Validation and application of arterial spin labeling MRI for cerebral perfusion
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GENERAL INTRODUCTION
AND OUTLINE
INTRODUCTION

Physiological background and rationale for perfusion imaging

The perfusion of brain tissue with a continuous supply of oxygenated blood and glucose is essential for a proper brain function. When the supply of blood is disrupted (locally or globally), the brain tissue will be deprived of oxygen, leading to tissue damage and eventually tissue death. Pathologies that acutely affect the cerebral blood flow (CBF) are therefore characterized by relatively high rates of cognitive and/or physical impairment and mortality (Go et al., 2014). Consequently, fast and accurate assessment of local CBF is of utmost importance in the acute clinical setting. For example, in the case of an acute stroke, information on local CBF is showing great promise to assess the extent of salvageable brain tissue and benefit of reperfusion therapy (Albers et al., 2006).

For pathologies that chronically affect the blood supply, baseline CBF alone may provide insufficient information for a correct assessment of vascular pathology. Chronic pathologies often exhibit normal baseline CBF though at maximum dilator capacity. Vascular reserve may be impaired, leaving the vessels unable to react to increased oxygen demand or decreased supply and causing chronic perfusion deficits in areas at risk. For instance, in the case of an internal carotid artery occlusion, baseline CBF often appears normal over the whole brain. However, when encountered with a perfusion stimulus, it can be seen that the affected side is unable to react as well to the stimulus as the unaffected side. In this case, the amount of decreased CBF reactivity could be an indication of chronic CBF deficits (Bokkers et al., 2011; Donahue et al., 2012).

Apart from the clinical research setting, CBF is rapidly gaining popularity as a parameter of interest in the field of drug research as well. For example, CBF levels and patterns are increasingly considered as potential parameters for the assessment of acute and long term medication effects in the brain (Chen et al., 2011; Schouw et al., 2013).

Clinical perfusion measurement techniques

Currently, the CBF can be measured with almost all imaging modalities available in the clinic (Wintermark et al., 2005). It can be assessed on a global manner by measuring the total amount of blood flowing to the brain, while local measurements image the perfusion distribution within the brain. Global perfusion can be estimated non-invasively with ultrasound in the brain feeding arteries, though it cannot directly measure the flow and rather probes velocities in the artery. Local perfusion can be assessed with positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT). These techniques can be categorized into invasive and non-invasive perfusion techniques. With the invasive perfusion techniques, a bolus of contrast-agent is injected in (preferably) the arm by means of a venous puncture. The contrast agent subsequently travels with the blood to the brain, where it causes a signal change as function of the time. This signal change is measured by the modality, after which the CBF image is calculated based on the Kety-Schmidt theorem (Kety and Schmidt, 1948).

Currently, $^{15}$O-$\text{H}_2\text{O}$ PET is regarded as the most accurate and reproducible perfusion imaging technique available in the clinic. Yet, the requirement of a cyclotron severely limits the clinical usage to a few highly specialized medical centers. Requiring solely a widely available CT system and coming with less contra-indications than MRI, Iodine-CT perfusion imaging is the preferred
method of choice in the acute clinical setting as for example with acute ischemic stroke. In the non-acute setting, where radiation exposure may be a concern, gadolinium enhanced MRI is currently the most applied technique. Applications here range from the detection of tumors to follow-up on ischemic strokes (Wintermark et al., 2005). However, it should be noted that both gadolinium-MRI and Iodine-CT use contrast agents which can induce nephropathy or nephrogenic systemic fibrosis in patients with impaired renal function (Marckmann et al., 2006; Rao and Newhouse, 2006). Technetium SPECT CBF imaging is nowadays not widely used in the clinic due to the relative high amount of radiation and decreased precision, compared to the other imaging techniques. However, the major drawback of all these invasive approaches, is the injection of contrast agent in the vein combined with either the usage of radiation (CT, PET and SPECT) or contrast agents which are toxic at higher dosages (gadolinium-MRI, Iodine -CT), limiting repeated usage within a short time frame.

Originally developed in the beginning of the 90s by Williams, Detre and colleagues (Detre et al., 1992; Williams et al., 1992), but only gaining popularity since a few years due to key technical developments, arterial spin labeling (ASL) MRI is capable to measure the CBF non-invasively. ASL employs the blood that travels to the brain as an endogenous contrast agent. The contrast induced by the magnetically labeled blood is then used to generate a perfusion weighted image. Since the major developments in ASL are relatively recent, the actual clinical usage is currently limited to highly specialized medical centers (Golay and Guenther, 2012). However, the non-invasive character of ASL and the ability for repeated measurements shows great promise for substituting current perfusion imaging techniques in a wide range of clinical pathologies. This includes the follow-up after an ischemic event, detection of tumors and assessment of arteriovascular malformations (Noguchi et al., 2008; Wolf et al., 2008, 2005).

**Arterial spin labeling**

**Measurement mechanism**

In ASL, the water molecules in the blood are magnetically labeled. Generally, this occurs in the brain feeding arteries at the height of the neck. The magnetically labeled blood then travels to the brain capillaries, where it causes a small attenuation of the brain magnetization. with respect to the non-labeled situation. This signal attenuation is proportional to the CBF and is the basis of ASL imaging. In practice, an ASL experiment consists of 2 separate measurements, namely a *label* measurement and a *control* measurement. Both measurements consist of a labeling period, a delay time (1.5-2 sec) to allow for the labeled blood to arrive in the brain capillaries, followed by acquisition of the brain magnetization. The single difference between both experiments is that in the control experiment the water molecules are not actually labeled. Subtraction of the labeled measurement from its control yields a perfusion weighted image. Since the blood occupies on average ~4% of the brain tissue (Ito et al., 2003; Leenders et al., 1990), the observed difference in blood signal is relatively small, compared to the total brain signal. In addition, the longitudinal relaxation time of the magnetically labeled blood (~1.65 sec at 3T (Lu et al., 2004; Varela et al., 2010)) is relatively short compared to the delay time, resulting in a small percentage of remaining label at the time of acquisition. A single subtraction image is therefore governed by noise and not reliable due to the low signal to noise ratio (SNR). For a
reliable perfusion image, the paired measurements are repeated multiple times (~30 times at 3T) to average out the noise (see figure 1) (Gevers et al., 2009).

![Figure 1: Example of a control and label image with the corresponding perfusion weighted ASL subtraction difference, after 1 and after 30 measurements.](image)

**Blood labeling approaches**

One of the most important aspects of ASL is the creation of a magnetically labeled bolus of blood. Several labeling methods have been proposed over the past decade. Historically, these methods are categorized into continuous ASL (CASL) (Detre et al., 1992; Williams et al., 1992), pulsed ASL (PASL) (Golay et al., 2005; Kim, 1995; Wang et al., 2002; Wong et al., 1997) and more recently also the velocity selective ASL (VS-ASL) (Duhamel et al., 2003; Schmid et al., 2014; Wong et al., 2006) labeling techniques (see figure 2) (Duhamel et al., 2003; Schmid et al., 2014; Wong et al., 2006). The CASL approach labels the blood by means of a thin labeling slice in the neck with a long low-power RF pulse, for a period of 1500 ms to 3000 ms). The moving blood-water spins traveling to the brain are inverted while traversing through the labeling plane, effectively creating the blood bolus as function of time. The CASL

![Figure 2: Illustration of the three major ASL labeling mechanisms. The CASL/pCASL and PASL techniques employ a labeling plane, while the VS-ASL techniques employ a blood velocity selective cut-off. Labeled blood is indicated in red, while non-labeled blood is indicated in blue.](image)
technique has the main advantage that it creates a well-defined blood bolus that is relatively insensitive to heterogeneities in the arrival time of the blood in the capillaries, while the major drawbacks are the relatively low percentage of created labeled blood (~68%, also known as the labeling efficiency) and decreased reproducibility with respect to the other ASL labeling approaches (Gevers et al., 2011; Wong et al., 1998). The PASL techniques label the spins almost instantaneously over a 80-100 mm slab along the neck by means of a high-power RF slab-selective inversion. The main advantage of the PASL sequence is the high labeling efficiency (~99%), while the most important disadvantage is the high sensitivity of the blood bolus to heterogeneities in the arrival time of blood in the brain, leading to a less well preserved blood bolus at arrival in the microvasculature. Attempting to obtain both a high labeling efficiency and well preserved blood bolus, Dai and colleagues proposed to modify the CASL technique to a pseudo-CASL (pCASL) labeling approach (Dai et al., 2010; Silva and Kim, 1999). By applying a long pulse train of short high powered RF pulses in a thin slab, a CASL like blood bolus can be created as function of time, yielding a higher labeling efficiency (85%) combined with low sensitivity to the bolus arrival time artifacts. The performance of pCASL has been investigated extensively over the years, showing a superior SNR and reliability when compared to the existing PASL and CASL techniques (Chen et al., 2011; Gevers et al., 2011). PCASL is therefore currently recommended by the ASL community as the preferred method of choice for clinical ASL studies. More recently, a new type of labeling sequences has been developed to resolve the remaining sensitivity to heterogeneities in the bolus arrival time as observed with pCASL. By labeling the blood in the brain based on a velocity or accelerative selective cutoff, perfusion weighted images can be generated (Norris and Schwarzbauer, 1999; Schmid et al., 2014; Wong et al., 2006). These VS-ASL techniques have shown great potential in dealing with the arrival time artifacts, since the blood is labeled closer to the microvasculature. However, the exact reliability and accuracy are still unknown, as is the exact origin of the obtained image contrast. Another major advantage of the VS-ASL techniques is the requirement of no separate labeling coil at higher magnetic fields, making them more suitable for usage on 7T MRI systems.

**Delay time implementations**

Following the labeling module, a delay time is applied to allow for the labeled blood to travel to the brain capillaries. Depending on the applied labeling method and clinical population, this delay ranges from 1.5-2 seconds and is essential for accurate and reliable CBF images. However, a major drawback is the “lost” imaging time where no action is performed. Therefore, several options have been proposed to utilize the delay time more effectively. Generally, background suppression pulses are applied to suppress the static brain tissue signal, for an improved SNR and precision of the acquired ASL images (Garcia et al., 2005; Gevers et al., 2011). The ASL signal difference comprises only 1-5% of the total magnetization. Therefore, noise variations in the remaining 95-99% of the static tissue greatly impact the SNR of the ASL derived difference images. The SNR in the ASL images can be significantly improved by reducing the static tissue and their respective noise contribution with background suppression pulses (figure 3) (Garcia et al., 2005; Ye et al., 2000). One could also consider avoiding the delay time and measure the in-and outflow of the label as function of time by means of multiple read-out acquisitions within
a single repetition time (TR). Quantitative STAR labeling of arterial regions (QUASAR) employs a PASL labeling pulse, directly followed by a Look-Locker sampling of the ASL signal as function of time (Petersen et al., 2006). Based on the Kety-Schmidt model revised for ASL perfusion imaging, the CBF images are subsequently calculated (Kety and Schmidt, 1948). The major advantage of QUASAR is that not only CBF information is gathered, but also knowledge on the bolus arrival time (BAT) and the arterial blood volume (aBV) are provided. However, the major drawback of the current QUASAR approach is the loss of full brain coverage and lower image resolution due to the Look-Locker read-out (Petersen et al., 2006). Recent advancements by means of Hadamard encoded pCASL and TURBO-QUASAR approaches show great potential for the acquisition of whole brain high SNR perfusion images combined with bolus arrival time information, though these approaches are still in the validation phase and not ready for widespread clinical usage (Petersen et al., 2013; Teeuwisse et al., 2014). As last, it was recently proposed to acquire an angiogram of the cerebral vasculature during the delay time, effectively acquiring two separate scans within the acquisition time of a single ASL scan (Suzuki et al., 2014).

Figure 3: The effect of background suppression on the noise in ASL brain images, with the corresponding noise effect in the difference signal. Error bars indicate the standard deviation over 30 temporal averages.

Read out approaches
The ASL read-out succeeding the delay period is nowadays mainly performed by either a single shot multi-slice EPI (Ms-SSh-EPI) read-out with a fast field echo (FFE) preparation, a SSh-3D
read-out with a spin echo (SE) preparation or a segmented 3D read-out with a SE preparation (Günther et al., 2005; Vidorreta et al., 2012; Ye et al., 2000) (see figure 4). The EPI read-out has the advantage that it is widely available on all commercial platforms. Yet the 3D-SE read-outs have a superior SNR and better background suppression, while being less susceptible to off-resonance artifacts. A minor drawback of the 3D approaches is blurring of the image in the slice direction. Where the SSh-3D read-out have shown the most potential, acquiring high quality whole brain images within a single TR, the reliability of these techniques are not yet fully validated for widespread clinical usage. Currently, a segmented 3D-read-out is recommended for routine clinical research based on its stability (Alsop et al., 2013).

![ASL read-out approaches](image)

**Figure 4:** An illustration of the major ASL read-out approaches in k-space, where the 3D approaches can be acquired in a single shot or a in a segmented manner (acquiring half of the spirals or planes within each TR instead of all).

**ASL quantification**

Following acquisition of the CBF weighted ASL images, it is essential to translate the derived MRI values into quantitative CBF values. Based on the blood flow model described by Kety-Schmidt (Kety and Schmidt, 1948), Buxton and colleagues derived a generic ASL solution, describing the CBF as function of the magnetization (Buxton et al., 1998) (see formula 1).

\[
\Delta M = 2 \cdot \alpha \cdot M_{a,0} \cdot f \cdot (c(t) \otimes (r(t) \cdot m(t)))
\]

Here \(\Delta M\) is the perfusion weighted difference signal as measured with ASL, \(\alpha\) the labeling efficiency, \(M_{a,0}\) the equilibrium magnetization of arterial blood, \(f\) the CBF, \(c(t)\) the delivery function, \(r(t)\) the residue function describing the wash-out of the label and \(m(t)\) the longitudinal magnetization effect. Based on the applied labeling and read-out methods, the delivery and magnetization function are adapted accordingly for an accurate quantification. The model can be implemented based on a one- or two-compartment assumption, whereby the main difference lies in the modeling of the longitudinal relaxation behavior of the magnetically labeled arterial blood. Where the one-compartment model assumes that the label decays with longitudinal relaxation time of arterial blood \(T1_R\) during the whole measurement, the two-
The one-compartment model assumes that when the blood arrives within the capillaries after a time $\delta$, the label decays with the longitudinal relaxation time of the tissue ($T_1$) (Wang et al., 2002) (see figure 5). While the one-compartment model is currently recommended as the generic model of choice for clinical ASL perfusion imaging (Alsop et al., 2013), its simplified label assumption may not hold in terms of quantitative accuracy.

**Figure 5:** The difference between 1 compartment (red) and the 2 compartment (pink) modeling of the blood magnetization as function of time. For the 2 compartment model it was assumed that after 1900 ms the blood magnetization decays with the relaxation rate of tissue instead of arterial blood.
CHAPTER 1

Objective and outline of this thesis

The rapid developments indicated above have now provided sufficient quality for the use of ASL in clinical and research applications beyond highly specialized MR centers. However, with the focus mainly on technical improvements, several clinically relevant aspects of ASL have not been fully investigated to date. These aspects include patient comfort and quantitative accuracy and precision. The main aim of this thesis was therefore to investigate such clinically relevant aspects. The chapters address the improvement of patient comfort in ASL imaging and the comparison of different ASL approaches with respect to $^{15}$O-$H_2O$ PET perfusion imaging.

To facilitate the applicability of ASL measurements in patients groups not eligible for an examination in common “tunnel like” MRI scanners, chapter 2 discusses the implementation and considerations of several ASL approaches on a 1T open bore scanner. Methods to reduce the intense acoustic noise produced by the pCASL labeling module are studied in chapter 3. To validate the performance of the community recommended pCASL technique, a thorough comparison of the reproducibility and accuracy of quantitative pCASL and $^{15}$O-$H_2O$ PET derived CBF measurements during baseline and hypercapnia is outlined in chapter 4. The accuracy of VS-ASL techniques with respect to $^{15}$O-$H_2O$ PET are investigated in chapter 5. As last, chapter 6 addresses the CBF and aBV agreement between QUASAR and $^{15}$O-$H_2O$ PET derived measurements.
LIST OF REFERENCES


