Review of Perfusion Imaging in Acute Ischemic Stroke
From Time to Tissue

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Perfusion imaging uses an intravascular tracer and serial imaging to quantify blood flow through the brain parenchyma. In acute ischemic stroke, perfusion imaging may increase diagnostic accuracy, aid treatment target identification, and provide prognostic information about functional outcome.[1] Moreover, perfusion imaging can identify patients who benefit from reperfusion beyond the conventional time window or in whom time of symptom onset is unknown.[2–4] Implementation of perfusion imaging in routine acute stroke care allows individualized treatment of stroke patients based on brain tissue status, rather than time-based treatment on the group level.

In this review, we give an overview of computed tomography perfusion (CTP) and perfusion magnetic resonance imaging (MRP) in acute ischemic stroke and discuss technical properties, clinical use, and pitfalls.

Acquisition of CT and MR Perfusion Imaging

Acquiring high-quality perfusion maps requires a scanning protocol that is optimized for high contrast sensitivity and low image noise and also ensures that bolus passage is captured in full with adequate temporal resolution. For CTP, these requirements must be balanced against the need to minimize radiation dose. Scan duration should generally be at least 60 seconds with a sampling rate of 2 seconds or faster. Besides technical considerations, advantages and risks differ between CT and MRI (Table I in the online-only Data Supplement). More details on injection protocol and radiation dose can be found elsewhere.[5]

Postprocessing of Perfusion Images

Background and Perfusion Maps

Perfusion source data are a 4-dimensional data set (3-dimensional volumes captured over time). This may be visualized as a movie in which tissue downstream to an occlusion typically shows delayed contrast arrival and prolonged bolus washout. Tracer kinetic models are used to estimate hemodynamic parameters for each voxel, converting the 4-dimensional data set into a set of perfusion maps that represent different hemodynamic properties. In essence, computation of the perfusion maps is based on a relationship between the bolus shape in the feeding vasculature, the arterial input function, and the contrast passage observed in each voxel. Mathematically, this relationship is determined using a so-called deconvolution algorithm which enables computation of perfusion parameters.

The fundamental hemodynamic properties of the tissue are cerebral blood volume (volume fraction of tissue, that is, vascularized, typically 2%–5%), cerebral blood flow (CBF; the volume of blood flow per minute per 100 mL of tissue) and mean transit time (the average transit time for a tracer particle to traverse the capillary bed). In addition, the delay of the bolus from the proximal vasculature to the tissue (time-to-maximum [Tmax]) is a popular metric.

Because of limitations of both CT and MRI, CBF is usually not considered quantitative but rather normalized to a presumed normal reference region of the brain and expressed proportionately, for example, 30% for CBF that is 70% depressed relative to the reference region. Multiple other parameter exist, such as time-to-peak and first moment. These metrics quantify properties of the curve without attempting to directly quantify hemodynamic properties, but they can be equally effective at predicting infarction as the hemodynamic parameters (eg, CBF, cerebral blood volume, and mean transit time) as long as properly normalized to a reference region.[6] Visual inspection of perfusion maps yields disparaging results between readers.[7] To obtain more consistent and objective results, perfusion maps are, therefore, usually subjected to some form of thresholding to exclude regions that are experiencing mild hypoperfusion with a low probability of infarction.

For clinical use, the goal is often to quantify (1) tissue that experiences significant hypoperfusion and is likely to infarct in the absence from reperfusion (termed penumbra) and (2) tissue that is likely irreversibly infarcted, termed the ischemic

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core. Application of thresholds enables quantification the volume of tissue that fall into each category, and these volume estimates can then be used to inform treatment decisions or form part of guidelines.

Software Packages

Multiple software products that produce perfusion maps and estimate volumes of ischemic core and tissue at risk are available. Perfusion processing is a nonstandard domain and substantial differences exist between vendors. Frequently, CBF, cerebral blood volume, and Tmax are calculated differently and are, therefore, not comparable between packages. Comparison of commercially available software shows significant differences in core and penumbra volume calculations, which may influence patient selection for reperfusion therapy.[8–10] It is, therefore, recommended to use software that has been validated on clinical data sets where it is known to what extent estimated volumes are meaningful for clinical use.[2,3] A benchmark tool is available which allows comparison to validated thresholds for various imaging parameters.[11]

Interpretation of Perfusion CT and MRI

Background

Occlusion of a cerebral blood vessel causes a variable decrease of blood flow in the downstream parenchyma proportionate to the degree of collateral circulation. In brain regions with poor collaterals, lack of oxygen and glucose, may result in electrical failure and ultimately failure of the cell's energy metabolism leading to tissue infarction.[12,13] Although both the ischemic core and penumbra are dysfunctional (and thus contribute to the patient's symptoms), the penumbra is viable upon restoration of blood flow.[12]

In the absence of reperfusion, the penumbra will eventually grow into the ischemic core. The rate of infarct growth is highly variable between individuals and is strongly dependent on the extensiveness of collateral circulation.[14] Genetic and environmental factors likely explain interindividual differences between native collateral circulation. Furthermore, several stimuli (eg, chronic hypoperfusion) may induce collateral formation.[15]

Assessment of Ischemic Core

CT-Based Methods

In contrast to MRI, CTP visualizes brain infarction indirectly based on perfusion changes. Therefore, small subcortical infarcts are more difficult to detect and CTP is more error-prone.[16,17] Validation of CTP parameters and thresholds for ischemic core identification is mostly based on final infarct volume on follow-up MRI in patients with complete reperfusion (Table II in the online-only Data Supplement). Variability in optimal perfusion parameter or threshold is explained by differences in imaging acquisition (mainly brain volume coverage, image acquisition rate, and scan duration), reference imaging, and data processing methods (among others arterial input function placement, deconvolution method, and delay and dispersion correction).[18,19]

Decreased CBF relative to normal brain tissue (rCBF) most consistently and accurately identifies the ischemic core. A rCBF threshold of <30% has been extensively validated (Table II in the online-only Data Supplement). Because only few studies used acute MRI for validation of ischemic core thresholds and because infarct growth may occur between CTP acquisition and reperfusion, validated CBF thresholds may overestimate ischemic core if perfusion imaging is acquired very early after symptom onset.[20–22] Similarly, the ischemic core may be overestimated if rapid reperfusion is achieved.[20] Although one would expect this to be especially the case for patients undergoing endovascular treatment (EVT), the threshold of rCBF <30% does not seem to overestimate and may underestimate final infarct volume in these patients.[21,23]

Lacunar or small subcortical infarcts are usually not detected using CTP thresholds, but visual inspection of in particular mean transit time, time-to-peak, and time-to-drain maps has a high specificity but moderate sensitivity for detection of these infarcts.[16,24,25] Sensitivity for infratentorial lesions is, however, low.[25]

Magnetic Resonance Imaging-Based Methods

Just minutes after stroke onset, cytotoxic edema, characterized by restriction of water molecule movement, develops in infarcted tissue. This is visualized as a decrease of the apparent diffusion coefficient and a hyperintensity on diffusion-weighted imaging (DWI).[26] An apparent diffusion coefficient threshold between 600 and 625×10^{-6} mm^2/s is a fairly robust parameter to delineate the ischemic core.[27] Reversibility of acute DWI lesions may be seen in on average 24% of cases and is associated with a shorter duration of ischemia and reperfusion.[28] Substantial and permanent DWI reversal in acute stroke patients undergoing reperfusion treatment is, however, rare and probably not clinically relevant.[29]

Identifying Tissue at Risk

Penumbra is derived from subtracting the ischemic core from the perfusion deficit (the total volume of brain tissue that is critically hypoperfused). CTP and MRP can successfully discriminate the perfusion deficit from normal brain tissue or benign oligemia, and a variety of perfusion parameters and thresholds have been described (Table III in the online-only Data Supplement). Optimal perfusion parameters are mostly validated by comparison to the final infarct on MRI in the absence of reperfusion (Table III in the online-only Data Supplement). Differences in optimal parameter and threshold are partially explained by deconvolution method and other postprocessing algorithms. Although deconvolved perfusion parameters are generally used, nondeconvolved maps may be equally accurate.[6,30] Typically, the perfusion deficit is identified using parameters related to the temporal profile of the concentration-time curve. The frequently used Tmax parameter with a delay >6 seconds provides a reasonable estimate of final infarction in patients without reperfusion.[31] Tmax may also be the most concordant parameter between CTP and MRP.[32]

Caveats and Pitfalls

Limitations of Perfusion Parameters and Thresholds

No perfusion parameter or threshold perfectly describes the perfusion deficit but rather reflects the probability of infarction

in the absence of reperfusion.[33] Infarction risk increases with hypoperfusion severity and duration of hypoperfusion. Short-lasting severe hypoperfusion may not result in tissue infarction, whereas longer-lasting hypoperfusion more likely will. It is also not uncommon to see a late increase in blood flow in irreversibly damaged tissue in patients with spontaneous recanalization or even with persistent vascular occlusion due to improved perfusion via collateral blood vessels.[34,35] This ischemic tissue may be readily visible on noncontrast CT but will not be identified as ischemic core on CTP if blood flow exceeds the threshold for ischemic core detection. Thorough inspection of noncontrast images for established infarction is thus necessary, especially in late-presenting patients. On MRI, apparent diffusion coefficient changes with time and reperfusion state.[36] A single apparent diffusion coefficient threshold may thus result in a different tissue fate depending on time from symptom onset and (subsequent) reperfusion.

Severity of hypoperfusion also influences tissue fate. Ischemic tissue with limited collateral circulation resulting in worse perfusion more rapidly progresses to infarction compared with better-perfused tissue.[37–39] This partially explains interindividual variability in infarct growth rate.[40] The hypoperfusion intensity ratio, the proportion Tmax >6 seconds lesion with Tmax >10 seconds, is a good predictor for collateral flow and infarct growth[38,39] (Figure 1). Besides Tmax and hypoperfusion intensity ratio, relative cerebral blood volume is associated with the degree of collateral circulation and is predictive of infarct growth.[39]

Limitations in Differentiating Normal From Pathological Tissue

In patients with chronic hypoperfusion (eg, because of hemodynamically significant stenosis or occlusion of supplying blood vessels), the perfusion deficit may be grossly overestimated if Tmax or mean transit time thresholds are surpassed.[41] Correction for delay and dispersion may increase reliability of perfusion imaging in such patients.

Absolute CBF values are abnormal in chronic vascular white matter changes.[42] Although the effect on rCBF changes is limited, perfusion imaging in patients with extensive chronic vascular lesions may be less reliable.

Clinical Use of Perfusion Imaging

The Mismatch Concept

The mismatch concept is a surrogate marker for the presence of a relevant volume of salvageable brain tissue and refers to a significant lesion volume difference (ie, mismatch) between the perfusion deficit and the ischemic core.

The definition of a mismatch pattern depends on the chosen ratio between core volume and perfusion deficit volume (ie, mismatch ratio [MMR]). In the DEFUSE study (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution), the concept of target mismatch (TMM) was introduced to describe patients with a greater response to reperfusion compared to the general mismatch population, defined as a MMR of at least 1.2 and minimal penumbra volume of 10 mL, in addition to a maximum core and severely hypoperfused tissue volume (respectively, DWI lesion and Tmax ≥8 seconds volume <100 mL).[37] The DEFUSE 2 study redefined the mismatch definition for EVT-eligible patients: MMR >1.8, penumbra >15 mL, DWI volume <70 mL, and Tmax >10 seconds volume <100 mL.[43]

Predicting Response to Reperfusion

In the DEFUSE study, the relationship between the perfusion profile and outcome was assessed in patients treated with alteplase 3 to 6 hours after known stroke onset.[37] Odds of achieving favorable outcome after reperfusion were only increased in patients with perfusion-weighted imaging/DWI mismatch and were greater in patients with TMM.[37] The EPITHET study (Echoplanar Imaging Thrombolytic Evaluation Trial) used MRP and the DEFUSE mismatch definition. They randomized patients to alteplase or placebo 3 to 6 hours after symptom onset.[44] No difference in outcome was found between mismatch and nonmismatch patients, possibly due to differences in the automated analysis. In the pooled DEFUSE and EPITHET population, thrombolysis was associated with a favorable outcome and attenuation of infarct growth in mismatch patients but not in nonmismatch or malignant profile patients, using automated software and a perfusion threshold of Tmax >6 seconds[45] (Figure 2). An observational study using CTP and a strict TMM definition adapted from DEFUSE 2 showed only TMM patients had a higher chance of achieving the excellent outcome and a lower chance of severe disability or death after thrombolysis[7] (Figure 2).

With regards to studies on EVT, the prospective cohort study DEFUSE 2 found a high rate of good outcome in reperfused patients with a TMM pattern.[43] This association was absent in non-TMM patients. CRISP (CT Perfusion to Predict Response to Recanalization in Ischemic Stroke Project) was, a prospective cohort study that confirmed the association between good functional outcome and reperfusion in TMM patients, regardless of time between stroke onset and imaging, suggesting that symptom duration is no modifier of reperfusion response in imaging-selected patients.[46]

Besides predicting response to reperfusion therapy, perfusion imaging can identify patients in whom reperfusion may be detrimental. In a pooled analysis of DEFUSE and EPITHET, 89% of reperfused patients with a malignant perfusion profile (Tmax >8 seconds volume of >85 mL) experienced poor outcome, versus 39% of patients without reperfusion.[47] Reperfusion was associated with symptomatic intracranial hemorrhage in the malignant profile group but not in the TMM group.[45] Observational data also showed an association between severe hypoperfusion (Tmax >14 seconds) and the occurrence of parenchymal hematoma after thrombolysis.[48] Similarly, thrombolysis was associated with poor outcome in patients without mismatch profile, although absolute numbers were low.[7]

Although randomized trials are lacking, a large ischemic core should not automatically preclude patients from EVT.[49,50] In the HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) meta-analysis which included 7 randomized controlled trials (RCTs) on EVT, larger ischemic core volume was associated with a lower chance of achieving function independence, and treatment effect was more time-dependent.[51] Benefit from EVT was, however, not modified by ischemic core volume. Notably, only 8.5% of patients included in the meta-analysis had a core volume

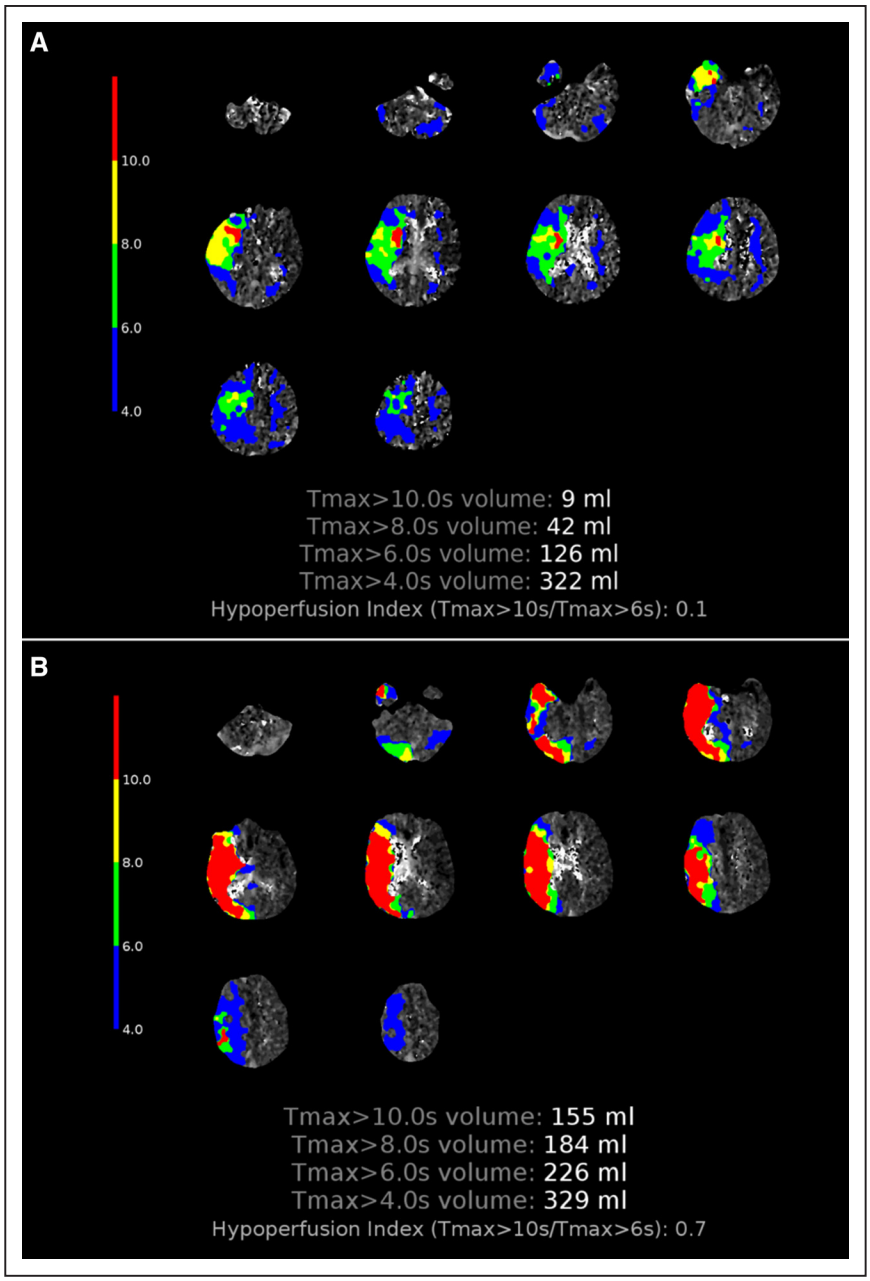

Figure 1. Computed tomography (CT) perfusion imaging processed by RAPID software showing different time-to-maximum (Tmax) thresholds. The Tmax >10 seconds / Tmax >6 seconds ratio is termed hypoperfusion intensity ratio (HIR). In a patient with a low HIR, slow ischemic core growth is expected (**A**). Below a patient with a high HIR is shown, in whom rapid ischemic core growth is expected (**B**).

≥70 mL. Although saving tissue at risk may be less pertinent, reperfusion in large core patients may improve functional outcome by inhibiting edema formation.[52] Whether patients with large cores (eg, >100 mL) benefit from reperfusion will need to be assessed in an RCT.

Mismatch Imaging for Treatment Selection

On a group level, thrombolysis within 4.5 hours after ischemic stroke onset without the use of perfusion imaging selection is safe and effective and time modifies treatment effect.[53] In EPITHET, a nonsignificant trend towards improved outcomes was seen in patients with an MMR >1.2 and minimal penumbra volume of 10 mL who were treated with alteplase between 3 and 6 hours after symptom onset.[44] Given the variability in infarct growth, recent clinical trials hypothesized benefit of reperfusion treatment in patients with a perfusion mismatch profile who presented in a later time window, or in whom symptom onset was unknown or occurred during sleep (ie, wake-up patients).[40] In the placebo-controlled EXTEND trial (Extending the Time for Thrombolysis in Emergency Neurological Deficits), benefit of thrombolysis in patients with a TMM profile between 4.5 and 9 hours after last seen well was evaluated.[4] Thrombolysed patients had better functional outcomes with a trend towards more symptomatic intracranial hemorrhage. Subgroup analysis did not show treatment differences in patients with wake-up stroke and patients treated between 4.5 and 6 hours or 6 and 9 hours from last seen well.

Another placebo-controlled study using alteplase in the same time window was stopped prematurely because of slow recruitment and failed to show a benefit of thrombolysis.[54] A study using tenecteplase in the 4.5 to 24 hours time window using perfusion imaging selection is ongoing (TIMELESS [A Phase III, Prospective, Double-Blind, Randomized,

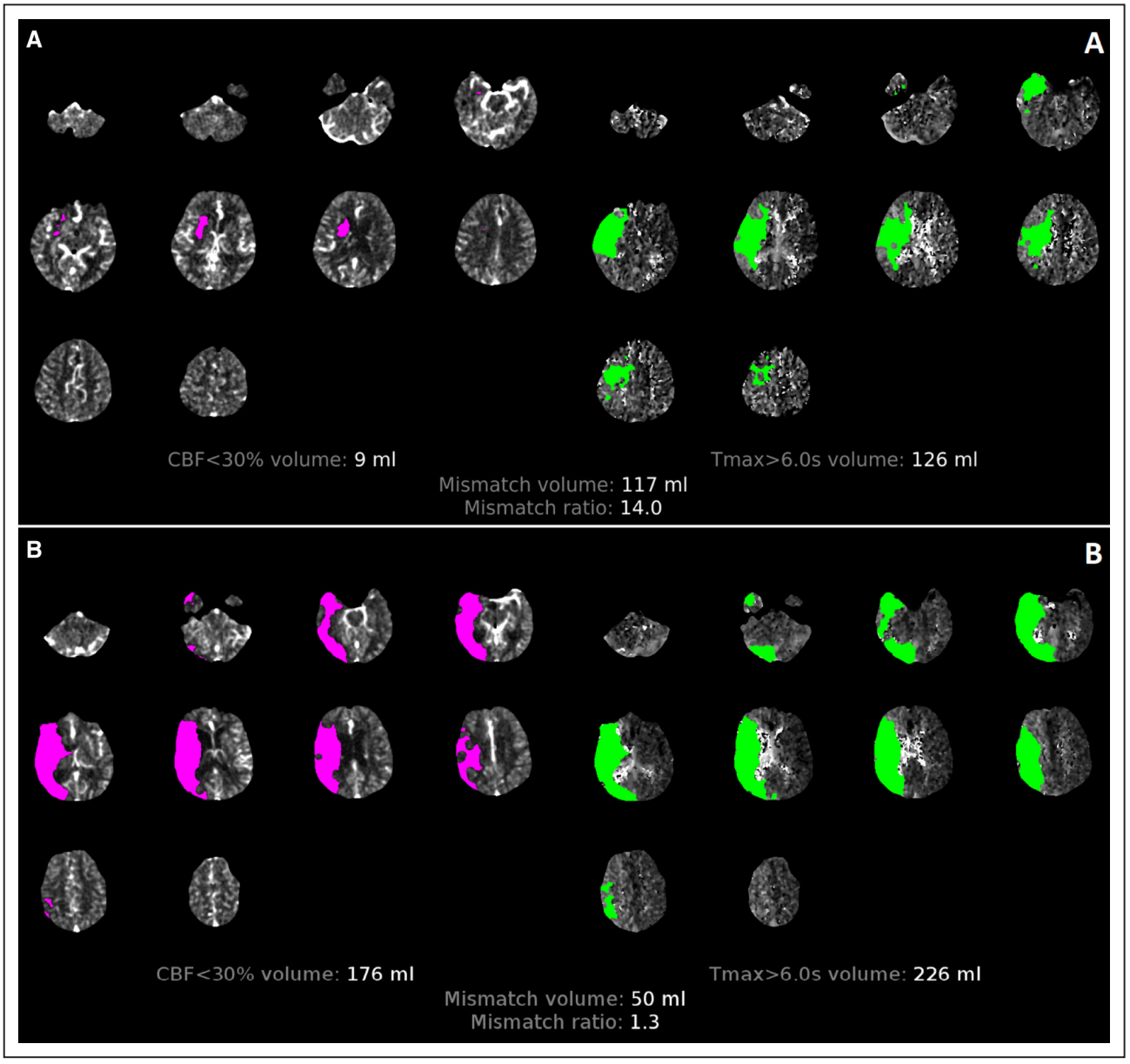

Figure 2. Computed tomography (CT) perfusion imaging processed by RAPID software showing the ischemic core and perfusion deficit. Above, a patient with an occlusion of the M1 segment of the right middle cerebral artery who has a target mismatch profile is shown (**A**), that is, small ischemic core (pink), considerable tissue at risk for infarction (green) and a large mismatch ratio. Below, perfusion imaging of a patient with a right-sided M1 occlusion and a malignant perfusion profile is shown (**B**). This patient has a large ischemic core (pink) which largely overlaps the perfusion deficit (green). CBF indicates cerebral blood flow.

Placebo-Controlled Trial of Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase]; URL: https://www.clinicaltrials.gov. Unique identifier: NCT03785678).

Most RCTs on EVT in the early time window did not use perfusion imaging for patient selection. EVT for stroke due to large vessel occlusion is associated with major benefit in (relatively) unselected patients and treatment effect is modified by time.[55,56] Two studies (partially) selected patients with TMM profile on MRP or CTP.[57,58] Compared with unselected patients, reperfusion in TMM patients resulted in increased functional independence (60%–71% versus 32.6%) and lower mortality (9% versus 21%) 90 days after treatment despite comparable baseline characteristics.[57–59]

Two RCTs demonstrated benefit of EVT between 6 and 16 to 24 hours after stroke onset or last seen well in the presence of a mismatch profile.[2,3] Ischemic core was identified as rCBF<30% on CTP or DWI lesion on MRI. In the DAWN trial (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo), mismatch between the ischemic core volume and clinical symptoms was used (National Institutes of Health Stroke Scale of at least 10 or 20, depending on age and ischemic core volume).[2] DEFUSE 3 used a Tmax threshold of >6 seconds to define the perfusion deficit and selected patients with ischemic core <70 mL, MMR ≥1.8 and at least 15 mL penumbra.[3] The proportion of good outcome in the intervention arm was similar to studies

in the conventional time window (45%–49%). Both studies included wake-up patients. Compared with patients with known symptom onset, neither study reported differences in treatment effect in patients in whom symptoms were discovered upon awakening or symptom onset was unknown.[2,3]

Although perfusion imaging is a powerful tool to identify those patients with treatment target, especially beyond the conventional treatment time window, absence of a perfusion deficit or TMM profile does not equal absence of reperfusion effect. Several trials on EVT in the early time window did not use perfusion imaging for patient selection and showed large treatment benefit in this population.[51,59] Moreover, observational data suggest that patients with large ischemic core volumes may also benefit from reperfusion.[51,52] Also, in the WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke), which used a DWI and fluid-attenuated inversion recovery (FLAIR) mismatch pattern on MRI as a surrogate marker for stroke with recent onset and randomized patients to thrombolysis or placebo if treatment was possible within 4.5 hours from symptom discovery, patients treated with thrombolysis had a higher chance of excellent functional outcome.[60] Although previous studies suggested a similar underlying mechanism, DWI-FLAIR and perfusion mismatch patterns can occur independently, again confirming that patients without mismatch pattern can benefit from reperfusion therapy.[61] Interestingly, patients may also present with a so-called total mismatch pattern, that is, the presence of a perfusion deficit in the absence of a DWI lesion.[62] Small, often lacunar, lesions may be undetectable on CTP but are visible on DWI. These patients, however, do seem to benefit from thrombolytic therapy.[63] Therefore, screening for either one of the aforementioned mismatch patterns might be most conclusive to select eligible patients for reperfusion therapy.

Other Considerations Regarding Perfusion Imaging

Not every center has implemented perfusion imaging for acute stroke. Although it is not required for therapeutic decision-making in early presenting patients, many advantages of perfusion imaging also apply to this population. Perfusion imaging improves diagnostic accuracy and detection of stroke mimics and enhances and expedites occlusion localization in patients with more distal occlusions.[1,64] Furthermore, it provides early prognostic information which may aid communication to patient and relatives and help guide early therapeutic decision-making beyond reperfusion therapy.[5,51]

These benefits need to be weighed against treatment time delays. Thrombolytic therapy can be started after exclusion of contra-indications on noncontrast CT and before or during perfusion imaging acquisition. When using MRI, rapid stroke imaging protocols are available and similar door-to-groin times can be achieved compared to CT imaging.[65]

Multimodal imaging for targeted thrombolytic therapy may be cost-effective, assuming that thrombolytic therapy is associated with higher hemorrhage risks or may be futile in certain subgroups.[7,48,66] Given the large benefit of endovascular therapy, screening for patients with treatment targets beyond the early time window is likely highly cost-effective.[2,3]

Summary and Future Directions

Perfusion imaging improves prognostication in acute ischemic stroke and enables identification of patients with treatment targets well beyond the conventional time windows for intravenous thrombolysis or EVT. There is now strong evidence for thrombolytic treatment of patients with a TMM profile up to 9 hours and for clot removal in patients with a TMM up to 24 hours after last seen well. Instead of relying on a uniform time window to determine whether to offer reperfusion therapy, perfusion imaging allows clinicians to tailor this decision based on the perfusion and tissue status of an individual patient's brain. Evidence for reperfusion treatment of specific patient populations (eg, large ischemic core volumes [beyond the 6 hours treatment window]) and the safety of treatment beyond 24 hours is sparse or lacking and will need to be addressed in RCTs. Likewise, identification of patients in whom early reperfusion treatment is futile or may cause more harm than benefit remains difficult.

Many factors challenge the widespread use of perfusion imaging in acute stroke treatment, among others the insufficient implementation of perfusion imaging in primary and comprehensive stroke centers, incomplete standardization of image processing and the lack of expertise in image interpretation. It is, however, increasingly clear that advanced brain imaging allows clinicians to move from time-based to individualized, tissue-based treatment to the benefit of late-presenting acute stroke patients.

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