



Arterial stiffness and cerebral hemodynamic pulsatility during cognitive engagement in younger and older adults[☆]



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ABSTRACT

This study examined central artery stiffness and hemodynamic pulsatility during cognitive engagement in younger and older adults.

Methods: Vascular-hemodynamic measures were completed in 19 younger (age 35 ± 1 yrs) and 20 older (age 69 ± 2 yrs) adults at rest and during a Stroop task. Aortic stiffness (carotid-femoral pulse wave velocity, PWV) and carotid pulse pressure (PP) were assessed using applanation tonometry. Carotid stiffness was assessed as a single-point PWV using Doppler Ultrasound. Middle cerebral artery (MCA) mean flow and flow pulsatility index (PI) were assessed using transcranial Doppler. Cognitive function was assessed as accuracy and reaction time from the Stroop task.

Results: Older adults had lower accuracy scores and longer reaction times on the Stroop task compared to younger adults ($p < 0.05$). Both age groups had similar increases in MCA mean flow during Stroop ($p < 0.05$). There were significant increases in aortic PWV, carotid PWV, carotid PP and MCA PI during Stroop in older but not younger adults ($p < 0.05$). Carotid PP and MCA PI assessed during Stroop were statistical mediators of the association between age group and Stroop performance metrics (accuracy and reaction time, $p < 0.05$), while aortic and carotid PWV were indirect statistical mediators of MCA PI through carotid PP ($p < 0.05$).

Conclusions: Older adults experience increases in large artery stiffness during cognitive engagement possibly preventing effective buffering of pulsatile hemodynamic energy entry into the cerebrovasculature. This is important as pulsatile flow during cognitive engagement, and not mean flow per se, was related to overall cognitive performance.

1. Introduction

The life expectancy of older Americans continues to increase, with persons aged ≥ 60 years representing the fastest growing segment of the US population (Wiener and Tilly, 2002). An untoward corollary of this extended lifespan is cognitive dysfunction. Aging is known to negatively impact memory, information processing/attention and executive functions (i.e. formulation of goals, developing strategies to achieve said goals, planning, action sequencing and monitoring, mental plasticity, inhibition, and updating working memory) (Glisky, 2007). Cognition is one of the most important determinants of overall health

status, quality of life and functional ability with advancing age (Borson, 2010; Castro-Lionard et al., 2011; Wilson et al., 2013).

While mechanisms governing cognitive decline with aging are multifactorial, much attention has recently been given to how the large elastic extracranial vessels (i.e. aorta and carotid) affect intracranial hemodynamics and cognition (Pase et al., 2012; Singer et al., 2014). With advancing age, the large central arteries become stiffer owing to numerous structural and functional aberrations. Arterial stiffness and subsequent loss of the intrinsic buffering capacity of these vessels increases hemodynamic pulsatility (Tarumi et al., 2014). The brain is an obligate high flow, low impedance target organ sensitive not only to the

Abbreviations: Ao, aortic; AIx, augmentation index; CCA, common carotid artery; DBP, diastolic blood pressure; Ep, elastic modulus; HR, heart rate; MAP, mean arterial pressure; MCA, middle cerebral artery; MnV, mean flow velocity; NA, negative area from reflected wave intensity; NA/W1, reflection coefficient; PP, pulse pressure; PWV, pulse wave velocity; PI, pulsatility index; RT, reaction time; SBP, systolic blood pressure; W₁, forward wave intensity; WIA, wave intensity analysis

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amount of total inflow received, but the manner in which that flow is delivered. Because the skull is a rigid structure, entry of excessive extracranial hemodynamic pulsatility into this non-expandable space may pervade the deep microcirculation of the brain (Bateman et al., 2008; Mokri, 2001) and can be detected even in the venous efflux (Bateman et al., 2008; Jolly et al., 2013). It has been posited that increased extracranial macrovascular stiffness with aging exposes the delicate cerebral microvasculature to excess hemodynamic pulsatility (Zarrinkoob et al., 2016) precipitating cerebrovascular damage (e.g. white matter hyperintensities, microbleeds and lacunar infarcts, leukoaraiosis, β -amyloid deposition) and thus cognitive decline (Tsao et al., 2016). Although an attractive theoretical model (i.e. stiffness begets pulsatility which begets damage and reduced function), this model presupposes cerebral damage as the ultimate arbiter of cognitive functional decline with aging (Cooper et al., 2016; Mitchell et al., 2011; Pase et al., 2016) and neglects the more immediate importance of cerebral perfusion in response to neural activation.

That cerebral blood flow increases with increases in regional neuronal-metabolic demand has been known for almost 120 years (Roy and Sherrington, 1890). Given limited energetic substrate storage in the brain, an increase in metabolic demand upon neuronal activation necessitates need for increased delivery via increases in regional blood flow. This matching of metabolic supply to neural demand is known as neurovascular coupling and has been suggested to be a significant determinant of cognitive performance (Novak and Hajjar, 2010; Sorond et al., 2013). Paradoxically, although aging is associated with reductions in resting cerebral flow (Tarumi et al., 2014), healthy older adults have an *augmented* cerebral flow response to cognitive engagement (Groschel et al., 2007; Hess and Ennis, 2012; Rosengarten et al., 2003; Sorond et al., 2008). Greater flow augmentation in this setting may be a compensatory mechanism due to greater neuronal activation and resource allocation aimed at maintaining function (Ennis et al., 2013). That is, there is recruitment of additional neural circuitry and thus greater cognitive effort to preserve task accuracy at the expense of processing speed in older adults (Groschel et al., 2007; Hess and Ennis, 2012; Rosengarten et al., 2003; Sorond et al., 2008). Taken together and these observations suggest that assessment of neurovascular coupling using mean flow may not be the most propitious way to survey the matching of flow delivery to neuronal activation. Assessment of flow pulsatility may offer additional insight into neurovascular coupling with aging.

Changes in vessel wall compliance can occur dynamically and may thus alter hemodynamic pulsatility. Hemodynamic pulsatility during cognitive engagement may directly and more instantaneously impact cognitive performance by altering overall flow delivery. The primary purpose of this study was to examine extracranial central artery stiffness and intracranial cerebral hemodynamic pulsatility *during* cognitive engagement in younger and older adults. A secondary purpose was to explore if age-associated differences in central vascular-hemodynamics *during* cognitive engagement in younger versus older adults are statistical mediators of cognitive performance. We hypothesized that cognitive engagement would instigate increases in aortic and carotid artery stiffness and increases in pulsatile central hemodynamics (carotid pulse pressure and cerebral flow pulsatility index) in older but not younger adults. We further hypothesized that arterial stiffness and central pulsatile hemodynamic load during cognitive engagement would be statistical mediators of differences in cognitive performance between younger and older adults suggesting a role for dynamic changes in central vascular-hemodynamics as effectors of neurovascular coupling and overall cognitive performance.

2. Methods

2.1. Study participants

Thirty-nine apparently healthy, right-handed adults between the

ages of 18 and 85 volunteered to participate in this study. Participants were split at the median age and divided into two groups: a younger group (age range 18–53) and an older group (age range 60–85). Exclusion criteria included history of smoking, stroke, Alzheimer's disease, neurological disease of any kind, head trauma resulting in concussion/loss of consciousness within the previous 6 months, diabetes mellitus, severe obesity (body mass index ≥ 35 kg/m²), pulmonary disease, peripheral artery disease, renal disease, Center for Epidemiologic Studies Depression Scale (CES-D) score > 18 signifying high depressive symptomology, Montreal Cognitive Assessment (MOCA) score < 24 signifying cognitive impairment, severe arrhythmia and color blindness. This study was approved by the Institutional Review Board of Syracuse University and all participants provided written informed consent prior to study initiation.

2.2. Study design

Participants reported to the Human Performance Laboratory on two separate occasions. Visits were carried out first thing in the morning (0600–0900) following an overnight fast. Following consent, participants completed a health history questionnaire, visual acuity test, Ishihara color-blindness test, body composition assessment via air displacement plethysmography (BodPod; COSMED, Concord, CA), urinalysis for the presence/absence of glucose, protein and ketones in the urine as well as urinary creatinine levels (Clinitek Status + Analyzer, Siemens, IL), fasting glucose and lipid assessment via finger stick (Cholestech LDX), depressive symptomology appraisal via the Center for Epidemiologic Studies Depression Scale and a global cognitive appraisal using the Montreal Cognitive Assessment.

Participants reported back to the Human Performance Lab on a second day approximately one week later for vascular and hemodynamic data acquisition. Vascular-hemodynamic testing was conducted in the morning following an overnight fast in a quiet, dimly lit, temperature-controlled laboratory. Participants were instructed to avoid vigorous exercise and avoid consuming caffeine/alcohol ≥ 12 h before testing. Participants also refrained from taking any vasoactive medications the morning of testing ($n = 4$). Following familiarization, participants were instrumented with all necessary equipment (brachial blood pressure cuff, ECG electrodes) and then required to remain in the supine position on a cushioned exam bed for a period of 15 min. Quiet rest was followed by acquisition of baseline measures of blood pressure (brachial and carotid), blood flow velocity (common carotid and middle cerebral), and arterial stiffness (carotid and aortic). All hemodynamic variables were then measured (in duplicate) during two separate 4-min blocks of a cognitive perturbation protocol (congruent and incongruent Stoop, randomized – described below). The two cognitive perturbation tasks were separated by 4-min recovery period. Pilot work from our lab has demonstrated that 4-min was sufficient time to ensure recovery of HR and brachial BP before initiating the second cognitive perturbation (Heffernan et al., 2015). Following vascular-hemodynamic measures, participants were escorted to a computer and assumed a seated position whereby they completed a 30-min computerized cognitive battery designed to assess multiple aspects of cognition. No vascular-hemodynamic measures were obtained during the seated global cognitive battery.

2.2.1. Neurovascular coupling

Participants remained in the supine position while a specialized wall mount was used to horizontally suspend a 42-inch flat screen television over the participant. A schematic of the research approach appears in Supplement Fig. 1. The television was approximately 40-inches above the participant as per manufacturer suggestions. The screen was slightly behind the participant, necessitating that participant tilt their head back slightly. This optimized participant position for carotid ultrasonography measurement. Font was focally displayed on a black background at a font size of 3-cm. This is a comparable extrapolation to

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