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Advances in Collateral Neuroimaging for Acute Ischemic Stroke: Redefining Time and Tissue Windows in the Reperfusion Era

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ABSTRACT

Cerebral collateral circulation is a critical determinant of infarct evolution, therapeutic response, and clinical outcomes in patients with acute ischemic stroke. While the concept of "time is brain" has traditionally guided reperfusion therapy, recent evidence—particularly from trials like DAWN and DEFUSE 3—suggests that collateral status more accurately determines the rate of infarct progression and the extent of salvageable tissue. This comprehensive review synthesizes advances in neuroimaging modalities for evaluating cerebral collaterals, emphasizing their role in refining stroke diagnosis, guiding patient selection, and informing personalized treatment strategies. Structural approaches such as multiphase and dynamic CT angiography, alongside perfusion-based parameters (e.g., cerebral blood volume, hypoperfusion intensity ratio, and Tmax delay maps), are examined. Cortical venous outflow, assessed via the cortical vein opacification score, emerges as an independent predictor of outcome, complementing arterial grading. Susceptibility-weighted imaging, arterial spin labeling, and metabolic and molecular techniques (e.g., PET imaging of inflammation and vascular remodeling) offer functional insights beyond traditional angiography. Biomarkers such as matrix metalloproteinase-9, integrin $\alpha v\beta 3$, and translocator protein–targeted PET ligands are discussed in relation to collateral vessel dynamics. Finally, we explore the integration of genetically informed brain atlases, spatial transcriptomics, and imaging–genomic platforms for high-resolution collateral phenotyping. Although promising, these modalities face challenges related to heterogeneity, limited validation, and the lack of standardization. A biologically informed, multimodal, and automated imaging paradigm may herald a new era of precision stroke medicine.

Ritwick Mondal and Shramana Deb contributed equally to this work and should be considered joint first authors.

1 | Introduction

Neuroimaging has established mismatch and penumbra as pivotal therapeutic targets in the management of acute ischemic stroke. The ischemic penumbra comprises hypoperfused yet potentially salvageable brain tissue that is at high risk of irreversible infarction unless timely reperfusion is achieved. This concept underpins the clinical axiom "time is brain," where the duration of ischemia critically determines tissue viability and treatment efficacy. However, mounting evidence suggests that penumbral viability can persist for up to 48 h in select patients—a variability governed mainly by the robustness of collateral circulation, which can delay infarct progression and improve outcomes [1].

The cerebral collateral gradient thus emerges as a key determinant of infarct evolution, distinguishing fast from slow progressors. Consequently, infarcts of similar etiology may evolve at markedly different rates depending on the status of the collateral network, reflecting a complex and individualized pathophysiological response. Despite recent advances in perfusion imaging—particularly following landmark trials such as DAWN and DEFUSE 3—the natural course of ischemic tissue and its interplay with collateral flow remain incompletely characterized [2]. Clinically, it has long been observed that many patients with severe atherosclerotic disease remain asymptomatic, largely due to the compensatory effect of well-developed collaterals. Even modest collateral perfusion may suffice to preserve penumbral tissue and avert permanent damage.

As a result, cerebral collateral circulation is now increasingly recognized as a critical determinant in acute stroke management, with significant implications for therapeutic decision-making, prognostication, and functional recovery. This review summarizes recent advances in neuroimaging techniques for visualizing and grading cerebral collaterals in ischemic stroke. It further explores the therapeutic and prognostic relevance of collateral status in guiding reperfusion strategies, highlighting emerging approaches that aim to modulate collateral flow to enhance reperfusion efficacy and improve clinical outcomes.

2 | Methods

A comprehensive literature search was conducted across five major databases—PubMed, Scopus, Web of Science, Embase, and the Cochrane Library—covering publications up to May 15, 2025. Tailored search strategies were applied to each database, incorporating both Medical Subject Headings and free-text terms. Key search terms included "collateral circulation," "acute ischemic stroke," "collaterelogenenesis," "angiogenesis," "cerebrovascular reserve," "collateral grade," "neuroimaging," "collateral imaging," "cerebral angiography," "cerebrovascular circulation," "reperfusion," "endovascular treatment," "thrombolysis," "thrombectomy," and "collateral enhancement."

In addition to electronic database searches, the reference lists of relevant articles were manually screened to identify additional studies not captured through the initial search. Relevant journal websites and major preprint repositories—including medRxiv, bioRxiv, and Preprints.org—were also examined for literature published between January 1, 2000, and May 15, 2025. To further mitigate publication bias, gray literature was reviewed by subject matter experts to capture pertinent unpublished or nonindexed sources.

3 | Results/Discussion

3.1 | The Impact of Demographic and Clinical Factors on Collateral Status

Cerebrovascular collaterals can be structurally categorized into three anatomical levels: the circle of Willis, which serves as the primary pathway; microvascular intracranial collaterals, such as leptomeningeal or pial vessels; and extracranial sources that contribute to collateral flow [3]. The circle of Willis provides a rapid redistribution of cerebral blood flow in the event of acute arterial occlusion. However, its efficacy is highly variable due to anatomical variation. Ideal configurations of the circle of Willis are observed in only a minority of individuals, with reported absence or hypoplasia of key components such as the anterior communicating artery in 1%, the proximal anterior cerebral artery in 10%, and the posterior communicating artery in up to 30% of the population [3, 4]. Moreover, the degree and pattern of anastomoses between distal cerebral arteries—particularly between anterior, middle, and posterior territories—also vary substantially. Beyond these structural aspects, collateral vessel lumen caliber and functional capacity differ widely [5]. Additionally, cerebral venous collaterals may play a compensatory role in maintaining cerebral perfusion, particularly in settings of extensive arterial occlusion or venous hypertension [6].

Sex-based differences in collateral dynamics have been reported. Women with acute large vessel occlusion often exhibit slower infarct core progression and smaller final infarct volumes compared to men, potentially due to enhanced collateral recruitment. Estrogen-mediated upregulation of endothelial nitric oxide synthase has been proposed as a mechanism promoting vasodilation [7]. However, these sex-specific findings have not been replicated in preclinical rodent models, suggesting a need to explore other determinants of sex-related collateral variability further [8].

Age is another critical modifier. Aging is consistently associated with impaired collateral function, manifesting as reduced vessel diameter, increased tortuosity, and diminished vasodilatory responsiveness [9]. Neurodegenerative changes, particularly late-onset Alzheimer's disease, may further exacerbate collateral rarefaction through dysfunctional endothelial nitric oxide synthase signaling [10]. Experimental models of permanent middle cerebral artery occlusion in transgenic Alzheimer's disease mice demonstrate accelerated infarct progression and reduced penumbral perfusion [11].

Similarly, chronic small vessel disease adversely affects collateral recruitment. In a cohort of 100 patients with large vessel occlusion stroke, Lin et al. [12] observed a dose-dependent relationship between chronic small vessel disease burden and poor collateral status. White matter hyperintensities, a hallmark of chronic small vessel disease, may impair leptomeningeal collateral function by reducing vascular compliance and impairing autoregulation [13]. These findings suggest that chronic small vessel disease and col-

lateral insufficiency may share overlapping pathophysiological and genetic underpinnings.

Systemic vascular risk factors, particularly hypertension and metabolic syndrome, also compromise collateral function. Fujita et al. [14] demonstrated that chronic hypertension impairs leptomeningeal collateral flow in large vessel occlusion stroke. Sim et al. [15] further reported that elevated systolic blood pressure at stroke onset was associated with worse collateral grades, particularly in cardioembolic stroke, highlighting the combined influence of blood pressure and stroke etiology on collateral recruitment. Interestingly, anterior circulation large vessel occlusion strokes due to cervical carotid atherosclerosis have been associated with more favorable collateral profiles and better 90-day outcomes following endovascular treatment compared to those caused by embolic etiologies.

Collectively, these data underscore the multifactorial nature of collateral variability, which is influenced by demographic, structural, hemodynamic, and genomic factors. The role of vascular genetics in modulating collateral architecture and function warrants further investigation, as it may hold the key to individualized risk stratification and targeted therapy.

3.2 | Implications of Collateral Variability in Acute Stroke Treatment: "Time" Is Brain, but Collaterals Set the "Pace"

The therapeutic efficacy of intravenous thrombolysis and endovascular therapy is primarily driven by the timely and successful restoration of blood flow, known as reperfusion. Current clinical guidelines define treatment windows of up to 4.5 h for intravenous thrombolysis and approximately 24 h for endovascular therapy based on pooled analyses from major randomized trials [16]. However, these rigid time-based criteria may fail to accommodate the substantial interindividual variability in collateral perfusion capacity. In real-world settings, this limitation could exclude many patients who may still harbor viable penumbral tissue beyond the standard time-based therapeutic window.

Recent data reiterate the importance of collateral status in modulating infarct evolution. Ospel et al. [17], analyzing 409 patients from the ESCAPE-NA1 trial, reported a median infarct growth rate of 4.74 mL/h. Collateral status was inversely associated with infarct expansion ($\beta = -0.81$; 95% confidence interval [CI] −1.20 to −0.41), confirming its prognostic significance. However, clinical and imaging predictors—including collateral grade—collectively accounted for only 23% of the variance in infarct growth, suggesting that while collaterals are important, they do not fully explain infarct dynamics. Moreover, each 1-mL/h increase in infarct growth rate was associated with a 4% decrease in the odds of a favorable outcome, reinforcing the need for individualized prognostic assessments.

The therapeutic implications of collateral status also encompass the ongoing debate between direct endovascular therapy and bridging therapy (intravenous thrombolysis followed by endovascular treatment). In a meta-analysis of 13 studies involving 3302 patients, Li et al. [18] found comparable overall outcomes for both strategies, although direct endovascular therapy was associated with a lower risk of symptomatic intracranial hemorrhage (relative risk = 0.76; 95% CI, 0.60–0.95; p = 0.02). While collateral status was not specifically assessed, patients with robust collaterals are likely better suited for direct endovascular therapy, as they may better tolerate delayed reperfusion.

These findings challenge the conventional notion that therapeutic windows should be strictly time-based. In many patients, infarct growth is influenced more by the quality and resilience of collateral circulation than by elapsed time alone. Although early reperfusion remains critical—capturing the essence of "time is brain"—the pace of neuronal loss is ultimately governed by the extent and functionality of the collateral network. Estimates suggest that neuronal loss during stroke may range from thousands to billions of neurons per minute, depending on collateral flow [19].

This substantial variability supports the need to move beyond fixed time thresholds and toward a more individualized approach. Advanced imaging capable of identifying salvageable tissue and assessing collateral status in detail may enable a more precise determination of the therapeutic window. Such a shift would allow a broader population of stroke patients to benefit from reperfusion therapies guided by physiological rather than purely temporal criteria.

However, recent evidence also highlights that in extended-window stroke interventions, collateral status alone is insufficient to protect against hemorrhagic complications when the infarct core is substantial. Even patients with robust collaterals may experience progressive growth of the infarct over time. For instance, Laflamme et al. [20] reported that several "slow progressors" exhibited significant early ischemic changes despite favorable collateral scores, indicating that strong collaterals do not guarantee slow infarct expansion. Post hoc analyses from clinical trials similarly suggest that collateral status, while informative, is insufficient to prevent infarct progression, necessitating caution when using it as the sole criterion for patient selection [20].

Collateral flow may temporarily sustain penumbral tissue, but without timely reperfusion, even initially favorable collateral patterns can fail, leading to core enlargement and heightened risk of hemorrhagic transformation [21]. Large infarct core volume is a well-established predictor of post-recanalization hemorrhage [22]. Studies extending thrombectomy beyond conventional time windows have reported elevated rates of symptomatic intracerebral hemorrhage in patients with sizable cores, despite good collaterals [21, 23]. For example, the MR CLEAN-LATE trial (6–24 h), which utilized collateral imaging for patient selection, found significantly higher rates of symptomatic hemorrhages in the endovascular group compared to the control group (7% vs. 2%) [23].

These findings underscore that patient selection in late-presenting stroke should not rely solely on collateral imaging. Advanced imaging techniques to quantify infarct core and penumbra are critical to avoid reperfusion of irreversibly damaged tissue, which carries a high risk of hemorrhagic conversion [20, 21]. Therefore, in patients beyond standard

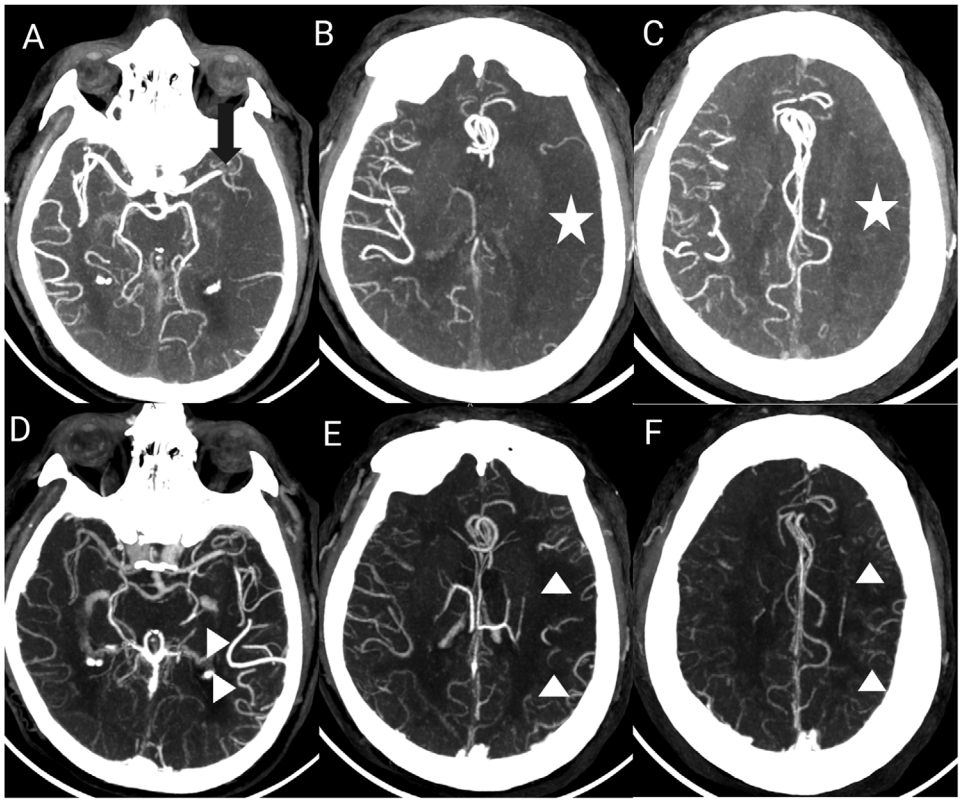

FIGURE 1 | A 68-year-old male presented with an acute onset of right-sided hemiplegia and expressive and receptive aphasia, with a symptom onset time of 4.5 h prior to arrival. (A–C) Axial images of maximum intensity projection (MIP) of the arterial phase of multiphasic CT angiography (m-CTA) showing an abrupt cutoff in the distal part of the M1 segment of the left middle cerebral artery (black arrow in A) and significant paucity of the distal left middle cerebral artery branches with a large area of hypoperfusion in panels B and C, respectively (represented by the "star"). (D–F) Axial images of MIP of the venous phase of m-CTA showing excellent reformation of the distal temporal branches of the left middle cerebral artery by the collaterals (arrowheads in D); however, significant paucity of the distal frontoparietal branches of the left middle cerebral artery is noted even in the venous phase (arrowheads in E and F).

treatment windows (i.e., more than 6 or 24 h), integrating infarct core assessment with collateral status is essential to minimize hemorrhagic risk and optimize outcomes.

3.3 | Refinements in Neuroimaging Modalities for Arterial Collateral Estimation

Recent advances in neuroimaging, particularly in multimodal CT angiography (CTA) and digital subtraction angiography, have significantly improved the detection, characterization, and grading of cerebral collaterals (Figures 1 and 2). These developments are complemented by integrated scoring systems that combine collateral evaluation with perfusion imaging metrics, such as CTA source image ASPECTS, the regional leptomeningeal collateral score, and cerebral blood volume (CBV) ASPECTS [24, 25]. Together, these tools have enhanced the ability to predict clinical outcomes and refine patient selection for reperfusion therapies. Crucially, they help mitigate futile interventions in patients with poor collateral status by identifying those most likely to benefit from endovascular treatment [26].

In a seminal review, Lin and Liebeskind [27] emphasized the value of multimodal CT/MRI in assessing cerebral hemodynamics and collateral flow to identify salvageable penumbra beyond conventional time thresholds. Martinon et al. [28] reported in a systematic review that dynamic CTA offers superior temporal and spatial resolution for collateral visualization compared to single-phase CTA and transcranial Doppler. Supporting this, the DAWN trial's collateral subanalysis by Liebeskind et al. [29] provided Level I evidence for the prognostic utility of collateral imaging in late-window thrombectomy candidates. Among 161 patients, collateral grades assessed via CTA (Tan scale) and digital subtraction angiography (American Society of Interventional and Therapeutic Neuroradiology scale) varied widely. Patients with better collateral grades had smaller infarct cores, slower infarct growth, and superior 90-day outcomes, with 43.7% achieving a modified Rankin Scale (mRS) score of 0–2 compared to 17.7% among those with poor collaterals ($p = 0.026$). These findings confirm the feasibility and clinical relevance of collateral imaging in selecting patients beyond 6 h from symptom onset.

Timely assessment of collateral status also plays a critical role in preventing massive cerebral infarction, which often results from proximal occlusions of the middle cerebral artery or internal carotid artery and carries a case fatality rate of 10%–80%. Chen et al. [30] proposed a combined scoring system that integrates ASPECTS with CTA collateral scores. In a cohort of 185 patients with occlusion of the anterior cerebral circulation, this combined model achieved an area under the receiver operating character-

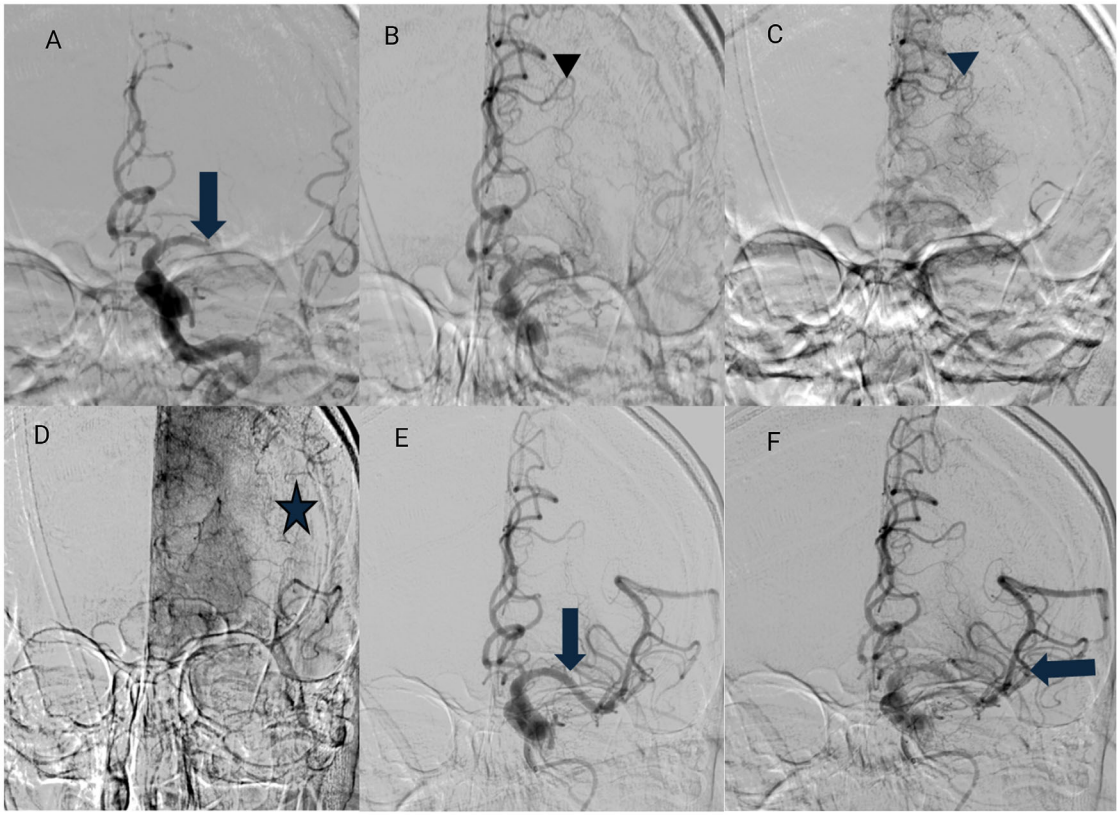

FIGURE 2 | Digital subtraction angiography images of the same patient. (A–D) Serial anteroposterior projection of the left internal carotid artery injection showing an abrupt cutoff in the distal part of the M1 segment of the left middle cerebral artery (black arrow in A). Panels B and C show pial–pial collaterals from the left anterior cerebral artery (represented by the "arrowheads"). Panel D shows a large area of hypoperfusion in the parenchymal phase of the angiography (represented by the "star"). The patient underwent mechanical thrombectomy by thromboaspiration. (E, F) Post-thrombectomy digital subtraction angiography images of anteroposterior projection of the left internal carotid artery injection showing recanalization of the left middle cerebral artery thrombus (black arrow in E) with established distal flow (black arrow in F).

istic curve of 0.918 for predicting massive cerebral infarction, outperforming the CTA collateral score alone, which had an area under the curve of 0.885. Bootstrap validation and decision curve analyses confirmed its superior clinical utility. Similarly, Catanese et al. [31] found that higher collateral scores on CTA at referring hospitals were independently associated with eligibility for endovascular therapy in 103 transferred stroke patients ($p = 0.02$), highlighting the importance of pretransfer triage in optimizing resources.

The relationship between stroke etiology and collateral status has also been explored. In a study of 191 patients, Sojak et al. [32] found that large-artery atherosclerosis and small-vessel disease were associated with better leptomeningeal collaterals (adjusted odds ratios [ORs] 3.72 and 4.19, respectively). In contrast, cardioembolic strokes were associated with significantly poorer collateral profiles (adjusted OR 0.17). These results suggest that the interpretation of collateral imaging should be contextualized within the stroke subtype to enhance precision.

Collectively, these studies demonstrate the central role of advanced neuroimaging in evaluating arterial collaterals. Nevertheless, challenges remain. The diversity of collateral grading systems, variability in imaging protocols, and heterogeneity in patient populations and stroke subtypes limit comparability across studies. Most current evidence is derived from retrospective analyses, with the DAWN trial being a notable prospective exception. Future studies should prioritize standardized grading systems, carefully stratified cohorts, and, importantly, the incorporation of collateral vascular genomics to improve precision in collateral assessment.

In addition to contrast-based techniques, susceptibility-weighted imaging (SWI)—a noncontrast, gradient-recalled echo T2-weighted MRI protocol—has emerged as a promising tool for collateral estimation. SWI is highly sensitive to deoxygenated hemoglobin and can detect early ischemic changes in the brain parenchyma and vasculature [33]. In a study of 152 patients with acute anterior circulation stroke, Lee et al. [34] demonstrated that intermediate and good SWI collateral grades independently predicted favorable outcomes (adjusted ORs 9.49 and 6.22, respectively; $p = 0.02$ and 0.03). This association remained significant after adjusting for age, National Institutes of Health Stroke Scale score, baseline diffusion-weighted imaging lesion volume, and reperfusion status. The linear correlation between SWI collateral grade and clinical outcome ($p = 0.008$) highlights the prognostic value of this modality.

Furthermore, combining SWI with diffusion-weighted imaging mismatch metrics has demonstrated improved predictive performance compared to SWI alone [35]. Despite these advantages, SWI remains less sensitive than advanced perfusion

techniques such as dynamic susceptibility contrast MRI and arterial spin labeling (ASL) [36]. However, recent advances in deep learning algorithms applied to collateral maps generated by dynamic susceptibility contrast MRI have led to improved accuracy in collateral grading. Quantitative susceptibility mapping, though still investigational, offers additional physiological insights into tissue oxygenation and microvascular integrity. In clinical practice, SWI may serve as a valuable noncontrast imaging option, particularly in patients with contraindications to contrast agents, and is best employed in conjunction with other MRI modalities for a comprehensive assessment of collateral status.

3.4 | Cortical Venous Outflow (VO) Imaging in Collateral Assessment

Cortical VO, typically assessed using the cortical vein opacification score (COVES) on CTA, has emerged as a promising independent biomarker of cerebral collateral status. Increasing evidence supports its strong association with tissue perfusion, infarct progression, and functional outcomes in acute ischemic stroke [37]. Unlike traditional arterial collateral imaging, VO captures downstream microvascular integrity and tissue-level hemodynamics, offering complementary prognostic insight. However, traditionally conducted single-phase CTA, which is frequently used in acute stroke imaging, may lack adequate venous opacification, potentially leading to misinterpretation of VO and falsely suggesting a lack of venous flow opacification. This occurs because the relatively faster imaging speeds of modern CT scanners can result in insufficient time for contrast to circulate through the venous system during a single-phase acquisition. To address this, the multiphase CTA is recommended, which involves an initial arterial phase and a delayed venous phase acquired after a short interval without any additional contrast injection [38].

In a pivotal study of 565 acute ischemic stroke patients, Faizy et al. [39] demonstrated that favorable venous outflow (COVES $\geq$ 3) was independently associated with excellent reperfusion (modified Thrombolysis in Cerebral Infarction 2c/3; OR 2.10, 95% CI 1.39–3.16; $p < 0.001$) and superior 90-day outcomes (mRS 0–2; OR 8.9, 95% CI 5.3–14.9); in the same model, single-phase CTA arterial collateral grading (modified Tan) did not predict excellent reperfusion (OR 0.87, 95% CI 0.58–1.30; $p = 0.48$). Consistently, Baydemir et al. [40] reported that mTAN collateral grade did not differentiate TICI 2b/3 recanalization rates (86% with good vs 88% with poor), but poor collaterals were strongly associated with futile recanalization (52% vs 8%; $p = 0.001$), higher mortality (32% vs 6%; $p = 0.001$), and independently predicted poor outcome (OR 6.89, 95% CI 1.60–29.62; $p = 0.009$).

Heitkamp et al. [41] further analyzed 784 patients with acute ischemic stroke due to large vessel occlusion, showing that VO declines with age (adjusted OR 0.83 per decade, $p = 0.006$), a relationship partially mediated by impaired microperfusion (hypoperfusion intensity ratio [HIR]). These findings underscore VO's sensitivity to microvascular function, which is especially relevant in older patients, where arterial collaterals may appear preserved despite underlying capillary dysfunction. In support of this, Li et al. [42] demonstrated that impaired VO correlated with increased extravascular–extracellular volume fraction, a marker of microvascular injury and edema risk. Although poor arterial collaterals were also associated with unfavorable VO (OR 0.102, $p < 0.001$), VO provided independent and additive prognostic value.

Van Horn et al. [43] evaluated 728 patients and confirmed that favorable VO (COVES $\geq$3) independently predicted reduced early edema progression ($\beta = -0.03$, $p = 0.002$) and better functional outcomes (OR 5.07, 95% CI 2.84–9.04, $p < 0.001$), after adjusting for infarct volume and arterial collateral status. These results underscore the unique prognostic role of VO in early infarct dynamics.

Notably, Gong et al. [44] assessed 440 patients undergoing late-window endovascular thrombectomy (6–24 h from symptom onset) and found that favorable VO (COVES 4–6) independently predicted functional independence (adjusted OR 2.25, $p = 0.003$), even in patients with poor arterial collaterals. These findings highlight the potential of VO to improve patient selection beyond traditional arterial imaging criteria. Similarly, Wang et al. [45] assessed 149 patients with acute ischemic stroke due to large vessel occlusion using whole-brain 4D-CTA/CT perfusion and found that delayed venous peak time was independently associated with poor prognosis, achieving 79.6% accuracy, thereby supporting the value of dynamic venous flow timing as a sensitive biomarker of collateral function. In a complementary dynamic CTA study of 35 acute anterior circulation occlusion patients who underwent successful endovascular reperfusion therapy, Shang et al. [46] reported that the extent, rather than the velocity, of cortical venous filling (CVF) on the affected side was associated with baseline collateral status and clinical outcomes. Poor CVF extent—defined as >50% reduction compared with the contralateral side—was linked to poor collaterals, larger final infarct volume, midline shift, higher discharge mRS, and increased in-hospital mortality, whereas slow CVF (delayed initial or terminal filling) was not significantly associated with these parameters, indicating that the overall extent of venous filling may be a more accurate and specific marker of venous drainage disturbance than velocity-based metrics [46].

Together, these studies provide strong and consistent evidence that VO assessment—especially using COVES and dynamic CTA—offers important and complementary information beyond that supplied by arterial imaging. VO reflects downstream perfusion and microvascular health, correlates with reperfusion success and infarct development, and maintains predictive value in patients with poor arterial collaterals and longer treatment windows.

However, several limitations still exist. Most studies are retrospective and prone to selection bias. Imaging protocols and collateral grading scales lack standardization, making comparisons and evaluations challenging. Nonetheless, the large multicenter cohorts and consistent results across different groups strongly support the clinical importance of VO. Moving forward, prospective validation and the development of standardized, and ideally automated, VO quantification tools will be crucial for wider clinical adoption.

3.5 | Metabolic Imaging in Cerebral Collateral Flow Assessment: Functional Insights Into Collateral Hemodynamics

The traditional evaluation of cerebral collateral flow in ischemic stroke has relied heavily on structural and hemodynamic imaging modalities, including CTA, magnetic resonance angiography, magnetic resonance perfusion imaging, and transcranial Doppler. While these techniques are valuable for anatomical and perfusion assessment, they offer limited insight into the metabolic and inflammatory status of collateral vessels and surrounding tissue [47]. In this context, metabolic imaging modalities are emerging as promising tools for assessing the functional viability of collaterals and their pathophysiological context.

Conventional MR-based methods that utilize proton contrast agents to enhance T_1 and T_2* signal properties are limited by their low sensitivity to subtle metabolic changes [48]. In contrast, hyperpolarized MRI offers a fundamentally different approach by increasing signals from non-proton nuclei, such as xenon-129 (ˆ129Xe), helium-3 (ˆ3He), and carbon-13 (ˆ13C) [49]. Shepelytskyi et al. [50] detailed the use of hyperpolarized xenon-129 MRI as an experimental, noninvasive technique capable of assessing cerebral perfusion and blood-–brain barrier permeability with high sensitivity to microenvironmental changes. Preclinical and early clinical studies suggest that hyperpolarized MRI may be particularly useful for detecting changes in cerebral blood flow associated with ischemia and collateral circulation.

In the field of neuroinflammation, Kolabas et al. [51] used PET imaging targeting the translocator protein to demonstrate that inflammation in the skull bone marrow might reflect broader neuroinflammatory processes, including those affecting cerebral collaterals. Hermanns et al. [52] built upon these findings in a mouse model of middle cerebral artery occlusion, where increased translocator protein uptake in the insular cortex at 7 days after stroke (3.8 ± 0.8 vs. 2.6 ± 0.7 %ID/g max, $p < 0.001$) was linked to a decrease in left ventricular ejection fraction ($r = -0.396$, $p = 0.027$). These findings highlight the potential of metabolic imaging to detect inflammatory activity in ischemic areas—often unseen with standard angiographic or perfusion imaging—and to reveal downstream systemic effects of stroke.

Conventional imaging remains crucial for managing acute strokes, but its limitations in detecting metabolic and inflammatory processes are increasingly acknowledged. Combining structural techniques like diffusion tensor imaging with functional and metabolic methods can enhance the evaluation of residual brain function and recovery potential. Specifically, PET imaging enables the detection of inflammation and neovascularization, offering mechanistic insights that go beyond the anatomical stenosis typically identified on CTA or magnetic resonance angiography [53].

Mokhber et al. [54] reviewed changes in cerebral perfusion associated with aging and cognitive disorders, highlighting that metabolic abnormalities often precede structural damage. This highlights the importance of metabolic imaging for the early detection of collateral failure, potentially before infarction occurs. In the context of moyamoya vasculopathy, Velo et al. [55] explained how functional and metabolic imaging can assist in diagnosis and surgical planning, as collateral networks develop in a manner distinct from atherosclerotic mechanisms.

Emerging technologies, such as functional ultrasound, as discussed by Deffieux et al. [56], also offer high temporal and spatial resolution for evaluating blood flow in small cerebral vessels. Functional ultrasound uses neurovascular coupling to map perfusion in real-time and has shown promise in preclinical models for assessing collateral recruitment. While its clinical use is still in early stages, functional ultrasound could become an important bridge between structural and metabolic imaging by offering dynamic, noninvasive data on collateral hemodynamics.

Despite their promise, metabolic imaging modalities face significant limitations, including lower spatial resolution compared to MRI or CTA, limited clinical availability, and the need for further validation in prospective studies. Nonetheless, incorporating these techniques into a multimodal imaging framework, alongside structural, hemodynamic, and molecular tools, may offer a more comprehensive understanding of collateral physiology. Such integration has the potential to improve patient stratification, guide treatment decisions, and identify novel therapeutic targets based on the metabolic and inflammatory biology of ischemic stroke [57]. Although these methods provide valuable insights into collateral dynamics, many remain impractical in acute stroke workflows due to the demands for rapid decision-making, constrained accessibility, and logistical challenges. Currently, their use is primarily limited to research settings or highly specialized centers.

3.6 | Recent Advancements in Perfusion Imaging Modalities in Assessing Cerebral Collateral Flow in Acute Stroke

Perfusion imaging, which employs intravascular tracers and serial image acquisition, enables the quantitative assessment of cerebral blood flow dynamics. Using both CT- and MRI-based modalities, this technique provides a functional evaluation of collateral circulation in acute ischemic stroke, particularly in extended time windows beyond conventional thrombolytic cutoffs. Key perfusion parameters such as CBV, CBV index, cerebral blood flow, and HIR are increasingly recognized for their prognostic and therapeutic relevance [58].

The CBV index is a perfusion-based metric that quantifies collateral perfusion by comparing relative CBV values. Specifically, it is calculated by dividing the mean CBV within hypoperfused tissue (typically with a Tmax greater than 6 s) by the mean CBV in normally perfused brain regions (Tmax ~4 s) [59]. In practical terms, the CBV index measures the degree to which collateral vessels can maintain blood volume in ischemic tissue. A higher CBV index (e.g., ≥0.8) indicates better collateral compensation. It has been consistently associated with more favorable outcomes after endovascular thrombectomy, including slower infarct growth, improved reperfusion success, and enhanced functional recovery. In contrast, a lower CBV index (<0.7) indicates poor collateral support and predicts a higher risk of infarct expansion, hemorrhagic transformation, and a poorer outcome. The CBV index,

therefore, provides a quantitative, physiologically meaningful surrogate for collateral status and may guide patient selection and risk stratification in both large and medium vessel occlusion strokes [59].

The HIR is another perfusion imaging metric used in acute ischemic stroke, defined as the ratio of brain tissue volume with a time-to-maximum (Tmax) of more than 10 s to that with a Tmax of more than 6 s on perfusion imaging [60]. The HIR reflects the severity of microvascular hypoperfusion and serves as a surrogate for collateral status, with higher values indicating poorer collateral flow and more severe tissue ischemia [60–63]. A lower HIR (commonly <0.4) is associated with better collateral circulation, slower infarct growth, reduced early edema progression, and improved functional outcomes after endovascular therapy—even in patients with large ischemic cores or delayed recanalization [61, 64–66]. Conversely, a higher HIR predicts larger infarct volumes, an increased risk of parenchymal hematoma after reperfusion, and worse neurological outcomes [67]. The HIR has demonstrated superior or comparable prognostic value to traditional collateral scoring methods and core infarct volume in predicting clinical outcomes and guiding thrombectomy eligibility [62–69]. Incorporating the HIR into clinical decision-making may enhance patient selection for mechanical thrombectomy and guide postintervention management, as it provides a rapid, automated, and objective assessment of tissue at risk and collateral status [60, 62, 69]. The optimal HIR threshold for predicting favorable outcomes varies across studies but is generally ≤0.3–0.4 [61, 63, 65, 66]. The HIR is now recognized as a valuable adjunct in acute stroke imaging protocols for both clinical care and research [60–63, 68].

In the DEFUSE 3 substudy, MacLellan et al. [70] retrospectively analyzed 84 patients who did not undergo reperfusion in the late window. Using RAPID software (Version 7.0, iSchemaView, Menlo Park, CA, United States, https://www.rapidai.com/), they derived collateral perfusion scores based on HIR (defined as Tmax >10 s volume / Tmax >6 s volume) and a CBV index. Unfavorable collateral profiles (HIR ≥0.34 and CBV index ≤0.74) were predictive of significant infarct expansion (>25 mL), with corresponding areas under the curve of 0.68 and 0.72, respectively. Patients with HIR ≥0.34 demonstrated markedly greater median infarct growth (73.2 vs. 23.4 mL; $p = 0.005$), underscoring that perfusion imaging can effectively assess collateral functionality and tissue viability, even in the absence of reperfusion therapy. Chen et al. [71] further validated the reliability of perfusion analysis, demonstrating strong agreement between UGuard (Version 1.6, Qianglian Zhichuang [Beijing] Technology, Beijing, China) and RAPID software for quantifying ischemic core volume and penumbral volume.

Expanding on this, Seners et al. [72] conducted a large multicenter cohort study involving 1127 patients with anterior circulation LVO. HIR emerged as the strongest independent predictor of rapid infarct progression (≥10 mL/h), with perfusion data consistently predictive across both CT and MR modalities. The study found that 37% of patients were "fast progressors," and HIR quartiles stratified this risk from 4% (best collaterals) to 77% (worst collaterals). These findings provide Level 2 evidence that perfusion imaging–derived metrics outperform both clinical and static angiographic predictors of infarct evolution.

Advanced imaging techniques, including perfusion CT and ASL MRI, allow noninvasive assessment of cerebral blood flow and collateral reserve beyond conventional anatomic imaging [73]. While ASL can detect delayed arterial arrival and hypoperfusion without the use of contrast agents [74], its clinical application remains limited due to its lower spatial resolution and sensitivity to transit time artifacts. Emerging computational models of perfusion based on MRI data may offer individualized predictions of hemodynamic responses [75], although current approaches cannot fully simulate the dynamic nature of collateral recruitment.

While the clinical utility of perfusion imaging in collateral assessment continues to grow, several methodological challenges remain. The absence of standardized protocols for acquisition, threshold definition, and postprocessing algorithms introduces variability that complicates interpretation and cross-study comparability. Perfusion maps generated from parameters such as cerebral blood flow, CBV, Tmax, and mean transit time can differ significantly depending on the software and settings used, which limits their generalizability and hinders widespread clinical implementation [76].

Therefore, despite strong evidence supporting perfusion imaging as a sensitive method for assessing collateral function, these methodological inconsistencies highlight the urgent need for standardization. Harmonizing acquisition parameters, processing techniques, and interpretation guidelines will be crucial to fully incorporate perfusion imaging into routine collateral assessment and treatment decisions in acute ischemic stroke.

3.7 | Emerging Molecular Imaging Biomarkers for Collateral Assessment

The evaluation of cerebral collateral circulation through molecular imaging is an evolving and multifaceted endeavor. It involves identifying specific molecular targets, developing highly selective imaging probes, and validating their correlation with the structural and functional integrity of collateral vessels [77]. These techniques aim to complement existing anatomical and perfusion-based modalities by providing a more profound understanding of the pathophysiological and cellular mechanisms underlying collateral formation, remodeling, and failure.

In human ischemic stroke, Gawlitza et al. [78] assessed fluid-attenuated inversion recovery vascular hyperintensities and four-dimensional magnetic resonance angiography as surrogate imaging biomarkers of leptomeningeal collaterals in anterior cerebral artery ischemia. Among 40 patients (41 affected hemispheres), vascular hyperintensities were present in 63.4% and correlated with time-to-peak lesion volume ($\rho = 0.4$, $p < 0.01$) and mismatch volumes, supporting their value in assessing collateral perfusion. Additionally, a modified collateral grading score derived from four-dimensional angiograms showed an inverse correlation with infarct volume ($\rho = -0.58$, $p < 0.01$). The lack of correlation between the two modalities suggests that they provide complementary information on collateral status.

Beyond imaging, molecular pathways central to angiogenesis and arteriogenesis provide promising targets for probe development.

Key regulators such as vascular endothelial growth factor, its receptor, and matrix metalloproteinases are critical to collateral vessel growth. In a rat model of nonischemic cerebral hypoperfusion, Hillmeister et al. [79] demonstrated the upregulation of protease inhibitors, including tissue inhibitors of metalloproteinase-1 and kininogen, during early arteriogenesis, as determined by gene expression profiling and immunohistochemistry. Although not directly applicable to molecular imaging, these findings provide a biological foundation for the future development of imaging probes.

A novel translational approach was presented by Kollikowski et al. [80], who quantified matrix metalloproteinase-9 release in blood drawn directly from collateral vessels prior to endovascular therapy in 132 patients. Elevated levels were associated with an increased risk of parenchymal hematoma and poor early outcomes (mRS ≥5). Each 1000-ng/mL increase in matrix metalloproteinase-9 raised the odds of hemorrhage by 1.54 and of poor functional outcome by 2.33, suggesting the potential of real-time molecular evaluation for risk stratification prior to reperfusion therapy.

Perhaps the most advanced example of targeted molecular imaging is provided by Wang et al. [81], who utilized superparamagnetic iron oxide nanoparticles conjugated to an arginine–glycine–aspartate peptide to target the integrin alpha-v beta-3, a known marker of angiogenic endothelium. In a rat model of ischemic stroke, this nanoprobe enabled magnetic resonance imaging of active collateral vessel development with high specificity [82]. Blocking experiments confirmed the selective binding of the probe, and temporal imaging demonstrated that antegrade reperfusion was the dominant mechanism of early infarct perfusion, highlighting the dynamic contribution of collaterals.

While promising, current research is constrained by small clinical sample sizes, the predominance of animal models, and heterogeneous imaging protocols. Furthermore, the quantitative relationship between molecular biomarker expression and functional collateral flow remains underexplored. These limitations notwithstanding, the integration of molecular imaging with conventional and advanced neuroimaging holds significant promise for improving the accuracy of collateral assessment and supporting personalized stroke care.

To build on these molecular insights, the next frontier in collateral imaging lies in decoding the genetic determinants that drive collateral heterogeneity. This requires the integration of spatially resolved genomic data into neuroimaging frameworks—an emerging paradigm discussed in the following section.

3.8 | Integrating Genetically Informed Brain Atlas Data in Neuroimaging Modalities: A Prospect for Cerebral Collateral Visualization

To advance our understanding of cerebral collateral circulation beyond correlation and into causation, it is essential to investigate the underlying genetic and transcriptomic mechanisms that govern collateral variability. While most current knowledge stems from rodent models, these studies consistently demonstrate that collateral genomics plays a critical role in determining both structural configuration and functional capacity [83]. However, current neuroimaging approaches remain limited in their ability to capture these deeper biological processes, as they predominantly reflect anatomical correlates and perfusion dynamics [84].

Integrating genetically informed brain atlas data, anchored in genome-wide association studies, spatial transcriptomics, and proteomics, into neuroimaging workflows may offer transformative insights into the cellular and molecular architecture of collateral function [85]. This approach enables high-resolution mapping of gene and protein expression across specific brain regions implicated in ischemic vulnerability, thereby refining the phenotyping of collaterals and informing individualized prognostication and therapeutic targeting.

Bonkhoff et al. [86] exemplified this approach by integrating lesion topography from diffusion-weighted imaging with white matter hyperintensity burden in a cohort of 928 patients with acute ischemic stroke. Using atlas-based parcellation and machine learning dimensionality reduction, they found that the burden of white matter hyperintensity amplified stroke severity in cortical regions, including the insular, opercular, and inferior frontal areas. These results underscore the interaction between lesion distribution, vascular integrity, and genetically mediated small vessel disease, suggesting that impaired collateralization may be partially genetically determined.

Similarly, the Stroke Neuro-Imaging Phenotype Repository introduced by Mohammadian Foroushani et al. [87] links brain imaging data with genetic and clinical variables from over 2200 stroke patients. The platform enables large-scale genotype–phenotype analyses using automated pipelines for image segmentation and registration aligned with high-resolution brain atlases. This repository serves as a model for the operationalization of genetically informed neuroimaging across multicenter stroke datasets.

Complementary work by Demyanenko and Uzdensky [88]employed spatial proteomic profiling to assess protein expression dynamics in the ischemic penumbra of rodent models. By quantifying 224 signaling molecules related to apoptosis, cytoskeletal remodeling, and synaptic activity, they revealed region- and time-specific changes in the molecular environment postinfarction. Although not directly integrated into genomic atlases, this work lays essential groundwork for understanding neurovascular injury from a molecular systems perspective.

Collectively, these efforts illustrate a promising trajectory: from anatomical collateral imaging toward genetically guided, spatially resolved, multimodal stroke phenotyping. Integrating genetic data into neuroimaging frameworks may not only enhance our understanding of collateral biology but also enable genotype-based patient selection and therapeutic innovation in cerebrovascular disease.

4 | Conclusion and Future Direction

In the era of reperfusion therapies for acute ischemic stroke, the presence of robust cerebral collateral circulation—visible on base-

line neuroimaging—has emerged as a key determinant of clinical outcome. Good collateral status is associated with slower infarct progression, improved tissue viability, and enhanced responsiveness to both intravenous thrombolysis and endovascular therapy. Despite these well-documented benefits, there remains little evidence for interventions that directly target or enhance collateral flow in the acute phase of stroke. Nevertheless, this area is the focus of growing research interest, with ongoing efforts exploring both pharmacologic and hemodynamic strategies to augment collateral perfusion.

Cerebral collateral recruitment following large vessel occlusion is a complex, dynamic, and highly individualized process. A wide array of factors, including age, sex, vascular comorbidities, genetic predisposition, neuroinflammatory milieu, and the structural configuration of the circle of Willis and leptomeningeal anastomoses, influences it. Recent advancements in neuroimaging—ranging from dynamic CTA and SWI to perfusion MRI, VO analysis, and even molecular and metabolic imaging—have enabled a more nuanced evaluation of both the anatomical and functional integrity of collateral pathways.

These imaging innovations have significantly enhanced patient selection in late-window trials such as DAWN and DEFUSE 3, which rely heavily on imaging-based criteria rather than rigid time thresholds. However, the lack of standardized, validated, and universally accepted grading systems for collateral circulation continues to limit the clinical application of these tools, particularly in time-sensitive emergency settings. Additionally, existing grading systems often suffer from interobserver variability and may not fully capture microvascular integrity or tissue-level perfusion.

Looking ahead, the future of collateral assessment lies in the integration of automated, rapid, and reproducible grading algorithms powered by machine learning and artificial intelligence. These tools should ideally incorporate multimodal inputs—structural, perfusion-based, venous, metabolic, and even genetically informed imaging—to provide a comprehensive collateral profile in real-time. Parallel advances in molecular and genetic profiling, including spatial transcriptomics and high-resolution brain atlases, will likely complement imaging biomarkers and offer insights into the biological determinants of collateral resilience and failure. However, these advanced modalities also face challenges related to availability, cost, and interpretation—especially in the hyperacute phase—and require further research to be integrated effectively into stroke evaluation and management.

In conclusion, cerebral collateral circulation represents both a critical diagnostic marker and a potential therapeutic target in acute ischemic stroke. The next phase in stroke care will require not only technological advancements in imaging but also standardized frameworks for interpreting and applying collateral data across diverse clinical contexts. Bridging the gap between anatomical visualization and molecular insight may ultimately enable a precision medicine approach to collateral-guided stroke therapy—one that maximizes reperfusion benefit while minimizing risk.

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Conflicts of Interest

The authors declare no conflicts of interest.

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