Title

Perfusion-Based Relative Cerebral Blood Volume Is Associated With Functional Dependence in Large-Vessel Occlusion Ischemic Stroke.

Journal

Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease, 13(23)

Authors

Lakhani, Dhairya
Balar, Aneri
Koneru, Manisha
et al.

Publication Date

2024-12-03

DOI

10.1161/JAHA.124.034242

Peer reviewed

Journal of the American Heart Association

ORIGINAL RESEARCH

Perfusion-Based Relative Cerebral Blood Volume Is Associated With Functional Dependence in Large-Vessel Occlusion Ischemic Stroke

Dhairya A. Lakhani, MD*; Aneri B. Balar, MD*; Manisha Koneru, MS; Sijin Wen, PhD; Burak Berksu Ozkara, MD; Justin Caplan, MD; Adam A. Dmytriw, MD; Richard Wang, MD; Hanzhang Lu, PhD; Meisam Hoseinyazdi, MD; Mehreen Nabi, MD; Ishan Mazumdar, MD; Andrew Cho, MD; Kevin Chen, MD; Sadra Sepehri, MD; Nathan Hyson, MD; Risheng Xu, MD; Victor Urrutia, MD; Licia P. Luna, MD, PhD; Argye Hillis, MD, MS, MBA; Jeremy J. Heit, MD, PhD; Greg W. Albers, MD; Ansaar T. Rai, MD, MBA; Tobias Faizy, MD; Max Wintermark, MD, MBA; Kambiz Nael, MD; Vivek S. Yedavalli, MD, MS

BACKGROUND: Pretreatment computed tomography perfusion parameter relative cerebral blood volume (rCBV) lesion volume has been shown to predict 90-day modified Rankin Scale score in small-core strokes with Alberta Stroke Program Early Computed Tomography Score ≥5, including those with medium-vessel occlusions (mid and distal M2 segment occlusions). Hence, in this study we aim to assess the performance of different rCBV lesion volume thresholds (rCBV <42%, rCBV <38%, and rCBV <34%) with 90-day modified Rankin Scale score including patients with large core (Alberta Stroke Program Early Computed Tomography Score <5) and strictly including only patients with anterior circulation large-vessel occlusion.

METHODS AND RESULTS: In this retrospective evaluation of our prospectively collected database, inclusion criteria were (1) Computed tomographic angiography confirmed anterior circulation large-vessel occlusion from September 1, 2017, to October 1, 2023; and (2) diagnostic computed tomography perfusion. Student *t* test, Mann–Whitney *U* test, and χ^2 test were used in the univariate data analysis. Spearman's rank correlation analysis was used to assess correlations. Outcome measure was dichotomized into good functional outcome (90-day modified Rankin Scale score, 0–2) and poor functional outcome (90-day modified Rankin Scale score, 3–6) for logistic regression and receiver operating characteristic analysis. $P \leq 0.05$ was considered significant. In total, 229 patients met our inclusion criteria. The majority of the patients (n=161) in our cohort had M1 occlusion. All the rCBV thresholds were significantly higher in patients with poor 90-day functional outcomes and were independently associated with the outcome. Spearman's rank correlation analysis revealed a slightly stronger correlation of rCBV <42% (ρ=0.27, P<0.001), as compared with rCBV <38% (ρ=0.25, P<0.001) and rCBV <34% (ρ=0.24, P<0.001) with functional outcome. Receiver operating characteristic analysis revealed that rCBV <42% (area under the curve, 0.67 [95% CI, 0.60–0.74]; P<0.001) performed marginally better than rCBV <38% (area under the curve, 0.66 [95% CI, 0.59–0.73]; P<0.001), and rCBV <34% (area under the curve, 0.65 [95% CI, 0.58–0.72]; P<0.001).

CONCLUSIONS: All the rCBV thresholds were independently associated with poor 90-day functional outcome; however, the rCBV <42% marginally outperformed rCBV <38% and rCBV <34% lesion volumes.

Key Words: poor functional outcome ■ rCBV <42% ■ relative cerebral blood volume

Correspondence to: Dhairya A. Lakhani, MD, Department of Neuroradiology, West Virginia University School of Medicine, Rockefeller Neuroscience Institute, 1 Medical Center Dr, Morgantown, WV 26506. Email: dhairyalakhani@gmail.com

*D. A. Lakhani and A. B. Balar contributed equally.

This manuscript was sent to Jose R. Romero, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Higher relative cerebral blood volume (rCBV) lesion volumes are independently and negatively associated with 90-day functional outcomes in patients with anterior circulation large-vessel occlusion.
- rCBV <42% threshold slightly performs better than rCBV <34% and rCBV <38% in predicting 90-day functional outcome.

What Are the Clinical Implications?

- rCBV <42% lesion volume by predicting 90-day functional outcome has the potential to serve as an adjunct marker in mechanical thrombectomy triage in anterior circulation large-vessel occlusion.

Nonstandard Abbreviations and Acronyms

AIS-LVO	acute ischemic stroke secondary to large-vessel occlusion
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
CTP	computed tomographic perfusion
ESCAPE-NA1	A Multicentre, Randomized, Double-Blinded, Placebo-Controlled, Parallel Group, Single-Dose Design to Determine the Efficacy and Safety of Intravenous NA-1 in Subjects With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy
IVT	intravenous thrombolysis
mRS	modified Rankin Scale
MT	mechanical thrombectomy
NIHSS	National Institutes of Health Stroke Scale
rCBV	relative cerebral blood volume
TENSION	The Efficacy and Safety of Thrombectomy in Stroke
T_{max}	time to maximum concentration

The computed tomographic perfusion (CTP) data are acquired by dynamic image acquisition of the head following intravenous contrast bolus administration. Several postprocessing software platforms are available that summarize these data into several CTP maps, which are more reproducible and less subjective in estimating penumbra and infarct core volume. Depending on the timing of bolus arrival and transit (time to maximum concentration [T_{max}] and mean transit time), cerebral blood flow and cerebral blood volume (CBV) are computed.[1–7]

The CBV in the territory of ischemia is an excellent quantitative marker to estimate compensatory response through collateral routes in the setting of acute ischemic stroke caused by large-vessel occlusion (AIS-LVO).[1–5] Several studies have shown that CBV is as an excellent marker for assessment of ischemic core and infarct growth.[6–8]

In AIS-LVO, there is a growing interest in quantitative estimation of CBV in the ischemic territory to quantify the degree of hypoperfusion in the affected parenchyma. Various definitions have been developed and studied that quantify CBV in ischemic territory, by several software platforms, and these definitions vary considerably. Most of the estimates quantified CBV in relation to the nonaffected hemisphere.[1–6,9,10] The RAPID (iSchemaView, Menlo Park, CA) platform quantifies CBV in the territory of T_{max} >6 seconds area within the affected hemisphere in relation to CBV in the unaffected parenchyma as defined by T_{max} ≤4 seconds area.[5,8]

Recently, ESCAPE-NA1 (A Multicentre, Randomized, Double-Blinded, Placebo-Controlled, Parallel Group, Single-Dose Design to Determine the Efficacy and Safety of Intravenous NA-1 in Subjects With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy) trial data in anterior circulation AIS-LVO established that increased rCBV lesion volumes (rCBV <42%, rCBV <38%, and rCBV <34%) were independent predictors of poor functional outcome at 90 days and that the rCBV <42% lesion volume outperformed rCBV <38% and rCBV <34% lesion volumes.[6] However, this prior study also included a small but significant proportion of medium-vessel occlusions. The success of large-core trials, which showed better outcomes in AIS-LVO treated with mechanical thrombectomy (MT) compared with those with medical management alone, resulted in shifting trends of managing patients large-core stroke with MT.[11,12]

Hence, in this study, we aim to assess the relationship of different rCBV thresholds lesion volume with 90-day modified Rankin Scale (mRS) in patients with anterior circulation AIS-LVO, including those with a large baseline ischemic core on admission CTP. We hypothesize that increased rCBV lesion volumes are independently associated with poor functional outcomes as defined by a 90-day mRS score of 3 to 6 and that rCBV <42% lesion volume will have a stronger association with the outcome compared with rCBV <38% and rCBV <34%.

METHODS

Data Availability

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Study Design

We performed a retrospective analysis of prospectively maintained stroke databases, and we identified consecutive patients from 2 comprehensive stroke centers from July 29, 2019, to October 1, 2023, who met our inclusion criteria. This study was approved through the Johns Hopkins Institutional Review Board (No. 00269637) and follows the Strengthening the Reporting of Observational Studies in Epidemiology checklist guidelines as an observational study.

Study Participants

The inclusion criteria for this study were (1) diagnostically adequate multimodal pretreatment computed tomography (CT) imaging including noncontrast head CT, CT angiography, and CTP; (2) AIS-LVO confirmed by CT angiography of the distal supraclinoid segment of the internal carotid artery, M1 segment of middle cerebral artery, and proximal M2 segment of the middle cerebral artery.[13–16]

The study was conducted in accordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Informed consent was waived by the institutional review boards given the retrospective study design. The decisions to administer intravenous thrombolysis (IVT) or perform MT were made on an individual basis following consensus of the stroke team evaluation per institutional protocols.

Data Collection

Baseline and clinical data were collected through electronic records, and stroke center databases for each patient are prospectively collected and managed, which include baseline demographics data; imaging markers on noncontrast CT, CT angiography, and CTP including Alberta Stroke Program Early Computed Tomography Score (ASPECTS), site of occlusion, and different RAPID-derived CTP variables; clinical variables including but not limited to premorbid mRS score, and National Institutes of Health Stroke Scale (NIHSS); various time parameters including last known well-to-door time, door-to-needle time, and door-to-groin puncture times; and outcome measures on imaging.

CTP Image Acquisition

Whole-brain pretreatment CTP was performed on the Siemens Somatom Force (Erlangen, Germany) with the following parameters: 70 kVP, 200 effective mAs, rotation time 0.25 seconds, average acquisition time 60 seconds, collimation 48 × 1.2 mm, pitch value 0.7, 4D range 114 mm × 1.5 seconds.

The lateral topogram field included vertex to the aortic arch, and the anteroposterior topogram included aortic arch to the vertex of the head, after which a noncontrast CT head was acquired from the skull base up to the vertex. Then, CTP data were acquired following injection of 50 mL of intravenous Omnipaque 300/30 mL saline at 5 to 6 mL/s. After a 6-second delay following initiation of contrast bolus administration, CT images were acquired continuously for 60 seconds over a 100- or 114-mm range. The frame rate was 3 to 5 seconds, and temporal resolution was 1 image per second. For the CT angiography head and neck acquisition following CTP, the slice at the level of the aortic arch was used for bolus tracking. About 50 to 70 mL of intravenous contrast at 5 to 6 mL/s was injected, while continuously acquiring the slice at the aortic arch level. When the Hounsfield units of the region of interest placed on the arch reached a desired level of enhancement (about 25 Hounsfield units), then the CT acquisition from the aortic arch to the vertex was manually triggered.

Image Analysis

All the CTPs were assessed by board-certified neuroradiologists with 9 years of working experience for diagnostic adequacy of the raw and postprocessed CTP data, where only those deemed diagnostic adequate were included in the study.

CTP source images were then postprocessed using commercial RAPID perfusion software version 5.2.2 (iSchemaView) to generate rCBV <34%, rCBV <38%, and rCBV <42% volumes.

Statistical Analysis

Categorical data were described using contingency tables including counts and percentages; continuous variables were summarized with median (interquartile range [IQR]). Student's *t* test was used in the data analysis for continuous variables, Mann–Whitney *U* test was used in the data analysis for ordinal data, and the χ^2 test was used for categorical data. Spearman's rank correlation analysis was used to assess strength and direction of relationship.

The outcome measure of 90-day mRS was dichotomized into a binomial variable for logistic regression analysis as good functional outcome (mRS score, 0–2) and poor functional outcome (mRS score, 3–6). The univariable and multivariable logistic regression models were used to estimate the association between rCBV <34%, rCBV <38%, and rCBV <42% lesion volume with 90-day mRS score. Multivariable logistic

regression model took into account important variables: age, hypertension, diabetes, IVT administration, admission NIHSS score, ASPECTS, and each CBV threshold. The outcomes were reported as unadjusted and adjusted odds ratio, 95% CI, and *P* value. R^2 was used to assess the impact of individual variables on the multivariable logistic regression model, which was as follows: clinical model with no rCBV, 0.267; clinical model + rCBV34; 0.432; clinical model + rCBV38, 0.446; and clinical model + rCBV42, 0.486.

The receiver operating characteristic (ROC) analysis was used to assess the strength of prediction with rCBV thresholds in discriminating patients with good and poor functional status at 90 days. Statistically significant analysis was described as $P \leq 0.05$, $P < 0.01$, and $P < 0.001$.

RESULTS

A total of 229 consecutive patients (median age, 68 years; 58% women) met our inclusion criteria. In total, 72 patients (31%) received IVT, and 184 patients (80%) underwent MT.

Of 229 patients, 161 (70%) had M1 segment occlusion, 45 (20%) had proximal M2 segment occlusion, and 23 (10%) had supraclinoid internal carotid artery occlusion.

Patient demographics, imaging parameters, and stroke treatment details are presented in Table 1. The patients with poor functional outcomes at 90 days were statistically significantly older (median age, 73 years), compared with those with good functional outcomes (median age, 65 years; *P*<0.001). The cohort with poor functional outcomes had a statistically significant higher proportion of patients with hypertension, patients with diabetes, and those who received IVT.

Distribution of rCBV Lesion Volume

Median rCBV <42% (13.0 mL [IQR, 0–53.5] versus 0.0 mL [IQR, 0–14.0]; *P*<0.001), rCBV <38% (10.5 mL [IQR, 0–47.5] versus 0.0 mL [IQR, 0–10.0]; *P*<0.001), and rCBV <34% (9.0 mL, [IQR, 0–41.5] versus 0.0 mL [IQR: 0–8.0]; *P*<0.001) lesion volumes were significantly higher in patients with poor functional outcomes as compared with those with good functional outcomes (Figure 1).

Correlation Analysis of rCBV Lesion Volume

On Spearman correlation analysis, the rCBV <42% lesion volume (ρ=0.27 [95% CI, 0.14–0.39]; *P*<0.001) showed stronger correlation with 90-day mRS as compared with rCBV <38% (ρ=0.25 [95% CI, 0.12–0.37]; *P*<0.001) and rCBV <34% (ρ=0.24 [95% CI, 0.11–0.36]; *P*<0.001) lesion volumes.

Regression Analysis of rCBV Lesion Volume

On logistic regression analysis, higher rCBV <42% (unadjusted odds ratio, 0.97 [95% CI, 0.96–0.98]; *P*<0.001), rCBV <38% (unadjusted odds ratio, 0.97 [95% CI, 0.96–0.98]; *P*<0.001), and rCBV <34% lesion volumes (unadjusted odds ratio, 0.97 [95% CI, 0.96–0.99]; *P*<0.001) were associated with poor functional outcome.

Multivariable logistic regression analysis adjusting for potential confounding markers showed that all the rCBV thresholds were statistically significant as independent variables in the multiple regression model (Tables 2–4).

ROC Analysis of rCBV Lesion Volume

All rCBV thresholds predicted the poor functional outcomes at 90 days. The rCBV <42% lesion volume (area under the curve [AUC], 0.67 [95% CI, 0.60–0.74]; *P*<0.001) ROC analysis was a little better compared with rCBV <38% (AUC, 0.66 [95% CI, 0.59–0.73]; *P*<0.001) and rCBV <34% (AUC, 0.65 [95% CI, 0.58–0.72]; *P*<0.001) lesion volume in predicting 90-day functional outcome; however, this was not statistically significant (Figure 2).

Other Clinical Parameters That Were Associated With 90-Day Functional Outcomes

Advanced age, hypertension, diabetes, lack of IVT administration, higher admission NIHSS score, and lower admission ASPECTS were associated with poor 90-day functional outcomes (Tables 2–4). However, adjusting for other confounding variables, only advanced age, diabetes, and higher admission NIHSS were associated with poor functional outcomes.

DISCUSSION

We found that all rCBV thresholds, rCBV <42%, rCBV <38%, and rCBV <34% lesion volumes were independently associated with 90-day functional outcomes in patients with AIS-LVO. In keeping with earlier observations in patients with small-core stroke, rCBV <42% lesion volume ROC analysis and correlation coefficient was slightly higher than rCBV <38% and rCBV <34% lesion volumes. This study further validates rCBV lesion volumes as an additional prognostic biomarker of 90-day functional outcome in this group of patients, slightly favoring rCBV <42%.

The rCBV threshold measures the compensatory response in the hypoperfused tissue by quantifying CBV in the region of ischemia (with T_{max} >6 seconds), relative to the CBV in normal parenchyma (with T_{max} ≤4 seconds).[5,8]

Table 1. Demographics of Study Population, Imaging Biomarkers, and Treatment Details

	90-day mRS score, 3–6 (n=116, 50.7%)	90-day mRS score, 0–2 (n=113, 49.3%)	Total (n=229)	*P* value
Demographics				
Age, y, median (IQR)	73.00 (64–82.5)	65.00 (53–73)	68.00 (58–79)	<0.001
Sex				
Female	69 (59)	63 (56)	132 (58)	0.57
Male	47 (41)	50 (44)	97 (42)	
Race				
Black	52 (45)	39 (35)	91 (40)	0.28
White	53 (46)	66 (58)	119 (52)	
Asian	6 (5)	5 (4)	11 (5)	
Others	5 (4)	3 (3)	8 (3)	
Comorbidities				
Hypertension	97 (84)	80 (71)	177 (77)	0.02
Hyperlipidemia	58 (50)	59 (52)	117 (51)	0.74
Diabetes	43 (37)	23 (20)	66 (29)	0.01
Heart disease	64 (55)	50 (44)	114 (50)	0.10
Atrial fibrillation	46 (40)	42 (37)	88 (38)	0.70
Smoking	56 (48)	52 (47)	108 (48)	0.83
Prior transient ischemic attack or stroke	22 (19)	23 (20)	45 (20)	0.79
Occlusion segment				
Supraclinoid Internal carotid artery	13 (11)	10 (9)	23 (10)	0.74
M1	82 (71)	79 (70)	161 (70)	
Proximal M2	21 (18)	24 (21)	45 (20)	
Premorbid mRS score				
0	69 (63)	78 (70)	147 (67)	0.06
1	8 (7)	17 (15)	25 (11)	
2	9 (8)	7 (6)	16 (7)	
3	21 (19)	9 (8)	30 (14)	
4	1 (1)	0 (0)	1 (0)	
5	1 (1)	0 (0)	1 (0)	
ASPECTS				
0	3 (3)	1 (1)	4 (2)	0.04
1	1 (1)	0 (0)	1 (0)	
2	3 (3)	2 (2)	5 (2)	
3	2 (2)	1 (1)	3 (1)	
4	4 (3)	0 (0)	4 (2)	
5	8 (7)	4 (4)	12 (5)	
6	14 (12)	3 (3)	17 (7)	
7	6 (5)	13 (12)	19 (8)	
8	16 (14)	19 (17)	35 (15)	
9	13 (11)	17 (15)	30 (13)	
10	46 (40)	53 (47)	99 (43)	
Stroke management details				
Intravenous thrombolysis	28 (24)	44 (39)	72 (31)	0.02
Mechanical thrombectomy performed	89 (77)	95 (84)	184 (80)	0.16
mTICI score				
0	7 (8)	3 (3)	10 (6)	0.19
1	2 (2)	2 (2)	4 (2)	
2A	5 (6)	0 (0)	5 (3)	

(*Continued*)

Table 1. Continued

	90-day mRS score, 3–6 (n=116, 50.7%)	90-day mRS score, 0–2 (n=113, 49.3%)	Total (n=229)	*P* value
2B	22 (26)	22 (26)	44 (26)	
2C	11 (13)	13 (15)	24 (14)	
3	38 (45)	46 (53)	84 (49)	
Admission NIHSS score, median (IQR)	18.50 (13.0–22.0)	12.00	16.00 (10.0–20.0)	<0.001
Time parameters, median (IQR)				
Last known well-to-door time, min	79.00 (38.0–144.0)	95.50	85.00 (48.0–263.0)	0.11
Door-to-CT time, min	31.00 (23.0–57.5)	28.00	30.00 (18.0–45.5)	0.22
Door-to-needle time, min	74.00 (52.0–83.0)	57.50	59.00 (44.0–78.0)	0.33
Door-to-groin puncture time, min	160.50 (132.0–246.0)	156.50	157.50 (126.0–226.0)	0.78
Groin puncture-to-recanalization time, min	32.50 (24.0–53.0)	29.00	29.00 (22.0–51.0)	0.79
CTP parameter, median (IQR)			0.00 (0.00)	
rCBV <34% lesion volume, mL	9.00 (0–41.5)	0.00 (0–8.0)	0.00 (0–23.0)	<0.001
rCBV <38% lesion volume, mL	10.50 (0–47.5)	0.00 (0–10.0)	5.00 (0–25.0)	<0.001
rCBV <42% lesion volume, mL	13.00 (0–53.5)	0.00 (0–14.0)	6.00 (0–32.0)	<0.001

Values are described as number (percentage) unless otherwise specified. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; CTP, computed tomography perfusion; IQR, interquartile range; mRS, modified Rankin Scale; mTICI, modified Treatment in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; and rCBV, relative cerebral blood volume.

This provides an estimate of the degree of hypoperfusion in the affected hemisphere. The normal homeostatic response to ischemia is to increase CBV in the ischemic area to facilitate oxygen extraction via vasodilation and pooling of blood via collateral routes. Conversely, poor compensatory vasodilation in patients manifests as decreased CBV in ischemic territory (higher rCBV lesion volume), leading to poor functional outcomes as compared with those patients with a robust compensatory response.[17–29]

Recently, the ESCAPE-NA1 trial data determined that all rCBV thresholds (rCBV <42%, rCBV <38%, and rCBV <34%) lesion volumes were significantly associated with lower functional independence as defined by 90-day mRS score, after adjusting for confounding variables. The ROC analysis showed a slightly higher AUC with the rCBV <42% lesion volume, as compared with the rCBV <34% and rCBV <38% lesion volume in predicting 90-day mRS score ≥3.[6] However, the ESCAPE-NA1 study had stringent inclusion criteria,

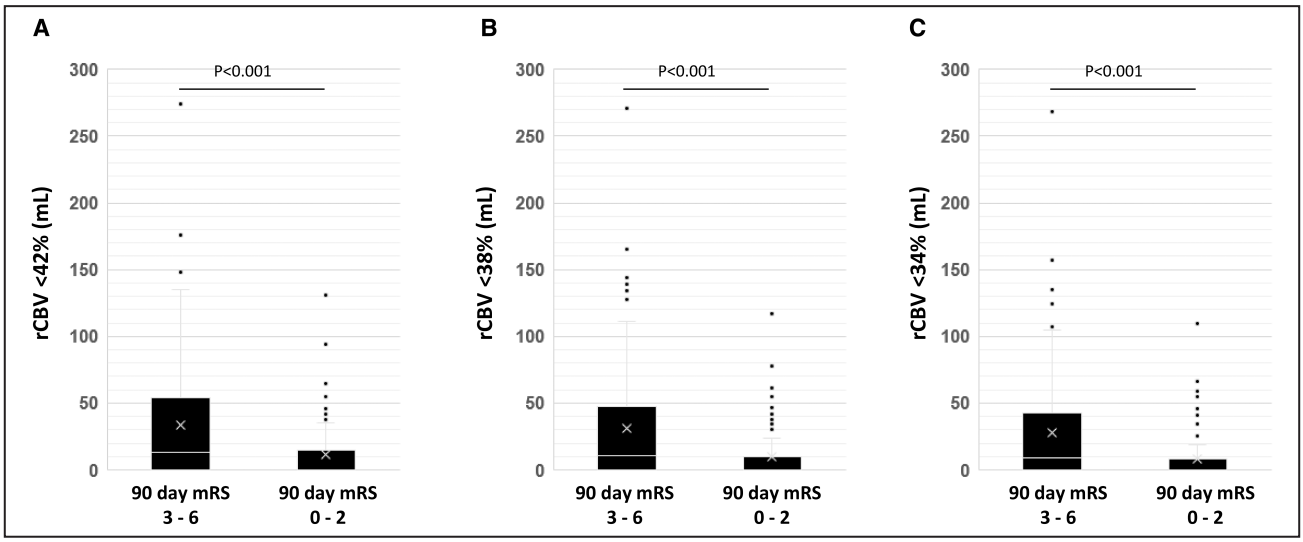

Figure 1. Distribution of rCBV thresholds in patients with poor (90-day mRS score, 3–6) and good functional outcomes (90-day mRS score, 0–2) at 90 days.
Box and whisker plot distribution of rCBV <42% (**A**), rCBV <38% (**B**), and rCBV <34% (**C**) lesion volume in patients with a poor 90-day mRS score of 3 to 6 and with a good 90-day mRS score of 0 to 2. Box plot represents median and interquartile range, whereas whiskers represent minimum and maximum values. *Y* axis represents volume in mL. mRS indicates modified Rankin Scale; and rCBV, relative cerebral blood volume.

Table 2. Multivariable Logistic Regression Analysis to Assess Association of rCBV <42% Lesion Volume With Follow-Up Poor Functional Outcome at 90 Days, as Defined by mRS Score of 3–6

Variables	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age, y	0.96 (0.95–0.98)	<0.001	0.95 (0.93–0.98)	<0.001
Sex	1.17 (0.69–1.97)	0.57		
Hypertension	0.48 (0.25–0.89)	<0.05	0.91 (0.42–1.98)	0.82
Hyperlipidemia	1.09 (0.65–1.84)	0.74		
Diabetes	0.43 (0.24–0.79)	<0.01	0.39 (0.19–0.83)	<0.05
Heart disease	0.65 (0.38–1.09)	0.09		
Atrial fibrillation	0.90 (0.53–1.53)	0.69		
Smoking	0.944 (0.561–1.590)	0.83		
Occlusion segment	1.00 (0.846–1.182)	0.99		
Prior transient ischemic attack or stroke	1.09 (0.57–2.10)	0.79		
Intravenous thrombolysis administration	2.00 (1.134–3.541)	<0.05	1.72 (0.85–3.50)	0.13
Mechanical thrombectomy	1.6 (0.82–3.10)	0.16		
Admission NIHSS score	0.882 (0.844–0.921)	<0.001	0.91 (0.87–0.95)	<0.001
ASPECTS	1.178 (1.043–1.330)	<0.01	1.17 (0.98–1.40)	0.08
rCBV <42% lesion volume	0.97 (0.96–0.98)	<0.001	0.98 (0.97–0.99)	<0.001

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and rCBV, relative cerebral blood volume.

where patients with large-core (ASPECTS <5), poor collateral status, minor stroke (NIHSS score <5), and last known well-to-door time of ≥12 hours were excluded. The ESCAPE-NA1 study also included medium-vessel occlusion (mid to distal M2 segment occlusions). The recent success of large-core trials has shown superior functional outcomes and lower mortality rate following MT compared with medical management alone, in patients with AIS-LVO with ASPECTS of 2 to 5.[11,30–34] Hence, in this study, we aimed to assess the performance of different rCBV thresholds in all cases of AIS-LVO, including those

Table 3. Multivariable Logistic Regression Analysis to Assess Association of rCBV <38% Lesion Volume With Follow-Up Poor Functional Outcome at 90 Days, as Defined by mRS Score of 3–6

Variables	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age, y	0.96 (0.95–0.98)	*P*<0.001	0.95 (0.93–0.98)	<0.001
Sex	1.17 (0.69–1.97)	0.57		
Hypertension	0.48 (0.25–0.89)	<0.05	0.92 (0.43–2.00)	0.84
Hyperlipidemia	1.09 (0.65–1.84)	0.74		
Diabetes	0.43 (0.24–0.79)	<0.01	0.39 (0.19–0.83)	<0.05
Heart disease	0.65 (0.38–1.09)	0.09		
Atrial fibrillation	0.90 (0.53–1.53)	0.69		
Smoking	0.94 (0.56–1.59)	0.83		
Occlusion segment	1.0 (0.84–1.18)	0.99		
Prior transient ischemic attack or stroke	1.0 (0.57–2.10)	0.79		
Intravenous thrombolysis administration	2.0 (1.13–3.54)	<0.05	1.74 (0.86–3.54)	0.12
Mechanical thrombectomy	1.6 (0.82–3.10)	0.16		
Admission NIHSS score	0.88 (0.84–0.92)	<0.001	0.91 (0.87–0.95)	<0.001
ASPECTS	1.17 (1.04–1.33)	<0.01	1.17 (0.98–1.40)	0.08
rCBV <38% lesion volume	0.97 (0.96–0.98)	<0.001	0.98 (0.96–0.99)	<0.001

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and rCBV, relative cerebral blood volume.

Table 4. Multivariable Logistic Regression Analysis to Assess Association of rCBV <34% Lesion Volume With Follow-Up Poor Functional Outcome at 90 Days, as Defined by mRS of 3–6

Variables	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age, y	0.96 (0.95–0.98)	*P*<0.001	0.95 (0.93–0.98)	<0.001
Sex	1.17 (0.69–1.97)	0.570		
Hypertension	0.48 (0.25–0.89)	<0.05	0.93 (0.43–2.02)	0.86
Hyperlipidemia	1.09 (0.65–1.84)	0.740		
Diabetes	0.43 (0.24–0.79)	<0.01	0.40 (0.19–0.83)	<0.05
Heart disease	0.65 (0.38–1.09)	0.090		
Atrial fibrillation	0.90 (0.53–1.53)	0.690		
Smoking	0.944 (0.561–1.590)	0.830		
Occlusion segment	1.00 (0.846–1.182)	0.990		
Prior transient ischemic attack or stroke	1.09 (0.57–2.10)	0.790		
Intravenous thrombolysis administration	2.00 (1.134–3.541)	<0.05	1.74 (0.86–3.53)	0.13
Mechanical thrombectomy	1.6 (0.82–3.10)	0.16		
Admission NIHSS score	0.882 (0.844–0.921)	<0.001	0.91 (0.87–0.95)	<0.001
ASPECTS	1.178 (1.043–1.330)	<0.01	1.17 (0.98–1.40)	0.08
rCBV <34% lesion volume	0.97 (0.96–0.99)	<0.01	0.98 (0.96–0.99)	<0.01

ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and rCBV, relative cerebral blood volume.

with large cores (ASPECTS ≤5). Furthermore, there is a difference in management of large- and medium-vessel occlusions, and hence, they were excluded from our study. Moreover, we also included patients with last known well ≥12 hours to reflect more real-world data. Nevertheless, our results were similar to the observation of ESCAPE-NA1 trial data,[6] and all rCBV thresholds (rCBV <42%, rCBV <38%, and rCBV <34%) were independently associated with poor 90-day functional outcomes, and the rCBV <42% lesion volume performed slightly better than the rCBV <38% and rCBV <34% lesion volume in predicting 90-day mRS, though it was not statistically significant.

Despite these differing inclusion criteria, our results nevertheless corroborate prior work in demonstrating that higher volumes of rCBV result in poor functional outcomes at 90 days.[5,8] Our findings support the underlying pathophysiological biomechanics of lower rCBV in capturing the degree of compensation, where patients who are unable to generate a sufficient response have poor functional outcomes.[21]

Our results also demonstrated that advanced age, diabetes, and higher admission NIHSS score were statistically significant as independent variables in the multiple regression model. These variables are already well established in the literature as a poor prognostic marker in patients with AIS-LVO.[18] Lower ASPECTS (larger infarct core) and lack of MT were associated with poor functional outcomes on univariable analysis.[33] However, in our study we did find any association of MT or ASPECTS with the outcomes, after adjusting for confounding variables on multivariable logistic regression analysis. Furthermore, sex, hypertension, hyperlipidemia, heart disease, atrial fibrillation, smoking, occlusion segment, and prior transient ischemic attack or stroke were not associated with 90-day functional outcome.

Limitations of our study include that of the retrospective study design and that CTP markers were measured on 1 commercial software, RAPID, which is computationally intensive and may not be available at all the centers. However, our study is strengthened by the sample size of 229 patients with anterior circulation large-vessel occlusion who are derived from 2 comprehensive stroke centers serving varying demographics.

Our results further validate the role of rCBV lesion volumes, especially rCBV <42% lesion volume, in estimating 90-day functional outcomes, and further adds to the potential role of rCBV as a prognostic markers.[35,36] More recently, large-core trials such as the TENSION (The Efficacy and Safety of Thrombectomy in Stroke) trial[33] showed the benefit of MT in large-vessel occlusion cases irrespective of ischemic core volume on pretreatment imaging. Hence, CTP-based rCBV lesion volumes may be used as an adjunct marker during MT triage of especially complex AIS-LVO cases where decision is more nuanced. Future studies are needed to expand our understanding of the adjunct

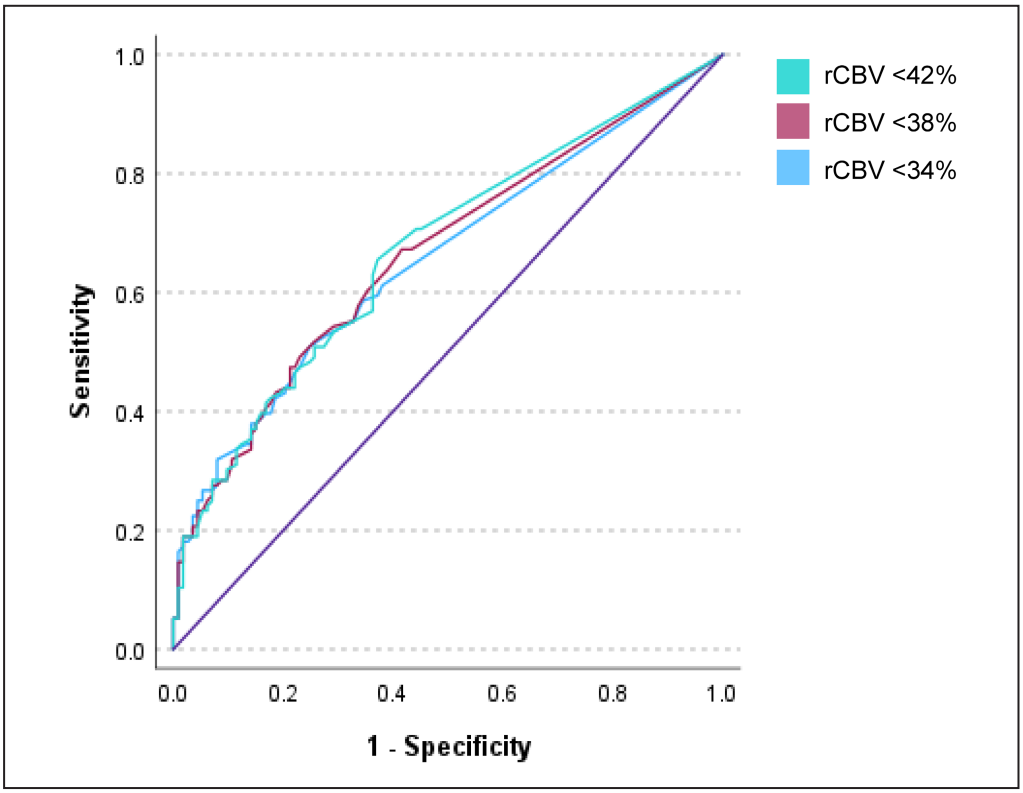

Figure 2. ROC curve analysis of rCBV lesion volume thresholds in predicting poor functional outcomes (defined as mRS score, 3–6 at 90 days).
The rCBV <42% lesion volume (AUC, 0.67 [95% CI, 0.60–0.74]; *P*<0.001) performed better than rCBV <38% (AUC, 0.66 [95% CI, 0.59–0.73]; *P*<0.001) and rCBV <34% (AUC, 0.65 [95% CI, 0.58–0.72]; *P*<0.001) lesion volume in predicting 90-day functional outcome. AUC indicates area under the curve; mRS, modified Rankin Scale; rCBV, relative cerebral blood volume; and ROC, receiver operating characteristic.

role of rCBV volumes with other similar pretreatment imaging-based markers in clinical evaluation and decision making in patients with AIS-LVO, particularly in the large-core subset of patients. In addition, more research is needed to investigate the biomechanisms of rCBV with respect to impaired cerebral autoregulation.

ARTICLE INFORMATION

Received January 3, 2024; accepted October 21, 2024.

Affiliations

The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, MD (D.A.L., A.B.B., R.W., H.L., M.H., M.N., I.M., A.C., K.C., S.S., N.H., R.X., L.P.L., V.S.Y.); Department of Neuroradiology, Rockefeller Neuroscience Institute, West Virginia University, Morgantown, WV (D.A.L., A.T.R.); Cooper Medical School of Rowan University, Camden, NJ (M.K.); Department of Biostatistics, West Virginia University, Morgantown, WV (S.W.); Department of Neuroradiology, MD Anderson Medical Center, Houston, TX (B.B.O., M.W.); Department of Neurology, Johns Hopkins University, Baltimore, MD (J.C., V.U., A.H.); Department of Radiology, Harvard Medical School, Boston, MA (A.A.D.); Department of Radiology, Stanford University, Stanford, CA (J.J.H., G.W.A.); Department of Radiology, Neuroendovascular Division—University Medical Center Münster, Münster, Germany (T.F.); and Department of Radiology and Biomedical Imaging, University of California, San Francisco (UCSF), San Francisco, CA (K.N.).

Acknowledgments

This study is supported by the Johns Hopkins University Department of Radiology Physician Scientist Incubator Program to Dr Yedavalli and the Johns Hopkins School of Medicine Physician Scientist Scholar Program to Dr Lakhani. Author Contributions: Dr Lakhani: writing—original draft, data curation, formal analysis, investigation, and methodology; Dr Balar: writing—original draft, formal analysis, investigation, and methodology; M. Koneru: data curation and investigation; Dr Wen: formal analysis; Dr Ozkara: data curation; Dr Dmytriw: methodology, supervision, and writing—review and editing; Dr Caplan: methodology, supervision, and writing—review and editing; Dr Wang: data curation; Dr Lu: data curation; Dr Hoseinyazdi: data curation; Dr Nabi: data curation; Dr Mazumdar: data curation; Dr Cho: data curation; Dr Chen: data curation; Dr Sapheri: data curation; Dr Hyson: data curation and investigation; Dr Xu: data curation; Dr Urrutia: methodology, writing—review and editing; Dr Luna: data curation and investigation; Dr Hillis: methodology, supervision, and writing—review and editing; Dr Heit: methodology, supervision, and writing—review and editing; Dr Albers: methodology, supervision, writing—review and editing; Dr Rai: methodology, supervision, and writing—review and editing; Dr Faizy: methodology, supervision, and writing—review and editing; Dr Wintermark: methodology, supervision, and writing—review and editing; Dr Nael: methodology, supervision, and writing—review and editing; Dr Yedavalli: resources, project administration, investigation, supervision, and writing—review and editing.

Sources of Funding

Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number 5U54GM104942–08. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Disclosures

Drs Lakhani, Albers, Heit, and Yedavalli are consultants for RapidAI (iSchemaView, Menlo Park, CA). The remaining authors have no disclosures to report.

REFERENCES

1. Sohn SW, Park HS, Cha JK, Kim DH, Kang MJ, Choi JH, Nah HW, Huh JT. Relative CBV ratio on perfusion-weighted MRI indicates the probability of early recanalization after IV t-PA administration for acute ischemic stroke. *J Neurointerv Surg*. 2016;8:235–239. doi: 10.1136/neurintsurg-2014-011501
2. Li BH, Wang JH, Yang S, Wang DZ, Zhang Q, Cheng XD, Yu NW, Guo FQ. Cerebral blood volume index may be a predictor of independent outcome of thrombectomy in stroke patients with low ASPECTS. *J Clin Neurosci*. 2022;103:188–192. doi: 10.1016/j.jocn.2022.07.006
3. Karamchandani RR, Strong D, Rhoten JB, Prasad T, Selig J, Defilipp G, Asimos AW. Cerebral blood volume index as a predictor of functional independence after basilar artery thrombectomy. *J Neuroimaging*. 2022;32:171–178. doi: 10.1111/jon.12933
4. Imaoka Y, Shindo S, Miura M, Terasaki T, Mukasa A, Todaka T. Hypoperfusion intensity ratio and CBV index as predictive parameters to identify underlying intracranial atherosclerotic stenosis in endovascular thrombectomy. *J Neuroradiol*. 2023;50:424–430. doi: 10.1016/j.neurad.2022.10.005
5. Cortijo E, Calleja AI, García-Bermejo P, Mulero P, Pérez-Fernández S, Reyes J, Muñoz MF, Martínez-Galdámez M, Arenillas JF. Relative cerebral blood volume as a marker of durable tissue-at-risk viability in hyperacute ischemic stroke. *Stroke*. 2014;45:113–118. doi: 10.1161/STROKEAHA.113.003340
6. Rex NB, McDonough RV, Ospel JM, Kashani N, Sehgal A, Fladt JC, McTaggart RA, Nogueira R, Menon B, Demchuk AM, et al. CT perfusion does not modify the effect of reperfusion in patients with acute ischemic stroke undergoing endovascular treatment in the ESCAPE-NA1 trial. *AJNR Am J Neuroradiol*. 2023;44:1045–1049. doi: 10.3174/ajnr.A7954
7. Park HS, Cha JK, Kim DH, Kang MJ, Choi JH, Huh JT. The rCBV ratio on perfusion-weighted imaging reveals the extent of blood flow on conventional angiography after acute ischemic stroke. *Clin Neurol Neurosurg*. 2014;122:54–58. doi: 10.1016/j.clineuro.2014.04.001
8. Arenillas JF, Cortijo E, García-Bermejo P, Levy EI, Jahan R, Liebeskind D, Goyal M, Saver JL, Albers GW. Relative cerebral blood volume is associated with collateral status and infarct growth in stroke patients in SWIFT PRIME. *J Cereb Blood Flow Metab*. 2018;38:1839–1847. doi: 10.1177/0271678X17740293
9. Schaefer PW, Souza L, Kamalian S, Hirsch JA, Yoo AJ, Kamalian S, Gonzalez RG, Lev MH. Limited reliability of computed tomographic perfusion acute infarct volume measurements compared with diffusion-weighted imaging in anterior circulation stroke. *Stroke*. 2015;46:419–424. doi: 10.1161/STROKEAHA.114.007117
10. Potreck A, Scheidecker E, Weyland CS, Neuberger U, Herweh C, Möhlenbruch MA, Chen M, Nagel S, Bendszus M, Seker F. RAPID CT perfusion-based relative CBF identifies good collateral status better than hypoperfusion intensity ratio, CBV-index, and time-to-maximum in anterior circulation stroke. *AJNR Am J Neuroradiol*. 2022;43:960–965. doi: 10.3174/ajnr.A7542
11. Palaiodimou L, Sarraj A, Safouris A, Magoufis G, Lemmens R, Sandset EC, Turc G, Psychogios M, Tsivgoulis G. Endovascular treatment for large-core ischaemic stroke: a meta-analysis of randomised controlled clinical trials. *J Neurol Neurosurg Psychiatry*. 2023;94:781–785. doi: 10.1136/jnnp-2023-331513
12. Sarraj A, Grotta JC, Pujara DK, Shaker F, Tsivgoulis G. Triage imaging and outcome measures for large core stroke thrombectomy—a systematic review and meta-analysis. *J Neurointerv Surg*. 2020;12:1172–1179. doi: 10.1136/neurintsurg-2019-015509
13. Faizy TD, Kabiri R, Christensen S, Mlynash M, Kuraitis G, Mader MM, Albers GW, Lansberg MG, Fiehler J, Wintermark M, et al. Association of venous outflow profiles and successful vessel reperfusion after thrombectomy. *Neurology*. 2021;96:e2903–e2911. doi: 10.1212/WNL.0000000000012106
14. Faizy TD, Kabiri R, Christensen S, Mlynash M, Kuraitis GM, Broocks G, Flottmann F, Marks MP, Lansberg MG, Albers GW, et al. Favorable venous outflow profiles correlate with favorable tissue-level collaterals and clinical outcome. *Stroke*. 2021;52:1761–1767. doi: 10.1161/STROKEAHA.120.032242
15. Lakhani DA, Balar AB, Koneru M, Hoseinyazdi M, Hyson N, Cho A, Greene C, Xu R, Luna L, Caplan J, et al. Pretreatment CT perfusion collateral parameters correlate with penumbra salvage in middle cerebral artery occlusion. *J Neuroimaging*. 2023;34:44–49. doi: 10.1111/jon.13178
16. Lakhani DA, Balar AB, Koneru M, Wen S, Hoseinyazdi M, Greene C, Xu R, Luna L, Caplan J, Dmytriw AA, et al. The compensation index is better associated with DSA ASITN collateral score compared to the cerebral blood volume index and hypoperfusion intensity ratio. *J Clin Med*. 2023;12:7365. doi: 10.3390/jcm12237365
17. Xu Y, Guo S, Jiang H, Han H, Sun J, Wu X. Collateral status and clinical outcomes after mechanical thrombectomy in patients with anterior circulation occlusion. *J Healthc Eng*. 2022;2022:7796700. doi: 10.1155/2022/7796700
18. Wang YJ, Wang JQ, Qiu J, Li W, Sun XH, Zhao YG, Liu X, Zhao ZA, Liu L, Nguyen TN, et al. Association between collaterals, cerebral circulation time and outcome after thrombectomy of stroke. *Ann Clin Transl Neurol*. 2023;10:266–275. doi: 10.1002/acn3.51718
19. Wan Z, Meng Z, Xie S, Fang J, Li L, Chen Z, Liu J, Jiang G. Correlation between hypoperfusion intensity ratio and functional outcome in large-vessel occlusion acute ischemic stroke: comparison with multi-phase CT angiography. *J Clin Med*. 2022;11:5274. doi: 10.3390/jcm11185274
20. Vagal A, Aviv R, Sucharew H, Reddy M, Hou Q, Michel P, Jovin T, Tomsick T, Wintermark M, Khatri P. Collateral clock is more important than time clock for tissue fate. *Stroke*. 2018;49:2102–2107. doi: 10.1161/STROKEAHA.118.021484
21. Uniken Venema SM, Dankbaar JW, van der Lugt A, Dippel DWJ, van der Worp HB. Cerebral collateral circulation in the era of reperfusion therapies for acute ischemic stroke. *Stroke*. 2022;53:3222–3234. doi: 10.1161/STROKEAHA.121.037869
22. Sperti M, Arba F, Acerbi A, Busto G, Fainardi E, Sarti C. Determinants of cerebral collateral circulation in acute ischemic stroke due to large vessel occlusion. *Front Neurol*. 2023;14:1181001. doi: 10.3389/fneur.2023.1181001
23. Singer OC, Berkefeld J, Nolte CH, Bohner G, Reich A, Wiesmann M, Groeschel K, Boor S, Neumann-Haefelin T, Hofmann E, et al. Collateral vessels in proximal middle cerebral artery occlusion: the ENDOSTROKE study. *Radiology*. 2015;274:851–858. doi: 10.1148/radiol.14140951
24. Shuaib A, Butcher K, Mohammad AA, Saqqur M, Liebeskind DS. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol*. 2011;10:909–921. doi: 10.1016/S1474-4422(11)70195-8
25. Rao VL, Mlynash M, Christensen S, Yennu A, Kemp S, Zaharchuk G, Heit JJ, Marks MP, Lansberg MG, Albers GW. Collateral status contributes to differences between observed and predicted 24-h infarct volumes in DEFUSE 3. *J Cereb Blood Flow Metab*. 2020;40:1966–1974. doi: 10.1177/0271678X20918816
26. Maguida G, Shuaib A. Collateral circulation in ischemic stroke: an updated review. *J Stroke*. 2023;25:179–198. doi: 10.5853/jos.2022.02936
27. Maas MB, Lev MH, Ay H, Singhal AB, Greer DM, Smith WS, Harris GJ, Halpern E, Kemmling A, Koroshetz WJ, et al. Collateral vessels on CT angiography predict outcome in acute ischemic stroke. *Stroke*. 2009;40:3001–3005. doi: 10.1161/STROKEAHA.109.552513
28. Liebeskind DS. Collateral lessons from recent acute ischemic stroke trials. *Neurol Res*. 2014;36:397–402. doi: 10.1179/1743132814Y.0000000348
29. Bang OY, Goyal M, Liebeskind DS. Collateral circulation in ischemic stroke: assessment tools and therapeutic strategies. *Stroke*. 2015;46:3302–3309. doi: 10.1161/STROKEAHA.115.010508
30. Huo X, Ma G, Tong X, Zhang X, Pan Y, Nguyen TN, Yuan G, Han H, Chen W, Wei M, et al. Trial of endovascular therapy for acute ischemic stroke with large infarct. *N Engl J Med*. 2023;388:1272–1283. doi: 10.1056/NEJMoa2213379
31. Yoshimura S, Sakai N, Yamagami H, Uchida K, Beppu M, Toyoda K, Matsumaru Y, Matsumoto Y, Kimura K, Takeuchi M, et al. Endovascular therapy for acute stroke with a large ischemic region. *N Engl J Med*. 2022;386:1303–1313. doi: 10.1056/NEJMoa2118191
32. Sarraj A, Hassan AE, Abraham MG, Ortega-Gutierrez S, Kasner SE, Hussain MS, Chen M, Blackburn S, Sitton CW, Churilov L, et al. Trial of endovascular thrombectomy for large ischemic strokes. *N Engl J Med*. 2023;388:1259–1271. doi: 10.1056/NEJMoa2214403
33. Bendszus M, Fiehler J, Subtil F, Bonekamp S, Aamodt AH, Fuentes B, Gizewski ER, Hill MD, Krajina A, Pierot L, et al. Endovascular thrombectomy for acute ischaemic stroke with established large infarct:

multicentre, open-label, randomised trial. *Lancet*. 2023;402:1753–1763. doi: 10.1016/S0140-6736(23)02032-9

34. Bendszus M, Bonekamp S, Berge E, Boutitie F, Brouwer P, Gizewski E, Krajina A, Pierot L, Randall G, Simonsen CZ, et al. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. *Int J Stroke*. 2019;14:87–93. doi: 10.1177/1747493018798558
35. Lakhani DA, Balar AB, Salim H, Koneru M, Wen S, Ozkara B, Lu H, Wang R, Hoseinyazdi M, Xu R, et al. CT perfusion derived rCBV <42% lesion volume is independently associated with followup FLAIR infarct volume in anterior circulation large vessel occlusion. *Diagnostics (Basel)*. 2024;14:845. doi: 10.3390/diagnostics14080845
36. Lakhani DA, Balar AB, Koneru M, Wen S, Ozkara BB, Lu H, Wang R, Hoseinyazdi M, Mei J, Xu R, et al. The relative cerebral blood volume (rCBV) <42% is independently associated with collateral status in anterior circulation large vessel occlusion. *J Clin Med*. 2024;13:1588. doi: 10.3390/jcm13061588