New Developments in Arterial Spin Labeling

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Summary
Arterial Spin Labeling is a magnetic resonance method for the measurement of cerebral blood flow. The perfusion signal is usually coming from the subtraction of two successively acquired images, one with, and one without proximal labeling of arterial water spins. Over the last decade, the method has moved from the experimental laboratory to the clinical environment. Furthermore, numerous improvements, ranging from new implementations to extensive theoretical studies have broadened its reach and extended its potential applications. In this lecture, after a short introduction to the techniques generally used, the latest developments and emerging techniques that emerged from this field in the last 2-3 years will be summarized. For a more complete overview of the literature on ASL, we refer the students to a recent review article (1).

Pulsed and Continuous ASL
There exist two main types of ASL methods to measure perfusion. The first one, dubbed continuous arterial spin labeling (CASL), utilizes a long radio-frequency (RF) pulse together with a linear gradient to continually invert the magnetization until a steady-state has been reached (2). In the second approach, dubbed pulsed arterial spin labeling (PASL), a thick slab of arterial blood is inverted at a single instance in time, and the image acquisition is performed after a time long enough for that spatially labeled blood to reach the tissue and exchange at the region of interest (3-5). In both methods, a control scan is performed in order to picture and compute the perfusion signal.
The signal difference between control and label images in perfusion imaging, which is only 0.5-1.5 % of the full signal, will depend on many parameters, such as the cerebral blood flow itself, the longitudinal relaxation time (T_1) of both blood and tissue, as well as the time it takes for the blood to travel from the labeling area to the imaging region, among others. With such a small signal available, many repetitions are usually needed to ensure sufficient SNR. Traditionally, conventional EPI readout has been used in ASL sequence, in order to get a large number of repetitions, necessary to get a reasonable SNR in these low SNR techniques (4,6,7). However, a few papers were recently introduced, in which new imaging techniques based on 3D sequences allow drastic improvement in the obtainable SNR (8,9).

High-field Clinical ASL
In the past few years, moderate and high field MR systems (≥ 3.0T) have been introduced in the clinical settings. Advantages of higher field strength have been demonstrated for magnetic resonance angiography (MRA) (10), functional MRI (fMRI) (11) and magnetic resonance spectroscopy (MRS) (12). An expected twofold SNR increase proportional to the magnetic field strength is the most appealing feature of 3T MR imaging, but other properties such as increased T_1 relaxation times may also provide great advantages for ASL. In fact, most CASL sequences

use a TR in the order of 5s, with the shortest possible echo times, resulting in proton density weighted images (6,13). Therefore, both the increase in T_1 and decrease in T_2 expected at 3T (14) will not affect the image contrast, and the native perfusion-weighted images will plainly profit from a twofold increase in SNR (15,16). Furthermore, the increase in arterial blood T_{1b} from 1400ms (17) at 1.5T to 1680ms (18) at 3.0T shall increase the contrast-to-noise ratio (CNR) of the images by ~ 20-30%, depending on the imaging parameters (8,19). In a study by Franke et al (20), both increase in signal as well as in T_{1b} were found to be the main contributors for the increase in CNR in ASL when going to higher field strength. Therefore, a reduction of the scan time by a factor of up to four for identical imaging parameters is expected when going from 1.5T to 3.0T; alternatively, this increase in SNR may be traded for increase image resolution.
In PASL sequences, usually an inversion (e.g. FAIR) (4) or pre-saturation (EPISTAR (3,7), TILT (21,22), QUIPSS (23,24)) pulse is followed 1-2 sec later by the acquisition sequence. These pulses will therefore be the main determinant of the contrast in the native (non-subtracted) image, which will show in most cases a T_1-weighting. For this reason, the expected SNR gain is less than that of CASL sequences (16) at high field strengths. However, the increased T_{1b} will still contribute to an increase in SNR.

ASL at multiple inversion times

In the majority of PASL or CASL studies, a single delay time TI between labeling and image acquisition is used to estimate CBF. In such case, the effects of arterial transit time on the CBF estimation are difficult to evaluate and can potentially cause errors in calculated perfusion values (13,25,26). This is especially true for patients with stroke and steno-occlusive disease of the carotid arteries for whom the labeled blood flowing via collateral vessels will cause an increased transit time in the affected area.
A possible approach to solve the transit time problem is based on the observation that, instead of minimizing the effect of transit time, this physiologically important hemodynamic parameter can also be measured in addition to CBF measurements by performing multiple ASL experiments at various TIs between ASL labeling and MR acquisition. Buxton and colleagues introduced the theoretical basis of this multiple TI method and proved the principles with an EPISTAR-like technique (27). The group of Alsop and Detre proposed a similar method based on a CASL sequence, and applied it to fMRI studies (28). Several studies have investigated the shape of ASL hemodynamic response curves, with the amount of ASL signal plotted against TI (29-31). Generally, an increase of the perfusion weighted signal is found at short TI for PASL sequences caused by the arrival of the labeled blood through the arterial system, followed by a decrease at longer TI, caused by a combination of washout of the tracer and T_1 relaxation, seen in both PASL and CASL (28). The main drawback of ASL at multiple inversion times is the considerably longer scan time than for single delay experiments, often rendering this technique impractical, especially in difficult patient populations.
Recently, Inflow Turbo Sampling FAIR (ITS-FAIR) and Turbo-TILT were introduced, both of which allow absolute quantification of CBF and arterial transit time in a single scan (32-34). Both techniques acquire a series of images at increasing delay times after one single inversion pulse by combining a pulsed ASL with a repeated small flip angle gradient echo (GRE) sampling strategy, in a way similar to the Look-Locker technique used for fast T_1 mapping (35). When applied to PASL sequences, the Look-Locker acquisition train allows monitoring the dynamics of blood inflow and tissue perfusion at high temporal resolution (50-200 ms). Finally, Petersen et al. recently utilized these multiple measurements at various time-points along the perfusion curve

to get an estimate of perfusion using a deconvolution technique (36) similar in its application as the one used in Gd-based perfusion sequences (37). The advantage of this technique over its corresponding is that it allows getting an absolute quantification by using a local estimation of the arterial input function, obtained by subtraction of and ASL signal acquired with and without crusher gradients to destroy the signal from the large arteries (36).

Selective ASL methods

Thus far, most ASL techniques have been used to measure tissue perfusion of the brain by non-selectively labeling of all of the brain feeding arteries. Edelman et al introduced selective labeling with a sagittal inversion slab for angiography, however no flow territory mapping or CBF quantification was performed in these studies (38). Local surface coils in CASL experiments can also be used for selective labeling of the right and left common carotid artery separately (39-42). Because the surface coils only allow for labeling of superficial arteries, this method is restricted to selective labeling of either internal carotid arteries (ICA), and no separate labeling of the posterior circulation can be usually achieved.

Using a similar PASL technique, Eastwood et al selectively labeled either the right or left carotid artery systems by alternating the application of spatially-selective inversion pulses in sagittal orientation (43). However, they were not able to get an absolute quantification using this technique. Recently, another PASL method for selective labeling of ICAs and basilar artery was implemented using two-dimensional labeling pulses forming a pencil beam profile (44). By planning this pencil beam with a Gaussian profile parallel to the slices of interest and below the circle of Willis, 2 to 4 cm of the left or right ICA or basilar artery could be labeled. However, a significant contamination of the perfusion territories of the non-labeled arteries was still present and no CBF values were obtained, due to the complex labeling scheme used and the absence of global control for magnetization transfer effects.

Hendrikse et al recently developed another technique based on TILT (21), called regional perfusion imaging (RPI) (45). With RPI, selective labeling is achieved by using the sharp labeling profiles of the concatenated TILT labeling pulses (22) and by interactively planning the spatially selective inversion slabs (45). RPI allows CBF quantification because of its inherent global control for MT effects independent of the angulation of the labeling slab (21,22). This technique has been successfully used in a large population study to study the variability in perfusion territories among the general population (46), as well as in a short study assessing the success of intra-extra-cranial bypass surgery in patients with complete occlusion of one of the internal carotid arteries or after endarterectomy (47).

However, this technique suffers from the problems of the transfer insensitive labeling technique upon which it is based. In particular, RPI is very sensitive to magnetic field inhomogeneities, and therefore the definition of the labeled bolus can deteriorate at field strength higher than 1.5 T. Furthermore, the slab-selective triple-pulse postsaturation sequence used originally will also be impaired due to the same problem, rendering RPI unusable at higher field. For this reason, we recently described a new sequence, called PULSAR (for PULsed STAR Labeling of Arterial Regions), in which an adiabatic-based signal targeting with alternating radiofrequency pulses sequence (EPISTAR) is proposed as a labeling scheme to solve the problems related to variations in local magnetic field, together with an improved four-pulse water suppression enhanced through T(1) effects technique (WET) as a presaturation scheme (48).

Velocity-encoded ASL

In general, most ASL techniques described so far are based on the proximal labeling of arterial magnetization followed by its measurement in the tissue of interest after a certain delay time. As expressed earlier, the main problem of such techniques is the finite arterial transit time between the labeling slab and the volume of interest. This transit time can be considerably longer in patients suffering from arterial occlusion, stroke or arterio-venous malformations for example. Furthermore, the transit time also depends on the actual relative position of the tissue to the labeling plane or slab. That is, the delay will generally be longer for more distal slices.

In an attempt to render such ASL techniques independent from these arterial transit delays, another class of arterial spin labeling techniques has recently been introduced, in which arterial spins are labeled everywhere according to their velocity (49,50), and further optimized and termed later velocity-selective ASL (VASL) by Wong et al (51). In this method, a series of non-selective 90º-180º-90º pulse sequence is used (DEFT sequence), with interleaved gradients to select spins of a particular velocity, in a way similar to MRI sequences used to obtain quantitative flow measurements in large vessels (52). For the control experiment, the same sequence is repeated with very low gradients. The main difference between this method and others ASL techniques is that flowing spins are labeled everywhere, including in the volume of interest, therefore minimizing the transit delay time necessary for the blood to reach any region of interest in the organ.

Conclusion

Tremendous improvements have appeared in the field of ASL over the last 12 years. Interestingly however, most up-to-date methods are still based on the original scheme proposed by Williams et al (2), except maybe some techniques based on velocity-selective ASL (49,51). ASL as a new way of measuring blood flow has been used widely in animal imaging, small clinical studies, as well as a potential surrogate to BOLD fMRI in neuroscience. From the original brain technique have emerged various methods specifically designed to measure blood flow in a large number of organs.

On the technical side, improvements in the techniques and control for the numerous potential artifacts have permitted the development of reliable multi-slice perfusion imaging, with a resolution often as good as, or even better, than most nuclear-medicine approaches. Despite all these improvements and the continuous research done in this domain, ASL is still an emerging technique *per se*, and has not replaced more invasive procedures for the assessment of blood flow in patients. Among the possible explanations for this are probably the relative complexity of the method, its intrinsic low SNR and relative high sensitivity to motion artifacts. However, some of the latest developments and the advent of high field clinical imagers might change this perception, and future advances ahead will definitely bring the robustness needed by this technique to be widely used in the clinics.

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