Value of pre-intervention CT perfusion imaging in acute ischemic stroke prognosis

Anubhav Katyal ⓘ
Sonu Menachem Maimonides Bhaskar ⓘ

ABSTRACT
Noninvasive imaging plays an important role in acute stroke towards diagnosis and ongoing management of patients. Systemic thrombolysis and endovascular thrombectomy (EVT) are proven treatments currently used in standards of care in acute stroke settings. The role of computed tomography angiography (CTA) in selecting patients with large vessel occlusion for EVT is well established. However, the value of CT perfusion (CTP) imaging in predicting outcomes after stroke remains ambiguous. This article critically evaluates the value of multimodal CT imaging in early diagnosis and prognosis of acute ischemic stroke with a focus on the role of CTP in delineating tissue characteristics, patient selection, and outcomes after reperfusion therapy. Insights on various technical and clinical considerations relevant to CTP applications in acute ischemic stroke, recommendations for existing workflow, and future areas of research are discussed.

From the Neurovascular Imaging Laboratory (A.K., S.B. ✉ *Sonu.Bhaskar@reprogramglobal.org*), Ingham Institute for Applied Medical Research, Clinical Sciences Stream, Sydney, Australia; Department of Neurology & Neurophysiology (S.B.), Liverpool Hospital & South West Sydney Local Health District (SWSLHD), Sydney, Australia; University of New South Wales (UNSW) (A.K., S.B.), South Western Sydney Clinical School, NSW, Australia; Ingham Institute for Applied Medical Research, Stroke & Neurology Research Group (S.B.), Sydney, Australia; NSW Brain Clot Bank (S.B.), NSW Health Statewide Biobank and NSW Health Pathology, Sydney, NSW, Australia; Thrombolysis and Endovascular WorkFLOw Network (TEFLON) (S.B.), Sydney, Australia.

Neuroimaging is currently the mainstay of acute stroke workflow as it is used to rule out hemorrhage and select patients eligible for systemic thrombolysis and endovascular thrombectomy (EVT) (1). Advanced imaging has shown promise in acute stroke; however, the prognostic utility of computed tomography perfusion (CTP) imaging has drawn considerable debate. Given that stroke is associated with long-term morbidity and mortality, efforts to develop diagnostic imaging biomarkers have been pursued. However, the clinical translation of certain imaging modalities has been limited, especially CTP imaging. This could be attributed to the limited availability of CTP in under-resourced settings, variations in the diagnostic accuracy of CTP maps, and differences in the thresholds used in creating perfusion maps. In this paper, we will present a comprehensive overview of various imaging modalities in acute stroke with a particular focus on the clinically relevant utility of CTP and provide roadmap for future research.

Current recommendations in stroke workflow

The 2018 (updated 2019) American Heart Association/American Stroke Association (AHA/ASA) recommendations provide a comprehensive guide to the management of patients presenting with acute ischemic stroke (AIS), through prehospital settings to 2 weeks post-stroke (1). Brain imaging is essential for the diagnosis of stroke and each imaging modality contributes to clinical decision making and prognostication. The current stroke recommendations are presented in Table 1. Briefly, noncontrast computed tomography (NCCT) is used to exclude stroke mimics, such as brain tumors, as well as intracerebral hemorrhage, which is a contraindication to intravenous thrombolysis. Computed tomographic angiography (CTA) is useful in confirming a large vessel occlusion that is amenable to EVT. Computed tomography perfusion (CTP) imaging and perfusion magnetic resonance imaging (MRP) provides tissue characteristics, including infarct and penumbral volumes (highlighting tissue at risk of infarction), hence reinforcing clinical decisions for thrombectomy in patients who present outside of the conventional time-window. A case study with the application of multimodal CT imaging in acute stroke is shown in Figs. 1 and 2. In the next section, we will discuss the various imaging techniques and look at current and emerging evidence regarding the use of these imaging modalities.

Role of noncontrast CT in initial stroke evaluation

The NCCT is the main imaging modality for the initial evaluation of patients with suspected stroke, allowing clinicians to identify hemorrhage, which produces a good contrast between the "bright", high attenuating clot, and the "dark" low attenuating cerebrospinal fluid (2). This is critical in selecting patients for intravenous thrombolysis (IVT) via tissue plasminogen activator (t-PA) within 4.5 hours since hemorrhage is an absolute contraindication and must be excluded (3). Moreover, the presence of various early ischemic changes (EIC), including parenchymal hypoattenuation, cortical sulcal effacement (4), and loss of grey-white matter differentiation may be visualized up to 6 hours from symptom onset and inform treatment decisions. In a multicenter trial, von Kummer et al. (5) showed that the presence of parenchymal hypoattenuation in over one-third of the middle cerebral artery (MCA) territory correlated with larger infarct size and worse long-term functional outcomes in patients despite reperfusion with t-PA. As an alternative to the qualitative one-third rule of von Kummer et al., the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was developed and validated to systematically detect and quantify EICs (6). The ASPECTS score is graded by deducting points for every region of the MCA territory demonstrating hypoattenuation, from a total of 10 (Fig. 1). ASPECTS has been used as an indirect measure of ischemic core size and has shown utility in assessing the duration and degree of tissue hypoperfusion (7). A baseline ASPECTS score ≤7 has been associated with worse 90-day functional outcomes and increased risk of symptomatic intracerebral hemorrhage (sICH) following t-PA (6, 8), supporting its use as a prognostic marker in clinical settings. However, the most significant limitation of ASPECTS is the subtle nature of EICs, which, despite adjustments to the CT window level in providing enhanced contrast of these lesions (9), still results in variability even amongst experienced clinicians (10); this is especially problematic given the fact that ASPECTS has been invoked in the inclusion criteria of multiple clinical trials (11).

Furthermore, a "hyperdense vessel" sign may be visualized on NCCT, providing evidence of a possible intraluminal thrombus indicative of a large-vessel occlusion (LVO). However, this hyperdense sign has limited clinical use because its diagnostic capability varies by location, often with high specificity but poor to moderate sensitivity (12). Although NCCT alone is useful in predicting patients most likely to be harmed by IVT, it is insufficient to guide the selection of patients in whom the benefits from reperfusion therapy outweigh the potential risks of sICH. The pooled meta-analysis by the Third International Stroke Trial (IST-3) Collaboration group demonstrated no statistically significant subgroup difference ($p = 0.94$) for IV alteplase effect on the functional outcome for ASPECTS subgroups (0–7 versus 8–10), or patients with hypo-attenuated arteries ($p = 0.517$) (13). This is consistent with the AHA/ASA guidelines whereby the use of ASPECTS and hyperdense MCA sign is not indicated for withholding t-PA treatment (1).

## CT angiography in identifying vessel status and patency

Computed tomographic angiography (CTA) of the head and neck enables clinicians to delineate the vasculature from the aortic arch to distal divisions of the intracranial vessels, allowing confirmation of LVOs, evaluation of the patency of blood vessels, and the assessment of collateral blood flow (14, 15). Studies have also demonstrated that in comparison to NCCT, CTA-source images (CTA-SI) provide greater visual demarcation between normal and abnormal tissue, enhancing the diagnostic capacity and providing greater concordance between clinicians regardless of their level of experience (14, 16). Compared to gold-standard digital subtraction angiography (DSA), CTA-SI has a sensitivity and specificity of 98%–100% for detecting large vessel occlusion (17, 18). The prognostic capacity of CTA has shown promise through the clot-burden score (CBS), a 10-point system analogous to the ASPECTS of NCCT, which quantifies the extent of intracranial thrombosis. Despite heterogeneity in diagnostic protocols and

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Main points

- CT perfusion (CTP) imaging has a value in stratifying subgroups of acute ischemic stroke patients who are more likely to respond favorably to appropriate reperfusion therapy intervention.

- In the milieu of endovascular thrombectomy, the prognostic value of CTP in determining the threshold of infarct core to accurately predict tissue status and clinical outcome is still not clear.

- Lack of standardized CTP methods, reporting variations, ambiguity in infarct thresholds, and differences in follow-up outcome measures are factors that need to be considered while designing future acute stroke trials.
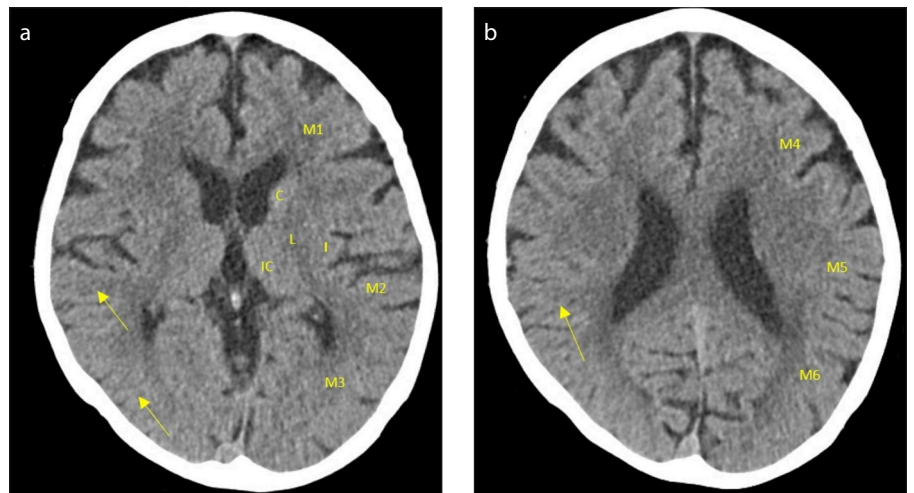
Figure 1. a, b. Noncontrast computed tomography (NCCT) and ASPECTS score in acute ischemic stroke. Axial NCCT image at the basal ganglia (**a**), and the supra-ganglionic (**b**) levels, respectively, show loss of grey-white matter differentiation in the M2, M3, and M5 territory of the right hemisphere, confirming a right middle cerebral artery (MCA) ischemic stroke *(arrows)* with an ASPECTS score of 7/10. The patient, in the 80–90 years age group, presented with left-sided hemiparesis and hemianesthesia. Following triage, the patient underwent NCCT, which indicated a right MCA stroke. IC, internal capsule; C, caudate nucleus; L, lentiform nucleus; I, insular ribbon; M1, anterior MCA cortex; M2, MCA cortex lateral to the insular ribbon; M3, posterior MCA cortex; M4, anterior MCA superior territory; M5, lateral MCA superior territory; M6, posterior MCA superior territory.
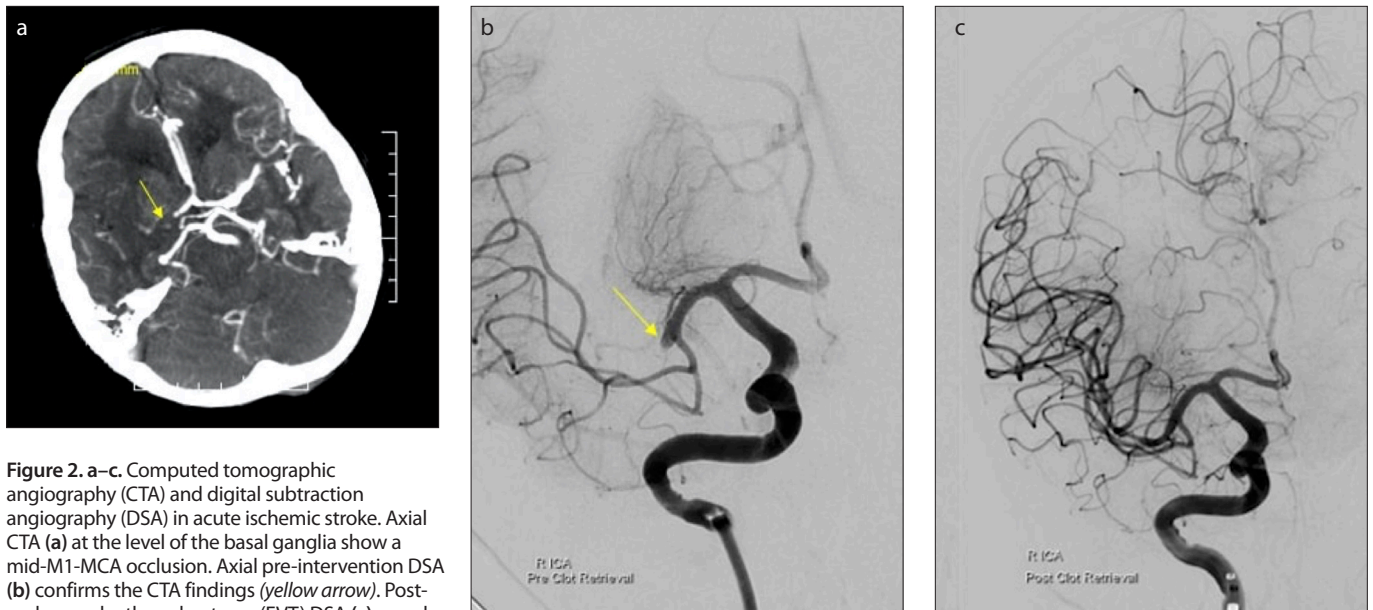
Figure 2. a–c. Computed tomographic angiography (CTA) and digital subtraction angiography (DSA) in acute ischemic stroke. Axial CTA (**a**) at the level of the basal ganglia show a mid-M1-MCA occlusion. Axial pre-intervention DSA (**b**) confirms the CTA findings *(yellow arrow)*. Post-endovascular thrombectomy (EVT) DSA (**c**) reveal restoration of the blood flow to the right cerebral hemisphere. The patient presented with left-sided hemiparesis and hemianesthesia. Following triage, the patient underwent NCCT, which indicated a right MCA stroke. The patient subsequently underwent EVT for the clot retrieval.

workflow across studies, lower CBS values have been validated to independently predict lower recanalization rates with t-PA, larger infarcts, poor functional outcomes, and greater risk of hemorrhagic transformation (19–21).

Given the transition of stroke care from IVT alone to additional EVT, CTA is critical in establishing a lesion amenable to neuro-intervention, typically an occlusion within the terminal internal carotid artery or MCA-M1 segment. Other MCA-segment occlusions require careful patient selection, for example, based upon the presence of leptomeningeal collateral supply, a key determinant in the progression of the salvageable tissue (known as the penumbra) to irreversible infarction (22, 23). Various collateral scoring systems exist; however, there is no standardization regarding the best scoring method. Nevertheless, the consensus is that good collateral supply correlates with smaller final infarct volumes (FIV) and good functional outcomes (24–28). However, key issues highlighted in these studies were marked variability in collateral supply between patients and limited accuracy in the evaluation of collateral supply in branches of the anterior and posterior cerebral arteries, often due to small vessel size and complex routes, which may impact infarct progression.

Fig. 2 compares CTA with DSA performed during the EVT procedure, highlighting the restoration of blood supply in the brain. Despite having utility in prognostication and guiding treatment decisions, the inability to visualize the penumbral tissue using CTA limits its ability in guiding the selection of patients who are more likely to have a poor outcome despite EVT. Patient selection based on collateral supply is classified under moderate recommendations as per the AHA/ASA guidelines (1) and requires further validation in clinical trials to be incorporated in standards of care in acute stroke.

Role of CT perfusion imaging in defining tissue characteristics

Computed tomography perfusion (CTP) maps demonstrate various parameters within the brain parenchyma, for example, cerebral blood flow within a region suspected of infarction. These perfusion maps are derived by measuring the attenuation of injected intravenous iodinated contrast through large arteries and the brain parenchyma over time, with post-processing conducted by software to generate CTP parameter maps (29). CTP parameters are explained in Table 2.

Diffusion-weighted imaging on magnetic resonance imaging (MRI) is typically considered the gold standard in detecting the ischemic core; however, it is less readily available compared to CTP and excludes patients with pacemakers and other metallic implants (12). In their comprehensive meta-analysis, Biesbroek et al. (30) established that CTP has a high sensitivity of 80% (95% confidence interval [CI]: 72%–86%) and very high specificity of 95% (95% CI: 86%–98%) in stroke detection, with false negatives mainly arising through a limited capability to detect smaller lacunar infarcts and infra-tentorial lesions. Despite this, the concordance between MRI- and CTP-identified mismatch has been demonstrated to be 90%, thus facilitating the use of either modality in acute stroke settings (31). However, there is still great contention about the extent of infarction using CTP. Previously, manual interpretation of CTP data required time and specialized skill, which was undesirable given that delays would result in greater neuronal loss. Moreover, visual assessment of CTP maps to identify penumbral tissue reveals moderate inter-rater reliability with inexperienced clinicians most likely to misinterpret these maps (32). Although this hurdle was overcome using automated software in calculating core and penumbral volumes, Bivard et al. (33) identified marked variability in computed volumes amongst different deconvolution techniques employed by different software packages. A key finding was that cerebral blood flow (CBF) best approximated the infarct core amongst all these algorithms, supporting results by Campbell et al. (34) and shifting away from the use of cerebral blood volume (CBV) in earlier studies (35); delay time (DT) may also be substituted

**Table 1.** Current recommendations by the AHA/ASA

Recommendation	Class	Evidence
Initial imaging		
All patients with suspected stroke should receive emergency brain imaging upon first arrival to the hospital before initiating specific therapy for AIS.	I	A
Systems should be established to ensure that brain imaging studies can be performed as quickly as possible in patients who may be candidates for IV fibrinolytics, mechanical thrombectomy or both.	I	B-NR
IV alteplase eligibility (within 4.5 hours of symptom onset)		
Both NCCT and MRI are effective to exclude ICH before IV alteplase administration. MRI: B-NR	I	CT: A
Administration of intravenous alteplase in eligible patients without first obtaining MRI to exclude CMBs is recommended.	I	B-NR
Since the benefit of alteplase therapy is time-dependent, treatment should be initiated as quickly as possible for eligible patients, and not delayed by additional multimodal neuroimaging, such as CTP/MRP.	I	B-NR
The extent and severity of acute hypoattenuation, early ischemic changes or the hyperdense MCA sign should not be used as a criterion to withhold IV alteplase therapy for patients who otherwise qualify.	III	B-R
Use of imaging criteria to select patients who awoke with stroke or have an unclear time of symptom onset for IV alteplase therapy is not recommended outside of a clinical trial.	III	B-NR
In patients with AIS who awake with stroke symptoms or have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.	IIA	B-R
Mechanical thrombectomy eligibility		
Noninvasive intracranial vascular study (using CTA/MRA) is recommended for patients deemed to be eligible for endovascular treatment. For patients with suspected LVO who have not had noninvasive vessel imaging as part of their initial imaging assessment for stroke, noninvasive vessel imaging should then be obtained as quickly as possible (e.g., during alteplase infusion if feasible).	I	A
For patients with suspected intracranial LVO who meet the criteria for endovascular treatment, it is reasonable to proceed with CTA before obtaining a serum creatinine concentration in patients without a history of renal impairment.	IIA	B-NR
In patients who are potential candidates for EVT, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, is reasonable to provide useful information regarding patient eligibility and endovascular procedural planning.	IIB	C-EO
It may be reasonable to incorporate collateral flow status into clinical decision making in some candidates to determine eligibility for mechanical thrombectomy.	IIB	C-LD
When evaluating patients with AIS within 6 hours of last known normal with LVO and ASPECTS of ≥6, selection for mechanical thrombectomy based on CT/CTA or MRI/MRA is recommended in preference to performance of additional imaging such as perfusion studies.	I	B-NR
In patients who have a large vessel occlusion in the anterior circulation from 6–24 hours of last known well, CTP/MRP/ DWI-MRI is recommended to aid in patient selection for mechanical thrombectomy, but only when imaging and other eligibility criteria from RCTs are strictly applied.	I	A

Class of recommendation:

I = strong recommendation (benefit >>>risk)

IIA = moderate recommendation (benefit >>risk)

IIB = weak recommendation (benefit ≥ risk)

III stratified into moderate recommendation (benefit = risk) and strong recommendation (risk > harm)

Level of evidence:

Level A: high quality evidence from more than 1 RCT, meta-analyses of high quality RCTs

Level B-R: moderate quality evidence from 1 or more RCTs, or meta-analysis of moderate quality RCTs

Level B-NR: moderate quality evidence from well-designed observational studies, meta-analyses of such studies

Level C-LD (limited data): moderate quality evidence from observational studies with flawed design

Level C-EO: expert opinions

Based on the American Heart Association/American Stroke Association (AHA/ASA) guidelines (1).
AIS, acute ischemic stroke; IV, intravenous; NCCT, noncontrast computed tomography; MRI, magnetic resonance imaging; ICH, intracerebral hemorrhage; CMB, cerebral microbleeds; CTP, computed tomography perfusion; MRP, perfusion magnetic resonance; MCA, middle cerebral artery; FLAIR, fluid-attenuated inversion recovery; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; LVO, large vessel occlusion; EVT, endovascular therapy; ASPECTS, Alberta Stroke Program Early CT Score; DWI, diffusion-weighted imaging; RCT, randomized controlled trial.

Table 2. Parameters of CT perfusion imaging

Parameter	Units	Definition	Hypoperfused state
Cerebral blood volume (CBV)	mL/100 g	Total volume of blood present within a region of the brain. Relative CBV (rCBV) is often calculated by dividing the average CBV values in the affected area with those of the contralateral hemisphere	Normal, elevated or decreased*
Mean transit time (MTT)	s	The average time difference between the arterial inflow and venous outflow in a region of brain	Increased
Cerebral blood flow (CBF)	mL/100 g/s	The flow rate of blood within a region of the brain. Calculated as CBV/MTT	Decreased
Time to peak (TTP)	s	The time from the beginning of contrast injection to the maximum concentration of contrast material within a region of interest	Increased
Time to maximum (T_{max})	s	The time to the maximum of the residue function, reflecting the delay of bolus between the site of the arterial input and the brain tissue	Increased
Delay time (DT)	s	T_{max} with mathematical correction for delay and dispersion of bolus	Increased

Adapted from (12). CTP maps are created demonstrating each of these parameters.
*In hypoperfused states, autoregulatory vasodilation may ensure normal or elevated CBV to preserve oxygenation in an otherwise hypoxic state (82). Therefore, it is not as clinically useful compared to CBF or T_{max}.
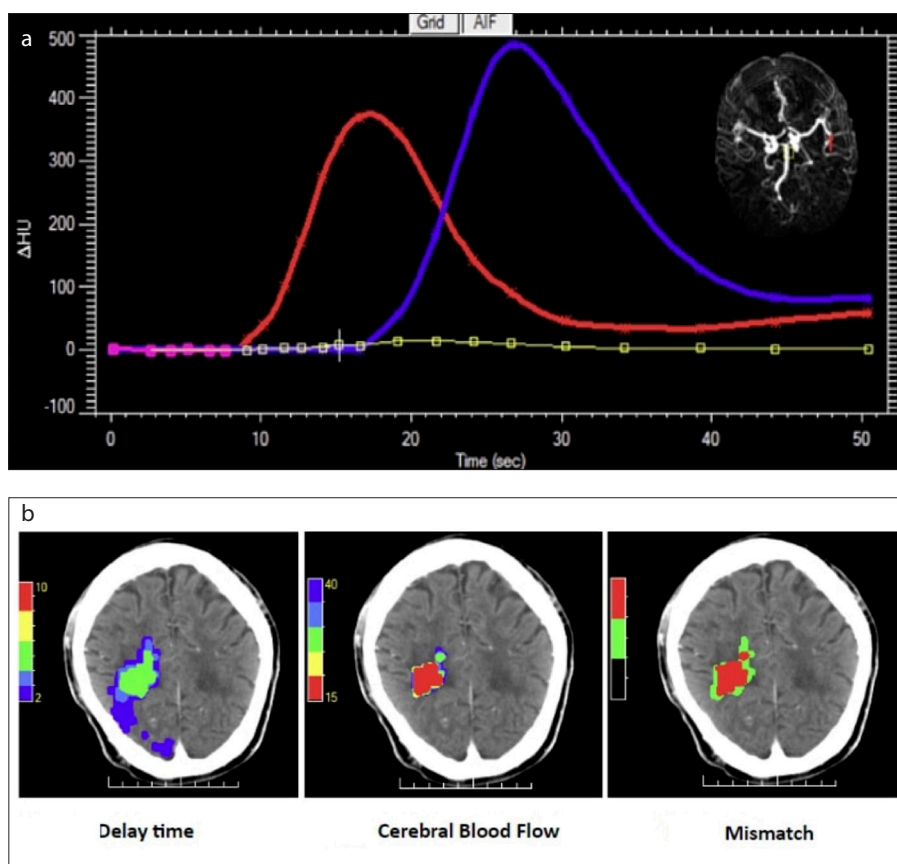
Figure 3. a, b. CTP perfusion maps in delineating the infarcted core and penumbra. The arterial *(red)* and venous *(blue)* input curves **(a)**, measured from the right MCA and the venous sinus, are shown. A MIP is shown in the top right **(a)**, showing an occlusion of the MCA. These maps were processed by MiStar™ to create perfusion maps **(b),** namely the delay time (DT) map, cerebral blood flow (CBF) map, and mismatch map (left to right). The axial DT map shows volumes of critically hypoperfused tissue, including both the infarcted core and the penumbral tissue at risk of infarction, based on various thresholds: DT >6.0 s, 0 mL; DT >4.0 s, 4 mL; DT >3.0 s, 12 mL; DT >2.0 s, 95 mL. A threshold DT >3.0 s indicated a volume of 12 mL. The axial CBF map shows the infarcted core volumes, based on various thresholds: CBF <40%, 7 mL; CBF <35%, 6 mL; CBF <30%, 5 mL; CBF <20%, 3 mL; CBF <15%, 1 mL. A threshold of CBF <30% indicated a volume of 5 mL (42% of the total lesion). The axial mismatch map shows the infarcted core and penumbra superimposed on the NCCT image to better identify the mismatch volume (7 mL, equivalent to 58% of the total lesion). The penumbral to the core volume ratio of 2.4. Hence, there is a benefit associated with endovascular thrombectomy within 24 hours of stroke symptom onset and in the absence of other clinical contraindications.

with time to the maximum of the residue function (Tmax), as demonstrated in a recent validation study (36). Heterogeneity in CTP parameter thresholds and imaging processing techniques amongst different commercial software result in significant variability in computed volumes with poor reproducibility (37), highlighting the need for standardization between stroke centers. Recent clinical trials have employed Rapid processing of perfusion and diffusion (RAPID) (iSchemaView©) software utilizing the thresholds Tmax>6 seconds for total hypoperfused tissue and CBF<30% for the infarcted core; the difference in the two volumes is the penumbra (8–41). RAPID has been validated to have 100% sensitivity and 91% specificity in a review by Straka et al. (42), whilst more accurately predicting FIV in comparison with Philips and Siemens (43). RAPID's extensive validation in the aforementioned trials has lent support to its widespread use for patient evaluation; however, its low availability necessitates the need for alternative platforms, techniques, or open-access software that can create perfusion maps that reliably assess perfusion parameters. Fig. 3 demonstrates the application of CTP maps in delineating the core and penumbral volumes.

Role of CT perfusion imaging in patient selection

The implementation of CTP has largely been marred due to its limited availability, increased radiation and contrast doses, and greater susceptibility to motion artifacts compared to NCCT (30, 44). Moreover, the additional benefit conferred by CTP im-

aging in guiding the selection of patients presenting more than 4.5 hours of the onset of stroke, initially demonstrated mixed results. In their meta-analysis, Mishra et al. (45) failed to demonstrate a statistically significant improvement in functional outcomes when t-PA was administered to patients with CTP-derived mismatch between penumbral and core volumes beyond 4.5 hours, reflecting the time-threshold in current AHA/ASA guidelines (1). Moreover, updated AHA/ASA guidelines for patients presenting within 6 hours of last known well and ASPECTS ≥6, advanced perfusion imaging such as CTP is not required for patient selection, because numerous multi-center randomized controlled trials (Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke (ESCAPE) (98), SWIFT PRIME (99), REVASCAT (100)) demonstrated the efficacy of EVT in patients selected using CTA/ magnetic resonance angiography (MRA).

Previously, the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial (46) investigating CTP mismatch-based patient selection for EVT using first-generation clot-retrievers had failed to demonstrate clinical significance; however, it was limited by a poor workflow that resulted in delays in receiving EVT and changes in clinical protocols during the 8-year trial. In contrast, the DEFUSE 2 trial (47) provided support for the use of magnetic resonance perfusion (MRP) in mismatch-based patient selection, despite being limited by its nonrandomized approach. Of prime importance was the trial's inability to establish a statistically significant difference between patients who were treated ≤6 hours and >6 hours in terms of a favorable response to EVT. This result has since been supported by recent trials, thus dispensing with the widely accepted belief that time from symptom onset was the principal determinant of success in EVT (22, 48, 49). This has provided support in recognizing the importance of collateral circulation in preserving the penumbral tissue for longer periods of time (50).

With the introduction of new stent-retrievers that have superior recanalization rates compared to first-generation clot-retrievers in 2012 and the abandoning of time-sensitive treatment modalities (12, 51), the recent multicenter, randomized controlled trials such as Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial Trial (EXTEND-IA)

(38), Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke Trial (DEFUSE-3) (39) and Diffusion-weighted imaging or computed tomography perfusion Assessment with clinical mismatch in the triage of Wake-up and late presenting strokes undergoing Neurointervention with Trevo Trial (DAWN) (41) were conducted to investigate the efficacy of EVT in an extended time window. In particular, the DEFUSE-3 trial (39) demonstrated that in patients with target mismatch (TMM), where the ratio of penumbral to core volume >1.8 who presented 6–16 hours after the onset of stroke, undergoing EVT provided greater rates of 90-day functional independence (modified Rankin Score, mRS: 0–2) compared to those in the control group receiving conservative medical management (45% versus 17%, $p < 0.001$), with no significant difference in rates of sICH (7% versus 4%, $p = 0.75$). This has been supported by a sub-analysis of the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment Trial (SWIFT-PRIME) trial (52), whereby patients with TMM profile at baseline had a highly favorable response to EVT with higher rates of reperfusion, smaller FIV, and better functional outcomes. The DAWN trial (41) highlighted the benefits of EVT by innovatively selecting patients with a mismatch between clinical indexes with perfusion imaging-derived baseline core volume, up to 24 hours from onset of stroke. This has been monumental towards extending the time window for EVT in the recent AHA/ASA guidelines (1) and lends support for further clinical trials in investigating the utility of combining imaging data and clinical scores in patient selection for reperfusion therapy.

## Current challenges in CTP based patient selection

The randomized controlled trials EXTEND-IA (38), DEFUSE-3 (39), and DAWN (41) each excluded patients with core volumes >70 mL, a parameter with great debate regarding its utility. Whilst previous studies have demonstrated that core volumes above this threshold have been associated with worse functional outcomes and higher mortality (53, 54), Sim et al. (55) highlighted that EVT may lead to a favorable shift in 90-day mRS scores compared to standard treatment. This has been supported by numerous studies (56–59); the recent Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES)-col-

laboration meta-analysis (59) incorporating 7 high-quality randomized controlled trials highlighted improved functional outcomes from treatment with EVT over a wide range of infarct core volumes, particularly in younger patients. A proposed explanation is that reperfusion of the infarct core may still enhance recovery by inhibiting edema formation, rather than saving tissue at risk (60). There is also limited evidence on the efficacy of EVT in patients with unfavorable mismatch volumes, where there is scarce penumbral tissue despite having small core volumes (61) (Fig. 4). This highlights the need for large prospective trials that explore the utility of higher baseline core volume thresholds and different penumbral patterns in patient selection for reperfusion therapy. Analysis of these randomized controlled trials also reveals the heterogeneity in the inclusion and exclusion criteria used for patient selection (Table 3). Coupled with inconsistencies in imaging modalities as MRP and CTP were used interchangeably at some centers, technical errors such as over-estimation of baseline lesions are likely. This highlights the need for standardizing criteria for patient selection in each neuroimaging modality (CTP and MRP) with consistency in the modality of follow-up imaging to streamline workflow across stroke centers.

Value of CTP imaging in prognosis and tissue fate

Baseline core volume

Pre-intervention CTP parameters may have value in predicting FIV and long-term functional outcomes, independently of receiving reperfusion therapy. An earlier retrospective cohort study by Zhu et al. (62) argued that imaging the penumbra would predict the FIV and functional outcome only if recanalization would be achieved. Indeed, Rao et al. (29) demonstrated in patients achieving >90% recanalization, the initial baseline core infarct correlated with the 24-hour FIV (r=0.83; $p < 0.0001$). However, since the recanalization status cannot be known when administering treatment, pre-intervention CTP may not be effective in predicting the FIV. Chen et al. (63) showed that the reperfused penumbral volume was a strong predictor of good functional outcome (area under the curve [AUC]=0.946, $p < 0.0001$). Moreover, the HERMES-collaboration meta-analysis (59) involving 1764 patients demonstrated that each 10 mL
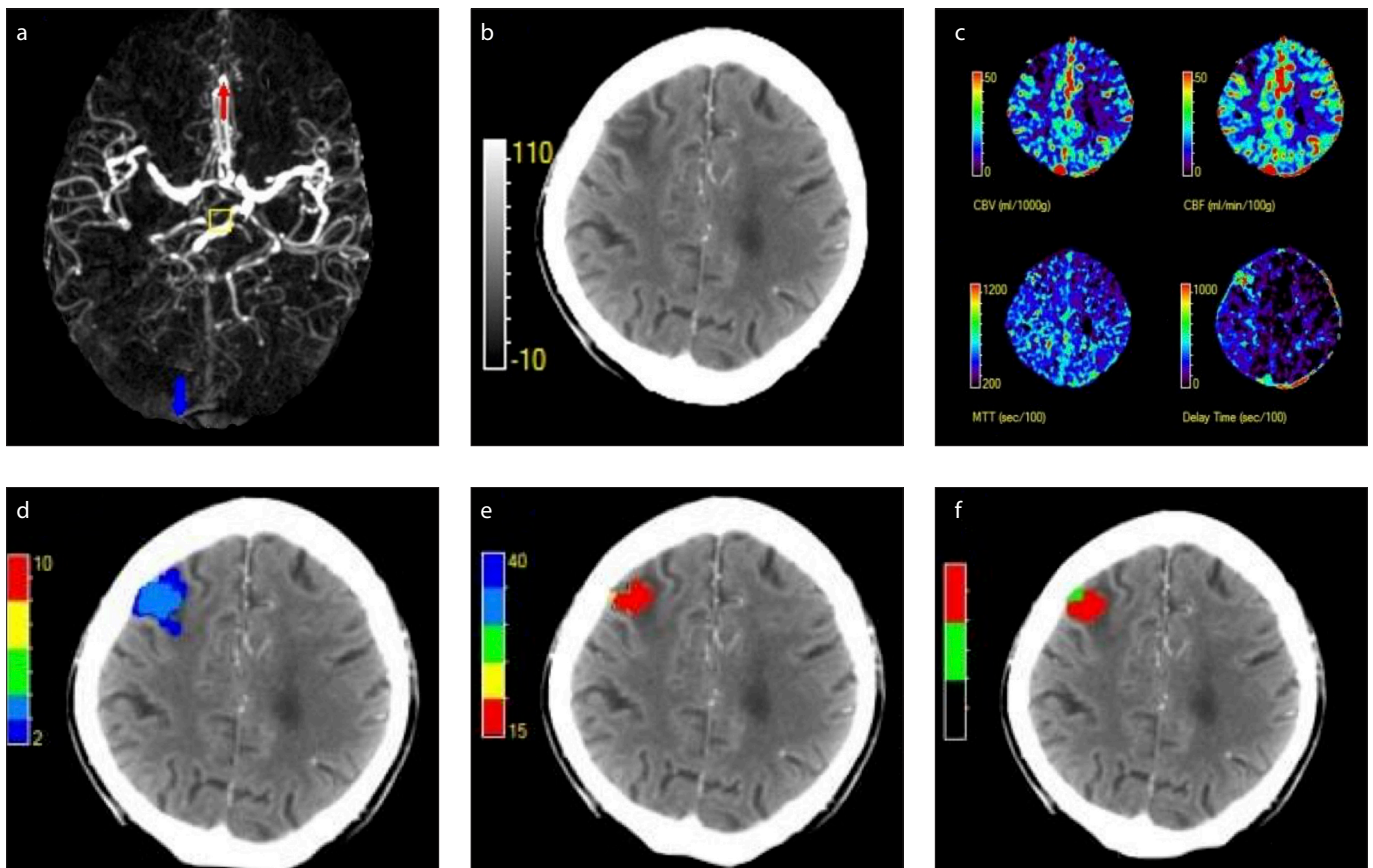
Figure 4. a–f. Penumbral pattern and its role in patient selection by CTP. A male patient in the 70–80 years age group presented with left-sided hemiparesis and hemianesthesia. Subsequently, he underwent multimodal CT imaging. Axial MIP image **(a)** shows a distal MCA stroke. Axial NCCT **(b)** shows acute ischemic changes in the M1-MCA territory. Axial CTP maps **(c)** show cerebral blood volume (CBV), cerebral flow (CBF), mean transit time (MTT), and delay time (DT) from left to right. Axial DT band map **(d)** shows the total hypoperfused volume. The volumes at various thresholds: DT>2.0s+, 10ml; DT>3.0s+, 5 ml; DT>4.0s+, 0 ml; DT>6.0s+, 0 ml. Axial CBF band map **(e)** shows the infarct core volume. The volumes at various thresholds: CBF<40%, 4 mL; CBF<35%, 4 mL; CBF<30%, 4 mL; CBF<25%, 3 mL; CBF<20%, 2 mL; CBF<15%, 1 mL. CTP-derived post-processed map using MiStar™ **(f)** demonstrates an infarct core volume of 4 mL (80%) and penumbral volume of 1 mL (20%), which constitutes to a mismatch ratio of 1.3. Scarce penumbral tissue and anticipated risks of treatment may outweigh the benefit of neurointervention. The DEFUSE 3 (39) used a threshold core to penumbral volume >1.8 as an inclusion criterion, hence this patient would not be considered for EVT in that context. Further clinical trials are required to verify appropriate penumbral patterns that are amenable to neurointervention and those that are not. DEFUSE 3, Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke Trial 3.

increase in CTP-derived baseline ischemic core volume was independently associated with reduced likelihood of 90-day functional independence by 20%–30% (odds ratio=0.77, 95% CI: 0.69–0.86, per 10 mL). However, the primary objective of the randomized controlled trials included in the HERMES meta-analysis was to investigate the efficacy of second-generation stent-retrievers; there is currently limited evidence on prospective trials that specifically analyze the linear relationship between baseline core volume, functional outcomes, and tissue outcomes in meaningful ways that may be implemented across stroke centers. Thus, the HERMES meta-analysis has paved the road for future trials in the assessment of patient prognosis using advanced neuroimaging modalities.

CTP ASPECTS

As an alternative to automated software, earlier studies adapted the semi-quantitative ASPECTS technique to CTP-source images and parameters. Parsons et al. (65) first established the additional benefit of CTP-SI and CBV-ASPECTS in more accurately predicting infarcted tissue and 90-day functional outcomes compared to NCCT or CTA-SI alone. Aviv et al. (66) further added information to this field by demonstrating that using a CBV-ASPECTS threshold of 8 discriminated patients with good long-term functional outcomes (mRS 0–2), providing moderate sensitivity of 60% and specificity of 100%. Numerous subsequent studies have demonstrated the utility of CBV-ASPECTS in predicting functional outcomes and FIV; how-

ever, these studies have demonstrated heterogeneity in the optimal thresholds (range, 6–9) used to discriminate between patients with good and poor functional outcomes (67–69). Moreover, using CBV-ASPECTS may be problematic given that CBV-ASPECTS can be affected by the presence of spontaneous recanalization in some patients, resulting in the reversibility of the CBV lesion (that defines the infarcted core) and an overestimation of the FIV (68). Taking this another step forward, Tang et al. (70) demonstrated in a retrospective analysis of 144 patients that the combination of CTA-SI-ASPECTS, the Regional leptomeningeal collateral score (rLMC) collateral scoring system in multimodal CT assessment, and CBV-ASPECTS provided a greater area under the

Table 3. Inclusion and exclusion criteria in the DAWN, DEFUSE 3 and EXTEND-IA trials

Study	Year	Patients (n)	Inclusion time (hours)	Inclusion criteria Clinical	Neuroimaging	Neuroimaging exclusion criteria
DAWN (38)	2018	206	6–24	1. Age ≥18 y 2. Ineligible for t-PA 3. NIHSS score ≥10	1. Infarct hypodensity <1/3 MCA territory on NCCT 2. A mismatch between NIHSS score and infarcted core volume measured using CTP/ MRP 3. Occlusion of intracranial ICA or M1 on CTA/MRA	1. Intracranial hemorrhage, significant mass effect and midline shift, or intracranial tumor on NCCT 2. Steno-occlusion or tortuosity of cervical ICA on CTA/MRA
DEFUSE 3 (39)	2018	182	6–16	1. Age 18–85 y 2. NIHSS score ≥6	1. Mismatch between penumbra and core volume (defined as core volume <70 mL, mismatch ratio ≥1.8, absolute penumbral volume ≥15 mL) measured on CTP/MRP 2. Occlusion of ICA and M1 on CTA/MRA	1. ASPECTS < 6 on NCCT 2. Intracranial hemorrhage, significant mass effect and midline shift, or intracranial tumor on NCCT 3. Dissection of cervical ICA 4. More than 1 vascular territory infarcted on CTA/MRA
EXTEND-IA (41)	2015	70	0–6	1. Age ≥18 y 2. NIHSS score ≥6	1. Infarct hypodensity <1/3 MCA territory on NCCT 2. A mismatch between infarct core and penumbra (defined as infarct core <70 mL, mismatch ratio >1.2 and absolute mismatch volume >10 mL) measured on CTP/MRP 3. Occlusion of ICA and M1 or M2 on CTA/MRA	1. Intracranial hemorrhage on NCCT/MRI 2. Difficulty or inability to access cerebral arteries (proximal stenosis or dissection)

t-PA, tissue plasminogen activator; NIHSS, National Health Institute Stroke Severity Score; MCA, middle cerebral artery, with M1 and M2 segments; NCCT, noncontrast enhanced computed tomography; CTP, computed tomography perfusion imaging; MRP, magnetic resonance perfusion imaging; ICA, internal carotid artery; CTA, computed tomographic angiography; MRA, magnetic resonance angiography; ASPECTS, Alberta Stroke Program Early CT Score; MRI, magnetic resonance imaging.

ROC curve (AUC=0.87) for the detection of poor functional outcomes following a stroke, significantly greater than for any single parameter used alone. This warrants further investigation in a larger prospective cohort of patients, in comparison with CTP-derived quantitative thresholds.

Collateral status

Collateral status has also been validated in an extensive meta-analysis of 29 studies in independently predicting functional outcomes, FIV, sICH, and mortality. Of notable importance, however, is that whilst 22 of these studies utilized CTA, only 3 studies utilized CTP imaging (71). CTP imaging is underutilized in determining collateral status because the function is fulfilled by CTA; both imaging modalities reflect similar pathophysiological aspects of ischemic stroke. Arenillas et al. (72) demonstrated a positive association between CTP-derived relative CBV (rCBV) and collateral circulation grade, which in turn predicted infarct growth in subgroups of patients in patients receiving EVT ($p = 0.038$). The use of rCBV as a prognostic marker has been supported by another study (73); however, limitations in sample size reduce the strength of their evidence. While Menon et al. (44) argues that multiphase CTA may be sufficient as a prognostic tool, there is limited evidence in the additional benefit of using CTP imaging over conventional CTA for collateral assessment. This offers opportunities to investigate a combination of baseline core volume and collateral status using CTP in predicting clinical and tissue-based outcomes.

Hemorrhagic transformation

Hemorrhagic transformation (HT) often occurs following reperfusion therapy, hypothesized to occur as a consequence of the disruption of blood-brain barrier integrity. Lin et al. (74) first highlighted the utility of permeability surface area product (PS) values, computed by measuring the extravasation of iodinated contrast into the brain, with elevated values in regions of infarction in patients with HT. Aviv et al. (75) further investigated this, highlighting that a PS threshold of 0.23 mL/min/100 g as demonstrating 77% sensitivity and 94% specificity for detection of HT. The utility of PS has been supported by various other retrospective studies, providing support for the role of PS in early identification of patients at risk of HT (76–79); however, these studies have been limited by small sample sizes. When validated in a larger cohort of 545 patients, Horsch et al. (80) concluded that although PS values predicted HT, it did not improve prediction compared to clinical parameters such as age above 60 years and admission stroke severity (determined using the National Institutes of Health Stroke Scale [NIHSS]). Key issues identified were the high number of patent exclusions (19%) due to technical processing difficulties and the substitution of follow-up CTP with MRI in some patients. As an alternative, Yassi et al. (81) utilized baseline CTP-parameters, showing that regions on CTP where Tmax >14 s exceeding a total of 5 mL enabled prediction of HT with a sensitivity of 79%, the specificity of 68%, and a negative likelihood ratio of 3.16. Overall, the disputed results of these trials highlight the need for larger prospective trials exploring the efficacy of CTP-based parameters in detecting HT and evaluating its utility in clinical settings in excluding patients for reperfusion therapy if required.

Limitations of CTP, technical and clinical considerations

Although various pre-intervention CTP parameters are useful in the assessment

Table 4. Various imaging modalities in acute stroke

Imaging techniques	Role in terms of current AHA/ASA recommendations	Further research avenues
Multi-modal computed tomography imaging		
NCCT	- Exclude hemorrhage and stroke mimics to guide t-PA administration within 4.5 hours of symptom onset - Should not withhold treatment based on hyperdense MCA sign or the extent of hypoattenuation	The utility of combining: - ASPECTS (6, 8, 13) and hyperdense MCA sign (12) with clinical indexes in centers without advanced neuroimaging modalities
CTA	- Confirm LVO in determining eligibility for EVT within 6 hours of symptom onset - Assessment of collateral supply to aid decision making	The utility of combining: - CTA-SI ASPECTS (17, 18) - Clot-burden score (19–21) - Collateral supply (24–27) in randomized trials in excluding patients for whom potential risks outweigh the benefits
CTP	- Selection of patients with anterior circulation stroke within 6–24 hours of symptom onset for EVT, based on strict inclusion criteria	- Altering baseline ischemic core threshold specific to CTP to facilitate greater patient inclusion (57–61) - Identifying patients with unfavorable mismatch (61) to prevent futile reperfusion - Combining imaging and clinical indexes for selection (41) - Patients with posterior circulation strokes - Prediction of FIV, functional outcomes, collateral status, and HT based on pre-intervention CTP features
Multi-modal magnetic resonance imaging		
MRI	- Exclude hemorrhage and stroke mimics to guide t-PA administration within 4.5 hours of symptom onset - Exclusion of cerebral microbleeds is not required before alteplase administration - In patients with AIS who awake with stroke symptoms or have an unclear time of onset >4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition	- Cerebral microbleeds demonstrate an increased risk of sICH and need to be investigated in randomized controlled trials. - FLAIR hyperintense signal should be investigated in terms of prognostic capacity and clinical utility, concerning HDMCA sign (88).
MRA	Same as CTA: - Confirm LVO in determining eligibility for EVT within 6 hours of symptom onset - Assessment of collateral supply to aid decision making	- Standardizing the technique for MRA across stroke centers (time of flight vs. contrast-enhanced MRA vs. phase contrast) in terms of maximum diagnostic capability in clinical settings
MRP	Same as CTP: - Selection of patients with anterior circulation stroke within 6–24 hours of symptom onset for EVT, based on strict RCT inclusion criteria	- Altering baseline ischemic core threshold specific to MRP to facilitate greater patient inclusion (57–61) - Identifying patients with unfavorable mismatch (61) to prevent futile reperfusion - Combining imaging and clinical indexes for selection (41) - Patients with posterior circulation strokes
MRI - ASL	Nil.	- Greater utilization of ASL in calculating CBF and thus facilitating the inclusion of patients with renal impairment. Investigating correlations between MRP and ASL for this purpose
Other modalities		
PET	Nil. Access to radiopharmaceuticals, long radioisotope uptake times, and lack of standardized protocols impede use in acute stroke situations.	- 18F-FDG is reduced in the ischemic core and transiently increased in the penumbral region (89, 90). F-FDG is also increased in perihematomal regions (91) - Infusion of 15-O bound to water can detect regional blood flow, oxidative metabolism, and cerebral metabolic rate for oxygen (CMRO2), thus highlighting regions of necrosis (<65μmol/100 gm/min) (92) - 11C-Choline or 68Ga-DOTATATE uptakes localized in areas of MRI confirmed ischemia (93) - Vulnerability of a carotid plaque to rupture can be detected by using 18F-FDG (94)
TCD	Nil. In acute stroke situations, diagnosis is confirmed through NCCT/MRI to exclude hemorrhage and extracranial carotid arteries are visualized through CTA/MRA to rule out dissection. TCD results are more operator dependent.	- Potential role in the investigation of cryptogenic stroke (with the use of echo contrast agent) and may be used as an adjunct to extracranial carotid sonography in determining cerebral hemodynamics (95). - Bedside assessment of prognosis: a normal TCD at 6 hours post-ischemic stroke predicts early improvement (96) and may predict spontaneous hemorrhagic transformation within 6 hours (97)

NCCT, noncontrast computed tomography; t-PA, tissue plasminogen activator; MCA, middle cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomographic angiography; LVO, large vessel occlusion; EVT, endovascular thrombectomy; CTP, computed tomography perfusion; FIV, final infarct volume; HT, hemorrhagic transformation; MRI, magnetic resonance imaging; AIS, acute ischemic stroke; FLAIR, fluid-attenuated inversion recovery; IV, intravenous; sICH, symptomatic intracranial hemorrhage; HDMCA, hyperdense middle cerebral artery sign; MRA, magnetic resonance angiography; MRP, perfusion magnetic resonance; RCT, randomized controlled trial; ASL, arterial spin labelling; CBF, cerebral blood flow; PET, positron emission tomography; TCD, transcranial Doppler ultrasound.

of patient prognosis, the current AHA/ASA guidelines mainly incorporate multimodal CT imaging as a diagnostic tool. Large multicenter randomized controlled trials are required to assess the potential for CTP as a prognostic tool and investigate its utility in individualizing stroke rehabilitation programs in clinical settings. Table 4 highlights areas where further research is warranted in improving guidelines for stroke intervention in the future. Further points of discussion are listed below:

1. As highlighted in Table 2, autoregulatory vasodilation may ensure normal or elevated CBV in hypoperfused tissue to preserve oxygenation in an otherwise hypoxic state (82). Therefore, reduced CBV is not consistent with the ischemic penumbra unlike other CTP parameters (CBF or Tmax), and should not be used for penumbral evaluation.

2. Perfusion maps can be inaccurate in patients with poor cardiac output, atrial fibrillation, and severe proximal arterial stenosis (83). Specifically, perfusion maps tend to overestimate MTT and underestimate CBF in these conditions. This can lead to an erroneous diagnosis of extensive hypoperfusion or ischemia. These limitations also apply due to poor placement of arterial and venous density regions of interest (84).

3. With the advent of improved efficacy of EVT and efficient stroke workflow in the future, ultra-fast reperfusion (≈60 min) may be achieved, hence alternative time-stratified CTP thresholds may need to be validated to accurately depict ischemic lesions (85, 86).

4. Standardized CTP protocols exclude a large volume of the brain, including the superior cerebral hemisphere and the posterior fossa as the scans are focused on the basal ganglia and supra-ganglionic level. This can cause erroneous diagnosis to patients with posterior circulation stroke. However, some studies have demonstrated that whole-brain CTP may provide additional diagnostic accuracy over conventional CTA/NCCT in detecting acute posterior circulation stroke (101, 102).

5. CTP maps are not good to evaluate lacunar infarcts due to their lower resolution and may result in false-negative results (30).

6. Patients presenting with seizures may cause a diagnostic dilemma in that post-ictal paralysis mimics stroke symptoms and CTP imaging may demonstrate hyperperfusion in the ictal region (87), which can lead to misinterpretation of hypoperfusion in the contralateral hemisphere.

Recommendation for future work

Various key issues have been highlighted in this article including heterogeneity in CTP-parameter thresholds and imaging processing techniques amongst different commercial software; the need for alternative platforms, techniques, or open-access software that can reliably create perfusion maps; the need to develop standardized inclusion criteria with advanced neuroimaging modalities (MRP or CTP) in selecting patients for reperfusion therapy; and further research regarding the utility of pre-intervention CTP features (baseline core volume, collateral status, permeability surface area product maps) in predicting tissue-based and clinical outcomes in patients with acute ischemic stroke. Future randomized controlled trials in exploring these key issues are warranted given that robust patient selection criteria and assessment of prognosis would enable a more streamlined and consistent workflow across stroke centers. Given the significant burden of disease posed by stroke globally, clinicians need to be adequately trained worldwide in using neuroimaging effectively so that patients can receive evidence-based treatment and have improved outcomes.

Conclusion

CTP perfusion imaging has a value in stratifying subgroups of acute ischemic stroke patients who are more likely to respond favorably to appropriate reperfusion therapy intervention. In the milieu of EVT, the prognostic value of CTP in determining the threshold of infarct core to accurately predict tissue status and clinical outcome is still not clear. Futile recanalization, which does not translate to clinical benefit, is an ongoing challenge. Lack of standardized CTP methods, reporting variations, ambiguity in infarct thresholds, and differences in follow-up outcome measures are factors that need to be considered while designing future acute stroke trials. For CTP imaging to be incorporated into routine clinical practice and appropriate guideline, further research leveraging randomized controlled trials are warranted.

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