

MR PERFUSION IMAGING

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Pak J Neurol Sci 2006; 1(3):162-6

Neuroimaging has become a powerful means to display both normal and abnormal brain physiology and function. Perfusion imaging is part of a recently developed spectrum of Magnetic Resonance (MR) imaging that allows visualization of tissue physiology and function. These techniques became available with the development of fast MR sequences, including echo planar MR imaging. These sequences allow imaging of a complete brain slice in 20 ms.¹

Perfusion-weighted magnetic resonance imaging (PW-MRI) is a technique that can provide information about the functional status of cerebral tissue with a high spatial resolution of CNS morphology. MR perfusion-weighted images (PWI) are acquired by serial imaging of the whole brain as a bolus of gadolinium contrast agent passes through the vasculature.³ The first perfusion MRI was done in 1991 by Belliveau and co-workers,² who injected an MR contrast agent and imaged the brain using echo-planar techniques to demonstrate that perception of visual stimuli increases blood volume in primary visual cortex.

Using the signal change that brain tissue experiences over time following administration of extracellular gadolinium-based contrast agents, important hemodynamics can be relatively accurately measured and mapped. Measurable parameters include cerebral blood volume (CBV), defined as the total volume of blood traversing a given region of brain, measured in milliliters of blood per 100 grams of brain tissue (ml/100 g).⁴ Another variable, cerebral blood flow (CBF),⁵ is defined as the volume of blood traversing a given region of brain per unit time, measured in milliliters of blood per 100 grams of brain tissue per minute (ml/100 g/min). Mean transit time (MTT) is more complex, but it can be thought of as the average time it takes for blood to traverse between arterial inflow and venous outflow, measured in seconds. Due to computational complications of achieving MTT, time to peak (TTP) can be directly and quantitatively derived from the measured curve and is used widely in ischemic pathologies.^{6,7}

TECHNIQUES AND PRINCIPLES

Three main techniques are used to perform MR perfusion imaging. Two of these, T2*-weighted dynamic susceptibility and T1-weighted dynamic contrast-enhanced perfusion require intravenous injection of a contrast agent. The third technique, arterial spin labeling, uses processes similar to MR angiography using time-of-flight sequences.⁵ Contrast-based techniques depend on the paramagnetic effects of gadolinium. This increases the signal on T1-weighted images and a signal drop on T2*-weighted images. Contrast-based images are more robust and therefore the most widely used in clinical applications. Of these T2*-weighted dynamic susceptibility imaging is preferred as it is possible to perform multiple samplings in a very short time allowing time activity curves to be calculated for the entire brain.

In this technique, T2* susceptibility effects of gadolinium are exploited, rather than utilizing the T1 shortening effects associated with contrast enhancement assessed in conventional imaging. A double-dose of gadolinium (0.2 mmol/kg) is typically injected, via an 18 or 20-gauge IV catheter, at a high rate (3-7 ml/sec) using a power injector. Serial images are then acquired during the first pass of contrast material through the brain. A time intensity curve is generated by mapping the drop in T2* signal caused by susceptibility effects of gadolinium on a voxel by voxel basis. The relative cerebral blood volume is then obtained by calculating the area under the curve and it is normalized with the contralateral non-diseased side. As arterial input function is not used in this method, the term 'relative' is used.

Another entirely different approach consists of T1-weighted contrast imaging primarily involved in evaluating disruption of blood brain barrier. A low dose of gadolinium (0.1 mmol/kg) is used and the injection is given over a slow rate. Multiple acquisitions are made in order for the contrast to leak out in extra vascular space and attain equilibrium.

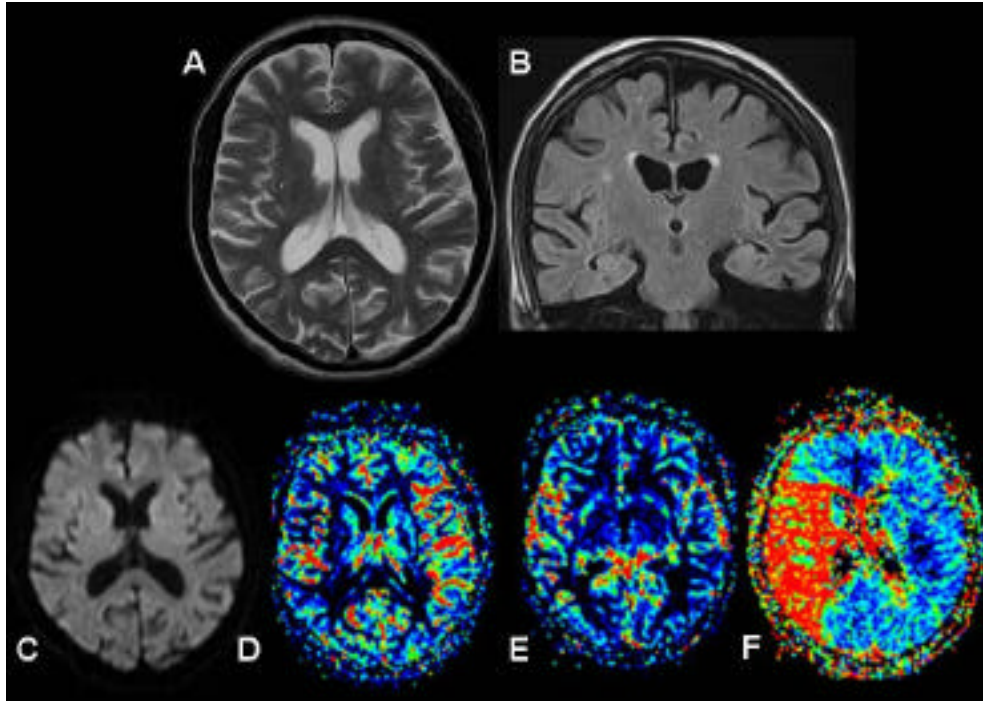


Figure 1

MR of the brain with diffusion and perfusion images demonstrating the ischemic penumbra. A 60-year-old male with acute onset of left-sided hemiparesis for 30 minutes. A: T2-weighted axial image is within normal limits. B: Coronal FLAIR images also within normal limits. C: b1000 Diffusion-weighted image shows no significant diffusion restriction. D: CBF map showing asymmetry with reduced blood flow in the right temporal and parietal lobes. E: CBV map showing asymmetry with some increased CBV in the corresponding area. F: MTT map demonstrating marked prolongation of MTT. Findings are those of impending infarction with no restriction of diffusion, reduced blood flow, or preserved blood volume. This is the area at risk - the penumbra.

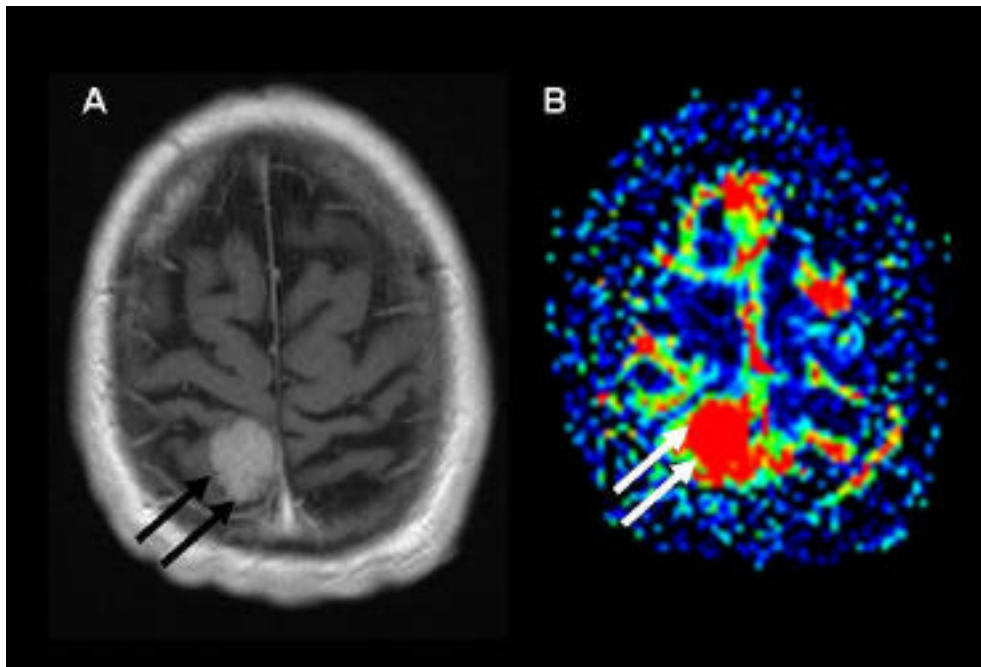


Figure 2

Perfusion-weighted MR scan showing hyper-vascularity in a tumour. A: T1-weighted contrast enhanced axial image. Enhancing lesion in the left para-sagittal lesion (black arrows). B: CBV map showing marked increase in the blood volume in the same lesion (white arrows). Diagnosis: Meningioma.

An inventive way of applying perfusion imaging is the arterial spin labeling technique (ASL).⁸ With ASL, a powerful magnetic gradient is applied to inflowing blood to invert its magnetization, effectively tagging the blood flowing upstream. This provides similar information as the above mentioned techniques with ASL flow maps showing better conspicuity than rCBV maps. However, due to long imaging times and decreased spatial resolution, widespread clinical applications have been halted.

CLINICAL APPLICATIONS OF PERFUSION IMAGING

Stroke

Significant research endeavors have been made in the subject of stroke due to its grave impact on the modern economy and society. While focusing on basic and clinical neuroscience, the core objective is to improve outcome at all stages of ischemic brain disease, not least in the acute stage of stroke. Mohr and colleagues⁹ documented that 85% of strokes were thromboembolic in origin resulting in ischemia with a significant time window between the onset of ischemia and death of cerebral tissue. Active explorations have been carried out to utilize this time frame with the discovery of better treatment options in ischemic disease in the acute stage with reperfusion or neuron protection.

Implementation of these advances requires a definitive diagnostic tool for assessing the degree of ischemia, reversibility of cerebral damage, distinguishing new infarcts from other lesions such as older stroke and hemorrhagic lesions, and mapping out the size and distribution of each of these in the brain.

Conventional CT and MR imaging have played a significant role in the detection of cerebral ischemia but have fallen short in significant parameters.¹⁰ Diffusion-weighted imaging, although of great accuracy, fails to depict the true size of the infarct with underestimation of the lesion.

Increase in resistance to blood flow may result in reduced perfusion to cerebral tissue. This may be due to gradual stenosis of a vessel or sudden occlusion as in embolism. Initially cerebral tissue is protected by various compensatory mechanisms such as decreased resistance to flow by dilatation of arterioles and venules hence maintaining CBF. As more time passes, the mechanism exhausts, resulting in decreasing CBF and electrical dysfunction.

The infarcted region is usually surrounded by a ring of reversible ischemic tissue known as the ischemic penumbra. This penumbral tissue is very transient and

rapidly deteriorates with time, while the risk of hemorrhage within the infarcted tissue increases.¹¹ Perfusion-weighted MR imaging provides information on the momentary hemodynamic state of brain tissue, since perfusion-weighted images reveal impaired tissue perfusion caused by arterial blood vessel obstruction. Therefore, perfusion-weighted imaging yields information about pathologically hypoperfused regions even before genuine structural brain tissue damage has taken place, and in particular during the first few hours after stroke onset.

In the literature the combination of diffusion and perfusion has been emphasized, as the mismatch between the two reveals the penumbral area.¹² Recent studies have proven that this combination results in overestimation of cerebral tissue and various perfusion parameters should be employed to determine the actual at-risk tissue prior to initiation of thrombolytic therapy.

Grandin et al¹³ suggested that the best perfusion parameter to determine penumbral tissue would be calculation of peak height and TTP from the measured concentration versus time tissue curves. Another study, conducted by Rüdiger et al,¹⁴ shows that a TTP of > 6 seconds is related to severe ischemia and warrants immediate intervention at this point to salvage valuable brain tissue.

Cerebral malignancies

Conventional MR imaging, although an established and worthy tool used in the diagnosis of brain tumors, fails to depict the correct classification and grading of gliomas despite optimization of sequences and protocols. The literature suggests a sensitivity of grading from 55.1% to 83.3%. Conventional MR imaging focuses on contrast enhancement, mass effect, peritumoral edema and necrosis in tumors rather than analysis of the physiological changes seen in brain tumors. Ginsberg et al¹⁵ demonstrated that lack of enhancement of supratentorial gliomas does not equate with low-grade gliomas. In another study, all low-grade tumors showed contrast material enhancement, but almost one-fifth of glioblastoma multiforme tumors did not.¹⁶

As novel therapies for patients with brain tumors are being developed, the role of imaging has begun to shift to provide information on tumor physiology, as well as anatomy. Perfusion methods are ideally suited to such physiological imaging. Other radiological techniques to evaluate tumor physiology, such as MR spectroscopy and ¹⁸F-fluorodeoxyglucose positron-emission tomography (FDG-PET) have also been utilized.

MR spectroscopy (MRS) relies on detection of metabolites within tumor tissue. MRS is often non-specific in physiology with poor spatial resolution. FDG-PET is based on tumor glucose metabolism and is also limited in availability, with poor spatial resolution of images.

In order to understand the application of perfusion imaging in CNS malignancies, a background of tumor physiology needs to be addressed.⁸ At commencement, the tumor derives its metabolic needs from preexisting vessels. After attaining a size of approximately 1-4 cm, the tumor starts outgrowing its preexisting supply, and the ensuing ischemia induces angiogenic factors that lead to neo-vascularization. These cytokines, such as vascular endothelial growth factor (VEGF), maintain and recruit the tumor blood supply as it grows. The net result of angiogenesis is a complex network of abnormal vessels in the peritumoral space with tumor vessels being more tortuous than normal vessels, thus affecting the distance that blood must traverse as it moves through the tumor. Vascular imaging reveals the visual correlate of vascular dilatation, increased blood volume and permeability. Based on these physiological principles, the application of rCBV, CBF and MTT are determined.

Various clinical applications have been analyzed in brain tumors. A very significant aspect is the preoperative grading of gliomas with differentiation between high-grade and low-grade tumors. Two major limitations are associated with histopathologic grading of gliomas: inherent sampling error associated with stereotactic biopsy, and inability to evaluate residual tumor tissue after cytoreductive surgery. Malignant gliomas are known to infiltrate the parenchyma by following vascular channels along white matter tracts. This may not be readily appreciated if there is no signal abnormality or contrast enhancement on conventional MR images. Hence, histopathologic grading of gliomas has disadvantages and intrinsic error. The advantage of state-of-the-art MR imaging techniques in evaluating cerebral gliomas is the ability to sample not only the entire lesion, but also the adjacent brain tissue for physiologic and morphologic alterations.

Due to histological variation between gliomas, a single lesion may contain foci of increased vascularity with heterogeneous rCBV maps. In such cases, the area with the highest rCBV value will decide the tumor grade. Law et al¹⁷ studied the accuracy of glioma grading utilizing perfusion parameters and revealed a sensitivity of 95%, indicating a high true-positive rate and low false-negative rate. Another literature review⁵ reports the sensitivity of pre-operative glioma grading as 100%. The rCBV values in these studies were taken to be 1.75 and 1.5, respectively. Erroneous sampling of the tumors during stereotactic biopsy is another clinical dilemma faced during conventional MR imaging. Histopathological grading will

prove to be inaccurate if the biopsy is not obtained from the most malignant region or the tumor has been incompletely resected. CT-guided stereotactic needle biopsy, a widely used method for evaluating brain neoplasms, relies on the assumption that the contrast-enhancing portion of the tumor corresponds to the most aggressive cell population. As already mentioned, contrast enhancement alone or the lack thereof is not a reliable indicator of tumor grade. MR perfusion imaging aids accurate sampling of tumors by revealing areas of high rCBV without evidence of gadolinium enhancement. Covarrubias⁵ reviewed that in a particular population of patients all of the 13 high-grade gliomas were correctly identified for biopsy, 3 of which did not enhance after contrast administration.

A significant clinical challenge lies in the distinction of radiation necrosis versus tumor recurrence, which leads to profound confusion on conventional neuro-imaging. Due to damage to the blood brain barrier there is contrast accumulation in the interstitium that can simulate a ring-enhancing lesion masquerading as recurrent tumor. Furthermore, the time frame of both changes is virtually the same, from 6 months to 3 years. Sugahara et al¹⁸ used gradient-echo dynamic susceptibility imaging to compare the two conditions and found that rCBV of > 2.6 gave a definite indication of tumor recurrence, while that of < 0.6 correlated with radiation necrosis. However, considerable overlap was found between the two values and thallium SPECT imaging had to be utilized in intermediate cases, rendering MR perfusion as an imperfect means for distinction.

Perfusion MR is a non-invasive imaging method for characterizing the functional properties of malignant processes, providing diagnostic information not available on conventional MRI and offering a functional parameter for assessing tumor grade and focal activity along with significant data on tumor grade and survival of the patient.

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