Association of Pulsatile and Mean Cerebral Blood Flow Velocity with Age and Neuropsychological Performance

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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 (β= 0.28, p < 0.05) and aortic (β= 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.

Key words: cerebral blood flow; cognition; neuropsychology; cerebrovascular; brain; blood pressure

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, characterised by increases in aortic stiffness and pulsatile blood pressure [5, 7]; both of which contribute to age-associated cognitive decline [8, 9].

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 [10]. 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 [11]. High pulsatile flow through the brain may damage small cerebral vessels, which remain exposed to high pressure flow throughout the cardiac cycle [11, 12]. 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 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 hypothesised 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[13], is thought to cause cognitive impairment through augmenting pulsatile brain blood flow [10, 12, 14]. 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 [15].

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 [16]). 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 [17]. 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 [17].

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 2MHz 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 five 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 [18, 19]. 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 [20]. 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. When examining the sample characteristics, unpaired t-tests were used to compare hemodynamic values between genders. Two-tailed correlational analysis was used to investigate the associations between age, blood pressure and cerebral hemodynamics. Significant correlations between blood pressure and cerebral hemodynamics were further examined in hierarchical linear regression models controlling for age, sex, body mass index, mean arterial pressure (MAP; calculated as (2 x diastolic BP + systolic BP)/3), use of lipid lowering medications and use of anti-hypertensive treatments

given that these factors are associated with CBF velocity or blood pressure [5, 6, 11, 16]. Relationships between flow velocity and cognition were also examined in hierarchical linear regression models controlling for specific confounding factors thought to be related to cognition and/or CBF velocity including age, gender, years of education, MAP, body mass index and use of blood pressure or lipid lowering medications [5, 6, 21]. Missing data was excluded from statistical analyses. Results were considered statistically significant at $p < 0.05$.

3. Results

3.1 Preliminary analyses

Of the 160 subjects enrolled in the study, MCA CBF velocities were successfully recorded in 130 participants. Brachial blood pressures were obtained for all participants while there were 12 missing cases for central blood pressures given that we excluded recording of inadequate quality (operator index < 79%). There were between 5-16 missing cases for the cognitive task results (see Table 3). This was predominantly due to the fact that we excluded data whereby participants performed worse than would be expected by chance (ie reflecting a failing to understand the task instructions or equipment failure).

3.2 Sample characteristics

Subjects were generally well educated and cognitively high functioning (Table 1). Across the whole sample, BP levels were normal, although systolic BP was high normal in males. The average CBF velocity and cognitive performance values of the sample can be seen in Tables 2 and 3 respectively. Inspection of Table 2, revealed that males had lower mean (t (1, 128) = -3.22, $p < 0.01$) and higher pulsatile (t (1, 128) = 1.92, $p = 0.05$) CBF velocities. Mean CBF velocities were similar to that reported by Grolimund and Seiler [1] (mean MCA velocity of 57.3cm/s) as well as Xu et al [5] (mean MCA velocity of 63cm/s and pulsatility index of

0.79). In comparison to the cohort used by Kidwell et al [6], pulsatile CBF velocity was lower in the present sample (pulsatility index of 0.77 vs 1.01).

In terms of cognitive performance (Table 3), males had faster one-choice reaction times (t (1, 153) = -3.05, $p< 0.01$), two-choice reaction times (t (1, 147) = -4.14, $p< 0.001$) and stroop (congruent) performance (t (1, 153) = -2.57, $p< 0.05$) in the present sample. Given these sex differences, gender was statistically controlled in all regression analyses.

3.3 Association of blood flow velocity with age and blood pressure

As shown in Figure 1, older subjects tended to have higher pulsatile ($r = 0.27$, $p < 0.01$) and lower mean MCA flow velocities ($r = -0.23$, $p < 0.01$). Higher brachial pulse pressure ($r = 0.24$, $p < 0.01$) and aortic pulse pressure ($r = 0.24$, $p < 0.05$) were each associated with higher pulsatile, but not mean, MCA flow velocities. The association between brachial pulse pressure and pulsatile CBF velocity remained significant after controlling for various confounding factors ($\Delta r^2 = 0.05$, $\beta = 0.28$, $p < 0.05$), as did the association between central pulse pressure and pulsatile CBF velocity ($\Delta r^2 = 0.04$, $\beta = 0.24$, $p < 0.05$). Systolic and diastolic blood pressures did not correlate with mean or pulsatile CBF velocity, when measured at the aorta or brachial arterial (data not shown).

3.4 Blood flow velocity and cognition

In the multivariate adjusted models (Table 4), neither mean nor pulsatile CBF velocity were associated with performance on any cognitive task.

4. Discussion

Consistent with previous research [1, 5, 6], the current study suggests that while mean CBF velocity declines with age, pulsatile flow velocity increases. Also consistent with past research [7], pulsatile flow velocity through the MCA was associated with both aortic and

peripheral pulse pressure; measures of aortic stiffness and arterial ageing known to predict cognitive impairment [22, 23]. The novel component of our study investigated the association between MCA pulsatile flow velocity and cognitive function. In the present sample, both MCA mean and pulsatile flow velocity were unrelated to cognitive performance.

Strengths of the current study include the use of a highly sensitive computerized cognitive test battery and the recruitment of a sample free from various confounding factors such as diabetes, smoking as well as cardiovascular and neurological disease. The use of TDU to measure CBF velocity is advantageous because it is non-invasive as well as fast and cheap to administer in clinical practice. A limitation of our study was the cross-sectional design which precludes us from making conclusion about the direction of causality. A further limitation is that we did not implement neuroimaging biomarkers of cerebrovascular disease given that we focused on behavioural outcomes. To better understand the effects CBF on brain health, future studies could complement neuropsychological assessment with neuroimaging biomarkers such as measures of white matter hyperintensities and microvascular infarcts.

Higher pulsatile CBF velocity was anticipated to predict inferior cognitive function on the basis of high pressure flow causing cerebral microvascular damage. In young healthy individuals the brain receives a steady stream of blood flow. However, with aortic stiffening and vascular ageing, pulsatile pressures are not adequately cushioned before entering the brain and as a result are increasingly absorbed by the cerebral circulation [11]. The results of the present study support the idea that aortic stiffening increases pulsatile stress in the brain given that pulse pressures were positively correlated with MCA pulsatile flow velocity. This was anticipated to have negative effects on cognitive performance given that small cerebral vessels remain dilated throughout the cardiac cycle and are continuously exposed to the potentially damaging forces of high pressure pulsatile flow [12]**.** However, our results found

that neither pulsatile nor mean CBF velocity were associated with neuropsychological function. This result may be partly due to the good health of the current sample.

We recruited a sample of individuals without neurological illness or cardiovascular disease in order to understand how age-associated differences in CBF velocity relate to brain function. As age was associated with both mean and pulsatile CBF velocity, the present results suggest that age-related variations in CBF velocity are not associated with cognitive performance. However, larger differences in CBF velocity, due to specific disease processes, such as peripheral vascular disease, may yield different associations with brain function. CBF velocity is associated with cardiovascular disease risk [16] meaning that poor cardiovascular health is associated with poor cerebral circulation. CBF velocity may therefore predict neuropsychological performance in those with very poor cerebral circulation due to underlying conditions such as cardiovascular disease. Supporting this idea, Kidwell et al.[6] reported associations between pulsatile CBF velocity and diffuse brain small vessel disease in a sample with vascular complications such as hypertension, coronary heart disease as well as neurological disease (ie cerebral infarction). Also supporting this idea, the subjects tested by Kidwell tended to have higher pulsatile CBF velocities than those of the current study. With a paucity of research in the area, future studies are required to clarify the association between pulsatile CBF, cerebrovascular disease and cognitive decline.

4.1 Conclusions

The current study is perhaps the first to report on the association between pulsatile CBF velocity and cognitive performance. We found that ageing was associated with lower mean coupled with higher pulsatile CBF velocity; yet both these factors were unrelated to neuropsychological performance. By showing a positive correlation between pulse pressure and pulsatile CBF velocity, this study lends further support to the idea that arterial ageing and

aortic stiffening augment pulsatile stress in the brain. However, age-related increases in pulsatile CBF velocity do not necessarily translate into poorer neuropsychological performance, at least in this relatively healthy sample. Further research is needed to examine the associations between CBF velocity and brain function in individuals with poor vascular health while also combining neuropsychological assessment with neuroimaging markers of cerebrovascular disease.

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6. Competing interests

There are no competing interests

7. References

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Figure Legend

Figure 1 Associations of mean and pulsatile middle cerebral artery blood flow velocity with age.

Table 1. Sample characteristics

Measure	Males	Females	Total
n	75	85	160
Age, y	59.88 (5.40)	58.74 (5.97)	59.28 (5.72)
Height, cm	177.76 (6.75)	164.84 (6.49)	170.93 (9.24)
Weight, kg	81.26 (11.79)	65.99 (10.75)	73.18 (13.57)
BMI	25.60 (3.08)	24.24 (3.61)	24.88 (3.43)
MMSE	28.07 (2.04)	28.21 (1.68)	28.14 (3.43)
Education, y	16.59 (3.65)	14.97 (3.34)	15.73 (3.57)
LDL, mmol/l	3.39 (0.74)	3.35 (0.76)	3.36 (0.75)
HDL, mmol/l	1.38 (0.33)	1.73 (0.38)	1.56 (0.40)
Triglycerides, mmol/l	1.44 (0.68)	1.00 (0.48)	1.20 (0.62)
Brachial SBP, mmHg	131.00 (17.18)	118.13 (18.75)	124.12 (19.10)
Brachial DBP, mmHg	79.59 (11.36)	73.44 (11.06)	76.30 (11.58)
Brachial PP, mmHg	51.41 (10.00)	44.69 (11.01)	47.82 (11.04)
Aortic SBP, mmHg	119.30 (17.04)	110.45 (16.41)	114.57 (17.23)
Aortic DBP, mmHg	80.35 (11.67)	74.21 (10.89)	77.07 (11.64)
Aortic PP, mmHg	38.95 (9.11)	36.24 (8.97)	37.50 (9.11)

BMI= body mass index, MMSE= mini mental state examination, SBP= systolic blood pressure, DBP= diastolic blood pressure, PP= pulse pressure

Table 2. Middle Cerebral Artery Blood Flow Velocity Values of Sample

Measure	Males	Females	Total
Mean, cm/s	54.76 (11.61)	61.28 (11.44)	58.17 (11.93)
Peak Systole, cm/s	82.81 (14.59)	87.45 (16.48)	85.24 (15.72)
End Diastole, cm/s	39.76 (10.02)	42.03 (9.33)	40.95 (9.69)
Pulsatility Index	0.81 (0.21)	0.75 (0.12)	0.77 (0.17)

Table 3 Cognitive performance of sample

	Males	Females	Total	n
Attention and processing				
Speed				
One-choice RT	268.15 (42.61)	288.94 (42.15)	279.15 (43.50)	155
Two-choice RT	425.52 (35.29)	447.37 (28.90)	436.81 (33.86)	149
Stroop (congruent)	714.05 (108.81)	758.23 (105.30)	737.42 (108.89)	155
Response inhibition				
Stroop (incongruent)	906.25 (157.85)	919.64 (134.73)	913.25 (145.88)	153
Memory				
Recognition Memory	1045.20 (111.51)	1046.84 (118.80)	1046.08 (115.08)	148
Spatial Working Memory	980.29 (156.01)	1027.46 (136.72)	1004.53 (147.80)	144
Contextual Memory	1005.88 (130.72)	1008.40 (124.77)	1007.21 (127.21)	154
Delayed Memory	1018.42 (125.60)	1012.90 (100.88)	1015.45 (112.60)	145

RT= Response Time

Table 4. Multivariate Adjusted Relationships between the Hemodynamic Variables and Cognitive Tasks

	MCA Mean flow		MCA Pulsatility Index	
DV	B ± SE	β	B ± SE	β
Attention and Processing Speed				
One-choice RT	-0.19 ± 0.34	-0.05	-13.16 ± 22.48	-0.05
Two-choice RT	0.09 ± 0.28	0.06	9.71 ± 18.54	0.05
Stroop (congruent)	-0.79 ± 0.90	-0.08	27.21 ± 59.36	0.04
Response inhibition				
Stroop (incongruent)	-0.03 ± 1.26	0.00	91.32 ± 82.82	0.11
Memory				
Recognition Memory	0.42 ± 0.99	0.04	26.96 ± 78.43	0.03
Spatial Working Memory	0.61 ± 1.27	0.05	51.23 ± 85.43	0.06
Contextual Memory	0.16 ± 1.01	0.02	114.61 ± 65.46	0.17
Delayed Memory	0.52 ± 0.94	0.05	-25.57 ± 73.91	-0.03

Note. All models adjusted for age, sex, body mass index, mean arterial pressure, hypertension treatment, statin use and years of education, MCA= middle cerebral artery, DV= dependent variable, B = unstandardized regression coefficient, SE = standard error, β= standardized regression coefficient, BP = blood pressure, RT = reaction time

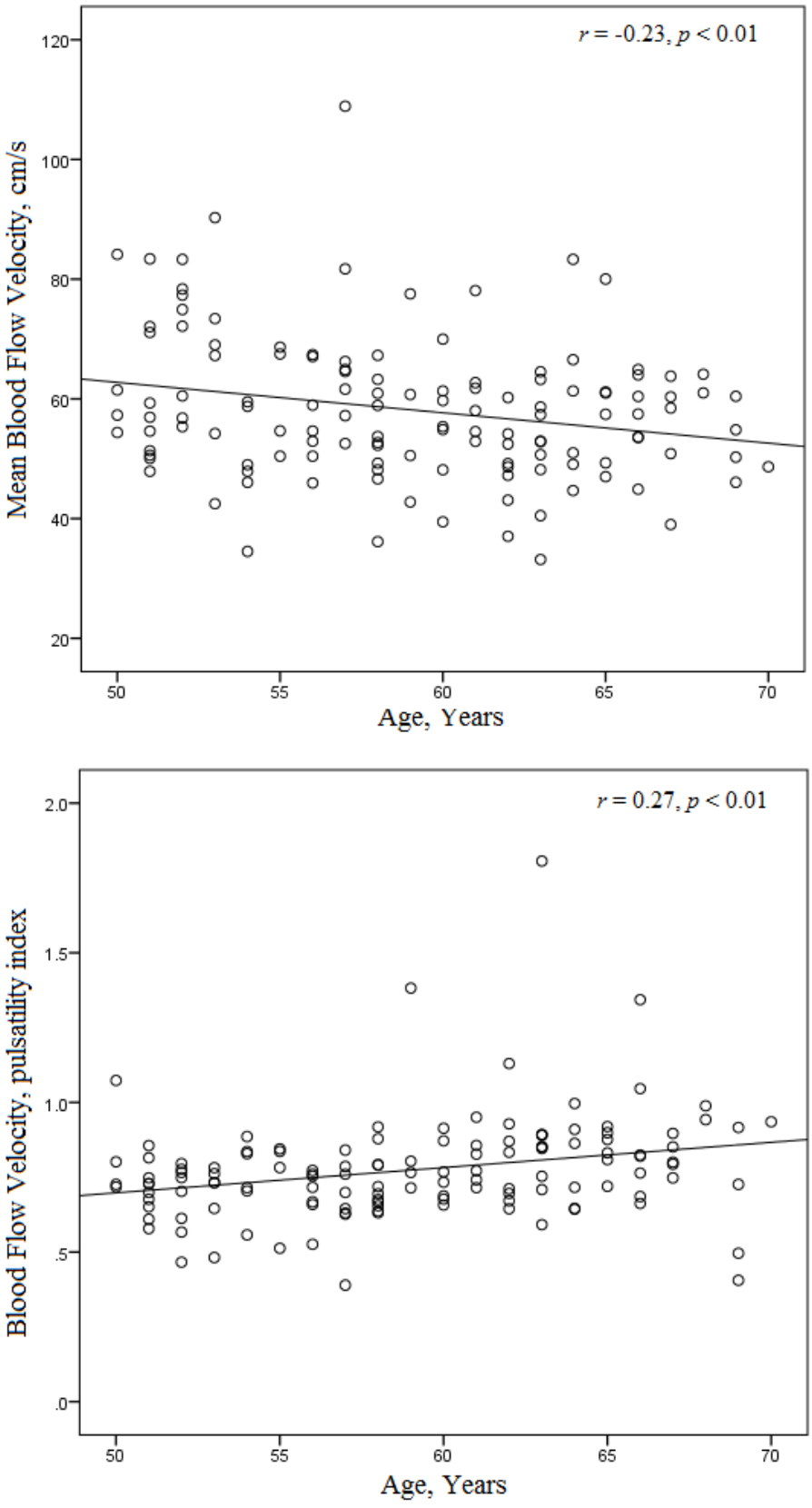
r = -0.23, p < 0.01
Mean Blood Flow Velocity, cm/s
120
100
80
60
40
20
50
55
60
65
70
Age, Years
r = 0.27, p < 0.01
Blood Flow Velocity, pulsatility index
2.0
1.5
1.0
.5
.0
50
55
60
65
70
Age, Years

Figure 1