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MR Perfusion Imaging of Alzheimer's Disease with Arterial Spin Labeling (ASL)

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Over the past decade, magnetic resonance imaging (MRI) methods have been developed that are sensitive to functional changes and provide resolution and contrast comparable with or exceeding that obtained with nuclear medicine techniques, without the use of ionizing radiation. Images sensitive to blood volume, blood oxygenation, and blood flow are now being routinely used for activation studies and the clinical evaluation of stroke and neoplasms. Such MRI techniques could be advantageous for studies of Alzheimer's disease (AD), because MRI is more widely available than PET, has higher spatial resolution than SPECT, and can produce high resolution, spatially coregistered, structural images. Blood flow MRI by arterial spin labeling uses electromagnetic labeling of the naturally existing water in the blood to acquire images sensitive to flow without any external contrast agents. Recent technical advances have made the acquisition of multiple slices and absolute quantification possible. Basic principle of arterial spin labeling technique and recent works on this technique in AD will be reviewed.

Key Words: *Alzheimer's disease, Arterial spin labeling, Magnetic resonance imaging*

INTRODUCTION

It has been suggests that increased expression and altered processing of the amyloid precursor protein (APP) and the resulting increase in the generation of β-amyloid peptides is one of the early events in the pathogenesis of amyloid plaque formation in Alzheimer's disease (AD)[1]. However, there is also experimental evidence that cerebral perfusion is decreased in Alzheimer's disease[2]. A causal relationship between vascular mechanisms and the development of sporadic AD has been hypothesized already a decade ago, suggesting that sporadic AD may represent a vascular disorder caused by impaired cerebral perfusion[3].

Fluorodeoxyglucose (FDG) positron emission tomography (PET), which is used to measure glucose metabolism, and technetium^{99}m hexamethylpropyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT), which is used to measure cerebral blood flow, consistently show reduction of cerebral metabolism or blood flow in studies of subjects with AD. The most characteristic reductions of metabolism or blood flow are seen in the temporoparietal association cortices, in the posterior cingulate cortex, and, to a lesser extent, in frontal association cortices with relative sparing of the primary motor and sensory cortices[4-6]. Several studies using these imaging techniques have suggested that AD can be detected at a very early stage, possibly even before the appearance of cognitive deficits[7, 8].

Arterial spin-labeling perfusion magnetic resonance (MR) imaging is another method used to assess brain perfusion and function in dementia[9]. To the extent that regional metabolism and perfusion are coupled, arterial spin-labeling MR imaging, at which arterial blood water is labeled as an endogenous diffusible tracer for perfusion, may depict functional deficiencies in a way similar to FDG PET and HMPAO SPECT[10].

UNDERSTANDING OF ASL SEQUENCE

Arterial spin labeling (ASL) is based on the principles of the indicator dilution theory. This theory was used for the first time by Kety and Schmidt to measure cerebral blood flow (CBF) in humans. Their method was based on the measurement of the arteriovenous dynamics of a freely diffusible tracer, nitrous oxide (N_2O), passed into the arterial system through the respiration. While the Kety-Schmidt method is rarely used in patients today, their theory has been applied for the estimation of rCBF in numerous techniques, mainly using

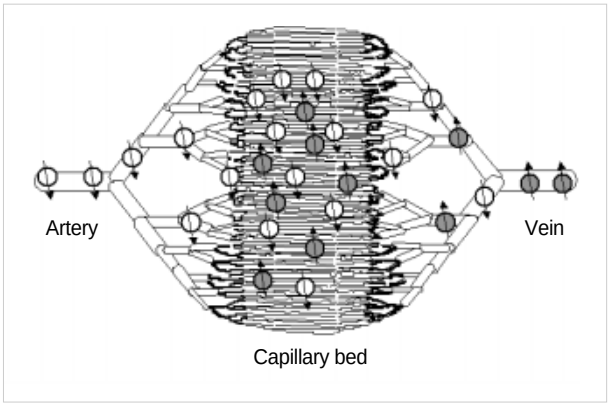

Fig. 1. Schematic description of the principles of freely diffusible tracer theory. Inverted magnetization (white) comes from the arterial tree (white arrow) and diffuses through the blood-brain barrier at the capillary level. There, spins are exchanged with the tissue magnetization (gray), and reduce its local intensity. The degree of attenuation is a direct measure of perfusion. Remaining tagged magnetization as well as exchanged water molecules flow out of the voxel of interest through the venous system (gray arrow).

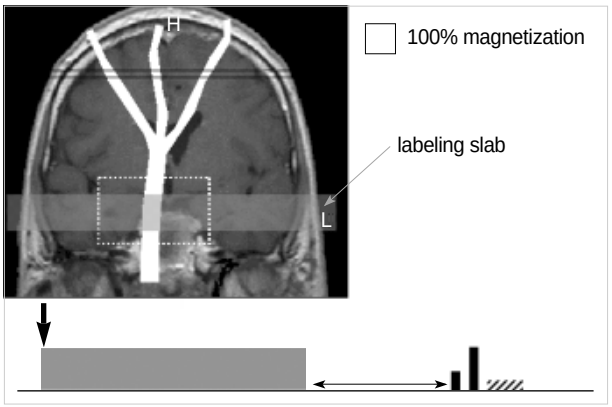

Fig. 2. In ASL techniques magnetization of inflowing blood is inverted with the use of labeling slab and magnetically labeled blood flowing into the slices of interest. Contrast agents are not required for these techniques.

radioactive tracers, such as $H_2{}^{15}O$ in positron emission tomography, or ^{99}mTc-ethylcysteinate-dimer in single-photon emission computed tomography. In ASL, no extrinsic tracer is used. Instead, a selective preparation sequence is applied to the arterial water spins, and the perfusion contrast is given by the difference in magnetization or apparent relaxation time induced by the exchange of these labeled spins with the tissue of interest[11-13] (Fig. 1).

MR image can be sensitized to the effect of inflowing blood spins if those spins are in a different magnetic state to that of the static tissue. ASL techniques uses this idea by magnetically labeling blood flowing into the slices of interest (Fig. 2). Contrast agents are not required for these techniques. This perfusion measurement is completely noninvasive. Blood flowing into the imaging slice exchanges with tissue water, altering the tissue magnetization. A perfusion-weighted image can be generated by the subtraction of an image in which inflowing spins have been labeled from an image in which spin labeling has not been performed (Fig. 3). Quantitative perfusion maps can be calculated if other parameters (such as tissue T1 and the efficiency of spin labeling) also are measured.

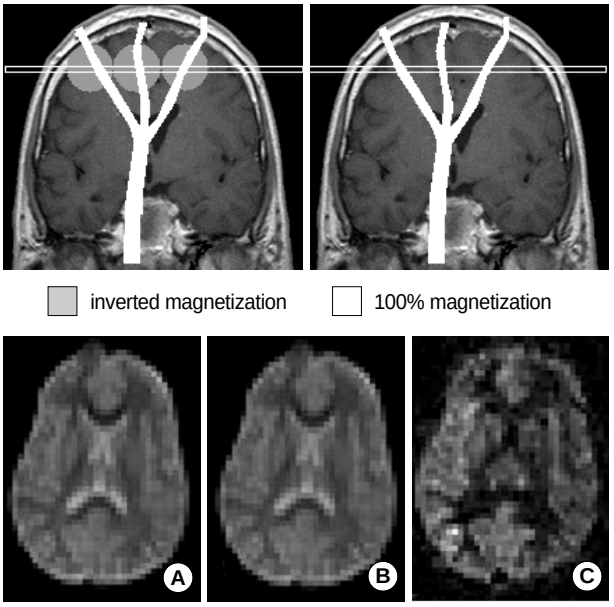

Fig. 3. Blood flowing into the imaging slice exchanges with tissue water, altering the tissue magnetization. A perfusion-weighted image (C) can be generated by the subtraction of an image in which inflowing spins have been labeled (A) from an image in which spin labeling has not been performed (B).

APPLICATION OF ASL IN ALZHEIMER'S DISEASE

A variety of studies in both animal models and human subjects have demonstrated that blood flow can be accurately quantified using ASL[9, 12, 14-18]. Such quantitative measurements of regional perfusion were previously obtainable only with exogenous tracer methods and ionizing radiation using positron emission tomography (PET), single photon emission computed tomography (SPECT) or xenon enhanced X-ray computed tomography (XeCT). The ability to obtain blood flow maps using a non-invasive and widely available modality such as MRI should greatly enhance the utility of blood flow measurement as a means of gaining

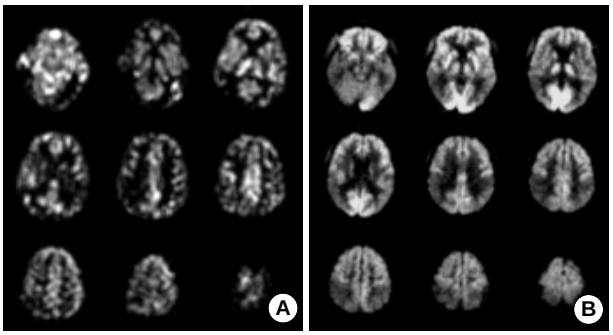

Fig. 4. Multislice-CASL image (A) of AD showed characteristic cerebral blood flow decrease in bilateral tempoparietal cortex. Cerebral glucose metabolism is decreased Decreased metabolism in the corresponding areas in FDG-PET (B) of the same patient.

further insight into the broad range of hemodynamically related physiology and pathophysiology.

Functional vascular abnormalties are one of the earlier clinical manifestations in AD[19]. Indeed, cerebrovascular abnormalities such as thickening of the microvascular basement membranes, decreased luminal diameter, and microvascular degeneration have frequently been observed in Alzheimer patients[20]. Sandson *et al.* have reported an initial evaluation of single-slice qualitative pulsed ASL imaging for functional studies of AD[21]. They were able to detect temporoparietal flow deficits relative to controls. Deter *et al*. evaluated multislice CASL perfusion MRI in a AD and frontotemporal dementia. Alzheimer's patients demonstrated very significant deficits bilaterally in parietal temporal, frontal and posterior cingulate cortex. In contrast, CBF deficits in frontotemporal dementia occurred in frontal and anterior temporal regions as well as superior parietal cortex[22, 23]. In the recent CASL perfusion MRI study in AD and mild cognitive impairment (MCI), Johnson *et al*. demonstrated patterns of hypoperfusion in subjects with mild to moderate AD. The brain regions involved were similar to those in previous FDG PET and HMPAO SPECT studies. Specifically, they found regional hypoperfusion in the parietal association cortices and posterior cingulate gyri of subjects with AD. These patterns of hypoperfusion were independent of underlying cortical gray matter atrophy. And they observed hypoperfusion of the right inferior parietal lobe in the MCI group [24].

CONCLUSION

Recent studies with ASL perfusion MRI suggest that this technique may depict patterns of reduced brain function in subjects with AD and subjects at risk for AD. These findings are similar to results previously observed with FDG PET or HMPAO SPECT (Fig. 4).

ASL perfusion MRI is completely noninvasive, and in conjunction with structural MRI offers the possibility of obtaining both functional and structural information during a single scanning session. Additional technical developments of ASL perfusion MRI are expected to further aid clinical research studies in detecting subtle brain changes at early stages of neurodegenerative disorders.

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