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REVIEW PAPER

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ASL (Arterial Spin Labeling) – historical and current perfusion MR methods

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ABSTRACT

Despite continuous scientific and technological advances in MR imaging, MR perfusion methods have not yet been widely deployed for routine clinical diagnostics. This is especially true for ASL (arterial spin labelling) methods used to evaluate cerebral perfusion. This method does not require a contrast agent, as new discoveries about gadolinium accumulation in the cerebellum and brain nucleus appear to be a valuable asset and provide the opportunity to be more widely deployed in clinical practice. The aim of this paper is to present the historical determinants of the development of MR perfusion techniques, the disadvantages and advantages and possible clinical applications and prospects of ASL development. Both historical articles published on MR in the 1990s and current research between 2006-2016 have been reviewed. The authors present in the work the MR perfusion method focusing on issues related to arterial spin labeling (ASL). Historically CASL (continuous ASL) and PCSL (pulsed ASL) techniques have been described and the pseudocontinuous ASL (pseudocontinuous ASL) 3D technique presents its technical and methodological considerations, advantages and disadvantages over previous methods. The methods of test protocol optimization and accompanying artifacts, as well as possible clinical applications and development perspectives, have been described.

Keywords. perfusion, MR, ASL

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Introduction

In Magnetic Resonance Imaging Tomography, typical functional morphologies can be obtained by using a variety of spin echoes and gradient echoes. Functional imaging shows processes far beyond the actual spatial MR resolution. Among the advanced MR imaging techniques, in addition to the diffusion imaging that has been shown to be important in the early detection of cerebral ischemia already implemented in the 1980s, we can also list methods for evaluating cerebral perfusion, whose use and clinical relevance go beyond the assessment of cerebrovascular disease and are increasingly widespread with recognized application in the evaluation of oncological processes taking place not only in the brain.

Arterial spin labelling (ASL) is a MR perfusion technique that is used to measure cerebral blood flow (CBF). ASL utilizes the ability of MRI to label arterial blood by spin inversion of innate water with radiofrequency pulses and noninvasively image without the use of contrast agents. In ASL, water serves as the natural biomarker for imaging arterial blood flow.

Among the perfusion techniques used in MR imaging, we can distinguish: DSCI (dynamic susceptibility contrast imaging), DCE (dynamic contrast enhanced) and ASL (arterial spina labeling). DSC most commonly used in clinical practice is based on the evaluation of the first pass of the contrast agent (gadolinium chelate) by the capillary bearing. DCE is a method based on the assessment of a change in the longitudinal relaxation time of T_1 induced by contrast agents, and ASL uses a method of marking arterial blood spins.

Advantage of ASL perfusion imaging is that no contrast agent is required, therefore, the study may be performed in patients with renal impairment, in allergic patients or in patients who do not agree to use contrast media. The other advantages are the possibility of multiple repetitions in a short time (under 24 hours), lack of geometric distortion Images and the fact that CBF (cerebral blood flow) is measured in ml/100g/min and does not depend on the type of coil.

ASL or AST (arterial spin tagging) is one of the MR perfusion methods that uses intrinsic water molecules as a marker, and unlike DSC and DCE, no contrast agent or other external marker is required. This technique for marking arterial blood spins was introduced in 1992 in MR research by John A. Detre and co-workers. Among the scholars who dealt with the development of ASL in perfusion studies, the names of Robert R. Edelman and David C. Alsop and Weiying Dai should also be noted. The MR technique of MR perfusion has evolved since the early 1990s through further methodological improvements from initial studies in one layer over very long acquisition times to the current high-quality 2D and 3D image of perfusion of the entire cerebral area within 5-6 minutes. ASL is currently available in most new MR devices and its reproducibility has been confirmed in numerous multicenter studies.

The basic principles and sequential steps for MR imaging in ASL are as follows:

1. Checkpoints of interest area (brain) in GE (gradient echo) or SE (spin echo) sequences.
2. Signaling of RF (radiofrequency) blood spins (water molecules) at the neck level through their saturation or inversion.
3. After post-label delay (PLD), marked spins water molecules in the arterial blood affect the interest (brain) and behave as a freely diffusing marker, changing the tissue magnetization by about 1-2%.
4. The area of interest (brain) is re-scanned (as in point 1), and the data obtained is subtracted from the control image, which allows calculation of parametric rCBF (regional cerebral blood flow) images, as local changes in tissue magnetization depend on blood flow parameters.

Under ASL perfusion, various techniques have been developed[1-3]:

— CASL (continuous ASL) with continuous RF pulse combined with electromagnetic field gradients applied to flowing blood,
— PASL (pulsed ASL) using intermittent RF pulse,
— EPISTARE (first PASL sequence - asymmetric spin marking),
— PICORE (asymmetric marking of water spins),
— FAIR (symmetrical marking of water spins),
— pCASL (pseudo-continuous ASL) - hybrid method,

CASL (Continuous Arterial Spin Labeling)

The first real ASL technique described by Detre et al. in 1992 used a constant, low-amplitude RF pulse in combination with electromagnetic field gradients causing inversion of blood flow perpendicular to the imaging layer.[4] Spine infiltration reduced the intensity of the stationary tissue signal to a lesser degree, which was possible due to subtraction.[5] This technique was abandoned in the late 1990s due to technical difficulties with its implementation in MR scanners due to the need for an additional RF pulse transmitter which resulted in a significant increase in tissue temperature. In addition, the inversion pulses used in CASL caused the phenomenon of magnetization transfer (MT), which, although marginal and non-specific, could undermine perfusion-related images. All ASL techniques must take into account the MT effect caused by the inversion impulse, which reduces the signal from the imaged area. To eliminate or reduce it, two solutions were proposed:

1. Apply the second inversion pulse during control imaging on the other side of the imaging area, symmetrically. The MT effect is then identical in the imaged layer to the labeled and control images, and during the subtraction is eliminated.

2. Inversion Impulse during control imaging is divided into two parts by amplitude modulation. When both parts of the pulse have only half the amplitude and are very close together, the MT effect disappears when the images are subtracted.

PASL (Pulsed Aretrial Spin Labeling)

The first PASL (Pulsed Aretrial Spin Labeling) technique introduced in the mid-1990s by Edelman - EPISTAR (Echo-Planar Imaging-Based Signal Targeting by Alternating Radiofrequency Pulses) was based on sequential application[6]:

1. 90 slice selective pulse and intermittent gradients for the initial saturation of the magnetization in the imaging layer.
2. A broad pulse of 180° proximal to induce inversion of incoming blood spins.
3. A control sequence in which repeated pulse 90° interrupted saturation of static tissues in the imaging layer and followed the mirror image spaced distances from the layers of imaging impulse 180°.
4. Subraction, which endured the undesirable effect of magnetization transfer.

EPISTAR gave the image of MR perfusion in a single layer and subsequent techniques (STAR, PULSAR, QUASAR) were already multilayer.[7]

PICORE (asymmetric marking of water spins) and FAIR (symmetrical marking of water spins)

The next PASL techniques developed are PICORE (Proximal Inversion with Control of Off-Resonance Effects), an asymmetric multi-layer PASL-like EPISTAR-like technique in which the tagging sequence was identical to EPISTAR, and the control sequence was different in that the re- Equivalent to the impulse in the tagging sequence but without the spatial gradient and FAIR (Flow-sensitive Alternating Inversion Recovery). FAIR was slightly different in symmetry with respect to the imaged marking technique. The marking sequence was started spatially bound to the area of the selected layer with an inversion pulse of 180° and in the control sequence the same inversion pulse 180° but without a layer selection gradient[8] was applied. The differences between the EPISTAR, PICORE and FAIR techniques depend in part on the geometry of the expected blood flow to the test volume (imaging area). PICORE marks only blood on one side and is therefore a sensible choice for axial imaging of cerebral perfusion, where all the incoming blood comes from the neck area. FAIR is more suitable when blood flow occurs from many directions (e.g. cerebral perfusion imaging or liver perfusion). FAIR is also more susceptible to signal pollution associated with unwanted venous infiltration and more difficult to implement in multilayer mode. In some situations, EPISTAR is preferable to other sequences, due to fewer artifacts due to balanced gradation gradients in labeled and control sequences.

pCASL (pseudo-continuous ASL)

pCASL (Pseudo-continuous Arterial Spin Labeling) is a Hybrid method proposed in 2008 by Dai *et al*., Using a narrow marking level (similar to CASL), which facilitates flow-dependent spin inversion. Marking of spins is just below the imaged volume and minimizes the loss of tagged blood. A series of very short RF pulses are used here, which imitate a single continuous pulse (as in CASL), but show much less energy in the imaging area and less on the RF power cycle. Compared to PASL, pCASL offers a higher SNR (signal to noise ratio) and is less susceptible to scattering and is highly sensitive to flow volume, compared to CASL for higher marking efficiency and can be used in modern MR scanners.[9,10]

From the point of view of the correct execution of the test and its optimization in the ASL technique the following values of parameters and rules[2,3] are taken into account:

1. PLD, that is, the spin time from their marking to the level of the imaged area should typically be between 1.5 and 2.5 seconds in healthy individuals. Longer PLD times should be considered in the elderly, patients with vascular pathology or low cardiac output, and in children, the PLD time should be shorter and should be about 1.0-1.5 s. This parameter is critical and directly affects the quality of the ASL test, where the marking and PLD depends on field strength, ASL technique and flow volume. For the brain in the 1.5 T field, the typical marking time for PASL is 700 ms, for pCASL about 1500ms, and the PLD is about 1800 ms. In the 3.0 T field the PLD times should be somewhat longer.
2. All ASL techniques perform better when imaging occurs in a transverse plane perpendicular to the direction of marked blood flow. Relevant symmetric neck and head alignment is important from the point of view of preparation.
3. ASLs are dependent on SNR, so it is best to use the MR with the highest available field strength, i.e. 3.0 T or possibly 1.5 T, and multi-channel coils are mandatory.
4. Repeat times (TR) should be greater than 3500ms and minimum echo time (TE).
5. Spatial resolution due to SNR should be low. For 2D ASL, the typical matrix is 64×64 or 128×128 with a 4-6mm layer thickness.
6. For maintaining a prudent SNR and a test time of 5 minutes, multiple averaging signals are required: for 2D techniques between 30 and 50 averaging signals at 3.0 T, and even more at 1.5T, and for 3D 2-4 signal averaging.

7. Background suppression is required for 3D image segmentation, which uses single excitation during TR, less effective for 2D multi-layer techniques.

Like other MR methods, ASL also exhibits the presence of artifacts associated with magnetic susceptibility, flow or movement, although some of them manifest themselves differently in ASL.[1,11] The most common are:

1. Artifacts of magnetic susceptibility.

Artifacts of magnetic susceptibility occurring at the level of the labeled layer may cause distortion of the CBF measurement. Artifacts of magnetic susceptibility at the level of the test layer (a test layer is a separate control image acquired without prior labeling of arterial spins) may mimic stroke.

2. Artifacts related to the sensitivity of the coil.

Spatial differentiation of the sensitivity of the receiving coil may mimic hyper areas or hypopituitarism in ASL images. This artifact can be minimized by image filtering and other postprocessing techniques.

3. Traffic related artifacts.

The movement of the patient between the marking phase and the control phase causes a rim ("halo") around the imaged area. Motion correction (patient stabilization) reduces the artifact. There may be differences in the brightness of this artifact between the imaging layers.

4. Artifacts related to downstream signal loss.

The common feature of ASL techniques is the reduction of the signal in the test layers away from the marking area. This is due to the longitudinal relaxation of T_1-labeled water protons between their inversion and the reading in the test layer. This phenomenon is more evident at 1.5 T field strength than in 3.0 T due to shorter T_1 blood pressure lowering times. This artifact can be reduced with the use of 3D sequences in the reading phase and parallel imaging techniques to shorten the acquisition time.

5. Intravascular signal artifact.

Delayed flow of labeled blood proton into the imaging area and lack of time to spread in tissues may cause them to be present during re-scan in the vascular bed. This artifact may also be due to a lack of accurate demarcation of the inversion pulse when marking blood proton, excessive shortening of PLD time or pathological delayed arrhythmia. In order to reduce high vascular signals, large bipolar gradients are often used along several axes just before the reading phase. Sometimes, despite the fact that these artifacts persist, they may be a significant clinical symptom reflecting the delayed arterial flow associated with vascular disease.

6. Artifacts related to unsuccessful saturation in the background.

Since the differences between the labeled and ASL control sequences are small (about 1%), all lesions in static tissues subjected to imaging can damage the perfusion images. This is particularly true in the ASL 3D method, and several types of background suppressions within the imaged volume are used to remedy this. If background saturation during the ASL test does not take place in postprocessing, the layers covered by this error may be removed, resulting in the failure to read the test.

Gadolinium significantly shortens the longitudinal relaxation time of T_1 blood proton, so between the inverse and read sequences, there is an almost complete return of longitudinal magnetization T_1. Thus, labeled and controlled images do not differ from each other, which, after subtracting them (image acquisition area of labeled spins subtracting from the control image), gives a picture in which there are no perfusion signals. After gadolinium administration, wait at least 8-12 hours before performing ASL imaging with normal renal function, and for accurate rCBF measurement, this time should be prolonged to 24-48 hours.[1]

Guidelines for proper ASL performance:

1. Do not perform ASL imaging with contrast agent, as there is no signal to create an image (CBF map).
2. Do not perform ASL if the images at the neck level are distorted due to the risk of false diagnosis e.g. occlusion of the carotid artery.
3. The neck placement of the patient should be accurate, without side deviation due to the possibility of the "right" or left hemisphere "shadow" artifact.
4. Properly delay the acquisition after spin marking should be used - the PLD value should be adjusted appropriately for age: in children 1.0-1.5 sec, in healthy patients 1.5-2.5 sec, in older patients and in stroke 2.5-3.0 sec.

Like other MR perfusion techniques, quantitative blood flow calculations are desirable but difficult to achieve. Differences in signal intensity data in the inversion and read phase allow for perfusion-dependent images. Translating these raw data into absolute blood flow measurement requires three steps: processing and filtering images to remove artifacts, acquiring separate maps in PD or T_1 images depending on the intensity of the signal, selecting data for the mathematical model to calculate the pixel blood flow.

Buxton's general kinetic model is the most widely used, and the final equation for calculating blood flow depends on many measurements and parameters, as well as the use of precision ASL pulse sequences.[10,12]

Areas of currently used and possible uses of ASL for cerebral perfusion are:[5,13-16]

1. Neurological diseases: vascular diseases (TIA, stroke, migraine, vascular malformations), brain tumors, neurodegeneration
2. Developmental and genetic effects
3. Functional and pharmacological MR imaging
4. Neuromodulation

In addition, it is possible to use selectively regional ASL (selective ASL region). This technique, by using a single 180° wide inversion impulse and applying thin-film impulses to the main blood supply vessels to the brain, is able to visualize separately the supply areas of each of the major cerebral blood vessels.

ASL is a very sensitive imaging technique (more than DSC), but not very specific.[15] An elevated signal on CBL mapping in ASL may be due to a wide range of vascular pathologies such as: decreased arterial flow, increased cortical flow, arteriovenous leakage. For accurate localization of signal disturbances in ASLs, image fusions with other more specific 3D sequences like TOF and SWAN are used. ASL is a sensitive method for evaluating perfusion mainly in the area of the cerebral cortex whereas, in fact, the white rate is limited to a low level compared to the gray matter and the MTT.[17] The use of 3D FSE ASL sequences enhances diagnostic efficacy in patients with aneurysms, clips, coils, and those with brain heme transformation as FSE sequences tend to reduce artifacts from magnetic susceptibility, as opposed to EPI sequences.[12,18]

Conclusions

In the literature, ASL perfusion has reached over 1,000 publications and is now of great interest, hence the desire to popularize this technique of MR perfusion on native soil. Numerous authors, apart from technical and methodological aspects, are concerned with the possibilities of implementing this technique in clinical practice, which is not easy due to its limitations and lack of popularization, due to the fact that it has only been available for several years in modern MR scanners. Nevertheless, the current work shows similar possibilities as in MR perfusion with DSC and comparable with CT perfusion assessment of cerebral perfusion and have wide application possibilities, also in functional MR imaging.[12,15,19] In Poland, few authors have attempted to assess the clinical relevance of ASL.[20] There is a 3D ASL technology available at the Medical Research Center of the University of Rzeszow, where the 1.5 T system is installed. Hopefully, in good cooperation with the Clinical Departments in Rzeszow, our experience and research will be documented. Due to the currently known side effects of the use of paramagnetic contrast agents in patients with chronic renal failure (NSF) and newly discovered brain gadolinium accumulation, the interest in "old" MR-ASL perfusion will increase.[21,22] Continuous technological progress is not difficult to imagine that this technique in the near future may be dominant in the assessment of cerebral perfusion in many clinically important areas.

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