Advanced Neuroimaging Applications

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INTRODUCTION

Faster MRI technology, the availability of paramagnetic contrast agents, and our understanding of intrinsic MR tissue contrast have combined to produce a new field of functional MR neuroimaging. Functional MRI techniques of perfusion have extended the capabilities of conventional methods to include the acquisition of tissue function maps that measure water proton diffusion and perfusion. With the achievement of these high-spatial, high-temporal resolution images, it has been possible to observe the functional, as well as structural, properties of regions of interest that hitherto remained obscure. We can now obtain MR images from which to calculate tissue blood flow, blood volume and blood oxygenation. Functional neuroimaging tools for mapping cerebral perfusion range from apparent diffusion mapping to assess flow-related alterations in microscopic flow and motion of water protons over a micron scale (diffusion weighted MRI), T2* bolus tracking of injected contrast agents to map rCBV and other hemodynamic parameters (perfusion weighted MRI), and mapping of arterial inflow into perfused slices (arterial spin- tagging).

The Need for Proton Perfusion Weighted Imaging (PWI). The mechanisms of perfusion are faster than those of diffusion, by approximately two orders of magnitude. The use of MR contrast media can provide unique information in the early detection of brain perfusion changes as well as improved delineation of a perfusion-deficient or perfusion-rich region in disease states. MR contrast media, such as gadolinium chelates or iron oxide particulates, which cause regional signal losses because of magnetic susceptibility-induced T2* shortening occurring largely in the microvasculature, have been shown to provide substantial contrast enhancement between ischemic and normally perfused brain. Because the long range magnetic field altering (T2*) effect in the microvasculature is pronounced due to the large surface area of the capillary bed that the passage of bolus injected T2* shortening agents is termed "perfusion". When a rapid imaging technique, sensitive to T1 or T2*, is used to obtain serial images of the same anatomic slice(s), the passage of a bolus of any susceptibility agent can be tracked as a transient increase or loss of signal intensity in the regions of arterial blood supply. The dynamics of this contrast agent transit can be used to assess the degree of contrast transit.

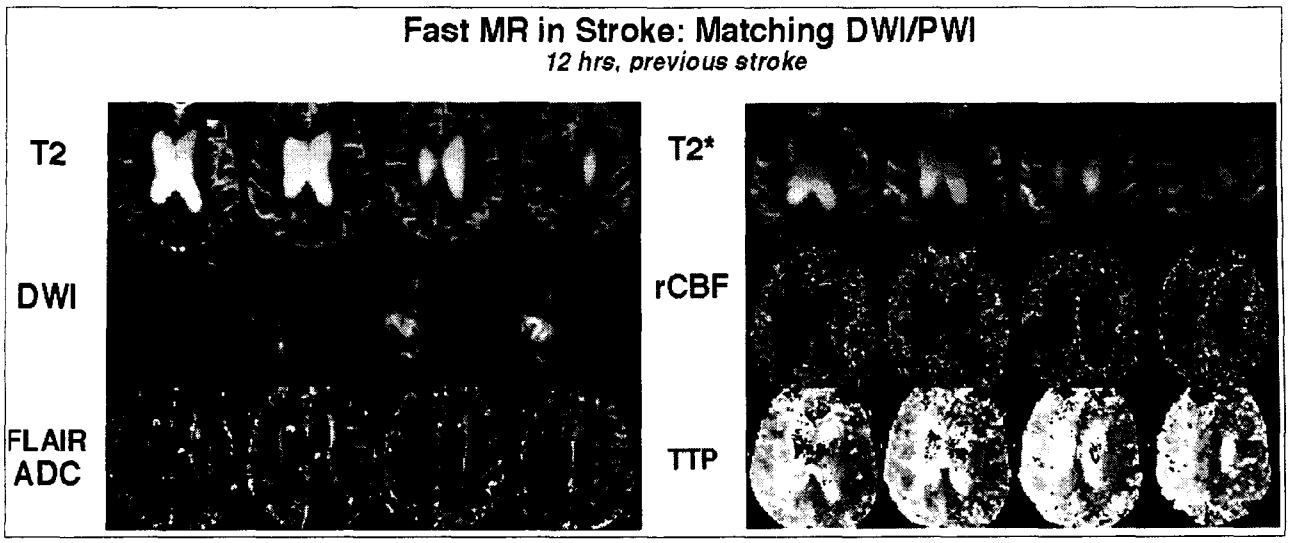


Figure 1. Integrated DWI and PWI exam. At early timepoints, T2 maps do not show presence or extent of the ischemic lesions, easily seen on DWI or on ADC maps. FLAIR ADC maps are often used to suppress bright CSF from the ADC maps, which obscures the lower-than-normal lesions. Correlating with this, the PWI maps show a lower than normal rCBF (determined from the rCBV and transit maps). Note however, that the entire hemisphere shows a longer transit index, indicative of a larger perfusion or hemodynamic difficult than the focal lesion seen on DWI.

Diffusion Weighted Imaging (DWI) and PWI in Stroke. Existing measures of cerebral stroke severity rely primarily on neurologic exams rather than physiological imaging. It is becoming reality that diffusion-weighted imaging (DWI) coupled with perfusion-weighted imaging (PWI) will become essential to the management of stroke patients in that an integrated exam can rapidly identify the extent, location, and circulation of the relevant lesion(s) and the underlying hemodynamic behaviors responsible for the clinical symptoms. Apparent diffusion coefficient (ADC) behavior derived from DWI can uniquely monitor the clinical evolution of tissue injury from acute ischemia to chronic infarction, and provide a rapid, non-invasive means for monitoring cellular energy failure, brain edema, and cellular necrosis. The hemodynamic patterns of tissue perfusion derived from PWI can confirm existing ADC behavior, and may predict evolving ADC behavior. A 30-minute integrated protocol of existing and improved DWI, PWI, and vascular imaging MR exams can be routinely performed in the setting of acute clinical stroke.

DWI has become a useful tool for the evaluation of acute brain ischemia in that the random movements of water are rapidly diminished in regions of acute brain ischemia, which is seen as a measured decrease in the ADC mediated by water movement from the extracellular space to the intracellular space (1-4). The crucial factor responsible for the intensity changes seen on DWI is cytotoxic edema resulting from early energy depletion during acute stroke. No changes can be seen when ischemia is too limited to produce energy depletion or cytotoxic edema (5), suggesting

that the ADC decreases only at CBF levels below a perfusion threshold. Because if the ADC threshold, reductions in CBF are not always matched by decreases in the ADC. The non-linearity results in the concept of the MR diffusion -to- perfusion "mismatch".

The Perfusion-Diffusion Mismatch in Stroke: The Clinical Value of CBF. The central goal of therapy in acute ischemic stroke is to salvage the ischemic penumbra. This can be accomplished by i) limiting the severity of ischemic injury by neuronal protection or ii) reducing the duration of ischemia and restoring blood flow to the compromised area by clot lysis and recanalization. Although they may be viable, neurons in the penumbra may act in a suboptimal manner, causing neurologic symptoms indistinguishable from those produced by infarcted tissue at clinical examination. Accordingly, it might be reasoned that DWI and perfusion imaging have implications to triage patients who would potentially benefit from advanced stroke therapy.

Perfusion abnormalities and measured CBF deficits (6) are found in most ischemic stroke patients, unless reperfusion occurred prior to the PWI study (7-11, 13-17). Almost all recent studies show acute perfusion abnormalities larger than the DWI lesions, leading many to believe that the "mismatch" represents viable tissue at risk, which may become recruited into the final infarct. Contrarily, if the PWI abnormality is the same size or smaller than the DWI lesion, the DWI lesion does not appear to expand significantly. With the combined use of DWI and PWI, many believe that it is possible to differentiate between patients with and without a sizable volume of potentially salvageable tissue.

The rationale for using PWI is that the perfusion thresholds for functional deficits in ischemia are slightly above that for reductions in ADC. Thus, if there is no DWI lesion, ischemia may still be the underlying cause of the patient's symptoms, which can be revealed by PWI. In these patients (perfusion deficit, but no DWI abnormality), blood flow appears to be impaired, but not severely enough to cause energy failure in the affected region, suggesting that most or all of the affected tissue is still potentially salvageable. It is thought that restoration of blood flow which raises the CBF above the ADC threshold can reverse the DWI-observed metabolic abnormalities. In addition, in those patients with documented reperfusion via intra-arterial thrombolytic agents, a reversal of large parts of DWI lesions has been documented (13). This suggests that the ADC is reversible when CBF rises above the critical ADC threshold within a critical period of time.
The PWI-DWI "mismatch" concept has nonetheless been clinically useful. Correlations of the PWI-DWI mismatch with the clinical impression (NIHSS and ESS) find that it is the larger of the two lesion volumes that provide the better correlation with the clinical scales. The measurements of Baird, et al., (12), Tong, et al. (11), and Barber, et al. (10) demonstrated the dynamic nature

of the ischemic lesion volume in stroke patients reporting that the DWI lesion volume increased by 200-300% when the initial PWI volume was greater than the DWI volume, but decreased by 40-80% when the initial PWI volume was smaller than or equivalent to the DWI volume. These three studies suggest that the initial PWI/DWI mismatches do indeed represent tissue at risk when PWI>DWI and that lesion growth represents recruitment of that tissue into the infarct.

The characteristic patterns of diffusion and perfusion, which may have potential implications on acute stroke therapy, might be proposed as follows:

CBF <12㎖/100g/min; CBV low, ADC 40-50% of normal, hyperintense DWI:

indicative of heavily injured or infarcted tissue

probably poor outcome

neuroprotection might be advantageous

12㎖/100g/min<CBF<20㎖/100g/min; CBV high; MTT high,

ADC normal or slightly reduced, DWI normal or slightly hyperintense:

indicative of tissue at highest risk and at limit of autoregulation and recruitment

lysis and neuroprotection may be effective

12㎖/100g/min<CBF<20㎖/100g/min; CBV low; MTT high, ADC normal, DWI normal:

an indicator of tissue at risk

lysis and neuroprotection may be effective

CBF higher than normal, normal or elevated CBV, ADC reduced, DWI hyperintense:

luxury perfusion and/or reactive hyperemia

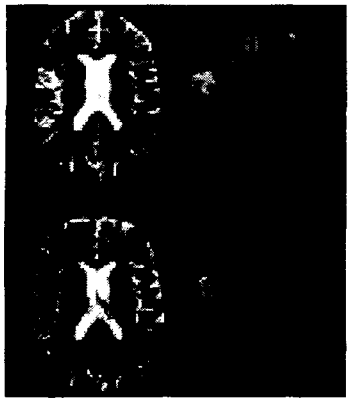
Appendix: Typical DWI PWI Stroke Protocol. In the MR exams, matching parameters are maintained wherever possible. These include FOV24 cm, TR>8000, 128x128 matrices for EPI, 1 average and slice thickness/gaps (5 mm skip 2 mm). Series of 20 slices are performed to increase coverage and reduce missed lesions in the brainstem and cord. The PWI bolus-tracking exam can acquire only a maximum of 12 slices at TR2000, however.

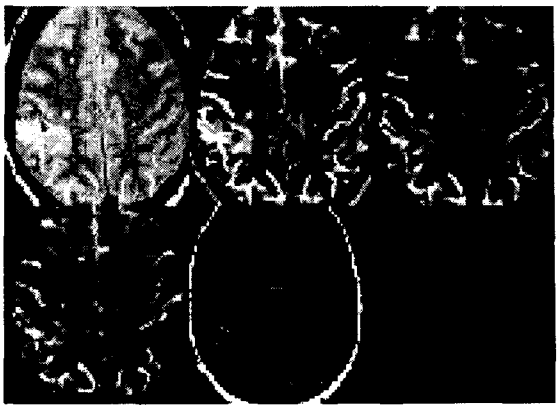
Table 1. Summary of DWI PWI Parameters

Sequence	Scan Time	Role in MR Exam
GRE Sagittal Localizer	0:36	Localizer with T2* sensitivity
3D TOF Vasc SPGR MRA 60 1mm slices; 24FOV	3:34	Vascular occlusion and stenoses Oblique coverage through Circle of Willis (COW).
Fast Spin Echo (TE17/85) 256x192; 24FOV; 5/2mm	3:12	Dual Echo- low T2* sensitivity Coverage 20slices (140mm).
FSE FLAIR (2D FSE) 256x192; 24FOV; 5/2mm	2:50	Improved T2W sensitivity Coverage 20slices (140mm).
SS FSE DWI (single-shot FSE) 128x128; 24FOV; 5/2mm X, Y, Z axes acquired.	1:40	DWI with SS FSE for comparison with EPI DWI Coverage 20slices (140mm). b=0 and b=500 sec/mm^2 acquired.
SE EPI DWI (epi2 rev) 128x128; 24FOV; 5/2mm X, Y, Z axes acquired.	0:48	Primary EPI DWI sequence Coverage 20slices (140mm). b=0, 500, and 1000 sec/mm^2 acquired.
GRE EPI (epi2 rev) 128x128, 24FOV; 5/2mm	0:06	Primary bleed screen Coverage 20slices (140mm)
Contrast-Enhanced (CE) MRA 128x256x16; 24x48FOV;	1:20	Large FOV coronal 3DMRA bolus-tracking; 5phases @ 16 seconds per phase; 0.1mmol/kg Gd
GRE EPI PWI (epi2 rev) 128x128; 24FOV; 5/2mm	1:20	Perfusion-wt bolus-tracking; 0.1mmol/kg Gd TR2000; 40phases = 80seconds.

Following a rapid GRE localizer sagittal scout series (0:36 seconds), the MRA sequence is a rapid 3D time-of-flight through the Circle of Willis (60 1mm slices from 2 slabs in 3:34 minutes). The MRA exam is used for large vessel occlusion and stenosis evaluations. The Fast Spin Echo (FSE) and FLAIR series are 256×192 resolutions with and without an initial inversion pulse (TI2200, TR10000, TE17/85, 1NEX) requiring 3:12 and 2:50 respectively.

The single-shot Fast Spin Echo (ssFSE) sequence compares favorably with the EPI DWI method in our hands (Figure 12 below left). The depiction of lesions in the brainstem and posterior circulation is superb at the expense of a slightly longer scan time (1.5 minutes for b=0 and b=500 sec/㎟). ADC maps are acquired from the varying b values either on-line from offline algorithms or on-line (on the scanner computer).





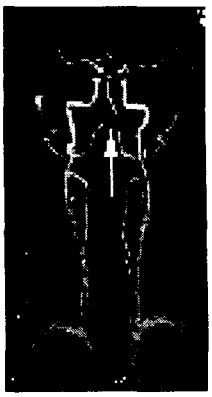


Figure 12 (Left). Comparison of single-shot EPI DWI (top) with the corresponding single-shot FSE DWI sequence (bottom) from one slice of 20 acquired. The b=0 and the b=500 sec/mm2 images are shown.

Figure 13 (Middle). MR detection of hemorrhage. Comparison of the dual-echo FSE and the T2W SE-EPI image (top row) with the corresponding GRE-EPI (TE60) and GRE (TE40) images (bottom) depict bleeds in various T2* sensitivities useful for detection as well as sizing.

Figure 14 (Right). Time-resolved contrast-enhanced MRA is becoming a useful tool in depicting vascular abnormalities in stroke. Note the tightening of the basilar artery in this arterial phase angiogram.

The SE-EPI DWI sequence is a commercially available FDA-approved product. The depiction of lesions in the brainstem and posterior circulation is less accurate than the SS FSE but is much faster (0:48 seconds for the b=0, 500, and 1000sec/㎟ series, 2 averages). ADC maps are acquired as above. For both the ssFSE and the EPI DWI series, the X, Y, and Z diffusion-weighted images are averaged, effectively eliminating all observable WM anisotropy. The b=0, the averaged and individual diffusion-weighted images, and the averaged ADC maps are available on the scanner console screen and are filmed for reading.

The GRE EPI bleed screen exam matches the EPI DWI exam for improved hemorrhage detection. A comparison of the GRE EPI, the SE EPI, and the FSE exams (matching parameters/coverage with differing T2* sensitivities) has been found by us to be effective in detecting and characterizing the true bleed location and extent (Figure 13 above middle).

For vascular depiction of relative flow from the aortic arch to the Circle of Willis, we use a large FOV (24×48) coronal-plane series of rapidly-acquired 3D MR angiograms obtained over 80 seconds (5 phases) while bolus-injecting Gd-DTPA (single-dose, 0.1mmol/kg Gd). An example is shown above in Figure 14 (above right). This sequence is ideal for depicting carotid or basilar artery stenoses or occlusions and adds critical formation to the 3DTOF MRA and PWI exams. The flow is visualized as regional shortening of T1 and has not interfered with the first-pass

T2*-shortening effect seen in the PWI series. By obtaining the contrast-enhanced MRA prior to the PWI series, both can be acquired with two separate single-dose injections.

A T2*-weighted GRE EPI pulse sequence is used for perfusion imaging with TR2000/TE60 and 12 slices, the maximum number of slices allowed by gradient duty-cycle limitations. Forty multislice image phases are obtained during bolus injection of gadolinium (single-dose, 0.1mmol/kg Gd). Bolus injections will be performed at 3ml/sec with an MR-compatible contrast power injector. The raw perfusion-weighted and calculated perfusion maps are reconstructed and displayed on the scanner console. For each slice, maps of relative blood volume (rCBV), bolus transit index (often called rMTT, as the first moment of the transit curve), and bolus arrival time (TTP in seconds) is constructed and used to look for regions of absent or markedly delayed and attenuated flow, compared to a similar region of brain in the non-ischemic hemisphere. Bolus time-to-peak (TTP) values are computed using a start time at which T2* changes are first observed in the MCA. The rMTT and the rCBF maps are further calculated from the rCBV and bolus transit index maps after measuring the arterial input behavior from either the T2*-wt EPI images. The perfusion images and maps are available for later viewing on the console.

A minimum of 20 slices is acquired for all MR exams giving coverage up to 140 mm (5mm skip 2mm slices). However, a maximum of only 12 slices can be acquired for the PWI exams yielding a coverage up to 84 mm (the twelve PWI slices are chosen to align exactly with the affected DWI EPI slices). In practice, this is sufficient, however, to cover the entire cortex where we expect observable perfusion deficits to occur. We chose the 5mm skip 2mm, 20 slices configuration to best cover the brain, allow for accurate diffusion, perfusion, and bleed comparisons.

Total exam time for the complete DWI, PWI, and bolus-tracking PWI exam is about 17 minutes. Of course, time for exam set-up, patient settling, and possible rescanning expands the MR stroke protocol to 30-45 minutes (our similar stroke protocol currently in use is presently 40 minutes only). Patient motion can affect all inter-image and intra-image studies, since series with differing b-values must be acquired for the ADC mapping. Images affected by excessive motion are presently rescanned as time allows.

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