Original Article

# Quantification of ASL Perfusion MRI in MCI Patients Using Single-Post Labeling Delay Model-Fitting Approach

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## Abstract

**Purpose:** Neuroimaging techniques hold many promises to detect Alzheimer Disease (AD) at early stages before clinical symptoms fully develop, suggesting decreased regional Cerebral Blood Flow (CBF). Perfusion deficiencies are present from very early clinical phases of AD, i.e. Mild Cognitive Impairment (MCI) and persist well into the latest stages, demonstrating a pattern of increased hypo-perfusion with the disease development. Accurate quantification such as quantification model and noise reduction method is necessary to achievement of good results in insufficient Post Labeling Delay (PLD) time.

**Materials and Methods:** Arterial Spin Labeling (ASL) is a non-invasive MRI technique to extract brain regional CBF, which in recent years gained wide acceptance for its value in clinical and neuroscience applications. In the present work, 44 participants in 2 groups were imaged (normal control and MCI) using single-Post Label Delay (single-PLD) model-fitting ASL Perfusion at 1.5T. Images were de-noised with Independent Component Analysis (ICA) algorithm and then preprocessing such as motion correction, distortion correction, normalization, and tissue segmentation analyzed with SPM12. Calibration image that needed to calculate absolute perfusion was estimated from the data by fitting a curve to the control images in the dataset. Absolute CBF values were finally extracted from the kinetic model quantification.

**Results:** Perfusion decreases in the right precuneus (28%), right inferior partial cortex (22%) and right middle frontal cortex (20%) cortex in MCI subjects.

**Conclusion:** According to the results, ASL-MRI is able to calculate perfusion changes associated with MCI.

## 1. Introduction

Arterial Spin Labeling (ASL) is a noninvasive perfusion Magnetic Resonance Imaging (MRI) technique that uses the labeled spins in arterial water as an endogenous tracer [1]. In principle, two different images are acquired; one control image with no blood labeling, and one tag image in which arterial blood is labeled. The technique has been developed two decades ago and although it is feasible on 1.5T scanners, it became increasingly popular with the introduction of higher field clinical 3T magnets [2]. Recent investigations highlight the utility of ASL in the domain of neurodegenerative diseases, notably Mild Cognitive Impairment (MCI) and Alzheimer's Disease (AD) [3].

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Structural MRI is commonly part of the work-up for Dementia, when volumetric studies have been effective in identifying specific regional atrophy at a group level, previous studies have shown atrophy in Medial temporal and hippocampal in Alzheimer subjects in 3T MR scanner [4, 5]. In the last decade FDG-Positron Emission Tomography (PET) perfusion has been used in brain imaging and currently used in clinical and research settings with the attempt to better diagnose and to study AD [6]. PET and Single-Photon Emission Computed Tomography (SPECT) have shown some utility for the diagnosis of AD, however, they require an injection of tracers that increase radiation exposure [7].

PET imaging has been generally regarded as the gold standard for the evaluation of brain perfusion [8]. Previous PET and SPECT studies have shown metabolic and perfusion reductions in AD in temporoparietal (18%), precuneus (29%), posterior cingulate cortex (PCC) (32%), and Medial Temporal Lobe (MTL) (26%) regions [9]. Nonetheless, PET scanning has several disadvantages compared to perfusion MRI, including the need for an injection of radioactive tracers and limited availability. ASL perfusion MRI uses water in arteries as an endogenous contrast agent to help visualize tissue perfusion and provide a quantitative assessment of Cerebral Blood Flow (CBF), without any excessive radiation or the need for an intravenous line, which eliminates the side effects of contrast media and exposure to radiation [10].

ASL technique is able to measure both CBF and Arterial Transient Time (ATT) [11]. While the former is still derivable from single- Post-Labeling Delay (PLD) imaging, the latter needs multi-PLD imaging. One potential method to implement single-PLD is pseudo-continuous ASL (pCASL) perfusion MRI which generates superior quality against other ASL Perfusion MRI techniques (namely PASL and CASL) [2].

In this study, we use single-PLD pCASL to get ASL images. The idea is that the single-PLD is set just longer than the longest ATT present in the subject. Under these conditions, the entire labeled bolus is delivered to the tissue prior to image acquisition.

Because poor Signal-to-Noise Ratio (SNR) typically degrades ASL perfusion acquisition quality, image de-noising is crucial as an essential preprocessing step to make ASL more robust and more useful in clinical and research applications, particularly at 1.5T. In this study, we implemented ICA algorithm to improve SNR in the ASL Perfusion acquisition [12].

## 2. Materials and Methods

### 2.1.Subjects

A total number of 44 subjects were recruited in this study, including 22 subjects for controls (15 men and 7 women, age range; 50-73 yrs old, mean of 61) and 22 subjects for MCI group (10 men and 12 women, age range; 52-74 yrs old, mean of 63).

### 2.2.ASL Perfusion MR Imaging

Data recording was performed on a clinical 1.5T MRI scanner (GE Optima 360; Zanjan, Iran). Multisection 3D pCASL was applied to acquire the Perfusion information; EPI imaging, 46 contiguous axial sections, 3mm thickness, 0mm spacing gap, TE of 11.2ms, PLD of 1525ms, the effective receiver bandwidth of 62.5Hz. The alternating single adiabatic inversion label and double adiabatic inversion control labeling planes were positioned near the cervicomedullary junction to acquire images of the entire cerebrum. The acquisition was repeated two times for signal-intensity averaging, resulting in the labeling duration of about 3.2 secs.

sMRI as well as T1 measurement were performed between the two ASL perfusion scans and auto pre-scans were performed to adjust the receiver gain.

### 2.3.Preprocessing

Figure 1 shows quantification flowchart. Images were processed using SPM12. Images were first corrected for motion and magnetic field B0 inhomogeneity. The M0 map was co-registered to the T1 images and the transformation parameters were used to co-register the CBF map in the same way. The T1 image was segmented, leading to five high definition maps (gray and white matter, cerebrospinal fluid, meninges, and bones). The first three served as a brain mask to exclude non-cerebral voxels from the CBF map. Gray and white-matter probability maps also served to calculate spatial normalization parameters to the Montreal National

 

Institute (MNI) space according to the DARTEL approach.

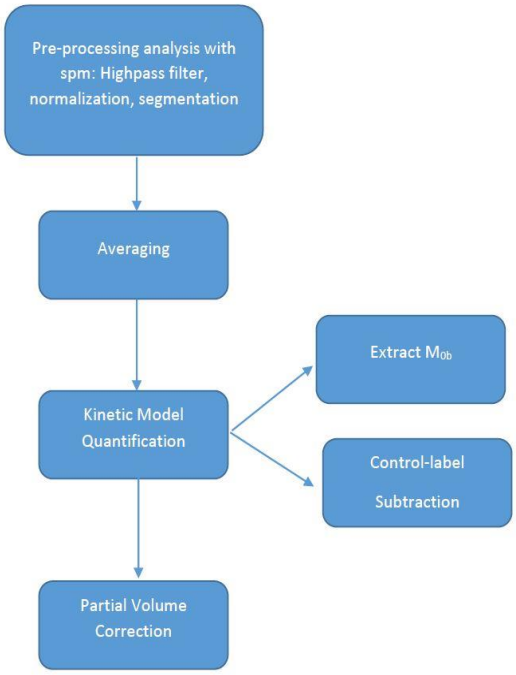


**Figure 1.** Quantification flowchart

## 2.4.Noise Reduction

De-noising techniques have been applied in MRI modalities, common methods are Anisotropic Diffusion (AD) filter, wavelet filter, Gaussian filter and Independent Component Analysis (ICA) filter [13]. Given the poor SNR typically obtained in ASL, de-noising is an important step in the pre-processing procedure [12]. ICA has proved a higher effect to eliminate random noise [12]. So we used ICA technique for noise reduction, aiming to distinguish and to extract random noise from the ASL data. Received ASL signal, $C_{jt}$, was assumed to be linear combination of the source signal components:

$$C_{jt} = \sum_{j=1}^{M} A_{jk}.S_{kt} + E_{jt}$$

Where $A_{jk}$ and $S_{kt}$ (where the columns of A represent component maps, and the row of S represent time courses of the respective component maps) are formed by the M independent components of the process, and $E_{jt}$ is spatially and temporally white noise. In spatial ICA we assumed that the columns of the matrix A = [$A_{jk}$] are statistically independent processes, whereas in temporal ICA the rows of S = [$S_{kt}$] are assumed [13]. The appropriate value of M, the number of sources, was set to maximize the SNR of image, so M was set to 10, based on preliminary analysis.

## 2.5.CBF Quantification

The pseudo-Continuous ASL (pCASL) is described by a general kinetic model [14]:

$$\Delta M(t) = \begin{cases} 0, & t < \Delta t \\ 2M_{0a}\alpha f T_{1app} e^{-\frac{\Delta t}{T_{1b}}}\left(1 - e^{-\frac{t-\Delta t}{T_{1app}}}\right), & \Delta t \le t < \Delta t + \tau \\ 2M_{0a}\alpha f T_{1app} e^{-\frac{\Delta t}{T_{1b}}} e^{\frac{-(t-\Delta t-\tau)}{T_{1app}}}\left(1 - e^{-\frac{\tau}{T_{1app}}}\right), & \Delta t + \tau \le t \end{cases}$$

where ΔM is the difference signal between control and label image, α is the tagging efficiency, f is the perfusion, $M_{0a}$ is the magnetization of the arterial blood when in the labeling region, $T_{1b}$ is the T1 of the arterial blood, τ is the label duration, $1/T_{1app}$ =1/T1 +f/ƛ, ƛ is the partition coefficient and Δt is the arterial transient time. The value of ƛ is 0.9 mL/g, T1b 1650 ms, α is 0.85.

To provide CBF in absolute units, $M_{0a}$ was also estimated from the data by fitting a curve voxel wise to the control images in dataset [15]:

$$M(t) = M_{0t}(1 - e^{-\frac{TR}{T1}})$$

Where $M_{0t}$ is the equilibrium magnetization of the tissue. Fitting was performed using Newton-Guass algorithm [16]. The parameters estimated from the data were tissue M0 and T1 values. The tissue M0 value was used to estimate the arterial M0 value by calculating a voxel-wise value for M0a using the relationship $M_{0a}=M_{0t}/ƛ$, where ƛ is the equilibrium tissue/blood partition coefficient of water, which was taken as 0.9 [2].

## 2.6.PV Correction

Considering the low spatial resolution, the GM, WM, and Cerebrospinal Fluid (CSF) may all contribute to the label/control difference signal, ΔM [17]. No ASL signal typically arises from CSF [1]; therefore, the signal ΔM at the spatial position i can be described as the Pseudo-

Continuous ASL (pCASL) is described by a general kinetic model [14]:

$$\Delta M_i = p_{iGM}\Delta M_{iGM} + p_{iWM}\Delta M_{iWM}$$

Where $p_{\_iGM}$ and $p_{\_iWM}$ are proportions of GM and WM in the voxel i, respectively. $\Delta M_{\_iGM}$ and $\Delta M_{\_iWM}$ are the difference magnetizations for GM and WM, respectively. In the current CBF calculation method, the CBF f of a tissue type is obtained by $f_{tissue}=((\Delta M_{tisuue})/M0)F_{tissue}$ where $F_{tissue}$ is a tissue-specific parameter, and M0 represents the equilibrium brain tissue magnetization obtained from the M0 image. For a mixed voxel, its CBF comes independently from the GM part and the WM part and can be described as:

$$CBF = f_{WM}^{p} + f_{GM}^{p} = \frac{p_{iWM}F_{WM}}{M_{i0}}\Delta M_{iWM} + \frac{p_{iGM}F_{GM}}{M_{i0}}\Delta M_{iGM}$$

For ASL perfusion studies, $p_{iWM}$ and $p_{iGM}$ can usually be estimated from a high resolution structural image of the same subject, and $F_{WM}$ and $F_{GM}$ can be derived from the two-compartment model for ASL data [18]. Therefore, for a CBF estimation of a mixed voxel, the key problem is to estimate the magnetization of GM and WM from multiple measurements [19].

## 3. Results

At baseline, 48 participants received MRI scan. 4 subjects had a poor signal because of motion correction and inaccurate PLD and were excluded from the analysis. Demographics of each subset of the cohort are provided in Table 1. Global cognitive and functional performance was assessed using clinical test results such as MMSE scores.

**Table 1.** Cohort demographics for the main cohort and two subsets, control and Mild Cognitive Impairment (MCI). (Mean±SD)

| Control | MCI | |
|---|---|---|
| Number | 22 | 22 |
| Age | 61±12 | 63±11 |
| Females | 7 | 12 |
| MMSE | 27±2 | 20±2 |

To calculate absolute CBF, calibration image (M0) calculated from proton density image, and PV correction algorithm applied to CBF to eliminate CSF effect in ASL signal. ICA algorithm applied to de-noising images from random noise.

CBF map shows In MCI subjects, both uncorrected whole brain and partial volume corrected CBF decreased in the right precuneus (28%), right inferior partial cortex (22%) and right middle frontal cortex (20%). (Table 2)

**Table 2.** Region of interest based Cerebral Blood Flow (CBF) values. (Mean±SD), in Mild Cognitive Impairment (MCI) and Control subjects

| | Control | MCI | p-value |
|---|---|---|---|
| **Right precuneus** | 58±2 | 45±3 | 0.024 |
| **Right inferior partial cortex** | 43±2 | 35±1 | 0.007 |
| **Middle frontal cortex** | 49±1 | 41±1 | 0.018 |

### 3.1.$M_0$ Estimation

Figure 2. shows M0 calibration image extract from proton density image, this procedure can describe as follows: 1- Medina filter 2- Erosion of voxels around the edge of brain 3- Extrapolation to refill the voxels we have eroded using the remaining values within the brain.

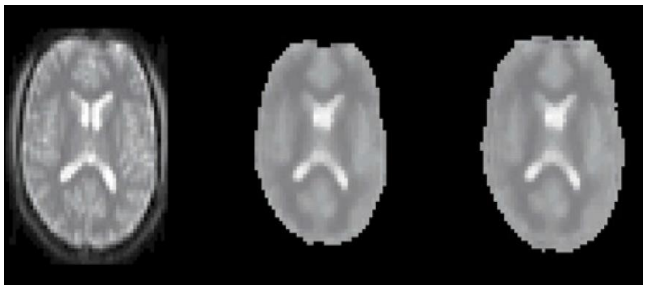

**Figure 2.** PD image (left). This has been smoothed with a median spatial filter and eroded to remove voxels around the edge of the brain that are only partially filled with brain tissue (center) and the extrapolated to refill the removed voxels with values based on those remaining (right), to generate a corrected image

### 3.2.De-Noising

Figure 3. shows error noise map that extracted from ICA algorithm. Mean and SD of noise map are 0.02 and 0.003, respectively. ICA method has no significant effect on our data which error in our data is due to inaccurate PLD.

 

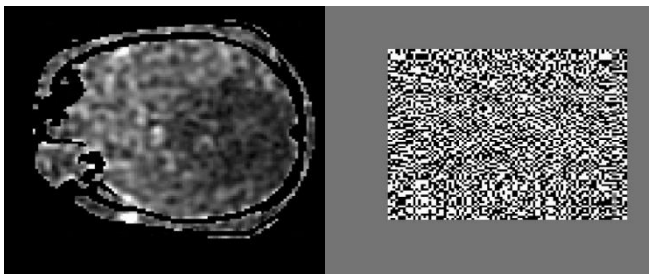

**Figure 3.** Error map (mean= 0.02 SD= 0.003) (left) and CBF map (mean=14.443 SD=0.390) (right)

### 3.3.CBF

Figure 4. shows apply PV correction algorithm to absolute perfusion and get GM proportion map and GM perfusion map and Figure 5 shows the subject's CBF images calculated using kinetic model quantification before and after PV correction.

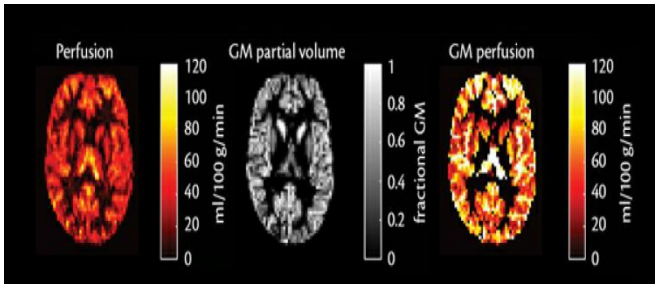


**Figure 4.** Absolute perfusion image using voxel-wise calibration (left) and after correction volume effects around the edge of brain (right)

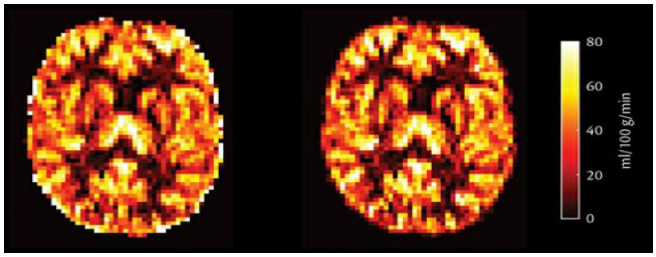


**Figure 5.** CBF map that extracted from kinetic model (left). The image of estimated PVs of gray matter (center), and the estimated gray matter perfusion (right)

## 4. Discussion and Conclusion

The first aim of this study was to find ASL perfusion MRI correlates of the first sign of MCI so quantitative CBF was measured at 1.5T. Our study shows that ASL-MRI is able to calculate perfusion changes associated with MCI. An initial voxel-wise analysis of the baseline perfusion data revealed a region of hypo-perfusion in the right precuneus, right inferior partial cortex and right middle frontal cortex in MCI subjects.

Global CBF was decreased in MCI which was not caused by a problem in the larger cerebral vessel. This shows that changes in CBF take place years before the onset of cognitive symptoms in subjects who eventually develop cognitive impairment. Among the techniques in ASL, PCASL has been recommended as the most sensitive ASL technique for the assessment of perfusion differences driven by metabolic changes due to neurodegeneration.

The second aim of this study was to improve the SNR of ASL signal with de-noising by ICA algorithm, our results show ICA has no significant effect on SNR that arises from inaccurate PLD time.

This study presents promising results that promote the use of ASL techniques for neurological diseases.

ASL imaging is a hopeful technique to extract markers of early diseases in MCI and AD and other dementias. ASL currently have some problems rather other modality of MRI but with widespread distribution of the techniques in progress, we hope this problem will be overcome and ASL will become a common tool in dementia diagnosis and research.

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