Quantitative Comparison of Cerebral Blood Volume between Patients with Alzheimer's Disease and Elderly Controls

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INTRODUCTION: Alzheimer's disease (AD) is one of the most common dementia that affects about 5 million people in the United States and more than 30 million worldwide (1). The pathogenesis of AD has not yet been clearly understood, however, and currently there is no cure despite of studies of decades. While AD has been known as a neuro-degenerative disease associated with insoluble senile plaques and neurofibrillary tangles, recent research has suggested that vascular factor is also an important feature of AD, which may be useful for better understanding and early marker of AD (2,3). In this work, we investigated Cerebral Blood Volume (CBV) of mild AD patients compared with age-matched controls to understand the relationship between the cerebrovascular dysfunction and the early progress of AD. There have been CBV studies on AD patients, but only relative CBV values for limited ROIs have been reported (4). Here, we assessed quantitative CBV in terms of ml-blood-per-100-ml-brain of the entire brain using a novel MR technique, Vascular-Space-Occupancy (VASO)-MRI (5). Brain regions that showed significant CBV differences between mild AD and controls were identified.

METHODS: We measured CBV maps for 12 mild AD patients (age 73.5±7.6, MMSE=27.0±3.9) and 11 age-matched elderly normal controls (age 74.6±5.2, MMSE=28.6±1.8) (age comparison, Student t test, p=0.68). The participants were recruited from the AD Center in our institution. The HIPAA compliant protocol was approved by the Institutional Review Board and informed written consents were obtained for all participants. We used 32 coronal slices (voxel size 2×2×5 mm^3) to cover the entire brain. The other imaging parameters were: FOV=192×192mm^2, matrix size=128×128, slice thickness=5mm, EPI factor=7, TE/TR=3.4ms/6s. An FDA-approved contrast agent, Gd-DTPA (Magnevist®), was used with a standard dosage (0.1 mmol/kg) via a power injector (MEDRAD). The post-contrast VASO scan was initiated 2 minutes after the injection in order to allow the contrast agent to be uniformly distributed. Each VASO scan took 2 min 36 s. In data processing, the pre- and post-contrast images were co-registered by Statistical Parametric Mapping (SPM) and the absolute CBV was calculated using algorithm described in the literature (5). In addition to the VASO images, a T1-weighted anatomical image with high resolution (1mm^3) was acquired for each subject. Images from individual subject were co-registered with a template image using an elastic registration algorithm (6). ROIs drawn on the template image by an experienced neuro-radiologist can then be transformed onto the individual image for identifying regional CBV values. We also performed voxel-based analysis on the co-registered CBV maps between the mild AD group and the control group, and voxels showing significant differences were overlaid on the anatomical images.

RESULTS and DISCUSSION: The CBV maps of a mild AD and a normal control are demonstrated in Fig. 1. By visual inspection, it can be seen that CBV images of the AD patient is darker than those of the normal control, indicating lower CBV values. The average CBV over the entire brain cortex showed that AD group has generally smaller CBV than the control group, but the difference was not yet significant (2.20±0.21 and 2.38±0.26 ml-blood/100-ml-brain for AD and control groups, respectively. two-tailed t test, p=0.083). This is possibly because CBV change due to AD does not occur uniformly over the entire brain. On the other hand, our ROI analysis reveals regions that have significant changes in CBV. Out of the regions we have investigated, 8 ROIs shows significant differences between the two groups (two-tailed t test, p<0.025 for each tail). The significant regions and their CBV values are listed in Fig. 2. Notably, all regions showed that the CBV in AD is lower than that in controls. None of the regions showed the opposite pattern. Consistent with path of spread of neurofibrillary tangles (7), parahippocampal gyrus (including entorhinal and perirhinal cortices) and cingulate gyrus showed involvement at this early stage. Interestingly, our data also show significant hypoperfusion in white matters. Our manually-drawn frontal/parietal white matter ROIs (not shown) also revealed a significant reduction of CBV for AD group (0.74±0.31 for AD, 1.08±0.25 for control, two-tailed t test, p=0.0086). This is consistent with recent diffusion tensor imaging (DTI) studies that found reduced fractional anisotropy in many white matter regions in early AD (8). The white matter CBV values in the elderly control group were slightly lower than those in young controls (5) (1.5ml-blood/100-ml-brain in young controls according to previous reports using similar techniques), probably due to normal aging process. Fig. 3 shows the result of voxel-based analysis. Student t test was performed between the AD and control groups on a voxel-by-voxel basis and the clusters with significant differences are presented. Similar to the ROI results, parahippocampal gyrus shows hypoperfusion in AD patients. In addition, orbital frontal regions manifest reduced CBV in the AD group. Cerebellum also showed decreased in CBV, in good agreement with recent volumetric studies (9). In summary, our study revealed that mild AD patients manifest significant reduction of CBV particularly at limbic system and basal ganglia regions, which can be assessed with the recently developed VASO-MRI technique.

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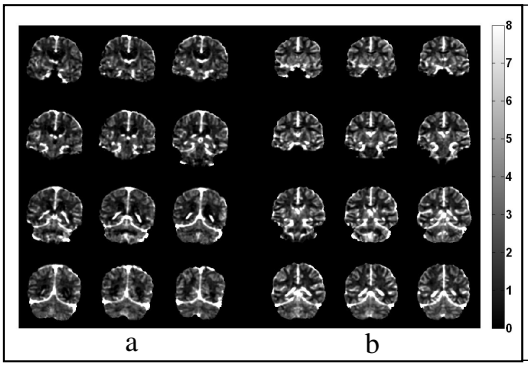

Fig. 1 CBV maps of a mild AD patient (a) (age=74, male) and an elderly control (b) (age=70, female). The gray scale indicates absolute CBV in ml/100-ml-brain

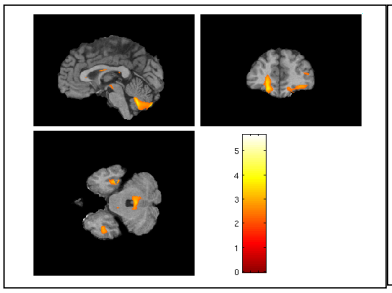

Fig. 3 Voxel-by-voxel analysis. The voxels in clusters showing significant difference are presented with the threshold of P=0.02 and cluster size = 500. The color-bar indicates Student t-statistic value.

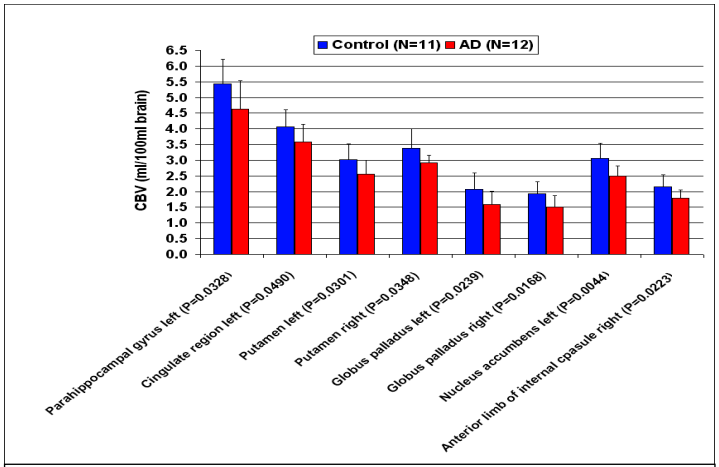

Fig. 2 ROI's showing significant differences of CBV between AD and Control groups. The percentage decrease of CBV for the eight compartments presented are 14.7, 11.7, 15.2, 13.8, 23.5, 21.4, 18.2, 16.2, and 16.8, respectively.