Arterial spin labeling: state of the art

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Abstract
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J Radiol 2009;90:1031-7

Arterial spin labeling (ASL) perfusion MR imaging is a technique by which water from circulating arterial blood is magnetically labeled and acts as a diffusible tracer allowing non-invasive measurement of cerebral blood flow. In this paper, the technique and current applications in neuroimaging will be reviewed.

Current status. First, the technical principles of ASL will be reviewed and both available techniques (continuous and pulsed ASL) explained. A review of the literature will demonstrate advances with the techniques of ASL and its clinical impact. Clinical research involves normal volunteers and patients with ischemic and tumoral pathologies.

Conclusion. Recent technical advances have improved the sensitivity of ASL perfusion MR imaging. The routine clinical use of ASL at 3.0 Tesla should increase over the next few years.

Key words: MRI. Perfusion. Arterial spin labeling. Cerebral blood flow.

Abbreviations
- ASL : arterial spin labeling
- CASL : continuous arterial spin labeling
- PASL : pulsed arterial spin labeling
- EPI : echo planar imaging
- CBF : cerebral blood flow
- CBV : cerebral blood volume
- MTT : mean transit time
- TTP : time to peak
- PET : positron emission tomography

Medicinal imaging allows the acquisition of morphological and functional data. The value of perfusion imaging has been established in the evaluation of cerebral ischemia, and more recently in the evaluation of follow-up of brain tumors. Perfusion MR imaging can be performed with techniques that require the intravenous injection of contrast and techniques that do not. The latter group includes techniques of arterial spin labeling or ASL, a technique developed over 20 years ago but becoming more accessible with the availability of higher field MR units. The clinical applications of ASL are under evaluation. Two techniques are currently available: continuous ASL and pulsed ASL. The principles of both techniques will be discussed. Technical advances have increased the signal from ASL and improved the acquisition of ASL sequences. Several clinical studies were published, on volunteers to demonstrate its feasibility, and on patients with ischemic and tumoral pathologies to compare with results from dynamic susceptibility-weighted contrast material-enhanced MR perfusion.


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Technical principles
Labeling
Perfusion MR imaging can be performed using a non-invasive technique where water nuclei in arterial blood are magnetically tagged before they enter into the tissue of interest. After a certain transition time through the plane of interest, the amount of labeling is measured and compared to a control image obtained without spin labeling. A subtraction of both images is performed and the tagged spins are identified because of their different magnetization. The signal intensity on the subtracted image is proportional to perfusion. This technique allows calculation of absolute cerebral blood flow (CBF) (fig. 1).

Continuous arterial spin labeling (CASL)
CASL is based on an adiabatic inversion pulse from a continuous low intensity RF pulse at the neck to tag arterial blood.
Because of continuous labeling, signal in the slice of interest will reach equilibrium. The labeling plane should as close as possible to the slice of interest (without introducing a magnetization transfer effect) while allowing enough time for the tagged spins to reach the region of acquisition, diffuse in tissue water and exit the intravascular compartment. Pseudo-continuous ASL is a technique where a train of short RF pulses is repeated. It is an alternative to implement CASL that combines the advantages of CASL and PASL with reduction of magnetization transfer effect and sensitivity to transit times while preserving a good SNR due to the prolonged labeling period (1).

**Pulsed arterial spin labeling (PASL)**

PASL is based on a short RF pulse with signal acquisition after a time delay TI. Again, the difference of signal on images prior to and after labeling indicates the quantity of tagged blood that reached the volume of interest after the time delay TI. PASL is less affected by magnetization transfer effects than CASL. However, similar pitfalls occur from variations in transit times. The effects of transit time variations may be decreased by the application of a saturation pulse on both tagged and control images, corresponding to the QUIPSS versions I and II (Quantitative Imaging of Perfusion using a Single Subtraction) (2). PASL is more advantageous in clinical practice and it is the most routinely used technique. In 1994, Edelman et al. (3) proposed this technique in association with a fast echo-planar imaging (EPI) technique, or EPISTAR (Echo Planar Imaging and Signal Targeting with Alternating Radiofrequency). Starting in 1995, other authors proposed a different technique with inversion-recovery (4-6). The latter is characterized by the use of a selective inversion pulse at the level of the slice of interest followed by a non-selective inversion pulse over the entire brain. Subtraction of both acquisitions results in a signal intensity proportional to perfusion. This technique is named FAIR (Flow sensitive Alternating Inversion Recovery). A wide variety of pulse sequences have emerged since then, most derived from the ones described above (PICORE, UNFAIR, BASE, STAR-HASTE, TILT or SMART). Confusion relating to these acronyms is unavoidable. As such, two different techniques are named FAIRER (7, 8), and the EST technique is similar to the UNFAIR technique (9).

**Acquisition and quantification**

A volumetric acquisition is possible with the acquisition of a stack of images over the region of interest. The labeling region (saturation band) should be proximal and as close as possible to the acquisition volume. Some manufacturers recommend an acquisition beginning 1 cm above the base of the cerebellum, making complete posterior fossa evaluation difficult. Quantification is made possible by the acquisition of non-labeled control images using parameters similar to the labeled images. Raw data from labeled and control acquisitions are saved, immediately reconstructed and converted into DICOM images. Both reconstructed acquisitions are then converted into quantitative CBF maps using an algorithm that varies with the type of sequence. It may be as follows.
Review of the literature and current technical advances

Technical advances

ASL was developed in the 90’s with both continuous and pulsed techniques to quantify perfusion. Since then, most advances were aimed at improving the SNR ratio. SNR is low due to the use of image subtraction with a small measurable difference between tagged and non-tagged images. This was first achieved with the use of high field MR units. In 2002, Wag et al. (13) were the first to compare ASL at 1.5T and 4.0T. They reported that the SNR ratio of grey matter on PASL at 4.0T was superior to the SNR ratio on CASL at 1.5T, which in turn is superior to the SNR ratio on PASL at 1.5T. The CNR ratio between grey and white matter was also superior on PASL at 4.0T. They discussed the possibility that magnetic susceptibility artifacts and physiologic noise could cause these differences. Another method to improve SNR is to reduce signal degrading distortions. In 2000, Ye et al. (14) suggested the use of a multiple-inversion background suppression technique (ASSIST method). However, the most significant improvements in spatial and temporal resolution results from the availability of phased-array surface coils combined with parallel imaging (15-19). Due to the geometry of the phased-array coils and absence of correlation of the noise recorded by each element, the SNR ratio will be superior to the SNR ratio of a large single element coil. Parallel imaging allows shorter RF pulses with improved multidimensional spatial discrimination and correction of patient related field inhomogeneities. This is most useful with the pseudo-CASL technique where multiple short RF pulses are used. In a recent publication, Wolf and Detre (15) reviewed recent technical advances in the field of ASL and showed that by combining high field strength, parallel imaging, pseudo-CASL and 3D imaging with background noise suppression, signal is 10-fold greater.

More recently, new methods have been developed to improve quantification with ASL. In 2006, Wong et al. (20) proposed a new method to quantify perfusion in patients with collateral or slow flow conditions (transit delay). Velocity-selective tags are applied that do not require spatial selectivity with threshold velocity under which tagged spins are not considered into the image.

Selective ASL allowing evaluation of regional perfusion is the latest innovation. By selectively tagging each vessel of the circle of Willis, a perfusion map of each vessel can be obtained. New functional hemodynamic parameters can then be assessed such as collateral flow, diseased vessel(s) (while considering inter-individual variation in vascular distribution), enabling distinction between thrombo-embolic and hemodynamic etiologies of CVA (21, 22).

A new dynamic MRA sequence based on ASL obtained early as the tagged protons are still intravascular in distribution can assist in determining the time delay in the arrival for each vessel (based on intravascular signal intensity) with creation of color-coded maps. This technique would be equivalent to transcranial Doppler US and superior to TOF MRA for the detection of collateral flow (23).

Clinical applications

Studies on normal volunteers

One of the first studies performed in 2000 on 12 healthy volunteers showed concordant results for CBF measurements between ASL at 1.5T MR and oxygen-15 water ($^{15}$O) positron emission tomography (24).

Since then, several studies have been performed on healthy volunteers to confirm the reliability and reproducibility of normal perfusion values on ASL. Reproducibility was good at 1 hour (25) and 7 weeks (26). However, there was no inter-subject reproducibility for age and sex matched subjects with variations as high as 100%, whereas intra-subject results were stable. Results as a function of age showed a progressive reduction of the GM/WM perfusion ratio of 0.79%/year. This reduction was mainly due to a reduction in gray matter perfusion (0.45%/year) and mainly at the frontal cortex (27). The same studies showed a 13% perfusion difference between males and females with higher values for females (25-27). The only study comparing ASL and dynamic susceptibility-weighted contrast material-enhanced MR perfusion in healthy volunteers was presented as RSNA in 2005 by Wang et al. (28). The study was performed on a 3.0T magnet using PALS in 10 healthy subjects. Results at PASL correlated with dynamic susceptibility-weighted contrast material-enhanced MR perfusion results.

Studies on patients

- Ischemic pathology (fig. 3)

Reports from the literature describe that perfusion imaging with ASL shows areas of hypoperfusion in acute ischemic strokes with eventual perfusion-diffusion mismatch correlating with the clinical presentation and evolution (29). Correlation with dynamic susceptibility-weighted contrast material-enhanced MR perfusion showed visual correlation for the areas of hypoperfusion (30, 31). Comparison studies were obtained correlating the rCBF on ASL and the rCBF, rCBV, MTT and

Fig. 2: Example of an algorithm for CBF quantification.
TTP on dynamic susceptibility-weighted contrast material-enhanced MR perfusion. Some studies showed a better correlation using the rCBF values (32, 33) while others showed that the MTT correlated best (34). The main reported limitation of the technique is delayed arterial transit time resulting in the persistence of intravascular labeled blood in patients with reduced blood flow that creates artifacts and may cause underestimation of parenchymal perfusion. However, some studies have shown that patients with such artifacts did not infarct in the areas of hypoperfusion suggesting that it could indicate the presence of underlying collateral circulation with good prognosis (29). The acquisition time of an ASL MR perfusion sequence is variable depending on the labeling technique, acquisition parameters and configuration by the manufacturer but it is possible to acquire a low resolution ASL sequence of satisfactory quality in 3 minutes 50 seconds (sequence provided by GE Healthcare). This sequence would then be usable in the setting of acute CVA, especially when taking into consideration the time spared by the absence of contrast injection.

- Tumoral pathology (fig. 4 and 5)

Based on reports from the literature, evaluation of tumor blood flow (TBF) with ASL yielded similar perfusion abnormalities compared to dynamic susceptibility-weighted contrast material-enhanced MR perfusion, irrespective of contrast enhancement related to disruption of the blood-brain barrier (35). Several studies have demonstrated the ability to distinguish between low grade and high grade gliomas on ASL similar to dynamic susceptibility-weighted contrast material-enhanced MR perfusion, and some suggest a TBF/contralateral CBF threshold ratio of 1.3 (35-37) that would be sensitive but non-specific. An rCBV value < 1.3 would be suggestive of a low grade tumor whereas an rCBV value > 1.3 would not discriminate between low and high grade tumors. However, results would be less reliable for oligodendrogliomas (37). ASL perfusion MR imaging could predict vascular density, a predictive factor of tumor grade, with strong correlation with histological findings and would be more reliable than contrast material-enhanced MRI (38, 39). Also, a large study has demonstrated that both ASL MR perfusion and dynamic susceptibility-weighted contrast material-enhanced MR perfusion were superior to MR spectroscopy in distinguishing glioblastomas from low grade gliomas, CNS lymphomas and metastases (40). Perfusion imaging of meningiomas with ASL and dynamic susceptibility-weighted contrast material-enhanced MR showed concordant results (41).

While it is generally accepted that perfusion MR imaging may distinguish between hyperperfused recurrent tumor and hypoperfused radiation necrosis, the ASL MR perfusion technique has not been validated as of 2008 for this indication (42). The main limitations of the technique reported in the literature are the underestimation of perfusion in low CBF conditions, as in elderly patients for example, and especially in white matter (35). Perfusion with ASL provides absolute CBF values while perfusion with dynamic susceptibility-weighted contrast material-enhanced MR typically provides CBV values. Several studies have attempted to quantify CBV and MTT on ASL perfusion MR but these are of little use since CBF and CBV seem to have similar diagnostic significance (10).
Fig. 4: **Left Rolandic region glioblastoma: 3.0T MRI.**

- **a** Axial postcontrast SE T1W image.
- **b** Axial FSE T2W image.
- **c** ASL: CBF map: hyperperfused tumor.
- **d** T2* perfusion: CBF map: hyperperfused tumor.

Fig. 5: **Right fronto-parietal meningioma: 3.0T MRI.**

- **a** Axial GRE T1W image.
- **b** Axial FSE T2W image.
- **c** ASL: CBF map: hyperperfused tumor.
- **d** T2* perfusion: CBF map: hyperperfused tumor.
Conclusion
Brain perfusion imaging with ASL, MRI is a technique that continues to be evaluated. Its main advantages are the absence of contrast material injection and direct quantification of absolute CBF. Recent technical advances and also the availability of higher field MR units have improved the signal-to-noise ratio. Early clinical studies show concordant results between ASL MR perfusion and dynamic susceptibility-weighted contrast material-enhanced MR perfusion.

References