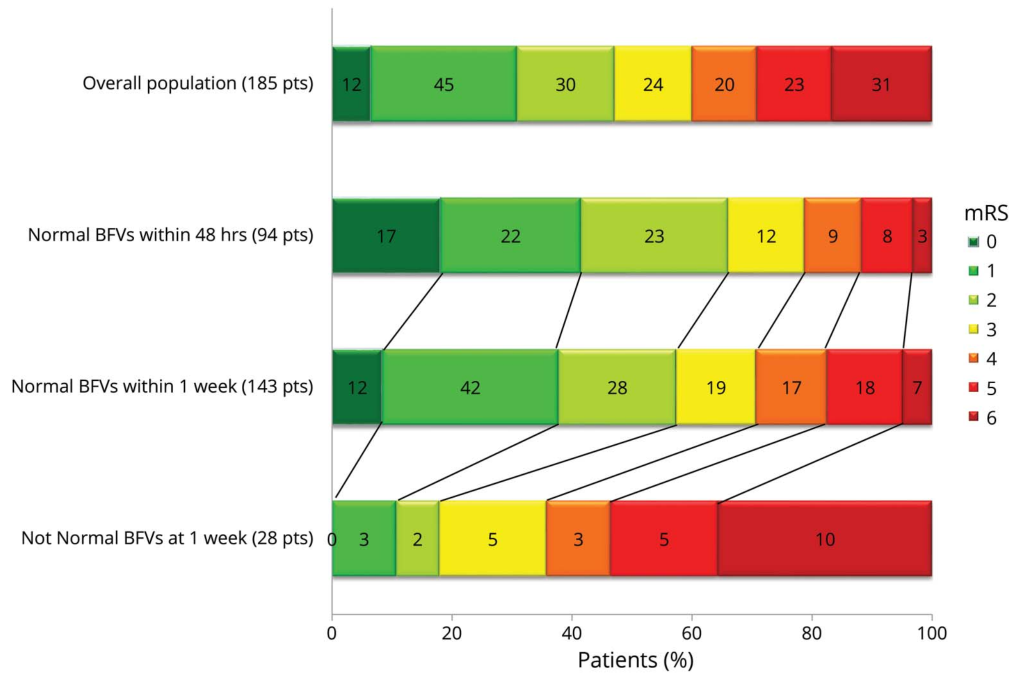
The first postprocedural TCCS was performed immediately after EVT; SonoVue was administered to 22 (11.9%) patients with an inadequate temporal bone window. No patient showed normal BFV in the treated vessel; in fact, the mean PSV ratio was 2.6 ± 0.2.

At 1 week from EVT, 14 (7.6%) patients had died (7 [58.3%] with mTICI grade 0–1, 2 [7.4%] with mTICI grade 2a, 5 [3.4%] with mTICI grade 2b–3), so 171 patients were reassessed by TCCS. BFV at the site of the recanalized arterial segment was decreased ($p < 0.05$) compared with immediate postoperative values. In patients with mTICI grade 2b to 3, the mean PSV ratio was 1.2 ± 0.1. Thereafter, no hemodynamic differences were observed at the 1-month, 6-month, and 1-year follow-up visits (table 2).

Taking all 171 survivors together, normal BFV values were more common after successful recanalization ($p < 0.001$). Notably, a normal PSV ratio was observed in 135 of 141 (95.7%) patients with mTICI grade 2b to 3 but also in 8 of 25 (32%) patients with mTICI grade 2a. No patients with mTICI grade 0 to 1 (0 of 5) had a normal PSV ratio.

Patients with successful EVT (mTICI grade 2b–3) and early (<48 hours) normalization of BFV (94 of 146, 64.4%) had the best prognosis (mRS score 0–2: 65.9%), followed by patients with normal velocities at 1 week, even if their initial mTICI grade was 2a (mRS score 0–2: 57.4%). Patients with pathologic BFV at 1 week had the

Figure Ninety-day outcome segmented by time to normalization of BFVs



BFV = blood flow velocity; mRS = modified Rankin Scale; pts = patients.

worst clinical outcome (mRS score 0–2: 17.8%; mRS score 3–6: 82.2%) (figure).

In univariate analysis, the following variables were identified as predictors of a good outcome at 3 months: younger age, absence of arterial hypertension, low baseline NIHSS score, MCA occlusion (vs ICA or tandem occlusion), bridging thrombolysis, successful revascularization, shorter time to revascularization, and normal PSV ratio at 48 hours and after 1 week from EVT. In multivariate analysis, mTICI grade 2b to 3 (OR 0.25, 95% CI 0.11–0.61) and normal PSV ratio at 48 hours (OR 0.22, 95% CI 0.15–0.64) and after 1 week (OR 0.11, 95% CI 0.07–0.31) from EVT were independent predictors of good outcome at 3 months. On the other hand, mTICI grade 0 to 1 (OR 10.22, 95% CI 1.47–45.53) and pathologic PSV ratio at 1 week from EVT (OR 15.23, 95% CI 4.54–46.72) were associated with a worse 90-day outcome (table 3).

Postinterventional brain CT examinations performed at 19 ± 5.4 hours showed an ICH in 21 of 146 (14.4%) patients with successful EVT (mTICI grade 2b–3: 10 [6.8%] were HI1, 6 [4.1%] HI2, 2 [1.4%] PH1, 1 [0.7%] PH2, 2 [1.4%] PHr1). ICH was symptomatic in 4 (2.8%) patients. These patients had arterial hypertension more often (20 of 21 [95.2%] vs 86 of 125 [68.8%], $p < 0.01$), more severe stroke symptoms (18 vs 16, $p = 0.01$), and a worse clinical outcome compared to patients without ICH (table 4). At the first post-EVT ultrasound evaluation, patients who subsequently would develop postinterventional ICH already showed a higher mean PSV ratio (3.5 ± 0.2 vs 2.4 ± 0.1, $p < 0.0001$) than those who would not develop ICH. At the 48-hour TCCS, they had persistently higher mean PSV ratio (2.4 ± 0.2 vs 1.9 ± 0.1, $p < 0.0001$) compared to patients without ICH. No difference was observed in the pulsatility index between patients with ICH and without ICH: 1.13 ± 0.32 vs 1.11 ± 0.31 (table 5). At 1 week from EVT, those 15 of 21 (71.4%) patients with ICH who resumed normal PSV values had a better 90-day outcome compared to those with abnormal PSV (mRS score 0 to 2: 6 vs 0; mRS score 3: 7 vs 0; mRS score 4: 2 vs 1; mRS score 5: 0 vs 2; mRS score 6: 0 vs 3). Arterial hypertension, NIHSS score at admission, and higher PSV ratio soon after EVT were associated with post-EVT ICH. However, on a multivariate analysis, only higher PSV ratio soon after EVT remained independently associated with postinterventional ICH (OR 8.474, 95% CI 3.066–45.122, $p < 0.01$). Concerning anesthetic management, 112 patients (60.5%) underwent EVT with conscious sedation and 73 patients (39.5%) with general anesthesia. The use of general anesthesia did not differ in patients with mTICI grade 2b to 3 (40.4%, $p = 0.71$), postinterventional ICH (57.1%, $p = 0.09$), and mRS score 0 to 2 at 3 months (39.1%, $p = 1.00$).

Discussion

This ultrasound post-EVT study on acute ischemic stroke investigated the time course of BFVs at the site of the recanalized artery, showing a strikingly variable time for

Table 3 Demographic, clinical, radiologic, and ultrasound characteristics of ischemic stroke patients with LAO of the anterior circulation after EVT vs outcome at 3 months

	Total patients (n = 185)	mRS score 0–2 (n = 87)	mRS score 3–6 (n = 98)	*p* Value, univariate analysis	*p* Value; OR (95% CI), multivariate analysis
Age, mean ± SD, y	69.5 ± 12.3	67.1 ± 11.4	71.6 ± 13.0	0.01	NS
Male, n (%)	109 (58.9)	52 (59.8)	57 (58.2)	NS	NS
Hypertension, n (%)	136 (73.5)	56 (58.6)	80 (86.7)	0.02	NS
Diabetes mellitus, n (%)	28 (15.1)	13 (14.9)	15 (15.3)	NS	NS
Hypercholesterolemia, n (%)	36 (19.4)	17 (19.5)	19 (19.4)	NS	NS
Smoking, n (%)	48 (25.9)	21 (24.1)	27 (27.6)	NS	NS
Coronary syndromes, n (%)	32 (17.3)	14 (16.1)	18 (18.4)	NS	NS
Atrial fibrillation, n (%)	56 (30.3)	24 (27.6)	32 (32.7)	NS	NS
Antiplatelet therapy, n (%)	88 (47.6)	47 (54.0)	41 (41.8)	NS	NS
Anticoagulant therapy, n (%)	23 (12.4)	11 (12.6)	12 (12.2)	NS	NS
NIHSS score, median (range)	18 (5–26)	14 (5–18)	19 (14–26)	0.0316	NS
Time to revascularization, mean ± SD, min	236 ± 52	228 ± 48	243 ± 53	0.0461	NS
ASITN/SIR score <2, n (%)	88 (47.6)	47 (54.0)	41 (41.8)	NS	NS
EVT for MCA occlusion, n (%)	150 (81.1)	77 (88.5)	73 (74.5)	0.0231	NS
EVT for ICA + MCA occlusion, n (%)	19 (10.3)	4 (9.2)	15 (11.2)	0.0268	NS
EVT for ICA occlusion, n (%)	16 (8.6)	3 (3.4)	13 (13.5)	0.0193	NS
Bridging thrombolysis, n (%)	110 (59.5)	59 (67.8)	51 (52.1)	0.0358	NS
mTICI grade 0–1, n (%)	12 (6.5)	0 (0)	12 (12.2)	0.0004	0.02; 10.22 (1.47–45.53)
mTICI grade 2a, n (%)	27 (14.6)	8 (0.9)	19 (19.4)	NS	NS
mTICI grade 2b–3, n (%)	146 (78.9)	79 (90.1)	67 (68.4)	0.0002	0.02; 0.25 (0.11–0.61)
Normal PSV ratio at 48 h from EVT, n (%)	94/185 (50.8)	62 (71.3)	32 (32.6)	0.0001	0.03; 0.22 (0.15–0.64)
Normal PSV ratio at 1 wk from EVT, n (%)	143/171 (83.6)	82 (94.3)	61 (62.2)	0.0001	0.02; 0.11 (0.07–0.31)
Still not normal PSV ratio at 1 wk from EVT, n (%)	28/171 (16.4)	5 (5.7)	23 (23.5)	0.0008	0.04; 15.23 (4.54–46.72)

Abbreviations: ASITN/SIR = American Society of Intervention and Therapeutic Neuroradiology/Society of Interventional Radiology; EVT = endovascular treatment; ICA = internal carotid artery; LAO = large artery occlusion; MCA = middle cerebral artery; mRS = modified Rankin Scale; mTICI = modified Treatment in Cerebral Infarction; NIHSS = NIH Stroke Scale; NS = nonsignificant; PSV = pulse wave velocity.

intracranial hemodynamic normalization that correlates with prognosis. In particular, early normalization of intracranial hemodynamics is an independent predictor of a good 90-day outcome, while pathologic findings at 1 week from EVT are associated with a worse prognosis. Furthermore, a high PSV ratio seems to be associated with postinterventional ICH and worse outcome at 3 months, while early normalization of regional BFV after endovascular thrombectomy appears to be a predictor of better clinical outcome even in partially recanalized (mTICI grade 2a) patients.

Previous studies have shown that early mechanical thrombectomy in association with IVT is efficient in timely restoration of blood perfusion after major intracranial artery occlusion.[21] Nowadays, EVT is the recommended treatment for acute ischemic stroke patients with LAO, leading to better clinical outcome in terms of residual disability.[22] Poststroke outcome was strictly dependent on the success of the endovascular procedure, with better prognosis being observed in optimal (mTICI grade 3) or suboptimal (mTICI grade 2b) recanalized patients compared to partial (mTICI grade 2a) or no recanalization (mTICI grade 0–1).[23,24] Yet, a considerable number of patients have a poor prognosis, despite angiographically successful recanalization, especially when hemorrhage occurs in the reperfused ischemic brain tissue. Moreover, good clinical outcome might be observed

Table 4 Demographic and clinical characteristics of ischemic stroke patients with LAO of the anterior circulation after successful EVT

	Total patients (n = 146)	No ICH (n = 125)	Post-EVT ICH (n = 21)	*p* Value
Mean age (±SD), y	68.3 ± 11.4	68.1 ± 11.4	69.7 ± 10.2	NS
Men, n (%)	82 (56.2)	70 (56.0)	12 (57.1)	NS
Hypertension, n (%)	106 (72.6)	86 (68.8)	20 (95.2)	0.01
Diabetes mellitus, n (%)	19 (13.0)	16 (12.8)	3 (14.3)	NS
Hypercholesterolemia, n (%)	26 (17.8)	22 (17.6)	4 (19.0)	NS
Smoking habit, n (%)	32 (21.9)	27 (21.6)	5 (23.8)	NS
Coronary syndromes, n (%)	24 (16.4)	20 (16.0)	4 (19.0)	NS
Atrial fibrillation, n (%)	43 (29.4)	36 (28.8)	7 (33.3)	NS
Antiplatelet therapy at admission, n (%)	68 (46.6)	58 (46.4)	10 (47.6)	NS
Anticoagulant therapy at admission, n (%)	13 (8.9)	11 (8.8)	2 (9.5)	NS
NIHSS score, median (range)	16 (5–26)	16 (5–26)	18 (10–23)	0.01
EVT for ICA occlusion, n (%)	13 (8.9)	11 (8.8)	2 (9.5)	NS
EVT for MCA occlusion, n (%)	119 (81.5)	102 (81.6)	17 (81.0)	NS
EVT for ICA + MCA occlusion, n (%)	14 (9.6)	12 (9.6)	2 (9.5)	NS
Bridging thrombolysis, n (%)	96 (65.7)	82 (65.6)	14 (66.7)	NS
Intrahospital mortality, n (%)	5 (3.4)	2 (1.6)	3 (14.3)	0.02
mRS score 0–2 at 90 d, n (%)	85 (58.2)	79 (63.2)	6 (28.6)	0.03
mRS score 3–5 at 90 d, n (%)	47 (32.2)	35 (28.0)	12 (57.1)	0.01
mRS score 6 at 90 d, n (%)	14 (9.6)	11 (8.8)	3 (14.3)	NS

Abbreviations: EVT = endovascular treatment; ICA = internal carotid artery; ICH = intracerebral hemorrhage; LAO = large artery occlusion; MCA = middle cerebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; NS = nonsignificant.

in a proportion of partially recanalized patients (mTICI grade 2a). This highlights that factors other than simple artery recanalization might play a role in clinical recovery of acute stroke patients, prompting further investigations into hemodynamic changes after EVT and possible hemodynamic predictors of clinical outcome.

The present study yielded valuable information about the hemodynamics of the treated artery immediately after EVT and during the following days, providing pathophysiologic clues as to what occurs in the ischemic territory after complete or partial arterial recanalization. A previous transcranial Doppler (TCD) study conducted in acute stroke patients who underwent intra-arterial thrombolysis found no significant increase of BFV in the treated arteries.[25] In contrast, our population showed early postprocedural alterations of cerebral hemodynamics as a constant though often temporary finding after artery recanalization. This discrepancy is most probably related to differences in timing of ultrasound monitoring, recruitment criteria, sample size, type of treatment,

Table 5 Post-EVT ultrasound findings in 146 successfully treated ischemic stroke patients for large vessel occlusion of the anterior circulation

	ICH (n = 21)	No ICH (n = 125)	*p* Value
Mean PSV ratio soon after EVT	3.5 ± 0.2	2.4 ± 0.1	<0.0001
PI Values after EVT	1.13 ± 0.32	1.11 ± 0.31	NS
Mean PSV ratio 48 hours after EVT	2.4 ± 0.2	1.9 ± 0.1	<0.0001

Abbreviations: EVT = endovascular treatment; ICH = intracerebral hemorrhage; PI = pulsatility index; PSV = peak systolic velocity.

and recanalization rate after the procedure. From a pathophysiologic point of view, early though transient BFV increase might be determined by 2 different mechanisms: residual stenosis causing focal BFV increase or distal arteriolar dilation resulting in post-EVT hyperperfusion.

In the first case, thrombus wall remnants might, for example, persist after EVT and dissolve subsequently with progressive BFV normalization. In fact, the vast majority of intracranial LAO is related to cardio-atheroembolism and not to primitive intracranial obstructive disease.[26] Alternatively, focal vasospasm of the treated artery could result in functional lumen narrowing that recedes in the following days. The second mechanism entails arteriolar dilation in the ischemic territory, with the aim of reducing distal blood flow resistances and improving regional perfusion. This is a well-known first-line compensatory mechanism as long as a terminal or near-terminal intracranial artery is occluded. In case of successful recanalization without arteriolar wall tone recovery, cerebral hyperperfusion ensues, possibly leading to vasogenic edema or hemorrhage.[27,28] Because conventional angiography did not detect a severe post-EVT stenosis in successfully recanalized patients, a residual or functional stenosis cannot account per se for such an impressive increase of BFV observed at the first ultrasound assessment. Consequently, our findings most probably are a result of hyperemia or a combination of both conditions (i.e., hyperemia and mild to moderate residual/functional stenosis).

The longitudinal evaluation of intracranial hemodynamics at the site of the recanalized artery also provided interesting information. As expected, hemodynamic normalization occurred more frequently and rapidly among patients with successful recanalization. Nonetheless, the process took place inhomogeneously within the whole sample and often lasted several days, revealing that the recovery of arteriolar wall tone does not develop immediately after EVT. At 1 week, 1 of 25 successfully recanalized patients still had an abnormal BFV. The reasons for such a delay between mechanical thrombectomy and hemodynamic normalization are unclear, especially when we compared TCD data obtained after intra-arterial thrombolysis. Apparently, EVT is associated with more persistent hemodynamic changes than intra-arterial thrombolysis despite a higher rate of recanalization and an improved postprocedural outcome. Further studies are warranted to better define the underlying pathophysiologic mechanisms and to understand the clinical significance of these changes.

Regarding the search of predictors of post-EVT clinical outcome, the prognostic role of microembolic signals after EVT has recently been investigated, showing that patients with microembolic signals have a worse outcome in terms of disability and mortality, an increased incidence of cardiovascular events, and a higher number of postinterventional ischemic lesions outside the major ischemic area.[29] Therefore, transcranial ultrasound already identified a predictor of poor outcome that was independent of angiography findings. However, no predictors were provided for the occurrence of ICH after successful EVT or for good clinical outcome in patients with mTICI grade 2a. In the present study, early and longitudinal TCCS evaluation identified BFV in the recanalized artery as a measure able to further stratify the prognosis among patients with similar EVT success. In fact, patients who would subsequently develop ICH had higher postprocedural mean PSV ratio, while among patients with ICH, early (<1 week) BFV normalization predicted a better outcome. The role of BFV normalization as an independent predictor of good prognosis in ischemic stroke patients was already proven in other ultrasound studies,[30,31] but this has never been demonstrated in EVT-treated patients. In the present study, among patients undergoing successful EVT, early (<48 hours) normalization of BFV predicted the best outcome, while enduring hemodynamic abnormalities at 1 week were associated with a poor clinical outcome.

Because clinical outcome correlates with the extent of brain infarct and both depend on several factors (e.g., successful recanalization, timing of recanalization, presence of recruitable intracranial collaterals, and metabolic status, including hyperglycemia, comorbidities, etc), postprocedural hemodynamics might represent a single comprehensive indicator of global injury severity: the larger the infarct, the more compromised the vasomotor reactivity beyond the recanalized artery, because necrotic brain tissue unlikely maintains the physiologic arteriolar tone. This hypothesis could explain why hemodynamic normalization at 1 week predicted better outcome regardless of EVT-related partial or complete recanalization. Future studies encompassing a detailed analysis of ischemic tissue extent will address this hypothesis, providing indirect support of the usefulness of TCCS monitoring after EVT.

Equally interesting were the hemodynamic findings in patients with intraparenchymal hemorrhage, which represents the most serious and feared complication in the acute phase of stroke reperfusion therapies. In our study, ≈1 of 7 patients with successful EVT (mTICI grade 2b–3) developed an ICH. In accordance with previous reports, we identified arterial hypertension and a worse initial NIHSS score as factors associated with postprocedural ICH.[32,33] Patients who experienced an ICH after recanalization were found to have a higher mean PSV ratio soon after EVT in the recanalized MCA compared to those who did not have an intracranial bleeding. These results, consistent with a previous TCD study,[34] suggest that hyperperfusion after mechanical recanalization of large vessel occlusion might have deleterious effects on several elements of the blood-brain barrier in the ischemic tissue due to reperfusion mediated injury.[35,36] Moreover, the persistence of abnormal hemodynamics at the 48-hour evaluation of patients with ICH after EVT might represent a more severe impairment of cerebrovascular reactivity as a predisposing factor for ICH or alternatively an abolished arteriolar wall tone within the ischemic brain tissue after hemorrhagic transformation. Finally, even among patients with ICH after EVT, TCCS evaluation provided valuable prognostic clues because hemodynamics normalization at 1 week predicted a better outcome at 3 months. Together, these results suggest that TCCS data collected soon after EVT might better stratify patients at risk of ICH and influence care decisions. In these cases, more aggressive blood pressure control might be required beyond current guidelines to prevent ICH and ultimately to improve clinical outcome. In addition, TCCS data collected on the following days are a strong predictor of outcome and might be useful to better understand the pathophysiology of post-EVT hemorrhage, suggesting that a poor hemodynamic response has a role in the genesis of ICH.

Although this study has the advantage of a consolidated diagnostic and interventional protocol performed in a large university hospital, it also has some limitations. First, operator dependence is an issue, as with all ultrasound studies. Consequently, this could represent an obstacle for study generalizability because availability of CTA is usually greater than TCCS expertise. This might not be true in rural hospitals where transcranial ultrasound is the only tool available for LAO diagnosis. Second, there is a greater likelihood of technical difficulties (e.g., absent acoustic window), limiting a TCCS study vs a CTA study fully evaluating all proximal arterial segments, although the use of ultrasound contrast agents has greatly reduced this limitation. Moreover, TCCS offers unique information on vessel compliance and dysperfusion, beyond mere restoration of vessel lumen, which is grossly measured by CTA. Third, blood pressure management of patients with mTICI grade 0 to 1 or a more severe clinical picture was no different from that in patients with good recanalization and a lower NIHSS score. This could be considered a limitation of the study, yet, according to current guidelines, it is reasonable to keep blood pressure values <185/90 mm Hg before treatment, whereas the usefulness of drug-induced hypertension after treatment is not well established. Finally, because this was a single-center study, the sample size is rather small, and the results might not be generalizable. However, all parameters found in the univariate analysis as good prognostic factors are reasonable and confirm the accuracy and generalizability of the results: younger age, absence of arterial hypertension, low baseline NIHSS score, MCA occlusion (vs ICA or tandem occlusion), bridging thrombolysis, successful revascularization, and shorter time to revascularization. Nonetheless, we hope that other stroke centers can perform a similar study and validate our results.

In the present study, we have shown that post-EVT ultrasound monitoring of stroke patients might be an effective bedside method for assessing treatment efficacy, shedding light on outcome variability and the pathophysiology of stroke after mechanical thrombectomy, and finally identifying patients at increased risk of postinterventional ICH.

Author contributions

Claudio Baracchini, MD, has made substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content; and gave his final approval to the version submitted. Filippo Farina, MD, has made substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data; statistical analysis; drafting the article and revising it critically for important intellectual content; and gave his final approval to the version submitted. Anna Palmieri, MD, Caterina Kulyk, MD, Alessio Pieroni, MD, Federica Viaro, MD, Giacomo Cester, MD, Francesco Causin, MD, and Renzo Manara, MD, have made substantial contributions to the conception and design of the study; acquisition, analysis, and interpretation of data; drafting the article and revising it critically for important intellectual content; and gave final approval to the version submitted.

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