Topic Review

MRI Perfusion Imaging in Acute Ischemic Stroke

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Introduction

Stroke remains a prevalent disease with an estimated 795,000 new or recurrent annual events in the U.S. and continues to be a leading cause of adult disability exacting an enormous financial toll on the health care system. [1] Ischemia accounts for the vast majority of stroke causes and occurs when vessel occlusion disrupts oxygenated blood perfusion to an area of the brain resulting in injury. The ability to image cerebral blood flow initially exploited angiographic techniques first created in the 1920's and subsequent radionuclide methods developed in the 1960's permitted in vivo brain perfusion measurements. [2] Investigation of magnetic resonance imaging (MRI) to assess perfusion began during the 1990's but has only recently evolved for clinical use over the past decade largely as a result of advancements in rapid image acquisition methods. [3]

MRI perfusion imaging (PWI) represents a form of functional imaging that assesses alterations in blood flow with additional information on metabolism and regional measures of a specific tracer. This technique has been employed for a variety of conditions, but it is most commonly used in cerebrovascular disorders, especially acute ischemia. The role of such imaging began to play a prominent role after publication of the National Institute of Neurological Disorders and Stroke (NINDS) recombinant Tissue Plasminogen Activator Stroke Study and the European Cooperative Acute Stroke Study (ECASS) results in 1995, when emphasis became geared towards timely identification and rescue of viable hypoperfused tissue with thrombolytics. [4-5]

While additional revascularization strategies have since been developed, the central premise behind treatment remains the same and aims to restore potentially salvageable ischemic brain tissue in order to prevent irreversible infarction. This territory of restorable tissue represents the "ischemic penumbra" and patients identified with a larger penumbra are more likely to benefit from recanalization therapies making it crucial to properly recognize them. [6-7] Multimodal MRI including perfusion sequences has been hypothesized to provide a visual representation of the ischemic penumbra prompting recent strong interest in this technique for implementation in acute stroke management. This paper will explore the basic concepts of MRI perfusion and its clinical utility in acute ischemic stroke as well as its current limitations.

Cerebral Perfusion in Ischemia

Measurement of perfusion is based on analysis of a hemodynamic time-to-signal intensity curve generated when a tracer passes through the cerebral circulation. (See Figure 1) This curve may be processed by different means to extract parameters that reflect either the cerebral blood flow (CBF), cerebral blood volume (CBV) or mean transit time (MTT) which are linked by the equation CBV = CBF × MTT, also known as the "central volume principle." In normal brain tissue, vessel autoregulation maintains CBF at 50-60 mL/100g/min., but during early ischemia, the CBF diminishes while CBV rises slightly or is maintained at near normal level due to dilatation of the vascular bed. When CBV begins to decrease or when CBF falls to < 20% of normal (10-12 mL/100gm/min), irreversible cell death has occurred. [8]

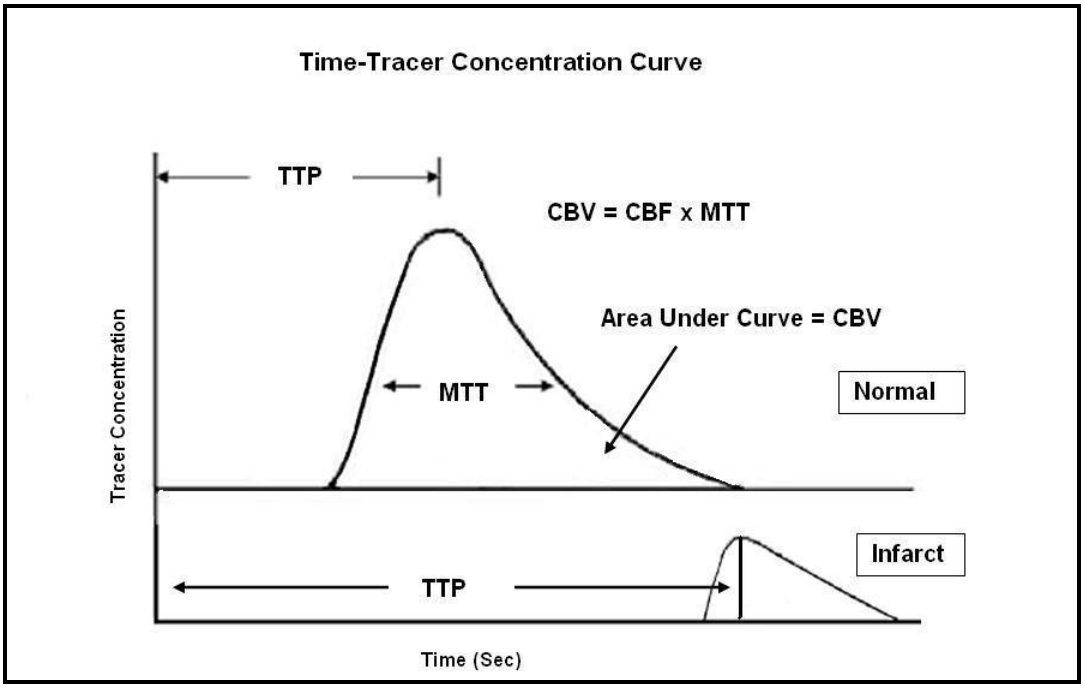

Figure 1: Time- Tracer Concentration Curve demonstrating the relationship of different perfusion parameters in normal tissue and during infarction. CBF = Cerebral Blood Flow. CBV = Cerebral Blood Volume. MTT = Mean Transit Time. TTP = Time To Peak.

This transition from ischemia to infarction not only depends on CBF values but also on the duration of the diminution in blood flow. [9] Transit times become delayed early in the course of the ischemia typically due to occlusive lesions and subsequently rise to immeasurable levels as infarction ensues and downstream resistance increases. Two parameters of transit time include MTT as well as time to peak (TTP), which reflects time from the beginning of the contrast injection to the peak enhancement within a region of interest. In general, tissue at risk of infarction will have normal or decreased CBF, normal or elevated CBV, and elevated MTT/TTP, while infarcted tissue will have decreased CBF and CBV with elevated MTT/TTP. [10-11] (See Table 1)

Tissue State	TTP	CBV	CBF
Normal	—	—	—
Benign Hyperemia	↑	—↑	—
At Risk Ischemia	↑	—↑	↓
Infarction	↑	↓	↓

Table 1: A simple representation of typical changes that occur with each perfusion parameter in normal brain tissue as it progresses towards infarction.

MRI Perfusion Techniques

Different MRI techniques are available for cerebral perfusion measurements in routine clinical practice, but a contrast-enhanced dynamic susceptibility T2* weighted technique remains the most common method. For this method, approximately 20 mL of gadolinium is injected at 4-6 mL/sec. and an echoplanar sequence is used to acquire whole brain coverage with ≥12 slices during a 90-120 second acquisition time. [12-13] The flow of paramagnetic contrast agent through the cerebral circulation produces a nonlinear signal loss due to the contrast susceptibility or T2* effect. [14] Tissue signal changes produced by this T2* effect are implemented to create the time-to-signal intensity curve. These signal intensity changes may then be used to create color-coded or intensity-coded hemodynamic maps from either raw data or processed data from deconvolution algorithms based on the arterial input function (AIF) which is often estimated from the middle cerebral artery and reflects the arterial concentration of contrast agent distributed in time. Various hemodynamic parameters such as relative CBF in mL/min, relative CBV in mL, MTT in sec., and TTP in sec. as well as Time to bolus arrival may be obtained (See Figure 1) and the contralateral brain tissue often serves as a normal control for which relative perfusion values may be compared.

The arterial spin labeling (ASL) technique is an additional technique that does not require the use of a contrast agent but rather utilizes the spins of endogenous water protons as a tracer. In the Pulsed Arterial Spin Labeling (PASL) method, the application of a short radiofrequency pulse tags arterial blood flowing upstream by inverting the spin polarity of protons flowing into the imaging plane. Another technique known as the Continuous Arterial Spin Labeling (CASL) method utilizes a continuous radiofrequency of weak intensity to label blood upstream of the slice. With either

method, subtraction of control from spin labeled images allows measurement of perfusion parameters. Although these methods remain promising for patients with gadolinium contraindications, ASL currently remains investigational as it is difficult to implement, especially on intermediate or low field strength below 1.5T and the signal to noise ratio is relatively low allowing for significant contamination from blood-oxygenation-level-dependent effects.[15-16] (See Figure 2)

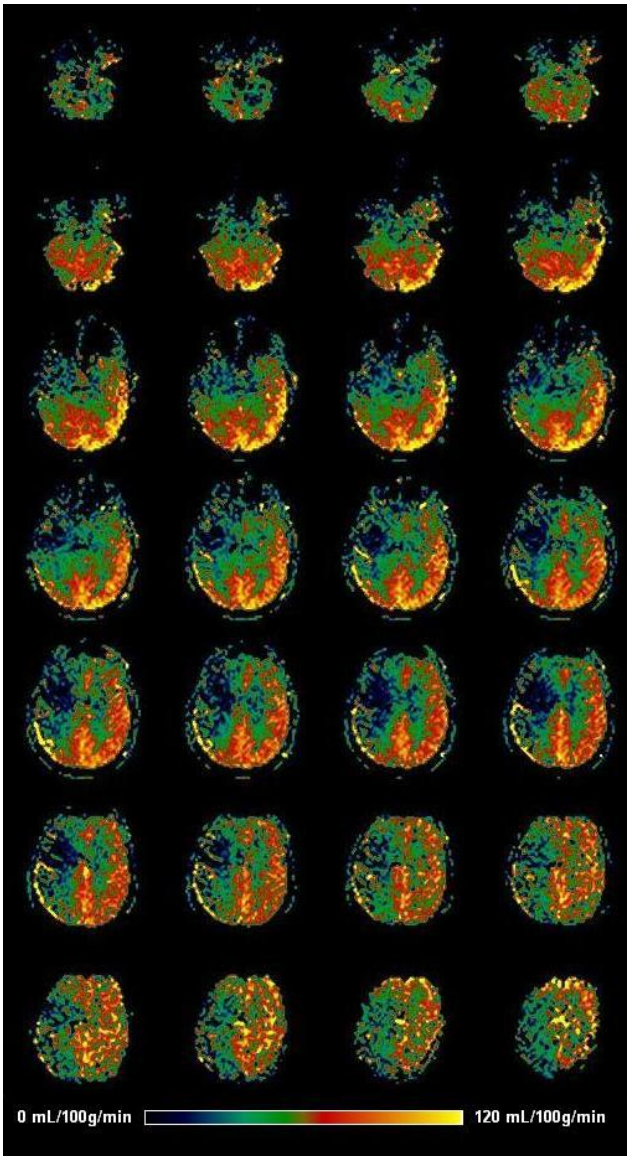

Figure 2: MRI brain perfusion image using color-coded ASL technique in a 57 year old female presenting with left sided hemiparesis and neglect for 2 hours. A CBF parameter map with multiple slices demonstrates significant asymmetry with decreased intensity (noted in blue) in the right middle cerebral artery territory.

The clinical role of each perfusion parameter and its function in accurately discerning ischemic penumbra from infarct core remains uncertain. Many studies employ TTP or MTT as evidence has demonstrated that these parameters are most predictive of final infarct size and are easy to obtain. [17-20] Measures of relative CBV changes are more difficult to measure with MRI perfusion techniques. Precise

measurement of other parameters remains under investigation as unresolved methodological constraints persist. A simple means of displaying perfusion information is to present images of relative perfusion values, so that an ischemic lesion may be visualized as an area of reduced flow compared to the other hemisphere. Additional complex mathematical processing techniques remain in development, but such calculations also rely upon accurate preconditions such as precise AIF derivation. [21] Proper AIF selection must correctly account for proper bolus arrival time and dispersion and its calculation has been shown to impact the size of a tissue perfusion abnormality defect. [22] In addition to optimal AIF selection,

Perfusion MRI techniques are highly dependent upon good temporal resolution with adequate signal-to-noise ratio and thus benefit from the improved signal strength provided by stronger magnetic fields. Spatial resolution is sacrificed for reduced scan times and limitation of artifacts from spatial distortion therefore sensitivity is diminished for small lesions. An additional limitation of this sequence in acute strokes entails the presence of hemorrhage which may create signal distortion resulting in artifactual perfusion measurements in that region. MRI effects such as distortion from saturation, partial volume effects, and local frequency shifts require further investigation. [23] Finally, important heterogeneous flow preconditions require consideration including factors such as the rate of injection, impaired cardiac output, proximal arterial stenosis, and areas of reduced flow which may produce low signal-to-noise levels. [24]

It is important to note that additional methods are currently available to assess cerebral perfusion including Single Photon Emission Computed Tomography (SPECT), CT perfusion, Xenon CT perfusion, as well as Positron Emission Tomography (PET), but discussion of these methods remains beyond the scope of this article. For ischemic strokes, the choice of perfusion MRI is largely based on logistics and institutional availability. General advantages of this technique include the ability to assess the entire brain, lack of radiation, avoidance of contrast with ASL as well as the detailed information provided when combined with other MRI modalities such as diffusion weighted imaging (DWI) and magnetic resonance angiography. The drawbacks of perfusion MRI currently include lack of quantitative measurements, longer examination time compared with CT, decreased sensitivity to hemorrhages and its limitation in patients with a contraindication to magnetic fields.

Clinical Use

The use of DWI to diagnose ischemic infarction on MRI has been described extensively elsewhere and has been clearly established as an important tool in the setting of acute stroke. [25] It is generally felt that DWI reflects irreversible infarct while PWI delineates an area of hypoperfusion and therefore the combined use of PWI

with DWI permits a simplified visual approach to discern infarct core from penumbra at risk. The volume difference between these two is noted as the "PWI/DWI mismatch" and patients without a mismatch demonstrate equal lesion volumes due to a theoretical lack of penumbral tissue either from normalization of prior hypoperfusion or completed infarction. [26-27] (See Figure 3) An important concern for this model is that a PWI lesion also assesses areas of benign hyperemia, which may not necessarily be at risk for infarct progression and that portions of DWI abnormalities may represent penumbra that may escape infarction in a phenomena described as "DWI reversal." [28-29] However, the emerging use of this clinical imaging modality is largely based on an important need to better identify acute stroke patients who are more likely to benefit from various revascularization therapies. Patients with a PWI/DWI mismatch pattern have been hypothesized to be more likely to benefit from reperfusion therapy than those without a mismatch based on several large acute stroke treatment trials that employed pre-treatment PWI/DWI imaging. [30-31]

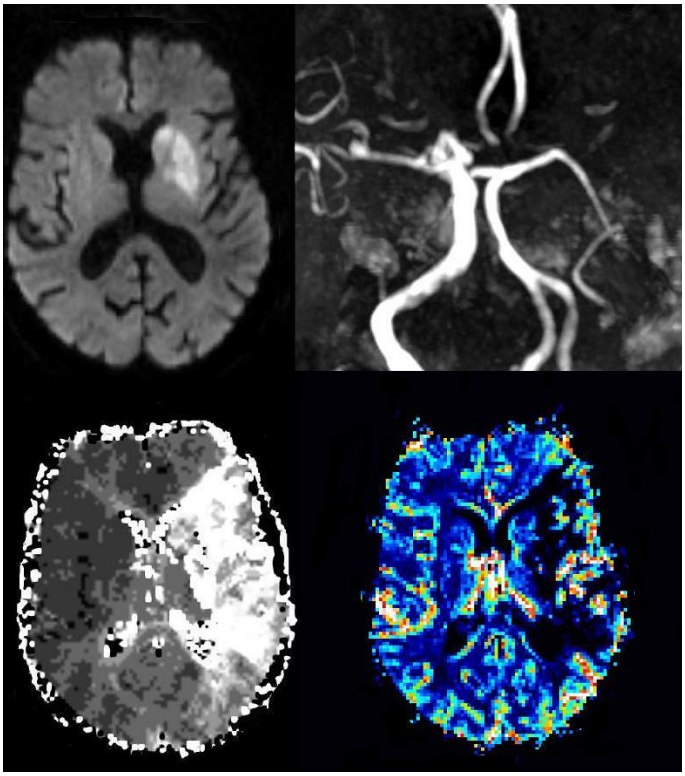

Figure 3: (Clockwise from Top-Left) Multimodal MRI of the brain in a 86 year old female presenting with aphasia and right hemiparesis for 6 hours. A) A DWI sequence demonstrates restricted diffusion in the left corpus striatum. B) A 3D time-of-flight MR angiogram of the brain reveals absence of flow related signal in the left internal carotid artery and the left middle cerebral artery. C) A CBF parameter map using contrast enhanced dynamic T2* perfusion sequence reveals a large region of decreased CBF in the left middle cerebral artery territory. D) A TTP parameter map using a contrast enhanced dynamic T2* perfusion sequence reveals prolonged TTP in a large region of left middle cerebral artery territory. Comparison with the DWI sequence is notable for a PWI/DWI mismatch.

The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was an important study that sought to determine whether tPA administration 3-6 hours after stroke onset would reduce infarct expansion in patients with PWI/DWI mismatch. This study found that 86% of randomized patients demonstrated a baseline mismatch defined as a PWI/DWI ratio > 1.2 but infarct growth at 90 days was not significantly different between tPA and placebo-treated patients. However, there was a strong trend to attenuation of DWI lesion expansion in patients treated with tPA and a non-significant trend toward good neurological outcome was observed in mismatch patients receiving tPA compared with those receiving placebo (50% vs. 37%). Post-hoc analyses indicate that the trial was underpowered and suggest that the mismatch definition may require modification. [32]

The Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) trial sought to determine if the benefit of tPA administered 3-6 hours after stroke onset would be enhanced in patients with mismatch. This study found that 54% of patients demonstrated mismatch and favorable clinical outcomes were significantly increased in target mismatch (PWI/DWI >1.2) patients with early reperfusion, relative to those who did not receive early recanalization (OR = 6.2). No relationship between early recanalization and favorable clinical response was seen in patients without mismatch. Patients with a malignant profile (PWI or DWI lesion >100mL) had a low rate of favorable outcomes and a 100% symptomatic intracranial hemorrhage rate with reperfusion. Conversely, all patients with a small lesion (PWI or DWI < 10ml) had favorable outcomes. The results of this study in conjunction with EPITHET trial suggest that mismatch imaging may play an important clinical role, but require further refinement in definition and standardization methods.

The Desmoteplase in Acute Ischemic Stroke (DIAS) and the related Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials used PWI-DWI mismatch during patient selection for thrombolytic use 3-9 hours after onset of stroke symptoms. [33-34] A dose-dependent rate of favorable clinical outcome was observed with desmoteplase, as compared to placebo for patients with a mismatch defined as PWI/DWI ≥ 1.2. However, a follow-up phase III prospective randomized trial (DIAS-2) failed to find a benefit for desmoteplase in selected patients with mismatch between 3-9 hours from stroke onset. [35] Despite the disappointing results, a tantalizing finding was that no difference in response rates were seen based on time, contradicting the notion that treatment is time dependent. Such notions should only bolster efforts to improve methods in identifying patients with a persistent penumbra.

Conclusion

Currently, there is no expert consensus opinion for the ideal clinical role of perfusion MRI in acute stroke. [25] Studies using PWI/DWI selection criteria have yielded mixed results, but still warrant further investigation after better understanding and improvement in imaging techniques are obtained. One of the main technical difficulties is the lack of a standardized and objective definition in perfusion measurements. There are a number of perfusion parameters that may be used to define the area at risk and head-to-head comparisons trials are needed. [36-37] While semi-quantitative perfusion maps are useful, quantitative values may yield improvements as comparative studies with PET do confirm that subjective visual inspection of TTP maps results in an over-estimation of the true volume at risk, due to the inclusion of regions with benign hyperemia. [38] Quantification of data requires processing algorithms which currently varies with software. Additionally, perfusion thresholds for infarct core and penumbra differ with the duration of ischemia and may be modified by recanalization and well as collateral circulation. All these variables may lead to significant disparities in mismatch percentage for the same patient in different institutions potentially leading to discrepancies in selecting patients for treatment. Finally, it remains unclear what constitutes a critical volume of mismatch tissue. Although a value of 20% has been implemented in several studies, this is an arbitrary ratio and there is some suggestion that a more conservative definition may be required to optimally select patients. Achieving a true penumbral imaging paradigm still remains elusive in stroke care, but the goal may be attainable after rigorous endeavors are undertaken to reconcile the above issues. Resolving these unsettled issues requires a collaborative effort and attempts are underway to begin addressing these concerns with the objective of standardizing perfusion parameters and definitions for future clinical studies. [13]

Summary

● MRI perfusion imaging may be utilized for the semi-quantitative evaluation of various parameters including cerebral blood flow, cerebral blood volume, time to peak and mean transit time, which become altered as normal cerebral tissue progresses from ischemia to infarction.

● Various MR imaging methods are available, but a contrast enhanced dynamic susceptibility weighted T2* technique is most frequently employed for strokes. Mean Transit Time or Time To Peak are commonly assessed parameters, used to visually compare suspected ischemic areas relative to the contralateral hemisphere.

● The usage of Multimodal MRI with perfusion imaging during an acute stroke permits evaluation of PWI/DWI mismatch which is hypothesized to provide a visual estimation of penumbra tissue from infarct core. Several studies have attempted to validate this method to guide therapeutic selection as well as to predict treatment response, but results currently remain insufficient to make definitive recommendations for routine clinical application.

● Further investigation is required to assess the value of quantification in perfusion parameters and attempts are in progress to improve processing algorithms that address heterogeneous precondtions and proper AIF selection. Additionally, collaborative efforts remain ongoing to apply standardized techniques and definitions for future studies as well as for clinical use.

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