MRI of Angiogenesis and Vasculature Alternations in Alzheimer's Disease Based on Endogenous BOLD Contrast

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Introduction: Affecting 10% of the world's population, Alzheimer's disease (AD) is one of the most common forms of dementia in the elderly. Despite enormous investigative efforts, the pathological basis for AD remains unclear. Recently, it was hypothesized that AD may be an angiogenesis-dependent disorder and anti-angiogenic drugs might be able to prevent and treat this disease [1]. Using the combination of the Scanning Electron Microscope (SEM) and vascular corrosion casting techniques, it was demonstrated that vasculature abnormalities and angiogenesis associated with AD [2]. Researchers suggest that imaging vascular alterations, such as angiogenesis, could serve as a biomarker for AD disease onset and progression. Here we present the first MRI demonstration of AD associated angiogenesis by using a technique based on endogenous blood oxygenation level dependent (BOLD) effect.

Methods: APP/ps1 transgenic (tg) mice (18-20 months, n=3) over-expressing human amyloid pathology were imaged at Varian 9.4T with gradient echo multi-slice imaging sequences under hyperoxia (100% O_2), normoxia (21% O_2) or hypoxia (15% or 8% O_2) inhalations. The imaging parameters were: TE=10ms, TR=0.5s, 0.5mm slice thickness, 20 slices, 58μm*58μm in-plane resolution and 10 signal averages for a total imaging time <25min at each inhalation. The cerebral blood volume (CBV) maps were calculated using a method presented by Newman et al.[3].

Results: Relative to normoxia, hypoxia (8% O_2) significantly reduces MR signal from cerebral vasculature, creating much higher BOLD effect than hyperoxia (100% O_2). While signal from AD plaques and normal brain tissue is less sensitive to oxygenation changes, resulting in a clear cerebral vasculature image (CBV map), with which the relationship between AD plaque and vasculature network can be characterized. Hyperoxia image in Figure 1A shows AD plaques concentrated especially in thalamus. Hypoxia image in Figure 1B shows low signal from both plaques and vessels, such as cortical veins and anterior choroidal arteries (AchA). CBV maps shown in Figure 1C and D demonstrate increased vasculature density surrounding regions of large plaques visible in images A and B. Plaques form "holes" from the vasculature network, confirming previous SEM observations [2]. Several large vessels originated from AchA are also clearly visible.

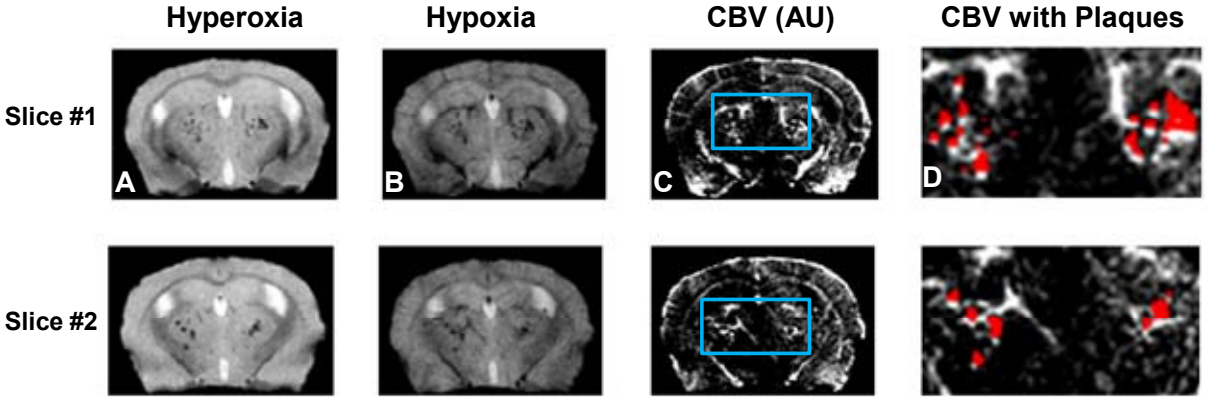

Figure 1. Two sample slices of MRI of AD associated angiogenesis. A and B show T_2* weighted images acquired at hyperoxia (100% O_2) and hypoxia (8% O_2) respectively. CBV map (C) constructed based on the ratio of image A and B shows cerebral vasculature. D shows the magnified CBV map from the selected region (highlighted in C). AD plaques are overlaid as red dots on the CBV map.

Conclusions: The results demonstrate that the endogenous BOLD effect induced by hypoxia enables the visualization of angiogenesis and vasculature alterations associated with AD pathology in mice. It avoids confounding factor due to vessels permeability in common in Dynamic Contrast Enhanced MRI (DCE-MRI) methods and produces much higher sensitivity than the endogenous contrast from Arterial Spin Labeling (ASL) MRI. This study represents the first MRI evidence of AD-associated angiogenesis. With further development, MRI of angiogenesis and vasculature alternations could serve as a sensitive tool for investigation of AD pathology, early diagnosis and testing therapeutic efficacy of novel drugs. We are working on further validation with histology and other MRI techniques including DCE-MRI or ASL.

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