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# Cerebral blood volume in Alzheimer's disease and correlation with tissue structural integrity

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**Abstract**

A vascular component is increasingly recognized as important in Alzheimer's disease (AD). We measured cerebral blood volume (CBV) in patients with probable AD or Mild Cognitive Impairment (MCI) and in elderly non-demented subjects using a recently developed Vascular-Space-Occupancy (VASO) MRI technique. While both gray and white matters were examined, significant CBV deficit regions were primarily located in white matter, specifically in frontal and parietal lobes, in which CBV was reduced by 20% in the AD/MCI group. The regions with CBV deficit also showed reduced tissue structural integrity as indicated by increased apparent diffusion coefficients, whereas in regions without CBV deficits no such correlation was found. Subjects with lower CBV tended to have more white matter lesions in FLAIR MRI images and showed slower psychomotor speed. These data suggest that the vascular contribution in AD is primarily localized to frontal/parietal white matter and is associated with brain tissue integrity.


*Keywords:* Alzheimer's disease; Cerebral blood volume; Cerebral blood flow; VASO; MRI; Tissue integrity

## 1. Introduction

Alzheimer's disease (AD) is neurodegenerative disease associated with neuritic plaques composed of beta amyloid and neurofibrillary tangles composed of hyperphosphorylated *tau* protein. While amyloid/tau pathology is the primary focus in the field, recent evidence indicates that vascular factors are important in the pathogenesis of AD (de la Torre, 2004). This evidence comes from a wide spectrum of studies, including postmortem studies showing severe cerebral angiopathy in AD patients (Chui et al., 2006; Jagust et al., 2008; Tian et al., 2006), epidemiologic studies showing that many of the risk factors for AD are also associated with vascular disease (hypertension, hypercholesterolemia, diabetes, and hyperhomocysteinemia) (reviewed in de la Torre (2002)), and neuroimaging studies showing that AD patients have greater volume of white matter hyperintensities of possible ischemic origin (Delano-Wood et al., 2008; Prins et al., 2004).

Brain vascular function can be assessed by several different methods. For in vivo studies, cerebral blood flow (CBF), the amount of blood reaching the tissue per unit time (Kety and Schmidt, 1948), is the most widely used parameter. Previous CBF studies in AD patients have found pronounced blood flow deficits in temporoparietal cortex, posterior cingulate cortex, and in some cases, frontal cortex (Alsop et al., 2000; Bartenstein et al., 1997; Ishii et al., 1997; Johnson et al., 2005; Kogure et al., 2000). CBF is known to be coupled to metabolic demand. Thus, although reduced CBF may be an indication of vascular dysfunction, it may also be simply due to lower metabolic demand in these regions (de Leon et al., 2001; Reiman et al., 2005; Small et al., 2000) in the face of relatively intact brain vasculature. In addition, CBF is also governed by many factors external to the brain, such

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as cardiac output, autonomic activity, and blood pressure. Therefore, it is necessary to study brain vasculature in AD with alternative vascular parameters.

Cerebral Blood Volume (CBV), the amount of blood per 100 ml of brain parenchyma, is an indicator of blood vessel lumen size and density. CBV has been less extensively studied than CBF, but was recently shown to be useful in assessing neovascularization in brain tumors (Law et al., 2004) and a good marker for angiogenesis and synaptogenesis (Pereira et al., 2007; Swain et al., 2003). In addition, the sensitivity of CBV to physiologic variation is about 38% of that of CBF (Grubb et al., 1974). Thus, CBV may be less dependent on the subject's depth and rate of respiration. We have recently developed a Vascular-Space-Occupancy (VASO) Magnetic Resonance Imaging (MRI) technique to quantitate CBV (Lu et al., 2005). In contrast with the Dynamic Susceptibility Contrast (DSC) MRI method, the VASO approach is based on steady-state signal and does not depend on arterial input function, which itself may be changed with disease. CBV measured by VASO shows a moderate correlation with that using DSC MRI, but also displays some deviations (Lu et al., 2005), suggesting that the two measures may have slightly different physiologic bases. The VASO technique also has the advantage that the sensitivity is sufficient to assess vascular health in white matter, which is ordinarily very difficult to assess due to very low vascularity.

In this study, we measured CBV in a group of patients with probable AD or Mild Cognitive Impairment (MCI), and identified regions with significant CBV decline compared to elderly non-demented controls. The relationship of CBV deficits to parenchymal damage was examined by correlating the regional CBV values to tissue water diffusion index as measured by diffusion tensor imaging (DTI), and the volume of white matter hyperintensities measured by FLAIR MRI. In addition, the CBV result was compared to neuropsychological test scores.

## 2. Methods

### 2.1. Participants

A group of probable AD/MCI patients ($n = 16$, 9M, 7F, age (years ± S.D.) = 70.7 ± 9.3) and a group of elderly controls ($n = 10$, 3M, 7F, age = 73.1 ± 4.4) were examined. The participants were recruited from the longitudinal cohorts maintained by the Alzheimer's Disease Center of University of Texas Southwestern Medical Center. The Health Insurance Portability and Accountability Act (HIPAA) compliant protocol was proved by the Institutional Review Board and written informed consent was obtained from all participants. Inclusion/exclusion criteria for all subjects were: (a) No contraindication to MRI scanning (pacemaker, implanted metallic objects, renal/liver disease), (b) general good health, with no serious or unstable medical conditions, (c) able and willing to provide informed consent (in the case of AD/MCI patients, caregivers co-signed consents), (d) age greater than 50, (e) no evidence of stroke in clinical MRI, and (f) Hachinski et al. (1975) score < 4. Additional criteria for the control group were normal cognition and Clinical Dementia Rating (CDR; Morris, 1993) score = 0. Additional criteria for the AD/MCI group included a diagnosis of probable AD based on NINCDS/ADRDA criteria (McKhann et al., 1984) or a diagnosis of MCI based on Petersen criteria (Petersen et al., 1997) with CDR score = 0.5–1. In this study, we grouped the probable AD (8 subjects, CDR = 1) and MCI (8 subjects, CDR = 0.5) patients together because of the evidence that MCI is a potential pre-clinical form of AD (Petersen et al., 2001) and considerable overlap between these two diagnostic entities. Special caution was used to exclude any subjects with clinically obvious cerebrovacular disease (DeCarli et al., 2004), including a history of stroke, focal neurologic findings, or MRI evidence of cerebral infarction. The demographic information for the participants is summarized in Table 1.

Table 1
Demographic information of the participants.

| Characteristic | Control group | AD/MCI group |
|---|---|---|
| Number of subjects | 10 | 16 |
| Mean age ± S.D. | 73.1 ± 4.4 | 70.7 ± 9.3 |
| Gender | | |
| Male | 3 | 9 |
| Female | 7 | 7 |
| Education (years) ± S.D. | 14.8 ± 2.6 | 14.8 ± 3.2 |
| MMSE score ± S.D. | 28.7 ± 1.9 | 26.6 ± 3.5 |

### 2.2. MRI methods

The MRI investigatons were performed on a 3 T MR system (Philips Medical System, Best, The Netherlands). A body coil was used for radiofrequency (RF) transmission and an 8-channel head coil with parallel imaging capability was used for signal reception. We measured CBV maps using the VASO MRI technique that was developed by our laboratory (Lu et al., 2003, 2005). For the VASO imaging protocol, we used 32 coronal slices (voxel size 2 mm × 2 mm × 5 mm) to cover the entire brain. The other imaging parameters were: FOV = 192 mm × 192 mm, matrix size = 96 × 96, slice thickness = 5 mm, echo-planar-imaging (EPI) factor = 7, TR/TE = 6000 ms/3.4 ms, duration = 2.5 min. The inversion time, TI, was selected to be 1088 ms in accordance with the blood T1 estimate, 1624 ms (Lu et al., 2004). The scan protocol included a pre-contrast scan, injection of contrast agent by an MRI Power Injector (MEDRAD, Pittsburgh, PA) and a post-contrast scan. An FDA-approved contrast agent, Gd-DTPA (Magnevist®), was used with a standard dosage (0.1 mmol/kg). The post-contrast VASO scan was initiated 2 min after the injection to avoid signal fluctuations due to bolus passes.

In addition to the CBV images, a T1-weighted high resolution (1 mm × 1 mm × 1 mm) anatomical image using a