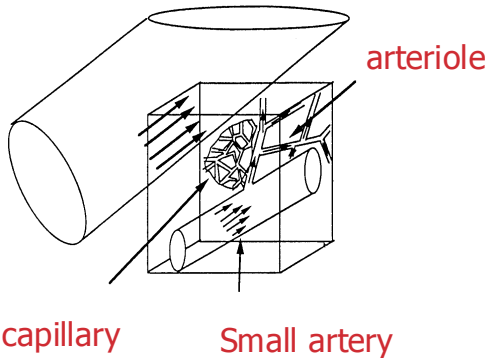


Absolute Beginners Guide to Perfusion Imaging

Dr. Laura M Parkes, Biomedical Imaging Institute, University of Manchester

What is Perfusion?



Perfusion is usually used synonymously with 'blood flow' to describe the supply of blood to the tissue. 'Supply' is an important part of the definition as we regard only blood which reaches the capillary network within our tissue voxel as contributing the perfusion. In this way the measurement is closely related to the metabolism of the tissue, which makes it a particularly useful measurement.

Units: ml of blood/ minute/ 100 ml of tissue.

There are two principle techniques for measuring perfusion using MRI: i) using an intravascular contrast agent as a tracer and ii) using labeled water in the blood as an endogenous tracer (arterial spin labeling or ASL). I will summarize each of these in turn and then discuss the relative merits and disadvantages of each.

Perfusion imaging with contrast agents: Dynamic-Susceptibility Contrast MRI or DSC-MRI

A bolus of intravascular tracer, usually a compound containing Gadolinium, is injected into the blood and T2 or T2*-weighted MRI is used to image the passage of the tracer as it passes through the vasculature. Fast imaging techniques are required in order to provide sufficient temporal resolution to capture the passage of the tracer. Following the tracer kinetic model of (Zieler, 1962), assuming the tracer remains intravascular, it is possible to calculate regional perfusion.

What can be measured?

As well as blood flow, a number of other physiological parameters can be measured:

- Blood volume – this is the relative volume of blood within the tissue, in units of ml/100ml of tissue. This is an important parameter as it is indicative of vasodilation which plays a key role in auto-regulation of blood flow to tissue.
- Mean transit time (MTT) is the time taken for blood to traverse the capillary bed.
- Temporal summary parameters including bolus arrival time and time to peak can also be measured, relative to the bolus injection or to the relative difference in timing of the tissue concentration upstroke in comparison to the arterial concentration. These parameters can provide information on the large vessels supplying the tissue.

How does it work?

Paramagnetic contrast agents reduce the T2 and T2* of tissue as they pass through in the vasculature. Contrast agents have different susceptibility than tissue and compartmentalization of the agent in capillaries leads to magnetic field inhomogeneities. These inhomogeneities cause dephasing and signal loss in T2*-weighted gradient echo images. A combination of field inhomogeneity and diffusion effects cause signal loss in T2-weighted spin echo images (Boxerman et al, 1995). T2 or T2*-weighted sequences are used and the concentration of contrast agent is calculated from the MR signal changes.

Quantification

There is a linear dependence of $\Delta R2^{(*)}$ on the concentration of the tracer (Rosen et al, 1990), hence by using the $R2^{(*)}$ value of the tissue before the arrival of the contrast as a reference, the concentration of the contrast agent in the tissue can be calculated. The area under the tissue concentration time-course is equivalent to the blood volume. In order to quantify perfusion the arterial input function (AIF) needs to be measured, i.e. the concentration time-course of the tracer as it passes through a large feeding artery. This can be found by selecting voxels in or near a large artery. Deconvolution of the AIF from the tissue concentration time-curve produces a function whose maximum value is equivalent to blood flow. The mean transit time can then be found as the ratio of blood volume to blood flow.

It should be noted that absolute quantification is unreliable as the AIF is not well characterized and the relaxivity in arterial blood and tissue is unknown (and often assumed to be equivalent) (Kennan and Jager, 2003). An assumed value for haematocrit is required for absolute quantification. Leakage of the tracer across the capillary wall (more of a problem outside the brain) and recirculation also limit the ability to quantify perfusion.

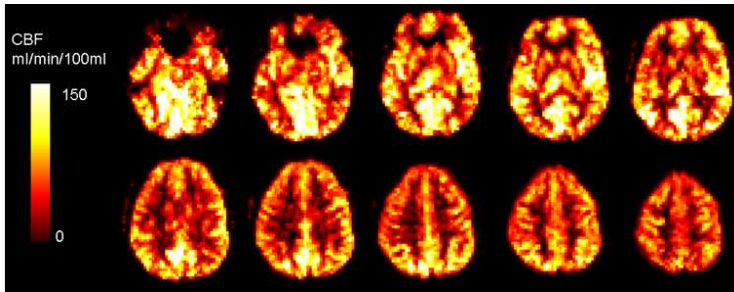
Spin echo techniques are more sensitive to the microvasculature than gradient echo techniques, but suffer from poorer contrast to noise (Boxerman et al, 1995). Gradient echo techniques will show high signal in large vessels that are not perfusing the tissue they are passing through, and hence may not represent a true measure of microvascular perfusion.

Applications

DSC-MRI has been applied much more widely than ASL, and is routinely used in clinical practice, particularly for the diagnosis and management of cerebrovascular disease. For a review of applications, see (Kennan and Jager, 2003). Key applications include acute

stroke where DSC can provide an immediate picture of regional tissue perfusion. When combined with diffusion-weighted imaging, DSC can be used to identify the ischaemic penumbra, representing potentially salvageable tissue. Other key applications include the characterization of haemodynamic disturbances following arterial occlusion, migraine, AVMs, the grading of brain tumors, dementia and trauma.

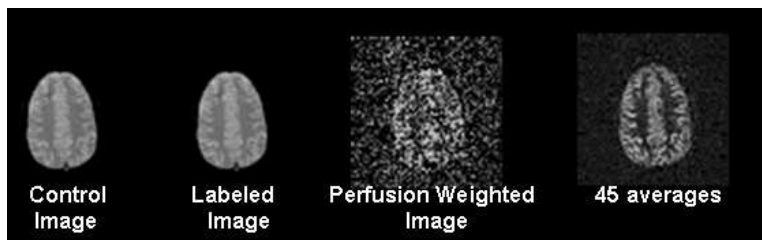
Perfusion imaging without contrast agent: arterial spin-labeling



An example ASL perfusion image at 3 Tesla.

How does it work?

The technique involves collection of a pair of images – a ‘label’ and ‘control’ image. The signal in the label image includes additional signal from ‘labelled’ blood that has entered the slice of interest. The control image contains the same signal (from background tissue etc) without the additional signal from the labelled blood. Thus, on subtraction of the two images we obtain a perfusion-weighted image as shown below. To be a little more precise, the labelled blood is carrying *negative* signal (the spins are inverted) and so the signal in the labelled image is slightly reduced compared to the control image.



Arterial Spin Labeling (ASL) is similar in essence to contrast agent studies of perfusion: a ‘tracer’ is introduced into the blood and the concentration of this tracer is tracked over time as it passes through the tissue of interest; usually the brain. In the case of ASL the tracer is endogenous water in the blood, which is labelled magnetically. Kinetic models suitable for freely diffusible tracers are used to calculate regional perfusion.

The difference in signal between the two images is on the order of only 1%, such that the perfusion-weighted subtraction image (left) is very noisy. Typically a number of averages are required to create a perfusion-weighted image with reasonable SNR. Recent developments include ‘background tissue suppression’ (Garcia, Duhamel et al. 2005) which uses a saturation pulse to reduce the signal from the static tissue. This increases the SNR.

The Labeling Pulse

Labeling is applied either Continuously through a plane – CASL, or Pulsed through a labeling volume - PASL. One problem for both techniques is to match the Magnetization Transfer (MT) effects of the labeling pulse in the control image. The labeling pulse causes off-resonant saturation of macromolecular spins in the tissue in the slices of interest. This then attenuates the free-water signal via MT.

CASL uses a spatially localized RF field to continuously invert the longitudinal magnetization of the protons in arterial blood water. MT effects are overcome by either using a separate labeling coil or a double inversion pulse in the control image (Alsop and Detre 1998). CASL is particularly suited to whole brain resting state perfusion measurements.

PASL techniques ‘label’ a large volume of spins using a short RF pulse. In the simplest FAIR technique (Kim 1995; Kwong, Chesler et al. 1995; Schwarzbauer, Morrissey et al. 1996) the labeling pulse is non-selective, whereas the control inversion covers only the slices of interest. There are a number of variants in labeling geometries. A number of strategies to reduce the sensitivity to transit time effects have been developed (Alsop and Detre 1996; Luh, Wong et al. 1999).

PASL is particularly suited to functional ASL studies, tracking perfusion changes over time.

Key advantages of PASL and CASL:

| PASL | CASL |
|--|--|
| Higher temporal resolution – good for fMRI | Easier to achieve whole brain coverage |
| Low power deposition – better at high fields | Higher CNR |
| Shorter transit times from label to tissue | |

With both techniques care must be taken to remove signal from large vessels, either by including diffusion gradients to dephase large vessel signal or by introducing a delay between labeling and signal collection to give time for labeled blood in large vessels to flow into smaller vessels. Recent technological developments include vessel-selective labeling (Wong 2007) and 3D acquisition (Gunther, Oshio et al. 2005) for whole brain coverage.

Quantification

In order to turn the subtraction images into accurate perfusion maps a number of factors need to be measured or assumed, including: i) the degree of arterial spin inversion, ii) the transit time from label to slice, iii) the T1 of blood and tissue, iv) the equilibrium

magnetization of arterial blood. Most applications use a single tissue compartment model (Detre, Leigh et al. 1992). Further developments include corrections for arterial transit time and restricted water diffusion (Parkes 2005). As well as blood flow, it is also possible to measure the arterial transit time from the labelling plane to the tissue. It is not possible to measure blood volume using arterial spin labeling as water does not remain intravascular.

Applications

A recent multi-centre reproducibility study showed promising results (Petersen and Golay 2008) providing the reliability measures needed to proceed to clinical studies an routine clinical use. Research applications, both clinical and basic science are increasing; a recent review paper (Brown, Clark et al. 2007) summarizes major research areas. These include:

Cerebrovascular disease: ASL has been used to study perfusion changes following stroke or carotid stenosis, correlating measures with clinical outcome. **Dementia:** A number of studies have found regions of hypo-perfusion in both Alzheimer's disease and mild cognitive impairment (Alsop, Detre et al. 2000; Johnson, Jahng et al. 2005; Du, Jahng et al. 2006). **Cancer:** ASL has been used to determine the grade of tumors (Chawla, Wang et al. 2007; Kim, Kim et al. 2008) and also to monitor the effect of treatment over time (Tourdias, Rodrigo et al. 2008). **Development and Aging:** The non-invasiveness of ASL lends itself to the study of development in babies and children (Miranda, Olofsson et al. 2006; Biagi, Abbruzzese et al. 2007); other work shows a decline in CBF with age (Parkes, Rashid et al. 2004). **Ex-Brain:** Studies outside of the brain are also increasing, including measurements of blood flow in muscle (Marro and Kushmerick 1997; Boss, Martirosian et al. 2006), kidney (Roberts, Detre et al. 1995; Michaely, Schoenberg et al. 2004), heart (McCommis, Zhang et al. 2008), retina (Li, Cheng et al. 2008), liver and lung. **Functional brain imaging:** One particular area of growth and interest is in the use of ASL for functional imaging where for certain applications it can provide valuable advantages. These include very low frequency tasks where the BOLD signal is unsuitable due to drift (Wang, Aguirre et al. 2003). For example the tracking of slow changes in mood, or the effect of a slow-acting drug infusion. In addition to this, for clinical fMRI studies where neurovascular coupling is altered, ASL is becoming an important tool for quantification of the component parts of the BOLD signal, allowing separate quantification of blood flow and oxygenation changes (Davis, Kwong et al. 1998; Buxton, Uludag et al. 2004).

While a larger number of applications have been highlighted here for ASL than for DSC, it should be noted that this is not representative as DSC applications are far more numerous.

The main advantages of ASL compared to DSC-MRI are:

1. Non-invasive
2. Provides quantitative measurements of blood flow
3. Serial measurements can be produced – can be used for fMRI

The main disadvantages are:

1. Low SNR
2. Long time required to produce reasonable maps (5 – 10 minutes)
3. Sensitivity to transit time from the labeling plane
4. Expertise required for implementation and analysis – not yet fully adopted by manufacturers

References

- Alsop, D. C. and J. A. Detre (1996). "Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow." *J Cereb Blood Flow Metab* **16**(6): 1236-1249.
- Alsop, D. C. and J. A. Detre (1998). "Multisection cerebral blood flow MR imaging with continuous arterial spin labeling." *Radiology* **208**(2): 410-416.
- Alsop, D. C., J. A. Detre, et al. (2000). "Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging." *Annals of Neurology* **47**(1): 93-100.
- Biagi, L., A. Abbruzzese, et al. (2007). "Age dependence of cerebral perfusion assessed by magnetic resonance continuous arterial spin labeling." *Journal of Magnetic Resonance Imaging* **25**(4): 696-702.
- Boss, A., P. Martirosian, et al. (2006). "Quantitative ASL muscle perfusion imaging using a FAIR-TrueFISP technique at 3.0T." *Nmr in Biomedicine* **19**(1): 125-132.
- Boxerman J.L., Hamberg, L.M., et al. (1995). "MR contrast due to intravascular magnetic susceptibility perturbations." *Magnetic Resonance in Medicine* **34**:555-566.
- Brown, G. G., C. Clark, et al. (2007). "Measurement of cerebral perfusion with arterial spin labeling: Part 2. Applications." *Journal of the International Neuropsychological Society* **13**(3): 526-538.
- Buxton, R. B., K. Uludag, et al. (2004). "Modeling the hemodynamic response to brain activation." *Neuroimage* **23**: S220-S233.
- Chawla, S., S. Wang, et al. (2007). "Arterial spin-labeling and MR spectroscopy in the differentiation of gliomas." *American Journal of Neuroradiology* **28**(9): 1683-1689.
- Davis, T. L., K. K. Kwong, et al. (1998). "Calibrated functional MRI: Mapping the dynamics of oxidative metabolism." *Proceedings of the National Academy of Sciences of the United States of America* **95**(4): 1834-1839.
- Detre, J. A., J. S. Leigh, et al. (1992). "Perfusion Imaging." *Magnetic Resonance in Medicine* **23**(1): 37-45.
- Du, A. T., G. H. Jahng, et al. (2006). "Hypoperfusion in frontotemporal dementia and Alzheimer disease by arterial spin labeling MRI." *Neurology* **67**(7): 1215-1220.

- Garcia, D. M., G. Duhamel, et al. (2005). "Efficiency of inversion pulses for background suppressed arterial spin labeling." *Magnetic Resonance in Medicine* **54**(2): 366-372.
- Gunther, M., K. Oshio, et al. (2005). "Single-shot 3D imaging techniques improve arterial spin labeling perfusion measurements." *Magnetic Resonance in Medicine* **54**(2): 491-498.
- Johnson, N. A., G. H. Jahng, et al. (2005). "Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: Initial experience." *Radiology* **234**(3): 851-859.
- Kennan R.P. and Jager H.R. (2003). Chapter 3 of "Quantitative MRI of the Brain", Wiley, editor P.S. Tofts.
- Kim, M. J., H. S. Kim, et al. (2008). "Diagnostic accuracy and interobserver variability of pulsed arterial spin labeling for glioma grading." *Acta Radiologica* **49**(4): 450-457.
- Kim, S. G. (1995). "Quantification of Relative Cerebral Blood-Flow Change by Flow-Sensitive Alternating Inversion-Recovery (Fair) Technique - Application to Functional Mapping." *Magnetic Resonance in Medicine* **34**(3): 293-301.
- Kwong, K. K., D. A. Chesler, et al. (1995). "Mr Perfusion Studies with T-1-Weighted Echo-Planar Imaging." *Magnetic Resonance in Medicine* **34**(6): 878-887.
- Li, Y. X., H. Y. Cheng, et al. (2008). "Mood-flow magnetic resonance imaging of the retina." *Neuroimage* **39**(4): 1744-1751.
- Luh, W. M., E. C. Wong, et al. (1999). "QUIPSS II with thin-slice T11 periodic saturation: A method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling." *Magnetic Resonance in Medicine* **41**(6): 1246-1254.
- Marro, K. I. and M. J. Kushmerick (1997). "Skeletal muscle perfusion measurements using adiabatic inversion of arterial water." *Magnetic Resonance in Medicine* **38**(1): 40-47.
- McCommis, K. S., H. Zhang, et al. (2008). "Feasibility study of myocardial perfusion and oxygenation by noncontrast MRI: comparison with PET study in a canine model." *Magnetic Resonance Imaging* **26**(1): 11-19.
- Michaely, H. J., S. O. Schoenberg, et al. (2004). "Renal disease: Value of functional magnetic resonance imaging with flow and perfusion measurements." *Investigative Radiology* **39**(11): 698-705.
- Miranda, M. J., K. Olofsson, et al. (2006). "Noninvasive measurements of regional cerebral perfusion in preterm and term neonates by magnetic resonance arterial spin labeling." *Pediatric Research* **60**(3): 359-363.
- O'Gorman, R. L., V. Kumari, et al. (2006). "Personality factors correlate with regional cerebral perfusion." *Neuroimage* **31**(2): 489-495.
- Parkes, L. M. (2005). "Quantification of cerebral perfusion using arterial spin labeling: Two-compartment models." *Journal of Magnetic Resonance Imaging* **22**(6): 732-736.
- Parkes, L. M., W. Rashid, et al. (2004). "Normal cerebral perfusion measurements using arterial spin labeling: reproducibility, stability, and age and gender effects." *Magn Reson Med* **51**: 736 - 743.
- Petersen, E. T. and X. Golay (2008). "Is Arterial Spin Labeling Ready for Primetime? Preliminary Results from the QUASAR reproducibility study." *Proceedings of the ISMRM*.
- Roberts, D. A., J. A. Detre, et al. (1995). "Renal Perfusion in Humans - Mr-Imaging with Spin Tagging of Arterial Water." *Radiology* **196**(1): 281-286.
- Rosen B.R., Belliveau J.W., et al (1990). "Perfusion Imaging with NMR contrast agents." *Magnetic Resonance in Medicine* **14**:249-265.
- Schwarzbauer, C., S. P. Morrissey, et al. (1996). "Quantitative magnetic resonance imaging of perfusion using magnetic labeling of water proton spins within the detection slice." *Magnetic Resonance in Medicine* **35**(4): 540-546.
- Tourdias, T., S. Rodrigo, et al. (2008). "Pulsed arterial spin labeling applications in brain tumors: Practical review." *Journal of Neuroradiology* **35**(2): 79-89.
- Wang, J. J., G. K. Aguirre, et al. (2003). "Arterial spin labeling perfusion AM with very low task frequency." *Magnetic Resonance in Medicine* **49**(5): 796-802.
- Wong, E. C. (2007). "Vessel-encoded arterial spin-labeling using pseudocontinuous tagging." *Magnetic Resonance in Medicine* **58**(6): 1086-1091.
- Zierler, K.L. (1962). "Theoretical basis of indicator-dilution methods for measuring flow and volume." *Circ Res* **10**:393-407.