Validation and application of arterial spin labeling MRI for cerebral perfusion
Heijtel, Dennis

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GENERAL DISCUSSION
AND FUTURE PERSPECTIVE
GENERAL DISCUSSION

Cerebral perfusion measurements with arterial spin labeling (ASL) provides information on the local cerebral hemodynamics. Contrary to the current perfusion imaging strategies available in the clinic, ASL employs the blood as an endogenous tracer thereby providing a non-invasive imaging method (Detre et al., 1992; Williams et al., 1992). Due to its relatively low spatial coverage, resolution and signal-to-noise ratio (SNR), the use of ASL imaging was initially limited to a few highly specialized MR centres, as research tool. To improve image quality, ASL research was mainly focussed on technical optimization and evaluation of the ASL acquisition. After introduction of the pseudo-Continuous ASL (pCASL) labeling scheme (Dai et al., 2008), background suppression (Garcia et al., 2005; Ye et al., 2000b) and 3D read-outs (Günther et al., 2005; Vidorreta et al., 2012), ASL image quality has improved in such a manner that is nowadays increasingly used in clinical research (Detre et al., 2012). Meanwhile, a wide variety of different ASL approaches have been proposed, each with their specific advantages and disadvantages (Detre et al., 1992; Golay et al., 2005; Kim, 1995; Petersen et al., 2006; Schmid et al., 2014; Williams et al., 1992; Wong et al., 2006, 1997). With the ASL research focus now shifted from technical optimization to its clinical application, this wide variety of ASL approaches has made it difficult for non-ASL experts to select an appropriate ASL protocol. Therefore, the ASL research community recently came to a consensus by indicating what imaging approach to use for clinical applications of ASL (Alsop et al., 2013).

The use of ASL is currently investigated for a wide variety of pathologies, ranging from ischemia and arteriovascular malformations to brain tumors (Wolf and Detre, 2007). However, before ASL can be translated from the clinical research setting to daily practice, several clinically relevant aspects of ASL have to be investigated. The main aim of this thesis was therefore to address some of these aspects, namely the improvement of patient comfort in ASL imaging and the validation of several ASL approaches with respect to $^{15}$O- $\text{H}_2\text{O}$ positron emission tomography (PET) perfusion imaging.

Improving clinical applicability of ASL

The applications of ASL have been investigated predominantly for cylindrical MRI scanners with a magnetic field strength of 1.5 T or higher (Wolf and Detre, 2007). However, in clinical practice certain patient populations are not eligible to undergo a MRI examination in regular MRI scanners (e.g. obese, paediatric and claustrophobic patients) (Bangard et al., 2007; Uppot et al., 2007). For these patient groups, a ‘hamburger shaped’ 1T open bore MRI scanner with direct tableside access has been developed, to allow the possibility to undergo an MRI examination. In order to facilitate the possibility of ASL measurements for these patients, we investigated the applicability of ASL on a 1T open bore scanner in chapter 2. We showed that ASL on a 1T open bore MRI scanner is feasible within a clinically acceptable acquisition time. First, the optimal ASL parameters were determined at 1T; such as the labeling approach, post-labeling delay, benefit of background suppression pulses as well as the most optimal read-out. Secondly, based on the optimized imaging parameters, the feasibility of ASL on 1T was illustrated by acquiring CBF-images in an obese woman not eligible for a conventional MRI examination. However, with the recent arrival of high field wide bore MR systems to accommodate the obese population, the necessity for translating ASL to a 1T open bore scanner might be less of an issue. Still, in contrary to open bore scanners, wide bore scanners do not allow for tableside access, limiting the applicability for paediatric and claustrophobic patients.
These patient groups often require tableside comfort of a relative during the examination and for them the implications of this research are still clinically relevant.

Recently, pCASL labeling has been recommended by the ASL community as the labeling approach of choice for clinical application of ASL. As proposed by Dai and colleagues, pCASL employs a 1500-1800 ms pulse train of 1 ms Hanning pulses to magnetically invert the blood-water (Dai et al., 2008). The corresponding 1 kHz-100 dB acoustic noise produced by the gradients during labeling is often perceived as very uncomfortable because it is loud as well as highly pitched. Particularly, the repeated transitioning from the ‘loud’ labeling to the ‘silent’ post-labeling delay (PLD) is experienced as aggravating. In chapter 3 we therefore performed simulations and MRI measurements in an effort to reduce the acoustic noise produced by the pCASL labeling module while preserving image quality. Simulations predicted three frequencies of interest that significantly could reduce the acoustic noise level. Measurements confirmed that by adapting the labeling frequency from 1.0 kHz to 0.71 kHz a 6.5 dB reduction in acoustic noise level could be achieved at the approximate location of the ear. PCASL imaging in nine volunteers with the original (1 kHz) and adapted (0.71 kHz) labeling frequency showed no significant difference in SNR between both approaches, indicating a preserved image quality. Still, one should take caution when translating these specific settings to a another scanner model, since the found minimum might differ from scanner-model to scanner-model. Yet, adjustment of the labeling interval is a relatively easy procedure that can be performed in most institutions and can be effortlessly replicated for a wide variety of scanner models.

Validating the performance of ASL with [15O]H2O PET

To validate ASL as a clinically acceptable perfusion technique, the performance of ASL has been compared with [15O]H2O PET in several studies (Bokkers et al., 2009; Henriksen et al., 2012; Kilroy et al., 2014; Maolin et al., 2010; van Golen et al., 2013; Xu et al., 2009; Ye et al., 2000a). However, the focus of these studies was predominantly on the accuracy without comparing the precision. Furthermore, each study concentrated on a single ASL approach, whereas a comprehensive evaluation of all the different ASL techniques within a single population could provide a more complete insight into the performance of ASL with respect to [15O]H2O PET.

The accuracy and precision of pCASL measurements with respect to the [15O]H2O PET was investigated in chapter 4. For the accuracy, consecutive ASL MRI and [15O]H2O PET imaging sessions were performed within a week. To assess the precision of both techniques, the paired imaging sessions were performed twice by means of a test re-test paradigm. Furthermore, CBF measurements were performed both during baseline as well as hypercapnic conditions to increase the CBF range of evaluation and to enable the evaluation of the cerebrovascular reactivity. For the CBF accuracy within the grey matter (GM), a one-on-one linear relationship was found between modalities. Voxel-wise analysis revealed several areas with systemic discrepancies between pCASL and [15O]H2O PET, predominantly originating from the applied background suppression settings and read-out approach. The intra- and inter-session reproducibilities were comparable for both modalities, indicating that both techniques have a similar precision, possibly dominated by physiological fluctuations. These results demonstrated that pCASL can be as quantitatively accurate and precise as the gold standard perfusion imaging method.
An important factor in the quantitative accuracy comparison is the CBF modeling. In this chapter we quantified the pCASL CBF based on the two-compartment approach as proposed by Wang et al. (Wang et al., 2002), while the more simple one-compartment model approach is currently recommended for clinical applications (Alsop et al., 2013). In addition, we performed a series of additional measurements to obtain person specific parameters to be employed in the quantification process as opposed to the more common approach of using literature values (Alsop et al., 2013; Aslan et al., 2010; Varela et al., 2010). These additional measurements require more scan time, while the exact benefit of person specific quantification values over literature constants remains to be proven. A further investigation into the quantitative accuracy differences between the one- and two-compartment modeling, combined with a cost-benefit analysis of the additional person-specific measurements, would provide important additional information for the application of quantitative pCASL imaging.

While the current pCASL implementation has proven to be as accurate and precise as $^{15}$OH$_2$O PET, an important remaining issue is the sensitivity of pCASL to increased blood arrival times. Proper timing of the post-labeling delay is still crucial for an accurate quantification. Especially in neuro-pathology, increased arrival time heterogeneities are often observed, which can lead to erroneous quantitative and qualitative CBF-maps. For example in the case of a symptomatic carotid artery occlusion, the blood arrival time in the affected hemisphere is often significantly prolonged. Single PLD pCASL imaging would show an underestimated CBF signal in the affected hemisphere due to the fact that not all label would have arrived yet at the time of imaging (Bokkers et al., 2009). Without specific knowledge on the ASL methodology, this could lead to misinterpretation of the underlying perfusion pathology. Velocity selective ASL (VS-ASL) techniques were proposed to resolve the blood arrival time sensitivity, by labeling the blood also within the brain based on specified cut-offs of the blood velocity or acceleration (Schmid et al., 2014; Wong et al., 2006). Although VS-ASL could provide a more accurate CBF contrast in populations with delayed arrival time (Qiu et al., 2012), a comprehensive comparison of the major available VS-ASL techniques with the gold standard has not yet been performed. Furthermore, it has been postulated that the image contrast in some VS-ASL scans might be partially cerebral blood volume weighted and a comparison with $^{15}$OH$_2$O PET could give an indication on the CBF-contrast agreement.

In chapter 5 we compared the three major VS-ASL techniques with $^{15}$OH$_2$O PET. In addition to a CBF comparison, we assessed the amount of the arterial blood volume (aBV) contribution to the VS-ASL image contrast. Solely the dual VS-ASL approach is suitable for quantification and therefore comparison of the absolute CBF-values was only done for this variant of VS-ASL. Dual VS-ASL significantly underestimated the GM CBF with respect to $^{15}$OH$_2$O PET. Qualitatively, we demonstrated that the signal contrast of all the analyzed VS-ASL methods show good agreement with $^{15}$OH$_2$O PET, whereby accelerative-ASL showed the highest correlation. With respect to aBV contribution of VS-ASL, only a minor contribution was found, indicating that the VS-ASL contrast is minimally influenced by aBV.

In the relative new field of VS-ASL, confirmation that the 3 major VS-ASL approaches provide predominantly CBF-weighted information, is an important step in the validation process of these techniques. However, further research has to be performed to assess the exact contribution of the influence of diffusion weighting as well as venous and capillary blood volume before VS-ASL.
can be introduced in the clinic. Especially in clinical pathology, knowledge on the exact origin of the signal is important for correct diagnosis. However, with the possibility to go beyond CBF and also measure the cerebral metabolic rate of oxygen (CMRO₂) (Bolar et al., 2011; Guo and Wong, 2012), the velocity selective labeling mechanism shows great promise to accompany pCASL and QUASAR measurements in clinical practice.

Even though the VS-ASL techniques appear to resolve the sensitivity to blood arrival time heterogeneities, it has been shown that the blood arrival time information itself might be a good reflector of hemodynamic failure (R P H Bokkers et al., 2009). The quantitative STAR labeling of arterial regions (QUASAR)-ASL technique as originally proposed by Petersen and co-workers (Petersen et al., 2006) was therefore developed to provide additional bolus arrival time and aBV information. By sampling the in- and out-flow of the blood bolus CBF, bolus arrival time and aBV can be calculated based on a similar approach as dynamic susceptibility contrast MRI. The QUASAR CBF has been compared previously with [¹⁵O]H₂O PET, with opposing results (Bokkers et al., 2009; Henriksen et al., 2012). Theoretically, QUASAR could be better suited for clinical applications than pCASL, since it is not hampered by arrival time heterogeneities and provides valuable aBV and blood arrival time information as well. In addition to CBF-information both [¹⁵O]H₂O PET and QUASAR provide aBV information as well, although this was not part of the aforementioned comparison studies. To provide decisive evidence on the quantitative performance of QUASAR MRI with respect to [¹⁵O]H₂O PET, the CBF and aBV agreement between both modalities was assessed in chapter 6. The gross patterns of CBF and aBV could be imaged in both modalities and moderate to high correlations were found between the modalities. However, significant quantitative discrepancies were observed, with QUASAR systematically underestimating CBF by 30% and aBV by 73%. After correction for these quantitative discrepancies, both modalities showed similar qualitative CBF and aBV images, indicating a voxel-wise agreement. These results demonstrate that QUASAR and [¹⁵O]H₂O PET provide similar hemodynamic information, though systematic quantitative discrepancies exist which have to be taken into account.

Beside the quantitative discrepancy, the major disadvantages of the current QUASAR application with respect to the pCASL implementation are the lower image resolution, reduced brain coverage and relatively poor SNR. Furthermore, the rather complex calculations necessary to obtain the CBF, aBV and bolus arrival time information, limit easy applicability in daily clinical practice. New developments as turbo QUASAR (Petersen et al., 2013) and time-encoded pCASL (Teeuwisse et al., 2014) show great promise to provide high resolution CBF and arrival time information in the near future. Yet, the sequence optimization as well as the evaluation of reliability of both techniques is still under investigation.

Overall, we compared three fundamentally different ASL approaches with [¹⁵O]H₂O PET, showing that qualitatively all the ASL techniques provide comparable CBF contrast with respect to [¹⁵O]H₂O PET. Yet, quantitatively solely pCASL imaging with CBF quantified by two-compartment modeling demonstrated quantitatively agreement with [¹⁵O]H₂O PET. The major drawback of the presented studies is that these were performed in healthy, young subjects without clinical pathology. Knowledge on the expected presence of certain pathology, could influence the choice for applying either pCASL, VS-ASL or QUASAR imaging, and therefore the current studies might present a preferential bias towards the most optimal method for healthy
subjects. However, the information from these studies does provide us with insight on the pros and cons of all these techniques by comparing the performance to the gold standard [15O]H2O PET, which should be taken into account when translating ASL towards clinical use.

To minimize the influence of physiological variation on the comparison, PET and MRI sessions would ideally be performed on the same day. Due to the different geographic locations of the scanners and the vast amount of preparation and aftercare for each imaging session, this was logistically not possible. Recently, Zhang and colleagues (Zhang et al., 2014) demonstrated the possibility of simultaneous pCASL and [15O]H2O PET acquisition on an integrated PET/MR system enabling a physiological more valid comparison, although both ASL and [15O]H2O PET in that study were acquired with suboptimal imaging settings.

Future perspective

In summary, the chapters in this thesis address several important steps necessary into making ASL a valid approach for use in daily clinical practice. To this end, chapters 2 and 3 were focused on improved patient comfort, and chapters 4 to 6 addressed the performance of different ASL approaches with respect to the gold-standard perfusion measurement.

However, before ASL can be widely applied in daily clinical practice, a few important issues still remain. First, to improve clinical usability, the different MR vendors should adopt a more or less similar ASL read-out and quantification protocol, to enable exchange of ASL scans between hospitals. Mutsaerts and colleagues investigated the quantitative differences between the standard GE and Philips pCASL imaging protocols and found significant qualitative contrast differences between the vendors, originating most likely from the different read-out protocols (Mutsaerts et al., 2014). Beside daily clinical care, this problem also hampers large scale clinical trials, since inclusion centers are often limited to a single MRI-vendor, because otherwise too large a variability would enter the perfusion data. Currently Groote and co-workers are investigating the application of identical ASL acquisition and quantification protocols on scanners of the three main MRI vendors to assess differences in ASL-imaging solely arising due to slight differences in hardware or reconstruction approaches.

Secondly, most clinical imaging is performed on 1.5 T scanners while the larger part of ASL research is performed on 3T. It is known that ASL performs best at 3T due to the increased SNR and longer relaxation rate of the arterial blood (Wang et al., 2002). However, for ASL to be widely accepted as a clinical perfusion imaging technique, clinically acceptable results have to be achieved at 1.5T as well.

Finally, with the qualitative performance of ASL assessed with respect to the gold standard, the next step should encompass a general consensus among clinicians on how and when to clinically apply ASL in the daily routine. The considerations that such a general consensus should include are: the current clinical quality of the recommended ASL implementation, the interpretation of ASL perfusion scans and the necessity of quantitatively accurate ASL CBF values. A major drawback of the currently recommended single PLD pCASL implementation, is the occurrence of artifacts in pathologies with prolonged arrival times due to slow flow or collateral supply. It should be decided whether to wait for a one-size fit all ASL approach or whether to adopt the current recommended ASL implementation and take the occurrence of
transit time artifacts into account when interpreting the CBF image. Turbo QUASAR (Petersen et al., 2013) and time-encoded pCASL (Teeuwisse et al., 2014) show great potential to realize such a one-size fit all measurement, yet both approaches are in early stage of development and it could take years before these will become clinically available. As demonstrated in this thesis, ASL has the capability to be quantitatively accurate. However, in clinical practice the main interpretation of an ASL perfusion image is mainly performed on a qualitative basis. While the qualitative ASL image can be easily calculated on the scanner console by simple subtraction and averaging, exact quantification by means of additional measurements requires the involvement of a physicist due to the complex post-processing. Therefore, the exact necessity of quantitative ASL imaging in the daily clinic should be addressed as well.

To conclude, ASL is on the verge of widespread usage in health care, though some important steps still have to be taken before it can replace existing perfusion techniques in daily clinical practice.

LIST OF REFERENCES


