Review

Endothelial glycocalyx injury after mechanical thrombectomy: Linking metabolic vulnerability to microvascular failure

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Abstract

Mechanical thrombectomy for acute ischemic stroke has made macrovessel reopening achievable, but angiographic success may not restore effective capillary flow or prevent cerebral target-organ damage. This hypothesis-driven narrative review examines endothelial glycocalyx injury as a blood-facing mechanism linking cardiometabolic vulnerability with post-thrombectomy microvascular failure. English-language literature from PubMed/MEDLINE, Web of Science, Embase, and Google Scholar

through 30 April 2026 was synthesized, focusing on thrombectomy, impaired microvascular reperfusion, blood-brain barrier and neurovascular-unit biology, glycocalyx shedding markers, cardiometabolic risk, imaging endpoints, and microcirculatory rescue. Experimental, biomarker, imaging, and therapeutic evidence suggests that ischemic priming, reperfusion stress, complement and metabolic injury, device-related trauma, distal embolization, and host vulnerability may converge on the glycocalyx. Glycocalyx loss may amplify leukocyte plugging, platelet adhesion, microthrombosis, vasomotor mismatch, blood-brain barrier destabilization, pericyte-associated resistance, capillary transit-time heterogeneity, and inefficient oxygen delivery. Direct proof in human thrombectomy remains limited. Serial, compartment-specific biomarkers integrated with peri-procedural perfusion and barrier imaging are needed to test whether endothelial glycocalyx injury contributes to incomplete tissue-level reperfusion after angiographically successful mechanical thrombectomy.

Keywords: Acute ischemic stroke, mechanical thrombectomy, endothelial glycocalyx, metabolic vulnerability, cerebral target-organ damage, microvascular reperfusion failure, blood-brain barrier, syndecan-1

INTRODUCTION: THE POST-THROMBECTOMY REPERFUSION GAP

Mechanical thrombectomy (MT) has shifted the therapeutic frontier in acute ischemic stroke caused by anterior-circulation large-vessel occlusion (LVO). In many patients, the immediate procedural challenge - reopening the target artery - can now be met, and randomized evidence has established the clinical value of endovascular therapy (EVT) across broad patient groups[1]. The unresolved problem is what happens after the artery is open. A substantial proportion of patients with modified Thrombolysis in Cerebral Infarction/expanded Treatment in Cerebral Ischemia (mTICI/eTICI)-defined success still do not regain meaningful neurological function, the dissociation commonly

described as futile recanalization[2]. From a target-organ damage perspective, the post-recanalization brain is not simply a reperfused tissue bed; it is a metabolically vulnerable microvascular organ interface exposed to abrupt hemodynamic, inflammatory, and oxidative stress.

This dissociation is not simply a flaw in an angiographic grading scale. It reflects a layered biological problem: parent-vessel patency, angiographic reperfusion, parenchymal perfusion, microvascular oxygen delivery, and clinical recovery are linked but not identical. The downstream vascular bed may remain hypoperfused, become hyperperfused, distribute flow inefficiently, leak across the BBB, or become compressed and metabolically ineffective even after proximal flow has been restored[3-5]. Reported rates of impaired microvascular reperfusion (IMR) or persistent hypoperfusion vary widely because studies differ in timing, imaging modality, reperfusion thresholds, and exclusion of competing causes[3]. Angiographic success is therefore necessary for tissue salvage but is not an adequate biological readout of it.

Several mechanisms have been proposed to explain the post-thrombectomy reperfusion gap: distal embolization, leukocyte plugging, microthrombi, pericyte contraction, endothelial swelling, BBB disruption, edema, HT, and impaired autoregulation[3-5]. These processes are often discussed separately. What is missing is a blood-facing structure that can plausibly connect hemodynamic stress, inflammation, immunothrombosis, endothelial barrier failure, and NVU dysfunction without forcing them into a single linear sequence.

The endothelial glycocalyx is well positioned for that role. It sits at the luminal surface of endothelial cells and is among the first cerebral microvascular structures exposed to ischemic priming, renewed shear stress, circulating inflammatory mediators, complement, platelets, leukocytes, thrombin, and device-related mechanical

perturbation[6-10]. Cardiometabolic vulnerability may further lower the resilience of this interface before MT occurs, particularly in patients with diabetes, hyperglycemia, hypertension, renal dysfunction, systemic inflammation, or endothelial dysfunction. The claim advanced here is intentionally narrow: endothelial glycocalyx injury is a plausible and testable contributor to post-MT microvascular dysfunction, incomplete tissue-level reperfusion, and cerebral target-organ injury. It should not be presented as the proven central cause of human MT-associated no-reflow or futile recanalization. The focus is anterior-circulation LVO, although the same reasoning may later prove relevant to posterior-circulation or other occlusion territories.

Scope of this review

This article is a hypothesis-driven narrative review and mechanistic translational perspective. It is not a systematic review, meta-analysis, guideline, or expert consensus statement, and it does not argue that glycocalyx injury has already been established as a dominant determinant of futile recanalization.

The literature base was assembled through targeted searches of PubMed/MEDLINE, Web of Science, Embase, and Google Scholar for English-language articles published through April 30, 2026. Search terms included combinations of mechanical thrombectomy, endovascular therapy, futile recanalization, no-reflow, impaired microvascular reperfusion, incomplete tissue-level reperfusion, endothelial glycocalyx, syndecan-1, heparan sulfate, hyaluronan, blood-brain barrier, neurovascular unit, metabolic vulnerability, cardiometabolic risk, hyperglycemia, diabetes, hypertension, renal dysfunction, target-organ damage, perfusion imaging, DSA parametric color coding, intra-arterial thrombolysis, and microcirculatory rescue. Additional references were identified from cited articles and selected for mechanistic relevance.

Because the purpose was conceptual synthesis rather than evidence grading, no PRISMA workflow, formal risk-of-bias assessment, or meta-analysis was performed. Priority was given to studies addressing MT, IMR, BBB/NVU biology, glycocalyx structure and shedding markers, cardiometabolic and endothelial vulnerability, microcirculatory rescue, and peri-procedural imaging. Where the evidence is indirect or extrapolated from non-MT settings, that limitation is stated rather than embedded repeatedly in every mechanistic sentence.

DEFINITIONS AND CONCEPTUAL HIERARCHY

A useful discussion of reperfusion failure after MT has to keep several terms apart. Figure 1 summarizes the conceptual hierarchy linking target large-vessel occlusion, macrovessel recanalization, angiographic reperfusion, tissue-level reperfusion, microvascular dysfunction, and clinical outcome, while Table 1 defines the key terms used throughout this review. Recanalization refers to reopening of the previously occluded macrovessel. Angiographic reperfusion describes contrast filling of the downstream territory, usually graded by mTICI/eTICI scales. Tissue-level reperfusion asks a different question: whether parenchymal perfusion and oxygen delivery are sufficient for threatened tissue to survive. Microvascular reperfusion is still more granular, referring to arteriolar, capillary, and venular patency, tone, permeability, rheology, and flow distribution. IMR or no-reflow denotes persistent microvascular dysfunction despite macrovessel recanalization; it is a mechanistic or imaging state rather than a clinical outcome by itself[3,5].

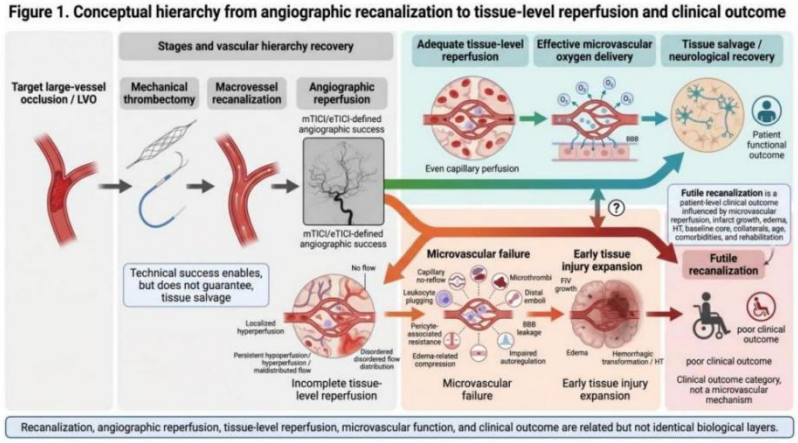

Figure 1. Conceptual hierarchy from angiographic recanalization to tissue-level reperfusion and clinical outcome. The diagram separates target large-vessel occlusion (LVO), macrovessel recanalization, mTICI/eTICI-defined angiographic reperfusion, tissue-level reperfusion, and patient-level clinical outcome. One route proceeds from target LVO to macrovessel recanalization, angiographic reperfusion, adequate tissue-level reperfusion, and tissue salvage. The alternative route shows that angiographic reperfusion may coexist with incomplete tissue-level reperfusion, followed by microvascular failure, FIV growth, edema, and/or HT, thereby increasing the likelihood of futile recanalization. Technical success enables but does not guarantee tissue salvage. Futile recanalization should be displayed as a clinical outcome category, not as a microvascular mechanism.

Table 1. Conceptual hierarchy of post-thrombectomy reperfusion failure.

Term	Definition	Typical measurement	Mechanistic meaning	Clinical limitation
Recanalization	Reopening of the occluded parent artery.	DSA, CTA, MRA; component of mTICI/eTICI assessment.	Restores proximal access for blood flow.	Does not prove parenchymal perfusion or tissue survival.
Angiographic	Contrast filling	mTICI/eTICI	Describes	Insensitive to

Term	Definition	Typical measurement	Mechanistic meaning	Clinical limitation
reperfusion	of the downstream vascular territory after treatment.	grade on DSA.	macroscopic flow restoration.	capillary flow, oxygen extraction, BBB leakage, and delayed infarct growth.
Tissue-level reperfusion	Adequate parenchymal perfusion and oxygen delivery to threatened tissue.	CTP, MRP, ASL, perfusion maps, and tissue outcome.	Intermediate layer between technical success and tissue salvage.	Definitions vary; may include hypoperfusion, hyperperfusion, or flow maldistribution.
Microvascular reperfusion	Functional arteriolar, capillary, and venular flow with preserved rheology, tone, and barrier function.	DSA-PCC, CTP/MRP/ASL, BOLD-CVR, experimental microscopy.	Reflects downstream vascular network function.	Difficult to measure directly in humans.
IMR / no-reflow	Persistent microvascular dysfunction despite macrovessel	Post-MT perfusion imaging, angiographic flow delay,	Mechanistic or imaging state involving obstruction,	Should not be equated with futile recanalization or 90-day mRS

Term	Definition	Typical measurement	Mechanistic meaning	Clinical limitation
	recanalization.	experimental capillary non-filling.	constriction, edema, or shunting.	alone.
Incomplete tissue-level reperfusion	Residual perfusion or oxygen-delivery abnormality after angiographically successful MT.	Hypoperfusion, hyperperfusion, CTH, BBB permeability, FIV growth, edema, HT.	Intermediate risk layer for infarct expansion and poor recovery.	Heterogeneous; may have multiple causes beyond glycocalyx injury.
Futile recanalization	Poor clinical outcome despite technically successful recanalization or reperfusion.	Usually a 90-day mRS threshold, often mRS 3-6 or 4-6.	Patient-level clinical outcome category.	Affected by age, baseline core, collaterals, cardiometabolic comorbidity, infection, rehabilitation, systemic complications, and target-organ reserve.

Incomplete tissue-level reperfusion is broader than classical no-reflow. It may include persistent hypoperfusion, regional hyperperfusion from autoregulatory failure,

microvascular shunting, capillary transit-time heterogeneity (CTH), impaired oxygen extraction, BBB leakage, edema, and evolving infarct growth[3,4]. Futile recanalization, by contrast, is a patient-level outcome category, most often defined by poor 90-day modified Rankin Scale (mRS) despite angiographically successful recanalization or reperfusion. It is shaped not only by reperfusion biology but also by age, premorbid status, baseline core volume, collateral status, stroke severity, infection, rehabilitation access, edema, HT, systemic complications, and comorbid disease[2].

Placing the glycocalyx hypothesis within this hierarchy is important. Glycocalyx injury should not be equated with futile recanalization. The more defensible position is that it may contribute to intermediate tissue and imaging states that increase the probability of poor recovery. In a metabolism and target-organ damage framework, these intermediate states can also be viewed as early expressions of cerebral microvascular target-organ injury in a host whose vascular surface may already be metabolically vulnerable. For that reason, this review uses angiographically successful reperfusion when referring to mTICI/eTICI-defined procedural success, rather than implying that tissue salvage has been achieved.

THE ENDOTHELIAL GLYCOCALYX AS A BLOOD-FACING BBB/NVU INTERFACE

The endothelial glycocalyx is a dynamic, carbohydrate-rich layer covering the luminal surface of endothelial cells. It contains glycosaminoglycans, including heparan sulfate, hyaluronan, and chondroitin sulfate; membrane-bound proteoglycans, including syndecans and glypicans; mucin-domain glycoproteins; sialylated glycoproteins; and plasma-derived proteins incorporated into the endothelial surface layer[7,8,11,12]. Its composition and thickness vary by vascular bed, flow state, inflammatory milieu, and disease context.

The cerebral glycocalyx should not be treated as a generic peripheral vascular coating simply relocated to the brain. Brain microvessels are embedded within the BBB and NVU, where endothelial cells, pericytes, basement membrane, astrocytic endfeet, microglia, neurons, and extracellular matrix jointly regulate barrier function, flow distribution, and metabolic coupling[9-11]. The glycocalyx is not synonymous with either the BBB or the NVU. It is the luminal endothelial surface layer operating within that specialized neurovascular environment.

That location is central to the hypothesis. An intact glycocalyx limits direct platelet and leukocyte contact with the endothelial membrane, supports antithrombotic and anticoagulant surface properties, contributes to permeability control, and transduces shear stress into endothelial nitric oxide (NO)-dependent vasomotor responses[6-8]. Experimental work also links glycocalyx integrity to suppression of endothelial transcytosis and preservation of BBB function after ischemic stroke[11]. These properties make the glycocalyx a plausible point of convergence between cardiometabolic endothelial vulnerability and acute reperfusion-associated cerebral target-organ damage.

Recent Nature work has sharpened the brain-specific relevance of this layer by showing that glycocalyx dysregulation and mucin-domain glycoproteins can influence BBB stability in aging and disease[12]. This strengthens the rationale for considering the glycocalyx as a BBB-associated luminal structure. It should not, however, be read as direct evidence that glycocalyx injury causes no-reflow after MT in patients; its value for the present argument is mechanistic, not clinical proof.

TRIGGERS OF GLYCOCALYX INJURY AFTER ANGIOGRAPHICALLY SUCCESSFUL MT

Glycocalyx instability after MT is unlikely to begin or end with a single insult. It is more plausibly produced by overlapping ischemic, reperfusion, mechanical, thromboinflammatory, metabolic, and host-related stresses that converge on an already vulnerable luminal surface. This framing is important because MT-associated cerebral injury may represent not only a procedural reperfusion problem but also an acute expression of pre-existing cardiometabolic endothelial vulnerability and target-organ susceptibility.

Ischemic priming. During arterial occlusion, endothelial hypoxia, ATP depletion, acidosis, ionic dysregulation, low shear stress, and local inflammatory signaling may weaken glycocalyx homeostasis before the occluded artery is reopened[6,11,29]. Reperfusion may therefore expose and amplify an injured surface rather than acting on a normal baseline.

Reperfusion-associated oxidative and inflammatory injury. Recanalization restores oxygen and substrate delivery, but it also brings reactive oxygen species, abrupt shear changes, neutrophil recruitment, thrombin generation, and inflammatory cytokines into the ischemic microvascular bed[6,28-30]. These processes may promote enzymatic shedding of glycocalyx components. Once the layer is thinned, adhesion molecules and procoagulant endothelial surfaces may become more accessible.

Complement activation and metabolic stress. Complement contributes to cerebral ischemia-reperfusion injury, and metabolic intermediates such as succinate can drive oxidative injury in experimental MT models[28,30]. Diabetes, acute hyperglycemia, insulin resistance, renal dysfunction, and systemic inflammation may intensify oxidative and inflammatory stress at the luminal surface, although these pathways are

not specific to the glycocalyx. They are best viewed as parallel or converging stressors that may injure the endothelial surface while also damaging other parts of the NVU.

Device-related endothelial trauma and altered shear stress. Stent retrievers, aspiration catheters, multiple passes, clot-device interaction, and rapid restoration of flow can perturb the endothelial surface[24-26]. Human and experimental studies support vessel-wall and endothelial trauma after MT, although direct visualization of cerebral glycocalyx damage from devices in patients is lacking. The anatomical inference is straightforward: the glycocalyx is the first endothelial layer encountered by devices and by newly restored flow fields.

Distal embolization and residual microthrombotic burden. Distal clot migration and residual microemboli can create patchy low-flow territories, maintain local thromboinflammation, and perpetuate downstream obstruction[5,27]. In these regions, glycocalyx loss could favor platelet and leukocyte-endothelial contact, while microemboli themselves may sustain endothelial stress.

Host vulnerability. Aging, diabetes, acute hyperglycemia, hypertension, dyslipidemia, renal dysfunction, infection, systemic inflammation, endothelial dysfunction, and peri-procedural blood-pressure fluctuation may lower the threshold for glycocalyx injury or slow recovery[2,6,12]. These factors are not downstream consequences of glycocalyx loss. They are background conditions that may determine whether the luminal surface remains resilient after recanalization and whether the reperfused brain behaves as a recoverable target organ or a vulnerable microvascular injury site.

MECHANISTIC PATHWAYS LINKING GLYCOCALYX INJURY TO TISSUE-LEVEL REPERFUSION FAILURE

The useful question is not whether glycocalyx loss explains every case of post-MT reperfusion failure. It almost certainly does not. The more testable question is whether injury to this blood-facing layer makes established no-reflow mechanisms more likely, more persistent, or more spatially heterogeneous [Figure 2].

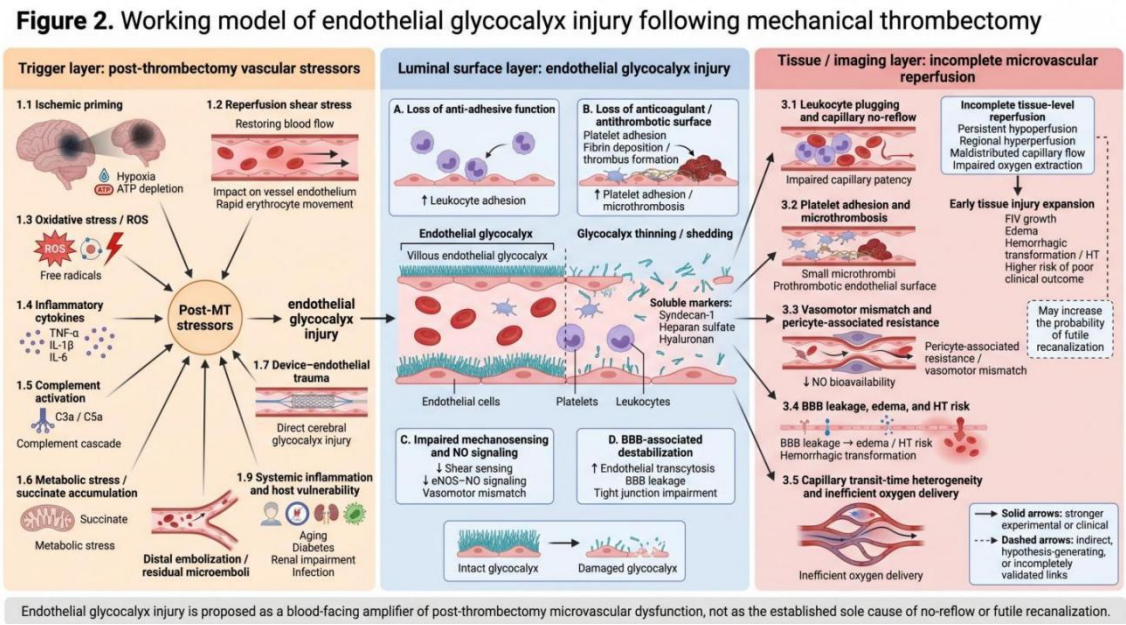

Figure 2. Working model of endothelial glycocalyx injury after mechanical thrombectomy. The model contains three layers: a trigger layer, a luminal surface layer, and a tissue/imaging layer. The trigger layer includes ischemic priming, reperfusion shear stress, oxidative stress, complement activation, metabolic stress, cardiometabolic vulnerability, distal embolization, device-endothelial trauma, systemic inflammation, and host vulnerability. The luminal surface layer includes glycocalyx thinning or shedding, endothelial activation, loss of anti-adhesive and anticoagulant surface properties, loss of mechanosensing, and BBB-associated destabilization. The tissue/imaging layer includes leukocyte plugging, platelet adhesion and microthrombosis, BBB leakage, edema, HT risk, pericyte-associated resistance, increased CTH, shunting, maldistributed perfusion, inefficient oxygen delivery, and

cerebral target-organ injury. Solid arrows indicate comparatively stronger experimental or clinical support. Dashed arrows indicate hypothesis-generating, indirect, model-based, or incompletely validated links rather than established causal relationships.

Loss of anti-adhesive function and leukocyte plugging. An intact glycocalyx separates circulating leukocytes from endothelial adhesion platforms. Thinning or shedding could make leukocyte rolling, adhesion, and capillary stalling more likely[6-8]. In a mouse thrombin model of middle cerebral artery occlusion with recanalization, neutrophil obstruction of brain capillaries was identified as a major contributor to no-reflow, with approximately 30% of capillaries remaining occluded after thrombolysis in that model[13]. This is strong animal evidence for leukocyte plugging as a no-reflow mechanism; it does not identify glycocalyx shedding as the initiating event in human MT.

Platelet adhesion, microthrombosis, and loss of antithrombotic surface properties. Glycocalyx loss may expose proadhesive and procoagulant endothelial surfaces, bring platelets closer to the endothelial membrane, and reduce local antithrombotic capacity[6-8]. The endothelial surface layer helps maintain a low-thrombogenic state through spatial organization of heparan sulfate, antithrombin-related effects, thrombomodulin-associated pathways, and shear-dependent endothelial signaling[6-8]. Microthrombi and fibrin-platelet aggregates are recognized components of no-reflow biology[5]. What remains unresolved is how much of the post-MT microthrombotic burden in patients is specifically driven by cerebral glycocalyx injury rather than by distal emboli, thrombin generation, stagnant flow, or systemic inflammation.

Impaired mechanosensing and NO-dependent vasomotor mismatch. Glycocalyx-dependent mechanotransduction links shear stress to endothelial NO

production and vasomotor regulation[7,8]. Abrupt recanalization changes shear conditions across vessels that have just experienced ischemia. If the glycocalyx is damaged, endothelial sensing of restored flow may become uneven, contributing to heterogeneous vasodilation, vasoconstriction, or autoregulatory failure. Clinical BOLD cerebrovascular reactivity (BOLD-CVR) data showing steal phenomena after angiographically successful EVT support persistent hemodynamic impairment, but they do not establish glycocalyx causality[31].

BBB destabilization, endothelial transcytosis, edema, and HT risk. Experimental stroke studies indicate that glycocalyx disruption can increase BBB permeability and endothelial transcytosis, even when tight-junction morphology is not the sole abnormality[10,11]. This makes glycocalyx loss a plausible contributor to edema and HT risk after reperfusion. Human evidence is still largely associative and biomarker-based, so the claim should remain focused: glycocalyx injury may participate in barrier failure, but it has not been shown to independently cause HT after MT.

Pericyte contraction and mural or extravascular resistance. Pericyte-mediated capillary constriction is a well-established experimental mechanism of post-ischemic no-reflow. Rodent and ex vivo studies show that pericyte dysfunction can persist after recanalization and reduce microvascular perfusion[14,15]. Glycocalyx injury could interact with this pathway through endothelial NO signaling, edema, oxidative stress, and leukocyte stalling. Direct endothelial glycocalyx-pericyte coupling after MT, however, remains an open experimental question.

Capillary transit-time heterogeneity, shunting, and impaired oxygen extraction. Theoretical and imaging work suggests that capillary flow heterogeneity can impair oxygen extraction even when total cerebral blood flow is not uniformly reduced[16-18]. Glycocalyx injury could contribute to this pattern by promoting patchy adhesion,

microthrombosis, vasomotor mismatch, and barrier leakage. The point is conditional, not universal: restored cerebral blood flow may coexist with inefficient oxygen extraction in selected settings, but perfusion-metabolic validation is needed to identify when this occurs.

INCOMPLETE TISSUE-LEVEL REPERFUSION AS AN INTERMEDIATE PHENOTYPE

Incomplete tissue-level reperfusion is best treated as the intermediate layer between technical success and clinical outcome. It is not synonymous with futile recanalization. It is a tissue and imaging state that may increase the likelihood of infarct growth, edema, HT, and poor neurological recovery. In the present framing, it also represents a candidate early phenotype of cerebral target-organ damage after recanalization, especially when the pre-existing endothelial surface is made vulnerable by cardiometabolic stress.

This state has several faces. Persistent hypoperfusion may reflect IMR, distal emboli, residual proximal or diffuse flow limitation, or edema-related compression. Hyperperfusion may signal autoregulatory failure and BBB vulnerability. Maldistributed capillary flow may produce shunting and inefficient oxygen extraction. BBB leakage may drive vasogenic edema, increase extravascular resistance, and contribute to HT. Follow-up imaging markers such as final infarct volume (FIV), infarct growth, edema, and HT are therefore closer to the biological consequences of reperfusion failure than the 90-day mRS alone[31-34].

The distinction has practical consequences. The 90-day mRS is shaped by many variables outside peri-procedural microvascular biology, including age, baseline core volume, collateral status, eloquence of the infarcted tissue, pre-stroke disability, infection, delirium, rehabilitation intensity, edema, HT, decompressive surgery,

systemic complications, and cardiometabolic comorbidity[2]. Mechanistic studies should therefore pair functional outcomes with early imaging endpoints. Those endpoints are more temporally proximate to vascular injury and better suited for testing whether glycocalyx-marker dynamics move with tissue-level reperfusion failure. In this view, glycocalyx injury is a candidate contributor to imaging-defined incomplete reperfusion and cerebral target-organ damage, not a direct label for poor clinical outcome.

BIOMARKER EVIDENCE: SYNDECAN-1 AS AN IMPERFECT PERIPHERAL SHADOW OF CEREBRAL GLYCOCALYX INJURY

The clinical evidence for the glycocalyx hypothesis is limited and should be read in layers. Most human studies use circulating shedding products - principally syndecan-1, heparan sulfate, and hyaluronan. These markers are practical because they can be sampled serially. Their weakness is the same feature that makes them easy to measure: they circulate systemically and are not specific to the cerebral microvasculature.

Closest human evidence. The most relevant human data come from LVO studies that sampled both intracranial and peripheral compartments. Intracranial and peripheral plasma syndecan-1 showed spatiotemporal heterogeneity, suggesting that distal occlusion-site signals and peripheral venous levels may not be synchronized[19]. This supports compartment-specific sampling, although the evidence remains constrained by small sample size and biomarker nonspecificity.

Peripheral studies and what they add. Longitudinal peripheral biomarker studies in EVT-treated LVO cohorts suggest that syndecan-1 dynamics are associated with neurological deterioration, 90-day mortality, or prognosis[20,21]. In thrombolysis-treated patients, higher plasma syndecan-1 has been associated with unfavorable outcomes[22]. A 2024 MT cohort reported that lower peripheral syndecan-1 on postoperative day 1

was associated with worse prognosis, a reminder that measurement timing can reverse intuitive interpretations[21]. Another study reported lower syndecan-1 levels after pre-thrombectomy intravenous thrombolysis, but this should be read as an association with peripheral shedding dynamics rather than proof of glycocalyx repair[23].

How temporal patterns might be interpreted. Early high syndecan-1 may reflect acute shedding and washout from injured endothelial surfaces. Later low levels could reflect depletion of endothelial reserve, altered clearance, impaired repair, or differences in systemic vascular contribution. Each explanation is biologically plausible; none is established. Serial paired intracranial and peripheral sampling is needed before a temporal biomarker pattern can be assigned mechanistic meaning.

What cannot be assumed. Peripheral syndecan-1 is not a real-time mirror of the cerebral microvascular glycocalyx. It may derive from lung, kidney, liver, gut, systemic endothelium, or traumatically injured vasculature. Levels may be influenced by diabetes, hypertension, renal dysfunction, infection, sepsis, chronic inflammation, anesthesia, contrast agents, heparin exposure, intravenous thrombolysis, blood-pressure management, number of device passes, reperfusion grade, and sampling time. A single peripheral blood draw is therefore unlikely to define the state of the cerebral luminal surface. At present, peripheral syndecan-1 is best regarded as an imperfect peripheral shadow of cerebral glycocalyx injury and should be interpreted together with cardiometabolic context and brain-specific imaging.

Table 2. Evidence map for the endothelial glycocalyx hypothesis.

Evidence domain	Representative evidence	Representative references	Relationship to glycocalyx hypothesis	Key limitations	Evidence strength
Brain	BBB glycocalyx	[9-12]	Supports the	Not	Animal

Evidence domain	Representative evidence	Representative references	Relationship to glycocalyx hypothesis	Key limitations	Evidence strength
endothelial glycocalyx and BBB/NVU biology	studies, ischemic stroke models, and mucin-domain glycoprotein work in aging/disease.		glycocalyx as a blood-facing BBB-associated surface.	specific to human MT; aging/disease data should not be overgeneralized.	evidence / mechanistic inference
Ischemia-reperfusion glycocalyx degradation	Organ ischemia-reperfusion literature and stroke BBB models.	[6,11,29,30]	Shows vulnerability of the luminal surface to reperfusion stress.	Most data are non-cerebral or experimental; pathways are not glycocalyx-specific in MT.	Animal evidence / mechanistic inference
Neutrophil plugging	Mouse no-reflow studies after recanalization.	[13]	Provides a downstream mechanism that glycocalyx loss could	Does not prove glycocalyx as the upstream driver in	Animal evidence

Evidence domain	Representative evidence	Representative references	Relationship to glycocalyx hypothesis	Key limitations	Evidence strength
			amplify.	humans.	
Pericyte contraction	Rodent and ex vivo studies showing capillary constriction and persistent no-reflow.	[14,15]	Could interact indirectly with endothelial NO and edema pathways.	Direct glycocalyx-pericyte causal coupling after MT is untested.	Animal evidence
CTH and oxygen extraction	Modeling and clinical perfusion-MRI work on capillary transit patterns.	[16-18,31]	Provides a hemodynamic state potentially amplified by patchy luminal injury.	Often model-based or indirect; not glycocalyx-specific.	Mechanistic inference / indirect clinical evidence
Intracranial versus peripheral syndecan-1 sampling	Local distal occlusion-site and peripheral syndecan-1 heterogeneity.	[19]	Supports compartment-specific biomarker study design.	Small cohorts; no direct visualization of cerebral glycocalyx.	Relatively direct human biomarker evidence
Peripheral shedding-marker	Serial EVT and MT cohorts; thrombolysis-rel	[20-23]	Suggests shedding-marker dynamics	Peripheral levels are nonspecific	Indirect human biomarke

Evidence domain	Representative evidence	Representative references	Relationship to glycocalyx hypothesis	Key limitations	Evidence strength
dynamics	ated syndecan-1 studies.		may be relevant to peri-procedural vascular injury.	and timing-dependent.	r evidence
DSA-PCC and perfusion imaging	Angio-suite PCC, CTP/MRP/ASL, BOLD-CVR, FIV/edema/HT biomarkers.	[31-34]	Can define the reperfusion states needed to test the hypothesis.	Imaging patterns are not specific to glycocalyx injury.	Indirect clinical evidence
Post-EVT microcirculatory rescue	CHOICE, PEARL, intra-arterial tenecteplase, and meta-analyses.	[35-40]	Shows that the post-EVT microcirculation may remain therapeutically actionable.	Does not demonstrate glycocalyx repair.	Direct human evidence for rescue concept; not direct glycocalyx evidence
Putative glycocalyx-directed therapies	Sulodexide, glycosaminoglycan restoration, and heparanase-relat	[41-44]	Potential mechanistic intervention class.	Mostly non-brain, non-MT, preclinical, sepsis,	Unproven assumption for acute post-MT

Evidence domain	Representative evidence	Representative references	Relationship to glycocalyx hypothesis	Key limitations	Evidence strength
	ed strategies.			diabetes, or vascular-injury settings.	stroke
Cardiometabolic vulnerability and cerebral target-organ susceptibility	Diabetes, hyperglycemia, hypertension, dyslipidemia, renal dysfunction, systemic inflammation, and endothelial dysfunction as host modifiers of reperfusion injury.	[2,6,12,29,30]	Frames the brain microvasculature as a target-organ interface in which pre-existing endothelial vulnerability may lower the threshold for glycocalyx injury.	Risk-context evidence is not proof of cerebral glycocalyx causality after MT; metabolic factors may also influence outcome through non-glycocalyx pathways.	Clinical context / mechanistic inference

THERAPEUTIC IMPLICATIONS

Established or near-clinical microcirculatory rescue

Adjunctive intra-arterial thrombolysis after angiographically successful EVT is the most clinically advanced example of post-recanalization microcirculatory rescue.

CHOICE suggested improved excellent outcome with intra-arterial alteplase after angiographically successful thrombectomy, but the trial was phase 2b and required replication[35]. PEARL subsequently reported a higher proportion of 90-day mRS 0-1 after intra-arterial alteplase in selected patients with eTICI-defined successful angiographic reperfusion[36]. Phase 1b/2a randomized evidence with intra-arterial tenecteplase supports procedural feasibility, dose selection, and safety signals, but does not yet establish clinical efficacy[37]. Contemporary meta-analyses support the broader idea that the post-EVT microcirculation can remain therapeutically actionable[38-40]. None of these data demonstrate glycocalyx repair. Their relevance is that tissue-level reperfusion may still be modifiable after the angiogram looks successful.

Mechanism-adjacent endothelial protection

Strategies targeting oxidative stress, complement activation, metabolic stress, endothelial inflammation, BBB disruption, and edema may indirectly stabilize the endothelial surface[28-30]. Hyperglycemia, renal dysfunction, blood-pressure variability, and systemic inflammation are clinically relevant host and peri-procedural modifiers, although their direct relationship to glycocalyx preservation after MT remains insufficiently defined. These approaches are therefore mechanism-adjacent rather than glycocalyx-specific. Their translational value will depend on patient selection, timing, safety, and concordance with imaging-defined reperfusion states. For a metabolism-oriented trial design, cardiometabolic phenotype should be treated as both a biological modifier and an adjustment variable, rather than as background clinical noise.

Putative glycocalyx-directed therapies

Sulodexide, heparanase inhibition, glycosaminoglycan restoration, preservation of hyaluronan or heparan sulfate, and strategies aimed at reducing enzymatic shedding are conceptually attractive[41-44]. The evidentiary problem is context. Much of the

supporting work comes from diabetes, sepsis, non-cerebral vascular injury, porcine or rodent models, and endothelial cell systems. Acute post-MT stroke differs in timing, bleeding risk, BBB vulnerability, concomitant antithrombotic exposure, and infarct biology. These therapies should therefore be described as conceptual, preclinical, cross-disease, or trial-enabling candidates, not as ready for routine clinical use in acute stroke.

Trial-enabling risk stratification

The near-term translational priority is not to give a glycocalyx-directed drug to every successfully recanalized patient. It is to identify the subgroup with imaging-defined incomplete microvascular reperfusion and, within that subgroup, to determine whether cardiometabolic vulnerability marks a higher-risk target-organ injury phenotype. Candidate tools include digital subtraction angiography parametric color coding (DSA-PCC), computed tomography perfusion (CTP), magnetic resonance perfusion (MRP), arterial spin labeling (ASL), BBB permeability imaging, BOLD-CVR, early FIV, infarct growth, edema, and HT[31-34]. A rational trial would first define a high-risk post-thrombectomy reperfusion state, then test whether targeted microcirculatory rescue or endothelial-surface stabilization improves mechanistic imaging endpoints and, secondarily, clinical outcomes.

Table 3. Imaging and tissue endpoints for future studies.

Imaging or tissue endpoint	Measurement window	Biological meaning	Advantages	Limitations	Recommended future use
DSA-PCC	Immediately post-recanalization.	Angio-suite flow delay and parametric	Available during the procedure; time-sensitive	Requires standardization, validation,	Candidate primary imaging endpoint for

Imaging or tissue endpoint	Measurement window	Biological meaning	Advantages	Limitations	Recommended future use
		hemodynamic state.	.	and software harmonization.	immediate IMR.
CTP	Early post-MT, ideally within 1-6 h and/or up to 72 h.	Parenchymal hypoperfusion, hyperperfusion, and perfusion delay.	Clinically familiar and accessible.	Protocol heterogeneity; thresholds vary; delayed scans may miss transient states.	Integrate with biomarkers and 24 h tissue outcome.
MRP	Early post-MT when feasible.	Parenchymal perfusion and transit delay.	Rich tissue characterization when paired with DWI/FLAIR.	Logistical barriers in unstable patients; protocol variability.	Use in mechanistic cohorts with MRI availability.
ASL	Early post-MT and follow-up.	Noncontrast cerebral blood flow and arterial transit effects.	Avoids contrast; repeatable.	Sensitive to transit artifacts and acquisition variability.	Use for serial perfusion trajectories.

Imaging or tissue endpoint	Measurement window	Biological meaning	Advantages	Limitations	Recommended future use
BBB permeability imaging	Early post-MT and 24 h when feasible.	Barrier leakage and edema/HT risk.	Mechanistically close to endothelial injury.	Limited availability; contrast and protocol issues.	Use in selected mechanistic cohorts.
BOLD-CVR	Early or subacute post-EVT when feasible.	Vasomotor reserve and steal physiology.	Captures autoregulatory dysfunction.	Less available acutely; not specific to glycocalyx injury.	Use as supportive hemodynamic endpoint.
FIV and infarct growth	Follow-up CT/MRI, typically 12-96 h; 24 h preferred for early trials.	Tissue injury expansion.	Closer to mechanism than 90-day mRS.	Downstream and multifactorial.	Use as secondary mechanistic endpoint.
Edema, HT, symptomatic intracranial hemorrhage (sICH)	Follow-up CT/MRI, typically 12-96 h.	Barrier failure, mass effect, and safety state.	Clinically important and safety-relevant.	Multifactorial; affected by infarct size and antithrombotics.	Use as safety and barrier-related endpoints.

Imaging or tissue endpoint	Measurement window	Biological meaning	Advantages	Limitations	Recommended future use
NIHSS change	24 h, 7 days, discharge.	Early neurological response.	Clinically meaningful and temporally closer than 90-day mRS.	Affected by eloquence, sedation, complications, and edema.	Use as clinical secondary endpoint.
90-day mRS	90 days.	Patient-level functional outcome.	Standard stroke efficacy endpoint.	Affected by age, premorbid status, rehabilitation, infection, and systemic complications.	Use as clinical endpoint, not sole mechanistic endpoint.

RESEARCH AGENDA

The next phase should move from broad plausibility to designs that can support, refine, or reject the hypothesis. Five priorities follow. First, the target state must be named precisely: no-reflow, IMR, persistent hypoperfusion, hyperperfusion, BBB leakage, edema, FIV growth, and futile recanalization are related but not interchangeable. Second, biomarker sampling should be serial and, whenever feasible, compartment-specific. Third, imaging and biomarker measurements need to be close enough in time to test temporal ordering. Fourth, analyses should examine mediation rather than simple association. Fifth, cardiometabolic vulnerability should be measured

explicitly so that diabetes, hyperglycemia, hypertension, dyslipidemia, renal dysfunction, and systemic inflammation can be tested as modifiers of glycocalyx injury and cerebral target-organ damage. Candidate soluble biomarkers for future studies are summarized in Supplementary Table 1.

Box 1. Proposed prospective cohort to test the glycocalyx hypothesis after MT.

Population: Adults with anterior-circulation LVO treated with MT who achieve near-complete or complete angiographic reperfusion, preferably mTICI/eTICI 2c-3, with prespecified sensitivity analyses restricted to eTICI 3. Baseline cardiometabolic phenotype should be recorded, including diabetes status, admission glucose, HbA1c if available, hypertension, dyslipidemia, renal function, systemic inflammation, and other target-organ damage indicators.

Sampling: Pre-MT peripheral venous blood; local arterial sampling proximal and/or distal to the occlusion if feasible; immediate post-recanalization; 1-6 h; 24 h; 72 h; and 7 days.

Biomarkers: Syndecan-1, heparan sulfate, hyaluronan, thrombomodulin, von Willebrand factor, matrix metalloproteinase-9 (MMP-9), C3a/C5a, cytokines, endothelial activation markers, coagulation-fibrinolysis markers, glucose, HbA1c when available, lipid profile, creatinine/eGFR, and inflammatory indices.

Imaging: DSA-PCC, early CTP/MRP/ASL, BBB permeability imaging when feasible, 24 h FIV, edema, and HT.

Primary mechanistic endpoint: Imaging-defined incomplete microvascular reperfusion, operationalized before study initiation. The definition should be prespecified according to the selected modality, such as DSA-PCC delay metrics,

CTP-defined persistent hypoperfusion, ASL-derived flow abnormality, or combined perfusion-barrier criteria.

Clinical endpoints: Early neurological improvement, 24-h National Institutes of Health Stroke Scale (NIHSS) change, 7-day NIHSS, discharge NIHSS, and 90-day mRS.

Analysis: Mediation pathway from glycocalyx-marker dynamics to imaging-defined IMR to tissue injury expansion and clinical outcome, with prespecified adjustment for core volume, collateral status, procedural variables, systemic inflammation, cardiometabolic risk factors, renal function, and treatment exposures. Interaction analyses should test whether metabolic vulnerability modifies the relationship between glycocalyx-marker dynamics and cerebral target-organ injury.

Limitations: Observational design, biomarker nonspecificity, sampling feasibility, timing mismatch, confounding, and absence of direct *in vivo* cerebral glycocalyx imaging.

LIMITATIONS OF THE GLYCOCALYX HYPOTHESIS

The glycocalyx hypothesis is appealing because it brings several luminal, thromboinflammatory, hemodynamic, and barrier-related processes into the same field of view. Five limitations define how far the argument can currently be taken.

First, cerebral microvascular glycocalyx disruption has not been directly visualized in patients immediately after MT. Much of the mechanistic confidence comes from animal models, ex vivo systems, non-cerebral vascular beds, or indirect human biomarker studies.

Second, peripheral syndecan-1, heparan sulfate, and hyaluronan cannot be assumed to represent the real-time cerebral microvascular glycocalyx. They are nonspecific, affected by systemic endothelial injury and clearance pathways, and sensitive to sampling time and treatment exposures.

Third, the temporal relationship between imaging-defined IMR or no-reflow and glycocalyx shedding has not been rigorously established. Without synchronized biomarker and imaging acquisition, cause, consequence, and shared response to severe ischemia-reperfusion injury are difficult to separate.

Fourth, pericyte contraction, distal embolization, microthrombosis, inflammation, complement activation, BBB injury, edema, and host vulnerability may occur upstream of, downstream of, in parallel with, or independently from glycocalyx injury. A network model is therefore more credible than a single-cause model.

Fifth, candidate glycocalyx-protective therapies are supported mainly by non-brain, non-MT, preclinical, diabetes, sepsis, or other vascular-injury evidence. Acute post-MT stroke introduces bleeding risk, BBB vulnerability, antithrombotic exposure, and a narrow therapeutic window that may change safety and efficacy. In addition, cardiometabolic risk factors may act as confounders, effect modifiers, or causal background conditions rather than simple covariates. These limitations do not weaken the rationale for study; they define the experiments and clinical designs that are needed.

CONCLUSION

Endothelial glycocalyx injury offers a plausible way to think about why an opened artery may still fail to deliver effective microvascular reperfusion. Its strength as a hypothesis is anatomical and biological: it sits at the blood-facing surface where shear stress, inflammation, coagulation, platelet and leukocyte interaction, endothelial

signaling, BBB stability, and metabolic vulnerability intersect. In this sense, the cerebral glycocalyx may be a translational interface between cardiometabolic stress and acute cerebral target-organ damage after reperfusion therapy.

The glycocalyx should therefore not be described as the established central cause of no-reflow or futile recanalization after MT. Peripheral syndecan-1 and related shedding markers provide indirect, nonspecific signals; post-EVT microcirculatory rescue trials show that the downstream circulation may be treatable, but they do not show that glycocalyx repair is the operative mechanism. The most productive next step is serial, compartment-specific biomarker research integrated with peri-procedural perfusion and barrier imaging.

If glycocalyx-marker dynamics are shown to track imaging-defined microvascular reperfusion failure and mediate subsequent tissue injury expansion, the hypothesis could support patient stratification and trial design. Until then, its immediate value for translational and neurointerventional practice is more practical than therapeutic: it sharpens attention to patients who remain biologically at risk despite angiographic success, particularly when cardiometabolic vulnerability may have already compromised the endothelial surface before MT.

DECLARATIONS

Authors' contributions

Conceived and designed the review: W.X, X.X;

Performed literature search and drafted the manuscript: W.X, M.S;

Contributed to literature screening, evidence synthesis, and interpretation: M.J, X.Y, L.G;

Provided administrative, technical, and material support: C.Z;

Critically revised the manuscript for important intellectual content and supervised the work: X.X;

All authors read and approved the final manuscript.

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Goyal M, Menon BK, van Zwam WH, et al., HERMES collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient

data from five randomised trials. *Lancet.* 2016 Apr 23;387(10029):1723-31.[DOI: 10.1016/S0140-6736(16)00163-X. Epub 2016 Feb 18. PMID: 26898852]

2. Shahid AH, Abbasi M, Larco JLA, et al., Risk Factors of Futile Recanalization Following Endovascular Treatment in Patients With Large-Vessel Occlusion: Systematic Review and Meta-Analysis. *Stroke Vasc Interv Neurol.* 2022 May 20;2(6):e000257.[DOI: 10.1161/SVIN.121.000257. PMID: 41582963; PMCID: PMC12778831]

3. Schiphorst AT, Turc G, Hassen WB, Oppenheim C, Baron JC. Incidence, severity and impact on functional outcome of persistent hypoperfusion despite large-vessel recanalization, a potential marker of impaired microvascular reperfusion: Systematic review of the clinical literature. *J Cereb Blood Flow Metab.* 2024 Jan;44(1):38-49.[DOI: 10.1177/0271678X231209069. Epub 2023 Oct 23. PMID: 37871624; PMCID: PMC10905632]

4. Barbagallo M, Zahn M, Zimmermann J, et al., Reperfusion failure after successful thrombectomy of large vessel occlusion stroke: clinical and imaging evidence. *Front Neurol.* 2025 Aug 22;16:1639880.[DOI: 10.3389/fneur.2025.1639880. PMID: 40917674; PMCID: PMC12411166]

5. Zhang Y, Jiang M, Gao Y, et al., “No-reflow” phenomenon in acute ischemic stroke. *J Cereb Blood Flow Metab.* 2024 Jan;44(1):19-37.[DOI: 10.1177/0271678X231208476. Epub 2023 Oct 19. PMID: 37855115; PMCID: PMC10905637]

6. Abassi Z, Armaly Z, Heyman SN. Glycocalyx Degradation in Ischemia-Reperfusion Injury. *Am J Pathol.* 2020 Apr;190(4):752-67.[DOI: 10.1016/j.ajpath.2019.08.019. Epub 2020 Feb 6. PMID: 32035883]

7. Zeng Y. Endothelial glycocalyx as a critical signalling platform integrating the extracellular haemodynamic forces and chemical signalling. *J Cell Mol Med.* 2017 Aug;21(8):1457-62.[DOI: 10.1111/jcmm.13081. Epub 2017 Feb 17. PMID: 28211170; PMCID: PMC5542909]

8. Fu BM, Tarbell JM. Mechano-sensing and transduction by endothelial surface glycocalyx: composition, structure, and function. *Wiley Interdiscip Rev Syst Biol Med.* 2013 May-Jun;5(3):381-90.[DOI: 10.1002/wsbm.1211. Epub 2013 Feb 7. PMID: 23401243; PMCID: PMC4157334]

9. Zhao F, Zhong L, Luo Y. Endothelial glycocalyx as an important factor in composition of blood-brain barrier. *CNS Neurosci Ther.* 2021 Jan;27(1):26-35.[DOI: 10.1111/cns.13560] Epub 2020 Dec 30. *Erratum in: CNS Neurosci Ther.* 2021 Jul;27(7):862.[DOI: 10.1111/cns.13652. PMID: 33377610; PMCID: PMC7804892]

10. Kutuzov N, Flyvbjerg H, Lauritzen M. Contributions of the glycocalyx, endothelium, and extravascular compartment to the blood-brain barrier. *Proc Natl Acad Sci U S A.* 2018 Oct 2;115(40):E9429-38.[DOI: 10.1073/pnas.1802155115. Epub 2018 Sep 14. PMID: 30217895; PMCID: PMC6176561]

11. Zhu J, Li Z, Ji Z, et al., Glycocalyx is critical for blood-brain barrier integrity by suppressing caveolin1-dependent endothelial transcytosis following ischemic stroke. *Brain Pathol.* 2022 Jan;32(1):e13006.[DOI: 10.1111/bpa.13006. Epub 2021 Jul 19. PMID: 34286899; PMCID: PMC8713524]

12. Shi SM, Suh RJ, Shon DJ, et al., Glycocalyx dysregulation impairs blood-brain barrier in ageing and disease. *Nature.* 2025 Mar;639(8056):985-94.[DOI: 10.1038/s41586-025-08589-9. Epub 2025 Feb 26. PMID: 40011765; PMCID: PMC11946907]

13. El Amki M, Glück C, Binder N, et al., Neutrophils Obstructing Brain Capillaries Are a Major Cause of No-Reflow in Ischemic Stroke. *Cell Rep.* 2020 Oct 13;33(2):108260.[DOI: 10.1016/j.celrep.2020.108260. PMID: 33053341]

14. Shrouder JJ, Calandra GM, Filser S, et al., Continued dysfunction of capillary pericytes promotes no-reflow after experimental stroke *in vivo*. *Brain.* 2024 Mar 1;147(3):1057-74.[DOI: 10.1093/brain/awad401. PMID: 38153327]

15. Korte N, Ilkan Z, Pearson CL, et al., The Ca2+-gated channel TMEM16A amplifies capillary pericyte contraction and reduces cerebral blood flow after ischemia. *J Clin*

Invest. 2022 May 2;132(9):e154118.[DOI: 10.1172/JCI154118. PMID: 35316222; PMCID: PMC9057602]

16. Jespersen SN, Østergaard L. The roles of cerebral blood flow, capillary transit time heterogeneity, and oxygen tension in brain oxygenation and metabolism. *J Cereb Blood Flow Metab.* 2012 Feb;32(2):264-77.[DOI: 10.1038/jcbfm.2011.153. Epub 2011 Nov 2. PMID: 22044867; PMCID: PMC3272609]

17. Angleys H, Østergaard L, Jespersen SN. The effects of capillary transit time heterogeneity (CTH) on brain oxygenation. *J Cereb Blood Flow Metab.* 2015 May;35(5):806-17.[DOI: 10.1038/jcbfm.2014.254. Epub 2015 Feb 11. PMID: 25669911; PMCID: PMC4420854]

18. Engedal TS, Hjort N, Hougaard KD, et al., Transit time homogenization in ischemic stroke - A novel biomarker of penumbral microvascular failure? *J Cereb Blood Flow Metab.* 2018 Nov;38(11):2006-20.[DOI: 10.1177/0271678X17721666. Epub 2017 Jul 31. PMID: 28758524; PMCID: PMC6259320]

19. Yin T, Hao J, Jiang Q, et al., Dynamics of intracranial and peripheral plasma Syndecan-1 after ischemic stroke with large vessel occlusion. *CNS Neurosci Ther.* 2022 Oct;28(10):1648-50.[DOI: 10.1111/cns.13898. Epub 2022 Jul 4. PMID: 35790077; PMCID: PMC9437231]

20. Liang D, Zeng X, Yao M, et al., Dynamic changes in the glycocalyx and clinical outcomes in patients undergoing endovascular treatments for large vessel occlusion. Front Neurol. 2023 Jan 26;14:1046915.[DOI: 10.3389/fneur.2023.1046915. PMID: 36779062; PMCID: PMC9909103]

21. Xu B, Yin T, Sun T, et al., Peripheral blood syndecan-1 levels after mechanical thrombectomy can predict the clinical prognosis of patients with acute ischemic stroke. *Acta Neurochir (Wien).* 2024 Mar 27;166(1):153.[DOI: 10.1007/s00701-024-06004-2. PMID: 38536487]

22. Zhao F, Wang R, Huang Y, et al., Elevated plasma syndecan-1 as glycocalyx injury marker predicts unfavorable outcomes after rt-PA intravenous thrombolysis in acute

ischemic stroke. *Front Pharmacol.* 2022 Jul 15;13:949290.[DOI: 10.3389/fphar.2022.949290. PMID: 35910391; PMCID: PMC9335363]

23. Xu B, Yin T, Sun T, et al., Venous thrombolysis prior to mechanical thrombectomy reduces glycocalyx damage in patients with acute ischemic stroke. Front Neurol. 2024 Aug 21;15:1321909.[DOI: 10.3389/fneur.2024.1321909. PMID: 39233682; PMCID: PMC11371720]

24. Teng D, Pannell JS, Rennert RC, et al., Endothelial trauma from mechanical thrombectomy in acute stroke: in vitro live-cell platform with animal validation. *Stroke.* 2015 Apr;46(4):1099-106.[DOI: 10.1161/STROKEAHA.114.007494. Epub 2015 Feb 24. PMID: 25712942]

25. Donnerstag F, Werlein C, Götz F, et al., Adhesion of vessel wall to stentriever during combined technique for mechanical thrombectomy in acute ischemic stroke: A histomorphological study. *Interv Neuroradiol.* 2023 Dec 6:15910199231216764.[DOI: 10.1177/15910199231216764. Epub ahead of print. PMID: 38056004]

26. Kasab SA, Bathla G, Varon A, et al., High-resolution vessel wall imaging after mechanical thrombectomy. *Neuroradiol J.* 2021 Dec;34(6):593-9.[DOI: 10.1177/19714009211017782. Epub 2021 May 20. PMID: 34014780; PMCID: PMC8649198]

27. Mohammaden MH, Stapleton CJ, Brunozzi D, et al., Risk Factors for Distal Clot Migration during Mechanical Thrombectomy of Anterior Circulation Large Vessel Occlusion. *Cerebrovasc Dis.* 2020;49(2):185-91.[DOI: 10.1159/000507341. Epub 2020 Mar 30. PMID: 32224607]

28. Alawieh A, Elvington A, Tomlinson S. Complement in the Homeostatic and Ischemic Brain. *Front Immunol.* 2015 Aug 12;6:417.[DOI: 10.3389/fimmu.2015.00417. PMID: 26322048; PMCID: PMC4533015]

29. Mizuma A, You JS, Yenari MA. Targeting Reperfusion Injury in the Age of Mechanical Thrombectomy. *Stroke.* 2018 Jul;49(7):1796-802.[DOI:

10.1161/STROKEAHA.117.017286. Epub 2018 May 14. PMID: 29760275; PMCID: PMC6019565]

30. Mottahedin A, Prag HA, Dannhorn A, et al., Targeting succinate metabolism to decrease brain injury upon mechanical thrombectomy treatment of ischemic stroke. *Redox Biol.* 2023 Feb;59:102600.[DOI: 10.1016/j.redox.2023.102600. Epub 2023 Jan 2. PMID: 36630820; PMCID: PMC9841348]

31. Bellomo J, Sebök M, Stumpo V, et al., Blood Oxygenation Level-Dependent Cerebrovascular Reactivity-Derived Steal Phenomenon May Indicate Tissue Reperfusion Failure After Successful Endovascular Thrombectomy. *Transl Stroke Res.* 2025 Apr;16(2):207-16.[DOI: 10.1007/s12975-023-01203-y. Epub 2023 Oct 25. PMID: 37880561; PMCID: PMC11976757]

32. Tian C, Chen J, Zhang J, Du F. Assessment of cerebral hemodynamic changes in acute ischemic stroke patients following mechanical thrombectomy using CT perfusion imaging. *Front Neurol.* 2025 Sep 25;16:1628717.[DOI: 10.3389/fneur.2025.1628717. PMID: 41079355; PMCID: PMC12507607]

33. Singer L, Sprügel M, Becker J, et al., Detection of Microvascular Failure After Thrombectomy Directly in the Angio-Suite Using Parametric Color Coding. *Clin Neuroradiol.* 2026 Mar;36(1):67-75.[DOI: 10.1007/s00062-025-01557-w. Epub 2025 Aug 19. PMID: 40828188; PMCID: PMC13009058]

34. Abraham S, Carone D, Mielke O, et al., Automatically quantified follow-up imaging biomarkers predict clinical outcomes after acute ischemic stroke. *Front Neurol.* 2025 Mar 19;16:1483138.[DOI: 10.3389/fneur.2025.1483138. PMID: 40177408; PMCID: PMC11963697]

35. Renú A, Millán M, San Román L, et al., Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients With Large Vessel Occlusion Acute Ischemic Stroke: The CHOICE Randomized Clinical Trial. *JAMA.* 2022 Mar 1;327(9):826-35.[DOI: 10.1001/jama.2022.1645. PMID: 35143603; PMCID: PMC8832304]

36. Writing Committee for the PEARL Investigators; PEARL Investigators. Intra-arterial alteplase after successful endovascular reperfusion in acute stroke: the PEARL randomized clinical trial. *JAMA.* 2025;334(19):1728-39.[DOI:10.1001/jama.2025.16876]

37. Hou X, Huang J, Wang L, et al., Intra-Arterial Tenecteplase After Successful Reperfusion in Large Vessel Occlusion Stroke: A Randomized Clinical Trial. *JAMA Neurol.* 2025 Sep 1;82(9):895-904.[DOI: 10.1001/jamaneurol.2025.2036. PMID: 40616333; PMCID: PMC12228979]

38. Al-Salihi MM, Al-Jebur MS, Saha R, Elazim AA, Siddiq F, Qureshi AI. Adjunctive Intra-Arterial Thrombolysis Following Endovascular Thrombectomy in Acute Ischemic Stroke: A Meta-Analysis. *J Neuroimaging.* 2025 May-Jun;35(3):e70054.[DOI: 10.1111/jon.70054. PMID: 40415217]

39. Mortezaei A, Al-Saidi N, Li YL, Yedavalli VS, Regenhardt RW, Dmytriw AA. Intra-arterial thrombolysis after successful endovascular reperfusion for large vessel occlusion stroke: A meta-analysis of randomized seven controlled trials. *Interv Neuroradiol.* 2025 Aug 13:15910199251367556.[DOI: 10.1177/15910199251367556. Epub ahead of print. PMID: 40801885; PMCID: PMC12350307]

40. Alkhiri A, Alturki F, Alamri AF, et al., Adjunctive intra-arterial thrombolysis after successful endovascular thrombectomy for large vessel occlusion: Meta-analysis of outcomes, dosage, and patient selection. *J Neurointerv Surg.* 2026 Mar 13;18(4):990-6.[DOI: 10.1136/jnis-2025-023404. PMID: 40506219]

41. Broekhuizen LN, Lemkes BA, Mooij HL, et al., Effect of sulodexide on endothelial glycocalyx and vascular permeability in patients with type 2 diabetes mellitus. *Diabetologia.* 2010 Dec;53(12):2646-55.[DOI: 10.1007/s00125-010-1910-x. Epub 2010 Sep 25. PMID: 20865240; PMCID: PMC2974920]

42. Li T, Liu X, Zhao Z, Ni L, Liu C. Sulodexide recovers endothelial function through reconstructing glycocalyx in the balloon-injury rat carotid artery model. *Oncotarget.*

2017 Aug 24;8(53):91350-61.[DOI: 10.18632/oncotarget.20518. PMID: 29207649; PMCID: PMC5710929]

43. Ying J, Zhang C, Wang Y, et al., Sulodexide improves vascular permeability via glycocalyx remodelling in endothelial cells during sepsis. *Front Immunol.* 2023 Aug 8;14:1172892.[DOI: 10.3389/fimmu.2023.1172892. PMID: 37614234; PMCID: PMC10444196]

44. Astapenko D, Gorskaja D, Zrzavecky M, et al., The modulation of endothelial glycocalyx by sulodexide on the porcine model of enzymatic endothelial glycocalyx damage - a pilot study. *Clin Hemorheol Microcirc.* 2025 Feb;89(2):181-8.[DOI: 10.1177/13860291241305514. Epub 2025 Feb 13. PMID: 39973431]