Clinical Implications of Hemodynamics in Symptomatic Intracranial Atherosclerotic Stenosis by Computational Fluid Dynamics Modeling: A Systematic Review

Supplemental materials

Liu Y*, et al. Stroke Vasc Neurol* 2025; 10:e003202. doi: 10.1136/svn-2024-003202

Supplemental Methods

Study selection

Two investigators (Y.L. and S.L.) screened the articles identified through literature search, removing duplicates, and excluding irrelevant articles by reading the titles and abstracts. Two investigators (Y.L. and X.L.) then examined the full text for eligible studies according to the inclusion criteria.

Data extraction

Two investigators (Y.L. and X.L.) independently extracted the following data from eligible studies: country/region of study, patient inclusion criteria regarding sICAS, lesion location (anterior and/or posterior circulation), number of cases, neurovascular imaging modality for detecting sICAS and providing source images for vessel segmentation, CFD modeling methods (generic or patient-specific inlet and outlet boundary conditions, rigid or elastic vessel wall assumption, Newtonian or non-Newtonian blood assumption, and steady or transient simulation). More importantly, we recorded the hemodynamic parameters of interest in each study, and the main findings regarding the associations of these hemodynamic metrics with other imaging markers (e.g., stenosis rate, plaque characteristics, and collateral and perfusion status) or clinical features/outcomes (e.g., risk of stroke recurrence, functional outcome, outcomes after certain treatment) in cross-sectional or longitudinal analyses. Discrepancy between the two investigators were resolved by consensus.

Liu Y, *et al. Stroke Vasc Neurol* 2025; 10:e003202. doi: 10.1136/svn-2024-003202

Risk of bias assessment

Two investigators (Y.L. and S.L.) independently assessed the risk of bias of included studies using a modified Newcastle-Ottawa Scale (mNOS),[1] covering 9 items in the following domains, subject selection, comparability and outcome. Items regarding the quality of outcomes were not assessed in the cross-sectional studies. Longitudinal studies scoring 7-9 and cross-sectional studies scoring 4-6 were considered as having a low risk of bias (Supplemental Appendix).

Supplemental Table S1. Search strategy for PubMed, conducted on 28th March 2024

Search#	Search queries	Number of items found
#1	**Search:** ((intracranial OR intracranial arter* OR intracranial large arter* OR intracranial large-arter* OR cerebral OR cerebral arter* OR cerebral large arter* OR cerebral large-arter* OR anterior circulation OR posterior circulation OR anterior-circulation OR posterior-circulation OR middle cerebral arter* OR anterior cerebral arter* OR posterior cerebral arter* OR basilar arter*) OR ((internal carotid arter* AND (intracranial OR siphon OR terminal OR distal OR C5 OR C6 OR C7 OR C5-7 OR C5-C7)) OR ((vertebral arter* OR vertebrobasilar arter*) AND (intracranial OR terminal OR V4)))) AND (steno* OR occlus* OR atherosclero*)	93,848
#2	**Search:** hemodynamic* OR haemodynamic* OR computational fluid dynamic* OR CFD	295,685
#3	**Search:** (#1) AND (#2)	6,769
#4	**Search:** (#1) AND (#2) Filters: Full text, English, from 2000 - 2024	3,752

Supplemental Table S2. Search strategy for Ovid, conducted on 28th March 2024

Search#	Search queries	Number of items found
#1	((intracranial OR intracranial arter* OR intracranial large arter* OR intracranial large-arter* OR cerebral OR cerebral arter* OR cerebral large arter* OR cerebral large-arter* OR anterior circulation OR posterior circulation OR anterior-circulation OR posterior-circulation OR middle cerebral arter* OR anterior cerebral arter* OR posterior cerebral arter* OR basilar arter*) OR ((internal carotid arter* AND (intracranial OR siphon OR terminal OR distal OR C5 OR C6 OR C7 OR C5-7 OR C5-C7)) OR ((vertebral arter* OR vertebrobasilar arter*) AND (intracranial OR terminal OR V4)))) AND (steno* OR occlus* OR atherosclero*).af.	114,678
#2	(hemodynamic* or haemodynamic* or computational fluid dynamic* or CFD).af.	407,081
#3	1 and 2	8,322
#4	limit 3 to (full text and english language and yr="2000 -Current")	1,473

Supplemental Table S3. Study characteristics of the 19 primary studies included in this systematic review

Study	Country	Patient inclusion criteria	Anterior/ Posterior circulation	Number of cases	Neurovascular imaging modality	CFD model setup					Hemodynamic parameters in CFD model	Main findings on clinical implications
						Inlet boundary condition	Outlet boundary condition	Vessel wall condition	Newtonian/ non-Newtonian blood	Steady vs Transient simulation		
Correlations with anatomical characteristics of the sICAS lesions in cross-sectional and longitudinal studies												
Nam et al. 2016[15]	China	50-99% sICAS	Anterior circulation	56	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR、SSR ratio、Velocity ratio	Lower PR (p<0.001) was found in sICAS lesions with severe (70-99%) stenosis than moderate (50-69%) stenosis.
Liu et al. 2017[11]	China	70-99% sICAS	Anterior & posterior circulations	11	CTA	Patient-specific	Generic LPM	Rigid, non-slip	Newtonian	Transient	PR	PR was not linearly proportional to the stenosis rate in patients with sICAS.
Zhang et al. 2021[16]	China	50-99% sICAS	Anterior circulation	40	TOF-MRA	Generic	Generic	Rigid, non-slip	Newtonian	Transient	PR、WSSR	Higher WSSR (medians 9.98 vs. 5.99, p=0.004) and higher WSS (means 53.99 Pa vs. 39.98 Pa, p=0.023) at the narrowest location in plaques with positive than negative remodeling; Positive correlation of the remodeling index (Pearson's r=0.376, p=0.026) and plaque area (Pearson's r=0.407, p=0.015) with WSSR; No significant association of PR (medians 0.92 vs. 0.96, p=0.260) with positive/negative remodeling.
Lan et al. 2020[13]	China	50-99% sICAS	Anterior & posterior circulations	39	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	rWSS measures	A higher maximum WSS (adjusted OR:1.20, 95%CI:1.03-1.39, p=0.019) and larger rWSS of the high-WSS region (adjusted OR:1.53, 95%CI:1.07-2.19, p=0.021), across the sICAS lesion or measured in the proximal and distal segments of the lesion, were independently associated with stenosis regression of sICAS over 1 year.
Correlations with collateral and perfusion status in cross-sectional studies												
Leng et al. 2018[17]	China	50-99% sICAS	Anterior circulation	85	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	Pressure gradient	A larger pressure gradient correlated with good leptomeningeal collaterals (adjusted OR for 10 mmHg increment in absolute pressure gradient:1.70, 95%CI:1.06-2.74, p=0.029).

Study	Country	Patient inclusion criteria	Anterior/ Posterior circulation	Number of cases	Neurovascular imaging modality	CFD model setup					Hemodynamic parameters in CFD model	Main findings on clinical implications
						Inlet boundary condition	Outlet boundary condition	Vessel wall condition	Newtonian/ non-Newtonian blood	Steady vs Transient simulation		
Lan et al. 2020[18]	China	50-99% sICAS	Anterior circulation	83	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR	Lower PR (means 0.79 vs. 0.90, p=0.015) and better leptomeningeal collateral status (56.7% vs. 34.5% with good LMCs, p=0.079) among patients with severe stenosis (70-99%) than those with moderate stenosis (50-69%); Cerebral perfusion supplying stenotic territory may depend more on leptomeningeal collateral flow (Pearson's r=0.038, p=0.051) in patients with severe stenosis but more on antegrade blood flow (Pearson's r=–0.605, p<0.001) in moderate stenosis.
Wang et al. 2023[19]	China	30-99% sICAS	Anterior & posterior circulations	18	Biplane DSA	Patient-specific	Patient-specific	Rigid, non-slip	Newtonian	Steady	PR	PR was negatively correlated with Tmax (Spearman's r=–0.73, p<0.01), the duration to the maximum of residue function.
Raynald et al. 2023[12]	China	50-70% sICAS	Anterior & posterior circulations	20	CTA	Generic	Patient-specific developed algorithm	Rigid, non-slip	Newtonian	Transient	Pressure、Velocity	Good agreement on blood flowrate derived from CFD modeling and TCD measurements (mean difference:-0.78 ml/s, p for Bland-Altman test=0.027); Less agreement on mean velocities derived from CFD modeling and TCD assessment (mean difference:-0.05 cm/s, p for Bland-Altman test=0.399).
Yin et al. 2024[10]	China	50-99% sICAS	Anterior & posterior circulations	10	CTA	Generic	Generic LPM	Rigid, non-slip	Newtonian	Transient	PR	Significantly lower PR in patients with apparent hypoperfusion than those with normal perfusion defined in 4D CTA (means 0.38 vs. 0.76, p< 0.01).
Correlations with stroke mechanisms in cross-sectional studies												
Feng et al. 2023[21]	China	50-99% sICAS	Anterior circulation	99	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR、WSSR	High WSS was an independent predictor of artery-to-artery embolism (adjusted OR:3.90, 95%CI:1.22-12.47, p=0.022) in sICAS patients of anterior circulation with low PR (PR≤median).
Li et al. 2024[22]	China	50-99% sICAS	Anterior circulation	84	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR	Low PR (PR≤median) was independently associated with internal borderzone infarcts (adjusted OR:4.22, p=0.026), but not cortical borderzone infarcts.
Correlations with cerebral small vessel disease in cross-sectional study												

Study	Country	Patient inclusion criteria	Anterior/ Posterior circulation	Number of cases	Neurovascular imaging modality	CFD model setup					Hemodynamic parameters in CFD model	Main findings on clinical implications
						Inlet boundary condition	Outlet boundary condition	Vessel wall condition	Newtonian/ non-Newtonian blood	Steady vs Transient simulation		
Zheng et al. 2024[24]	China	50-99% sICAS	Anterior circulation	112	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR、WSSR	Abnormal PR (PR≤median) and WSSR (WSSR≥fourth quartile) were associated with moderate-to-severe white matter hyperintensities (adjusted OR:10.12, p=0.018), cortical microinfarcts presence (adjusted OR:5.25, p=0.003), and moderate-to-severe cerebral small vessel disease burden (adjusted OR:12.55, p=0.033) in the ipsilateral hemisphere to sICAS.
Correlations with the risk of stroke recurrence in medically treated sICAS patients												
Leng et al. 2014[14]	China	70-99% sICAS	Anterior & posterior circulations	32	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR、SSR ratio、Velocity ratio	Higher SSR ratio (HR:1.03, 95%CI:1.00-1.05, p=0.023) and higher velocity ratio (HR:1.03, 95%CI:1.00-1.06, p=0.035) were associated with recurrent ischemic stroke in the same-territory within 1 year.
Leng et al. 2019[7]	China	50-99% sICAS	Anterior & posterior circulations	245	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR、WSSR	Low PR (PR≤median, adjusted HR:3.16, 95%CI:1.15-8.72, p=0.026) and high WSSR (WSSR≥4th quartile, adjusted HR:3.05, 95%CI: 1.25-7.41, p=0.014), separately or combined, were independently associated with recurrent same-territory ischemic stroke within 1 year.
Tian et al. 2022[25]	China	50-99% sICAS	Anterior & posterior circulations	245	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR、WSSR	A nomogram incorporating diabetes, dyslipidemia, hemodynamic significance (PR and WSSR) of sICAS, hypertension and age ≥50 years could be a useful tool to stratify sICAS patients receiveing medical treatment for the risk of recurrent ischemic stroke in the same-territory.
Feng et al. 2020[26]	China	50-99% sICAS	Anterior & posterior circulations	157	CTA	Generic	Generic	Rigid, non-slip	Newtonian	Steady	PR	Low (≤130mmHg) systolic blood pressure level (HR:5.08, 95%CI:1.05-24.49, p=0.043) may be associated with increased risk of recurrent stroke in the same-territory in sICAS with a large translesional pressure gradient.
Correlations with functional outcome in sICAS patients receiving acute reperfusion therapy												

Study	Country	Patient inclusion criteria	Anterior/ Posterior circulation	Number of cases	Neurovascular imaging modality	CFD model setup					Hemodynamic parameters in CFD model	Main findings on clinical implications
						Inlet boundary condition	**Outlet boundary condition**	**Vessel wall condition**	**Newtonian/ non-Newtonian blood**	**Steady vs Transient simulation**		
Wu et al. 2022[27]	China	Patients receiving intravenous thrombolysis or acute endovascular treatment with 50-99% sICAS	Anterior circulation	120	TOF-MRA	Generic	Patient-specific	Rigid, non-slip	Newtonian	Steady	PR、WSSR	WSSR before intravenous thrombolysis or acute endovascular treatment (OR:0.86, 95%CI:0.75-0.99, p=0.041) and difference in WSSR before and after such treatment (OR:0.72, 95%CI:0.52-1.03, p=0.043) were correlated with functional outcome at 3 months; Adding the two WSSR measures yielded higher predictive ability for the functional outcome, compared with prediction models including clinical variables only (p<0.05).
Changes of the hemodynamic parameters in sICAS with stenting treatment												
Zhang et al. 2022[28]	China	70-99% sICAS	Anterior circulation	51	3DRA	Generic	Generic	Rigid, non-slip	Newtonian	Transient	Pressure、Velocity、Vorticity、WSS	Endovascular stent angioplasty could reduce the pressure loss (means 6.46 Pa vs. 12.84 Pa, p<0.001) across the sICAS lesion compared with that before stenting.
Zhou et al. 2023[29]	China	70-99% sICAS	Posterior circulation	62	3DRA	Generic	Generic	Rigid, non-slip	Newtonian	Transient	Pressure、Velocity、Vorticity、WSS	Significantly reduced WSS (means 14.84 Pa vs. 139.49 Pa, p<0.001) at the stenosis segment after stenting treatment.

sICAS, symptomatic intracranial atherosclerotic stenosis, symptomatic intracranial atherosclerosis; CTA, computed tomography angiography; TOF-MRA, time of flight-magnetic resonance angiography; DSA, digital subtraction angiography; 3DRA, three-dimensional rotational angiography; LPM, lumped parameter model; PR, pressure ratio; SSR, shear strain rate; WSSR, wall shear stress ratio; rWSS, relative wall shear stress; WSS, wall shear stress; OR, odds ratio; CI, confidential interval; TCD, transcranial doppler ultrasound; HR, hazard ratio

Supplemental Table S4. Risk of bias assessment of 19 studies included in the systematic review using a modified Newcastle-Ottawa Scale

Study	Selection				Comparability	Outcome			Risk of bias
	Representativeness of the sample	**Sample size**	**Assessment of sICAS**	**Demonstration of clinical implications of hemodynamic parameters**	**Comparability of studies on the basis of the design or analysis**	**Assessment of Outcome#**	**Was follow-up long enough for outcome to occur#**	**Adequacy of follow-up#**	
Longitudinal studies									
Leng et al. 2014[2]	*		*	*	*	*	*	*	7
Leng et al. 2019[3]	*	*	*	*	**	*	*	*	9
Feng et al. 2020[4]	*	*	*	*	*	*	*	*	8
Lan et al. 2020[5]	*		*	*	*	*	*	*	7
Zhang et al. 2022[6]	*		*	*		*		*	5
Wu et al. 2022[7]	*	*	*	*	*	*		*	7
Tian et al. 2022[8]	*	*	*	*	*	*	*	*	8
Zhou et al. 2023[9]	*		*	*		*		*	5
Cross-sectional studies									
Nam et al. 2016[10]	*		*	*		—	—	—	3
Liu et al. 2017[11]	*		*	*		—	—	—	3
Leng et al. 2018[12]	*		*	*	**	—	—	—	5
Lan et al. 2020[13]	*		*	*	*	—	—	—	4
Zhang et al. 2021[14]	*		*	*		—	—	—	3
Wang et al. 2023[15]	*		*	*		—	—	—	3
Raynald et al. 2023[16]	*		*	*		—	—	—	3
Feng et al. 2023[17]	*		*	*	**	—	—	—	5
Yin et al. 2024[18]	*		*	*		—	—	—	3

Liu Y, *et al. Stroke Vasc Neurol* 2025; 10:e003202. doi: 10.1136/svn-2024-003202

Zheng et al. 2024[19]	*	*	*	*	*	—	—	—	5
Li et al. 2024[20]	*		*	*	*	—	—	—	4

sICAS, symptomatic intracranial atherosclerotic stenosis

#Not assessed in cross-sectional studies

Supplemental Table S5. Software for CFD modeling in 19 primary studies included in the systematic review

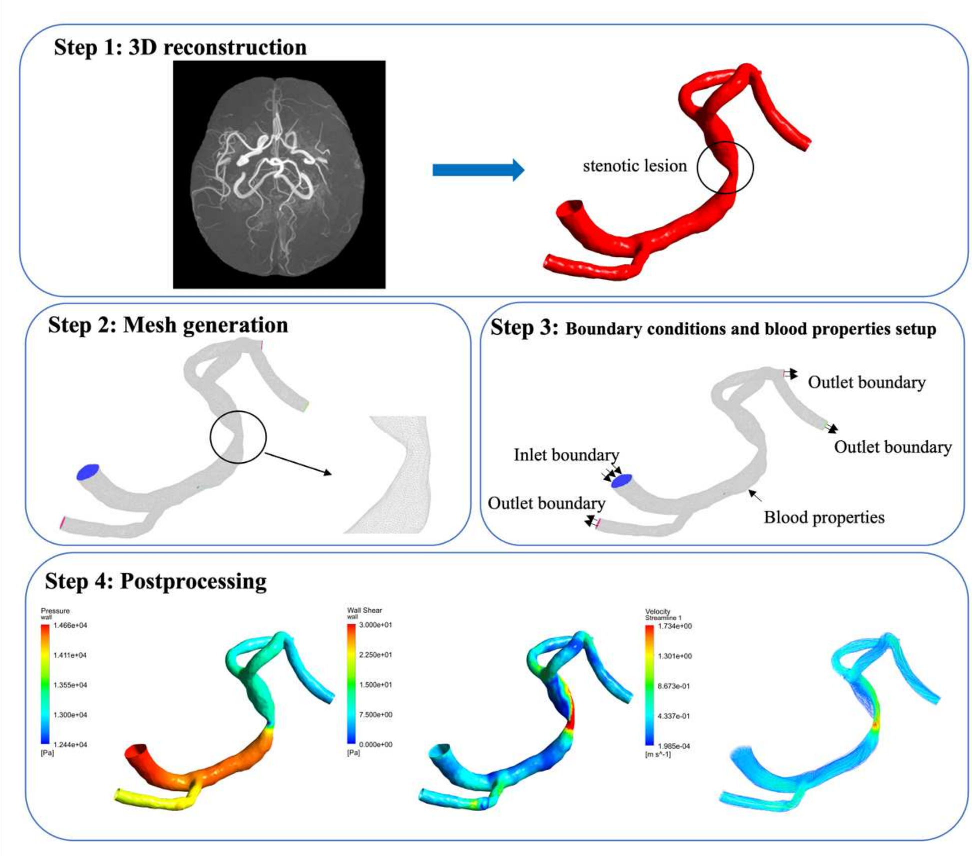
Study	3D reconstruction	Mesh generation	Boundary condition setup & Simulation	Postprocessing
Leng et al. 2014[2]	Vascular Modeling Toolkit	ANSYS ICEM CFD	ANSYS CFX	ANSYS CFD-Post
Nam et al. 2016[10]	Unknown	ANSYS ICEM CFD	ANSYS CFX	Unknown
Liu et al. 2017[11]	Mimics	ANSYS ICEM CFD	ANSYS CFX	Unknown
Leng et al. 2018[12]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Leng et al. 2019[3]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Lan et al. 2020[13]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Feng et al. 2020[4]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Lan et al. 2020[5]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Zhang et al. 2021[14]	Mimics	ANSYS ICEM CFD	ANSYS Fluent	Unknown
Zhang et al. 2022[6]	Amira	Sharc Harpoon	ANSYS	Ensight
Wu et al. 2022[7]	Mimics	ANSYS ICEM CFD	ANSYS Fluent	CFD-Post

Study	3D reconstruction	Mesh generation	Boundary condition setup & Simulation	Postprocessing
Tian et al. 2022[8]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Wang et al. 2023[15]	AccuFFicas	AccuFFicas	AccuFFicas	AccuFFicas
Raynald et al. 2023[16]	Mimics	ANSYS ICEM CFD	ANSYS CFX	Unknown
Feng et al. 2023	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Zhou et al. 2023[9]	Amira	Sharc Harpoon	ANSYS	Ensight
Yin et al. 2024[18]	Mimics	SimVascular	Unknown	Paraview
Zheng et al. 2024[19]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post
Li et al. 2024[20]	Mimics	ANSYS ICEM CFD	ANSYS CFX	CFD-Post

Liu Y, *et al. Stroke Vasc Neurol* 2025; 10:e003202. doi: 10.1136/svn-2024-003202

Supplemental Figure S1. Workflow of CFD modeling

CFD modeling for ICAS mostly involves the following steps: 1) Reconstruction of the arteries of interest from source images of neurovascular exams; 2) Generation of a mesh in the vessel lumen, wall and inlet/outlet; 3) Setup of boundary conditions on inlet/outlet and blood properties; 4) Simulation of blood flow by solving fluid dynamics equations; 5) Postprocessing of hemodynamic parameters.
Abbreviations: CFD, computational fluid dynamics; ICAS, intracranial atherosclerotic stenosis; 3D, three-dimensional



Appendix. The modified Newcastle-Ottawa Scale for risk of bias assessment of the longitudinal and cross-sectional studies included in the systematic review

Selection

1. Representativeness of the subjects:

a. Truly representative of the target subjects. *

b. Somewhat representative of the target subjects.

c. Selected group of users.

d. No description of the derivation of the included subjects.

2. Sample size:

a. Sample size ≥100. *

b. Sample size <100.

3. Assessment of sICAS:

a. Standard assessment using imaging methods. *

b. Non-standard imaging methods used.

b. No description.

4. Demonstration of clinical implications of hemodynamic parameters

a. Yes *

b. No

Comparability

5. Comparability of studies on the basis of the design or analysis:

a. study controls for the most important cofounding factor (e.g., demographics like age and sex). *

b. study controls for other confounding factors (other baseline characteristics, e.g., stenosis severity, leptomeningeal collateral status). *

Outcome

6. Assessment of Outcome#:

a. Valid/reliable measurement. *

b. Outcome data collected directly from the subjects.

c. Method of outcome assessment not described.

d. No description

7. Was follow-up long enough for outcome to occur#:

a. At least 12 months of follow-up. *

b. Less than 12 months of follow-up.

c. Length of follow-up not reported.

8. Adequacy of follow-up#:

a. No or small loss to follow-up. *

b. Large amount of loss to follow-up.

c. No statement.

#Not assessed in cross-sectional studies.

This scale for risk of bias assessment has been adapted from the Newcastle-Ottawa Scale[1]. For longitudinal study, the scale ranges from 0 to 9, with ≥ 7 indicating low risk of bias and < 6 indicating high risk of bias. For cross-sectional study, the scale ranges from 0 to 6, with ≥ 4 indicating low risk of bias and < 3 indicating high risk of bias.

Liu Y*, et al. Stroke Vasc Neurol* 2025; 10:e003202. doi: 10.1136/svn-2024-003202

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