Arterial spin labeling perfusion MRI: reproducibility & clinical applications
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General Introduction & Outline
Chapter 1

General introduction and outline

Introduction
Cerebral Perfusion Imaging

Cerebral perfusion refers to the delivery of oxygen and nutrients to the brain, by means of blood flow. Cerebral perfusion is also called cerebral blood flow (CBF) and is expressed in mL/g/min, reflecting the amount of blood that supplies a certain brain mass per unit of time. Knowledge on the distribution of CBF provides insight in the local metabolic demands. Cerebral perfusion imaging plays a crucial role in the evaluation of brain disease and its progression. Since the early forties of the last century, various methods have been introduced to measure cerebral perfusion. Among these are Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Xenon enhanced Computed Tomography (Xe-CT), Dynamic Perfusion Computed Tomography (perfusion CT) and Dynamic Susceptibility Contrast MRI (DSC-MRI). Each technique has its own pros and cons, which mainly depend on the involvement of radio-active tracers, exogenous contrast agents or ionizing radiation and on acquisition and post-processing time, brain coverage, spatial resolution and reproducibility of the measurement.

In current clinical practice, DSC-MRI and perfusion CT are most often used. DSC-MRI can be added to existing MR protocols whereas perfusion CT is fast and easy to perform in an emergency setting. The disadvantage of those techniques is that both techniques require injection of exogenous contrast agents that can be harmful to patients with impaired renal function. Iodine based contrast agents can lead to nephropathy while gadolinium based contrast agents can induce nephrogenic systemic fibrosis. Moreover, concern exists among the use of ionizing radiation leading to cancer. In 1992 Williams and Detre introduced an alternative MRI perfusion imaging technique in which arterial blood is used as an endogenous contrast agent. This completely non-invasive perfusion imaging modality can be used for visualization and quantification of perfusion.

Arterial Spin Labeling MRI

Arterial Spin Labeling (ASL) is a non-invasive perfusion imaging technique that uses arterial blood water protons as an endogenous tracer of arterial blood flow. Its non-invasiveness renders ASL especially suitable for repeated measurements or measurements in vulnerable patient populations like the pediatric population. In ASL perfusion MRI, arterial spins are magnetically labeled upstream by means of inversion, and exchange their magnetization with local tissue water after arriving downstream a little later. This reduces MR signal slightly (only a few percent of tissue magnetization). To identify this slight decrease in MR signal, images are acquired with and without previous magnetic labeling. In the ideal situation, the signal that comes from the surrounding static tissue is identical in both the label and control condition. In that case, subtraction of labeled images and control images yields perfusion weighted images, purely composed of the signal coming from inflow of the inverted blood spins (Figure 1).
The percentage of signal change is only small, 0.5-1.5% of the full signal and is dependent on many factors such as blood flow, longitudinal relaxation time (T1) of arterial blood and the time it takes the spins to travel from the labeling plane towards the capillary bed (arterial transit or arrival time).

Generally, repeated acquisitions (30 to 40 paired subtractions) are gathered and averaged, in order to obtain sufficient perfusion signal, resulting in acquisition times of 5 to 10 minutes per ASL scan.11,12

During the last two decades, numerous ASL sequences have been developed. Those can grossly be divided into continuous and pulsed ASL sequences. In continuous ASL (CASL) long radiofrequency pulses (1-3 seconds) and a slice selection gradient are applied in a thin labeling plane, placed perpendicularly to the carotid arteries, for flow driven inversion of arterial blood water spins.13 The moving arterial spins will experience a radiofrequency pulse causing inversion, while surrounding tissue spins will be saturated. Generally, the labeling efficiency of arterial spins in CASL experiments is around 80-95%.10,14 The labeling efficiency is influenced by blood velocity, angulation of the labeling slab with respect to the vasculature, RF amplitude and gradient strength.12 The efficiency with which labeling occurs is important for the magnitude of the eventual perfusion signal and for quantification of perfusion.

A drawback of the CASL technique is the need of long radiofrequency (RF) pulses and high RF power leading to high specific absorption rates (SAR). To limit SAR levels in CASL, a separate coil is used for transmission. Moreover, the application of long radiofrequency pulses in the labeling condition can cause magnetic labeling of the protons in the backbones of macromolecules, inducing the possibility of magnetization transfer (MT) when those macromolecules exchange their magnetization with magnetization of free water. This phenomenon could result in an overestimation of the ASL perfusion signal if MT is only present in the labeling condition. To overcome MT effects, different modifications of the original sequence have been proposed, such as the sinusoidal modulation of the radiofrequency waveform for the control condition, that was introduced by Alsop and Detre and continuously inverts two planes at the same time.15 Using this double inversion, MT effects are identical in the label and control situation, resulting in net zero MT after paired subtraction.
subtraction. A limitation of this modification is the doubled RF power, leading to higher SAR levels and the reduced labeling efficiency (ca 70%)\textsuperscript{16}.

Recently a variant of the CASL method has been introduced, called pseudo-continuous ASL (P-CASL)\textsuperscript{17}. In P-CASL a train of discrete labeling pulses is applied in a thin labeling plane, resulting in relatively high labeling efficiency and SNR, with low RF power and SAR. In addition, P-CASL allows for body coil transmission and array coil reception, increasing the SNR of the images\textsuperscript{18}.

In pulsed ASL (PASL) short (approx. 10 milliseconds) spatial inversion of arterial blood water spins, is applied over a long trajectory of the brain feeding arteries. To get an adequate signal to noise ratio (SNR), the thick labeling plane is positioned just below the imaging volume. As in CASL, the image is acquired after a delay time (the postlabeling delay) that is sufficient to allow for the labeled spins to reach the brain parenchyma. Depending on the way labeling is applied with respect to the imaging volume, PASL techniques can be subdivided in symmetric and asymmetric techniques. Symmetric techniques similar to the flow-sensitive alternating inversion recovery (FAIR) technique are based on a scheme proposed by Kwong et al\textsuperscript{19;20}. In this scheme labeling is performed with a slice-selection gradient, while non-selective inversion is applied in the control situation. Asymmetric techniques include all sequences based on the EPISTAR sequence ("echo-planar imaging with signal targeting by alternating radiofrequency pulses")\textsuperscript{21}. EPISTAR sequences use a selective inversion pulse proximal to the imaging volume for magnetic labeling of arterial spins. This inversion pulse is applied distally to the imaging volume in the control condition.

Because reduced RF power is needed in PASL experiments compared to CASL, MT effects are less important than in CASL. Another advantage is the relatively high labeling efficiency that can be reached using the large inversion slab. However, the difficulty of this technique resides in the estimation of timing parameters like the arterial transit time (the time it takes for the labeled bolus to reach the brain parenchyma) or the temporal bolus width (the time from arrival of the labeled spins in the brain parenchyma till clearance of the labeled bolus). Wrong estimation of these parameters can cause errors in perfusion quantification. To better define the length of the tag, Wong et al have introduced the QUIPSS method ("QUantitative Imaging of Perfusion using a Single Subtraction") in which additional saturation pulses are applied approximately 500-800 ms after labeling. The use of those pulses in both the label and control condition also limits the signal that comes from remaining intravascular label\textsuperscript{11;22;23}.

Instead of minimizing the effect of the arterial transit time, this hemodynamic parameter could also be measured together with cerebral perfusion. This can be done by performing multiple ASL experiments with varying delay times between labeling and acquisition. The theory behind this method was introduced by Buxton et al\textsuperscript{24}. The newer sequences using multiple inversion times (TIs), like ITS-FAIR, Turbo TILT (Transfer Insensitive Labeling Technique) and QUASAR (QUAntitative Star labeling of Arterial Regions), acquire a series of images at increasing delay times after initial labeling\textsuperscript{25-27}.

The common labeling strategies and their characteristics are summarized in Table 1 and illustrated in Figure 2.
Table 1. Overview of continuous, pulsed and pseudo-continuous arterial spin labeling (CASL, PASL and P-CASL).

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<tr>
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<th>CASL</th>
<th>PASL</th>
<th>P-CASL</th>
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<tr>
<td>Coils</td>
<td>Body coil</td>
<td>Body coil</td>
<td>Train of discrete labeling pulses</td>
</tr>
<tr>
<td>Transmit/Receive</td>
<td>Transmission</td>
<td>Transmission</td>
<td></td>
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<tr>
<td>Labeling</td>
<td>Continuous</td>
<td>Pulsed</td>
<td></td>
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<tr>
<td>Duration</td>
<td>Seconds</td>
<td>Milliseconds</td>
<td>Seconds</td>
</tr>
<tr>
<td>Slab</td>
<td>Thin</td>
<td>Thick</td>
<td>Thin</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Low</td>
<td>High</td>
<td>Intermediate</td>
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<tr>
<td>SAR level</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
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<tr>
<td>SNR</td>
<td>High</td>
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Figure 2: the position of the imaging volume and the labeling plane for the different labeling strategies. The imaging volume is indicated by a solid rectangle whereas the labeling plane is indicated a dotted rectangle.

Selective Arterial Spin Labeling

Besides global cerebral perfusion imaging, ASL can also be used for selective labeling of the individual cerebral arteries, allowing for visualization and quantification of perfusion in the flow territories of these arteries. Currently, intra-arterial digital subtraction angiography (DSA) is the gold standard for visualization of the cerebral vasculature and the different patterns of collateral flow. Other than selective ASL, DSA is an invasive method that does not provide quantitative information on perfusion in the flow territories of the individual arteries. Numerous sequences have been developed for selective ASL based on CASL or PASL labeling approaches. By using the CASL approach selective labeling of one of the common carotids can be achieved by applying an additional surface coil or by oblique positioning of the selective labeling slab. Hendrikse et al. developed a regional perfusion imaging method that was based on anatomy driven spatially selective labeling. Recently, Wong et al. introduced planning-free vessel-encoded pseudo-continuous ASL, in which the labeling plane is spatially manipulated in the anterior-posterior direction and in the left-right direction,
allowing for separate labeling of the internal carotid and vertebrobasilar circulation. Labeling of single intracranial arteries can be performed by superselective P-CASL developed by Helle et al.

Quantification of perfusion

Quantification of perfusion in ASL depends on multiple parameters. Originally, perfusion was estimated based on the tracer clearance theory, proposed by Kety and Schmidt and adapted to ASL experiments by Detre and Williams et al. In this single compartment model, it is assumed that the labeled arterial blood water is provided to the brain parenchyma as a uniform plug that exchanges its magnetization with tissue water directly after arrival in the capillary bed. The modified Bloch equation for the longitudinal magnetization in the presence of perfusion, including the flow dependent exchange term, becomes:

\[
\frac{\Delta M(t)}{\Delta t} = \frac{M_0 - M_f(t)}{T_1}, f \left( \frac{M_{0a} - M_f(t)}{\lambda} \right),
\]

in which \( M_T \) is the longitudinal magnetization of the tissue with an equilibrium value \( M_0 \), \( M_{0a} \) is the magnetization of the inflowing arterial blood, \( T_1 \) is the longitudinal relaxation time of tissue, \( f \) is the blood flow in ml/g/s and \( \lambda \) is the blood brain partition coefficient. The first models for perfusion estimation did not take into account the arterial transit time or the temporal bolus width. This parameter was added to the equation in the general kinetic model described by Buxton et al. Furthermore, it has been recognized that the labeled blood relaxes with the longitudinal relaxation rate of arterial blood until it reaches the brain parenchyma. After reaching the brain parenchyma it relaxes with the relaxation rate of tissue as implemented in the models of Alsop and Detre and Wang et al.

Difficulties encountered in Arterial Spin Labeling MRI

Although ASL is a very promising tool for non-invasive measurement of cerebral perfusion, clinical implementation remains challenging. This is due to several difficulties that are frequently encountered in ASL imaging. First of all, spatial and temporal resolution is low compared to other perfusion imaging techniques, like DSC-MRI and perfusion CT. Full brain coverage cannot always be reached. Moreover, the technique has a low intrinsic SNR due to the 0.1-1.5 % signal change induced by magnetic labeling. To get sufficient perfusion signal with multiple acquisitions, ASL scanning times are relatively long. Better SNR can be achieved by the use of additional background suppression pulses to exclude noise coming from fluctuations in the magnetic field. Another way to reduce those fluctuations is by using fast (single shot) 3D GRASE (gradient and spin echo) imaging sequences that reduce the possibility of movement between acquisitions. The latter could be of great value for the clinical applicability of ASL since movement is a high frequency source of artifacts.

As a resultant of the low SNR and also because of prolonged arterial arrival times in the white matter, the sensitivity of ASL to detect white matter perfusion has for long been a matter of debate. Recently, van Osch et al., have shown that the increased SNR achieved by the implementation of P-CASL labeling combined with additional background
suppression pulses at 3 Tesla, is sufficient to measure perfusion in most of the deep white matter.\textsuperscript{36}

Besides low spatial and temporal resolution, low SNR and low sensitivity to white matter perfusion, the definition of arterial timing parameters remains an important issue. Those timing parameters directly influence perfusion estimates. Knowledge on arterial timing parameters is especially important in patients with delayed arrival of arterial blood, due to vessel stenosis or occlusion and blood travelling via collateral pathways. Also, remaining intravascular label that has entered the imaging volume but has not yet reached its final destination in the capillary bed, can lead to overestimation of perfusion. In PASL, the QUIPSS method can be used to influence the temporal bolus width and to minimize effects of remaining intravascular label and the multiple TI sequences can be used to measure the arterial timing parameters. Additionally, flow-weighting gradients can be used to crush the vascular signal, however at the cost of a reduced SNR.\textsuperscript{39}

Whereas previous studies claimed that venous outflow of labeled blood water protons could lead to an underestimation of CBF, especially at long postlabeling delays or in high flow conditions, a recent study by Liu et al., has shown that virtually all spins exchange to tissue when passing the capillary bed and only very few remain to enter the vein.\textsuperscript{22,40} The latter has important implications for the choice of a sufficient postlabeling delay in patients in whom arterial arrival could be delayed.

Other potential issues are: bolus dispersion, inducing a spread in the arrival of spins that have been labeled at the same time, or the equilibrium magnetization of arterial blood needed for CBF quantification.

Because of these challenges, ASL has for long been portrayed as a technique that can only be used in specialized imaging centers. However, technical advances and the introduction of 3.0 Tesla MR systems (higher SNR and longer relaxation time of the labeled spins) have solved some of the problems.\textsuperscript{41}

Reproducibility

The complex set up of ASL experiments and the possible sources of errors in quantification raise the question whether the same perfusion values are found when ASL experiments are repeated. The reproducibility of ASL is essential for its applicability in clinical routine. Several single center studies have been performed to assess the robustness of whole brain and flow territory perfusion estimates, based on either continuous or pulsed labeling schemes and on standard perfusion templates.\textsuperscript{42-45} Those studies were carried out in single imaging centres at 1.5 Tesla scanners and describe ASL reproducibility with test-retest timeframes of at least one hour to several weeks. The signal variability within scanning sessions was not tested. Only recently, the first multicenter ASL reproducibility study was published by Petersen et al., dubbed the QUASAR (QUAntitative Star labeling of Arterial Regions) reproducibility study.\textsuperscript{27} This study has shown that ASL is a reliable perfusion imaging technique that can be used in clinical routine without the need for special hardware or dedicated personnel.

It is still uncertain however, whether comparable perfusion values would be obtained when scanning the same subjects multiple times at different imaging sites. The latter will determine whether reference values for CBF could be used in clinical decision-making.
making, or whether each imaging center should first gauge its own perfusion values in healthy controls. Also, reproducibility studies performed thus far focused on the quantitative assessment of reproducibility of perfusion estimates. The behavior of regional variability patterns in ASL perfusion imaging however is still unknown. Knowledge on regional variability patterns is valuable when ASL perfusion maps will be used in the diagnostic process in patients with local cerebrovascular pathology and can provide insight in the most important sources of variation for the different ASL techniques.

Clinical applications

Over the past years the utility of ASL as a diagnostic and research method has been demonstrated. The latter is illustrated by the broad spectrum of clinical studies that have been reported. ASL has been used in patients with acute and chronic cerebrovascular disease. In those populations sequences with multiple TIs -that can also be used for calculation of arterial arrival time- or sequences with long delay times have appeared to be most suitable. Furthermore, ASL was performed to measure changes in regional CBF that occur in epilepsy or in degenerative disease including Alzheimer’s dementia, frontotemporal dementia and HIV. In brain tumor patients, ASL can be used for grading of the tumor. ASL has been used in the pediatric population (for example in children with sickle cell disease and children with arterial ischaemic stroke) in whom the non-invasiveness of ASL is especially beneficial. Since ASL perfusion imaging is free of any harm, it is helpful in monitoring disease progression and response to treatment. Finally, selective ASL has been demonstrated to be of added value in classification of borderzone infarcts.
Outline of this thesis

The overall aim of this thesis was to study the reproducibility of state of the art ASL sequences at 3 Tesla and to study its applicability in different patient populations. This thesis consists of three parts.

The first part focuses on the reproducibility and acquisition time of different labeling strategies. In Chapter 2, the amplitude modulated CASL sequence described by Alsop and Detre was implemented at a 3T MR system. It was hypothesized that higher field strength would result in shorter scanning times, since fewer averages could suffice to obtain sufficient perfusion signal. Also, it was hypothesized that acquisition related reproducibility would improve at high field strength. In Chapter 3, intra- and multicenter reproducibility of all main labeling strategies were assessed by scanning healthy volunteers multiple times and at multiple sites. All sites were equipped with comparable 3 Tesla Philips MR scanners, to exclude measurement differences between vendors, from the analysis. Not only global perfusion was studied but regional variability patterns were taken into account as well. Chapter 4 describes the robustness and reproducibility of flow territory mapping by planning-free, vessel-encoded pseudo-continuous ASL.

The second part of this thesis focuses on the applicability of different labeling methods in three different patient populations. The purpose of Chapter 5 was to determine the usefulness of ASL based pharmacological MRI in the assessment of serotonergic dysfunction in ecstasy users, by examining the hemodynamic response evoked by citalopram infusion (selective serotonin reuptake inhibitor). In Chapter 6 ASL with multiple acquisition times was used to study cerebral perfusion long term after therapeutic balloon occlusion of the internal carotid artery in patients with giant aneurysms who tolerated balloon test occlusion. Chapter 7 investigated the use of ASL in patients with sickle cell disease, in whom ASL imaging is challenging because of their chronic anaemia and hyperaemia.

The third part of this thesis consists of a general discussion, conclusions and implications (Chapter 8).
Chapter 1
Reference List


31. Wong EC, Kansagra AP. Mapping Middle Cerebral Artery Branch Territories with Vessel Encoded Pseudo-Continuous ASL: Sine/Cosine Tag Modulation and Data Clustering in Tagging Efficiency Space. ISMRM 16th Scientific Meeting & Exhibition Proc. ISMRM #182. 2008. ISMRM Toronto. Ref Type: Conference Proceeding


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