

Expanding the capabilities of arterial spin labeling MRI Zhang, X.

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Chapter VI

In Vivo Blood T₁ Measurements at 1.5 T, 3 T, and 7 T

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Abstract

The longitudinal relaxation time of blood is a crucial parameter for quantification of cerebral blood flow by arterial spin labeling and is one of the main determinants of the signal-to-noise ratio of the resulting perfusion maps. Whereas at low and medium magnetic field strengths (B_0), its in vivo value is well established; at ultra-high field, this is still uncertain. In this study, longitudinal relaxation time of blood in the sagittal sinus was measured at 1.5 T, 3 T, and 7 T. A nonselective inversion pulse preceding a Look-Locker echo planar imaging sequence was performed to obtain the inversion recovery curve of venous blood. The results showed that longitudinal relaxation time of blood at 7 T was ~ 2.1 s which translates to an anticipated 33% gain in the signal-to-noise ratio in arterial spin labeling experiments due to T_1 relaxation alone compared with 3 T. In addition, the linear relationship between longitudinal relaxation time of blood and B_0 was confirmed.

Key words:

longitudinal relaxation time; magnetic field; arterial spin labeling; T_1 ; 7 T

Introduction

The longitudinal relaxation time of blood $(T_{1, blood})$ plays a critical role in perfusion imaging based on arterial spin labeling (ASL) techniques (1,2). ASL techniques use an endogenous contrast agent by detecting the distribution of magnetizationtagged blood. In the tagged image, the magnetization of inflowing arterial blood water is inverted. After a short time delay to allow the labeled spins to reach the capillary bed and to exchange with tissue, a so-called "label" image is acquired. A second image, the control image, is acquired using exactly the same imaging parameters without the inversion pulse. The perfusion weighted image is formed by subtraction of these two images, removing signals from the static tissues, thereby showing the distribution of the endogenous tracer (3,4).

The value of $T_{1, blood}$ determines how fast this endogenous tracer decays: because this value is between 1 and 2 s for 1.5 T and 3 T field strengths; there is a compromise between the signal-to-noise ratio (SNR) of the perfusion- weighted scan and a sufficient long inflow time to allow the labeled blood to reach the microvasculature (5,6).Therefore, $T_{1, blood}$ is one of the main determinants of the SNR of the resulting perfusion map and limits the ability of ASL to measure perfusion in regions with low flow.

For single phase homogeneous substances, the relationship between T_1 and the Larmor frequency (ω_0) is governed by the Bloembergen-Purcell-Pound theory (7,8), which shows that T_1 increases with increasing Larmor fre-quency and, therefore, static magnetic field strength (B_0). This theory is only strictly applicable to pure substances, and the relationship between T_1 and B_0 is much more complicated for human tissues. Some in vitro measurements of $T_{1, \text{ blood}}$ between 1.5 T and 9.4 T have shown a linear relationship (9), but in contrast some earlier nuclear magnetic resonance and in vivo measurements showed a sublinear relationship between 0.02 T and 7 T (8,10). Only a single in vivo human study has so far provided measurements of $T_{1, \text{ blood}}$ at 7 T, and this value of 2600 ms (10) was much higher than the in vitro measurements of 2212 ms (9).

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 T_1 values and a corresponding improvement of SNR for ASL acquisitions should be anticipated for higher magnetic field strengths. In addition, an accurate estimate of the $T_{1,}$ value is important for the calculation of quantitative cerebral blood flow (CBF) values in ASL as well as for cerebral blood volume measurements using the Vascular Space Occupancy technique, which requires the exact T_1 value to null the blood signal (11–13).

The goal of this study is to measure the T_1 of blood in the sagittal sinus at 7 T and to compare it to measurements obtained at 1.5 and 3 T, thereby determining the relationship of $T_{1, \text{ blood}}$ as a function of magnetic field strength, and predicting the expected gain in SNR for ASL by moving to 7 T.

METHODS

Theory: SNR of ASL as a Function of T_{1, blood}

In terms of the implications for ASL, the dependence of the SNR of continuous ASL on the $T_{1, \text{ blood}}$ can be calculated by using the following equation (assuming a $T_{1, \text{ blood}}$ of 1650 ms at 3 T, a $T_{1, \text{ blood}}$ of 2212 or 2600 ms at 7 T, a typical labeling duration (LD) of 1650 ms, and a post labeling delay (PLD) of 1500 ms):

SNR
$$\propto \int_{PLD}^{LD+PLD} e^{-\frac{t}{T_{1,blood}}} dt$$
 [1].

This would result in a 63% increase in SNR by going from 3 T to 7 T when assuming a $T_{1, blood}$ of 2600 ms at 7 T, compared with only 40% if the value from the in vitro measurements (2212 ms) would be applied. In a similar manner, the influence on the SNR of pulsed ASL can be approximated by

$$SNR \propto e^{\frac{PLD}{T_{1,blood}}}$$
 [2].

This would result in a 40% increase in SNR for the longest T_1 of blood, compared with only 25% for the value from the in vitro measurements. Therefore, for both continuous ASL and pulsed ASL, increased SNR can be anticipated with prolonged longitudinal relaxation time.

Subjects and MR Acquisitions

Six healthy subjects (three males, three females) aged between 24 and 38 years (mean age: 31 ± 6 years) were recruited and scanned randomly over the three field strengths within 1 month. All protocols were approved by the Leiden University Medical Center and Utrecht University Medical Center Committee for Medical Ethics. MRI experiments were performed on scanners with a field strength of 1.5 T, 3 T and 7 T (Philips Healthcare, Best, The Netherlands) using 15 channel (1.5 T) and 32 channel (3 T and 7 T) receive coils. Measurement of $T_{1, \text{ blood}}$ was performed by the technique proposed by Varela et al. shown in Figure 1 (14).



FIG. 1. Overview of the MRI sequence which starts with a nonselective 180 inversion pulse followed by a slice-selective Look-Locker echo-planar imaging with 95° flip angles. The interval between read-out pulses was 150 ms and the imaging slice was planned perpendicular to the sagittal sinus.

It starts with an adiabatic nonselective 180°global inversion pulse (hyperbolic secant pulse, B_1 value /duration of the pulse = 13.5 µT/13 ms at 1.5 T and 3 T, while 17 µT/10.5 ms at 7 T) followed by a slice-selective Look-Locker echo-planar imaging read-out with 95° flip angles. This approach is based on the assumption that within the imaging plane the blood in the sagittal sinus is completely refreshed between two consecutive read out pulses. The inversion recovery curve was sampled 60 times every 150 ms, resulting in an effective measurement time of 9 s. The following parameters were used: Look-Locker echo-planar imaging: $\alpha_{LL} = 95^\circ$, slice thickness 2 mm, voxel size 1.5 mm × 1.5 mm, pulse repetition time 10 s (1.5 T and 3 T) and 20 s (7 T), SENSE-factor 3.5 (3 T and 7 T) and 3 (1.5 T), number of signal average 6, first inversion time (TI) 190 ms, Δ TI 150 ms, number of TI values 60.

Analysis

The Nelder-Mead search method (function fminsearch, MATLAB, The MathWorks) was used to obtain the $T_{1, blood}$ estimation by fitting the signal of each voxel as a function of three parameters (M_0 , offset, and $T_{1, blood}$):

$$M(nTI) = abs\left(M_0 * \left[1 - 2 * e^{\frac{offset + firstTI + (nTI - 1) * \Delta TI}{T_{1,blood}}}\right]\right)$$
[3]

The offset was included in the model to correct for possible imperfect inversion, for example due to T_2 -effects during the pulse or inhomogeneities of the radio-frequency field, and the labeling efficiency (a) was calculated by using the following equation: $\alpha = e^{-\frac{offset}{T1,blood}}.$

Four to eight voxels in the sagittal sinus were selected and the signals from these voxels were fitted to Eq. [3]. The estimated $T_{1, \text{ blood}}$ values from these voxels were subsequently averaged to obtain the reported overall value of $T_{1, \text{ blood}}$ for each subject.

RESULTS



FIG. 2. Signal intensity time course in a representative subject, stars represents data points and solid lines are the fitted signals, blue is 1.5 T, green 3 T, and red 7 T.

Figure 2 shows the inversion recovery curves from a sin-gle voxel at 1.5 T, 3 T, and 7 T in a representative subject, resulting in an estimated $T_{1, \text{ blood}}$ in this subject of 1439 ms at 1.5 T, 1592 ms at 3 T, and 2007 ms at 7 T.

| | 1.5 T | | 3 T | | 7 T | |
|-----------|-----------------------|--------|-----------------------|--------|-----------------------|--------|
| | T _{1, blood} | α (%) | T _{1, blood} | α (%) | T _{1, blood} | α (%) |
| Subject 1 | 1499 | 99 | 1734 | 98 | 2066 | 96 |
| Subject 2 | 1556 | 99 | 1728 | 97 | 2169 | 98 |
| Subject 3 | 1538 | 98 | 1580 | 98 | 2254 | 99 |
| Subject 4 | 1408 | 100 | 1652 | 98 | 2101 | 98 |
| Subject 5 | 1451 | 100 | 1608 | 99 | 2070 | 100 |
| Subject 6 | 1427 | 98 | 1594 | 98 | 1864 | 96 |
| Mean ± SD | 1480 ± 61 | 99 ± 1 | 1649 ± 68 | 98 ± 0 | 2087 ± 131 | 98 ± 1 |

Subjects 1-3 are females and subjects 4-6 are males.

Table 1

Table 1 shows all the $T_{1, blood}$ values obtained from the six subjects at the three different field strengths. In each subject, a clear increase in $T_{1, blood}$ is apparent at higher magnetic field strengths. As in previous studies, the average value of $T_{1, blood}$ of female subjects is consistently higher than that of male subjects (Table 2) (15).

| | Females | Males |
|-------|---------------|------------|
| 1.5 T | 1531 ± 29 | 1429 ± 21 |
| 3 T | 1681 ± 87 | 1618 ± 30 |
| 7 T | 2163 ± 94 | 2012 ± 119 |

 Table 2: The Average Values and Standard Deviations of T_{1, blood} (Values in ms) Showing

 Higher Values for Females than Males

The inversion efficiency for the nonselective inversion pulse was found to be 99.2%, 98.1%, and 98.3%, respectively, at 1.5 T, 3 T, and 7 T. Table 1 also lists the averaged results of $T_{1, \text{ blood}}$ for the three different field strengths. When the measured values of all volunteers are plotted against field strength the graph is highly linear, as shown in Figure 3, with a fitted equation:

$$T_{1, blood} = 110 \text{ ms/T} * B_0 + 1316 \text{ ms} (R^2 = 0.903)$$
 [4],

which is similar to the results of previous in vitro measurements (9).



FIG. 3. Blood T_1 as a function of the magnetic field strength showing a linear increase between 1.5 T and 7 T.

DISCUSSION

The main findings of this study are 3-fold: first, the $T_{1,\text{blood}}$ in the sagittal sinus at 7 T was 2.1 s, significantly lower than has been reported previously (10); second, $T_{1,\text{blood}}$ increases linearly with magnetic field strength with a very high correlation coefficient; and third, the average $T_{1,\text{blood}}$ of males were lower than females at all field strengths.

Using Eqs. [1] and [2], the observed $T_{1, blood}$ of 2.1 s translates to an SNR increase for continuous ASL (only taking the effect of longitudinal relaxation into account) of 33% and for pulsed ASL of 25% when moving from 3 T to 7 T. This $T_{1, blood}$ (2.1 s) as measured in this study is much shorter than that reported by Rooney et al. (2.6 s), which implies that the anticipated gain in SNR for ASL scans at 7 T due to the longer T_1 compared with 3 T is decreased by almost a factor-of-two compared with these previous measurements, even though measurements of $T_{1, blood}$ were performed at the same location, i.e., the sagittal sinus. The discrepancy

between our results and those of Rooney et al. can probably be explained by the fact that we used an optimal sequence for measuring the $T_{1, \text{ blood}}$ as compared with the sequence of Rooney et al. which was designed to enable measurement of the longitudinal relaxation times in many different, mostly static cerebral structures. The sequence in our present study, originally proposed by Varela et al., exhibits very efficient suppression of back-ground signal due to the 95° radiofrequency-pulse in the Look-Locker echo-planar imaging readout, thereby significantly reducing partial volume effects with cerebral spinal fluid. Even a very minor inclusion of cerebral spinal fluid-signal would give rise to a significant increase in the observed $T_{1, \text{ blood}}$ due to the much longer T_1 of cerebral spinal fluid.

The differences between male and female subjects can be explained by the higher hematocrit in males. This is in agreement with the study of Lu et al. which showed a decrease in $T_{1 \text{ blood}}$ for a higher hematocrit (15). However, this difference did only reach significance at 1.5 T and not at 3 T and 7 T (Student's t-test). This can most probably be attributed to the small sample size (only three males versus three females). In Lu et al.'s study, it was also observed that the arterial $T_{1 \text{ blood}}$ is slightly higher than the venous $T_{1, blood}$ and that it decreases at a slower rate for lower hematocrits. In this study, only the venous $T_{1, \text{ blood}}$ was measured because the arterial $T_{1 \text{ blood}}$ is difficult to quantify due to the inflow of uninverted blood into the imaging slice, which prevents a reliable measurement of $T_{1 \text{ blocd}}$. The main difference between venous and arterial blood is the oxygen fraction, and so far only a single study has investigated the arterio-venous T_1 difference as a function of magnetic field strengths, showing a quadratic dependence (15). At 1.5 T, arterial and venous blood T_1 values are virtually the same, whereas arterial blood T_1 is 79 ms higher than venous blood T_1 at 3 T and 330 ms at 4.7 T. Therefore, arterial blood T_1 would be anticipated to be ~940 ms higher than venous blood at 7 T, although one must recognize that this is based on extrapolation of data leading to high uncertainty and experimental verification is therefore needed.

One assumption of the employed method in our study is that the observed spins in the sagittal sinus do not experience any read-out radiofrequency pulses before detection and that these spins were fully inverted. If inflowing blood which passed through the imaging slice is perturbed by the read-out pulses before detection in the sagittal sinus, this would affect the detected signal and lead to errors in the T_1 measurement. In addition, inflowing blood in the imaging voxel at the end of the experiment might not have been inverted, because an effective measurement time of 9 s is longer than the mean transit time of the cerebral vasculature (~4 to 6 s). To study the extent of these effects, curve fitting was repeated for only the first half of the data (up to 4.5 s). This analysis gave essentially identical results, and supporting the conclusion that this potential mitigating factor is not significant. In addition, any potential effects of radiation damping (which would reduce the measured relaxation time) are expected to be quite small due to the very low quality factor of the loaded coil at 7 T, and the fact that each element of the array samples only small fraction of the total volume of the brain.

The SNR benefit for ASL when going to ultra-high magnetic field not only depends on the $T_{1, \text{ blood}}$ but also on other factors such as the T_2^* of the tissue and blood, and the general increase in SNR at higher field strengths, etc. The T_2^* of brain has been measured as 65 ms at 1.5 T, 48 ms at 3 T, and 28 ms at 7 T, the arterial T_2^* at 7 T is currently not known, but values have been measured at lower fields of 125 ms at 1.5 T and 71 ms at 3 T (16). Assuming a typical echo time of 22 ms, by moving to 7 T, the signal loss in the tissue compartment is 1.48 times faster than 3 T. Including the higher signal intensity at ultra-high magnetic field, the longer $T_{1, \text{ blood}}$ and the shorter T_2^* , the SNR gain in the tissue compartment would be anticipated to be 123% by performing ASL at 7 T rather than 3 T.

To assess the variation on CBF quantification due to blood T_1 variation, a single-compartment ASL model can be used as a first-order approximation: $\Delta s = f * 2\alpha \frac{M_0}{\lambda} re^{-\frac{T}{T_{L,blood}}}$ where Δs is the ASL-signal, α is the labeling efficiency, and the product f^*t is the amount of tagged blood. This shows that an underestimation of CBF of about 25% would be observed if a $T_{1, blood}$ of 2600 ms would be used instead of the measured value of 2100 ms. Furthermore, an underestimation of CBF by 3% would be observed in females and an overestimation of 3% in males when assuming a single, mean value of $T_{1, blood}$ (calculations based on the mean T_1 -values in males and females).

So far, blood T_1 has been measured both in vivo and in vitro in many studies. Both approaches have their advantages and disadvantages. For in vitro measurements, oxygen level and hematocrits can be controlled and imaging can be performed at sufficient resolution to circumvent partial volume effects. However, blood is measured in a static condition or a complicated flow set-up is needed, which increases the required volume of human blood considerably. In vivo experiments reflect the true physiological situation at the expense of the risk of partial volume effect. Moreover, such in vivo experiments could potentially be included in a quantitative ASL protocol for inter-individual calibration of the decay rate of the tracer, i.e., the ASL-label.

In conclusion, $T_{1, blood}$ at 7 T was measured in the sagittal sinus to be ~2.1 s, which is shorter than reported from previous measurements. Performing ASL at 7 T, the gain in SNR due to the increased T_1 relaxation time is still improved by a factor of 1.3 compared with 3 T. To get an accurate CBF quantification, it would be better to combine the experiment with a T_1 measurement. Combined with the general higher SNR at 7 T, this leads to the conclusion that 7 T remains a promising candidate for ASL perfusion imaging.

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Chapter 6 | *In Vivo* Blood T₁ Measurements

Chapter VII

Discussion and Summary

Discussion and Summary

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 e 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 \sqrt{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 T_2 *=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 883ms<PLD<2176ms, while it was relatively stable for PLDs > 2176ms. The fast compartment of the conventional IVIM experiment showed comparable apparent diffusion values to the ASL-signal with PLDs between 1747ms and 2176ms. 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 (PLD>2176 ms) was found to be $\sim 1.9 \pm 1.4 \times 10^{-3}$ mm2/s, which is two times lower than the D* using the mono-exponential model (~4.0±2.8×10-3 mm2/s) and two times higher than the diffusion coefficient of the slow compartment $(0.90\pm0.05\times10-3 \text{ mm2/s})$ 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 T_1 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 T_1 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, 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, 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, was measured in the sagittal sinus which represents venous blood T₁, while the slightly higher arterial blood T₁ 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 T₁. Recently, Li et al. proposed applying an adiabatic inversion RF pulse followed by a Look-Locker segmented TFE acquisition to measure arterial blood T₁ 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 T₁ (~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 arterialvenous T₁ 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).

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Chapter 7 | Discussion and Summary