Ref: Ro J Neurol. 2021;20(4)
DOI: 10.37897/RJN.2021.4.3

Diagnostic and prognostic utility of brain collaterals in acute ischaemic stroke: Current knowledge and insights on treatment decision-making

Akansha Sinha[1,2], Miriam Priglinger-Coorey[3], Peter Stanwell[4], Negman Alvarado[5], Murray Killingsworth[1,3,6], Sonu Menachem Maimonides Bhaskar[1,2,7,8]

[1] University of New South Wales (UNSW), South Western Sydney Clinical School, NSW, Australia
[2] Neurovascular Imaging Laboratory, Clinical Sciences Stream, Ingham Institute for Applied Medical Research, Sydney, Australia
[3] Department of Neurology, Royal North Shore Hospital and Northern Sydney Local Health District, Sydney, Australia
[4] School of Health Sciences, Faculty of Health, University of Newcastle, Callaghan, New South Wales, Australia
[5] Instituto Regional de Bioingeniería (IRB), Universidad Tecnológica Nacional (UTN), Facultad Regional Mendoza (FRM), Mendoza, Argentina
[6] Correlatively Microscopy Facility, Department of Anatomical Pathology, NSW Health Pathology, Sydney, Australia
[7] NSW Brain Clot Bank, NSW Health Pathology, Sydney, Australia
[8] Department of Neurology and Neurophysiology, Liverpool Hospital and South Western Sydney Local Health District, Sydney, Australia

ABSTRACT

Stroke is a leading cause of death and disability worldwide. The advent of acute reperfusion therapy, intravenous thrombolysis and endovascular thrombectomy, has revolutionised the field of stroke medicine, and neurology in general. Recent studies have implicated a major role of cerebral collaterals in the trajectory of acute ischemic stroke patients receiving reperfusion therapy. Collaterals sustain blood supply to the tissue in the setting of acute ischaemia which prevents further expansion of the hypoperfused tissue, playing an important role in determining outcomes after acute ischaemic stroke. The use of collateral assessment in routine practice in acute ischaemic stroke, let alone in reperfusion therapy, is far from universal and limited. Future work in embedding collateral assessment in standards of care in acute stroke and management is warranted. This article provides a comprehensive update on the diagnostic and prognostic utility of collaterals in acute ischaemic stroke and recommendations on collateral-based decision making in acute stroke and steps that can be taken for its rapid uptake in clinical practice.

Keywords: collaterals, acute ischaemic stroke, reperfusion therapy, reperfusion, cerebrovascular disease

Abbreviations

AHA	American Heart Association/American Stroke Association
AIS	Acute ischaemic stroke
IVT	Intravenous thrombolysis
EVT	Endovascular thrombectomy
HT	Haemorrhagic transformation
BBB	Blood-brain barrier
ICH	Intracranial haemorrhage
NCCT	Non-contrast computed tomography
CT	Computed tomography
CTA	Computed tomography angiography
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
CTP	Computed tomography perfusion
DSA	Digital subtraction angiography
sCTA	Single-phase computed tomography angiography

Corresponding author:
Sonu Bhaskar
E-mail: sonu.bhaskar@reprogramglobal.org; sonu.bhaskar@uon.edu.au

Article history:
Received: 15 September 2021
Accepted: 20 December 2021

mCTA	Multi-phase computed tomography angiography
ASL	Arterial spin labelling
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
	Diffusion-weighted imaging
DWI	Gradient recalled echo
GRE	
FLAIR	T2 weighted fluid-attenuated inversion recovery
PWI	Perfusion weighted imaging
CE-MRA	Contrast-enhanced magnetic resonance imaging
TOF-MRA	Time-of-flight magnetic resonance imaging
AUC	The area under the curve
dMRA	Dynamic magnetic resonance imaging
mRS	Modified Rankin scale
sICH	Symptomatic intracerebral haemorrhage
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
DEFUSE 3	The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke
CAS	Carotid artery stenosis
Delayed-LCVF	Delayed cortical vein filling during the late venous phase
SPG	Sphenopalatine ganglion
ECP	External counterpulsation
MCA	Middle cerebral artery
SENTIS	Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke
EC	Extracranial
IC	Intracranial
HDT	Head down tilt

INTRODUCTION

The global prevalence of ischaemic stroke in 2017 was 82.4 million, a 16.1% increase since 2007 (1,2). Its increasing prevalence and global burden justify a comprehensive understanding of the factors mediating stroke outcomes (3,4). Reperfusion therapy is the only approved treatment for AIS and includes intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) (5). Other reperfusion strategies for AIS, including intra-arterial, ultrasound, combined intravenous and intra-arterial thrombolysis, as well as the use of glycoprotein IIb/IIIa (GP IIb / IIIa) antagonists, or increased collateral flow through electrical stimulation of the sphenopalatine ganglion, are being investigated (6). Baseline collateral status has been demonstrated to impact prognosis following reperfusion therapy after an acute ischaemic stroke (AIS) (7,8). Baseline collateral status may inform clinical decision-making when selecting AIS patients for reperfusion therapy (9). The 2018 American Health Association (AHA) guidelines support the use of baseline collateral status to select patients for EVT with weak evidence (Class IIb) due to the gaps and discrepancies in knowledge surrounding collaterals (10). This article presents an overview of imaging modalities used to assess collaterals, their prognostic capability, automation of the process of baseline collateral assessment and finally, and collaterals-based decision-making.

STATIC AND DYNAMIC ASSESSMENT OF COLLATERALS – CLINICAL INDICATIONS

AHA guidelines for stroke assessment

The 2018 AHA guidelines state that the primary goal of emergency imaging after an AIS is to exclude an intracranial haemorrhage (ICH) and a non-contrast computed tomography (NCCT) is the ideal modality to do so. By no means should any vascular or perfusion imaging delay the initial IVT treatment. Once IVT has commenced, and a patient has met the criteria for endovascular treatment, non-invasive intracranial vascular imaging such as computed tomography angiography (CTA) can be carried out. Additional imaging, other than computed tomography (CT), CTA, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), to aid with selection for EVT is not recommended in patients who are < 6 hours since the onset of symptoms. However, there is strong evidence supporting additional imaging, such as CT perfusion (CTP), diffusion-weighted MRI or MRI perfusion for EVT selection in patients who are within 6 to 24 hours since the onset of symptoms. The 2018 AHA guidelines state that there is weak evidence supporting the use of collateral status to select patients for EVT (10). Multiple studies have highlighted the clinical benefits of good baseline collateral status, meaning that appropriate imaging modalities to assess collaterals, and the clinical indications to utilise them, should be explored (11,12).

Static vs. dynamic assessment

Collaterals can be assessed in either a static or dynamic manner. The static assessment provides a snapshot of collaterals at a single point in time. This often raises issues wherein the contrast medium has not fully dispersed throughout the vessels, leading to underestimation of collaterals. Dynamic assessment involves observing blood flow through collaterals over a period, allowing for an adequate amount of time for the contrast to reach, and thus

visualise all vessels. Imaging modalities used to assess collaterals statically include single-phase CTA (sCTA) and MRA. Digital subtraction angiography (DSA), multi-phase CTA (mCTA,or 4D-CTA/time-resolved CTA), CTP and arterial spin labelling (ASL) MRI can be used to assess collaterals in a dynamic manner (13).

Digital subtraction angiography

Multivessel DSA is the gold standard for assessing both primary and secondary collaterals in AIS patients. Its ability to assess arterial, capillary and venous contrast enhancement phases allows it to assess collaterals in a dynamic manner (14). However, conducting a DSA requires arterial catheterisation, making it an invasive procedure that increases risks of complications such as iatrogenic stroke (8). It is highly operator dependent, commonly performed by an interventional radiologist, its use requires knowledge regarding catheter insertion, disease pathology and vascular anatomy, requiring angio-suite and specialised procedure and equipment (14). DSA also has a long acquisition and procedural time and low accessibility (15). Furthermore, images are obtained via injection of a single artery. Most cerebral DSA procedures involve separate studies (called runs) where each vessel is selected individually, and contrast injected for each run. If there are complications, a catheter can be placed in the arch and injected to capture all vessels, but still, likely need multiple injections with different patient position to reduce superimposition of anatomy. Thus, collaterals that branch off other arteries may not be visualised (16). As such, despite being the gold standard to assess collaterals, it is not commonly used.

Computed tomography

In the context of collateral assessment, subtypes of CT such as CTA, mCTA and CTP can be used. sCTA is the most widely used imaging modality to assess collaterals and is used in most clinical trials assessing the impact of collaterals on clinical outcome following reperfusion therapy after an AIS (17). Tan et al. found that combining information from a static and dynamic mode of visualising collaterals, specifically CTA and CTP (18,19), provides the most accurate assessment of collaterals (20). mCTA allows dynamic visualisation of collateral status. In the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial, the pial arterial filling visualised on mCTA was reported to have good inter-rater reliability and ability to determine the good clinical outcome (13).

Magnetic resonance imaging

Although CT is the most used imaging modality during an AIS work-up, an MRI can provide a lot more clinical information which may be relevant to determining outcomes following an AIS. A full MRI protocol involves conducting diffusion-weighted imaging (DWI), gradient recalled echo (GRE), T2 weighted fluid-attenuated inversion recovery (FLAIR), MRA and perfusion-weighted imaging (PWI). An MRA and PWI can provide static and dynamic information respectively regarding the collateral status of an AIS patient. There are two forms: MRA-contrast-enhanced MRA (CE-MRA) and time-of-flight MRA (TOF-MRA). The use of contrast in CE-MRA enables the visualisation of collaterals. TOF-MRA does not involve using contrast and, instead, relies on direction and velocity of blood flow. Though this makes it an ideal imaging modality for those who are allergic to contrast media or have impaired renal function, TOF-MRA is an insensitive method of assessing collateral blood flow (21). It can be argued that arterial spin labelling (ASL) is also a form of contrast-enhanced MR, which uses an endogenous agent, i.e., magnetically labelled water.

Arterial spin labelling

Arterial spin labelling (ASL) is a non-invasive and non-ionising MRI technique, used to measure tissue perfusion (22), and can be applied to assess collateral blood flow (23). A high density of collateral circulation delays overall arterial transit time and appears as an intra-arterial sign (IAS) or hyperintense signals. As such, collateral status on ASL is determined by analysing these hyperintense signals. A retrospective cohort study by Morofuji et al. confirmed that hyperintense signals distal to the site of occlusion are indicative of angiographic collaterals. However, the study also notes that overestimation of collaterals is possible when using ASL because hyperintensity of the cerebral cortex or cerebrospinal fluid space is sometimes observed. Conversely, collaterals may be underestimated if the collateral flow is weak and hyperintensities distal to the site of occlusion are hard to detect (23).

DIAGNOSTIC COMPARISON BETWEEN CTA, DSA AND MRA

As mentioned previously, DSA is the gold standard imaging modality to assess primary and secondary collateral circulation. CT or MRA, on the other hand, can visualise primary collateral with moderate-to-good diagnostic performance, but the ability to visualise and evaluate secondary collaterals are limited (13).

CTA/CTP VS DSA

CTA, DSA and MRA have varying levels of diagnostic accuracy, especially when considering the in-

terobserver reliability context of CTA, mCTA is a more accurate method of assessing collaterals when compared to sCTA (24). Garcia-Tornel et al. found that good collaterals (sCTA: defined as collateral supply filling >50% but >100% of occluded vascular territory; mCTA: compared to the asymptomatic contralateral hemisphere, there is no delay or delay in one phase in filling in of peripheral vessels and prominence and extent are the same/increased) detected on both sCTA and mCTA are associated with smaller infarct volume (24). However, good collaterals detected on mCTA, as opposed to sCTA, were more likely to be associated with better clinical outcomes, specifically NIHSS score and mRS at 90 days. This study also confirmed that sCTA often underestimates collateral supply – patients who had bad collaterals on sCTA (defined as sCTA static collateral score of 0-1 on modified American Society of Interventional and Therapeutic Neuroradiology (ASITN) scale where 0 corresponds to absent collaterals and 1 refers to collaterals filling 50% or less of the occluded territory) but good collaterals on mCTA (defined as mCTA collateral score of 3-4 where 3 corresponds to complete collateralization of the ischemic site by the late venous phase and 4 refers to the complete collateralization of the ischemic site before the venous phase) had a high probability of a good functional outcome (mRS 0-2 at 3 months) (24). CTP collects images in a time-resolved series during injection of contrast media, its images can be used to reconstruct mCTA images. Kauw et al. compared collateral visualisation on sCTA to that of CTP derived 3-phase CTA and mCTA images (17). In the static assessment of collaterals, sCTA, 3-phase CTA and mCTA had an interobserver agreement of 0.69, 0.58 and 0.67 respectively. In the dynamic assessment of collaterals, 3-phase CTA and mCTA had an interobserver agreement of 0.52 and 0.54 respectively. Concordance between all CT and DSA images, the latter of which was the reference standard, was poor. This was attributed to the lack of standardisation of collateral grading scale for different imaging modalities, incomplete data regarding collaterals since contralateral ICA and posterior circulation was not assessed in anterior circulation stroke and the inability of CTA to time-resolved blood flow in collateral circulation (17). Furthermore, 3-phase CTA and mCTA, not DSA, assessed collateral grading was associated with clinical outcome.

MRA VS. DSA

A study by Yuan et al. assessed the ability of TOF-MRA to assess pial collaterals compared to DSA. The sensitivity and specificity of TOF-MRA were found to be 0.7 and 0.93 respectively. Compared to DSA, the area under the curve (AUC) of collateral grading using TOF-MRA was 0.83. However, this study has several shortcomings, the main one being that the TOF-MRA images were not obtained within a few hours of the onset of symptoms - the median time from onset of symptoms to TOF-MRA was 7.5 days (25). As such, the results of this study cannot be applied to an acute setting. Furthermore, the results from the study by Yuan et al are contested in a review by Merino et al. who state that TOF-MRA is an insensitive method of assessing collaterals (21).

A study by Hernandez-Perez et al. aimed to evaluate the ability of dynamic MRA (dMRA) in assessing cerebral collaterals. It was found that grading collateral status on dMRA using the ASITN/SIR scale was highly correlated to infarct core and hypoperfusion intensity ratio. As such, Hernandez-Perez et al. recommend it as a fast and reliable method to assess collateral status in AIS patients. However, the study notes that the clinical application of its results are limited by the small cohort of 25 patients and by the fact that dMRA was not compared to DSA (26).

Transcranial Doppler (TCD) or carotid duplex ultrasonography (CDU)

A major collateral pathway for ophthalmic and cerebral artery blood supply is the external carotid artery (ECA) (27). In ipsilateral ICA occlusion patients with recurrent symptoms, the ECA is an essential collateral pathway, which may guide the need for emergency surgery, or planning thereof, in stenotic ECA patients requiring revascularization (28, 29). Isolated ICA occlusions may not warrant immediate surgery and change in patient care is not necessitated. The difference between near occlusion and total occlusion is clinically important (30). Patients with near occlusion may be eligible for surgery, while patients with complete occlusion are not. In the event of a near or complete occlusion of the common carotid artery (CCA), flow direction in the ECA may be reversed through collateral recruitment to a patent ICA (31). Combination of the cut-off of an ECA peak systolic velocity (PSV) ≥200 cm/s with the presence of colour aliasing demonstrates the high diagnostic capability for ≥ 50% ECA stenosis, based on CTA, with sensitivity (90%), specificity (96%), positive predictive value (83%), and negative predictive value (98%) and the area under the curve of 0.97 (27).

THE PROGNOSTIC CAPABILITY OF ARTERIAL COLLATERALS

As mentioned previously, the 2018 AHA guidelines support collateral assessment as a part of clinical decision making with weak evidence. Several studies investigate the correlation between clinical outcome and collateral supply. To solidify its incor-

poration into routine stroke workflow, several studies have investigated the impact of baseline collateral status on clinical outcomes following reperfusion therapy in AIS patients. Multiple parameters can be considered when assessing clinical outcome. For example, the Modified Rankin Scale (mRS) is a 7-point scoring system that quantifies a patient's degree of disability following a neuropathological event. Low scores (mRS 0-2) indicate functional independence while higher scores indicate disability (mRS 3-5) and death (mRS 6). mRS, alongside other parameters such as mortality rates, successful reperfusion, infarct growth and incidence of complications such as symptomatic intracerebral haemorrhage (sICH), can be used to assess clinical outcomes. Recent meta-analyses support the widely accepted hypothesis that good collateral status is correlated with better clinical outcomes (32-36). However, results from meta-analyses must be interpreted cautiously. Due to the selection criteria adopted by these meta-analyses, wherein articles must be full-text and in English, a significant degree of selection bias is involved. Heterogeneity amongst primary studies, *vis a vis* results reported, and scales used to assess collaterals limits the ability of meta-analysis to conduct subgroup analyses. The limited availability of primary studies assessing specific outcomes also contributes to this. Although meta-analyses support the widely accepted hypothesis, there is a discrepancy amongst primary studies wherein some support the hypothesis, while others contest this direct correlation (12,37,38).

Association with functional outcomes

Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) is a multicentre RCT that randomised eligible patients into treatment groups (usual care or intraarterial treatment and usual care) (39). Through a post hoc analysis of data from the MR CLEAN registry, Jansen et al. found that better baseline collateral status was associated with lower mRS score, even when adjusted for confounders such as age, baseline NIHSS score, history of diabetes mellitus or previous stroke, and occlusion location (12). Several other studies support this correlation (11,38,40,41). However, Jansen et al. added that a large portion of patients with poor/absent collaterals who were treated at the end of the 6-hour time window also achieved functional independence at 90 days. Thus, collaterals status may not alone mediate the benefit from reperfusion therapy. Instead, a multivariate approach wherein other patient factors are considered is recommended. A unique strength of the MR CLEAN registry is its inclusion of patients with absent/poor collaterals. However, only one reader assessed collaterals status, making this process prone to inaccuracies. Furthermore, sCTA was used to assess collateral status, which may have led to its underestimation, and the impact of stroke aetiology on collaterals was not considered. These limitations must be considered when interpreting the results of this trial.

Association with mortality

A prospective cohort study by Yeo et al. found that the presence of posterior communicating artery was significantly associated with reduced mortality rate, independent of baseline leptomeningeal collateral status (40). The inclusion of patients with good perfusion status in this study introduces selection bias and as such, these results should be interpreted cautiously. Despite this, the correlation between good collateral status and reduced mortality rates is also highlighted by results from the MR CLEAN registry and retrospective cohort studies by Park et al. and Kim et al. (12,38,41).

Association with infarct growth

Endovascular Therapy Following Imaging Evaluation for Ischaemic Stroke (DEFUSE 3) is a multicentre RCT wherein AIS patients were randomised into standard medical therapy or EVT and standard medical therapy (42). A sub-group analysis of the data collected by DeHavenon et al. found that patients with good collateral status had smaller infarct growth and an overall smaller absolute ischaemic core at the 24-hour follow-up imaging (37). A major limitation of the DEFUSE 3 trial is that due to the inclusion of patients with wake-up stroke, the exact time of stroke onset in these patients is not known. This may have caused inaccurate documentation of initial infarct size and the degree of infarct growth over time. Despite this limitation, prospective and retrospective studies by Nambiar et al. and Sheth et al. respectively, corroborate the results from DEFUSE 3 (11,43).

Association with recanalisation

The DEFUSE 3 trial showed no difference in recanalization rates between groups with good and poor collaterals (37). These results are contested by several other studies which suggest a correlation between good collaterals and higher recanalisation rates (11,35,44,45). A potential explanation for the unexpected results in DEFUSE 3, concerning recanalisation and sICH, is a progressive worsening of collateral status over time. This may cause patients who initially had a good collateral status to eventually develop the same clinical profile as patients with poor collateral status. As such, no differences will be observed in the clinical outcomes between the two groups.

Association with sICH

No association was observed between collateral status and rates of sICH in sub-analyses of the DEFUSE 3 and MR CLEAN trials as well as other prospective/retrospective cohort studies (12,37,46,47). However, other studies have observed higher rates of sICH amongst patients with poor collaterals (45,48,49). Such a dichotomised perspective of this correlation may be due to reperfusion injury and the unknown extent to which it offsets the beneficial effects of reperfusion therapy.

Association with stroke aetiology

Recent studies have found an interesting connection between stroke aetiology and baseline collateral status. In a retrospective cohort study, Al-Dasuqi et al. noted that patients with carotid artery stenosis (CAS)-related stroke were more likely to have a good baseline collateral status (47). This correlation was previously noted by Rebello et al. who found that, as opposed to cardioembolic strokes, steno-occlusive diseases are independently associated with moderate/good collateral circula-

TABLE 1. Summary of the studies assessing the impact of baseline collateral status on clinical outcome following reperfusion therapy

Study	Study design (Cohort size)	Clinical outcomes	Main findings
Jansen et al. (12)	Post-hoc analysis (n = 1412)	mRS at 90 days	Good baseline collateral status is associated with a lower mRS score, independent of time to treatment (OR 1.5, 95% CI 1.4 – 1.7)
		Mortality	Good baseline collateral status is associated with lower mortality rates.
		sICH	Good baseline collateral status is not associated with lower sICH rates.
Yeo et al. (40)	Prospective cohort study (n = 147)	mRS at 90 days	The presence of an anterior communicating artery is associated with good clinical outcome, independent of baseline leptomeningeal collateral status.
		Mortality	The presence of a posterior communicating artery is associated with a reduced mortality rate.
de Havenon et al. (37)	RCT sub-analysis (n = 130)	Infarct growth	Good baseline collateral status is associated with smaller infarct growth and an overall smaller absolute ischaemic core.
		Recanalisation	No difference was found in recanalisation between the groups with good and poor baseline collaterals
		sICH	No difference was found in the rates of sICH between groups with good and poor baseline collaterals
		mRS	No difference was found in the rates of functional independence between groups with good and poor baseline collaterals. (OR 0.61, 95% CI 0.26 – 1.45)
Nambiar et al. (11)	Prospective cohort study (n = 84)	Infarct growth	Infarct growth was significantly lower in patients with good baseline collateral status who achieved recanalization.
		Recanalisation	Patients with intermediate/good collaterals were more likely to experience successful recanalisation compared to patients with poor collaterals.
		mRS	Patients with intermediate/good collaterals who experienced successful recanalization showed a significant correlation with good clinical outcome (mRS 0-2).
Park et al. (38)	Retrospective cohort study (n = 119)	sICH	Higher rates of sICH in patients with poor leptomeningeal collaterals score, although this correlation was not clinically significant.
		mRS	Higher rates of favourable functional outcome amongst patients with good leptomeningeal collaterals score. (OR 5.14, 95% CI 1.62 – 16.26)
		Mortality	Lower rates of mortality amongst patients with good leptomeningeal collaterals score.
Kim et al. (41)	Retrospective cohort study (n = 554)	HT	Higher rates of HT in patients with poor collaterals.
		mRS	Patients with good collateral better 3-month mRS profiles compared to those with poor collaterals.
		Mortality	Mortality rates were higher in patients with poor collaterals.
Al Dasqui et al. (47)	Retrospective cohort study	Stroke aetiology	Patients with CAS related stroke aetiology are more likely to have good baseline collaterals.
Rebello et al. (50)	Retrospective cohort study	Stroke aetiology	Patients with steno-occlusive diseases are more likely to have moderate/good collaterals.

mRS, modified Rankin score; sICH, symptomatic intracerebral haemorrhage; HT, haemorrhagic transformation

tion (50). Table 1 provides a summary of the main findings of the association of collaterals with stroke aetiology.

The prognostic capability of venous collaterals

Several studies regarding cerebral collateral circulation are based on arterial collaterals. As mentioned previously, venous collaterals play an equally important role in determining prognosis following reperfusion therapy after an AIS. Yu et al. found that prominent medullary veins on the contralateral hemisphere were more common in patients with good clinical outcome (mRS<3) after 3 months (51). Furthermore, other studies found that favourable velocity and extent of cortical vein drainage was also associated with good clinical outcome (52,53). Such findings support the involvement of the venous circulation and its impact on prognosis.

Delayed cortical vein filling during the late venous phase (delayed-LCVF) was found to be independently associated with poor baseline collaterals (54). Bhaskar et al. assessed the impact of delayed-LCVF on reperfusion status at 24 hours and functional outcome at 90 days. It was found that patients with delayed-LCVF had poor reperfusion at 24 hours. No significant difference was found in functional outcome at 90 days between patients with or without delayed-LCVF (55). Gaps in knowledge such as this, alongside the general lack of studies focusing on venous collaterals, warrant further research into this field.

Through the analysis of various studies, it becomes obvious that although there is a consensus

TABLE 2. Summary of studies using automated collateral assessment in acute ischemic stroke

Source	Automated assessment method	Imaging modality/ Grading system	Findings
Boers et al. (56, 57)	1. identify the affected territory at risk 2. segmentation of the vessels 3. comparison of vessel presence between the hemispheres	CTA/Tan	· Was strongly correlated to the manual method. · Had reliable correlations with functional outcome and tissue death · Was better able to distinguish between favourable and unfavourable outcomes (manual AUC: 0.66; automated AUC: 0.76).
Aktar et al. (58)	ACCESS (Automatic Collateral Circulation Evaluation in iSchemic Stroke) - The collateral score is defined as the ratio of unfilled vessels to full vasculature	4DCTA/ ASPECTS	Average AUC of 0.85.
Verdolotti et al. (59)	ColorViz - Is a semi-automatic, post-processing software that uses a colourimetric map to assess collaterals	Colour-coded maps using mCTA/ 3-point scale based on the arrival time of contrast	Good accordance among operators when evaluating CTA and ColorViz images (r = 0.962 and r = 0.89 respectively)
Su et al. (60)	1. define the relevant anatomical region 2. deep learning to extract vessel structure 3. quantification - comparison of affected and non-affected hemispheres	3DCTA/Tan	The automated assessment method had an accuracy of 0.8.
Shieh et al. (61)	Comparison of the contralateral hemisphere	NCCT/ ASPECTS	AUC of 0.902
Frolich et al. (62)	4DCTA was processed using a commercial software package. Temporal maximum intensity projection fuse contrast opacification across the duration of 4DCTA and show densely opacified arterial and venous structures	4DCTA/ rLMC	Intraclass correlation of 0.78
Zhang et al. (63)	4D CTA images were reviewed and reconstructed using commercial software. Collateral scores were assigned using the velocity of blood flow and extent of collaterals.	4DCTA/ rLMC	AUC of 0.8
Kersten et al. (64)	Intensity differences between left & right hemisphere	4DCTA/ ASPECTS	Correlation of automated method to radiologist had r^2 of 0.71

CTA, computed tomography angiography; 4DCTA, 4-dimensional computed tomography angiography; AUC, area under the curve; ASPECTS, Alberta stroke programme early CT score; mCTA, multi-phase computed tomography angiography; NCCT, non-contrast computed tomography; rLMC, regional leptomeningeal score; AUC, area under the curve

that links good baseline collateral status to good clinical outcome, results from studies do not always support this direct correlation. As such, further research must be conducted to validate the prognostic value of collaterals and their use in patient selection for reperfusion therapy.

Automated collateral assessment

The post-processing of radiological imaging used to assess collaterals is often done manually, making it time-consuming and prone to a poor interobserver agreement due to potential bias or error. As such, automating this process may be beneficial. Boers et al. conducted a post hoc analysis of 70 patients from the MR CLEAN database to test the reliability of automatic collateral scoring compared to manual collateral scoring. The automated process involved identifying the affected territory, segmentation of the vessels and comparison of vessel presence between the hemispheres. It was found that the automated method was strongly correlated with the manual method and showed reliable correlations with functional outcome and tissue death. The automated method had a better discriminative power between favourable and unfavourable functional outcome compared to the manual method (56). A follow-up retrospective study by the same authors assessed the value of the same automated collateral grading in 442 patients from the MR CLEAN database. Through this study, it was further confirmed that the automated collateral grading system was an independent predictor of mRS at 90 days and follow-up infarct volume (57). Other studies which assess the reliability of automated assessment of collaterals have been listed in Table 2.

CONCLUSIONS

Cerebral collaterals are a major determinant of stroke outcomes. In the context of reperfusion therapy, the role of collaterals in AIS merit consideration given their role in the viability of salvageable, ischaemic tissue or in assisting to deliver thrombolytic agents to the site of occlusion, both of which impact prognosis following reperfusion therapy. Furthermore, given the use of collateral assessment in routine practice in acute ischaemic stroke, let alone in reperfusion therapy, is far from universal and limited; efforts towards incorporating collateral assessment into routine acute stroke workflow should be pursued.

Funding

Funding for the NSW Brain Clot Bank (Chief Investigator: Dr Bhaskar) from the NSW Ministry of Health (2019-2022) is acknowledged. The funding body has no role in the study design, data collection, analysis, interpretation of findings and manuscript preparation. The content is solely the responsibility of the authors and does not necessarily represent the official views of the affiliated/funding organization/s.

Acknowledgements

We would like to acknowledge the support of the administrative staff and our NSW wide partnering clinicians and investigators.

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. *Circulation.* 2020; 141(9):e139-e596.
2. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke.* 2013;44(7):2064-89.
3. Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. *Circ Res*. 2017;120(3):472-95.
4. Diseases GBD, Injuries C. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet.* 2020; 396(10258):1204-22.
5. Bhaskar S, Stanwell P, Cordato D, Attia J, Levi C. Reperfusion therapy in acute ischemic stroke: dawn of a new era? *BMC Neurol.* 2018;18(1):8.
6. Oliveira-Filho J, Samuels OB. Approach to reperfusion therapy for acute ischemic stroke2021. Available at: https://www.uptodate.com/contents/approach-to-reperfusion-therapy-for-acute-ischemic-stroke/print.
7. Liebeskind DS. Collateral circulation. *Stroke.* 2003;34(9):2279-84.
8. Ravindran AV, Killingsworth MC, Bhaskar S. Cerebral collaterals in acute ischaemia: Implications for acute ischaemic stroke patients receiving reperfusion therapy. *Eur J Neurosci.* 2021;53(4):1238-61.
9. Bang OY, Saver JL, Kim SJ, Kim GM, Chung CS, Ovbiagele B, et al. Collateral flow averts hemorrhagic transformation after endovascular therapy for acute ischemic stroke. *Stroke.* 2011;42(8):2235-9.
10. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/ American Stroke Association. *Stroke.* 2019;50(12):e344-e418.
11. Nambiar V, Sohn SI, Almekhlafi MA, Chang HW, Mishra S, Qazi E, et al. CTA collateral status and response to recanalization in patients with acute ischemic stroke. *AJNR Am J Neuroradiol.* 2014;35(5):884-90.
12. Jansen IG, Mulder MJ, Goldhoorn RB, Boers AM, van Es AC, Yo LS, et al. Impact of single phase CT angiography collateral status on functional outcome over time: results from the MR CLEAN Registry. *J Neurointerv Surg.* 2019;11(9):866-73.
13. Bang OY, Goyal M, Liebeskind DS. Collateral Circulation in Ischemic Stroke: Assessment Tools and Therapeutic Strategies. *Stroke.* 2015;46(11):3302-9.
14. Bashir Q, Ishfaq A, Baig AA. Safety of Diagnostic Cerebral and Spinal Digital Subtraction Angiography in a Developing Country: A Single-Center Experience. *Interv Neurol.* 2018;7(1-2):99-109.
15. Lin MP, Liebeskind DS. *Imaging of Ischemic Stroke*. Continuum (Minneap Minn). 2016;22(5, Neuroimaging):1399-423.

16. Raymond SB, Schaefer PW. Imaging Brain Collaterals: Quantification, Scoring, and Potential Significance. *Top Magn Reson Imaging*. 2017;26(2):67-75.
17. Kauw F, Dankbaar JW, Martin BW, Ding VY, Boothroyd DB, van Ommen F, et al. Collateral Status in Ischemic Stroke: A Comparison of Computed Tomography Angiography, Computed Tomography Perfusion, and Digital Subtraction Angiography. *J Comput Assist Tomogr.* 2020;44(6):984-92.
18. Katyal A, Bhaskar S. CTP-guided reperfusion therapy in acute ischemic stroke: a meta-analysis. *Acta Neurol Scand.* 2021;143(4):355-66.
19. Katyal A, Calic Z, Killingsworth M, Bhaskar SMM. Diagnostic and prognostic utility of computed tomography perfusion imaging in posterior circulation acute ischemic stroke: A systematic review and meta-analysis. *Eur J Neurol.* 2021;28(8):2657-68.
20. Tan JC, Dillon WP, Liu S, Adler F, Smith WS, Wintermark M. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann Neurol.* 2007;61(6):533-43.
21. Merino JG, Warach S. Imaging of acute stroke. *Nat Rev Neurol.* 2010;6(10):560-71.
22. Bhaskar S, Bivard A, Stanwell P, Parsons M, Attia JR, Nilsson M, et al. Baseline collateral status and infarct topography in post-ischaemic perilesional hyperperfusion: An arterial spin labelling study. *J Cereb Blood Flow Metab.* 2017;37(3):1148-62.
23. Morofuji Y, Horie N, Tateishi Y, Morikawa M, Yamaguchi S, Izumo T, et al. Arterial Spin Labeling Magnetic Resonance Imaging Can Identify the Occlusion Site and Collateral Perfusion in Patients with Acute Ischemic Stroke: Comparison with Digital Subtraction Angiography. *Cerebrovasc Dis. 2*019;48(1-2):70-6.
24. Garcia-Tornel A, Carvalho V, Boned S, Flores A, Rodriguez-Luna D, Pagola J, et al. Improving the Evaluation of Collateral Circulation by Multiphase Computed Tomography Angiography in Acute Stroke Patients Treated with Endovascular Reperfusion Therapies. *Interv Neurol.* 2016;5(3-4):209-17.
25. Yuan HW, Ji RJ, Wang AL, Lin YJ, Chen HF, Xu ZQ, et al. A Grading Scale for Pial Collaterals in Middle Cerebral Artery Total Occlusion Based on Time-of-flight MR Angiography Source Images. *Magn Reson Med Sci.* 2019;18(1):62-9.
26. Hernandez-Perez M, Puig J, Blasco G, Perez de la Ossa N, Dorado L, Davalos A, et al. Dynamic Magnetic Resonance Angiography Provides Collateral Circulation and Hemodynamic Information in Acute Ischemic Stroke. *Stroke.* 2016;47(2):531-4.
27. Kronick MD, Chopra A, Swamy S, Brar V, Jung E, Abraham CZ, et al. Peak systolic velocity and color aliasing are important in the development of duplex ultrasound criteria for external carotid artery stenosis*. J Vasc Surg.* 2020;72(3):951-7.
28. Boontje AH. External carotid artery revascularization: indications, operative techniques and results. *J Cardiovasc Surg* (Torino). 1992;33(3):315-8.
29. Tahmasebpour HR, Buckley AR, Cooperberg PL, Fix CH. Sonographic examination of the carotid arteries. *Radiographics.* 2005; 25(6):1561-75.
30. Thanvi B, Robinson T. Complete occlusion of extracranial internal carotid artery: clinical features, pathophysiology, diagnosis and management. *Postgrad Med J.* 2007;83(976):95-9. Epub 2007/02/20.
31. Bajko Z, Balasa R, Motataianu A, Maier S, Chebut OC, Szatmari S. Common carotid artery occlusion: a case series. *ISRN Neurol.* 2013; 2013:198595.
32. Qian J, Fan L, Zhang W, Wang J, Qiu J, Wang Y. A meta-analysis of collateral status and outcomes of mechanical thrombectomy. *Acta Neurol Scand.* 2020;142(3):191-9.
33. Wufuer A, Wubuli A, Mijiti P, Zhou J, Tuerxun S, Cai J, et al. Impact of collateral circulation status on favorable outcomes in thrombolysis treatment: A systematic review and meta-analysis. *Exp Ther Med.* 2018;15(1):707-18.
34. Leng X, Lan L, Liu L, Leung TW, Wong KS. Good collateral circulation predicts favorable outcomes in intravenous thrombolysis: a systematic review and meta-analysis. *Eur J Neurol.* 2016;23(12):1738-49.
35. Leng X, Fang H, Leung TW, Mao C, Miao Z, Liu L, et al. Impact of collaterals on the efficacy and safety of endovascular treatment in acute ischaemic stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2016;87(5):537-44.
36. Leng X, Fang H, Leung TW, Mao C, Xu Y, Miao Z, et al. Impact of Collateral Status on Successful Revascularization in Endovascular Treatment: A Systematic Review and Meta-Analysis. *Cerebrovasc Dis.* 2016;41(1-2):27-34.
37. de Havenon A, Mlynash M, Kim-Tenser MA, Lansberg MG, Leslie-Mazwi T, Christensen S, et al. Results From DEFUSE 3: Good Collaterals Are Associated With Reduced Ischemic Core Growth but Not Neurologic Outcome. *Stroke.* 2019;50(3):632-8.
38. Park JS, Kwak HS, Chung GH, Hwang S. The Prognostic Value of CT-Angiographic Parameters After Reperfusion Therapy in Acute Ischemic Stroke Patients With Internal Carotid Artery Terminus Occlusion: Leptomeningeal Collateral Status and Clot Burden Score. *J Stroke Cerebrovasc Dis.* 2018;27(10):2797-803.
39. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372(1):11-20.
40. Yeo LL, Andersson T, Holmberg A, Mpotsaris A, Soderman M, Holmin S, et al. Posterior communicating and anterior communicating arteries on pre-thrombectomy computed tomography scans are associated with good outcomes irrespective of leptomeningeal collateral status. *Interv Neuroradiol.* 2019;25(4):364-70.
41. Kim BM, Baek JH, Heo JH, Nam HS, Kim YD, Yoo J, et al. Collateral status affects the onset-to-reperfusion time window for good outcome. *J Neurol Neurosurg Psychiatry*. 2018;89(9):903-9.
42. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med.* 2018;378(8):708-18.
43. Sheth SA, Sanossian N, Hao Q, Starkman S, Ali LK, Kim D, et al. Collateral flow as causative of good outcomes in endovascular stroke therapy. *J Neurointerv Surg*. 2016;8(1):2-7.
44. Cao R, Qi P, Liu Y, Ma X, Shen Z, Chen J. Improving Prognostic Evaluation by 4D CTA for Endovascular Treatment in Acute Ischemic Stroke Patients: A Preliminary Study. *J Stroke Cerebrovasc Dis.* 2019;28(7):1971-8.
45. Sallustio F, Motta C, Pizzuto S, Diomedi M, Giordano A, D'Agostino VC, et al. CT angiography-based collateral flow and time to reperfusion are strong predictors of outcome in endovascular treatment of patients with stroke. *J Neurointerv Surg.* 2017;9(10):940-3.
46. Liebeskind DS, Tomsick TA, Foster LD, Yeatts SD, Carrozzella J, Demchuk AM, et al. Collaterals at angiography and outcomes in the Interventional Management of Stroke(IMS) III trial. *Stroke.* 2014;45(3):759-64.
47. Al-Dasuqi K, Payabvash S, Torres-Flores GA, Strander SM, Nguyen CK, Peshwe KU, et al. Effects of Collateral Status on Infarct Distribution Following Endovascular Therapy in Large Vessel Occlusion Stroke. *Stroke.* 2020;51(9):e193-e202.
48. Nordmeyer H, Webering N, Chapot R, Hadisurya J, Heddier M, Stracke P, et al. The association between collateral status, recanalization and long term outcome in stroke patients treated with stent retrievers - Are there indications not to perform thrombectomy based on CT angiography? *J Neuroradiol.* 2017;44(3):217-22.
49. Liebeskind DS, Jahan R, Nogueira RG, Zaidat OO, Saver JL, Investigators S. Impact of collaterals on successful revascularization in Solitaire FR with the intention for thrombectomy. *Stroke.* 2014;45(7):2036-40.
50. Rebello LC, Bouslama M, Haussen DC, Grossberg JA, Dehkharghani S, Anderson A, et al. Stroke etiology and collaterals: atheroembolic strokes have greater collateral recruitment than cardioembolic strokes. *Eur J Neurol.* 2017;24(6):762-7.
51. Yu X, Yuan L, Jackson A, Sun J, Huang P, Xu X, et al. Prominence of Medullary Veins on Susceptibility-Weighted Images Provides Prognostic Information in Patients with Subacute Stroke. *AJNR Am J Neuroradiol.* 2016;37(3):423-9.
52. van den Wijngaard IR, Wermer MJ, Boiten J, Algra A, Holswilder G, Meijer FJ, et al. Cortical Venous Filling on Dynamic Computed Tomographic Angiography: A Novel Predictor of Clinical Outcome in Patients With Acute Middle Cerebral Artery Stroke. *Stroke.* 2016;47(3):762-7.
53. Parthasarathy R, Kate M, Rempel JL, Liebeskind DS, Jeerakathil T, Butcher KS, et al. Prognostic evaluation based on cortical vein score difference in stroke. *Stroke.* 2013;44(10):2748-54.

54. Bhaskar S, Bivard A, Parsons M, Nilsson M, Attia JR, Stanwell P, et al. Delay of late-venous phase cortical vein filling in acute ischemic stroke patients: Associations with collateral status. *J Cereb Blood Flow Metab.* 2017;37(2):671-82.
55. Bhaskar S, Bivard A, Stanwell P, Attia JR, Parsons M, Nilsson M, et al. Association of Cortical Vein Filling with Clot Location and Clinical Outcomes in Acute Ischaemic Stroke Patients. *Sci Rep.* 2016;6:38525.
56. Boers AMM, Sales Barros R, Jansen IGH, Slump CH, Dippel DWJ, van der Lugt A, et al., editors. Quantitative Collateral Grading on CT Angiography in Patients with Acute Ischemic Stroke. Molecular Imaging, Reconstruction and Analysis of Moving Body Organs, and Stroke Imaging and Treatment. Springer International Publishing, 2017.
57. Boers AMM, Sales Barros R, Jansen IGH, Berkhemer OA, Beenen LFM, Menon BK, et al. Value of Quantitative Collateral Scoring on CT Angiography in Patients with Acute Ischemic Stroke. *AJNR Am J Neuroradiol.* 2018;39(6):1074-82.
58. Aktar M, Tampieri D, Rivaz H, Kersten-Oertel M, Xiao Y. Automatic collateral circulation scoring in ischemic stroke using 4D CT angiography with low-rank and sparse matrix decomposition. *Int J Comput Assist Radiol Surg.* 2020;15(9):1501-11.
59. Verdolotti T, Pilato F, Cottonaro S, Monelli E, Giordano C, Guadalupi P, et al. ColorViz, a New and Rapid Tool for Assessing Collateral Circulation during Stroke. *Brain Sci.* 2020;10(11).
60. Su J, Wolff L, van Es A, van Zwam W, Majoie C, D WJD, et al. Automatic Collateral Scoring From 3D CTA Images. *IEEE Trans Med Imaging.* 2020;39(6):2190-200.
61. Shieh Y, Chang CH, Shieh M, Lee TH, Chang YJ, Wong HF, et al. Computer-aided diagnosis of hyperacute stroke with thrombolysis decision support using a contralateral comparative method of CT image analysis. *J Digit Imaging.* 2014;27(3):392-406.
62. Frolich AM, Wolff SL, Psychogios MN, Klotz E, Schramm R, Wasser K, et al. Time-resolved assessment of collateral flow using 4D CT angiography in large-vessel occlusion stroke. *Eur Radiol.* 2014; 24(2):390-6.
63. Zhang S, Chen W, Tang H, Han Q, Yan S, Zhang X, et al. The Prognostic Value of a Four-Dimensional CT Angiography-Based Collateral Grading Scale for Reperfusion Therapy in Acute Ischemic Stroke Patients. *PLoS One.* 2016;11(8):e0160502.
64. Kersten-Oertel M, Alamer A, Fonov V, Lo B, Tampieri D, Collins L. *Towards a Computed Collateral Circulation Score in Ischemic Stroke.* Available at: https://arxiv.org/abs/2001.07169.