A review of perfusion imaging in acute ischemic stroke: "from time to tissue"

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1. Background

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 CT perfusion (CTP) and perfusion MRI (MRP) in acute ischemic stroke and discuss technical properties, clinical use and pitfalls.

2. 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 60s with a sampling rate of 2s or faster. Besides technical considerations, advantages and risks differ between CT and MRI (Table I of the supplemental data). More details on injection protocol and radiation dose can be found elsewhere (5).

3. Post-processing of perfusion images

a. <u>Background and perfusion maps</u>

Perfusion source data is a 4-dimensional data set (3-dimensional volumes captured over time). This may be visualised 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 dataset 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 (AIF), 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 (CBV; volume fraction of tissue that is vascularized, typically 2-5%), cerebral blood flow (CBF; the volume of blood flow per minute per 100mL of tissue) and mean transit time (MTT; the average transit time for a tracer particle to traverse the capillary bed). In addition, the delay of the bolus from the proximal vasculartur 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, e.g. 30% for CBF that is 70% depressed relative to the reference region. Multiple other parameter exist, such as time-to-peak (TTP) and First Moment (FM). 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, CBV, MTT) 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 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.

4b. 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 non-standard domain and substantial differences exist between vendors. Frequently CBF, CBV 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 datasets 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).

4. Interpretation of perfusion CT and MRI

17a. 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 (e.g. chronic hypoperfusion) may induce collateral formation (15).

b. Assessment of ischemic core

i. Computed tomography-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 of the supplemental data). 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 AIF 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 of the supplemental data). 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 MTT, TTP and time to drain (TTD) maps has a high specificity but

moderate sensitivity for detection of these infarcts (16, 24, 25). Sensitivity for infratentorial lesions is however low (25).

ii. 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 (ADC) and a hyperintensity on DWI (26). An ADC threshold between 600-625 x 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).

c. 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 of the supplemental data). Optimal perfusion parameters are mostly validated by comparison to the final infarct on MRI in the absence of reperfusion (Table III of the supplemental data). Differences in optimal parameter and threshold are partially explained by deconvolution method and other post-processing algorithms. Although deconvolved perfusion parameters are generally used, non-deconvolved 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 > 6s 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).

d. Caveats and pitfalls

i. 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 occlusiondue to improved perfusion via collateral blood vessels (34, 35). This ischemic tissue may be readily visible on non-contrast CT, but will not be identified as ischemic core on CTP if blood flow exceeds the threshold for ischemic core detection. Thorough inspection of non-contrast images for established infarction is thus necessary, especially in late-presenting patients. On MRI, ADC changes with time and reperfusion state (36). A single ADC 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 to better perfused tissue (37-39). This partially explains interindividual variability in infarct growth rate (40). The hypoperfusion intensity ratio (HIR), the proportion Tmax > 6s lesion with Tmax > 10s, is a good predictor for collateral flow and infarct growth (38, 39) (Fig 1). Besides Tmax and HIR, rCBV is associated with the degree of collateral circulation and is predictive of infarct growth (39).

ii. Limitations in differentiating normal from pathological tissue

In patients with chronic hypoperfusion (e.g. due to hemodynamically significant stenosis or occlusion of supplying blood vessels), the perfusion deficit may be grossly overestimated if

Tmax or MTT 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.

5. Clinical use of perfusion imaging

a. 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 (i.e. "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, 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 severly hypoperfused tissue volume (respectively DWI lesion and Tmax ≥ 8s 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 > 10s volume <100ml (43).

b. Predicting response to reperfusion

In the DEFUSE study the relationship between the perfusion profile and outcome was assessed in patients treated with alteplase 3-6 hours after known stroke onset (37). Odds of achieving favorable outcome after reperfusion were only increased in patients with PWI/DWI mismatch and were greater in patients with TMM (37). The EPITHET study used MRP and the DEFUSE mismatch definition. They randomized patients to alteplase or placebo 3-6 hours after symptom

onset (44). No difference in outcome was found between mismatch and non-mismatch patients, possibly due to differences in the automated analysis. In the pooled DEFUSE and EPITHET population, thrombolysis was associated with a favourable outcome and attenuation of infarct growth in mismatch patients but not in non-mismatch or malignant profile patients, using automated software and a perfusion threshold of Tmax > 6s (45) (Fig 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 excellent outcome and a lower chance of severe disability or death after thrombolysis (7) (Fig 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, a prospective cohort study, 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 >8s volume of > 85 ml) experienced poor outcome, vs. 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 > 14s) 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 meta-analysis which included 7 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. Noteably, only 8.5% of patients included in the meta-analysis had a core volume ≥ 70ml. 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 (e.g. > 100mL) benefit from reperfusion will need to be assessed in a RCT.

c. Mismatch imaging for treatment selection

On a group level, thrombolysis within 4.5h after ischemic stroke onset without the use of perfusion imaging selection is safe and effective and time modifies treatment effect (53). In EPITHET, a non-significant trend towards improved outcomes was seen in patients with a MMR > 1.2 and minimal penumbra volume of 10mL who were treated with alteplase between 3 and 6 h 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 (i.e. "wake-up patients") (40). In the placebo-controlled EXTEND trial, benefit of thrombolysis in patients with a TMM profile between 4.5 and 9h 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 – 6h or 6 – 9h from last-seen-well.

Another placebo-controlled study using alteplase in the same time window was stopped prematurely due to slow recruitment and failed to show a benefit of thrombolysis (54). A study using tenecteplase in the 4.5-24h time window using perfusion imaging selection is ongoing (TIMELESS; clinicaltrials.gov reference 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 to unselected patients, reperfusion in TMM patients resulted in increased functional indepence (60-71% vs. 32.6%) and lower mortality (9% vs. 21%) 90 days after treatment despite comparable baseline characteristics (57-59).

Two RCTs demonstrated benefit of EVT between 6 and 16 to24h 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, mismatch between the ischemic core volume and clinical symptoms was used (NIHSS of at least 10 or 20, depending on age and ischemic core volume) (2). DEFUSE 3 used a Tmax threshold of > 6 s 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 to 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 suggests that patients with large ischemic core volumes may also benefit from reperfusion (51, 52). Also, in the WAKE-UP trial, which used a DWI-FLAIR mismatch pattern as a surrogate marker for stroke with recent onset and randomized patients to thrombolysis or placebo if treatment was possible within 4.5h 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, i.e. 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. .

d. 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 non-contrast 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).

6. 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 (e.g. large ischemic core volumes [beyond the 6h 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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Conflict of interest

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Figure legends

Figure 1.

CT perfusion imaging processed by RAPID software showing a patient with a low hypoperfusion intensity ratio (HIR), i.e. Tmax 10/Tmax6 lesion volume (A). In this patient, slow ischemic core growth is expected. Below a patient with a high HIR is shown, in whom rapid ischemic core growth is expected (B).

Abbreviations: CT = computed tomograpy

Figure 2.

CT perfusion imaging processed by RAPID software showing a target mismatch profile in a patient with an occlusion of the M1 segment of the right middle cerebral artery (A), i.e. 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).

Abbreviations: CT = computed tomography

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