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Chapter VII

Discussion and Summary
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Arterial spin labeling (ASL) MRI employs radiofrequency pulses to magnetically label blood water as an endogenous tracer, and it has the desirable properties of being completely non-invasiveness, reproducible, quantitative and fast. Since its first appearance in the 1990s (1,2), cerebral perfusion measurements based on ASL-MRI have become an important and competitive tool for diagnosing brain diseases. During the last two decades, the ASL community has been very active in proposing new ASL techniques. These techniques can be grouped into three categories based on the temporal and spatial layout of the labeling sequence: (pseudo-) continuous ASL (3,4), pulsed ASL (5–9), and velocity selective ASL (10,11). They have been successfully implemented in the brain as well as other organs both in a clinical and research environment (12–15). A recently-published ASL white paper provides clear guidelines on the clinical implementation of ASL, and represents a milestone in the field of ASL-MRI (16). In this thesis, several new ASL techniques are proposed to detect different aspects of cerebral perfusion, and to extend the capabilities of ASL-MRI.

Vessel-encoded dynamic ASL: fast cerebral territory mapping

Information on cerebral flow territories is important in understanding the mechanisms of cerebrovascular disease, for instance, it can be used to identify which particular artery is the source of emboli in acute stroke patients (17,18). Vessel-encoded pCASL (VE-pCASL) is by far the most promising non-invasive and planning-free whole-brain territory mapping technique based on ASL-MRI for clinical research. Discrimination between the flow territories of different feeding arteries is achieved by gradient-induced spatial variations of the labeling efficiency, and subsequent image post-processing (19,20). Although all the main territories are identified in a single scan, it is still frequently considered too long (~5 min) for inclusion in clinical protocols, especially for the acute clinical setting.

In chapter II a new technique termed vessel-encoded dynamic arterial spin labeling (VE-DASL) was proposed to achieve fast (<30 seconds) cerebral flow territory mapping. The main concept behind VE-DASL is to create a continuous inflow of label/control blocks with different encoding patterns for each feeding artery. This approach leads to unique signal evolutions within each flow territory and accelerates the identification of flow territories. This in contrast to VE-pCASL, which is based on several images in which the encoding pattern of the labeling is varied between these images. To optimize VE-DASL, different settings such as flip
angle, labeling block duration, labeling configuration and scan duration were studied. The validation was performed by comparing the territory maps acquired by VE-DASL with the ‘gold standard’ reference maps obtained from VE-pCASL. The conclusion is that VE-DASL has the potential to map the main flow territories with whole brain coverage in 30s, enabling use in, for example patients with acute stroke.

The main drawback of VE-DASL is the lack of CBF quantification, since VE-pCASL does provide quantitative CBF and territory maps simultaneously (21–24). As a future prospective for VE-DASL one can imagine the development of a more advanced signal evolution model of VE-DASL that would enable the quantification of CBF and identification of mixed perfusion regions, for example using linear regression analysis (25).

**ASL-PRESS: can spectroscopic readout increase the SNR, especially for white matter perfusion measurement?**

The main drawback of ASL-MRI is the low SNR because inflowing labeled molecules comprise only a few percent of tissue signal in the gray matter (GM) (26), and an even lower percentage in the white matter (WM). So far, the majority of cerebral perfusion measurements by ASL-MRI have focused on CBF in GM. ASL-based white matter perfusion measurements have proven to be difficult and studies are relatively scarce, mainly due to the much lower perfusion in WM resulting in low SNR of the measurements. Recently, ASL with a PRESS spectroscopic readout has been hypothesized to enhance the sensitivity for the measurement of WM perfusion (27), although this claim was, unfortunately, not experimentally verified. If measurement noise is assumed to be the dominant noise-contributor, the SNR is proportional to the voxel-volume (V) and readout time (T) (28,29).

Assuming a comparable scan time T for both ASL PRESS and ASL EPI, the SNR is proportional to the voxel size V. Defining the size of the spectroscopic VOI as N*V (i.e. N EPI-voxels fit in the PRESS VOI), the SNR of spectroscopic readout will be increased by a factor of N, while the SNR of imaging, when averaging the voxels within the VOI, will only be increased by a factor of √N. Therefore, the SNR of ASL PRESS will be √N higher than the SNR of ASL EPI. In addition to the SNR increase due to the lower spatial resolution, PRESS is less sensitive to T₂* dephasing while gradient-echo EPI could result in ~25% signal loss due to T₂* (assuming TE=14 ms and gray matter T₂*=48 ms at 3T).

In chapter III, time-encoded pCASL in combination with a PRESS spectroscopic readout was proposed to detect multi-phase cerebral perfusion changes in white
matter in a highly time efficient manner. Moreover, the temporal SNR of white matter perfusion signal acquired by te-pCASL PRESS was compared to that acquired by te-pCASL EPI. The results showed, however, no significant difference. This study demonstrated the potential use of time-encoded pCASL to measure localized white matter perfusion changes in a highly time-efficient manner, ~12.5 min compared to over one hour in other studies. However, changing the readout module to PRESS instead of EPI did not result in an additional temporal SNR gain. The inconsistency of theoretical SNR gain using spectroscopic readout and the experimental results could be explained by: 1) imperfect shimming can result in signal cancelations showing as line broadening in ASL spectroscopy; 2) variations in labeling efficiency and physiological fluctuations in WM CBF could be the dominant source of noise for this application, and both of these sources of variation are independent of the readout resolution. This study therefore provides support for the use of a conventional imaging readout for WM ASL experiments, because this enables more irregular shaped ROIs for WM perfusion measurements, rather than the clinically available rectangular-shaped ROI of the PRESS readout. Moreover, measurements can be performed at multiple locations, such as the left and right hemispheres, increasing the relative efficiency even further.

Although the current study implies that spectroscopic readout has a limited future in ASL for increasing sensitivity for WM perfusion measurement, one could speculate that ASL in combination with a spectroscopic readout would enable the monitoring of metabolic changes within or near the microvasculature. The limited SNR of such an approach is, however, an important limitation.

**ASL-IVIM: unraveling the signal origin of IVIM**

Intravoxel incoherent motion imaging (IVIM) is an alternative non-invasive MRI technique for perfusion measurements (30–32). Although IVIM has regained significant interest during the last decade (33–42), application of IVIM in the brain still lags behind. The basic assumption of IVIM is that blood flow in the capillaries, known as cerebral perfusion, can be considered as a pseudo-diffusion process due to the random directions within the capillary network. However, a major concern is that a distribution of velocities as well as non-random orientation could result in a more complex relation than the mon-exponential assumption of the fast compartment. In chapter IV, to better understand the IVIM-signal, ASL prepared IVIM was proposed to study the arterial IVIM signal as a function of post-labeling delays and diffusion-weighting to measure exclusively the diffusion properties of different sub-parts of the vascular tree. This is especially important for a proper
interpretation of cerebral IVIM studies. The pseudo-diffusion coefficient $D^*$ as calculated from ASL-IVIM data using the mono-exponential model was found to decrease exponentially for $883\text{ms}<\text{PLD}<2176\text{ms}$, while it was relatively stable for $\text{PLDs}>2176\text{ms}$. The fast compartment of the conventional IVIM experiment showed comparable apparent diffusion values to the ASL-signal with PLDs between $1747\text{ms}$ and $2176\text{ms}$. A two-compartment was also applied to further distinguish the contributions from the intra- and extra-vascular compartments (42,43). Similar results were found as from the mono-exponential model, although the bi-exponential fitting was found to describe the ASL signal more accurately as a function of $b$-value. The averaged extra-vascular $D$ at long PLDs ($\text{PLD}>2176\text{ ms}$) was found to be $-1.9\pm1.4\times10^{-3}\text{ mm}^2/\text{s}$, which is two times lower than the $D^*$ using the mono-exponential model ($-4.0\pm2.8\times10^{-3}\text{ mm}^2/\text{s}$) and two times higher than the diffusion coefficient of the slow compartment ($0.90\pm0.05\times10^{-3}\text{ mm}^2/\text{s}$) of the conventional IVIM-experiment, indicating that the ASL-signal does not exchange with the complete extravascular compartment, but with only a sub-part. The comparison between the ASL-IVIM and conventional IVIM showed much more complicated diffusion properties of the vascular signal than the conventionally assumed single $D^*$ of the perfusion compartment in the two-compartment model of IVIM. This should be taken into account when interpreting IVIM studies of the brain.

As a future prospective the development of more complex models for IVIM can be envisioned which take the various velocities and non-random directions of blood flow in the different subparts of the capillary tree into account. Furthermore, ASL-IVIM can be used to distinguish between spin compartments by combining the current approach with a TRUST-module to measure the $T_2$ of the ASL-signal (44,45) or to obtain more information on the microvascular architecture. Similarly, mirroring the method of diffusion MRI-based fiber tracking (46), directional tracking on the fast diffusion compartment could enable visualizing the microvascular structure in the brain (43). Therefore, a bold prediction is that ASL prepared tensor imaging may be able to map the structure of the whole vascular tree as well as probe its microvascular characteristics.

**Labeling efficiency measurement: more accurate CBF quantification**

pCASL is now the most widely-accepted ASL approach and labeling efficiency is one of the most important parameters for accurate pCASL CBF quantification (16). However, to date, there is no reliable method to calibrate the labeling efficiency of pCASL perfusion imaging in a clinically acceptable manner, and usually a constant value (e.g. 0.85) obtained from simulations is adopted (4,47).
However, variation in labeling efficiency is thought to contribute to the relatively high intra- and inter-subject variability observed in quantitative pCASL (48,49). Considering that the asymmetry of brain perfusion is an important indicator for clinical diagnosis in patients and the labeling efficiency may vary between feeding arteries, an artery-specific labeling efficiency measurement accompanying the standard brain pCASL imaging would be crucial for the use of quantitative pCASL measurements in the individual patient.

In chapter V, a sequence for measuring the labeling efficiency of pCASL was optimized and validated. The sequence was optimized by studying the stability of the labeling efficiency measurement with regard to the use of cardiac triggering, flow compensation and vein signal suppression. To validate the sequence, in vivo labeling efficiency was deliberately changed by modifying the pCASL flip angle, and then the measured labeling efficiency as a function of pCASL flip angle was compared to simulations and the acquired pCASL perfusion signal intensity in the brain. The conclusion is that the pCASL labelling efficiency measurement sequence can robustly measure the in vivo labeling efficiency and can be used to calibrate the pCASL perfusion signal and improve accuracy of pCASL CBF quantification. The main limitations are that the technique requires careful planning and that the labeling plane needs to be placed lower than the conventional position for standard pCASL cerebral perfusion mapping, resulting in longer arterial transit time and slight SNR loss for the cerebral perfusion signal; furthermore, some user-interaction is required when quantifying the labelling efficiency.

As future perspectives one could see the integration of the labeling efficiency measurement into a normal pCASL scan without SNR penalty, e.g. by using time-encoded principles (50), and to validate the method by comparing the pCASL labeling efficiency corrected perfusion map with other ‘golden-standard’ techniques like PET.

**Blood T₁ measurement: how much do we gain in ASL by moving to ultra-high magnetic field?**

ASL is frequently quoted as an example of a technique that will benefit most from going to ultra-high field MRI (7 T and above), because longer T₁ values and a corresponding improvement of SNR for ASL acquisitions can be anticipated at higher magnetic field strengths (51,52). For ASL this would especially be important since the longer T₁ at ultra-high magnetic field would allow the use of longer post-labeling delay times, which would lead to better compensation for
long arterial transit times as often found in patients with neurological diseases or greater age (53).

In chapter VI, the in vivo blood $T_1$ in the sagittal sinus was measured at three different magnetic fields (1.5T, 3T and 7T) to predict the gain in SNR for ASL by moving to ultra-high magnetic field. Blood $T_1$ was found to increase linearly with magnetic field strength with a very high correlation coefficient. The conclusion is that performing ASL at 7T the gain in SNR due to the increased $T_1$ relaxation time is improved by a factor of 1.3 compared to 3T for (pseudo-) continuous ASL when taking into account only the effect of longer longitudinal relaxation times. The limitation of this prediction is that blood $T_1$ was measured in the sagittal sinus which represents venous blood $T_1$, while the slightly higher arterial blood $T_1$ should actually be employed to accurately predict the SNR gain of ASL. However, the arterial blood $T_1$ is difficult to quantify due to the inflow of uninverted blood into the imaging slice, which prevents a reliable measurement of arterial blood $T_1$. Recently, Li et al. proposed applying an adiabatic inversion RF pulse followed by a Look-Locker segmented TFE acquisition to measure arterial blood $T_1$ in the internal carotid artery (ICA) (54). The technique is intrinsically similar to our method, but the adiabatic inversion RF pulse was optimized to be very insensitive to $B_0/B_1$ inhomogeneity. By applying the optimized RF pulse to a large volume covering the chest area (heart, lung, aorta, common carotid artery etc.) followed by a segmented TFE readout, the inverted blood signal in the ICA can be detected and the motion artifacts due to the arterial blood flow pulsation can be minimized. The results show longer blood $T_1$ (~1840 ms at 3 Tesla) in the ICA compared to the value in the sagittal sinus (~1650) as expected. The main difference between venous and arterial blood is the oxygen fraction, the arterial-venous $T_1$ difference as a function of magnetic field strengths has been found to show a quadratic dependence (55).

Despite the intrinsic advantage of higher SNR, the implementation of ASL at ultra-high magnetic field is still very challenging, mainly due to the increased $B_1$ and $B_0$ inhomogeneity, and increased risk of RF heating. Future perspectives include optimization of adiabatic inversion pulses which are less sensitive to $B_1$ inhomogeneity (56); separate labeling coils and multi transmit methodology to reduce the magnetic transfer effects and SAR; high permittivity pads to improve $B_1$ homogeneity (57,58); and image-based shimming to improve $B_0$ homogeneity(59,60).
References


