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Applications of Diffusion/Perfusion Magnetic Resonance Imaging in Experimental and Clinical Aspects of Stroke

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Abstract

The acute evaluation of stroke patients has undergone dramatic advances in the recent past. The increasing availability of novel magnetic resonance imaging (MRI) techniques, such as diffusion and perfusion MRI, provides a plethora of information to clinicians evaluating patients suspected of having an acute stroke. This review focuses on recent advances with experimental and clinical applications of perfusion and diffusion imaging and their utility in identifying potentially salvageable ischemic tissue in rat stroke model and stroke patients.

Introduction

Diffusion-weighted magnetic resonance imaging (MRI) has become an established method for the noninvasive evaluation of cerebral ischemia in both animal models and humans. Although the biophysical mechanism(s) underlying apparent diffusion coefficient (ADC) reduction remain incompletely understood, diffusion-weighted imaging (DWI) is widely recognized for its ability to noninvasively detect ischemic brain injury within minutes after its onset, whereas other conventional imaging techniques (such as T1- and T2-weighted MRI and computed tomography [CT]) fail to detect such injury for many hours [1–5].

Brain tissues with cerebral perfusion deficits below a critical threshold experience metabolic energy failure, membrane depolarization, and subsequent cellular swelling (cytotoxic edema) [6]. These changes precipitate a reduction in the ADC of brain water and are manifested as a hyperintense region on DWI [1]. During the first few minutes in animal models to a few hours in human stroke (*ie*, the acute phase), the anatomic area defined by DWI is initially smaller than the area of perfusion deficit. However, most of this DWI-defined ischemic region expands and eventually coincides with the abnormal area defined by perfusion-weighted imaging (PWI). The difference in the abnormal region defined by the PWI and DWI in the acute phase of stroke, commonly referred to as the “perfusion-diffusion” mismatch, was suggested to be potentially salvageable ischemic tissue [7]. Other MRI parameters, such as proton density (M0) and T1 and T2 relaxation times, are generally unaffected early after stroke onset and only begin to change with the advent of vasogenic edema (typically > 6 hours) [8].

The perfusion-diffusion mismatch region is presumed to approximate the ischemic penumbra, which is a region of moderately ischemic tissue with diminished cerebral blood flow (CBF) and impaired electrical activity but preserved cellular metabolism. The transition from reversible to irreversible injury is complex and highly dependent on the duration and severity of ischemia, and as such, different areas of the penumbra could have variable outcomes. Re-establishing tissue perfusion and/or administering neuroprotective drugs in a timely fashion are expected to salvage some ischemic tissues [9]. To potentially help to expand the time window for thrombolytic therapy and to provide individualized diagnosis and treatment, it will

likely be important to have an imaging-based identification of the “tissue signature” and “clock window” of ischemic tissue in order to achieve the maximum benefit and to avoid the occurrence of a devastating intraparenchymal hemorrhage [9].

Perfusion/Diffusion Imaging in Animal Stroke Models

The precise fate of ischemic tissue characterized by the perfusion-diffusion mismatch, however, remains poorly understood and controversial. Consequently, clinical decision making based on perfusion and diffusion imaging has not yet reached its fullest potential. Animal models in which the perfusion-diffusion mismatch can be reproducibly studied under controlled conditions are important to fully characterize the tissue fates of ischemic injury (*ie*, salvageable vs nonsalvageable tissues) and to evaluate the efficacy of therapeutic intervention.

The most widely used perfusion MRI technique is based on dynamic susceptibility contrast imaging [10], in which an intravenous bolus of a blood-pool MR contrast reagent such as Magnevist (Berlex, Montville, NJ) is injected while T2* or T2 imaging is performed. This technique is generally qualitative due to inaccurate determination of the arterial input function, and generally is performed only once due to recirculation of the contrast reagent and potential side effects. Nonetheless, dynamic susceptibility contrast imaging has widespread clinical utility. An alternative technique is based on the arterial spin-labeling technique that involves noninvasively and magnetically labeling the blood water protons as they flow into the imaging slices (no need for exogenous contrast reagents) [10]. Most arterial spin-labeling techniques are, however, limited to one or a few imaging slices and are also generally qualitative. Williams *et al.* [11] invented a two-coil continuous arterial spin-labeling (cASL) technique that overcame many of the limitations of the conventional arterial spin-labeling technique, providing quantitative CBF multislice imaging across the entire brain. With this technique, repeated measurements can be made for signal averaging at relatively high spatial and temporal resolution.

Applications of the cASL technique with the two-coil setup to evaluate the spatio-temporal progression of stroke rats during the acute phase are shown in Figure 1. The ADC and CBF maps clearly delineate regions of hypointense abnormality (Fig. 1A). Areas with ADC reduction grow from 30 to 180 minutes after ischemia, eventually reaching the CBF lesion volume. Pixel-by-pixel CBF-ADC scatterplot analysis shows additional information that is not readily evident by inspecting the ADC and CBF per se (Fig. 1B). In the left hemisphere, there is a single cluster with high ADC and CBF. In the right hemisphere at 30 minutes, there are three clusters: 1) the “normal” cluster, with normal CBF and ADC; 2) the “core” cluster, with markedly reduced CBF and ADC; and 3) the “mismatch” cluster, with reduced CBF but slightly reduced ADC. At 180 minutes, essentially all the mismatch pixels migrated to the core in the permanent occlusion model. Tissue volumes and ADC and CBF values of each tissue cluster on the CBF-ADC scatterplots can be automatically and statistically resolved using cluster analysis, and each cluster can be mapped back onto the image spaces, providing a powerful and objective tool for pixel-by-pixel visualization of different tissue fates [12–14]. The group-averaged lesion-volume evolutions in permanent ($n = 6$) and temporary (60 minutes; $n = 6$) occlusion are summarized in Figure 1C. In the permanent occlusion group, ADC lesion volume grows until it reaches CBF lesion volume at 180 minutes, which correlated with the triphenyltetrazolium chloride infarct volume determined at 24 hours. Reperfusion performed at 60 minutes after occlusion clearly demonstrates the perfusion-diffusion mismatch can indeed be salvaged, with ADC lesion volume at 180 minutes reaching approximately 50% of the permanent occlusion group [15,16,17].

In addition to anatomic imaging based on tissue perfusion and diffusion, functional MRI (fMRI) of stroke animals can also be performed to evaluate the functional status of the perfusion-diffusion mismatch. fMRI is a noninvasive imaging modality and has been widely exploited for mapping brain processes, ranging from perceptions to cognitive functions [18]. The most widely used fMRI technique is based on the blood oxygen level-dependent (BOLD) signal or CBF signal. The BOLD contrast originates from the intravoxel magnetic field inhomogeneity induced by paramagnetic deoxyhemoglobin in erythrocytes. Changes in regional deoxyhemoglobin content can be visualized in susceptibility-sensitized (*ie*, T2*-weighted) BOLD images. The BOLD fMRI technique is based on a principle discovered over 100 years ago, in which neuronal activity is intricately coupled to CBF [19]. When a task is performed, regional blood flow increases disproportionately (which can be also measured using the cASL technique), overcompensating the stimulus-evoked increase in oxygen consumption needed to fuel the elevated neural activity, resulting in a regional reduction in deoxyhemoglobin concentration. Thus, the BOLD signal increases following elevated activity relative to basal conditions, making it possible to dynamically and noninvasively map changes in neural activities. Most fMRI studies had been performed in normal humans and animal models to map brain functions. Recent developments have made the fMRI techniques fast and robust, and a wide range of disease applications are emerging. Figure 1D shows the CBF-based functional MRI maps of a normal and stroke (permanent occlusion) rat [20]. Bilateral forepaw somatosensory stimulation activates the somatosensory cortices of both hemispheres in a normal rat. In the stroke rat 30 minutes after occlusion, activations in the somatosensory cortices are not detected in the ischemic hemisphere. Functional MRI in stroke should be useful in determining whether risky therapeutic intervention should be performed if the perfusion-diffusion mismatch is already nonfunctional. Recent development allows the addition of oxygen-consumption imaging to map oxidative metabolism and neural-vascular coupling in stroke rats [19]. It is now possible for perfusion, diffusion, and functional (including oxygen-consumption) imaging to be routinely carried out within 30 minutes at reasonably high spatial resolution.

The combined use of perfusion, diffusion, and functional MRI provides a powerful tool for complete characterization of ischemic injury, for evaluation of drug efficacy, and potentially for statistical prediction of ischemic tissue fates. Tissue volumes, tissue perfusion, and diffusion and functional characteristics of ischemic tissue that is subsequently salvaged or evolves to become infarcted can now be quantitatively evaluated on a pixel-by-pixel basis at high spatio-temporal evolution. Animal stroke models in which the perfusion-diffusion mismatch and its functional status can be reproducibly studied under controlled conditions will be highly valuable to establish the foundation of various MRI modalities and to characterize ischemic tissue fates.

Diffusion/Perfusion MRI Applications in Acute Stroke Patients

Diffusion/perfusion MRI has now been utilized for patient care for almost a decade, and both MRI techniques have become increasingly available in routine clinical practice. Performing diffusion/perfusion MRI studies in the setting of suspected acute stroke provides much useful information to the clinician [21]. These studies, along with magnetic resonance angiography (that is also typically part of the acute stroke imaging battery), confirm that acute brain ischemia is indeed present. This confirmation may not be available for many additional hours with standard CT and MRI techniques. They provide information about the localization of the ischemic event, thus distinguishing small subcortical ischemic lesions from larger cortically based ones [22]. A surprising revelation derived from diffusion/perfusion MRI is that up to 25% of acute stroke patients in some series have evidence of multiple acute ischemic lesions [23]. This observation, especially in distinct vascular territories, should imply a cardiac or aortic source for emboli and guide the search for such a source of multiple emboli. A recent

study suggested that 15% of ischemic stroke patients had a second event outside of the initially hypoperfused region, suggesting that sub-acute stroke recurrence is not uncommon and that large artery atherosclerosis was the most common stroke mechanism associated with recurrence [24]. An early concern with the use of MRI as the initial imaging modality for assessing acute stroke patients was that intracerebral hemorrhage might not be detected. Recent studies with gradient-echo (GRE) MRI sequences appear to have alleviated this concern. When both CT and an MRI battery containing GRE sequences are obtained in close temporal approximation, it appears that susceptibility-weighted MRI is at least as sensitive as CT for detecting intracerebral hemorrhage, and perhaps slightly more so [25]. At this time, if a comprehensive MRI battery is readily available, it appears to be the optimal imaging approach for acute stroke patients.

Using Diffusion/Perfusion MRI for Patient Treatment Decisions and Clinical Trials

Currently, the only approved therapy for acute ischemic stroke is tissue plasminogen activator (tPA) initiated within 3 hours of stroke onset [26]. The approval and use of tPA in this clinical setting is derived from the results of the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial [27], which randomized patients such that 50% had to be started on therapy within 90 minutes after stroke onset. A reanalysis of this trial indicated that starting tPA earlier in the time window was associated with a substantially better outcome 3 months later [28]. The presumed target of acute stroke therapy is the ischemic target, with the goal of reducing ultimate infarct size to improve clinical outcome [29]. The relationship of time to treatment and ultimate outcome is consistent with the concept that the ischemic penumbra evolves at least in part from potential salvageability to irreversible injury over time. Therefore, treating earlier with thrombolytic therapy in patients selected based upon their clinical status and exclusion of hemorrhage by CT should be associated with a better chance for clinical improvement because there is likely more penumbra to salvage the earlier treatment is initiated. Another approach to identifying patients who might respond to thrombolytic or even neuroprotective therapy is to use diffusion/perfusion MRI (Fig. 2). It is now widely appreciated that a diffusion/perfusion mismatch persists for many hours after stroke onset in some patients [30]. Several recent studies demonstrated that patients with a diffusion/perfusion mismatch identified before initiating tPA therapy beyond 3 hours after stroke onset and subsequent evidence of reperfusion were more likely to improve than patients without such a mismatch [31,32]. In one study, the best MRI predictor of favorable outcome was a rapid reduction in the hypoperfused volume by more than 30%, supporting the concept that early reperfusion likely salvages ischemic but not yet infarcted tissue and, therefore, improves outcome [33•]. In another recent study, it was observed that complete recanalization/reperfusion on a combined analysis of magnetic resonance angiography and perfusion MRI after tPA was associated with a better outcome than patients who had no recanalization [34•]. Interestingly, minimal and partial recanalization/reperfusion were also associated with better outcome, and there was no obvious difference between the partial recanalization/reperfusion group and the complete recanalization/reperfusion group. These studies were not blinded or placebo controlled, so evaluation of patient selection with diffusion/perfusion MRI for delayed tPA treatment is now ongoing in appropriate clinical trials.

Initially, it was assumed that reduced ADC values identified early after stroke onset with diffusion MRI represented irreversibly damaged ischemic tissue. Recent animal and human studies have dispelled that notion and clearly have demonstrated that initial ADC reductions are indeed potentially reversible with early intervention such as reperfusion [35,36]. However, secondary ADC declines after initial normalization also have been observed, adding to the complexity of data analysis and predictability modeling. An updated view of the identification of stroke patients more likely to respond to treatment or for inclusion in clinical trials recognizes that the diffusion/perfusion mismatch only approximates the ischemic penumbra and that a

more sophisticated paradigm will evolve that recognizes the contribution of absolute ADC and perfusion parameters towards distinguishing ischemic core and penumbra [37••].

The potential uses for using diffusion/perfusion MRI to help stroke drug development are manifold [38]. As discussed, these imaging modalities can provide an approximation of the ischemic penumbra and, therefore, help to target the randomization of patients into acute stroke therapy trials most appropriate for inclusion. Another use of diffusion/perfusion for the inclusion or exclusion of patients in clinical trials is the ability of these MRI techniques to rapidly identify the precise localization of ischemic brain injury. For example, if a clinical trial is designed to exclude small, subcortical lacunar stroke patients or patients with brainstem strokes, diffusion/perfusion MRI can reliably accomplish this task, whereas clinical assessment is likely to be somewhat less accurate. Diffusion/perfusion MRI can also be employed to assess therapeutic effects. For neuroprotection, a biologically relevant endpoint would be the effect of treatment on ischemic lesion growth from baseline to pretreatment on diffusion imaging to delayed infarct size at days 30 to 90 as measured by T2 or fluid-attenuated inversion recovery imaging. The natural history of lesion growth in patients with middle cerebral artery territory ischemia imaged within 6 hours of stroke onset is that ischemic lesion volume will increase by mean percentage of 50% to 100% [35]. Therefore, with a relatively modest number of patients per treatment group (eg, 50 to 100), a trial can be appropriately powered to detect a 25% to 30% effect on lesion growth. Another approach is to use a responder analysis, with a favorable response defined as no lesion growth or shrinkage. With this approach, even smaller patient numbers are likely to be needed to identify no treatment effect, which would lead to the rapid identification of doses that are ineffective at reducing ischemic lesion evolution and should, therefore, be abandoned. For thrombolytic drugs, the effects of treatment on reperfusion efficacy measured on perfusion imaging pretreatment and then several hours later can be used to identify dosage regimens that are effective on re-establishing flow or that are ineffective. For both neuroprotection and thrombolysis, these treatment effects are biologically plausible and relevant and should, therefore, be acceptable to regulatory agencies as potential surrogate markers of drug efficacy.

Another relevant application of diffusion/perfusion MRI is that the same techniques can be used in preclinical stroke models and clinical drug development programs. The preclinical evaluation of potential acute stroke treatments has been quite variable in extent [39]. For both neuroprotective and thrombolytic drugs, the major initial assessment tool has been the reduction of infarct size, typically measured 1 to 7 days after stroke onset. With diffusion MRI, treatment effects can be measured dynamically in vivo, beginning within minutes after stroke onset and continued for many hours [40]. With perfusion MRI, the effects of thrombolytic agents on the extent of brain hypoperfusion can be assessed, in addition to determining effects on ischemic lesion volume with concomitant diffusion MRI [41]. Many neuroprotective drugs and a few thrombolytic drugs have been evaluated with these imaging paradigms, providing useful information about in vivo treatment effects, dosing kinetics, and time-to-treatment response effects. This useful information can then be applied when the drug begins clinical development, especially if diffusion/perfusion MRI-based clinical trials are also used in the drug development process.

Several clinical trials have incorporated diffusion/perfusion MRI. The initial MRI stroke trials were part of the phase III program because the drugs were already in advanced development when the MRI technology became available. MRI-based assessment of two neuroprotective agents, the glycine antagonist GV150526 and the maxi-K channel antagonist BMS204352, showed absolutely no effect on ischemic lesion growth [38]. A trial with citicoline used MRI to assess treatment effects and both showed no statistically significant effects on ischemic lesion growth. The trial was stopped prematurely by the sponsor, and 81 patients completed the final evaluation at day 90. The mean increase in lesion volume from the baseline diffusion

MRI scan to the day 90 T2 scan was 180% in the placebo group and 34% in the citicoline group. The study did not achieve statistical significance because of the large variability in percent lesion growth and the small sample size [42]. Another citicoline trial used MRI as part of a larger phase III trial, again including patients up to 24 hours after stroke onset [43]. A significant reduction in ischemic lesion growth was observed in patients treated with citicoline who had any baseline cortical lesion on diffusion MRI. The alpha-amino antagonist YM872 was evaluated by assessing lesion growth from a pretreatment baseline diffusion MRI to a delayed T2 MRI in a phase II-B study that apparently showed no treatment effect and was, therefore, stopped for futility. Another phase II study evaluated the thrombolytic agent desmoteplase. This study enrolled patients between 3 and 9 hours after stroke onset and used perfusion MRI to evaluate reperfusion efficacy on a second scan performed several hours after completion of treatment [44]. In a dose-escalation study, the highest weight-adjusted dose of desmoteplase demonstrated substantially better reperfusion effects than vehicle-treated patients. This result is currently being evaluated in a second trial. These initial clinical trials incorporating diffusion/perfusion MRI have provided valuable lessons concerning how to use these MRI technologies in the acute stroke trial setting and hints of biologically relevant treatment effects. It is anticipated that the role of diffusion/perfusion MRI in acute stroke drug development will expand and that these techniques will help to achieve regulatory approval of additional therapies in the near future.

Conclusions

The clinical utility of diffusion/perfusion MRI is rapidly expanding, and these MRI techniques along with fMRI are widely incorporated into experimental studies in animals and humans. They provide much useful information for stroke clinicians and experimentalists that will continue to help to improve our ability to diagnose, treat, and understand the pathophysiology of this common and devastating disorder. The capabilities of these MRI techniques will continue to increase at a rapid rate and should remain a mainstay of stroke imaging for many years to come.

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Figure 1.

A, Cerebral blood flow (CBF) and apparent diffusion coefficient (ADC) maps at 30 and 180 minutes of permanent focal ischemic rat (ADC: 0 to $2 \times 10^{-3} \text{ mm}^2/\text{s}$; CBF: 0 to 3 mL/g/min.) **B**, Pixel-by-pixel CBF-ADC scatterplots of the left hemisphere (LH) and right hemisphere (RH) at 30 and 180 minutes after stroke. **C**, Lesion-volume evolution in permanent ($n = 6$) and temporary (60 minutes) ($n = 6$) occlusion rats, and their correlations with triphenyltetrazolium chloride (TTC) infarct volumes. **D**, Functional CBF-based magnetic resonance imaging maps of a normal (overlaid on anatomic images) and a stroke (overlaid on CBF images) rat. Bilateral forepaw somatosensory stimulation used 0.3 ms, 3 Hz, 6 mA under 1.1 % isoflurane [20] (cross-correlation coefficient of 0.3 [$P < 0.05$] to 0.8).

Figure 2.

Representative diffusion magnetic resonance image (MRI) (*panel A*), perfusion MRI mean transit time (MTT) map (*panel B*), and magnetic resonance angiography (MRA) (*panel C*) from a stroke patient initially imaged 2.5 hours after stroke onset. These images demonstrate occlusion of the middle cerebral artery on MRA with a large area of hypoperfusion on MTT maps and only a small lesion of the diffusion MRI scan. The patient received intravenous tissue plasminogen activator. Reperfusion on the MRA and perfusion MRI with minimal expansion of the diffusion lesion, supporting successful thrombolysis and likely tissue salvage on images obtained 24 hours later (*panels D, E, and F*). (DWI—diffusion-weighted imaging.) (Courtesy of M. Selim, MD).