Flow-based arterial spin labeling: from brain to body

Franklin, S.L.

Chapter 7

Summary and general discussion

This thesis presents research done on the translation of MRI perfusion techniques from brain to body applications. In the section below the main findings and implications are summarized and discussed, followed by key points that need to be addressed in future work to take the next steps in body ASL.

Flow-based ASL forms a promising set of techniques for body applications due to their inherent properties of labeling non-spatially selective (i.e. no labeling slab needs to be planned), and transit time insensitivity, enabling application in organs with multiple feeding vessels and/or slow flow. First, a more general property, which is not limited to body applications, was studied in brain, where the technique is already more established. **Chapter 2** describes the work done on measurement of the cardiac cycle sensitivity of a single VS-ASL and Acc-ASL module. The sequence was designed in such a way to minimize other contributions to the signal, that are influenced by the cardiac cycle, i.e.: inflow of 'fresh' unlabeled spins, the distance that the label travels into the vasculature, and venous signal. Results showed that the amount of arterial label generated by a single VS-ASL and Acc-ASL module differed by ~36% and 64%, respectively, over the cardiac cycle. However, because in ASL, multiple repetitions are acquired, this effect is expected to average out and not have a major effect on the resulting perfusion measurement. On the other hand, these results provide an interesting starting point to develop a measure for microvascular pulsatility, by mapping variation of the generated ASL-signal over the cardiac cycle, i.e. highly pulsatile blood flow will lead to high variation, and low pulsatility will lead to low variation over the cardiac cycle. Scan time, however, would need to be shortened dramatically to make it clinically feasible.

In **Chapter 3**, different flow-based ASL techniques (VS-ASL, Acc-ASL, mm-VSASL, and VSI-ASL) were compared to spatially-selective ASL techniques in brain (pCASL) and kidney (pCASL and FAIR). In brain, volunteers were presented with a visual task to induce a perfusion increase in the visual cortex, which was used to validate the measurements. Results showed that VSI-ASL had a similar sensitivity as pCASL for picking up this perfusion increase, while the other flow-based techniques showed less sensitivity. In kidney, FAIR had a higher temporal SNR (tSNR) than all other techniques. All flow-based ASL-techniques showed a similar tSNR. For VSI-ASL, severe subtraction artefacts were observed in areas with low B_1, which were likely related to a combination of reduced inversion efficiency of the background suppression pulses as well as VSI-ASL labeling efficiency. From the results in the brain it is clear that VSI-ASL has the highest potential as flow-based technique, but only when used in relatively homogenous magnetic field conditions. However, for body applications, it is vital that adjustments are made so that VSI-ASL becomes more robust to field imperfections. Because of the issues regarding field imperfections, VS-ASL, instead of VSI-ASL, was used in a following study in breast cancer patients.

Feasibility of VS-ASL in breast cancer patients is described in **Chapter 4**. Overall, lesions were well visible with VS-ASL, and artifacts could be distinguished from the ASL-signal. Importantly, by using a flow-based ASL technique, the whole breast could be covered, while this is not feasible when using spatial-selective ASL techniques as FAIR. A comparable morphology was seen for the signal observed with VS-ASL as for the early phases of the ultrafast DCE scan. This confirms that VS-ASL is a measure for perfusion and vascularity, similar as the early phases of ultrafast DCE. In addition, an unexpected observation was made concerning segmental patterns of increased perfusion around some lesions, which corresponded to areas including prominent vessels, which seemed to form either feeding or draining vessels of the lesion. In patients with dense breast, VS-ASL exhibited stronger artifacts, due to the high contrast between glandular and fat tissue on the raw images, leading to subtraction artefacts when even minor motion was present. This first attempt at applying VS-ASL in breast cancer patients showed promising results for the development of a non-contrast alternative for perfusion imaging for breast cancer. Therefore, VS-ASL holds the potential to have a major impact on breast cancer screening, since it could limit the use of gadolinium-based contrast agents. Such an approach would be in line with the current attempts to employ a multi-parametric breast protocol to improve diagnostic accuracy, in which several non-contrast enhanced scans are added to the traditional breast exam. This allows integration of different and complementary information contained in these images. Until now there was no non-contrast alternative to DCE-MRI, that is sensitive to blood flow and perfusion. By replacing DCE-MRI by VS-ASL, all scans would be non-contrast enhanced: reducing costs and patient discomfort considerably. Now we have established the feasibility of VS-ASL in breast cancer patients, the repeatability and sensitivity of the method should be investigated in larger patient groups, especially for smaller lesions. To improve SNR it would be interesting to use VSI-ASL, although then, either the field imperfections in breast or the sensitivity of VSI-ASL to B_0/B_1 inhomogeneity would likely need to be reduced. In addition, it would be desirable to reduce the occurrence of subtraction artifacts, which were especially observed in patients with dense breast. A possible approach would be to optimize background suppression to, in addition to fat signal, also minimize glandular tissue signal.

In both the kidney as well as the breast study, EPI was used as readout technique, because of its time efficiency and thus motion insensitivity. However, EPI is also known for its sensitivity to off-resonance effects in the phase-encoding direction, leading to signal loss and image distortions. In both the kidney as well as breast study, artefacts were observed as a result of this off-resonance sensitivity. In kidneys, distortions, i.e. elongation of the kidneys were observed with EPI-readouts. Elongation of the kidneys was relatively stable, thereby not producing noticeable subtraction artifacts. However, occasional signal voids around the colon due to pockets of air, obscured parts of the kidneys in some volunteers. In breast, EPI-induced distortions due to the filling and emptying of the lungs during the respiratory cycle were observed. These distortions

were dealt with by performing a non-rigid motion correction. However, even when performing non-rigid motion correction, there is always the chance of residual registration errors, leading to subtraction artifacts in the resulting ASL-image. An additional source of subtraction artifacts were fat signal ghosts, which still occurred even though an image-based shimming tool, dedicated to breast MRI, SPAIR fat suppression and background suppression were used. Although in most cases the subtraction artifacts could be easily distinguished from ASL-signal, it would be desirable to have a readout method that is less sensitive to off-resonance.

These B_0-related problems for body ASL are addressed in **Chapter 5**. Here an alternative readout to EPI was implemented that is more robust to B_0 field inhomogeneity and susceptibility-induced T_2^* dephasing, i.e. spatio-temporal encoding (SPEN). The feasibility of combining SPEN with ASL was demonstrated for brain perfusion imaging, confirming the higher robustness of SPEN to susceptibility-induced artifacts compared to spin echo (SE)-EPI and gradient echo (GE)-EPI, without a cost in SNR. A TR-dependence was observed for ASL-images with SPEN readout: a minimal delay of ~1000 ms is advised between the SPEN-excitation pulse and start of the next labeling module, to prevent SNR loss. The TR-dependence is likely caused by the chirp pulse as used in SPEN, which affects all spins within reach of the transmit coil. The chirp pulse will have a saturation effect on the hydrogen nuclei in blood proximal to the labeling plane, reducing the labeling efficiency of pCASL of the following repetition. This study did have some limitations: it was performed with a single-slice readout, and used relatively large voxels for the SPEN-images. T_2-decay during readout prevented a smaller voxel size. Improvements to the sequence are necessary to enable multi-slice/3D-scanning and allow improved resolution in combination with larger FOVs, such as parallel imaging approaches.

In **Chapter 6**, we studied the B_0/B_1-sensitivity of VSI-ASL that lead to significant artefacts as observed in Chapter 3, especially focusing on the hyperbolic secant background suppression pulses and the VSI-ASL labeling module. Simulations using the Bloch equations were performed for field conditions that can be expected at 3T in anatomies close to the lungs, such as kidneys and breast (B_1-level = [0.4, 1.2], and B_0 = ± 300 Hz[127], [128], [190]). Simulations of the VSI-ASL label- and control modules showed that there is a severe reduction in labeling efficiency for the expected B_0 and B_1-levels, when using a velocity-compensated control module. They furthermore show that velocity-insensitive control modules are more robust to B_0 and B_1 inhomogeneity and thereby provide a good alternative. Simulations of the inversion efficiency of background suppression pulses were performed for hyperbolic secant (standard), BIR-4, and FOCI, at two different B_1-levels. Results showed that BIR-4 pulses can provide a higher robustness in terms of B_1, but only in areas where there is almost no frequency offset. For both B_1-levels hyperbolic secant provided the best inversion efficiency when both B_0 and B_1-imperfections are present. Therefore, it was concluded that the hyperbolic secant pulse still provides the best compromise for background suppression for ASL in body applications.

In conclusion, the studies of this thesis demonstrated great potential for flow-based ASL for body applications in general, and breast and kidney specifically. Considering the next steps, there are two main technical domains where improvements are warranted to improve performance of flow-based ASL in body applications:

1) Improvements need to be made to the labeling method; to get a B0/B1-robust flow-based ASL method that matches the SNR of the standard spatially-selective technique, e.g. pCASL and/or FAIR.
2) Improvements need to be made to the readout technique, to make it more B_0/B_1-robust than EPI without a cost in SNR, resolution, or affecting labeling efficiency of the next measurement.

There technical topics, as well as the next steps for flow-based ASL in clinical studies, will be discussed in more detail below.

Future outlook: Improving B0/B1-sensitivity of VSI-ASL

This work has shown that ASL, and in particular flow-based ASL is feasible in kidney and breast applications. It has also unveiled prevailing issues that prevent the widespread use of flow-based ASL in the body at the moment and especially at 3 Tesla. VSI-ASL is the most promising flow-based ASL technique in brain, showing a similar sensitivity as pCASL to pick up on regional perfusion increases, as demonstrated in chapter 2. However, when applied in kidneys, as described in chapter 2 and 5, B_1-sensitivity of the VSI-labeling sequence compromised labeling efficiency as well as decreased inversion efficiency of background suppression pulses. This is likely also an issue for other anatomies associated with reduced B_1, i.e. organs in proximity to the lungs, such as breast. By using a VS-ASL technique based on saturation, promising results were obtained in breast cancer patients, as reported in chapter 4. However, to be able to also visualize smaller, and more early-stage lesions, as well as make a clearer distinction between ASL-signal and subtraction artifacts, it is necessary to improve the SNR of the labeling technique. VSI-ASL has the potential to provide such increased perfusion sensitivity, if the B_0/B_1-robustness can be improved for these body applications. Because currently, VSI-ASL still has a higher sensitivity to field imperfections than VS-ASL[192].

The VSI-ASL sequence used in this work already included MLEV phase-cycling of the refocusing pulses inside each VSI-module to improve B_0/B_1-robustness[122]. Recently, dynamic phase-cycling of the refocusing pulses was introduced to further improve the field robustness[193]. Here, VSI-ASL is used with an additional 90-degree phase-increment to the refocusing pulses for every dynamic. In addition, a velocity-insensitive control module is employed, which, as also shown in chapter 5, enhances the robustness to B_0 and B_1-inhomogeneity considerably [53]. This results in B_0/B_1-robustness for field conditions typical for brain at 3T, i.e. B_0 of

±300 Hz and B_1-level of 1.0 ± 0.2. It is yet unclear how this technique would perform in more challenging anatomies in terms of field inhomogeneity, as well as movement. Dynamic phase-cycling relies on averaging of the four dynamics to average out signal from static spins and the so-called stripe artifact[193], which is likely not compatible with organ movement as encountered in e.g. kidney ASL.

An alternative adaptation of the VSI-ASL sequence, i.e. "sinc-VSI-ASL", was presented for measuring perfusion in myocardium[125]. Here, the amplitude of the VSI-ASL sub-pulses were optimized based on the expected B_0/B_1-range and motion in the myocardium, to improve labeling efficiency and prevent spurious labeling of myocardial tissue[125]. Here the amplitude of the VSI-ASL sub-pulses followed a windowed sinc-modulation, instead of the more traditional rectangular shape. This resulted in a more rectangular Mz-velocity profile (instead of a sinc-profile), providing sharper edges of the velocity field-of-view. In addition, a velocity-insensitive control module was used. The superior B_0/B_1-robustness of this sinc-modulated VSI-ASL method with velocity-insensitive control was confirmed in a later study [192], although it still has a higher sensitivity to field imperfections compared to the saturation-based BIR-8 VS-ASL approach[192].

Although a separate optimization per anatomy might be undesirable, due to the added complexity, labeling efficiency could in a similar manner be improved for other organs by optimizing for the specific motion and field conditions[125]. Myocardium has stringent constraints on the stopband due to the amount of motion, but this is less of an issue in e.g. breast, potentially allowing a higher labeling efficiency. This would be an interesting area to pursue in future studies.

FUTURE OUTLOOK: IMPROVING B0-SENSITIVITY OF THE READOUT

In this work we have demonstrated the feasibility of combining SPEN with ASL in brain, enabling a higher robustness to susceptibility-induced artifacts. This thesis furthermore discussed off-resonance related artifacts and distortions for kidneys as well as breast. A logical next step would be to investigate SPEN-ASL in abdomen applications. Alterations to the SPEN implementation, used in this thesis, have been proposed to enable multi-slice[164], 3D scanning[178], and improve spatial resolution. Multi-slice scanning is enabled by the use of an additional pulse after excitation that returns all spins outside of the slice back to equilibrium. This has the added benefit that, when combined with ASL, the saturation effect of the chirp pulse on incoming unlabeled blood, as shown in chapter 5, will likely be minimal in the smaller arteries. However, imperfections will exist in the reinversion of the spins in the larger

arteries, where flow is higher. Using these state-of-the-art SPEN-implementations for ASL body applications is an interesting approach which could potentially form a solution for the off-resonance and distortion artifacts discussed in this thesis.

Besides SPEN and multi-slice 2D EPI, various 3D readouts have been developed specifically for ASL body applications, to deal with the challenges of movement and field inhomogeneity. Compared to EPI and GRASE, 3D fast spin echo (FSE) is inherently more robust to susceptibility artifacts[194], making it an interesting candidate for body applications. To limit its scan time, 3D FSE has been combined with compressed sensing in renal ASL[176]. In another approach, 3D segmented FSE was combined with a Cartesian acquisition and spiral profile reordering to improve robustness[177]. Further research is needed to compare these readout approaches with SPEN for ASL measurements in body.

FUTURE OUTLOOK: CLINICAL STUDIES

This work has shown feasibility of flow-based ASL in body, mostly on healthy volunteers, with the exception of the study in breast cancer patients. Before these techniques can be used in a clinical setting, a comparison of spatially selective and flow-based ASL techniques is needed in specific patient groups. Alterations in flow conditions can occur depending on the pathology and organ, e.g. increased transit times in case of a stenosis.

In addition, it is essential to have acceptable repeatability and reliability for a specific application, measured in larger patient cohorts, before the technique can have a widespread clinical use. Repeatability can be measured, e.g. by performing repeated measures on different days. Reliability is more complicated to measure because of a lack of a golden standard perfusion technique [18] to compare ASL to. Care should be taken when validating the ASL against DCE-MRI, because these techniques do not measure exactly the same phenomena. ASL is a pure perfusion technique, while the signal of DCE-MRI is a mixture of perfusion and vessel wall permeability. Because vessel wall permeability is an effect that mainly comes into play at later phases after contrast injection, ASL signal can be compared to the flow-dominated early-phases of ultrafast DCE-MRI, as was done in chapter 4. In a recent study, ASL, as measured by FAIR, was shown to be the most repeatable perfusion method in kidney [195].

To further develop flow-based ASL in specific patient groups, it would be helpful when vendors would provide research institutes with 'works-in-progress' versions, so that these new approaches can easily be tested in clinical patients. Harmonization of such sequences among vendors would also be needed, similar as what has been achieved with pCASL for brain applications[13].

In summary, this thesis provides a major step in the application of flow-based ASL in body applications, and describes challenges that need to be overcome before widespread clinical use is possible.