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Review

Delving Into the Significance of Brain's Collateral Circulation in the Era of Revascularization Therapy

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Abstract

Purpose of review This narrative review summarized the major studies focusing on the association between revascularization therapies (intravenous thrombolysis and endovascular thrombectomy) and collateral circulation status in terms of outcome and safety. Our aim is to elucidate, drawing upon the latest scientific evidence, the pivotal role that collateral circulation plays in shaping the prognosis and potential therapeutic in patients with ischemic stroke.

Recent findings The data currently available suggest that pre-treatment assessment of collateral circulation may be crucial, as a good collateral circulation status appears to be associated with better outcomes in terms of both early revascularization and long-term disability. There is limited literature about the assessment of collateral circulation prior to acute reperfusion therapy.

Summary The role of the intracranial collateral circulation is gaining increasing attention in the field of ischemic stroke, both in terms of outcome prognosis and therapeutic interventions. These findings need to be confirmed by more structured randomized controlled trials (RCTs), but they suggest that investigating therapeutic strategies to maintain and support collateral circulation may represent the future of ischemic stroke therapy.

Introduction

Acute ischemic stroke (AIS) is the second most common cause of mortality and the first cause of disability worldwide [1]. In the last 30 years, we have witnessed an increase in diagnostic tools and acute-phase therapeutic strategies, leading to a significant rise in survival rates and a reduction in residual disability. The recent introduction of new neuroimaging techniques has also expanded therapeutic windows both for intravenous thrombolysis and endovascular thrombectomy procedures [2]. The therapeutic window for thrombolytic therapy has been extended up to 9 h from the last well-known time in patients meeting the EXTEND criteria for core-penumbra mismatch in CT or MR perfusion studies [3, 4]. On the other hand intra-arterial treatment with mechanical thrombectomy (MT) in AIS with large vessel occlusion is the standard treatment in addition to endo-venous thrombolysis for AIS if performed within 6 h since symptom onset [5, 6]. According to results from the trials DAWN and DEFUSE-3, MT is an effective and safe procedure when it is used from 6 to 24 h from symptoms onset in patients with specific perfusion imaging features [6, 7]. The extension of the time windows during which a patient can benefit from acute-phase treatments is associated with the presence of ischemic lesions with a small infarct core and a large salvageable ischemic penumbra [8].

Ischemic penumbra refers to that portion of tissue subjected to hypoperfusion that will inevitably progress to irreversible damage if perfusion is not restored [9]. The presence and maintenance of penumbra are attributed to the adequate blood support derived from collateral circulation. The brain's collateral circulation refers to interconnected arterial pathways that can provide essential perfusion to a brain area in case the primary blood flow is diminished or compromised [10] (Fig. 1).

Collateral circulation can be categorized into primary and secondary systems [11]. The primary collaterals include the interconnected vessels within the circle of Willis, while the secondary collaterals comprise the ophthalmic artery and the leptomeningeal vessels. Additionally, an anatomical classification differentiates extracranial collaterals, involving anastomoses with the ophthalmic and dural arteries, from intracranial collaterals, which include connections between the anterior and posterior circulations [11].

In the event of a vascular occlusion and the ensuing ischemic episode, a series of intricate biochemical and mechanical processes are initiated. These include the vasodilation of pre-existing collateral vessels, the stimulation of arteriogenesis resulting in the development of new anastomotic connections, and the induction of neoangiogenesis, which culminates in the establishment of novel capillary networks [12]. The relationship between collateral circulation and the extent of tissue damage underscores the potential prognostic value of collateral assessment, indicating its usefulness in guiding treatment decisions. In this review, our aim is to summarize the most significant data regarding the impact of cerebral collateral circulation in the context of acute reperfusion therapies.

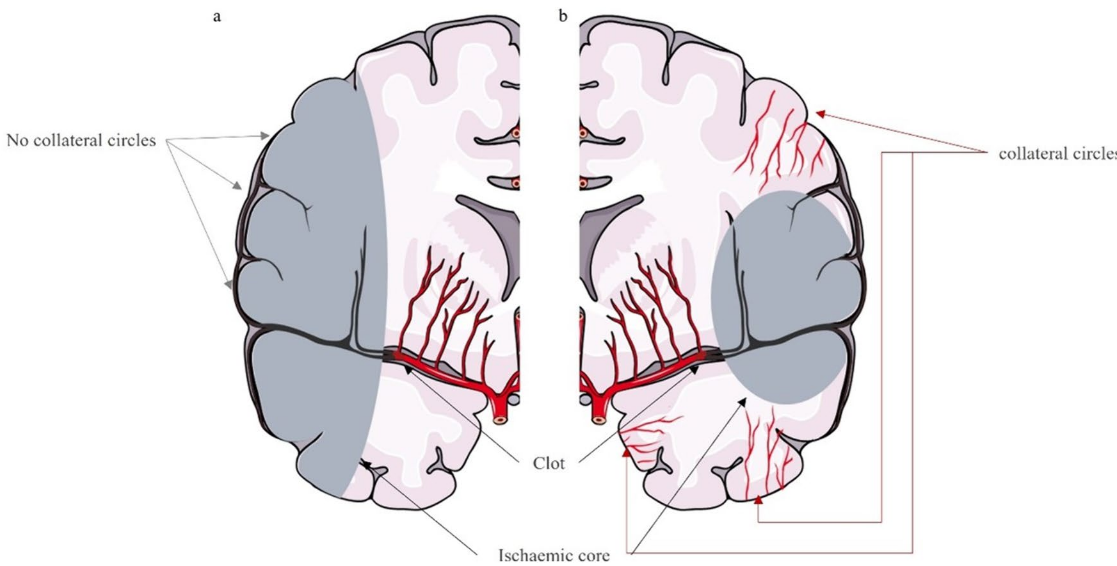

Fig. 1 Effect of good collateral circulation on the ischemic core. **a** The absence of collateral circulation leads to a large ischemic core. **b** The leptomeningeal collaterals perfuse the tissue, slowing the transformation of the penumbra into the core and effectively reducing the size of the ischemic lesion. Image modified from open-source images of smartservier.com

Methods

Literature searches will be conducted in PubMed. Combinations of keywords and MeSH terms used, including "stroke ischemic," "mechanical thrombectomy," "thrombolysis," "collateral circulation," "CT angiography," "digital subtraction angiography," "prognostic value," and "functional outcome." The search limited to studies published in English, with no time restrictions, to include the broadest and most relevant literature possible. Original studies evaluating the impact of pre-thrombolysis and pre-thrombectomy collateral circulation assessment on functional outcomes in ischemic stroke patients will be included in the review. This includes prospective and retrospective studies, clinical trials, and cohort analyses. Review articles, commentaries, letters to the editor, animal studies, and articles not providing quantitative outcome data were excluded.

Results

Imaging of collateral circulation

Several imaging techniques are available to assess the collateral circulation. Some of them provide anatomical information while others are able to inform about its function. Digital subtraction angiography (DSA) is the gold standard technique for the imaging of collateral vessels and allows the direct visualization of extracranial and intracranial vessels, including the circle of Willis and the leptomeningeal vessels [13]. However, it is an invasive and time-consuming procedure that uses ionizing radiations and contrast medium. Therefore, at present, it is mostly used in the setting of endovascular thrombectomy. In the setting of acute ischemic stroke, one commonly used technique is computed tomography angiography (CTA) that allows the visualization of the vessel occlusion by means of IV infusion of contrast medium followed by image acquisition and 3-D reconstruction. While single-phase CTA captures the image at one single point in time, multiphase CTA involves the acquisition of the image at multiple points. The latter guarantees a good interrater reliability, while the former technique may lead to an overestimation of the collateral vessels if the image is acquired during the late venous phase [8]. A novel technique is 4D-CTA, also referred to as time-resolved CTA or dynamic CTA, that combines the non-invasive nature of CTA with the dynamic acquisition of DSA. It evaluates the flow dynamics of intracranial vessels through several subsequent CT acquisitions or through a continuous volume CT acquisition for a period of time [14]. 4D-CTA was shown to be comparable to cerebral angiography in detecting arteriovenous malformations and in discriminating antegrade and retrograde flow across vessel occlusion [13, 14]. The advantage of dynamic CTA is that it provides information about late filling collaterals [8]. Perfusion techniques give quantitative and qualitative information about cerebral perfusion: cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to maximum. Such parameters, derived from CT perfusion, are an indirect measure of the extent of collateral vessels and of the ongoing viability of the tissue at risk of infarction [8, 15]. Arterial spin labeling (ASL) is an MR imaging technique that does not require contrast medium and can be used to study collaterals in patients with ischemic stroke [16].

Collateral vessel grading

The quality of collateral circulation is among the factors that determine the speed of infarct growth and the outcome of patients with ischemic stroke. Therefore, several scales have been developed to assess the quality of collaterals, some of which are based on manual assessment and others involving the use of automated software. The most widely used grading system is the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) which assesses the collateral flow as poor, moderate, or good. Among the various grading methods, the scores by Maas and Miteff have demonstrated a high sensitivity in predicting the functional outcome and may thus be used in clinical decision-making in the setting of acute ischemic stroke [10, 17]. Automatic assessment of collateral circulation, based on machine learning, promises to solve issues such as interrater reliability. Furthermore, they are based on quantitative information and are less time-consuming. Software already on the market includes e-CTA by Brainomix, StrokeSENS by Circle Neurovascular Imaging, StrokeViewer by NICO.Lab, and ColorViz by Healthcare Fast Stroke. However, automatic assessment has not yet been widely implemented in routine imaging, and companies must still solve issues like the lack of diversity, accuracy, and reproducibility of the datasets that are used to train the machine learning models [8, 10, 18].

Thrombolysis

Recently, there has been increasing support that the presence of adequate collateral support appears to be correlated with a higher rate of early recanalization with thrombolytic treatment [19]. The first studies showed that a poor collateral circulation, despite a time to treatment within 3 h, independently correlated with an increased risk and a larger volume of hemorrhagic infarction [20, 21]. An early and important study is the one conducted by Angermaier et al. [22] that examined the relationship between favorable outcomes of thrombolytic therapy and collateral circulation. This study acknowledges that the extent of the final infarct area is directly influenced by residual blood flow and, consequently, the promptness of recanalization. The patients were assessed using CT angiography and the "CTA collateralization score" (CTA-cs) was utilized to evaluate collateral presence. A higher CTA-cs correlated with a smaller infarct volume, indicating that early collateral assessment could predict infarct size following intra-arterial thrombolysis [22]. Furthermore, Nicoli et al. in 2013 in a retrospective analysis [23] explored the use of an innovative score known as the nCCD (collateral circulation deficit index), defined using MR perfusion imaging to indirectly quantify collateral circulation deficit. This index is based on the ratio between the volume of the critically hypoperfused area (absolute Tmax value exceeding 6 s) and the volume of the moderately hypoperfused area (absolute Tmax value between 2 and 6 s). The study involved 64 patients with ischemic stroke due to M1 segment occlusion of the middle cerebral artery who underwent intravenous thrombolysis. The results demonstrated an inverse correlation between nCCD and baseline stroke severity, lesion volume, and functional outcomes, along with a correlation with recanalization rate assessed at 24 h using CT angiography. These findings suggest that the quality of collateral circulation may influence the effectiveness of IV thrombolysis, especially within the first 3 h after stroke onset [23]. Two additional studies that evaluated groups of patients with AIS undergoing thrombolysis and with prior assessment of collateral circulation report similar findings. Calleja et al. assessed collateral circulation using CT perfusion source images [24], while Zhang et al. evaluated rapid collateral filling with PWI. In the latter study, it is interesting to note that the velocity, rather than the extent, of collateral filling was associated with 24-h post-IVT recanalization. This condition has been hypothesized to correlate with increased shear stress at the thrombus level and thus a higher likelihood of its fragmentation [25•]. The limitations of these two studies could primarily be the small sample sizes and the lack of consideration for two confounding factors that, as mentioned earlier, independently associate with early recanalization (ER). These factors include the length of the thrombus and the site of occlusion (considered only by Zhang et al.) [24, 25•].

Two meta-analyses have focused on the relationship between collateral circulation status and outcomes in patients with acute ischemic stroke (AIS) treated with thrombolysis [26, 27$p < 0.001$). Additionally, it underscored that good collaterals are associated with favorable functional outcomes (mRS 0–3 at 3 months) and, as already stated, with reduced hemorrhagic complications and smaller final infarct volumes [26••]. Similar results were found by Leng et al. that performed a systematic review and meta-analysis with 28 studies (3057 patients) on IVT-treated AIS patients. It highlighted the doubled rate of favorable functional outcomes in patients with good collateral circulation, along with reduced risks of symptomatic intracranial hemorrhage (sICH) and increased early neurological improvement [27•]. Poor collateral circulation, in addition to being independently associated with a higher incidence of hemorrhagic transformation, has been observed to correlate with increasing grade of radiographic cerebral edema [28].

In the era of bridging therapy, it could be crucial to evaluate the criteria suggesting which patients might benefit from early recanalization with thrombolytic therapy before endovascular treatment. In a French study involving 224 patients eligible for both intravenous and endovascular therapy, it was observed that those with good collateral circulation [29••] (assessed using the PWI map method previously validated by Kim et al.) [30] exhibited a higher rate of early recanalization, defined as angiography mTICI score of 2b-3 [31].

Furthermore, in the same study, a good status of collateral circulation correlates clearly and independently with a lower NIHSS at onset and a smaller volume of lesions on DWI sequences, factors that themselves correlate with better outcomes and a higher rate of recanalization after IVT [29••]. However, we have to underline that in this study [29••], the number of patients with an excellent collateral circulation (grade 4) [30] is small, and such findings should be confirmed in larger populations.

Thrombectomy

Mechanical thrombectomy stands as the foremost reperfusion strategy for large cerebral vessel occlusions [6]. In selecting candidates for this intervention, clinical assessment plays a pivotal role, in addition to confirming the presence of a treatable occlusion. Key clinical determinants include the NIHSS score, which should be 5 or higher, and the mRS that should not surpass two points score [6]. These criteria are crucial as they gauge the intensity of the stroke and the likelihood of the patient's recovery. Newest guidelines further recommend the employment of CT perfusion imaging in cases of significant vessel occlusion occurring within a 6–24-h timeframe [6]. This imaging technique is instrumental in evaluating the core-to-penumbra ratio, thereby enabling the estimation of potentially recoverable brain tissue. Pre-thrombectomy collateral circulation assessment can provide an additional parameter to highlight the need for endovascular treatment. The prognostic value of collateral circulation as an indicator of functional outcomes at 3 months has been examined in various studies. Weiss et al. [32•] conducted a prospective randomized study involving 84 patients with anterior circulation stroke. Collateral circulations were assessed using CT angiography (CTA) through the Miteff [33], Maas [34], modified TAN score [35], and Opercular Index [36] scores. The aim was to evaluate the predictive capabilities of these indices for outcomes measured by mRS at 3 months, comparing them with those obtained from CT perfusion (CTP). The results revealed significant differences between patients with favorable outcomes (mRS ≤ 2) and those with poor outcomes in relation to the collateral scores assessed with all four metrics. Notably, the Miteff and Maas scores emerged as the most reliable predictors. The Miteff score showed high sensitivity for predicting positive outcomes with a cut-off of 1.75, despite lower specificity. From logistic regression analysis, the Maas score was identified as the sole independent predictor of a positive outcome, also showing a correlation with the mRS at 3 months, though not statistically significant [32•]. The IMS-1, IMS-2, and IMS-3 studies also emphasized the importance of pre-thrombectomy collateral circulation assessment [37, 38••]. IMS-1 and IMS-2, involving 28 patients, utilized the capillary index score (CIS) in digital subtraction angiography (DSA), finding a positive correlation between the score and the presence of good outcomes [37]. IMS-3 examined 276 individuals through the ASINT scale in DSA, demonstrating a significant relationship between efficient collateral circulation and an mRS ≤ 2 at 3 months, as well as correlations with the NIHSS score and ASPECTs [38••]. Further retrospective analyses of patients from the DAWN [7], DEFUSE 3 [39], MR CLEAN, SWIFT PRIME [40] trial, and ETIS [41•] registry expanded the understanding of the prognostic efficacy of collateral circulation. A retrospective analysis of 161 patients, including 91 treated with thrombectomy and 70 controls from the DAWN trial [7] exploring thrombectomy in the 6–24-h window, was conducted [42]. Collateral circulations were examined in 144 subjects using CTA and TAN grade and in 57 patients with the ASITN grading system in DSA. The results demonstrated a significant correlation between the collateral score and an mRS at 3 months ≤ 2 ($p < 0.026$) [42]. The post hoc analysis of DEFUSE 3 [39] did not show significant correlations with functional outcomes but rather with the size of the infarct. This result could be attributed to the low percentage of patients with poor collateral circulation and the variety of lesion locations, leading to different clinical manifestations and mRS scores. The SWIFT study, comparing the safety and efficacy of MERCI devices with the Solitaire FR stent retriever [40], assessed collateral circulation through the ASINT score in DSA, associating efficient collateral circulation with better outcomes measured by mRS at 3 months, ASPECT scores at baseline and 24 h, NIHSS at 7 days, and improved reperfusion grade (TICI 2b/3) [43]. An analysis of ETIS registry data [41•] on 2020 patients, including 959 with good collateral circulation assessed in CTA with ASITN, confirmed the correlation with mRS at 3 months [44]. This study also highlighted that the timing and degree of reperfusion are associated with positive outcomes regardless of the quality of collateral circulation, which, however, significantly influences symptom improvement [44]. Finally, a meta-analysis including 39 studies, such as IMS I-II-III and sub-analyses of SWIFT and DEFUSE 2, showed that a good pre-endovascular treatment collateral status doubles the functional outcome at 3 months. This study revealed a relative risk for a good outcome of 3.23 for good collateral compared to poor collateral in subjects undergoing EVT and 4.45 in subjects undergoing intra-arterial thrombolysis [45••]. Table 1 summarizes the overall cited studies.

Table 1. The overall cited studies

	Type of study	Number of patients	Evaluation method (CT or DSA)	Score used	Statistical correlation with 3-month mRS	Therapy	Additional notes
Angermaier et al. [22]	Prospective	25	CTA	CTA-cs score	–	IAT	Higher CTA-cs scores had smaller infarct volumes
Nicoli et al. [23]	Retrospective analysis	64	MR perfusion	nCCD (collateral circulation deficit index)	nCCD (OR 0.988, 95% CI 0.977–0.999, p 0.042)	IVT	The nCCD is associated with baseline NIHSS and lesion volume
Calleja et al. [24]	Prospective	54	Perfusion CT-source images	LMC score	Good LMCs is associated with a good outcome [OR 21.02 (95% CI 2.23–197.75), $p = 0.008$]	IVT	Good LMCs is associated with smaller volumes ($p < 0.001$) and a higher recanalization rate
Zhang et al. [25•]	Retrospective analysis	66	MR perfusion	Velocity of collateral filling was defined as arrival time delay (ATD)	–	IVT	ATD predicted the occurrence of recanalization (area under curve = 0.69, 95% CI, 0.558–0.815, $p = 0.009$)
Seners et al. [29••]	Retrospective analysis	224	MR perfusion	ASITN-cg	–	IVT	Good collaterals are associated with early recanalization ($p = 0.029$)
Wufuer et al. [26••]	Meta-analysis	4053	–	–	$p < 0.001$	IVT	Good collaterals are associate with higher rate of recanalization ($p < 0.001$)

Table 1. (continued)

	Type of study	Number of patients	Evaluation method (CT or DSA)	Score used	Statistical correlation with 3-month mRS	Therapy	Additional notes
Leng et al. [27•]	Meta-analysis	3057	–	–	RR = 2.45; 95% CI, 1.94–3.09; $p < 0.001$	IVT	Good recanalization (RR, 1.34; 95% CI, 0.87–2.07; $p = 0.19$), and lower ICH (RR, 0.38; 95% CI, 0.16–0.90; $p = 0.03$)
Weiss et al. [32•]	Prospective	84 patients	CTA	Miteff, Maas, mTAN, Opercular Index	**Maas** $r_s = -0.14$, $p = 0.12$, AUC (95% CI) 0.61 (0.48–0.75), sensitivity 96%, specificity 23% (cut-off: 1.75)	EVT	Maas and Miteff show higher correlation with 3-month mRS
Al-Ali et al. [37]	Prospective (IMS I–II trial)	28 patients	DSA	CIS (capillary index score)	$p > 0.25$	EVT IAT	
Liebeskind et al. [38••]	Prospective (IMS III trial)	331 patients	DSA	ASITN/SIR	$p = 0.035$	IAT IVT EVT	No correlation between collateral status and TICI
Liebeskind et al. [42]	Retrospective (DAWN)	161 patients	144 in CTA, 57 in DSA	mTAN (CTA), ASITN/SIR (DSA)	$p < 0.026$	EVT	
de Havenon et al. [52]	Retrospective (DEFUSE 3)	130 patients	CTA	TAN Maas	$p = 0.8$	EVT	
Rao et al. [53]	Retrospective (DEFUSE 3)	123 patients	CTP	HIR (hypoperfusion intensity ratio)	$p = 0.154$	EVT	

Table 1. (continued)

	Type of study	Number of patients	Evaluation method (CT or DSA)	Score used	Statistical correlation with 3-month mRS	Therapy	Additional notes
Anadani et al. [44]	Retrospective (ETIS registry)	2020 patients	DSA	ASITN/SIR	OR = 1.5, CI 95% 1.19–1.88, $p < 0.001$ (adjusted with risk factors)	EVT	No correlation between collateral status and recanalization rate but association between successful reperfusion and early neurological improvement stronger in the good collateral group (OR 5.63, 95% CI 3.13 to 10.13)
Liebeskind et al. [43]	Retrospective (SWIFT PRIME)	119 patients	DSA	ASITN/SIR	$p < 0.001$	EVT	

CTA computed tomography angiography, *CTAcs* Angio Computed Tomography collateral score, *IAT* intra-arterial thrombolysis, *IVT* intravenous thrombolysis, *nCCD* collateral circulation deficit index, *ASITN* American Society of Interventional and Therapeutic Neuroradiology, *LMCs* LeptoMeningeal Collateral score, *ATD* arrival time delay, *ASITN-cg* American Society of Interventional and Therapeutic Neuroradiology collateral grading, *DSA* digital subtraction angiography, *EVT* endovascular therapy

Discussion

In the era of revascularization therapy, every factor that could impact prognosis and therapeutic efficacy in AIS gains heightened importance. Literature data underscore the growing strategic role of early comprehensive imaging studies in patients with acute ischemic stroke. Assessing the status of collateral circulation could not only assist in prognostic evaluation but also increase the precision in selecting patients for the most appropriate therapeutic intervention. The most significant finding from the reviewed studies is the notable correlation between good collateral circulation and favorable outcomes at 3 months in patients AIS. From a pathophysiological perspective, efficient collateral networks influences the velocity of the conversion of the ischemic penumbra into ischemic core, slowing down this process [8]. Consequently, patients with good collateral circulation exhibit a reduced infarct size and lower NIHSS scores compared to those with poor collaterals [23, 26, 29]. The status of collateral circulation also appears to influence the effectiveness of reperfusion therapy. Thrombolysis remains the primary urgent therapeutic strategy, combined or not with endovascular therapy [4]. Patients with robust collateral networks undergoing thrombolysis exhibit a significantly higher rate of recanalization, and poor collateral circulation could become a radiological predictor of lower likelihood of recanalization [19, 29]. This phenomenon could be attributed to various mechanisms. It has been postulated that the presence of more efficient collaterals is associated with increased flow around the thrombus, leading to heightened shear stress, which in turn enhances the likelihood of thrombus fragmentatio [25•]. Additionally, well-developed collaterals may also serve to transport thrombolytic agents to the distal end of the thrombus, thereby amplifying the treatment's effectiveness [19]. Therefore, the status of collateral circulation could indeed serve as an additional predictive factor for the successful efficacy of thrombolytic treatment [8] such as low NIHSS at onset, occlusion of distal vessels, small thrombus, incomplete vessel occlusion, and ASPECT score [29••]. The presence of a low ASPECT score acts as a contraindication for both thrombolytic and endovascular interventions. Yet, recent research findings suggest that good collateral circulation can result in favorable outcomes even amidst low ASPECT conditions [35]. This highlights a potential subgroup of patients who might derive benefit from treatments otherwise deemed unsuitable under standard criteria.

In endovascular treatment, collateral circulation is a key prognostic indicator for 3-month functional outcomes. Although it is reasonable to assume that this finding is also associated with a correlation between good collateral circulation and a higher TICI score after endovascular treatment, there is still a lack of strong evidence in the literature [38••, 44]. Nonetheless, patients with strong collateral networks who achieve successful recanalization tend to show better clinical improvements than those with weaker collaterals, despite similar recanalization success [44]. This clinical improvement, regardless of recanalization rate, may be due to a longer window before the ischemic penumbra becomes ischemic core, suggesting that good outcomes are possible even with delayed thrombectomies [8].

These studies underscore the significance of collateral circulation and the management of factors that may influence its status. Notably, patients with poor collaterals are often characterized by the presence of hypertension, a history of smoking, and diabetes mellitus [42–44]. Future research directions might pivot towards developing therapeutic interventions aimed at augmenting collateral circulation-induced perfusion in ischemic stroke patients [15]. Among the promising avenues being explored is the electrical stimulation of the sphenopalatine ganglion, which has been shown to enhance cerebral blood flow through parasympathetic nervous system activation [46].

Furthermore, statins have been implicated in bolstering cerebral collateral circulation, possibly through the upregulation of nitric oxide (NO) synthase. Notably, studies have revealed that patients with acute ischemic stroke (AIS) who were already on statin therapy exhibited reduced infarct volumes and improved collateral circulation [47]. Additionally, nitric oxide inhalation has been demonstrated in rodent models to cause targeted vasodilation in ischemic penumbra regions, thereby diminishing infarct size [48, 49]. Despite these promising animal studies, the application of transdermal NO in human subjects has not yet achieved comparable success [50]. Multiple compounds are currently being investigated for their potential to enhance the brain's collateral circulation, including PEGylated carboxyhemoglobin (PP-007) and hemoglobin-based oxygen carriers [51].

Conclusions

The evaluation of collateral circulation is poised to assume a pivotal role in the future of stroke management, serving as a critical determinant in the selection of candidates for reperfusion therapy. Emerging evidence indicates a compelling association between robust collateral circulation and heightened rates of early recanalization, translating into improved outcomes at the 3-month mark. This positive correlation holds true for various reperfusion modalities, encompassing thrombolysis, thrombectomy, and combined therapies. Notwithstanding these promising findings, it is imperative to underscore the necessity for specific randomized controlled trials that can substantiate and refine the preliminary data gleaned from existing literature. Rigorous scientific inquiry is essential to establish a solid foundation for the integration of collateral circulation assessment into clinical decision-making processes. Looking ahead, the trajectory of research endeavors should be directed towards formulating therapeutic strategies geared towards augmenting perfusion facilitated by collateral circulation in ischemic stroke patients. By delving into innovative approaches and interventions, researchers can explore avenues to enhance and optimize the natural compensatory mechanisms, ultimately refining the landscape of ischemic stroke treatment.

This pursuit of knowledge will undoubtedly contribute to the evolution of stroke care and fortify the foundation upon which future therapeutic interventions are built.

Author Contribution

Conceptualization: M.M., S.S.R., B.A.; methodology: M.M., S.S.R., B.A., G.I.; validation: M.M., F.R.P., A.M.; investigation: M.M., S.S.R., G.I.; Fig. 1 prepared by B.A.; Table 1 prepared by S.S.R., B.A., G.I.; writing—original draft preparation: M.M., S.S.R., B.A., G.I.; writing—review and editing: M.M.; supervision: A.S., P.E., F.R.P., G.DR. All authors reviewed the manuscript.

Compliance with Ethical Standards

Conflict of Interests
The authors declare no competing interests.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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