Flow-based arterial spin labeling: from brain to body

Franklin, S.L.

Chapter 1

General introduction

Blood is vital for survival of our organs. It delivers the oxygen and nutrients, necessary for cells to survive and perform their function. In addition, it transports waste products to the kidneys and liver[1]. Blood is pumped from the heart into the vascular tree. From the aorta, which has a diameter of approximately 3.2 cm[2], blood is transported to ever smaller arteries, and eventually into the microvasculature. The microvasculature consist of arterioles and capillaries, which have a diameter of approximately 5-100 µm and 5-10 µm, respectively[1]. It is at the capillary level, that the exchange of oxygen, nutrients and waste products takes place with the tissue[1].

Blood flow at the level of the microvasculature, i.e. perfusion, can provide important information about the function of the organ[3]. In case of e.g. tumorous tissue, blood flow can be increased, because the abnormal growth of cells requires an increased amount of oxygen and nutrients[4]. But there are also diseases associated with an abnormally low blood flow, e.g. acute kidney injury[5]. Here perfusion levels drop below the level required for the metabolic needs, resulting in impairment of kidney function.

This work covers development and optimization of magnetic resonance imaging (MRI) techniques to measure perfusion. Besides MRI, various other perfusion methods exist [6]; e.g. positron emission tomography (PET), single photon emission computed tomography (SPECT), Xenon-enhanced computed tomography (XeCT), and Doppler ultrasound. In PET, SPECT, and XeCT, radioactive tracers are used to generate contrast between blood and surrounding tissue. Although they use tracers with a relatively short half-life, examinations are still associated with a radiation dose of ~2 mSv for PET, and ~10 mSv for SPECT and XeCT. Considering that the average risk for developing cancer is estimated to increase with 0.012% for every mSv[7], caution is necessary with respect to the frequency that these techniques are employed. In addition, these techniques have a high cost and long examination times. $H_2{}^{15}O$-PET is the most expensive due to the requirement of an on-site cyclotron[6], [8]. Doppler ultrasound on the other hand, is completely non-invasive, but there is a limitation to which vessels can be examined and there is a large operator dependence[9].

MRI does not require radioactive tracers, but is often used in combination with gadolinium-based contrast agents (GBCAs) [10], i.e. Dynamic Contrast Enhanced (DCE-) MRI [11] and Dynamic Susceptibility Contrast (DSC) MRI [12]. However, there are also MRI-techniques that do not require administration of GBCAs. Arterial Spin Labeling (ASL) is a cluster of MRI-perfusion techniques, which is completely non-invasive, and which can provide a perfusion map, instead of assessing separate vessels, as in the case of Doppler ultrasound. Clinically, ASL is primarily used for brain applications [8], [13], [14], e.g. in patients with stenosis of brain feeding artery[8], [15], stroke[8], [16] or vascular dementia[8], [17]. However, there are various body applications where ASL could add considerable value[18], [19].

In this work, applications of ASL for perfusion measurements in kidneys and breast were developed, and solutions to the encountered technical challenges were investigated. This introduction will first discuss technical aspects and limitations of contrast enhanced MRI. Followed by an introduction to ASL, including spatially-selective and flow-based ASL, specific challenges that arise in body applications of ASL, i.e. field inhomogeneity, and a possible solution in terms of an alternative readout technique, i.e. spatial encoding (SPEN). Lastly, clinical applications will be discussed.

CONTRAST ENHANCED MRI

In contrast enhanced MRI, GBCA's are used to create contrast between blood and the surrounding tissue[20]. GBCAs are paramagnetic and induce magnetic susceptibility effects, they thus shorten both T_1 and T_2/ T_2*. Which effect dominates, depends on sequence parameters, as well as the location and concentration of the GBCA. The susceptibility effects are most pronounced when the GBCAs remain intravascular, causing magnetic field gradients that extend well beyond the vessel wall. This leads to T_2^*-shortening, in and around the vessels, and a subsequent *loss* in signal[21]. At the same time GBCAs also shorten T_1, which will *enhance* the signal on a T_1-weighted sequence. For perfusion measurement, there are two types of dynamic contrast enhanced MRI, i.e. DSC-MRI and DCE-MRI. DSC exploits the T_2/T_2* shortening induced by the contrast agent, while DCE exploits the T_1-shorterning properties.

In DSC-MRI[12], T_2 or T_2*-weighted images are dynamically acquired before and after injection, to image the first pass of the bolus. It is mainly applied in brain, because the effect relies on GBCAs to remain intravascular, and an intact blood-brain-barrier prevents quick extravasation into surrounding tissue[21]. Evaluating the loss of signal during the first pass of the bolus, allows quantification of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and timing parameters such as time-to-bolus peak (TBP)[21]. DSC is mainly used for evaluation of cerebral ischemia and brain tumors[22].

In DCE-MRI, T_1-weighted images are acquired dynamically before, and after administration of the GBCA, to enable kinetic analysis of the contrast "wash-in" and "wash-out" phase[22]. During the "wash-in" phase the signal is mainly characterized by blood flow. However, there is a second effect that is often exploited in oncology. With time, contrast agent leaks from the intravascular compartment into the extravascular space, from which it will be slowly cleared. This provides a measure of vessel wall permeability. This effect slowly takes over, and dominates the "wash-out" phase of the kinetic curve. Multiple analysis methods exist for DCE-MRI, e.g. evaluation of the shape of the kinetic curve and more advanced modeling allowing the quantification of blood flow, blood volume, and well as the rate at which the contrast agent

diffuses from blood to tissue, e.g. K_{trans}[23]. DCE-MRI is used in many different diseases and organs, e.g. imaging of tumors[10], monitoring therapy response[23], kidney function[23], and neurodegenerative diseases [10]. Permeability measures are employed to discriminate between benign and malignant tumors, since angiogenesis in malignant tumors lead to a higher vessel wall permeability[24], [25]. A rapid decrease in the "wash-out" phase of the kinetic curve, characterizes higher vessel wall permeability, giving a strong indication for malignancy[24], [26].

However, contrast agents should be used cautiously, especially in specific patient groups. About fifteen years ago, nephrogenic systemic fibrosis (NSF), a rare disease in patients with severe renal failure, was first linked to the use of GBCAs[10]. This prompted strict guidelines regarding the use of GBCA in patients with severe kidney failure and/or previous severe reactions to GBCAs[27], including recommendations on dosage and type of GBCA. Since then, the number of NSF incidences has been greatly reduced[10], [27], [28]. However, there are still concerns due to another recently identified side-effect, i.e. retention of contrast agent in organ tissue. Since 2014, numerous studies have been published showing retention of contrast agents in parts of the brain, skin and bones, even in healthy individuals, with unknown clinical and long-term effects[10], [28], [29]. The amount of retention is dependent on the type of contrast agent[29], [30] with macrocyclic agents showing less retention than linear GBCAs, but all seem to show some amount of retention[29]. For this reason, in addition to the important benefits of not requiring an intravenous injection, and enabling repeated measurements, non-contrast enhanced perfusion techniques, such as Arterial Spin Labeling (ASL) have gained a lot of traction.

ARTERIAL SPIN LABELING

In contrast to DCE-MRI, ASL does not create contrast between blood and surrounding tissue by using a contrast agent. Instead, blood itself is used as an endogenous tracer [31]. The magnetization of blood is modulated to create a difference in magnetization between blood and tissue, and thus contrast. In ASL, two types of images are acquired alternatingly; an image where the magnetization of blood is modulated, i.e. labeled, followed by an image without labeling: the control image. Subtracting the label image from the control image results in the ASL image, which only shows signal of the labeled blood while other signals cancel out. Because ASL-signal is based on a difference in longitudinal magnetization, it will relax with T_1, causing a drop in SNR with time[32]. The amount blood compared to tissue is relatively low; e.g. the brain's gray matter has a vascular volume of about 5%[33], even though it is one of the most highly perfused organs, receiving 15-20% of the cardiac output[34]. In an ASL

experiment you can expect to obtain a signal intensity of ~1% of the relaxed brain signal[13]. This means that ASL is an inherently SNR-starved technique.

To maximize SNR multiple ASL techniques have been developed, which vary in the way blood is labeled, and what blood is labeled[32]. This work is mostly focused on flow-based ASL techniques; they label blood on flow velocity or acceleration, whereas more conventional ASL techniques label based on spatial location.

Another key component of the ASL sequence is background suppression. Background suppression aims to minimize all other sources of label/control differences, e.g. caused by motion or physiological noise, to prevent subtraction errors and improve SNR [13], [35], [36]. Background suppression consist of two or more non-selective inversion pulses in combination with a saturation pulse at the beginning of the sequence. The timings are optimized based on Bloch simulations of the magnetization to minimize the signal of relevant background signals at the time of acquisition. Because they are applied in both label and control condition, the difference between label and control, and thus the ASL-signal, is untouched. There is only a small loss due to imperfect inversion of the background suppression pulses[37].

SPATIALLY SELECTIVE ARTERIAL SPIN LABELING

In spatially selective ASL, either a labeling plane is planned: such that all blood flowing through gets labeled, e.g. pseudo continuous ASL (pCASL)[38], or a volume is labeled: as in the case of pulsed ASL techniques, e.g. flow alternating inversion recovery (FAIR). The labeling takes place upstream of the imaging region. Which means that there is a delay, the transit delay or arterial transit time, before the labeled blood has reached the microvasculature in the imaging region.

The transit delay is not a physiological constant, but varies between regions, gender, age, pathology, and just generally between individuals[16], [39]–[42]. For example, MoyaMoya disease results in significantly increased, and a higher inter-subject variation of transit delays[43]. Image acquisition takes place at a certain delay, the post-labeling-delay (PLD), after labeling, to grant the labeled blood time to reach the microvasculature. The PLD ideally needs to be longer than the longest transit delay to make sure all labeled blood has reached the imaging region, and prevent perfusion underestimation[13]. However, because the ASL signal decays with T_1 there is a limit to the length of PLD. The T_1 of arterial blood is approximately 1.65s at 3T, so at a PLD of 1.65s already 63% of ASL-signal has decayed. This can cause limitations in organs with naturally slow blood flow, e.g. the breast[44]. Because the transit delay is usually not known beforehand, multiple PLDs can be acquired to improve perfusion quantification[13].

The recommended ASL technique for brain is pCASL [13]. For brain applications, the pCASL labeling plane is planned in the neck-region, on the carotids and vertebral arteries. The labeling plane is planned at a specific location to make sure that all feeding arteries are perpendicular to the labeling plane. This ensures that all blood flowing into the brain, is inverted [13], [38]. For body applications, planning of the labeling slab can be challenging. First, because of movement, e.g. due to respiration, it can be challenging to plan the plane at the right location. Movement of the organ into the labeling plane needs to be prevented, to prevent direct labeling of the tissue. Second, the vascular bed can be complex, complicating planning of the labeling plane such that all incoming blood flow is labeled correctly, i.e. so that all feeding arteries are perpendicular to the labeling plane. For example, the breast is fed mainly by the internal thoracic artery, but also to some extent by the intercostal and lateral thoracic arteries[45]. These different feeding arteries can all slightly differ in orientation, which can affect labeling efficiency[38]. Third, field inhomogeneity at the labeling location can reduce labeling efficiency, e.g. in the lung area[38], [46], [47]. For example, in renal applications, the labeling slab is planned on the aorta; it should be placed high enough to prevent kidneys from moving into the labeling slab during respiratory cycle; but should not be placed too high to prevent loss in labeling efficiency due to off-resonance around the lungs.

An alternative spatially-selective ASL approach is FAIR [48]. FAIR does not suffer from the same planning issues as pCASL, but there are other considerations that need to be taken into account during planning. In FAIR, difference between label and control is generated by using either a selective or non-selective inversion pulse, followed by a PLD and finally image acquisition. The selective inversion covers the imaging region with a certain additional width, to ensure proper inversion in the whole imaging region[48]. After subtraction, the ASL-signal will consist of the blood signal which was outside of the selective inversion pulse during labeling, and flowed into the imaging region during the PLD. So to label aortic blood, the aorta should be left out of the selective inversion pulse, which can be a challenge for e.g. renal ASL. When the coronal plane of the kidneys (partly) includes the aorta, then it will not be possible to include this part of the kidney in the imaging region, preventing whole kidney coverage.

FLOW-BASED ARTERIAL SPIN LABELING

Flow-based ASL does not suffer from planning issues and transit time sensitivity[49], [50]. In flow-based ASL, blood is labeled non-spatially selective, based on either a cut-off velocity or acceleration. By choosing this cut-off low enough, blood is no longer only labeled upstream to, but also within the imaging region, essentially eliminating the transit time issues [49]. Various flow-based ASL techniques have been published which are either based on labeling blood by saturation, such as velocity-selective ASL (VS-ASL)[49], acceleration-selective ASL

(Acc-ASL)[51], VS-ASL with multiple VSASL-modules (mm-VSASL)[52], or inversion, i.e. velocity selective inversion-based ASL (VSI-ASL)[53]. Because flow-based ASL is inherently transit-time insensitive and does not require planning of a labeling slab, it is especially interesting for body applications.

VS-ASL was first introduced in 2006[49]. Velocity dependence is realized by a set of two bipolar gradients. Bipolar gradients have a zeroth gradient moment of zero, meaning that in case the hydrogen nuclei are static during application of the labeling module, the phase build up by each separate gradient cancel out[54]. However, when the hydrogen nuclei move, there will be a net phase build up, which depends on the velocity[54]. By summing the phase accrual of all velocities while assuming a laminar flow profile, the relation between longitudinal magnetization and velocity will form a sinc-profile [49]. At a velocity of zero, the magnetization remains untouched, while after the first zero-crossing of the sinc, the longitudinal magnetization is significantly reduced. The cut-off velocity is defined as the first zero-crossing and the magnetization is assumed to be saturated above this value[49]. The cut-off velocity is determined by the gradient strength and the delays in between the gradients. It is usually set to 2 cm/s, corresponding to the flow velocity found in the penetrating arteries of the brain's cortical surface[55], at which level within the arterial tree a laminar flow profile is still found[56]. The sequence is only sensitive to velocity in the direction of the gradient. However, because of increased tortuosity of smaller vessels, VS-ASL with a cutoff velocity < 4 cm/s has been found to be relatively independent on the direction of velocity encoding [49]. The VS-ASL sequence consists of a labeling module including bipolar gradients in the label condition, and a control module without bipolar gradients in the control condition. These modules are followed by a PLD, and a second labeling module right before readout. This second labeling module is applied in both the label and control condition and includes bipolar gradients in both conditions. It acts as a vascular crusher, and ensures that only labeled blood that decelerated from above the cutoff velocity during the first labeling module, to below the cutoff velocity during the second module, gets imaged. This means that only arterial blood gets imaged, and venous blood does not, because arterial blood will decelerate as it flows further into the vascular tree, while venous blood does the opposite. The other important reason for having the second labeling module is that it enables quantification of perfusion. The second labeling module cuts off the bolus, and you need to know the bolus length to properly quantify the ASL-signal[49]. Note, that in VS-ASL, the PLD cannot be chosen too short. Even though labeling already takes place in the imaging region, the labeled blood needs enough time to decelerated below the cutoff velocity during the PLD, otherwise it will be crushed by the last VS-ASL module, and SNR will be compromised[49], [56]. In addition, if the PLD is too short, eddy currents induced by the gradients in the VS-ASL labeling module can lead to subtraction errors in the perfusion image[57].

After the introduction of the original VS-ASL approach, several flow-based techniques have been introduced to improve SNR. Acc-ASL is based on similar principles as VS-ASL, only in this case, the gradients in the labeling module are unipolar, introducing an acceleration-sensitivity instead of velocity[51]. In Acc-ASL, the second labeling module is not necessary to remove the venous component from the signal, because higher acceleration (or actually deceleration) mainly occurs on the arterial side and Acc-ASL therefore inherently labels arterial blood. The absence of the second labeling module means Acc-ASL can provide a higher SNR than VS-ASL. The second labeling module removes a significant part of the signal, i.e. all velocities larger than the cutoff velocity. However, a consequence is that quantification is not possible, because the bolus length will not be known[51]. Mm-VSASL is a variation of VS-ASL, where an additional labeling/control module is added to increase the amount of generated label[52]. VSI-ASL on the other hand, is based on a completely different principle. The VSI-ASL labeling module consists of a train of sub-pulses with bipolar gradients and refocusing pulses in between. Spins are inverted in small steps based on the Fourier principle; by using a rectangular amplitude envelope of the sub-pulses a sinc-shaped velocity profile is obtained[53], [58]. But theoretically, the amplitudes of the sub-pulses can be adjusted in such a way to obtain any desired velocity profile[58]. Contrary to VS-ASL, VSI-ASL inverts the static spins while the faster flowing spins retain their magnetization. For this reason VSI-ASL is usually combined with an odd number of background suppression pulses to keep the static tissue positive[53]. Because VSI-ASL is based on inversion instead of saturation it has a theoretical factor 2 SNR advantage compared to the other flow-based techniques. However, this is not met in practice, largely because the block pulses used in the VSI-module introduce a B_1-sensitivity which reduces labeling efficiency[53]. VSI-ASL can be used with either a velocity-insensitive control module, i.e. the same RF pulse train as the labeling module, with gradients turned off, or a velocity-compensated control module, i.e. the same RF pulse train and gradient lobes as the labeling module, only with a unipolar gradient orientation[53]. In the original implementation a velocity-compensated control module is used, because the velocity-insensitive control module the diffusion sensitivity of the label module is not compensated by the control. This could lead to an overestimation of blood flow[53]. However, the velocity-compensated control has B_1-sensitivity which could reduce labeling efficiency already at B_1-levels of 1 ± 0.1[53]. Although this does not provide clear issues in brain, it could potentially become a problem in body applications.

MAGNETIC FIELD INHOMOGENEITY

One of the mechanisms through which the local B_0 is disturbed is through variations in magnetic susceptibility. Magnetic susceptibility is a tissue characteristic which determines the degree to which the tissue becomes magnetized when placed in an external magnetic field[59].

Variations in magnetic susceptibility result in local changes to the precession frequency, so that these hydrogen nuclei are mapped to the wrong location within the MR-image, resulting in distortions of the imaged object[59]. In addition, large variations in susceptibility over a small distance can lead to additional dephasing, i.e. shortening of T_2*, and consequently loss of signal[59]. These mechanisms affecting the homogeneity of B_0 are larger in the body compared to brain due to more air-tissue interfaces, e.g. in the vicinity of the bowel and lungs[60]. This can complicate body applications of ASL in organs close to the lungs, such as breast and kidney.

Another mechanism affecting the B_0 experienced by hydrogen nuclei, is their molecular environment. The molecular environment determines the degree to which the hydrogen nucleus is shielded from the externally applied magnetic field B_0[54]. The effect is a difference in precession frequency between different types of molecules, which results in a displacement between different tissue types, i.e. chemical shift. The most well-known chemical shift effect is that between water and fat.

Also the B_1-field is less homogeneous in body compared to brain. The object to be imaged is typically larger for body imaging, which means it can become of similar dimensions as the 'standing wave' effect[60], [61]. The standing wave effect occurs when various electromagnetic waves interact within the sample, causing either constructive or destructive interference, leading to large spatial variations in B_1.

Similar to VSI-ASL, inhomogeneity in the B_1 and B_0-field can also affect the labeling efficiency of other ASL-techniques. Much is still unknown about the performance of flow-based ASL-techniques in the kind of field conditions found in body. Next to affecting labeling efficiency, field inhomogeneity can also affect the readout. In ASL, single-shot echo-planar imaging (EPI) is an often used as readout. EPI is a fast readout, making it relatively insensitive to motion, which is especially important for body applications. However, the speed of EPI comes at the cost of a sensitivity to B_0-field offsets, especially in the phase-encoding direction, because of limited gradient strength in this direction.

READOUT METHODS

Segmented 3D turbo spin echo (TSE) or gradient- and spin-echo (GRASE) approaches have been recommended for brain ASL[13]. This is mainly because they enable optimized background suppression for the whole FOV, instead of only the first couple of slices, as is the case in 2D multi-slice EPI. In kidney, due to limited clinical experience with 3D readouts, 2D spin-echo echo planar imaging (SE-EPI) is recommended[62], despite its sensitivity to field-inhomogeneity.

Spatio-temporal encoding (SPEN) is a readout technique that is more robust to field inhomogeneity than EPI, while keeping similar readout times[63]. In SPEN, a frequency swept pulse is used in combination with a gradient, which imparts a quadratic phase profile[63]. The result is that resonance frequencies are spread out over the FOV. So contrary to EPI, not all locations will get excited at the same time. Thus each location will experience the excitation gradient for a specific time, leading to a specific phase-build up after excitation[64]. A refocusing pulse, followed by blips of an acquisition gradient will then sequentially unwind the phases belonging to specific parts of the FOV, leading to a signal that is spatially encoded in time. Because the signal in time is already directly proportional to the spin density at a certain location, there is no need for Fourier analysis.

SPEN is usually applied in the direction equivalent to the phase-encoding direction in EPI. An important advantage of SPEN is that it enables use of a stronger acquisition gradient compared to EPI [63], see appendix chapter 4. In addition, by choosing the proper timings, all points will get T_2* refocusing[63], instead of only the center of k-space as is the case in EPI, see the appendix of chapter 4. These properties make SPEN more robust to field inhomogeneity than EPI. So, it would be interesting to see whether SPEN can be used in conjunction with ASL, especially when considering body applications or patient groups with implants. See appendix chapter 4 for formulas and theoretical background on SPEN.

CLINICAL APPLICATIONS OF ASL

Although ASL is still traditionally seen as a brain technique, numerous body applications have started to emerge[18], [19]. In this work, we will explore the application of ASL in kidney and breast cancer.

In kidneys, perfusion provides the driving force for glomerular filtration, and thus the metabolic activity of the kidneys, as well as delivery of oxygen and nutrients to support general organ function [18]. Furthermore, hypoxia as a result of inadequate blood supply has shown to be associated to the initiation and progression of acute kidney injury (AKI) and chronic kidney disease (CKD)[18]. Being able to measure the perfusion of kidneys locally thus has great potential for the clinic, and would allow to study these diseases better. However, the use of contrast agent is restricted in patients with severe CKD, AKI or in patients who previously experienced severe reactions to GBCAs[27]. In addition, multiple contrast-enhanced measurements within a short time frame are not recommended, since retention of contrast agent remains a concern[27]. ASL provides a non-contrast enhanced alternative for renal perfusion measurements. The relatively short acquisition time and the fact that it does not require administration of contrast agents make repeated measurements possible, enabling monitoring

of perfusion over time, for example to study drug or treatment response[18]. At this point, FAIR or pCASL with a coronal oblique orientation of the imaging slices is recommended[62]. But transit time artefacts, and in particular planning of the labeling slab complicate the use of spatially-selective ASL in kidneys [62]. Flow-based ASL provides a transit time insensitive alternative that does not require planning of the labeling slab.

Also in breast cancer there is a clear potential for flow-based ASL. Screening for breast cancer with mammography has reduced breast cancer mortality with approximately 30% [65]. However, the sensitivity of mammography is limited, especially in the high-risk population[66]–[68]. In addition, mammography has a tendency to be less sensitive to aggressive tumor subtypes[69]. Breast MRI on the other hand, has a sensitivity approximately twice as high as mammography for breast cancer detection, a good specificity, and is specifically more sensitive to the detection of aggressive tumors[66], [69]. Breast MRI consists of a multi-parametric protocol, with as main workhorse DCE-MRI. Tumors require growth of new vessels, i.e. angiogenesis, to grow larger than 2-3mm^3[70]. DCE-MRI can measure this increase in perfusion, as well as the increase in vessel permeability, making it especially sensitive to aggressive tumor types[66]. However, compared to mammography, breast MRI is expensive; the main contributors being the required staff, because of the time required for administration of contrast agent, the length of the examination, and cost of the contrast agent itself[71]. High costs lead to the decision to recommend breast MRI only for the high-risk population[65], [71], [72]. Women who fall in this high-risk category, e.g. carriers of the BRCA1 and/or BRCA2 mutation, get annual breast MRI for screening from the age of 30[65]. However, because of the cumulative effect of gadolinium retention with every GBCA-administration[73], and because the vast majority of these women are healthy, a non-contrast enhanced alternative would be very valuable. If ASL proves to be sensitive to breast lesions, it has the potential to prevent gadolinium retention and to lower costs, which could even open up the possibility for breast MRI screening in the average-risk population.

Previous studies have shown feasibility of FAIR implementations in breast, although in a single slice setting[74]–[77]. Because the labeling takes place outside the field-of-view (FOV), the distance labeled blood needs to travel is reduced in single-slice imaging. The main feeding artery of the breast, i.e. the internal mammary artery, has a blood flow of approximately 19cm/s[44], while the main feeding artery of the brain, i.e. the carotids, have a blood flow of approximately 39cm/s[78]. So it is likely that, because of the slow flow in breast, multi-slice FAIR would suffer from significant SNR loss due to increased transit delays. Flow-based ASL can provide a transit-time insensitive alternative, by labeling directly within the imaging region, thereby potentially enabling whole-breast coverage.

THESIS OUTLINE

This work focusses on technical challenges concerning various aspects of ASL image acquisition in body applications. As motivated above, flow-based ASL methods have a lot of potential for body applications. First, a more general aspect of VS-ASL was studied, which was not necessarily limited to body applications. Blood velocity changes constantly as a function of the cardiac cycle, so it was hypothesized that the amount of label that is generated with velocity-selective ASL would be dependent on the phase of the cardiac cycle at which flow-based labeling is applied. This was studied in brain and is discussed in **Chapter 2**. Secondly, to investigate which flow-based ASL technique has the best performance, a comparison was made between four flow-based ASL techniques. Because different conditions apply in terms of e.g. field homogeneity, this comparison was done both in brain and kidney. Results of this study are discussed in **Chapter 3.** Thirdly, after successful application of flow-based ASL in kidney, the feasibility of velocity selective ASL was studied in breast cancer patients, to study whether enough contrast is generated to pick up hyper-perfusion in breast cancer lesions. Results of the study are shown in **Chapter 4**. When applying ASL in the kidneys and breast, it became apparent the EPI readout lead to subtraction artefacts in these applications, due to inhomogeneity of the B_0-field. **Chapter 5** discusses the technical feasibility of combining ASL with Spatial Temporal Encoding (SPEN) readout to enable a more robust readout. Lastly, the study in kidneys also demonstrated issues related to B_1-sensitivity of the background suppression pulses and VSI-ASL module. **Chapter 6** describes simulations of different non-selective inversion pulses, and VSI-ASL labeling and control modules, to find out how they perform under field conditions as they are found in body, and whether more robust alternatives can be found.