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# Association of pulsatile and mean cerebral blood flow velocity with age and neuropsychological performance

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## HIGHLIGHTS

- Older age predicted higher pulsatile and lower mean brain blood flow velocity.
- Higher pulse pressure was associated with higher brain pulsatile flow velocities.
- However, brain blood flow velocity was unrelated to cognitive function.

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## ABSTRACT

Low cerebral blood flow velocity is associated with cognitive decline. However, the association between pulsatile brain blood flow velocity and cognition has not been investigated. High pulsatile hemodynamic stress in the brain may impair cognitive function through damage to small cerebral vessels. The current objective was to examine the cross-sectional association of pulsatile and mean cerebral blood flow velocity with age and neuropsychological performance. We also examined whether cerebral blood flow velocity was associated with aortic pulse pressure, a measure of arterial ageing and aortic stiffness. Cerebral blood flow velocity was measured in the middle cerebral artery using Transcranial Doppler Ultrasonography (TDU) while neuropsychological performance was measured using a computerized cognitive test battery. Aortic pulse pressure was non-invasively derived from applanation tonometry of the radial artery. The sample comprised 160 healthy adults aged 50–70 years. Results indicated that increasing age correlated with lower mean ($r = -0.23$, $p < 0.01$) and higher pulsatile ($r = 0.27$, $p < 0.01$) brain blood flow velocity. In multivariate adjusted models, both peripheral ($\beta = 0.28$, $p < 0.05$) and aortic ($\beta = 0.24$, $p < 0.05$) pulse pressure were associated with higher pulsatile flow velocity through the middle cerebral artery. In adjusted models, neither mean nor pulsatile cerebral blood flow velocity was associated with performance on any cognitive task. In conclusion, arterial ageing was associated with increased pulsatile hemodynamic stress in the brain. However, this was not associated with impaired neuropsychological performance.



## 1. Introduction

Resting blood flow in the brain decreases with advancing age [1]. Arterial inflow and cerebral blood flow (CBF) velocity are also diminished in Alzheimer's disease [2–4] and are associated with cognitive decline in non-demented subjects [3]. Despite reduction in mean CBF velocity, several small studies suggest that pulsatile CBF velocity augments with ageing [5,6]. This is partly due to the ageing of large arteries, characterized by increases in aortic stiffness and pulsatile blood pressure [5,7]; both of which contribute to age-associated cognitive decline [8].

A young healthy aorta cushions pulsatile blood flow ejected by the left ventricle such that blood is delivered to peripheral organs in a steady stream [9]. However, when aortic compliance diminishes with age, the aorta is less able to cushion the pulsatile component of the cardiac output meaning that more pulsatile energy is transferred to peripheral organs [10]. High pulsatile flow through the brain may damage small cerebral vessels, which remain exposed to high pressure flow throughout the cardiac cycle [10,11]. Supporting this idea, augmented pulsatile CBF velocity is associated with cerebrovascular insults [6] as well as both vascular dementia and Alzheimer's disease [4].

Thus, vascular ageing may contribute to cognitive impairment in two ways (1) by reducing mean blood flow and therefore cerebral perfusion and (2) by increasing pulsatile stress in the brain causing

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cerebral microvascular damage. Despite documented associations between pulsatile CBF velocity and cerebral pathology [6], to our knowledge, the relationship between pulsatile CBF velocity and neuropsychological performance has gone unexamined.

The primary aim of the current study was to examine the cross-sectional association between CBF velocity and cognitive performance in a group of adults without diagnosed cardiovascular, neurological or psychiatric illness. It was hypothesized that higher pulsatile CBF velocity would be associated with poorer neuropsychological function. This was expected on the basis that 1) higher pulsatile CBF velocity is associated with cerebral pathology [6] and 2) aortic stiffness, which has been associated with cognitive decline in meta-analysis[12], is thought to cause cognitive impairment through augmenting pulsatile brain blood flow [9,11,13]. On the basis of past research [3], we also expected lower mean CBF velocity to be associated with poorer cognitive performance.

The secondary aims of the study were to examine the associations of pulsatile CBF velocity with age and pulse pressure. These associations were investigated because preliminary reports suggest that pulsatile CBF velocity increases with advancing age [5,6] and with increasing aortic stiffness [5], which can be measured indirectly with aortic pulse pressure [14].

## 2. Method

This study explored the cross-sectional association between CBF velocity, neuropsychological performance, age and blood pressure. The present study explored these associations using baseline data obtained from a larger clinical trial conducted between February 2010 and December 2011 (Australian Clinical Trial Registry Number 12611000094976). The study involved community dwelling participants who voluntarily attended our university laboratory in Melbourne, Australia.

### 2.1. Study population

Non-dietetic participants aged 50–70 without a history heart, neurological (including stroke and dementia) or psychiatric disease were recruited from the general population in Melbourne, Australia, by way of newspaper advertisements and word of mouth. This restricted age-range was chosen to limit the heterogeneity in cognitive test performance associated with age. We chose a sample of individuals without the aforementioned health problems in order to understand how age-associated differences in CBF velocity relate to brain function (whilst limiting the effects of various confounding factors like cardiovascular disease, which is known to affect CBF velocity [15]). Participants were screened for the above contraindications in a clinical interview relying on patient self-report. All participants were non-smokers given that nicotine has acute effects on cognitive function. Participants were largely white Caucasian.

A total of 377 participants were contacted about participating in the present study. Of these people, 113 were deemed to be ineligible while 104 declined to participate or failed to show up for testing. A total of 160 individuals gave written informed consent to participate in the study (75 males and 85 females) and provided baseline data for the present analyses. The sample size of 160 was determined in order to provide adequate statistical power for the larger clinical trial rather than the present study. Nevertheless, others have reported significant associations between CBF velocity and age as well as between CBF velocity and measures of brain health in a sample of 55 individuals [6]. Thus, the present sample size was deemed large enough to investigate the research aims. The study was approved by the Swinburne University Human Research Ethics Committee and all procedures were conducted in accordance with the Declaration of Helsinki (2008).

### 2.2. Assessment of cognition

Multiple domains of cognition were measured using a validated computerized cognitive test battery called the Swinburne University Computerized Cognitive Assessment Battery (SUCCAB). Details of this battery have been published previously [16]. In short, participants were presented with the following tasks in the following order; one choice reaction time, two choice reaction time, simple recognition memory (immediate memory of abstract pictures), colour-word stroop (with congruent and incongruent conditions), spatial working memory (working memory with a spatial component), contextual recognition memory (immediate recall of pictures in specific spatial locations) and delayed picture recognition (delayed recall component of simple recognition memory). For each task, the outcome measure was response time to correct stimuli (ms) which was measured with millisecond precision. To minimize the effects of learning on task performance, a brief standardized practise run preceded each task. The SUCCAB tasks are well validated and highly sensitive to the effects of age [16].

### 2.3. Assessment of blood flow velocity

A trained research assistant used transcranial doppler ultrasonography (TDU; Compumedics device) to calculate CBF velocity in the left middle cerebral artery (MCA) using a 2 MHz probe. Measurements were completed with the participant seated in a quiet temperature controlled room. To measure CBF velocity from the left MCA, the TDU probe was gently pressed against the participants' left temple (over the temporal bone where the skull is thin enough to allow the TDU signal to penetrate into the MCA). Once an adequate TDU signal was obtained, a continual trace of CBF velocity was saved for later analysis. From an electronic graph of the acquired data, peak systolic and end diastolic blood flow velocity were measured and averaged across 10 consecutive cardiac cycles for each participant. This process was completed for all participants by a single researcher with qualifications in cardiac technology who was blind to the respective cognitive scores. Traces with significant artefact or ectopic flow velocity waveforms were not analysed. Mean CBF velocity was calculated automatically by the software. Pulsatility flow index (PI) was defined as (peak systolic − end diastolic blood flow velocity) / mean cerebral blood flow velocity. TDU differs to other imaging methods such as functional magnetic resonance imaging because TDU measures CBF velocity from a single artery rather than measuring blood oxygenation to a region of the cortex.

### 2.4. Assessment of brachial and aortic blood pressure

Blood pressure (BP) was measured from the brachial artery with the participant seated and after a 5 minute rest period. This assessment was completed by an experienced research assistant and a cardiac technologist using an automatic sphygmomanometer (Omron, 705IT) validated according to both the European Hypertension Society (EHS) and the British Hypertension Society (BHS) protocols [17,18]. The average of three recordings was used in statistical analysis. Aortic BP was automatically calculated with a SpygmoCor system (AtCor Medical) using applanation tonometry of the radial artery with central pressures derived through a validated automatic transfer function calibrated with brachial blood pressure [19]. Aortic pressures were calculated directly after the assessment of brachial BP under the same conditions. Pulse pressure was defined as the systolic − diastolic BP.

Each participant completed all assessments on the same day. Participants were not permitted to consume alcohol or caffeinated beverages on the day of testing.

### 2.5. Statistical analysis

Data analysis was performed using IBM Statistical Package for the Social Sciences (version 19). Values are presented as means ± SDs.