Cardiovascular Disease Risk and Cerebral Blood Flow Velocity

Matthew P. Pase, PhD.c; Natalie A. Grima, Dpsyc.c; Con K. Stough, PhD; Andrew Scholey, PhD; Andrew Pipingas, PhD

Background and Purpose—Cardiovascular disease risk predicts cognitive decline although the mechanisms underpinning this association remain unclear. Increasing cardiovascular risk may impair cerebral blood flow predisposing to cerebrovascular damage, cognitive decline, and dementia.

Methods—This study examined the association between the Framingham General Cardiovascular Risk Profile and cerebral blood flow velocity in 160 healthy middle-aged adults. Blood flow velocity was assessed in both the common carotid and middle cerebral arteries using Doppler.

Results—In adjusted linear regression models, cardiovascular risk predicted higher pulsatile (common carotid artery $\beta=0.56$, $R^2=0.19$, $P<0.001$; middle cerebral artery $\beta=0.40$, $R^2=0.09$, $P<0.001$) and lower mean flow velocity (common carotid artery $\beta=-0.49$, $R^2=0.14$, $P<0.001$; middle cerebral artery $\beta=-0.27$, $R^2=0.04$, $P<0.05$). Cardiovascular risk predicted common carotid artery mean and pulsatile flow over and above the effects of age ($\Delta R^2=0.11–0.19$, $P<0.001$) and sex ($\Delta R^2=0.03–0.03$, $P<0.05$). In contrast, cardiovascular risk remained a significant predictor of middle cerebral artery pulsatile, but not mean flow velocity, when controlling for age ($\Delta R^2=0.05$, $P<0.05$) and sex ($\Delta R^2=0.06$, $P<0.01$).

Conclusion—Cardiovascular risk has divergent effects on mean and pulsatile blood flow velocity, each of which may independently contribute to cerebral pathology and cognitive impairment. (Stroke. 2012;43:2803-2805.)

Key Words: blood flow ▪ brain ▪ cardiovascular ▪ cerebral ▪ cognition ▪ hypertension

The Framingham General Cardiovascular Risk Profile is a validated algorithm used to quantify an individual’s risk of general cardiovascular disease (CVD). CVD risk also predicts declining cognitive function, an increased risk of later-life dementia as well as cerebral pathology including the volume of white matter hyperintensities in individuals without stroke or dementia.

It is unclear how a high CVD risk causes cerebral pathology. One mechanism may be through the reduction of cerebral perfusion. Single CVD risk factors such as hypertension predict decreases in cerebral blood flow. Although mean cerebral flow declines with age, perhaps partly explaining age-associated cognitive decline, little attention has been paid to how CVD risk affects the pulsatile nature of cerebral blood flow. Higher brain pulsatile flow (peak systolic minus end diastolic flow) may also contribute to cerebral pathology and cognitive impairment through the shearing of the small vessel endothelium.

The current study aimed to examine the association between general CVD risk and cerebral blood flow velocity in a group of healthy adults. We hypothesized that higher Framingham General Cardiovascular Risk Profiles would be associated with lower mean and higher pulsatile blood flow velocity in both the middle cerebral (MCA) and common carotid artery (CCA).

Method

Participants

The sample comprised 160 healthy adults without diagnosed CVD, neurological disease, psychiatric disease, or diabetes. Participants were aged 50 to 70 years, predominantly white, nonsmokers, and were not taking psychoactive medications. Participants provided informed consent and all procedures were performed in accordance with the Declaration of Helsinki (2008). The study was approved by the Swinburne University Human Research Ethics Committee.

Assessment of Blood Flow

Cerebral blood flow velocity was calculated in the left MCA and CCA using transcranial Doppler (Compumedics) with a 2- and 4-MHz probe, respectively. Blood flow velocity was measured with the participant seated in a quiet temperature-controlled room. For each participant, peak systolic and end diastolic CCA and MCA blood flow velocity were extracted for 10 cardiac cycles and averaged. Pulsatility index was calculated as peak systolic minus end diastolic blood flow velocity divided by the mean.
Blood flow velocity was generally healthy (Table 1). Blood flow velocity was examined in the CCA and MCA was successfully obtained for 153 and 142 participants, respectively. Higher CVD risk was associated with higher pulsatility index (MCA: $r=0.24$, $P<0.01$; CCA: $r=0.39$, $P<0.001$) and lower mean blood flow velocity (MCA: $r=-0.22$, $P<0.05$; CCA: $r=-0.39$, $P<0.001$).

In hierarchical linear regression (Table 2), CVD risk was a significant predictor of both CCA and MCA pulsatility index, explaining 19% ($R^2=0.19$) and 9% ($R^2=0.09$) of the variance, respectively. These relationships were not entirely due to age and sex, which are incorporated into the CVD risk profiles. Specifically, CVD risk explained 19% ($R^2=0.19$) of the variance in CCA pulsatility index above and beyond the effects of age and $3\%$ ($R^2=0.03$) above the effects of sex. CVD risk explained $5\%$ ($R^2=0.05$) of the variance in MCA pulsatility index above and beyond the effects of age and $6\%$ ($R^2=0.06$) above the effects of sex.

CVD risk was also a significant predictor of both CCA and MCA mean flow velocity explaining $14\%$ ($R^2=0.14$) and $4\%$ ($R^2=0.04$) of the variance, respectively. When controlling for age or sex, CVD risk remained a significant predictor of CCA mean flow velocity explaining an additional $3\%$ and $11\%$ ($R^2=0.03$–$0.11$) of the variance, respectively. CVD risk did not predict MCA mean flow velocity when controlling for either age or sex.

### Table 1. Sample Characteristics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>160</td>
</tr>
<tr>
<td>Males, %</td>
<td>39.5</td>
</tr>
<tr>
<td>Age, y</td>
<td>59.27 (5.72)</td>
</tr>
<tr>
<td>CVD risk</td>
<td>9.28 (6.93)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>24.88 (3.43)</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>3.36 (0.75)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.56 (0.40)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.20 (0.62)</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>124.12 (19.10)</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
<td>76.30 (11.58)</td>
</tr>
<tr>
<td>CCA mean, cm/s</td>
<td>57.00 (12.60)</td>
</tr>
<tr>
<td>MCA mean, cm/s</td>
<td>23.01 (5.29)</td>
</tr>
<tr>
<td>CCA pulsatile index, cm/s</td>
<td>0.77 (0.17)</td>
</tr>
<tr>
<td>MCA pulsatile index, cm/s</td>
<td>2.41 (0.04)</td>
</tr>
</tbody>
</table>

CVD indicates Framingham General Cardiovascular Disease Score; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure; CCA, common carotid artery flow velocity; MCA, middle cerebral artery flow velocity.

### Assessment of CVD Risk

The Framingham General CVD risk score was used to assess CVD risk. Through the use of an algorithm, this score combines information pertaining to sex, age, treated and untreated systolic blood pressure, diabetes, total cholesterol, and high-density lipoprotein cholesterol. Cholesterol was measured from overnight fasting blood samples. The average of 3 blood pressure recordings was calculated with the participant seated and after a 5-minute rest period.

### Statistical Analysis

Data were analyzed using IBM SPSS Version 19. The association between CVD risk and cerebral blood flow velocity was examined using 2-tailed correlations. Significant associations were further examined using hierarchical multiple linear regression models controlling for various confounding covariates expected to relate to cardiovascular and neurological health based on past research. These included mean arterial pressure, physical activity, education, lipid-lowering medications, body mass index, age, and sex.

### Results

Review of the cohort demographics indicated that participants were generally healthy (Table 1). Blood flow velocity in the CCA and MCA was successfully obtained for 153 and 142 participants, respectively. Higher CVD risk was associated with higher pulsatility index (MCA: $r=0.24$, $P<0.01$; CCA: $r=0.39$, $P<0.001$) and lower mean blood flow velocity (MCA: $r=-0.22$, $P<0.05$; CCA: $r=-0.39$, $P<0.001$).

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CVD risk was also a significant predictor of both CCA and MCA mean flow velocity explaining 14% ($R^2=0.14$) and 4% ($R^2=0.04$) of the variance, respectively. When controlling for age or sex, CVD risk remained a significant predictor of CCA mean flow velocity explaining an additional 3% and 11% ($R^2=0.03$–$0.11$) of the variance, respectively. CVD risk did not predict MCA mean flow velocity when controlling for either age or sex.

### Discussion

As hypothesized, higher CVD risk predicted lower mean and higher pulsatile blood flow velocities. These associations may explain previously reported associations between CVD risk and cognitive decline.2 Pulsatile cerebral blood flow may predispose to cognitive impairment through the shearing of the small vessel cerebral endothelium.9 Because the brain is not protected by vasoconstriction upstream, small cerebral vessels endure the force of high pressure flow through the entire cardiac cycle.9 High pulsatile flow velocity through the MCA has previously been associated with cerebral white matter disease6 and appears to be augmented in Alzheimer disease and vascular dementia.10 MRI has also confirmed that arterial inflow is also lower in Alzheimer disease despite higher pulsatile flow.11 Thus, CVD risk may predict cognitive decline and cerebrovascular damage through increases in

### Table 2. Multivariate Adjusted Relations Between Cardiovascular Risk Profiling and Blood Flow Velocity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DV Beta</td>
<td>t</td>
<td>$\Delta R^2$</td>
</tr>
<tr>
<td>CCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.49‡</td>
<td>-5.10</td>
<td>0.14</td>
</tr>
<tr>
<td>Pi</td>
<td>0.56†</td>
<td>5.65</td>
<td>0.19</td>
</tr>
<tr>
<td>MCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.27*</td>
<td>-2.41</td>
<td>0.04</td>
</tr>
<tr>
<td>Pi</td>
<td>0.40‡</td>
<td>3.47</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Each model is adjusted for education, physical activity, body mass index, lipid-lowering treatments, and mean arterial pressure. Model 2 is further adjusted for sex and Model 3 is further adjusted for age. DV indicates dependent variable; CCA, common carotid artery; Pi, pulsatility index; MCA, middle cerebral artery.

* $P<0.05$.
‡ $P<0.01$.
† $P<0.001$. 
pulsatile cerebral blood flow velocity in addition to decreases in cerebral perfusion.

Our study was limited by the cross-sectional design, meaning that causality cannot be established between CVD risk and blood flow velocity. A large amount of variance in cerebral blood flow appears to be due to factors not assessed by the current study. Our study was limited because we did not assess the following factors potentially related to cerebral blood flow including autoregulatory capacity, cerebrovascular reactivity, and arterial stiffness.

In conclusion, cardiovascular risk appears to have divergent effects on mean and pulsatile blood flow velocity, each of which may independently contribute to cerebral pathology and cognitive impairment.

Sources of Funding
These data are part of a larger industry-sponsored intervention trial (Swisse). This article presents baseline findings of little relevance to the funded trial (<$10 000).

Disclosures
None.

References
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