Vascular and Microstructural Markers of Cognitive Pathology

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Abstract

Background: Arterial stiffness may play a role in the development of dementia, presumably through its effects on white matter integrity and hyperintensities (WMH). However, relationships among arterial stiffness, white matter microstructure, and WMH volumes remain poorly understood. Arterial stiffness increases monotonically with age and its increase is accelerated by cardiometabolic disorders (e.g., hypertension, metabolic syndrome, diabetes). Further exploration of these relationships is key to the development of targeted therapies, early management, and detection.

Method: Arterial stiffness was measured using carotid-femoral pulse wave velocity (cfPWV) in ADRC participants with baseline systolic blood pressure (SBP) measurements, detailed cognitive testing, cognitive adjudication, and brain MRI. We examined associations of cfPWV and SBP with cognitive function (Montreal Cognitive Assessment [MoCA], Preclinical Alzheimer's Cognitive Composite [PACC5], and domain measures of memory and executive function) and brain MRI measures of: macrostructure (volume of gray matter [GM] and WMH from T1-weighted and FLAIR imaging), white matter microstructure (neurite orientation dispersion and density imaging [NODDI] free water [FW] and diffusion tensor imaging [DTI] fractional anisotropy [FA]), and cerebral blood flow (CBF) in white matter (WM) and GM. Age, race, gender, education, and APOE-4 status were included as covariates and in interaction terms in linear regression analyses.

Result: Among 458 participants with a mean age 70±8 years and cognitive adjudication (44 dementia, 157 MCI, 257 normal cognition; Table 1), higher cfPWV was associated with worse cognitive performance (MoCA, PACC5), as was SBP (MoCA, PACC5, executive domain, language domain; Table 2). Higher cfPWV was associated with differences in WM microstructure (higher FW, lower FA) and higher WMH volume. While no overall associations between cfPWV and CBF were detected, cfPWV had stronger associations with FW, FA, and WMH in men. Higher SBP was associated with higher FW, higher WMH volume, and lower WM and GM CBF (Table 3).
SBP had stronger associations with WMH in younger participants (<70y) and GM CBF in Black/AA participants and participants with impaired fasting glucose. No other interactions were detected.

**Conclusions:** Arterial stiffness is associated with microstructural and macrostructural differences and poorer global and executive cognitive function.

| Table 1. Demographics and Neuropsychological Assessments by Cognitive Status |
|-----------------------------------------------|
| Normal Cognition (n = 257) | Mild Cognitive Impairment (n = 157) | Dementia (n = 44) | P-value |
| Age (years) | 68.6 | 71.8 | 74.4 | 8.1 | 7.7 | 8.2 | <0.001 |
| Women | 190 | 74% | 94 | 60% | 26 | 59% | 0.005 |
| Race | White | 228 | 89% | 125 | 80% | 39 | 89% | 0.032 |
| Black | 29 | 11% | 32 | 20% | 5 | 11% | 0.097 |
| Education | 16.1 | 2.3 | 15.1 | 2.6 | 15.6 | 3.0 | <0.001 |
| Systolic Blood Pressure | 129.7 | 18.0 | 134.1 | 18.3 | 135.9 | 21.3 | 0.020 |
| Diastolic Blood Pressure | 69.8 | 10.4 | 71.1 | 9.2 | 71.7 | 9.7 | 0.292 |
| BMI (kg/m²) | 27.6 | 5.6 | 27.5 | 5.1 | 25.8 | 4.1 | <0.001 |
| Hypertension Status | Present | 171 | 67% | 126 | 81% | 35 | 80% | 0.007 |
| Absent | 83 | 33% | 30 | 19% | 9 | 20% | 0.007 |
| Montreal Cognitive Assessment (MoCA) | 26.4 | 2.4 | 22.0 | 3.3 | 16.8 | 4.8 | <0.001 |
| Craft Story | 20.8 | 5.6 | 13.8 | 6.1 | 4.6 | 6.1 | <0.001 |
| mPACC5 (z-score) | 0.0 | 0.6 | -1.3 | 0.8 | -3.4 | 1.4 | <0.001 |
| Global Dementia Scale | 1.2 | 1.7 | 1.8 | 2.1 | 2.3 | 2.0 | <0.001 |
| Clinical Dementia Rating Scale | 0.3 | 0.6 | 1.1 | 0.9 | 4.7 | 2.4 | <0.001 |
| Carotid-femoral Pulse wave velocity (m/s) | 7.8 | 1.6 | 8.2 | 1.9 | 8.1 | 1.9 | 0.131 |

Hypertension defined as Stage 1, Stage 2 hypertension, or antihypertension medications.
Modified Preclinical Alzheimer’s Cognitive Composite (mPACC5) version FCSRT96 is reported.
Note: Sample restricted to participants with at least one of the 5 MRI measures reported plus PWV measurement and all 3 covariates (age, gender, race).
BMI: Body mass index.
Table 2. Standardized cognitive test performance associated with vascular factors

| Cognitive Test             | Carotid-femoral pulse wave velocity (cPWV, m/s) | Systolic blood pressure (SBP, mmHg) |
|---------------------------|-----------------------------------------------|------------------------------------|
|                           | N     | B (SE) | P-value | N     | B (SE) | P-value |
| Global Cognition (MoCA)   | 454   | -0.066 (0.025) | 0.009 | 454   | -0.010 (0.002) | < 0.001 |
| mPACC5                    | 446   | -0.101 (0.035) | 0.004 | 446   | -0.011 (0.003) | < 0.001 |
| Memory Domain             | 457   | -0.006 (0.030) | 0.834 | 457   | -0.003 (0.003) | 0.345  |
| Executive Domain          | 457   | -0.041 (0.024) | 0.097 | 457   | -0.006 (0.002) | 0.007  |
| Language Domain           | 456   | -0.013 (0.022) | 0.553 | 456   | -0.005 (0.002) | 0.026  |
| Attention Domain          | 457   | -0.003 (0.027) | 0.911 | 457   | -0.003 (0.003) | 0.173  |
| Visuospatial Domain       | 454   | 0.015 (0.028) | 0.598 | 454   | 0.001 (0.003) | 0.765  |

Unadjusted models of cognitive measures normed for age, gender, race, and education presented as z-scores.
Regression coefficients correspond to change in cognitive test performance corresponding to a one SD increase in PWV or SBP.

Table 3. Linear regression coefficients of vascular factors and brain MRI measures.

|                  | NODDI Free Water WM | Fractional Anisotropy WM | White Matter Hyperintensity Volume | Gray Matter Cerebral Blood Flow | White Matter Cerebral Blood Flow |
|------------------|----------------------|--------------------------|-----------------------------------|---------------------------------|----------------------------------|
|                  | (n = 451)            | (n = 478)                | (n = 495)                         | (n = 459)                       | (n = 458)                        |
|                  | N   | beta | SE   | P-value | N   | beta | SE   | P-value | N   | beta | SE   | P-value | N   | beta | SE   | P-value |
| cPWV (m/s)       |     |      |      |         |     |      |      |         |     |      |      |         |     |      |      |         |
| Model 1          | 422 | 0.208 | 0.045 | < 0.001 | 446 | -0.105 | 0.051 | 0.038 | 463 | 0.098 | 0.043 | 0.024 | 431 | -0.068 | 0.047 | 0.151 | 430 | 0.027 | 0.051 | 0.603 |
| Model 2          | 417 | 0.184 | 0.045 | < 0.001 | 441 | -0.094 | 0.052 | 0.070 | 458 | 0.075 | 0.044 | 0.094 | 426 | -0.043 | 0.048 | 0.370 | 425 | 0.055 | 0.052 | 0.290 |
| SBP (mmHg)       |     |      |      |         |     |      |      |         |     |      |      |         |     |      |      |         |
| Model 1          | 451 | 0.117 | 0.043 | 0.007 | 478 | -0.081 | 0.046 | 0.080 | 495 | 0.093 | 0.039 | 0.018 | 459 | -0.110 | 0.044 | 0.012 | 458 | -0.116 | 0.048 | 0.015 |
| Model 2          | 451 | 0.090 | 0.045 | 0.047 | 441 | -0.069 | 0.050 | 0.168 | 458 | 0.085 | 0.043 | 0.045 | 426 | -0.093 | 0.046 | 0.046 | 425 | -0.101 | 0.051 | 0.030 |

Model 1 adjusted for age, gender, race, and education. Model 2 adjusted for age, gender, race, education, and hypertension treatment, with SBP and cPWV in the model together.
Regression coefficients correspond to change in cognitive test performance corresponding to a one SD increase in PWV or SBP.