Special Section: 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.

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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. AT1-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

volume = 22 cm^3, acquired isotropic spatial resolution = 0.77 mm, TE = 2.7 ms, TR = 7.4 ms, flip angle α = 10°, bandwidth = 83.3 KHz, and 14,000 projection angles. Scan acquisition time was approximately 7 minutes. Hemodynamic evaluation was conducted using the velocity vector data acquired via the PC VIPR scans. Segmentation of the arterial tree was performed in MATLAB (The MathWorks, Natick, MA, USA) from PC angiograms constructed from the PC VIPR data. EnSight (CEI, Apex, NC, USA) was used for interactive flow visualization and manual selection of vessel planes for quantitative analysis. For this analysis, planes were placed 5 mm from the MCA origin and in the distal petrous portion of the ICA. Four-dimensional-flow MRI data were used to generate two-dimensional cine images with through-plane velocities at the selected planes; mean blood flow (mL/min) was calculated. Blood flow through the left and right MCAs and blood flow through the left and right sICAs were added together and divided by 2 to calculate an average blood flow for the MCAs and sICAs [16].

2.4. Cerebral tissue perfusion—pcASL

Cerebral perfusion was measured using background-suppressed pcASL MRI [10]. Images were acquired using a 3D fast spin echo spiral sequence, with a stack of variable density 4-ms readout and eight interleaves. The scan parameters for pcASL were as follows: TR = 6000 ms, TE = 21 ms, FOV = 240 × 240 × 160 mm, matrix size = 128 × 128, slice thickness = 4 mm no gap, number of excitations = 3, and labeling radiofrequency amplitude = 0.24 mG. Postlabeling delay was 2025 ms. A fluid-suppressed proton density (PD) scan was acquired without radiofrequency labeling, but using the same imaging sequence/slab parameters as the pcASL scan. As described previously, the three excitations were averaged to improve signal-to-noise ratio, and the PD sequence was used for flow quantification and image registration [5]. Scan time was approximately 4.5 minutes.

Postacquisition processing of the pcASL scans was performed using SPM12. Each participant's PD image was colocalized to their T1 image, and the derived transformation matrix was applied to the CBF map. Subsequently, the coregistered CBF map was spatially normalized to the MNI template with resampling to a 2 × 2 × 2 mm voxel size via the deformation field produced during tissue segmentation. The normalized CBF maps were then smoothed using an 8-mm full-width at half-maximum Gaussian kernel. Grand mean scaling to a value of 50 and proportional normalization were applied in all voxel-wise regression analyses [5]. A gray matter mask (created with SPM12 ImCalc, thresholded at 0.2) was applied to the resulting SPM.mat file to limit analyses to voxels with greater than 20% probability of containing gray matter.

2.5. Atherosclerotic Cardiovascular Disease risk score

The Atherosclerotic Cardiovascular Disease (ASCVD) risk score, developed by the American College of Cardiology

and the American Heart Association, estimates an individual's risk of a major cardiac event (myocardial infarction and stroke) in the next 10 years [17]. The score is comprised of systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, age, sex, race, diabetes status, smoking status, and antihypertensive medication status. These data were acquired at the study visit closest to the MRI date. Analyses of ASCVD risk included 154 participants because one participant was missing complete ASCVD data. Owing to a nonnormal distribution, this score was log-transformed before inclusion in statistical models.

2.6. Genetic risk

Genotyping was conducted by LGC Genomics (Beverly, MA, USA) using competitive allele-specific PCR-based KASP genotyping assays, and quality control was performed as described previously [18]. Apolipoprotein E (*APOE*) risk was calculated as a polygenic risk score according to the odds ratio (OR) of the ε2/ε3/ε4 genotype, as indicated in the meta-analysis of *APOE* genotype frequencies reported in AlzGene [19]. The specific ORs used were based on studies of Caucasian individuals for consistency with the current sample and were calculated using the ε2/ε2 genotype as the reference (ε2/ε2 OR = 1) as follows: ε2/ε3 OR = 1.38, ε3/ε3 OR = 2.00, ε2/ε4 OR = 4.45, ε3/ε4 OR = 6.78, ε4/ε4 OR = 25.84 [18]. Analyses of *APOE* risk included 151 participants because four participants were missing genetic data.

2.7. Statistical analyses

SPSS statistics (version 23, IBM) was used to conduct analyses investigating relationships between perfusion, arterial flow, and hypothesized moderators (age, ASCVD risk, and *APOE* risk). Statistical significance was defined as $P < .05$. Multiple linear regression models tested the relationship between mean arterial flow (MCAs or sICAs) as the predictor variable and mean perfusion as the outcome variable, with age and sex as covariates. Bivariate correlations were conducted to assess the relationship between age and flow (perfusion, arterial flow). Multiple linear regression models (including age and sex covariates) were conducted to examine the relationship between blood flow (e.g., mean perfusion, mean arterial flow) and (1) ASCVD risk score or (2) *APOE* risk score.

Voxel-wise analyses were conducted using SPM12. Whole-brain voxel-wise multiple linear regression models included mean arterial flow (MCAs or sICAs) as the predictor variable, age and sex as covariates, and whole-brain cerebral perfusion as the outcome variable. Three subsequent multiple linear regression analyses added the following terms to the aforementioned model: (1) interaction of age × mean arterial flow, (2) main effect of ASCVD risk score and interaction of ASCVD risk score × mean arterial flow, and (3) main effect of *APOE* risk score and interaction of *APOE* risk score × mean arterial flow. A false discovery rate (FDR) correction at

the $P < .05$ level and a cluster extent of >100 voxels was applied to adjust for multiple comparisons. For exploratory purposes, an uncorrected $P < .001$ threshold at the voxel level was also applied, and results are reported as trends.

3. Results

3.1. Sample characteristics

The sample was on average late middle-aged, highly educated, female, and Caucasian (see Table 1). The sample was enriched for AD risk with 71% with parental history of AD and 40% at genetic risk for AD. Mean 10-year risk of an atherosclerotic cardiovascular event was 9%.

3.2. Relationship between arterial flow and cerebral perfusion

Mean flow in the MCAs and sICAs accounted for a significant amount of variance in mean perfusion, after adjusting for covariates of age and sex (MCA: $\beta = 6.96$, $t = 10.23$, $P < .001$; sICA: $\beta = 3.32$, $t = 6.82$, $P < .001$; see Fig. 1). A voxel-wise analysis revealed a statistically significant positive relationship between MCA flow and perfusion in a large cluster that encompassed several cortical regions, with peak voxels in the superior parietal lobe (postcentral gyrus) and lateral temporal lobe (superior temporal gyrus). Similarly, significant positive relationships were observed between sICA flow and cerebral perfusion in bilateral parietal and occipital regions, with a peak voxel also in the superior

Table 1
Sample characteristics

Characteristic	Value
N	155
Age (mean years; SD; range)	61.1 (8.5; 45–86)
Sex (N; % female)	111; 72%
Education (mean years; SD)	16.46; 2.356
Race/ethnicity	97.4% Caucasian
Positive parental history of dementia (N; %)	110; 71%
APOE ε4 positive (N; %)	61; 39.4%
Mini-Mental State Examination (mean; SD; range)	29.31; 0.883; 26–30
Mean perfusion, mL/g/min tissue (mean; SD; range)	33.77; 5.90; 15.22–51.38
MCA mean flow mL/min (mean; SD; range)	160.2; 32.4; 67.2–265.7
sICA (petrous portion) mean flow mL/min (mean; SD; range)	270.1; 49.9; 173.05–497.01
ASCVD 10-y risk score % (mean; SD; range)	9.1%; 11.7; 0.3%–69%
Diagnosed with diabetes (N; %)	12; 7.7%
Systolic blood pressure, mmHg (mean; SD)	127.5; 14.2
Diastolic blood pressure, mmHg (mean; SD)	73.7; 9.2
Total cholesterol (mean; SD)	195.5; 35.9
HDL cholesterol (mean; SD)	63.2; 20.1
Taking blood pressure–lowering medication (N; %)	46; 29.7%

Abbreviations: *APOE*, apolipoprotein; ASCVD, Atherosclerotic Cardiovascular Disease; MCA, middle cerebral artery; sICA, superior portion of the internal carotid artery.

parietal lobe (postcentral gyrus). Regions exhibiting positive relationships between MCA and sICA flow and cerebral perfusion are displayed in Fig. 2. No negative relationships between sICA or MCA flow and perfusion were observed.

3.3. Potential moderators of relationship between arterial flow and cerebral perfusion

3.3.1. Age

Age was negatively associated with mean flow in the MCAs ($r = -.39$, $P < .001$), sICAs ($r = -.31$, $P < .001$), and mean cerebral perfusion ($r = -.39$, $P < .001$). In voxel-wise analyses, the interaction term age $\times$ MCA flow or age $\times$ sICA flow on whole-brain perfusion was not statistically significant at the FDR-corrected threshold. Trends in the positive direction were observed for the interaction term of age $\times$ MCA mean flow on perfusion in parietal regions (inferior parietal lobule, postcentral gyrus), cuneus, and middle temporal gyrus (uncorrected $P < .001$; see Fig. 3). These findings suggest a potentially stronger relationship between MCA flow and perfusion in older age. In contrast, there was no relationship between age and sICA flow on perfusion (FDR corrected $P < .05$ or uncorrected $P < .001$).

3.3.2. Cardiovascular risk

ASCVD risk score accounted for a nearly significant amount of variance in mean MCA flow ($\beta = -0.4$, $t = -1.85$, $P = .067$) and mean sICA flow ($\beta = -0.6$, $t = -1.93$, $P = .056$), and a statistically significant amount of variance in mean cerebral perfusion ($\beta = -8.8$, $t = -4.46$, $P < .001$), after accounting for variance associated with covariates of age and sex. The interaction of ASCVD risk score and MCA or sICA flow on perfusion was not statistically significant at the FDR-corrected threshold. Trends in the positive direction were observed, suggesting that higher ASCVD risk scores were associated with a stronger relationship between MCA flow and perfusion in left parietal and frontal regions (uncorrected $P < .001$; see Fig. 3). The interaction between ASCVD risk score and sICA mean flow was not significant at both FDR-corrected and uncorrected $P < .001$ thresholds.

3.3.3. Genetic risk

There were no significant relationships between the *APOE* risk score and mean flow in MCAs ($P = .62$), sICAs ($P = .997$), or mean perfusion ($P = .78$), after accounting for variance associated with age and sex. Similarly, voxel-wise analyses resulted in no significant interactions between *APOE* risk score and mean flow in MCAs or sICAs on perfusion, as well as no main effect of *APOE* risk score on perfusion.

4. Discussion

In this cognitively healthy late middle-aged sample enriched for AD risk, mean blood flow in the MCAs and sICAs
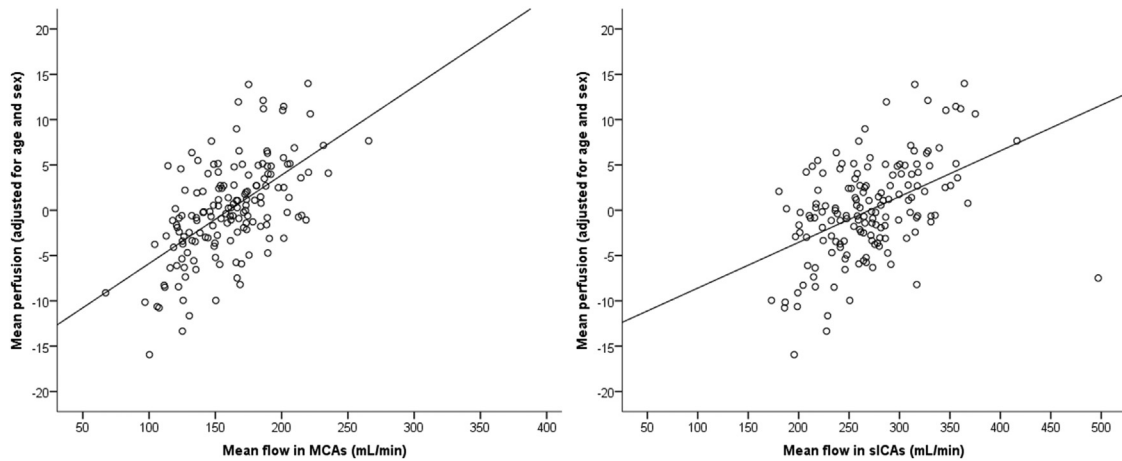
Fig. 1. Significant positive relationship between mean perfusion and mean flow in MCAs (left) and sICAs (right), adjusted for age and sex in cognitively healthy middle-aged and older adults enriched for Alzheimer's disease risk (*n* = 155).

was positively associated with cerebral perfusion across a majority of the cortex after adjusting for age and sex, supporting our hypothesis. Flow in the MCAs and sICAs was associated with perfusion in similar brain regions (postcentral gyrus); however, MCA flow was uniquely associated with perfusion in the superior temporal gyrus and frontal regions. Furthermore, results suggest that the relationship between macrovascular and microvascular blood flow may be disrupted by age and cardiovascular risk factors. In contrast, macrovascular or microvascular blood flow was not associated with the *APOE* status.

Prior studies have reported that increased age and greater cardiovascular risk factors are associated with lower perfusion in middle-aged at-risk adults [20]. This study extended prior results by demonstrating that elevated age and cardiovascular risk are associated with lower flow in the MCAs and ICAs. Furthermore, trends (e.g., uncorrected *P* < .001) in the positive direction were observed, suggesting a stronger relationship between flow in the MCAs and perfusion in parietal-occipital regions with older age and in frontal-parietal regions with higher cardiovascular risk. These findings suggest that with increasing age and greater
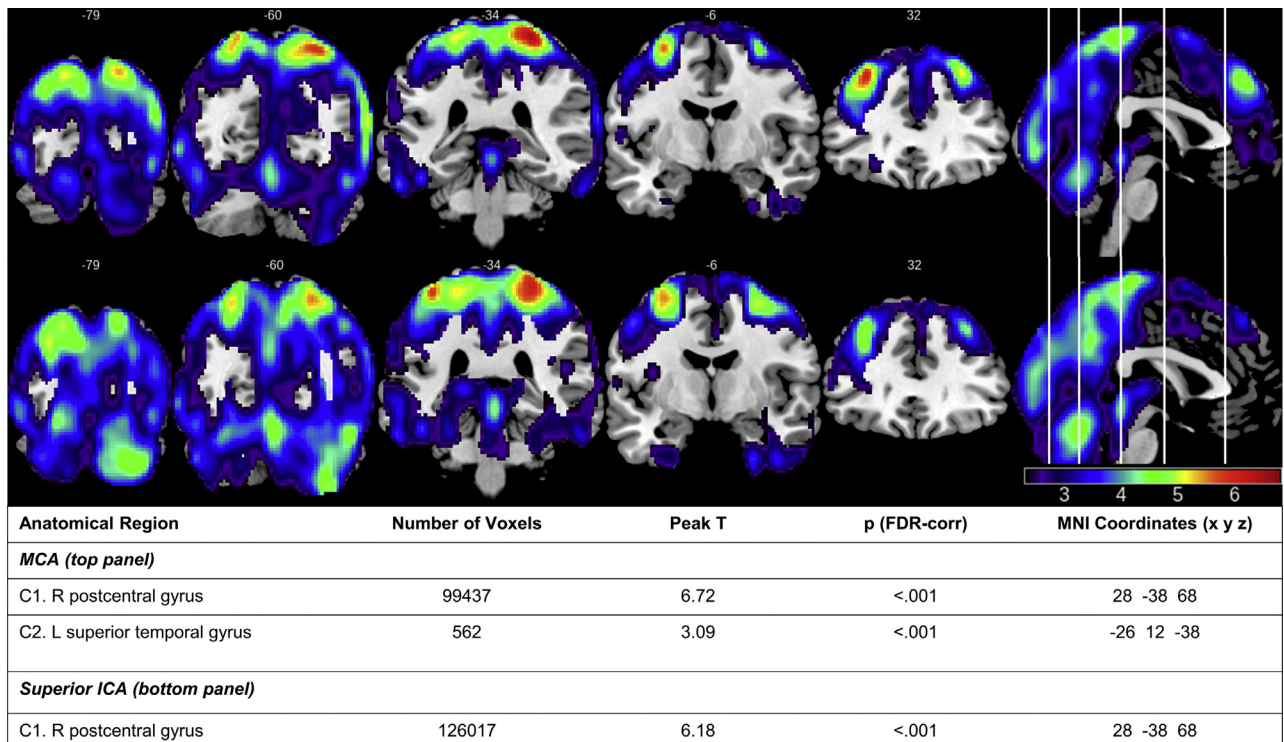

Anatomical Region	Number of Voxels	Peak T	p (FDR-corr)	MNI Coordinates (x y z)
MCA (top panel)				
C1. R postcentral gyrus	99437	6.72	<.001	28 -38 68
C2. L superior temporal gyrus	562	3.09	<.001	-26 12 -38
Superior ICA (bottom panel)				
C1. R postcentral gyrus	126017	6.18	<.001	28 -38 68

Fig. 2. Results of voxel-wise analyses (*t* statistic map) demonstrating a positive relationship between mean flow in MCAs (top) and sICAs (bottom) and regional perfusion in cognitively healthy middle-aged and older adults (*n* = 155; *P* < .05 FDR corrected; cluster extent = 100).
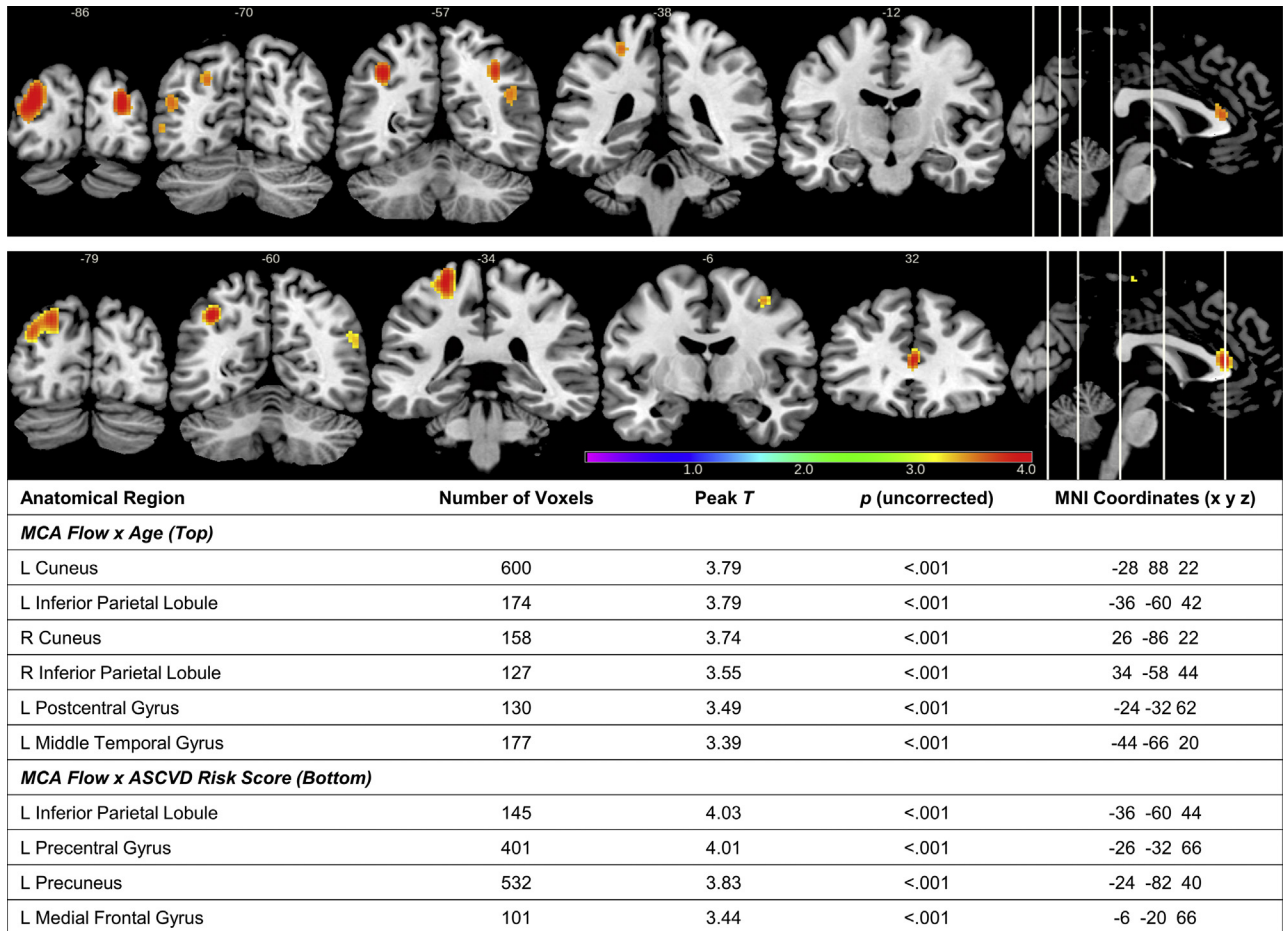
Anatomical Region	Number of Voxels	Peak T	p (uncorrected)	MNI Coordinates (x y z)
MCA Flow x Age (Top)				
L Cuneus	600	3.79	<.001	-28 88 22
L Inferior Parietal Lobule	174	3.79	<.001	-36 -60 42
R Cuneus	158	3.74	<.001	26 -86 22
R Inferior Parietal Lobule	127	3.55	<.001	34 -58 44
L Postcentral Gyrus	130	3.49	<.001	-24 -32 62
L Middle Temporal Gyrus	177	3.39	<.001	-44 -66 20
MCA Flow x ASCVD Risk Score (Bottom)				
L Inferior Parietal Lobule	145	4.03	<.001	-36 -60 44
L Precentral Gyrus	401	4.01	<.001	-26 -32 66
L Precuneus	532	3.83	<.001	-24 -82 40
L Medial Frontal Gyrus	101	3.44	<.001	-6 -20 66

Fig. 3. Results of voxel-wise analyses (*t* statistic map) displaying clusters in which perfusion was positively associated with the age × MCA mean flow interaction term (top panel; *n* = 155; *P* < .001 uncorrected; cluster extent = 100) or the atherosclerotic cardiovascular disease (ASCVD) risk score × MCA mean flow interaction term (bottom panel; *n* = 154; *P* < .001 uncorrected; cluster extent = 100).

cardiovascular risk, perfusion rate in the capillary beds may be more dependent on inflow from the MCAs; however, these results should be considered with caution and require replication. One potential confounder is that validated composite measures of vascular risk burden, including ASCVD, include age as a component of the risk score calculation. Therefore, it is possible that the associations with vascular risk are driven by age, rather than other factors such as hypertension or cholesterol levels. However, the regions in which age versus vascular risk score moderated the relationship between large-vessel flow and perfusion did not completely overlap, suggesting that there may be a component of the ASCVD score that independently affects this relationship above and beyond age. Future studies will continue to explore these questions through analyses investigating relationships between specific vascular risk factors and CBF. Although no similar relationships were observed in the sICAs in the present study, a recent study conducted by our group demonstrated a similar uncoupling of macrovasculature and microvasculature in the ICAs in cognitively healthy at-risk adults with higher insulin resistance [16].

Overall, these findings suggest that perfusion measured via pcASL is strongly dependent on inflow from larger cerebral arteries and, therefore, may not be an optimal functional imaging technique of neurometabolism in populations in which large-vessel flow is suspected to be compromised. Mechanisms underlying the development of hypoperfusion and potential alterations in macrovasculature and microvasculature require further investigation. Changes in vasculature that become more common with advanced age, such as atherosclerosis and vessel stiffening, can disrupt blood flow–based delivery of essential nutrients to neurons. In addition, elevated cerebrovascular resistance is commonly observed in individuals diagnosed with dementia due to AD [21,22] and is postulated to contribute to pathologic changes in the cerebrovascular system, including atherosclerosis within intracranial vessels [23]. In turn, stenosis of cerebral arteries may partially cause reduced cerebral perfusion in AD [23]. In addition to large-vessel changes, growing evidence indicates that progressive disturbances in capillary flow may be a response to maintain adequate oxygenation of tissue and that decoupling of blood flow with metabolism occurs across both presymptomatic and postsymptomatic disease phases [24]. Furthermore, age

and vascular risk factors are associated with altered capillary morphology, including increased permeability of the blood-brain barrier, which may contribute to capillary dysfunction [24], hippocampal atrophy, and early cognitive impairment [25]. Further studies are needed to examine relationships among vessel diameter, stiffness, and flow to clarify if hypoperfusion in preclinical AD can be explained by cerebrovascular pathology. In addition, while the current results demonstrate a strong positive relationship between perfusion and arterial blood flow, more investigation is needed on the direct effect of intracranial vascular health on glucose metabolism, as FDG-PET data were not available for these participants.

Limitations of this study should be noted. Blood flow within the MCAs and sICAs was examined specifically because of hypotheses based on prior reported associations with global atrophy and dementia. However, it is possible that collateral flow in the circle of Willis that was not examined (e.g., basilar artery) may moderate relationships between the vessels examined and perfusion in aging and vascular risk. In addition, future studies assessing contributions of AD biomarkers, blood-brain barrier integrity, vessel stiffness, mean arterial pressure, and cerebrovascular resistance are needed to provide greater context for the current results. This study also did not collect data on extracranial carotid artery status or cardiac dysfunction which may affect CBF, and future studies investigating the relationship between extracranial and intracranial flow in this population are needed. Furthermore, the sample is enriched for AD risk, and these results may not generalize to other cognitively healthy middle-aged populations. It is also important to acknowledge that the current sample is primarily composed of Caucasian participants (97.4%), and thus, findings may lack generalizability to broader populations. With a concerted effort to enroll more participants in our studies from groups traditionally underrepresented in research, future studies will be able to investigate cerebrovascular function in a more generalizable and diverse sample. Despite these limitations, our study provides evidence of a strong relationship between intracranial arterial flow and capillary perfusion and suggests future directions to explore potential breakdown in this connection in the middle age.

A recent study based on a large sample of older adults enrolled in the Alzheimer's Disease Neuroimaging Initiative reported that reduced CBF may be the first abnormality that is detectable in the progression of AD, even before amyloid and tau alterations [26]. Therefore, developing and applying sensitive measures of cerebrovascular function (PC VIPR and pcASL) in the earliest stages of disease before development of clinical symptoms will be essential to improving understanding of mechanisms underlying hypoperfusion. In addition, as vascular health during midlife is associated with dementia risk in late life [27], understanding alterations in CBF in cognitively healthy adults at risk for AD is important for development of effective secondary prevention strategies to improve cerebrovascular health and ultimately slow cognitive decline.

RESEARCH IN CONTEXT

1. Systematic review: We examined relevant literature via PubMed. Although MRI methods of arterial spin labeling and intracranial 4D-flow imaging have been used independently to study cerebral blood flow in individuals at risk for Alzheimer's disease (AD), information was limited on the comparison between these modalities and the relationship between large-vessel blood flow and tissue perfusion in this population.

2. Interpretation: Our findings suggest that there is a strong relationship between intracranial arterial vessel flow and local tissue perfusion in cognitively healthy adults at risk for AD. These relationships are moderated at a trend level by age and cardiovascular disease risk.

3. Future directions: Follow-up studies should include extension to a larger sample, examination of longitudinal relationships between large-vessel blood flow and perfusion alterations, and contributions of AD biomarkers to hypoperfusion. In addition, studies exploring the impact of cerebrovascular health on measures of neuronal function in asymptomatic at-risk adults are warranted.

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