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Vascular Contributions to Alzheimer's Disease

Macrovascular and microvascular cerebral blood flow in adults at risk for Alzheimer's disease

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Abstract

Introduction: Capillary hypoperfusion is reported in asymptomatic adults at-risk for Alzheimer's disease (AD), but the extent that can be explained by reduced flow in intracranial arteries is unknown.

Methods: One hundred fifty-five asymptomatic adults enriched for AD risk (mean age 61 years) completed arterial spin labeling (pcASL) and 4D-flow MRI sequences. Voxel-wise regression models investigated the relationship between mean flow in bilateral cerebral arteries and capillary perfusion, and tested potential moderators of this relationship.

Results: Mean arterial blood flow through middle cerebral arteries (MCAs) and internal carotid arteries was positively associated with perfusion in large cortical clusters ($P < .05$, false discovery rate corrected). Trends were observed for the interactions MCA flow × age and MCA flow × cardiovascular risk on cerebral perfusion ($P < .001$, uncorrected).

Discussion: These findings provide evidence that capillary perfusion measured via pseudocontinuous arterial spin labeling is strongly dependent on inflow from larger cerebral arteries. Further studies are warranted to investigate possible alterations between macrovascular and microvascular flow in advanced age and elevated cardiovascular risk in asymptomatic adults at risk for AD.

Keywords: Cerebral blood flow; Alzheimer's disease; Cerebrovascular disease; Phase-contrast MRI; Arterial spin labeling; Vascular imaging

1. Introduction

Reduced cerebral blood flow (CBF), or hypoperfusion, may be an early marker of neurodegeneration that initiates a cascade of events preceding cognitive decline in Alzheimer's disease (AD) [1]. For example, cardiovascular risk factors may increase risk of cognitive decline by

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reducing CBF, which may in turn initiate increased production of β-amyloid and capillary hypoperfusion, ultimately inducing neuronal dysfunction [2]. Supporting this assertion, hypoperfusion is observed more frequently in individuals at risk for AD such as older adults [3] and those with a positive family history or genetic risk for AD [3–6].

Prior studies suggest that cerebral perfusion closely parallels cerebral glucose metabolism and that perfusion measures may be used as surrogate measures for glucose metabolism (e.g., fluorodeoxyglucose [FDG]) without requiring radioactive tracer injection [7]. In favor of this interpretation are consistent patterns of hypoperfusion (measured via pseudo-continuous arterial spin labeling [pcASL] MRI or 15-O-water positron emission tomography [PET]) and hypometabolism (e.g., FDG-PET) among people at risk for AD and with symptomatic disease [8–10]. However, signal from pcASL is likely influenced by both neurometabolic activity and the health of the supplying arteries. Although prior studies of CBF in asymptomatic adults at risk for AD have investigated parenchymal capillary perfusion, there is little information regarding the effect of macrovascular health on perfusion in this population.

Measuring the relationship between intracranial vessel flow and cerebral perfusion was previously challenging because of practical limitations, including motion artifacts, lengthy scan times, and complex implementation [11]. However, a recently developed 4D-flow MRI technique termed phase-contrast vastly undersampled isotropic projection (PC VIPR) imaging uses radial undersampling, allowing for improved temporal and spatial resolution compared with 2D methods in clinically feasible scan times [12,13]. Using this technique, lower mean blood flow and higher pulsatility (a marker of vessel stiffness) were observed in individuals with dementia due to AD compared with age-matched cognitively healthy peers, both of which were observed in anterior vessel segments (internal carotid arteries [ICAs] and middle cerebral arteries [MCAs]) [14]. Moreover, across a sample of cognitively healthy and cognitively impaired participants, lower flow in the MCAs and superior ICAs (sICAs) was associated with greater global brain atrophy [15].

Identifying early markers of cerebrovascular dysfunction that contribute to hypoperfusion and cognitive decline will be important for future secondary prevention strategies aiming to slow the impact of AD on cognition. Therefore, we investigated the relationship between cerebral macrovascular and microvascular blood flow in a sample of cognitively asymptomatic adults enriched for AD risk. To reduce the number of comparisons, only vessel segments that exhibited consistent detriments in prior studies were investigated (e.g., sICAs and MCAs). Furthermore, we investigated modifiable and invariable risk factors related to increased dementia risk as potential moderators of the relationship between microvascular and macrovascular CBF. We hypothesized there would be a positive relationship between mean arterial flow in the MCAs and sICAs (as measured via 4D-flow) and cerebral perfusion (as measured via pcASL). We also hypothesized that advanced age, greater cardiovascular risk, and genetic risk for AD would modify the relationship between intracranial arterial flow and cerebral perfusion.

2. Methods

2.1. Participants

Participants were enrolled in the Wisconsin Alzheimer's Disease Research Center clinical core, completing a comprehensive neuropsychological battery, physical examination, and fasting lipid panel. Study data were reviewed in a clinical consensus conference, and participants deemed cognitively healthy were included in the present study. One hundred sixty-two cognitively healthy participants underwent PC VIPR scans with complete MCA and sICA flow measurements and pcASL scans. Seven participants were excluded because of poor pcASL scan quality ($n = 3$), anatomic anomalies (hydrocephalus, cysts, prior neurosurgery, $n = 3$), or a recent head injury ($n = 1$). Of the 155 participants included in analyses, 119 were enrolled in the Investigating Memory in People at Risk, Causes and Treatments (ages 40–65 years) cohort and 36 were enrolled in the older adult (age >65 years) control cohort. The sample was enriched for participants at risk for AD (71% with positive parental history of AD). The University of Wisconsin Institutional Review Board approved all study procedures, and each participant provided signed informed consent.

2.2. Magnetic resonance imaging

Magnetic resonance imaging (MRI) scans were completed on a clinical 3T scanner (Discovery MR750; GE Healthcare, Waukesha, WI, USA) using an eight-channel head coil (Excite HD Brain Coil; GE Healthcare). All participants were instructed to abstain from food, tobacco, and caffeine at least 4 hours before the scan. A T1-weighted structural scan (BRAVO) was acquired axially using the following imaging parameters: 3D fast spoiled gradient echo sequence, inversion time = 450 ms; repetition time (TR) = 8.1 ms; echo time (TE) = 3.2 ms; flip angle = 12°; acquisition matrix = 256 × 256; field of view (FOV) = 256 mm; and slice thickness = 1.0 mm. In postprocessing, the T1-weighted volume was segmented into tissue classes using the updated segmentation feature in Statistical Parametric Mapping version 12 (SPM12, www.fil.ion.ucl.ac.uk/spm). The segmentation procedure also produced a deformation field, allowing the T1 image to be mapped to Montreal Neurological Institute (MNI) standard space.

2.3. Intracranial arterial flow—PC VIPR

Blood flow within the bilateral MCAs and sICAs was measured using PC VIPR. The scanning parameters were as follows: velocity encoding (venc) = 80 cm/s, imaging