ASL Perfusion Imaging: Concepts and Applications

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INTRODUCTION

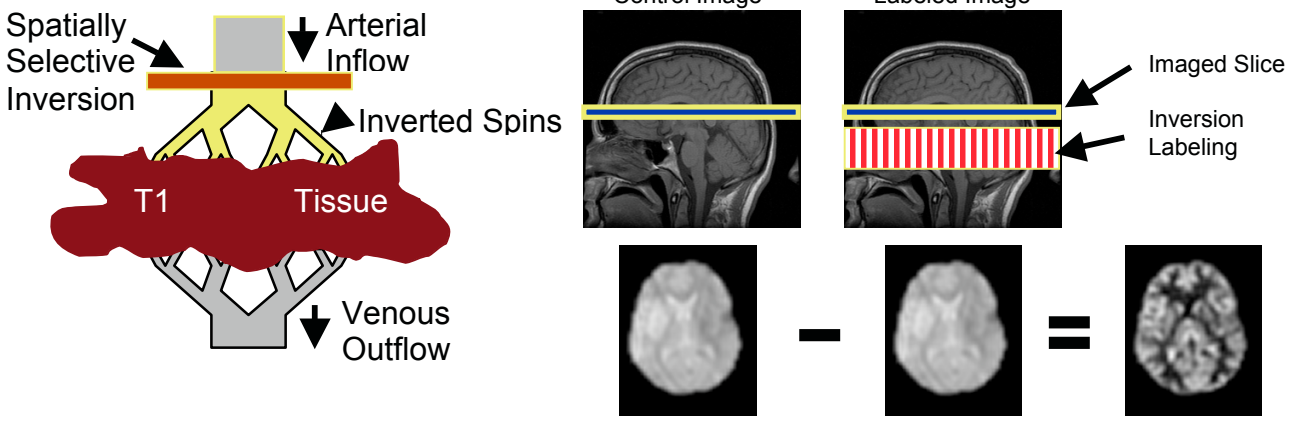
Arterial Spin Labeling (ASL) perfusion imaging in the brain, or cerebral blood flow(CBF) imaging, adds an exciting new functional dimension to noninvasive evaluation of the brain with MRI. In considering the impact of ASL, it is important to remember that there are a number of established techniques for imaging of brain function and CBF which both provide insight into clinical applications of CBF imaging and also could compete with ASL for use. Both PET imaging with H_2O^{15} and SPECT imaging with Tc-HMPAO and other tracers have been available for some time and widely used to explore disease. PET imaging of glucose utilization, a metabolic measure, also deserves mention as a functional measure because of its high quality and somewhat greater availability than H_2O^{15} PET. CBF can also be measured with stable Xenon as an inhaled tracer in X-ray CT and with intravascular tracers both with CT and MRI.

The strengths of ASL relative to these other approaches are substantial. ASL requires no contrast injection or inhalation. It can be performed as one of a number of MRI imaging techniques in a single study which both reduces cost and provides intrinsically co-registered anatomic and functional information. ASL can be repeated as often as needed and its intrinsic temporal resolution is on the order of a few seconds. ASL can be acquired with good SNR at spatial resolution better than any nuclear medicine technique and with absolute quantification. Because timing can be used to limit the vascular contribution to the ASL signal, it does not produce strong vascular artifacts as in bolus contrast CT or MRI. ASL can be acquired with robust sequences like Fast Spin Echo and need not suffer from susceptibility signal loss as in gradient echo bolus contrast MRI. The water used as a tracer in ASL is largely free diffusible and even when not, ASL is less sensitive to this assumption than H_2O^{15} PET.

ASL's greatest weakness is rapid T1 decay of the tracer. This makes it particularly challenging to study slow flow and cerebrovascular disease. ASL is also a SNR limited technique so spatial resolution and imaging time are limited by the available SNR. Finally, ASL cannot be performed after an injection of Gd-DTPA or other T1 contrast agent as the T1 shortening of the blood precludes further ASL acquisition. These benefits and limitations of ASL will become apparent in the discussion of individual clinical applications below.

ASL METHODS

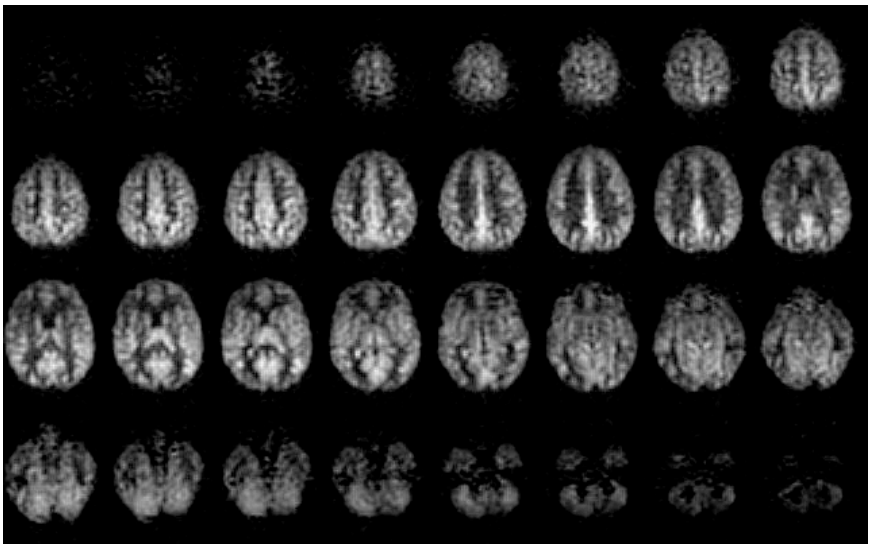
ASL[1,2] uses spatially selective inversion of inflowing arterial blood as a method to label blood flow. The MRI signal from inverted blood is made negative relative to uninverted blood. When the labeled blood reaches the tissue, it attenuates the signal from the image of that tissue. Subtraction of a labeled image from a control image gives a measure of the amount of label which flowed into the tissue. This quantity is closely related to the tissue perfusion. A typical change in image intensity between labeled and control is 1% so SNR is lower than for a comparable



proton density image and sensitivity to motion is greater. For these reasons reduced spatial resolution and motion insensitive sequences are frequently used for ASL.

Quantification of blood flow in physiologic units is relatively straightforward with ASL[1,3]. The greatest uncertainty is whether sufficient time has been allowed for the labeled blood to enter the tissue, or at least to arterial vessels smaller than the voxel size. In subjects with cerebrovascular disease or other pathologies leading to very low flow, the long arrival time of labeled blood can be a limitation for ASL[4]. Knowledge of the T1 of the tissue and blood is also required for quantification.

A number of more extensive reviews of ASL techniques have been published[5-8]. Here we will just highlight some of the more recent developments that impact the utility and applications of ASL. Sensitivity enhancement has been made possible by two important general developments. First, the use of higher field strengths has increased ASL signal both because of intrinsically higher SNR at high field and the lengthening of blood T1 which accompanies increased field strength[9]. An additional SNR advantage has come from the increasing use of array coils for signal reception. While array coils can require new approaches to labeling because of body coil transmission, solutions to these issues have already been developed[10]. An example of a routine 5 minute, 3 Tesla array coil study in an elderly subject is shown below.



The combination of high field strength and array coils has greatly improved ASL signal but has further emphasized the contribution of motion and other nonthermal noise sources to the noise in ASL. The use of background suppression by the application of multiple inversion pulses[11-13] has become more attractive to improve ASL robustness and true SNR. Thanks to background suppression, the promise of susceptibility insensitive, spin echo based imaging sequences has been realized in multi-shot volumetric acquisitions, and more recently, with the incorporation of parallel imaging, single-shot acquisition of the whole brain has been achieved[14-16]. Single-shot acquisition with whole brain coverage is particularly attractive for fMRI using ASL, as it provides similar temporal resolution and spatial coverage to BOLD without susceptibility artifacts and with improved temporal stability.

Clinical applications of ASL have demonstrated the challenges of optimizing labeling timing, in particular the post-labeling delay or TI time, to allow all labeled blood to enter the microvasculature while not losing too much signal to T1 decay because of excessive wait times. While measurement of ASL signal at multiple delay times is an option, it has reduced SNR per unit time relative to averaging at the optimal timing. An alternative would be to obtain a quick, low resolution estimate of arrival time which could be used to set the wait time for the longer ASL acquisition in much the way timing boluses are used for timing of bolus contrast angiography.

NEUROSCIENCE APPLICATIONS OF ASL

ASL can be useful either as a baseline measure of function compared across groups or as a serial measure in individual subjects. As a serial measure, it can be used for shorter time scale changes within a single scanning session, much like BOLD fMRI, or for changes on longer timescales, hours to years, with subjects removed from the scanner between scans.

Scanning with ASL can be used to image the changes in the brain with normal aging[17], either by comparing groups or, ultimately, measuring changes over time in individual subjects. ASL is particularly attractive in the study of brain development in newborns and children[18,19] because nuclear medicine methods are considered undesirable, and rapid changes in flow and metabolism occur over the period of months.

ASL can be used to monitor the neurological effects of pharmacologic agents[20]. The repeatability and noninvasiveness of ASL are attractive for such studies, though, as with all hemodynamic indicators, vascular and neuronal effects of ASL cannot be separated. ASL in combination with BOLD imaging has been suggested an indicator of oxygen utilization[21,22]. Further development of this technique might permit the separation of neuronal and vascular changes with drug administration, as well as the mechanisms of flow metabolism coupling in general.

The temporal stability of ASL relative to BOLD makes it attractive for the study of brain activation changes that process on longer timescales[23]. A number of important neural functions, such as memory consolidation, emotional state, sleep and hunger and satiety, proceed over many minutes. Activation studies with ASL may improve or enable studies of these functions.

ASL studies across large groups also offers promise for the detection of neural substrates of group differences. Correlation of resting state with neurologic or physiologic indicators could be helpful in probing intersubject differences that are not readily modulated, such as personality[24]. The wide availability and low risk and discomfort of ASL MRI make such studies more practical.

CLINICAL APPLICATIONS OF ASL

Stroke and Cerebrovascular Disease

Since stroke is a disease of insufficient blood flow, it would seem to be a natural application for perfusion MRI. Several studies of ASL in acute stroke have been reported[4,25]. Not surprisingly, in each of these studies, there is a concern that ASL underestimates flow in many of the cases and imaging performed with a longer wait before acquisition, either post-labeling delay or TI, was more consistent with other findings[26,27]. ASL does offer the possibility of confirming a hemodynamic abnormality, which could serve to confirm the diagnosis, and could be used to demonstrate reperfusion, which would suggest that thrombolytic therapy was no longer necessary. The repeatability of ASL could also be used to monitor reperfusion following interventions. However, the oversensitivity to stenosis and delay, combined with relatively low SNR, makes ASL appear poorly suited to prediction of tissue at risk of infarction. Reduction of the labeling to tissue distance with single-slice acquisitions or possibly velocity selective labeling may help to improve the utility of ASL tissue risk characterization in acute stroke. Techniques to overcome these limitations cannot increase the acquisition time of the images too much, however, as time is of the essence for treating acute stroke.

Chronic cerebrovascular disease has also been explored with ASL(27-29). Here the target of imaging is usually to assess the hemodynamic significance of a stenosis or occlusion. Occasionally patients exhibit abnormalities of resting blood flow but more often even baseline blood flow is relatively normal, at least when the patients is resting supine in the MRI scanner, but the ability to augment flow is compromised. Challenge studies using CO2 inhalation or acetazolamide administration can be used to assess the available cerebrovascular reserve[29]. ASL is well suited to reserve measurements because of its repeatability and absolute measurement capability. Reserve can be measured with ASL in normal controls and CVD patients. A growing literature relates patterns of abnormal reserve with a much heightened risk of later stroke and cognitive impairment so reserve measurement has implications for the selection of surgical or stent based treatment. In patients with very significant stenosis and slow collateral circulation, ASL may still have trouble with long transit times and underestimation of flow.

Dementia

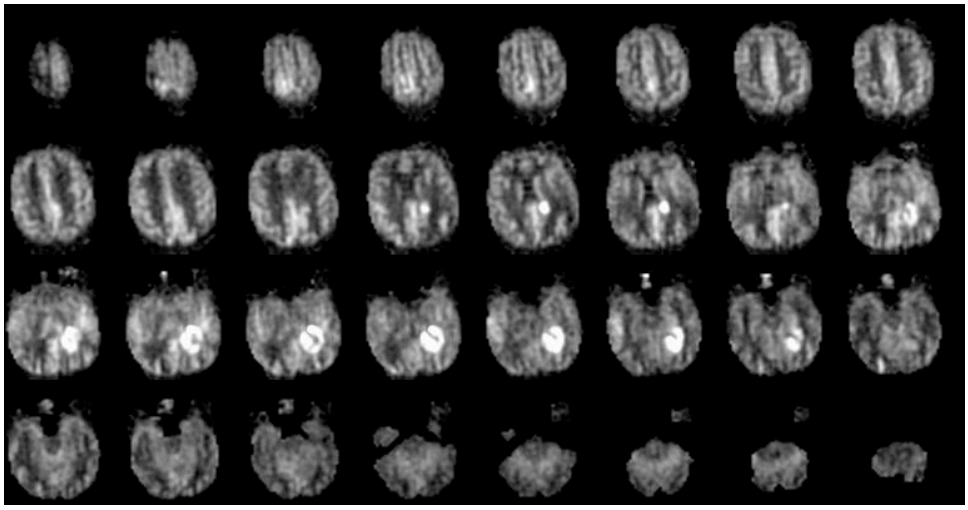
Dementia, including Alzheimer's Disease, Frontotemporal Dementia and Parkinsonian Dementia, is a major public health problem. While current therapies for these diseases are of very limited success,

improved knowledge of the molecular mechanisms of these diseases has spawned intense development of drug therapies. Imaging can play an important role in assessing the effectiveness of treatment to halt these slowly evolving diseases and can also be used to guide diagnosis once more effective therapies are available.

Loss of tissue and metabolic function are important hallmarks of these dementias though the two types of abnormalities are not always closely coupled. In Alzheimer's disease, very early and severe loss of tissue is detected in the medial temporal lobes including the hippocampus and entorhinal cortex. Metabolic imaging with FDG PET and to a lesser extent flow imaging with PET and SPECT, have demonstrated functional decreases in association cortex including the posterior-inferior temporal cortex, the superior temporal-parietal association cortex, the posterior cingulated cortex, and to a lesser extent the frontal association cortex. We have applied ASL perfusion MRI to patients diagnosed with AD and found similar regions of decreased function in these patients[30]. ASL MRI offers the possibility of acquiring functional and structural information in the same MRI study. We also found relative preservation of blood flow in the medial temporal, superior temporal and inferior frontal regions[31]. This dichotomy of functional abnormalities in AD suggests different pathologic mechanisms at work in these two regions. ASL may be useful in the early detection of AD related changes in subjects with mild cognitive impairment[32].

Brain Tumors

Blood flow is of importance for the characterization of tumors for two reasons. One is that more aggressive tumors typically have higher blood flow and hence blood flow measurement can be an indicator of tumor grade. Another is that treatments that block the development of tumor blood supply have become promising approaches to tumor therapy. ASL offers several important advantages for tumor blood flow assessment. Because it is insensitive to vascular permeability, measurement of blood flow is not complicated by permeability factors as in dynamic susceptibility contrast. ASL offers absolute quantification that can be used to compare tumor blood flow values measured throughout the duration of therapy. With state-of-the-art sequences, ASL is insensitive to susceptibility variations that can result from surgical interventions and hemorrhage. Another key strength of MR blood flow measurement in brain tumors is the coregistration with outstanding anatomical imaging obtained in the same scanning session. The need for such coregistration between anatomical and functional information cannot be overstated as the interpretation of just the functional information without anatomical guidance is problematic. The need for such coregistration has spawned the development of entire instruments, PET CT, for oncology purposes but ASL and MRI pre and post arguably offer superior information in the brain. Initial clinical



3D FSE ASL in a patient with high grade glioma. The ASL imaging and associated sensitivity and T1 mapping required just 6 minutes.

experience with ASL in human brain tumors has been reported by two groups[33-35] and interest in this area is accelerating. ASL changes following anti-angiogenic therapy of renal cell carcinoma metastases has shown promise for predicting response to therapy[36,37] and similar results were found n a preliminary trial of thalidomide therapy in glioma[38]. ASL signal prior to therapy has been shown to correlate with tumor grade[39].

Epilepsy

ASL blood flow MRI can serve as a surrogate for metabolic measures of activity in assessment and treatment planning for epilepsy. In temporal lobe epilepsy, an important application is the determination of laterality by the measurement of interictal hypometabolism. Studies comparing ASL determination of laterality with PET and surgical outcomes have been reported[40,41]. Determination of seizure focus in atypical presentations of epilepsy is an important application but the ideal signature would be the ictal hypermetabolism. This can be performed with ASL MRI or BOLD MRI[42] if the seizure or at least some kind of subclinical ictal activity occur during a scan but for rarer events, SPECT Tc-HMPAO blood flow imaging has the advantage that the isotope is long-lived so an injection of the label during the seizure in a monitoring unit can reveal the focus hours later in when a SPECT scan is feasible.

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