

Exploring Differences in Vascular Aging and Cerebrovascular Hemodynamics between Older
Adults of White Caucasian and South Asian Origin

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

In Canada, the number of older adults has been on the rise over the past several decades. As the aging population continues to rise, the prevalence of chronic illnesses is projected to correspondingly increase at an unprecedented rate. Another factor contributing to the rise of chronic diseases is the significant disparities in disease burden that exist among certain ethnic minority groups in Canada's multicultural society. South Asians (SA) constitute the largest minority group in Canada and suffer from a disproportionately high burden of heart disease and stroke compared to the rest of the population. Arterial stiffness is a hallmark characteristic of vascular aging and a recognized process that is linked to the development of cardio- and cerebrovascular diseases. A recent study conducted in our laboratory on healthy Caucasian (CA) older adults has found that elevated arterial stiffness is associated with increased cerebrovascular resistance, and this is in turn associated with reduction in brain blood flow (aCBF). This finding presents the possibility that SAs, who are reported to have elevated levels of arterial stiffness compared to their CA counterparts, may exhibit greater cerebrovascular resistance and greater reduction in aCBF, and as a consequence they may be more prone to cerebral hypoperfusion and subsequent ischemia. The primary purpose of this thesis was to examine differences in central arterial structure and function and cerebrovascular hemodynamic properties in CA and SA older adults matched for age and gender, and to explore ethnic differences in the relationship between arterial stiffness and aCBF. The secondary objective was to compare physical activity as well as cognitive performance between CAs and SAs and explore their relationship with characteristics of central arterial and cerebrovascular health. This study found that older adults of SA origin have greater arterial stiffness compared to older adults of CA origin, and that this was associated with greater cerebrovascular resistance and correspondingly greater reduction in aCBF in SAs. In

addition, arterial wall thickness, IMT, appeared to be less pronounced in SAs compared to CAs, yet IMT was associated with greater resistance and pulsatility of blood flow in the cerebral vessels in SAs compared to CAs. SA older adults in this study lived a relatively sedentary lifestyle compared to CA older adults; nonetheless, physical activity of daily living among SA older adults was associated with lower glycemic levels and lower abdominal obesity (approximated by waist circumference and waist-to-hip ratio). With regards to cognitive performance, SAs performed slower on reaction time tasks compared to CAs. No significant relationships between cognitive performance and central arterial and cerebrovascular health were observed. Taken together, the findings from this study suggest ethnic disparities between CAs and SAs in vascular aging properties that may contribute to more pronounced alterations in cerebral hemodynamics in SAs.

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Table of Contents

Author's Declaration.....	ii
Abstract.....	iii
Acknowledgements.....	v
Table of Contents.....	vii
List of Figures.....	ix
List of Tables.....	x
List of Abbreviations.....	xi
1 Literature Review.....	1
1.1 Vascular Health and Disease with Aging.....	1
1.1.1 Definition of Vascular Aging.....	1
1.1.2 Vascular Aging and Disease.....	3
1.1.3 Vascular Age Assessments.....	4
1.1.4 Role of Central Vascular Aging on Cerebral Hemodynamics.....	5
1.2 Ethnic Differences in Vascular Aging.....	7
1.2.1 Arterial Stiffness in South Asians.....	7
1.2.2 Altered Cerebral Hemodynamics in South Asians.....	8
1.3 Implications of Cerebrovascular Carbon Dioxide Reactivity.....	11
2 Objectives.....	13
3 Hypotheses.....	14
4 Methods.....	15
4.1 Study Population.....	15
4.2 Overview of Experimental Design.....	16
4.3 Part One: Morning Session.....	17
4.3.1 Biochemical and Basic Anthropometric Measurements.....	17
4.3.2 Comprehensive Questionnaire, Cognitive Testing and Laboratory Tour.....	17
4.4 Part Two: Afternoon Session.....	19
4.4.1 Overview.....	19
4.4.2 Continuous Measurements.....	20
4.4.3 Baseline Vascular Characteristics.....	21
4.4.4 Brachial-Ankle Pulse Wave Velocity.....	21
4.4.5 Carotid Pulse Pressure.....	21
4.4.6 Carotid Arterial Wall Structure and Function.....	22
4.4.7 Cerebral Blood Flow.....	22
4.4.8 Cerebrovascular Reactivity to Carbon Dioxide.....	23
4.5 Data Acquisition and Analysis.....	25
4.5.1 Biochemical Analysis.....	25
4.5.2 Anthropometric Calculations.....	26
4.5.3 Cardiovascular Variables.....	26
4.5.4 Brachial-Ankle Pulse Wave Velocity.....	28
4.5.5 Carotid Pulse Pressure.....	29
4.5.6 Carotid Intima-Media Thickness.....	29
4.5.7 Carotid Compliance and Distensibility.....	30
4.5.8 ICA Blood Flow and Anterior Cerebral Blood Flow.....	30

4.5.9	Indices of Cerebrovascular Function	31
4.5.10	Cerebrovascular Hemodynamic Properties.....	32
4.5.11	Classification and Quantification of Physical Activity Level.....	34
4.5.12	Reaction Time Tasks.....	35
5	Statistical Analysis.....	36
6	Results.....	38
6.1	Participant Characteristics.....	38
6.2	Physical Activity	39
6.3	Cognitive Performance Outcomes	40
6.4	Arterial Structure and Function and Cerebral Blood Flow	41
6.5	Cerebrovascular Hemodynamic and Cardiovascular Variables in Supine and Seated Rest Positions	42
6.6	Cerebrovascular Reactivity to Carbon Dioxide	43
6.7	Relationships with Arterial Structure and Function and Cerebrovascular Hemodynamic Properties.....	43
6.8	Relationships between Physical Activity and Arterial Structure and Function and Cerebrovascular Hemodynamic Properties	46
7	Discussion	70
7.1	Ethnic Disparities in Arterial Stiffness and Arterial Structure and Function.....	71
7.1.1	Arterial Stiffness and Arterial Function	71
7.1.2	Potential Explanations for Elevated Arterial Stiffness in South Asians.....	74
7.1.3	Ethnic Disparities in Vascular Structure.....	77
7.2	Ethnic Disparities in Cerebrovascular Hemodynamics.....	78
7.2.1	Cerebral Blood Flow.....	78
7.2.2	Cerebrovascular Function.....	81
7.3	Ethnic Disparities in the Effects of Arterial Stiffness on Cerebral Blood Flow	83
7.4	Potential Ethnic Disparities in Plaque Burden	85
7.5	Ethnic Disparities in Health Factors.....	87
7.5.1	Blood Biomarkers	87
7.5.2	Physical Activity.....	88
7.5.3	Benefits of Physical Activity	89
7.6	Ethnic Disparities in Cognitive Performance.....	92
8	Limitations	93
9	Future Directions	102
10	Conclusion	105
	References.....	107
	APPENDIX A – INCLUSION AND EXCLUSION CRITERIA.....	138
	APPENDIX B – AGING HEALTH QUESTIONNAIRE	139
	APPENDIX C – SELF-REPORTED PHYSICAL ACTIVITY SCORING GUIDELINE	154
	APPENDIX D – SUPPLEMENTARY ANALYSES.....	155

List of Figures

Figure 1. Schematic Diagram Representing Pressure Waveforms in Compliant (Left) and Stiff (Right) Central Arteries.	2
Figure 2. Cardiovascular and Cerebrovascular Responses to Hypocapnia and Hypercapnia in White Caucasian and South Asian Older Adults	57
Figure 3. Age-Associated Increase in Arterial Stiffness in CA and SA Older Adults	58
Figure 4. Relationship between Age and Anterior Cerebral Blood Flow in SA and CA Older Adults	59
Figure 5. Relationship between Arterial Stiffness and Anterior Cerebral Blood Flow in CA and SA Older Adults	60
Figure 6. Relationship between Carotid Artery Compliance and Cerebrovascular Resistance in SA Older Adults.....	62
Figure 7. Relationship between Cerebral Blood Flow and Cerebrovascular Resistance in SA Older Adults.....	63
Figure 8. Relationship between Carotid Artery Distensibility and Pulse Pressure in CA and SA Older Adults.....	64
Figure 9. Relationship between Carotid Artery Compliance and Pulse Pressure in CA and SA Older Adults.....	65
Figure 10. Relationship between Common Carotid Artery Intima-Media Thickness and Middle Cerebral Artery Pulsatility Index in CA and SA Older Adults	66
Figure 11. Relationship between Common Carotid Artery Intima-Media Thickness and Middle Cerebral Artery Resistive Index in CA and SA Older Adults.....	67

List of Tables

Table 1. Participant Characteristics	49
Table 2. Biochemical Characteristics	50
Table 3. Participant Medications	51
Table 4. Qualitative and Quantitative Measures of Physical Activity	52
Table 5. Participant Performance on Simple and Choice Reaction Time Cognitive Tasks	53
Table 6. Measurements of Arterial Structure and Function and Cerebral Blood Flow in the Supine Rest Position	54
Table 7. Cerebrovascular and Cardiovascular Variables in Supine and Seated Rest Positions ...	55
Table 8. Cerebrovascular Reactivity to Carbon Dioxide under Hypercapnic and Hypocapnic Conditions	56
Table 9. Correlations between Arterial Structure and Function and Cerebrovascular Properties in CA and SA Older Adults	61
Table 10. Correlations between Arterial Stiffness, Anthropometric Measurements and Blood Biomarkers in CA and SA Older Adults.....	68
Table 11. Pearson Correlations between Quantitative Measures of Physical Activity, Arterial Structure and Function, Cerebrovascular Hemodynamic Properties, and Blood Biomarkers in CA and SA Older Adults.....	69

List of Abbreviations

ABP	Arterial blood pressure
BMI	Body mass index
BP _{MCA}	Mean arterial blood pressure at the level of the middle cerebral artery
CA	Caucasian
CBF	Cerebral blood flow (a- anterior)
CC	Compliance Coefficient
CCA	Common carotid artery
CO ₂	Carbon dioxide
CPP	Cerebral perfusion pressure
CRP	C-reactive protein
CVR	Cerebrovascular resistance (pressure/flow)
CVRi	Cerebrovascular resistance index (pressure/ flow velocity)
DBP	Diastolic blood pressure
DC	Distensibility Coefficient
ECG	Electrocardiogram
ETCO ₂	End-tidal carbon dioxide
HOMA-IR	Homeostasis model of assessment – insulin resistance index
HR	Heart rate
ICA	Internal carotid artery
ICP	Intracranial pressure
IMT	Intima-medial thickness
MAP	Mean arterial blood pressure
MBF	Mean blood flow
MCA	Middle cerebral artery
MFV	Mean flow velocity
P _{ET} CO ₂	Partial pressure of end-tidal carbon dioxide
PI	Pulsatility Index
PWV	Pulse wave velocity (ba- brachial-ankle)
Q	Cardiac output
RI	Resistance index
SA	South Asian
SBP	Systolic blood pressure
SWA	Senswear armband
TCD	Transcranial Doppler ultrasound
WHR	Waist-to-hip ratio

1 Literature Review

1.1 Vascular Health and Disease with Aging

1.1.1 Definition of Vascular Aging

Vascular aging is a natural process by which the vasculature undergoes progressive changes during aging. The major structural changes include the breakdown of elastin and deposition of collagen protein fibers, vascular remodeling, vascular smooth muscle cell proliferation and hypertrophy, and endothelial dysfunction (Nichols *et al.*, 2011). With advancing age, these alterations promote arterial stiffening and vessel wall thickening that substantially affect arterial function and regulation of blood flow.

When the heart contracts and ejects blood into the circulatory system, pressure pulse waves are generated and propagate along the arterial tree. The first conduit vessels that receive blood from the heart are central elastic arteries that are structurally designed to accommodate the ejected blood and functionally designed to distend and recoil to reduce the pulsatility of pressure waves generated by each heartbeat. In this way, the central arteries ensure constant blood flow and protect the small distal arteries from the transmission of high pulsatile energy. Normally, as pressure waves travel forward from central to peripheral arteries, they reflect back to the center when they encounter regions of impedance mismatch, such as branch points, which arise from differences in diameter and structural composition of vessels along the arterial tree (Latham *et al.*, 1985). In turn, the reflected waves amplify the incoming waves in late systole and early diastole (Nichols *et al.*, 2011). The resultant pressure waves drive blood flow during both systole and diastole that is necessary for adequate delivery of oxygen and nutrients to meet the metabolic demands of downstream organs and tissues in the human body.

Wave propagation and reflection vary considerably with age. The mechanical stretching and recoil of central arteries with each heartbeat can cause molecular and structural changes that accumulate over time with advancing age, which in part, causes the elastin fibers in the arterial wall to fatigue and breakdown while stiff collagen fibers begin to predominate (Samila & Carter, 1981). This natural degenerative process, along with the other aforementioned structural alterations, increase arterial stiffness and reduce central arterial compliance. Consequently, these changes influence hemodynamic properties, whereby the pressure waves move faster and reflect early to return in systole rather than diastole, resulting in amplified systolic and reduced diastolic pressure of incoming waves (**Figure 1**). In this situation, low resistance downstream vascular beds near organs that demand high volume of blood flow to meet their energy needs, such as the brain, are exposed to these high pulsatile pressure waves that potentially can cause substantial damage to the vessels and surrounding tissues.

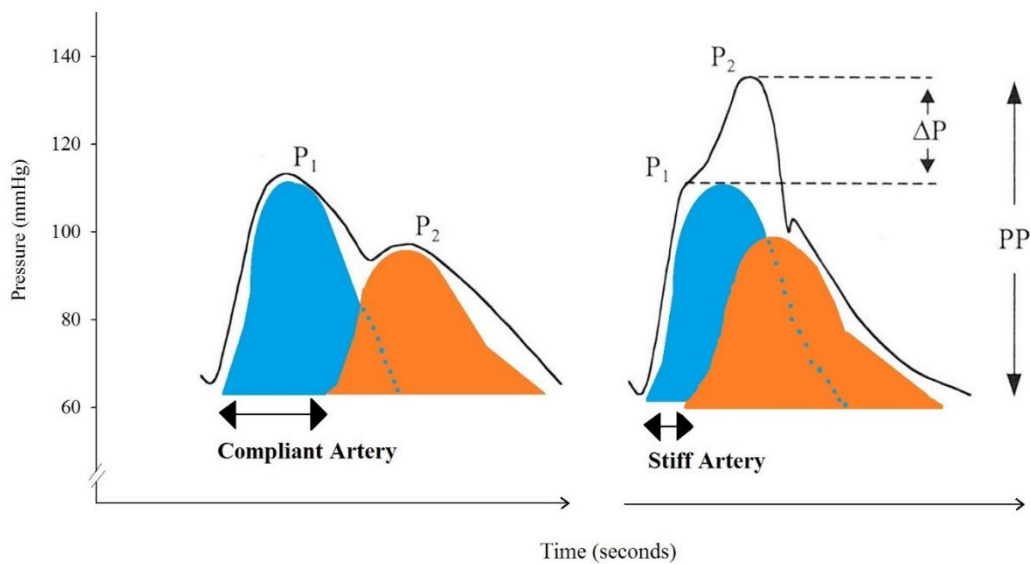


Figure 1. Schematic Diagram Representing Pressure Waveforms in Compliant (Left) and Stiff (Right) Central Arteries. In a healthy, young elastic artery, the forward wave (P1) created by the contraction of the heart determines the systolic blood pressure, and a reflected wave generated in the periphery (P2) returns towards the heart and amplifies the pressure during diastole. As the central arteries begin to age and stiffen, blood travels faster, and the reflected wave (P2) returns earlier, thereby increasing systolic blood pressure (ΔP) and pulse pressure (PP). Modified from Oliver & Webb (2003).

1.1.2 Vascular Aging and Disease

The physiological changes of the human vasculature with aging contribute to the decline in cardiovascular function. Many of the chronic diseases older adults suffer from are to some extent related to the long-term consequences of altered hemodynamic blood flow patterns associated with vascular aging. For instance, increased central arterial stiffness is associated with organ failure, including end-stage renal damage (Safar, 2002), as well as cerebrovascular diseases, such as stroke (Laurent *et al.*, 2003). In addition, increased risk of stroke and myocardial infarction is related to increased arterial thickness in older adults (O'Leary *et al.*, 1999). Together, these findings suggest that individuals with greater vascular changes (*i.e. accelerated* vascular aging) are at a greater risk of developing cardiovascular and cerebrovascular diseases compared with their age-matched counterparts. Therefore, it is important to understand differences in the extent of vascular changes during aging among individuals because these changes may help stratify risk and identify those most vulnerable to cardiovascular events.

In addition to age, hypercholesterolemia (Wilkinson *et al.*, 2002), hyperglycemia (Aoun & Blacher, 2001; Schram *et al.*, 2004), and increased levels of inflammatory markers (Mattace-Raso *et al.*, 2004), are associated with increased arterial stiffness. Nevertheless, arterial stiffness can be modified by lifestyle habits, such as physical activity. Individuals who are regularly active have less central arterial stiffness and largely preserved vascular health with age (Rogers *et al.*, 1990; Vaitkevicius *et al.*, 1993; Ainslie *et al.*, 2008; Miyazaki *et al.*, 2011). Even light intensity activities confer health benefits among older adults (Gando *et al.*, 2010). As such, promoting physical activity holds great promise in attenuating the age-related changes of the vasculature, thereby delaying the risk of associated diseases.

1.1.3 Vascular Age Assessments

Several non-invasive techniques have emerged to quantify the age-related changes in the vasculature. Indicators of arterial stiffness and thickness are commonly measured to provide information about arterial structure and function. For instance, arterial stiffness is evaluated by pulse wave velocity (PWV) and central pulse pressure analysis. PWV refers to the speed that pressure pulse waves travel over a defined distance along an arterial segment, which increases with greater arterial stiffness. Central pulse pressure (the difference between systole and diastole) is derived from pressure waveforms at the common carotid artery. Normally, the pressure waveform changes as it travels from central to peripheral arteries; the systolic peak gradually increases as a function of wave reflection (Kroeker & Wood, 1955; Wilkinson *et al.*, 2001). This pressure wave amplification phenomenon is not present in older adults because central arteries become stiff, and therefore, central pulse pressure is similar to peripheral pulse pressure. For this reason, arterial pulse pressure is considered an appropriate marker of arterial stiffness in older adults compared to young adults.

Thickening of the arterial wall is another hallmark characteristic of aging (Howard *et al.*, 1993). The vessel wall is made of three layers: adventitia, which is the outermost layer composed of connective tissues; media, which is the middle layer composed of smooth muscle cells, elastin and collagen fibers; and intima, which is a single layer of endothelial cells that line the vessel lumen. Thickness is visually assessed using ultrasound, which allows for visualization of the vessel wall. The common carotid artery (CCA) on either side of the neck is commonly used for measuring intima-medial thickness (IMT). CCA is the major artery that supplies oxygen-rich blood to the brain (Sojkova *et al.*, 2010). IMT is defined as the measured distance between the lumen-intimal interface and the media-adventitial interface of the far wall. IMT is a major indicator of arterial

health and an early detection measurement for atherosclerosis and its progression (Persson *et al.*, 1994).

Together, arterial stiffness and IMT measurements provide a comprehensive evaluation of vascular health. They are both considered valuable measurements because they improve risk prediction for future cardio- and cerebrovascular diseases and are related to mortality and morbidity in older adults, as well as in the general population (Meaume *et al.*, 2001; Mattace-Raso *et al.*, 2006; Willum-Hansen *et al.*, 2006; Lorenz *et al.*, 2007). Although cardiovascular risk factors (*e.g.*, hypertension, fasting plasma glucose levels, cholesterol, and smoking) can contribute to the increased risk of cardio- and cerebrovascular diseases in older adults, evidence suggests that arterial stiffness and thickness measurements independently predict future cardiovascular events after adjustments are made for these risk factors (Simons *et al.*, 1999; Sutton-Tyrrell *et al.*, 2005; Mitchell *et al.*, 2010; Lunder *et al.*, 2012).

1.1.4 Role of Central Vascular Aging on Cerebral Hemodynamics

Evidence suggests that faster PWV, an indicator of increased arterial stiffness, is associated with the prevalence and severity of cerebral infarctions and white matter hyperintensities (Hatanaka *et al.*, 2011; Saji *et al.*, 2011, 2012b; Poels *et al.*, 2012b). Several studies have also shown that increased arterial stiffness is associated with cognitive dysfunction (Scuteri *et al.*, 2007; Waldstein *et al.*, 2008; Triantafyllidi *et al.*, 2009; Watson *et al.*, 2011). These findings have major implications for older adults given that arterial stiffness increases with advancing age. Older adults are at high risk of cerebral microvascular damage associated with increased arterial stiffness (Tsao *et al.*, 2013). The link between age-related central arterial stiffness and cerebrovascular damage might be mediated by highly pulsatile pressure and flow, which are transmitted to the small vessels in the brain (Kidwell *et al.*, 2001; Hirata *et al.*, 2006; Mitchell *et al.*, 2011; Xu *et al.*, 2012; Webb

et al., 2012a). Therefore, increased arterial stiffness could contribute to the pathogenesis of cerebral small vessel disease in older adults.

Previous work in our laboratory on older adults without clinically overt cardio- and cerebrovascular diseases has shown that increased central arterial stiffness is associated with increased cerebrovascular resistance, which corresponds to reduction in CBF (Robertson *et al.*, 2010). Increased resistance to flow may represent a protective mechanism that limits the transmission of high pulsatile pressure and flow in the cerebral microcirculation in an attempt to prevent any severe damage to the blood vessels and surrounding brain tissue (Tarumi *et al.*, 2011). Chronically low CBF as a consequence of increased cerebrovascular resistance has the potential to compromise normal tissue perfusion and increase the risk for ischemic tissue damage if metabolic needs of brain tissues are not sufficiently met (Nichols *et al.*, 2011). Normally, resting CBF declines with aging (Buijs *et al.*, 1998; Scheel *et al.*, 2000), which indicates that older adults have a compromised cerebral perfusion state due to their advanced age. The brain has a high metabolic rate and requires continuous CBF for sufficient supply of oxygen and metabolic substrates for normal brain function and tissue integrity. Even a slight decrease in resting CBF that is not directly mediated by the changes in the brain's metabolic demands could compromise adequate tissue perfusion. These circumstances could trigger ischemic events, such as stroke, due to an inadequate supply of oxygen and nutrients to the brain (Powers *et al.*, 1985). This means that older adults with chronically elevated arterial stiffness may be at greater risk for cerebral hypoperfusion because they likely have diminished CBF that is mediated by increased cerebrovascular resistance.

Although the mechanisms underlying these relationships are not entirely understood, there is evidence to suggest that vascular aging of central arteries is associated with altered cerebral

hemodynamics and may be involved in the manifestation of cerebrovascular diseases associated with aging.

1.2 Ethnic Differences in Vascular Aging

Vascular changes with aging occur in all populations, although the rate and related consequences of these changes are not necessarily the same. Ethnicity can explain some of the variation in arterial stiffness not accounted for by aging and traditional cardiovascular risk factors. Ethnicity is a non-modifiable risk factor that has been identified as a marker of increased risk for cardiovascular and cerebrovascular diseases, such as stroke (Sheth *et al.*, 1999; Anand *et al.*, 2000; Chiu *et al.*, 2010).

1.2.1 Arterial Stiffness in South Asians

South Asian (SA) ethnicity refers to individuals originating from the southern region of the Asian continent, which includes India, Pakistan and Sri Lanka. In Canada, SAs are currently the largest and one of the fastest growing visible minority group. They account for the largest proportion of immigrants settled in Canada in recent decades, and this trend is projected to continue in the coming years (Statistics Canada, 2009). People of SA ethnicity have been recognized to have a higher risk of cardio- and cerebrovascular disease than those of other ethnic groups. In particular, SAs have the highest prevalence and incidence of heart disease, stroke, and small vessel disease (Gunarathne *et al.*, 2009a; Boparai *et al.*, 2011). Evidence suggests that the increased susceptibility to these diseases among SAs could be attributed to the increased degree of arterial stiffness. SAs have significantly faster PWV and increased pulse wave reflection compared to age- and gender-matched Caucasians (CA), independent of established cardiovascular risk factors (Din *et al.*, 2006; Gunarathne *et al.*, 2008b). Furthermore, SA stroke patients are reported to have greater

arterial stiffness compared to stroke patients from other ethnic groups (Gunarathne *et al.*, 2009a; De Silva *et al.*, 2009). Based on these observations, SAs appear to have adverse changes in vascular structure and function compared to CAs at any given age. Age is a significant independent predictor of arterial stiffness in both ethnicities, and it seems that SAs have an “accelerated” vascular aging process, which could contribute to the early pathology and excess risk of vascular diseases. Unfortunately, studies currently direct little attention to hemodynamic changes in the cerebral circulation that might be associated increased arterial stiffness in SAs. Given that SAs have elevated arterial stiffness, blood flow to the brain could be transmitted at high pressure, potentially inducing cerebral vessel remodelling and damage and having adverse effects on cerebral hemodynamics. Hence, the differences observed in the severity and associated risk of developing cerebrovascular disease between SA and CA ethnic groups could be related to the ethnic differences in the degree of arterial stiffness and its impact on the cerebral circulation.

1.2.2 Altered Cerebral Hemodynamics in South Asians

Middle-aged SAs are reported to have elevated blood flow velocity, pulsatility, and cerebrovascular resistance in the cerebral circulation compared to age- and gender-matched CAs (Bathula *et al.*, 2011). These findings support the notion that SAs have altered cerebral hemodynamics, which might contribute to increased risk of cerebrovascular damage and cerebrovascular disease. Surprisingly, the study did not find a significant difference in arterial stiffness between the two ethnic groups, implying that arterial stiffness may not necessarily explain the cerebrovascular hemodynamic differences observed between the SA and CA group. The researchers found that ethnic differences in cerebral hemodynamics was abolished when glycemic status was considered, and therefore, suggest that hyperglycaemia may explain the abnormal cerebral hemodynamics observed in SA group (Bathula *et al.*, 2011). However, the study design

raises several caveats that need to be addressed when interpreting the results. First, there is a significant number of comorbidities (*e.g.*, diabetes, metabolic syndrome, and coronary heart disease) in the study population that other studies suggest are independently associated with increased arterial stiffness (Salomaa *et al.*, 1995a; Scuteri *et al.*, 2004; Mattace-Raso *et al.*, 2006). Such comorbidities are also related to altered cerebrovascular hemodynamics. For instance, cerebral blood flow velocity and cerebrovascular resistance are significantly elevated in diabetic patients compared to healthy patients, implying that hyperglycemia could be a major factor influencing cerebral hemodynamics (Lee *et al.*, 2000). Such comorbidities appear to synergistically augment the vascular structural and functional changes with aging, and therefore, produce considerable amount of variability in the measures of arterial stiffness among individuals. Therefore, the presence of these comorbidities in the study conducted by Bathula and colleagues (2011) could have confounded the ethnic differences in arterial stiffness, and hence, non-significant difference in pulse wave velocity were reported ($p=0.10$). The SA group in Bathula and colleagues' (2011) study had a greater proportion of diabetics compared to the CA group (28.4% and 6.3%, respectively). This disproportionate number of diabetic patients among the ethnic groups may have influenced the relationship reported between hyperglycemia and altered cerebrovascular hemodynamics in SA group. A more appropriate approach would be to study cerebrovascular hemodynamic properties in the absence of diabetic patients to elucidate whether the differences between the ethnic groups are in fact due to glycemic status. Therefore, it is important to evaluate healthy individuals without comorbidities to minimize such confounding factors that limit or mask the true interpretation of the data, especially when understanding the mechanisms associated with disease development and risk among populations that display differential susceptibility.

Although the study conducted by Bathula and colleagues (2011) was not specifically designed to assess the role of arterial stiffness in cerebral hemodynamic patterns among SAs and CAs, the researchers found a positive correlation between PWV and cerebrovascular resistance ($r=0.338$, $p<0.0001$), and a negative correlation between PWV and mean cerebral blood flow velocity in the middle cerebral artery ($r= -0.157$, $p=0.01$) in the *total* study sample. These results suggest that *both* CAs and SAs in the study sample exhibited a significant relationship between age-related changes in central vascular structure and function and cerebrovascular hemodynamic properties. Significant findings have emerged from this study, yet there is still a need for direct evidence to support the role of central vascular changes in cerebral hemodynamics in SAs.

In recognition that middle-aged SAs have increased arterial stiffness and exhibit altered cerebral hemodynamic properties in comparison to age-matched CAs, there is a need to ascertain whether a difference in arterial stiffness between SAs and CAs persist with aging, and if it is linked to ethnic differences in cerebral hemodynamics. It is possible that SA older adults experience an even greater decline in CBF with aging as a consequence of having both greater arterial stiffening and increased cerebrovascular resistance compared to CA older adults. In other words, increased arterial stiffness may explain the increased risk of ischemic damage and cerebrovascular disease in SAs compared to CAs.

Taken together, research on SAs is particularly important considering that they are the largest growing minority group in Canada and have the highest prevalence of cardio- and cerebrovascular disease compared to other ethnic groups. The rising number of SA population urgently calls for understanding ethnic differences to implement appropriate effective prevention strategies to maximize the likelihood of healthy aging for all individuals in Canada's multicultural society.

1.3 Implications of Cerebrovascular Carbon Dioxide Reactivity

In addition to the observed reduction in resting CBF with aging, the dynamic regulation of CBF declines with age (Galvin *et al.*, 2010). Cerebrovascular reactivity to carbon dioxide (CO₂) is commonly used to assess the capacity to which cerebral microvessels respond to changes in arterial blood CO₂ by adjusting their radius, thereby changing the resistance to flow. The vessels dilate with increased CO₂ (hypercapnia) and constrict with decreased CO₂ (hypocapnia). Cerebrovascular reactivity to CO₂ is used to assess endothelial function of small cerebral vessels and cerebrovascular integrity. A relatively low cerebral vasomotor reactivity to CO₂ reflects impaired cerebral capacity to appropriately respond (increase CBF) to vasoactive stimuli, which can be detected prior to clinical presentation of cerebrovascular disease, and is associated with increased risk of ischemic events in the brain (Bakker *et al.*, 1999; Markus, 2001). This method challenges small cerebral vessels to reveal cerebrovascular hemodynamic abnormalities that may become more pronounced in a dynamic test than when it is examined at rest.

The cerebral vessels regulate CBF through a myogenic response to changes in blood pressure. Cerebrovascular tone is also mediated by endothelium-dependent mechanisms (Schmetterer *et al.*, 1997; Lavi *et al.*, 2003, 2006; Barnes *et al.*, 2012). The vascular endothelium is a monolayer of cells that forms an interface between circulating blood and the medial layer of the vessel wall that is comprised of smooth muscle cells. The endothelium releases agents that act on the vascular smooth muscles to regulate vascular tone (Sandoo *et al.*, 2010). As such, the maintenance of endothelium integrity and function is critical for the preservation of cardiovascular health.

Endothelium-derived nitric oxide (NO) is a major mediator of vasodilation, and decreased NO production and bioavailability is characteristic of endothelial dysfunction of peripheral vessels

(Vallance *et al.*, 1989). Endothelial function progressively declines with age and is considered an early pathological condition that is linked to the increased risk of cardiovascular disease (Celermajer *et al.*, 1992; Gerhard *et al.*, 1996). Several studies support the involvement of endothelium derived-NO in mediating the cerebral vessel response to CO₂ (Lavi *et al.*, 2003, 2006; Ainslie *et al.*, 2007); however, the precise role of NO in cerebral vasodilation is not entirely clear. Cerebrovascular reactivity is impaired in patients with peripheral endothelial dysfunction (Lavi *et al.*, 2006), suggesting a potential link between peripheral and cerebral vasomotor activity. These findings are particularly important because SAs are reported to have impaired peripheral endothelial function compared to age-matched CAs (Murphy *et al.*, 2007), yet little is known regarding the dilatory capacity of cerebral vessels among SAs. Adverse cerebrovascular hemodynamics are reported in SAs (Bathula *et al.*, 2011), which may be a consequence of morphological changes or impaired endothelial function of cerebral vessels. Therefore, this thesis examined cerebrovascular reactivity to CO₂ in SAs for a more comprehensive assessment of cerebrovascular function and the regulation of CBF. This assessment could shed light on potential mechanisms to better understand ethnic differences in cerebrovascular disease risk.

2 Objectives

Primary Objective:

- 1) Compare structural and functional vascular health and cerebral hemodynamics between CA and SA older adults matched for age and gender.
- 2) Ascertain whether arterial stiffness is associated with resting cerebral blood flow (aCBF) and whether this relationship differs between CAs and SAs.

Secondary Objective:

- 1) Explore relationships between the structural and functional vascular properties and cerebral hemodynamics in CA and SA older adults.
- 2) Examine differences in blood biomarkers and physical activity between CAs and SAs.
- 3) Examine differences in cognitive performance between CAs and SAs and explore the relationship between central arterial and cerebrovascular health and cognitive performance.

3 Hypotheses

1. SA group will exhibit greater central arterial stiffness compared to CA group.
2. Baseline aCBF will be lower in SAs relative to CAs.
3. Cerebrovascular reactivity during hypercapnia will be lower in SAs relative to CAs.
4. Baseline aCBF will be negatively correlated with indices of central arterial stiffness and that this relationship will be stronger in SAs compared to CAs.
5. Fasting levels of metabolic markers will be higher in SAs compared to CAs.

4 Methods

Experimental procedures and data collection techniques were consistent in both ethnic groups to ensure accurate comparability of data. Some modifications, additional methods, as well as methodological and analytical considerations, are highlighted in this section. All experimental procedures and measurements have been reviewed and approved by the Office of Research Ethics at the University of Waterloo (ORE#19197).

4.1 Study Population

i) SA participants

Twenty-two community-dwelling older adults of SA origin (11 males, 11 females) participated in the study. SAs determined by self-report, were defined as individuals with both parents born in the Indian subcontinent (e.g., India, Pakistan, Bangladesh). Participants were recruited from a senior community center, various religious temples, and the public community at large in the Waterloo and Peel Regions of Ontario. Participants volunteered freely after receiving information about the study from public presentations, radio advertisements, as well as through word of mouth. Interested participants were phone interviewed to review their medical history in light of the inclusion and exclusion criteria for this study (**Appendix A**). Eligible participants were scheduled for testing and given specific instructions to standardize the methods and minimize possible physiological variability on the day of testing, which included refraining from alcohol consumption (Riff *et al.*, 1969; Kupari *et al.*, 2009); caffeine (Whitsett *et al.*, 1984; Lunt *et al.*, 2004); and nicotine for 24 hours (Benowitz *et al.*, 1984); as well as to avoid exercise for at least 12 hours prior to testing day. Every participant was also told to fast overnight for at least 8 hours prior to arrival in order to obtain early-morning venous blood samples.

ii) CA participants

Twenty-two SAs were age- and gender-matched to CA participants whose data had been previously collected from this lab and can be found in Dr. A.D. Robertson's thesis dissertation (Robertson, 2013). Whereas data from each CA participant were collected over a span of two days, data collection from each SA participant in the current study was condensed into a single day for logistic reasons.

4.2 Overview of Experimental Design

The study was conducted at the University of Waterloo Vascular Aging and Brain Health Laboratory. The study protocol was divided into two sections: morning and afternoon. In brief, participants arrived in the morning and signed the informed consent; then, fasting blood samples were drawn, and height and weight were measured. Once the measurements were complete, a health status questionnaire was administered face to face, followed by an assessment of cognitive performance. The experimental testing took place early afternoon for all participants, similar to when testing had been previously conducted on CA group, to minimize the variability in the cardio- and cerebrovascular measures associated with the time of day (Diamant *et al.*, 2002; Ainslie *et al.*, 2007). Testing procedures included measurements of arterial structure and function, resting baseline aCBF, and cerebrovascular reactivity to CO₂. At the end of the test, participants were given a wireless activity monitor to take home and wear for 3 consecutive days to provide an estimate of their current physical activity patterns. They were instructed to wear the armband on the right upper arm over the triceps muscle for 3 whole days, while continuing with their normal daily routines and activities, and to remove it only when showering or swimming. Once complete, each participant returned the monitor in person.

4.3 Part One: Morning Session

4.3.1 Biochemical and Basic Anthropometric Measurements

After the written consent was obtained, approximately 25 mL fasting blood sample was drawn from each participant by a trained and certified technician who performed a venipuncture of an antecubital vein in the forearm according to standard procedures. The blood sample was analyzed for fasting glucose, glycosylated hemoglobin (HbA_{1c}), hematocrit, triglycerides, cholesterol, and C-reactive protein (CRP). Insulin and glycated albumin were two additional blood markers analyzed in only SA group based on literature suggesting the involvement of insulin resistance and abnormal glycemic control in cardiovascular disease risk (McKeigue *et al.*, 1991; Selvin *et al.*, 2011; Moon *et al.*, 2012; Song *et al.*, 2012; Mebazaa *et al.*, 2013). Glycated albumin has gained considerable clinical interest as a short-term measure of glycemic changes and has been proposed as a more accurate and useful measure of glycemic status than HbA_{1c} (Schleicher *et al.*, 1993; Ohkubo *et al.*, 1995; Juraschek *et al.*, 2012; Montagnana *et al.*, 2013). After blood collection was complete, height and weight were measured with participants wearing no shoes using a balance-beam and a wall-mounted stadiometer, respectively. Then, participants ate a light breakfast.

4.3.2 Comprehensive Questionnaire, Cognitive Testing and Laboratory Tour

The health status questionnaire, modified from Robertson (2013) (**Appendix B**), was administered verbally in Punjabi by the bilingual author, and then, the author translated the answers into English and filled out the questionnaire. Participants self-reported their sociodemographic information, such as age, ethnicity, marital status, education level, employment status, as well as current and past health behaviors, such as alcohol intake and smoking status, and physical activity. In addition, each participant was asked about his or her personal and family

medical history, including current and past medical conditions, such as heart attack, stroke, diabetes, as well as neurological or other chronic disorders. Current medications (prescribed and over-the-counter) were also recorded, including the dosage and total years of medication use.

Upon completion of the questionnaire, participants performed two computer-administered cognitive tasks: simple (sRT) and choice (cRT) reaction times. These tasks are classified as psychomotor tasks that involve attention and motor skills; sRT is considered a basic cognitive task that involves one stimulus and one response, whereas cRT is more complex because it requires decision-making to choose one of multiple responses depending on the stimulus presented. These tasks were chosen for this study because they are simple, culture-free assessments that have shown to be reliable when comparing between populations of different ethnic backgrounds (Hagger-Johnson *et al.*, 2014). For sRT task, participants were instructed to respond as fast as they could by pressing the button on the keyboard with the index finger when the letter ‘O’ appeared over the target in the middle of the computer screen; this was assessed for both the left and right index fingers. For cRT task, participants were asked to respond with either their left or right index finger, depending on whether the target letter was ‘O’ or ‘X’. The sRT task was comprised of 8 sets of trials (4 trials for each finger), and the cRT was comprised of 4 sets of trials; each of these trials contained a total of 20 targets. Participants were given a practice trial before each task prior to the test trials. sRT and cRT reaction times were collected using E-Prime software (E-Prime, Psychology Software Tools Inc., Pittsburgh PA, USA). The tasks and trials within each task were automatically randomized by the software for every participant.

After completing the cognitive tasks, participants were given a tour of the laboratory and an overview of the experimental protocol and equipment to relieve initial anxiety before proceeding with the experimental testing. This familiarization session was intended to reduce possible

physiological response to stress that could confound the cardiovascular variables during testing (Hickam *et al.*, 1948).

4.4 Part Two: Afternoon Session

4.4.1 Overview

The experimental test was performed at least 1-2 hours after breakfast to minimize the possible confounding effects of food consumption on cardiovascular measures. Room temperature, barometric pressure, and relative humidity were monitored during every test to ensure that environmental conditions were similar and maintained. Participants rested comfortably in supine position on an examination bed for at least 15 minutes before performing any assessment. During this time, they were instrumented for measurement of heart rate (HR), arterial blood pressure (ABP), exhaled CO₂, cardiac output (Q), and blood flow velocity (BFV) at the right middle cerebral artery (MCA). These variables were recorded continuously throughout the entire test at 1000 Hz using a data-acquisition system (PowerLab, ADInstruments, Colorado Springs CO, USA) and the corresponding computer software (LabChart 7, ADInstruments, Colorado Springs CO, USA). Once the signal quality of each device was optimized and stable, manual blood pressure was measured twice, one minute apart, using a sphygmomanometer to calibrate the Finometer blood pressures for offline analysis. Then, baseline vascular properties were examined: regional and central arterial stiffness were assessed by measuring brachial-ankle pulse wave velocity (baPWV) and CCA pulse pressure (PP_{car}), respectively; the arterial wall structure was examined by ultrasound measurements of CCA IMT; and the arterial wall function was evaluated by measurements of CCA compliance and distensibility. In addition, bilateral internal carotid artery (ICA) diameter and blood flow velocity were imaged using ultrasound to estimate aCBF. Lastly,

the participants were assisted in transitioning from supine to a seated position for the final assessment of cerebrovascular reactivity.

4.4.2 *Continuous Measurements*

While participants rested supine on the examination bed, they were instrumented with an electrocardiogram (ECG Module, Finapres Medical Systems, Amsterdam, NL) to measure HR using the CM5 electrode placement (the left and right shoulder below the collar bone, and the left fifth intercostal space). Beat-to-beat ABP (systolic blood pressure, SBP; diastolic blood pressure, DBP; and mean arterial pressure, MAP) were continuously measured on the left middle or index finger using a photoplethysmographic cuff from the Finometer (Finometer Pro, Finapres Medical Systems, Amsterdam, NL). Once stable signals were obtained, brachial artery pressure waveforms were reconstructed by the device from the finger waveforms via waveform filtering (transfer function) (Bos *et al.*, 1996; Guelen *et al.*, 2003). Additionally, the return-to-flow calibration on the device was performed to calibrate the finger pressure to brachial pressure by means of an automated upper arm cuff (Gizdulich *et al.*, 1997). The height corrector was taped onto the participant at heart level to avoid the effect of hydrostatic pressure (Gizdulich *et al.*, 1996). The Finometer also provided beat-to-beat estimates of Q based on a Modelflow algorithm.

Breath-by-breath exhaled CO₂ were collected through a nasal cannula and analyzed using infrared spectroscopy (Datex-Ohmeda 5200 CO₂ Monitor, Mundelein IL, USA). The peak percent CO₂ concentration at the end of every exhaled breath was used to represent end-tidal CO₂ (ETCO₂), and was converted to millimeters of mercury, mmHg, to be expressed as partial pressure of CO₂ (P_{ET}CO₂). P_{ET}CO₂ was calculated by multiplying the CO₂ concentration by the difference in barometric and vapor pressure at room temperature. Changes in P_{ET}CO₂ were used as a proxy for

changes in the partial pressure of arterial CO₂ when cerebrovascular reactivity results were interpreted (Young *et al.*, 1991).

BFV at the right MCA was measured by transcranial Doppler ultrasound (TCD; Doppler Box, Compumedics DWL, Singen, GE) using a 2 megahertz (MHz) transducer. This method has been conventionally used in literature to assess global cerebral blood flow velocity since the MCA is one of the largest intracerebral vessels supplying a large proportion of the total blood flow to the brain (Schoning *et al.*, 1994). The participants wore an adjustable headband (Marc 600, Spencer Technologies, Seattle WA, USA) that held the transducer steady on the right temporal region to insonate the M1 segment of the MCA throughout the test. At insonation depth between 50 to 60 mm, the probe position and angle were adjusted accordingly to identify the MCA and to obtain the most optimal flow velocity signals directed toward the probe for each participant (Aaslid *et al.*, 1982; Pellerito & Polak, 2012).

4.4.3 *Baseline Vascular Characteristics*

This section outlines the measurement techniques and the next section (Data Acquisition and Analysis) describes the equations and evaluation of these measurements.

4.4.4 *Brachial-Ankle Pulse Wave Velocity*

Pulse waves at the right brachial and posterior tibial arteries were recorded sequentially for 20-30 cardiac cycles using pressure transducers (MLT1010, Pulse Transducer, ADInstruments, Colorado Springs CO, USA) placed directly on the surface of the skin and were used to compute baPWV.

4.4.5 *Carotid Pulse Pressure*

Beat-by-beat CCA pulse pressure (PP_{car}) was recorded non-invasively by applanation tonometry for 15-20 consecutive cardiac cycles (SPT-301, Millar Instruments, Houston TX, USA).

Briefly, the left CCA pulse was located by palpating the surface of the neck, and the hand-held tonometer probe was then placed directly over the center of the pulse with enough pressure to “flatten” the circumferential shape of the carotid artery against underlying adjacent tissue or bone. In this way, the probe recorded the internal pressure in the artery (Kelly *et al.*, 1989). To obtain reliable carotid pulse signals, the hold-down pressure of the probe was adjusted accordingly until persistent maximum amplitude waveforms with a stable baseline appeared on the recording software on the computer screen (Drzewiecki *et al.*, 1983). Ideally, the probe should be applied over the center of the vessel, and the vessel should be flattened.

4.4.6 Carotid Arterial Wall Structure and Function

Brightness-mode (B-mode) echo ultrasonography (M5 system, Mindray Bio-Medical Electronics Co., Shenzhen, CN) using an 8-12 MHz linear array transducer (L14-6s) was used to image the left and right CCA. The water-soluble ultrasonic gel was applied to the transducer that was placed against each participant’s neck to insonate the CCA within 1-2 cm of the carotid bifurcation. Images of the left and right CCA that captured the thickest part of the far arterial wall over 3 consecutive cardiac cycles were used for mean and maximum IMT measurement. IMT was defined as the distance from the lumen-intimal interface to the media-adventitial interface of the far wall of the artery (Touboul *et al.*, 2006). ECG signals were simultaneously recorded on the images and used for data analysis purposes. In addition, the B-mode images of the left CCA were used, in combination with PP_{car} , to calculate arterial compliance and distensibility (See Data Acquisition and Analysis for further details).

4.4.7 Cerebral Blood Flow

Extracranial blood flow through bilateral ICA was estimated using duplex ultrasonography (M5 system). For diameter measurements, the 8-12 MHz linear array transducer was used to

collect longitudinal B-mode images of the ICA at least 1-2 cm distal to the carotid bifurcation; for velocity measurements, a beat-to-beat spectral velocity trace was collected using Doppler mode (PW-mode). The sample volume for the velocity trace was taken from the same location as the vessel diameter measurements. The sample volume cursor was positioned in the center of the vessel, parallel to the wall, and its gate was adjusted to encompass the full width of the vessel diameter. The angle of insonation (angle between the direction of the ultrasound beam and the direction of blood flow) was kept at or less than 60 degrees. The vessel diameter and velocity measurements were used to calculate the mean blood flow (CBF) in both the left and right ICA, and the bilateral sum of the CBF volumes was used to calculate aCBF (**Equation 1.11**, See Data Acquisition and Analysis section for further details).

4.4.8 *Cerebrovascular Reactivity to Carbon Dioxide*

After participants transitioned from supine to a seated position, cerebrovascular reactivity to hypocapnia (LOWCO₂) and hypercapnia (HICO₂) were examined. In preparation for these assessments, a 5-litre non-diffusing gas bag (Series 6000, Hans Rudolph, Shawnee KS, USA) was inflated with a gas mixture (5% CO₂, 21% O₂, and balance N₂). Then, the bag was attached to a breathing tube connected to a mouthpiece.

After a 5-minute rest in the seated position, manual blood pressure was again measured twice for the purpose of calibrating the Finometer blood pressure signals in this posture before beginning the assessment. Then, the nasal cannula was removed and replaced with a nose clip and a mouthpiece sealed air tight. In addition, the sampling line from the CO₂ monitoring device was attached to the mouthpiece. A three-way valve (Three-way T-shape Stopcock Type, Hans Rudolph, Shawnee KS, USA) on the bag was used to manually switch between the delivery of

room air and hypercapnic gas during the assessment. Beat-to-beat recordings of ABP, PETCO₂, and BFV at the MCA were simultaneously recorded for data analysis of cerebrovascular reactivity.

The assessment began with each participant breathing room air for 3 minutes through the mouthpiece at their normal breathing rate to obtain baseline values, followed by the induction of hypocapnia achieved through mild hyperventilation. Participants were instructed to hyperventilate for 2 minutes to reduce P_{ET}CO₂ ~5-10 mmHg from their baseline. Their breathing rate was paced by using an electronic metronome (Seiko Digital Metronome 440 Hz) set at a frequency of 20 breaths per minute. Then, participants returned to their normal breathing rate while continuing to breathe through the mouthpiece for 3 minutes to recover from hyperventilation before proceeding to the second condition (hypercapnia). To achieve hypercapnic conditions, first the bag-valve was switched from room air to the gas mixture contained in the bag. Participants then inhaled the gas for 3 minutes and were told to maintain a constant breathing frequency. Based on the pre-established threshold for obtaining adequate signal-to-noise ratio of BFV signals from the TCD, a minimum of ~5 mmHg increase and decrease in P_{ET}CO₂ were sufficient to induce hypercapnic and hypocapnic conditions, respectively (Robertson, 2013). ETCO₂ and BFV signals on the computer screen were closely monitored to ensure these thresholds were being met and maintained during each condition. The assessment ended when the valve was turned back to room air.

After the entire study procedure was complete, all equipment and devices were removed from the participants, and waist and hip circumference were the final measurements. While participants stood still, waist circumference was measured using a measuring tape between the costal margin and iliac crest at the end of a normal expiration, and hip circumference was measured around the widest portion of the buttocks.

4.5 Data Acquisition and Analysis

4.5.1 Biochemical Analysis

Blood samples obtained from each participant were collected in plain tubes (for whole blood and serum analyses) and in Ethylenediaminetetraacetic acid (EDTA) anticoagulant-treated tubes (for plasma analysis). Immediately after collection, one plain tube containing the whole blood sample was analyzed for fasting glucose (Glucose: Accu-Chek Aviva, Roche, Mannheim, DE, USA); HbA_{1c} (A1cNow+, Bayer Health Care, Sunnyvale CA, USA); and hematocrit (microcapillary tube centrifugation at 1000 rounds per minute (rpm) for 5 minutes). The remaining tubes containing the blood sample were put in dry ice, after which they were centrifuged at 2800 rpm for 15 minutes at room temperature in order to separate the serum in the plain tubes and the plasma in the EDTA-treated tubes. The serum and plasma were carefully transferred into separate Eppendorf tubes using a pipette and then stored in a -80°C freezer.

Commercially available assay kits were used to analyze fasting plasma levels of glycosylated albumin (Human Glycosylated Albumin ELISA Kit [Order No. E01G0293], Bluegene SA, China) and CRP (CRP sensitive [Cat. No. K9710s], ALPCO Immunoassays, Salem NH, USA), as well as serum levels of insulin (Insulin Coat-A-Count Kit [Cat. No. TKIN1], Siemens Medical Solutions Diagnostics, Los Angeles CA, USA); triglycerides (Triglycerides-GPO Reagent Set, Pointe Scientific, Inc., Canton MI, USA); total cholesterol (Cholesterol Reagent Set, Pointe Scientific, Inc., Canton MI, USA); high-density lipoproteins (HDL) and low-density lipoproteins (LDL) (HDL Cholesterol Precipitating Reagent Set, Pointe Scientific, Inc., Canton MI, USA). Insulin (in microunits per millilitre, $\mu\text{U}/\text{mL}$) and glucose (in millimole per litre, mmol/L) levels were used to estimate insulin resistance using the Homeostasis Model of Assessment - Insulin Resistance index (HOMA-IR, **Equation (1.1)**). In current literature, this equation is considered a feasible and

reliable surrogate measure of insulin sensitivity as it has been previously validated with the golden standard euglycemic-hyperinsulinemic clamp techniques in humans (Matthews *et al.*, 1985; Bonora *et al.*, 2000).

$$\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/mL}) \cdot \text{fasting glucose (mmol/L)}] / 22.5 \quad (1.1)$$

4.5.2 Anthropometric Calculations

Height (in meters, m) and weight (in kilograms, kg) were used to calculate body-mass index (BMI; **Equation (1.2)**). These measurements were also used in the Dubois and Dubois formula to estimate body surface area (BSA; **Equation (1.3)**) to correct Q for body size.

$$\text{BMI (kg/m}^2\text{)} = \text{weight (kg)} / \text{height (m)}^2 \quad (1.2)$$

$$\text{BSA (m}^2\text{)} = 0.007184 \cdot \text{weight (kg)}^{0.425} \cdot \text{height(cm)}^{0.725} \quad (1.3)$$

Waist and hip circumference measurements (in cm) were assessed individually and as a waist-to-hip ratio (WHR; **Equation (1.4)**).

$$\text{WHR} = \text{Waist Circumference (cm)} / \text{Hip Circumference (cm)} \quad (1.4)$$

4.5.3 Cardiovascular Variables

All cardiovascular variables were expressed as an average over the last 30 seconds in each position (supine and sit) and in each condition during cerebrovascular reactivity. As previously mentioned in the methods section, manual measurements of blood pressure using the traditional auscultation method were performed 5 minutes after participants rested in supine and seated

positions to compare and correct the blood pressure readings from the Finometer since this device has the tendency to overestimate systolic pressure readings (Rongen *et al.*, 1995) During offline analysis, the time point when manual BP were measured, simultaneous BP readings from the Finometer were averaged over 15 beats, and if the BP values differed between the two methods by > 10 mmHg, then the BP readings from the Finometer were corrected to the manual BP values.

Q (in litres per minute, L/min) was estimated by the Modelflow algorithm from the Finometer device. The Modelflow algorithm uses the three-element Windkessel model to compute an aortic flow waveform and estimate stroke volume. The three elements represent the major properties of the arterial system: aortic impedance, arterial compliance, and systemic (peripheral) vascular resistance. Aortic impedance and compliance depend on the elastic properties of the aorta and are estimated from the non-linear aortic pressure-area relationship, which was an empirical model originally studied/derived from *post-mortem* human aortas (Langewouters *et al.*, 1984). For each ABP waveform, values for these parameters are computed and then used in the algorithm that takes into account each participant's age, gender, height and weight to estimate beat-to-beat Q. Q for each participant was corrected for body size by computing a cardiac index (Qi; **Equation (1.5)**)

$$Q_i \text{ (L/min/m}^2\text{)} = Q \text{ (L/min)} / \text{BSA (m}^2\text{)} \quad \text{(1.5)}$$

Beat-by-beat total peripheral resistance (TPR, mmHg/L/min) was calculated as MAP, generated from the Finometer at heart level, divided by Q in **Equation (1.6)** below:

$$\text{TPR (mmHg/L/min)} = \text{MAP (mmHg)} / Q \text{ (L/min)} \quad \text{(1.6)}$$

4.5.4 *Brachial-Ankle Pulse Wave Velocity*

Rather than the gold standard carotid-femoral PWV method, baPWV was an alternative method used that reflects the stiffness of both central and peripheral muscular arteries. The key advantage of the baPWV method was that it was an appropriate method that respects the comfort level of older participants in a research laboratory setting compared to carotid-femoral PWV method. baPWV has a modest correlation with carotid-femoral PWV (Yu et al., 2008; Tanaka et al., 2009) and has been validated and shown to be a reproducible measure (Yamashina et al., 2002). Other studies have found that baPWV and carotid-femoral PWV are associated with similar cardiovascular disease risk factors and clinical cardio- and cerebrovascular events (Turin et al., 2010; Vlachopoulos et al., 2010; Ninomiya et al., 2013). Therefore, baPWV was a reasonable surrogate marker of arterial stiffness in this study.

The anatomic distance from the suprasternal notch to each arterial site (brachial artery, Lb, and posterior tibial artery, La) was measured using a tape measure, as previously performed in CA group (Robertson, 2013). The difference between these measured distances was used in **Equation (1.7)** to calculate baPWV (in metres/second, m/s). In addition, a digital low-pass filter with a maximum cut-off frequency of ~20 Hz was applied to the recorded signals to reduce the noise and distortion in the original arterial pressure waveforms, thereby improving the signal-to-noise ratio (Goldberger & Ng, 2010). Then, the average transit time for brachial (Tb) and posterior tibial (Ta) arteries were measured from the foot of the pressure pulse waveforms gated to the R-spike of the ECG over the last 25-30 cardiac cycles of recording. The foot of each waveform was identified as the minimum point just before the initial systolic upstroke of the wave.

$$\text{baPWV (m/s)} = [L_a - L_b] / [T_a - T_b] , \quad (1.7)$$

where L_a and L_b are the distances (in metres, m) from the suprasternal notch to the posterior tibial and brachial artery, respectively. T_a and T_b are the average times (in seconds, s) from the R-spike to the foot of the wave at the posterior tibial and brachial artery, respectively.

4.5.5 Carotid Pulse Pressure

CCA pulse waveforms (expressed in volts, V) measured by applanation tonometry using the Millar transducer was converted into pressure waveforms (in mmHg) by calibrating them to the brachial MAP and DBP measured from the Finometer. This is a method originally proposed by Kelly *et al.*, (1989), and is based on the concept that MAP and DBP do not change considerably along the arterial tree; invasive studies have shown that MAP and DBP from the central to peripheral arteries differ only slightly (Schnabel *et al.*, 1952; Kroeker & Wood, 1955; Pauca *et al.*, 1992). The average MAP and DBP values simultaneously recorded from the Finometer during the assessment were used to estimate PP_{car} . Carotid SBP was calculated by extrapolation to the peak of each carotid pulse wave. Therefore, to ensure the accuracy of PP_{car} measurements, the brachial artery pressure waveforms had to be reconstructed by the Finometer device and manual blood pressure was taken prior to the assessment. PP_{car} was computed as an average over a minimum of 15 consecutive beats when the pressure waveforms had a stable baseline, and the maximal amplitude was consistent among the waveforms recorded.

4.5.6 Carotid Intima-Media Thickness

Mean and maximum IMT were measured on B-mode longitudinal ultrasound images of the CCA obtained from both sides of the neck. A set of 8 electronic calipers were equally placed over a 1-cm segment along the far wall of the artery on frozen images during diastole (at the R-spike on the ECG signals), and an average was taken over 3 consecutive beats. The mean IMT (in

millimeters, mm) was computed by combining the average IMT measurements from the left and right CCAs. Similarly, the thickest wall of the left and right CCAs were averaged to calculate the maximal IMT. Reporting the average CCA IMT measurements from both sides as opposed to one side only is believed to be reproducible and more precise, as inter-observer errors are low (Schmidt & Wendelhag, 1999).

4.5.7 Carotid Compliance and Distensibility

The left CCA systolic and diastolic diameters were measured from longitudinal B-mode images. Calipers were used in triplicates to measure from the top wall intima to bottom wall intima, perpendicular to the vessel, over 3 consecutive cardiac cycles. Systole and diastole were determined as the largest and smallest diameters during the cardiac cycle. An average diameter value for each phase, along with the calculated average PP_{car} , were used to calculate distensibility coefficient (DC) (**Equation (1.8)**) and compliance coefficient (CC) (**Equation (1.9)**) (Van Bortel *et al.*, 2002; Reneman *et al.*, 2005).

$$CC \text{ (mm}^2\text{/MPa)} = [\pi \cdot \Delta D(\text{mm}) \cdot D(\text{mm})] / [2 \cdot PP_{car} \text{ (MPa)}] \quad (1.8)$$

$$DC \text{ (10}^{-3}\text{/kPa)} = [2 \cdot \Delta D(\text{mm}) \cdot D(\text{mm}) + \Delta D(\text{mm})^2] / [D(\text{mm})^2 \cdot PP_{car} \text{ (kPa)}] \quad (1.9)$$

4.5.8 ICA Blood Flow and Anterior Cerebral Blood Flow

The left and right ICA mean blood flow volumes were determined as the product of the average cross-sectional area of the blood vessel and the mean flow velocity (MFV, in cm/s) using **Equation (1.10)**). The diameter was measured during end-diastole (gated to the R-spike) in triplicates using electronic calipers on B-mode images that were averaged over 3 consecutive cardiac cycles. MFV was obtained from the PW mode images by averaging the velocity over 4-5

consecutive cardiac cycles. aCBF (in mL/min) was computed as the sum of the left and right ICA blood flow volumes (**Equation (1.11)**).

$$\text{ICA Blood Flow (mL/min)} = [\text{MFV (cm/s)} \cdot \pi \cdot \text{diameter (cm)}^2 / 4] \cdot 60 \text{ s/min} \quad (1.10)$$

$$\text{aCBF (mL/min)} = \text{left ICA CBF} + \text{right ICA CBF} \quad (1.11)$$

4.5.9 Indices of Cerebrovascular Function

Cerebrovascular function was evaluated by measuring the change in MCA MFV from the TCD in response to the change in P_{ETCO_2} . Several studies have described a linear relationship between TCD-measured MFV at the MCA and P_{ETCO_2} (Hauge *et al.*, 1980; Peebles *et al.*, 2007; Ainslie & Duffin, 2009; Zuj *et al.*, 2012), whereas others have argued a non-linear relationship (Ide *et al.*, 2003). For the present study, a linear relationship was assumed in order to compare reactivity between ethnic groups. The mean values of MFV and P_{ETCO_2} at baseline, hypocapnia, and hypercapnia were obtained from averaging the last 30 cardiac cycles of data in each condition and were used to calculate cerebrovascular reactivity to hypocapnia (LOWCO₂, **Equation (1.12)** and **(1.13)**) and hypercapnia (HICO₂, **Equation (1.14)** and **(1.15)**). Cerebrovascular reactivity for each condition was expressed as an absolute and as a percent change in MFV from baseline (breathing room air at a normal breathing rate) over the mmHg change in P_{ETCO_2} (Ide *et al.*, 2003; Cummings *et al.*, 2007; Peebles *et al.*, 2007). Furthermore, ABP was continuously recorded during the assessment to monitor its potential effects on MFV values (Dumville *et al.*, 1998; Hetzel *et al.*, 1999; Panerai *et al.*, 1999; Edwards *et al.*, 2002; Battisti-Charbonney *et al.*, 2011).

$$\text{LOWCO}_2 (\Delta\text{cm/s}/\Delta\text{mmHg}) = \frac{[\text{MFV}(\text{hypocapnia}) - \text{MFV}(\text{baseline})]}{[(\text{P}_{\text{ET}}\text{CO}_2(\text{hypocapnia}) - \text{P}_{\text{ET}}\text{CO}_2(\text{baseline}))]} \quad (1.12)$$

$$\text{LOWCO}_2 (\Delta\text{cm/s}/\Delta\text{mmHg}) = \frac{[\text{MFV}(\text{hypocapnia}) - \text{MFV}(\text{baseline})] / \text{MFV}(\text{baseline}) \cdot 100 \%}{[(\text{P}_{\text{ET}}\text{CO}_2(\text{hypocapnia}) - \text{P}_{\text{ET}}\text{CO}_2(\text{baseline}))]} \quad (1.13)$$

$$\text{HICO}_2 (\Delta\text{cm/s}/\Delta\text{mmHg}) = \frac{[\text{MFV}(\text{hypercapnia}) - \text{MFV}(\text{baseline})]}{[(\text{P}_{\text{ET}}\text{CO}_2(\text{hypercapnia}) - \text{P}_{\text{ET}}\text{CO}_2(\text{baseline}))]} \quad (1.14)$$

$$\text{HICO}_2 (\Delta\text{cm/s}/\Delta\text{mmHg}) = \frac{[\text{MFV}(\text{hypercapnia}) - \text{MFV}(\text{baseline})] / \text{MFV}(\text{baseline}) \cdot 100 \%}{[(\text{P}_{\text{ET}}\text{CO}_2(\text{hypercapnia}) - \text{P}_{\text{ET}}\text{CO}_2(\text{baseline}))]} \quad (1.15)$$

4.5.10 Cerebrovascular Hemodynamic Properties

MCA flow velocity waveforms derived from the TCD waveform signals, including peak-systolic (SFV) and end-diastolic (DFV) flow velocities, were used to compute indices that describe cerebrovascular hemodynamics and regulation. Pourcelot's resistance index (RI, **Equation (1.16)**) was used to reflect the resistance to flow of downstream cerebral microvessels. Gosling's pulsatility index (PI, **Equation (1.17)**) was used to describe the pulsatile blood flow pattern in the cerebral vessels that is dependent on the downstream resistance of microvessels in the brain.

$$\text{RI} = [\text{SFV (cm/s)} - \text{DFV(cm/s)}] / \text{SFV (cm/s)} \quad (1.16)$$

$$\text{PI} = [\text{SFV (cm/s)} - \text{DFV (cm/s)}] / \text{MFV (cm/s)} \quad (1.17)$$

An additional index of cerebrovascular resistance (CVRi) was examined to account for the influence of ABP on MFV, which is ignored in RI and PI calculations. Cerebrovascular resistance is traditionally calculated as the ratio between cerebral perfusion pressure (CPP) and CBF. CPP is the pressure that drives blood flow to the brain, and is calculated as the difference between

systemic ABP (MAP) and intracranial pressure (ICP). Unfortunately, ICP measurements often require invasive methods, which is impractical in the present study. In healthy individuals, ICP is described as being low and relatively stable; therefore, the contribution of ICP to CPP is much smaller relative to MAP. For this reason, and in accordance with relevant studies, ICP was assumed to have a negligible impact on CPP, and thus MAP was used to represent CPP when determining CVR_i (Liu *et al.*, 2005; Panerai *et al.*, 2005; Robertson *et al.*, 2010; Robertson, 2013).

Supine CVR for each participant was computed by taking the average MAP over the last 30 beats in that position and the measured aCBF value (**Equation (1.18)**). In addition, an index of CVR, CVR_i, for each position and each condition of cerebrovascular reactivity was computed by taking the average MAP and MFV over the last 30 beats. MFV was used to represent CBF when computing CVR_i under the assumption that the MCA diameter remained constant. The majority of research provides convincing evidence that MFV is a reliable index of CBF (Valdúeza *et al.*, 1997; Schreiber *et al.*, 2000). Some studies have confirmed that MCA diameter does not change in different conditions, such as during hyperventilation when P_{ET}CO₂ is decreased (hypocapnia) or when P_{ET}CO₂ increases (hypercapnia). In addition, others have shown that changes in MFV correlate with changes in CBF (Bishop *et al.*, 1986; Sorteberg *et al.*, 1989; Egashira *et al.*, 1994; Clark *et al.*, 1996). Therefore, supine CVR_i was calculated using **Equation (1.19)**, and supine CVR was calculated using aCBF in place of MFV. Seated CVR_i was calculated by first correcting MAP to the height level of the MCA (MAP_{MCA}) to account for the hydrostatic pressure gradient in head-up positions (**Equation (1.20)**).

$$\text{CVR (mmHg/mL/min)} = \text{MAP (mmHg)} / \text{aCBF (mL/min)} \quad (1.18)$$

$$\text{CVR}_i \text{ (mmHg/cm/s)} = \text{MAP (mmHg)} / \text{MFV (cm/s)} \quad (1.19)$$

$$\text{CVRI (mmHg/cm/s)} = \text{MAP}_{\text{MCA}} \text{ (mmHg)} / \text{MFV (cm/s)}, \text{ where} \quad (1.20)$$

$$\text{MAP}_{\text{MCA}} \text{ (mmHg)} = \text{MAP (mmHg)} - [0.78 \cdot \text{mmHg/cm} \cdot \text{distance from heart to TCD probe (cm)}]$$

4.5.11 Classification and Quantification of Physical Activity Level

Each participant's current physical activity level was assessed using both self-reported data and direct measures. Self-reported physical activity, derived from the health status questionnaire, was scored and entered into one of three categories: Inactive, active, or highly active lifestyle (Refer to **Appendix C** for the scoring guideline). Direct measures of physical activity were obtained from the SenseWear™ armband (SWA) (SenseWear™ Body Monitoring System, BodyMedia Inc., Pittsburgh PA, USA). Validation studies of SWA in different populations have been published (Fruin & Rankin, 2004; St-Onge *et al.*, 2007), including in older adults (Mackey *et al.*, 2011). This device is a two-axis accelerometer with multiple sensors that monitor heat flux, skin conductivity, and skin temperature (Jones *et al.*, 2011). These measures, in combination with the participants' demographic information (age, gender, height, weight, smoking status, and handedness), were processed in an algorithm carried out by the accompanying analysis software (The SenseWear™ Professional Software) to provide minute-by-minute estimates of energy expenditure (EE) during awake and sleep states and during different levels of physical activity. After each armband was returned, data were uploaded to a computer and exported into Microsoft Excel. The time period selected for data output was three days since previous studies have found that three-day scores provide an accurate estimate of EE in older adults (Hart *et al.*, 2011; Mackey *et al.*, 2011).

SWA was used to make quantitative estimates of physical activity, which included number of steps, energy expenditure from activities of daily living (AEE), and physical activity EE (PAEE), all expressed as daily averages. Total EE (TEE) is composed of basal metabolic rate

(BMR), thermal effects of food (TEF), and AEE (Insel *et al.*, 2003; Colbert *et al.*, 2011; Tanhoffer *et al.*, 2012). Therefore, AEE was calculated using **Equation (1.21)**, where TEE was obtained from the SWA (TEESW); BMR was represented by the sleeping metabolic rate, which was calculated by taking the mean of the average EE over the last 60 minutes prior to waking each morning (Heiermann *et al.*, 2011); and TEF was considered 10% of daily TEE (Vaughan *et al.*, 1991; Westerterp, 2004; Middleton *et al.*, 2011). PAEE was defined as the amount of energy expended by physical activities ≥ 3 METs (AEE_{sw}) over the amount of time spent exercising. AEE_{sw} was user defined by setting the METs threshold level on the SWA analysis software. PAEE was corrected for BMR; that is, the BMR was not considered part of EE from physical activity (**Equation (1.22)**).

$$AEE \text{ (kcal/day)} = TEE_{sw} \text{ (kcal/day)} - BMR \text{ (kcal/day)} - TEF \text{ (kcal/day)} , \quad (1.21)$$

where $TEF = 0.1 \cdot (TEE_{sw})$

$$PAEE \text{ (kcal/day)} = [AEE_{sw} \text{ (kcal/min)} - (BMR \text{ (kcal/min)} \cdot PA_{time} \text{ (min)})] \cdot \text{day}/60 \text{ min} , \quad (1.22)$$

where PA_{time} is the duration of physical activity

4.5.12 Reaction Time Tasks

sRT and cRT were analyzed using the E-DataAid software program. A cutoff range of <100 and >1000 ms were used to eliminate trials where participants seemed to be anticipating a response rather than reacting to the target or not be paying attention to the target. An overall average sRT and cRT were calculated over all the trials for the left and right index fingers. In addition, the coefficient of variance (defined as the standard deviation divided by its mean and expressed as a percentage) was also computed for each individual, and then a group average was determined to compare the relative intra-individual variability in reaction times between the groups.

5 Statistical Analysis

Normality probability and histograms were created for each continuous variable to determine whether the requirements of the normality assumption were satisfied for the measured variables used in the statistical tests outlined below. Non-normal data were either natural-log or square root transformed accordingly. Parametric tests were employed and all statistical tests were considered significant at a significance level of $p \leq 0.05$, while trends were reported at $0.05 \leq p \leq 0.10$. Statistical data analyses and graphs were completed using SigmaStat 12.5 (Systat Software Inc., Chicago, IL, USA). CA and SA group mean differences of continuous variables were compared using two-tailed t-tests and were presented as mean \pm standard deviation. Categorical variables (demographics, health status, medications, smoking and drinking status) were compared using z-tests and presented as frequency (%). Differences in baseline cardio- and cerebrovascular variables between ethnic groups prior to the cerebrovascular reactivity assessment were evaluated using unpaired t-test. The change (i.e., delta, Δ) in these variables from baseline condition to hypocapnia and to hypercapnia were also compared between groups using two-tailed t-test. Pearson product correlations and multivariate linear regression analyses were used to examine the association between indicators of arterial stiffness and aCBF. Ethnic status (0=CA, 1=SA) and an interaction term between ethnic status and arterial stiffness were added into the model as an independent variable to assess whether ethnic status modifies the association. If the interaction term was statistically significant ($p < 0.05$), then stratified (by ethnic group) linear regressions were performed to test how much the relationship between differed between CA and SA ethnic groups.

Secondary analyses included performing Pearson product correlations to explore relationships between measures of central arterial structure and function, cerebrovascular hemodynamics (MFV, CVR, CVRi, RI and PI), performance on cognitive tasks (sRTs and cRTs),

and measures of physical activity obtained from the Sensewear™ armband monitoring device in each ethnic group. Significant relationships observed in each ethnic group between measures of arterial structure and function and cerebrovascular hemodynamics were further explored in linear regression models to determine whether the relationships differed between the two ethnic groups.

6 Results

6.1 Participant Characteristics

The characteristics of the study participants, separated by ethnic group, were presented in **Table 1**. The mean age of the participants in each group was 71 years, ranging from 64 to 82 years. SA participants were all born outside of Canada (n=22), whereas over a quarter of CA group were immigrants (n=6). No significant differences were detected between the two ethnic groups with respect to weight, BMI, and hip circumference, although SA participants had larger WHR (p=0.003) and waist circumference (p=0.006) compared to CA participants. SA participants were also shorter (p=0.027) and had smaller body surface area (p=0.033) than CA participants. Both ethnic groups were comprised of a greater proportion of participants who were married; however, there were more divorced (p=0.028) and widowed participants (p=0.051) in CA group compared to SA group. Education level was significantly different between the groups, where CA participants had more years of education than SA participants (p<0.001). More SA participants were without a high school diploma (p=0.018), and very few had attained post-secondary education or higher (p=0.003) compared to CA group. All SA participants were non-smokers, whereas just under a half of the CA group were current smokers (p=0.006). In addition, alcohol consumption was greater in CA group than SA group (p<0.001).

No significant differences in medical conditions were noted; the prevalence of hypertension and hyperlipidemia were similar across the two groups. Two SA participants had reported to have diabetes. Furthermore, no differences were seen between CA and SA group for metabolic syndrome, which was characterized in accordance to the American Heart Association diagnostic criteria for metabolic syndrome (Grundy *et al.*, 2005). The prevalence of other relevant

cardiovascular risk factors, including family history of cardiovascular diseases, stroke and hypertension, were not significantly different between CA and SA group.

Several notable differences in blood markers were detected between the two ethnic groups (**Table 2**). Fasting glucose levels were lower in SA group compared to CA group ($p=0.031$), but conversely, SA group had significantly higher HbA_{1c} ($p<0.001$). These differences still remained significant even after excluding the two diabetics in SA group (Glucose: CA: 5.39 ± 0.48 mM ($n=22$), SA: 4.96 ± 0.72 mM ($n=20$), $p=0.027$; HbA_{1c}: CA: 5.29 ± 0.38 % ($n=22$), SA: 5.88 ± 0.60 % ($n=20$), $p<0.001$). Levels of HDL and LDL were also higher in SA group compared to CA group ($p=0.006$ and $p=0.013$, respectively). No differences in average hematocrit, TG, total cholesterol, TC/HDL ratio, and CRP inflammatory marker were detected between the groups. Levels of glycated albumin, insulin, and HOMA-IR were evaluated in SA group, but not previously in the CA group; therefore, no t-tests were performed for these markers. The self-reported use of prescription medications, specifically antihypertensive, antithrombotic and antiinflammatory drugs, was similar across the two groups (**Table 3**). The number of CA participants taking vitamin D supplement was significantly higher than SA group ($p=0.032$).

6.2 Physical Activity

Physical activity profiles for CA and SA group determined by subjective and objective methods were presented in **Table 4**. Three CA participants did not complete the questionnaire. SWA data were not available for 2 SA participants, and data collected over 2 consecutive days as opposed to three days were available in 2 CA participants and 7 SA participants due to technical difficulties that prevented complete data collection. However, the number of days did not significantly influence the data, given that no differences were observed for total energy

expenditure per day and daily number of steps between participants with two-day and three-day SWA data in each group (CA: $p=0.198$, $p=0.819$; SA: $p=0.231$, $p=0.979$, respectively, **APPENDIX D, Supplementary Table 1**). Therefore, participants who wore the armband for at least 48 hours and for at least 90% of that time were used to analyze physical activity. In addition, no differences in physical activity were found between participants whose SWA data collection period included the weekend and those whose data were collected on weekdays only (**APPENDIX D, Supplementary Table 2**). A significant difference in the level of physical activity was found between the study groups; more CA participants were highly active compared to SA participants ($p<0.001$). No CA participant was physically inactive; conversely, more than half of the participants in the SA group were inactive ($p<0.001$). Similarly, quantitative data obtained objectively from SWA revealed that the number of steps per day was significantly greater in CA group than SA group ($p=0.006$). Although differences in daily METs, AEE, PAEE, and the duration of physical activity were not detected, CA group generally engaged in more high-level intensity activities compared to SA group, and thus, tended to expend more energy (TEE) ($p=0.096$).

When data only from participants who had three complete days of SWA were analyzed (i.e., participants who wore the SWA for less than three consecutive days were removed from the analysis), the differences between CA group and SA group still remained, where the average daily steps were significantly lower in SA group (CA: 8052 ± 2651 ; SA: 5636 ± 2665 , $p=0.016$).

6.3 Cognitive Performance Outcomes

Natural log-transformed average reaction time scores for sRT and cRT tasks by ethnic group were presented in **Table 5**. Compared to CA participants, SA participants had significantly

slower sRT and cRT for both the left and right index fingers. Although the standard deviations appeared to be larger in SA group compared to CA group, the coefficient of variance was not different between the groups; in other words, the intra-variability in response time from trial-to-trial for each participant was similar for both groups. Pearson correlation analyses of the total study sample showed that faster log-transformed RTs were closely related to greater years of education (right index finger sRT: $r = -0.683$, $p < 0.001$; left index finger sRT: $r = -0.66$, $p < 0.001$; right index finger cRT: $r = -0.59$, $p < 0.001$; left index finger cRT: $r = -0.53$, $p < 0.001$). After controlling for years of education as a covariate in the analysis of variance, differences in RTs between the groups remained significant (Right sRT: $p < 0.001$; left sRT: $p = 0.0025$; right choice RT: $p = 0.0035$; left choice RT: $p < 0.001$).

6.4 Arterial Structure and Function and Cerebral Blood Flow

The measurements of arterial stiffness, structural and functional arterial properties, and cerebral blood flow by ethnic group are presented in **Table 6**. PP_{car} was significantly higher in SA participants compared to CA participants (CA: 46 ± 10 mmHg; SA: 59 ± 18 mmHg, $p = 0.005$), and a trend for faster baPWV was also observed in SA participants (CA: 11 ± 2 m/s; SA: 12 ± 2 m/s, $p = 0.080$). Mean carotid IMT tended to be lower in SA participants than in CA participants ($p = 0.073$), and maximum (or peak) IMT were significantly higher in CA participants than in SA participants ($p < 0.001$). Conversely, carotid compliance was significantly lower in SA participants ($p = 0.048$). In addition, SA participants appeared to have lower carotid distensibility compared to CA participants, although this did not reach statistical significance ($p = 0.109$).

A trend was observed for SA group to have higher right ICA (CA: 268 ± 76 mL/min; SA: 349 ± 153 mL/min, $p = 0.062$) and anterior CBF (aCBF) (CA: 536 ± 134 mL/min; SA: 660 ± 233

mL/min, $p=0.065$) compared to CA group, although not statistically significant. Higher blood flow velocity (MFV) through the right ICA observed among SA participants ($p=0.046$). The left ICA MFV also appeared to be higher in SA group, but it was not statistically significant ($p=0.140$). No differences were observed in the ICA diameters between the two groups. Furthermore, no within-group differences in MFV and diameter were observed between the left and right ICA.

6.5 Cerebrovascular Hemodynamic and Cardiovascular Variables in Supine and Seated Rest Positions

The cerebrovascular and cardiovascular variables in resting supine and seated postures are presented in **Table 7**. TCD data was not collected in 7 SA participants during supine and 6 SA participants during seated positions due to poor transparency of the ultrasonographic temporal bone windows. During the supine assessment, SFV in the MCA tended to be higher in SA group compared to CA group ($p=0.063$); this difference became statistically significant in the seated position ($p=0.030$). In addition, DFV, MFV, RI and PI in both supine and seated positions appeared to be elevated in SA group, but they did not achieve statistical significance. A trend for lower CVR was noted in SA group compared to CA group ($p=0.063$). Furthermore, SA group had lower DBP ($p=0.017$) and TPR ($p=0.035$), and higher Qi ($p=0.003$) in the supine position compared to CA group, but these differences were not evident in the seated position. No differences were found in HR, SBP and MAP between the two ethnic groups in either position. Of note, P_{ETCO_2} was significantly higher in SA group compared to CA group in both the supine (CA: 37 ± 3 mmHg; SA: 41 ± 3 mmHg, $p<0.001$) and seated positions (CA: 36 ± 4 mmHg; SA: 40 ± 4 mmHg, $p=0.005$).

6.6 Cerebrovascular Reactivity to Carbon Dioxide

Cerebrovascular reactivity to CO₂ evaluated under hypocapnic and hypercapnic conditions is presented in **Table 8**. The absolute and relative change in MFV per change in P_{ET}CO₂ were calculated in each condition. No differences in cerebrovascular reactivity to CO₂ between the two groups were found.

The cerebrovascular and cardiovascular responses to hypocapnia and hypercapnia for CA and SA group are illustrated in **Figure 2**. Both groups began the cerebrovascular reactivity assessment during baseline at similar MFV (CA: 50 ± 12 cm/s; SA: 57 ± 17 cm/s, p=0.130), CVRi (CA: 1.53 ± 0.53; SA: 1.44 ± 0.36, p=0.553), HR (CA: 66 ± 10 bpm; SA: 67 ± 11 bpm, p=0.814), MAP (CA: 100 ± 10 mmHg; SA: 104 ± 19 mmHg, p=0.396), and P_{ET}CO₂ (CA: 37 ± 4 mmHg; SA: 39 ± 5 mmHg, p=0.116). In hypocapnic condition, the response was similar in both groups; MAP, P_{ET}CO₂ and MFV decreased, whereas HR and CVRi increased from baseline. In hypercapnic condition, SA group exhibited a greater increase in P_{ET}CO₂ (CA: +9 ± 2 mmHg; SA: +12 ± 5 mmHg, p=0.011) and MFV (CA: +17 ± 7 cm/s; SA: +25 ± 13 cm/s, p=0.022) compared to CA group. The absolute change in HR (CA: +0.6 ± 3; SA: +1.8 ± 4), MAP (CA: +10 ± 8 mmHg; SA: +12 ± 6 mmHg) and CVRi (CA: -0.22 ± 0.22 mmHg/cm/s; SA: -0.26 ± 0.18 mmHg/cm/s) from baseline were not different between the two groups during hypercapnic conditions.

6.7 Relationships with Arterial Structure and Function and Cerebrovascular Hemodynamic Properties

A linear relationship between age and arterial stiffness (baPWV) was observed in both CA (r=0.47, p=0.029) and SA groups (r=0.44, p=0.045) (**Figure 3**); this relationship was not different between the groups (ethnicity*age interaction term: β=0.05, p=0.654, adjusted R²=0.20).

Furthermore, a linear trend was noted between age and reduced aCBF in the total sample ($r = -0.26$, $p = 0.098$, **Figure 4**), but this relationship was not seen when the groups were examined separately (CA: $r = -0.12$, $p = 0.626$; SA: $r = -0.34$, $p = 0.118$).

A linear regression analysis revealed that baPWV was not a significant predictor of the log-transformed aCBF in the study groups (CA: adjusted $R^2 = 0.11$, $\beta = 0.03$, $p = 0.086$; SA: adjusted $R^2 = 0.00$, $\beta = 0.01$, $p = 0.376$) (**Figure 5**). In addition, when the interaction term between ethnicity and baPWV was entered into the regression model for log-transformed aCBF as a function of baPWV, it was not significant; that is, the effect of ethnicity on this relationship was not significant (ethnicity*baPWV interaction term: $\beta = -0.02$, $p = 0.433$, adjusted $R^2 = 0.10$).

Higher P_{ETCO_2} levels during supine assessments were observed in SA participants in comparison to CA participants. P_{ETCO_2} was correlated with lower CVR ($r = -0.32$, $p = 0.048$) and higher aCBF ($r = 0.34$, $p = 0.033$) in the total study sample. A multiple linear regression analysis revealed an interaction effect between ethnic group and P_{ETCO_2} in predicting aCBF (adjusted $R^2 = 0.18$; ethnicity* P_{ETCO_2} interaction term: $\beta = 0.028$, $p = 0.031$), suggesting that high P_{ETCO_2} in SA group explained some of the difference in aCBF between the two groups.

Pearson correlation analyses between the central and peripheral arterial properties and cerebrovascular hemodynamics during resting supine position revealed several notable relationships in each ethnic group (**Table 9**). In CA group, baPWV was associated with lower resting supine MFV ($r = -0.74$, $p < 0.001$) and greater CVRi ($r = 0.75$, $p < 0.001$), which were not observed in SA group. In addition, baPWV was modestly correlated with reduced cerebrovascular reactivity to CO_2 under both hypercapnic ($r = -0.46$, $p = 0.03$) and hypocapnic conditions in CA group ($r = -0.55$, $p = 0.008$); these relationships were not seen in SA group. For SA group, lower central artery compliance (CC) and distensibility (DC) were associated with greater

cerebrovascular resistance (CC and CVR: $r = -0.41$, $p = 0.059$ (**Figure 6**); CC and CVR_i: $r = -0.57$, $p = 0.025$; log-transformed DC and CVR_i: $r = -0.58$, $p = 0.023$). No direct relationships between CC or DC and aCBF were observed. Although, a strong negative correlation was found between CVR and aCBF ($r = -0.96$, $p < 0.001$), thereby indicating an indirect link between central arterial stiffness and brain blood flow in SA group. A similar relationship between CVR and aCBF was observed in CA group ($r = -0.93$, $p < 0.001$), but SA group displayed a greater decline in aCBF with CVR (**Figure 7**). The regression slopes were $\beta = -2.02$, $p < 0.001$ for CA group and $\beta = -3.03$, $p < 0.001$ for SA group. Furthermore, no significant relationship between CC and CVR or DC and CVR was observed in CA group.

For both groups, CC and log-transformed DC were inversely related to PP_{car} , and a subsequent multiple regression analysis indicated that ethnicity significantly modified these association (ethnicity*log-transformed DC interaction term: $\beta = -38.78$, $p = 0.01$, adjusted $R^2 = 0.59$; ethnicity*CC interaction term: $\beta = -0.03$, $p = 0.02$, adjusted $R^2 = 0.53$). Specifically, SA participants with less compliant and distensible carotid arteries had significantly higher PP_{car} compared to CA participants (**Figure 8** and **Figure 9**).

In both groups, a link between carotid artery IMT and altered cerebral blood flow properties was observed, where increased IMT was associated with higher MCA PI during the supine rest assessment (**Table 9**, CA: $r = 0.46$, $p = 0.032$; SA: $r = 0.83$, $p < 0.001$). This relationship differed significantly between CA and SA groups; a multiple linear regression analysis revealed that ethnicity had a significant effect on the relationship between IMT and PI, where a unit increase in IMT was associated with a greater increase in PI in SA group compared to CA group (**Figure 10**). IMT was also associated with a greater RI in SA group ($r = 0.81$, $p < 0.001$, **Figure 11**); however, this was not seen in CA group. Similar relationships were observed between IMT and PI and RI

in the seated position in SA group (seated PI: $r=0.71$, $p=0.002$; seated RI: $r=0.68$, $p=0.004$), but these were not seen in CA group (seated PI: $r=0.21$, $p=0.359$; seated RI: $r=0.10$, $p=0.669$).

Additional correlation analyses were performed to explore the relationship between the indicators of arterial stiffness (that were statistically significant between the two groups) and anthropometric measurements and blood biomarkers in each ethnic group (**Table 10**). No significant relationships were observed in the CA group except for the correlation between baPWV and WHR ($r=0.44$, $p=0.04$). In SA group, height was correlated with baPWV ($r=0.46$, $p=0.036$), whereas BMI ($r=-0.44$, $p=0.05$) was inversely related to baPWV. In addition, a positive relationship was seen between height and CC in SA group ($r=0.44$, $p=0.04$). No significant relationships were detected between the blood markers and indicators of arterial stiffness in either ethnic group.

Relationships with the performance on cognitive tasks and structural and functional arterial properties and cerebrovascular hemodynamics were sought; however, no relevant correlations were found.

6.8 Relationships between Physical Activity and Arterial Structure and Function and Cerebrovascular Hemodynamic Properties

Correlations between SWA-measured physical activity and indices of arterial stiffness, arterial structural and functional properties, cerebrovascular variables, and clinically-relevant blood markers for each ethnic group are presented in **Table 11**. In the CA group, lower BMI was associated with greater daily AEE ($r=-0.43$, $p=0.045$), square root transformed PAEE ($r=-0.46$, $p=0.033$), and square root transformed duration of physical activity ($r=-0.54$, $p=0.009$). Similarly, in SA group, negative trends were observed between BMI and duration of physical activity ($r=-0.42$, $p=0.063$) and number of steps per day ($r=-0.41$, $p=0.069$). The same SWA variables in SA

group were significantly correlated with lower waist circumference ($r = -0.56, p = 0.01$ and $r = -0.48, p = 0.003$, respectively). Also, duration of PA and PAEE were associated with lower WHR in SA group ($r = -0.62, p = 0.003$ and $r = -0.57, p = 0.009$, respectively), whereas CA group showed a positive association between PAEE and WHR ($r = 0.42, p = 0.055$). Other unexpected results observed in CA group were that TEE, PAEE, and the duration of physical activity were associated with greater baPWV ($r = 0.43, p = 0.049$; $r = 0.50, p = 0.017$; $r = 0.50, p = 0.017$, respectively). Likewise, in SA group, average daily steps was associated with greater baPWV ($r = 0.45, p = 0.054$). No other relationships between arterial structural or functional measurements and SWA-measured physical activity were observed in the CA group. In SA group, positive linear trends between TEE and log-transformed DC and CC were observed (DC: $r = 0.40, p = 0.080$; CC: $r = 0.43, p = 0.058$), but no other significant relationships were detected.

In both ethnic groups, greater number of daily steps was correlated with greater aCBF (CA: $r = 0.52, p = 0.023$; SA: $r = 0.46, p = 0.043$, **Table 11**). AEE, PAEE, and duration of physical activity were also associated with greater aCBF in CA group ($r = 0.49, p = 0.03$; $r = 0.55, p = 0.016$; $p = 0.56, p = 0.012$; $p = 0.52, p = 0.023$, respectively); however, these relationships were not detected in the SA group. In addition, these variables in CA group were associated with lower MFV (AEE: $r = -0.43, p = 0.044$; PAEE: $r = -0.49, p = 0.019$; log-transformed duration of physical activity: $r = -0.51, p = 0.015$), and with lower CVR (AEE: $r = -0.51, p = 0.026$; PAEE: $r = -0.55, p = 0.015$; log-transformed duration of physical activity: $r = -0.55, p = 0.015$). In contrast, no significant relationships between SWA-measured physical activity and MFV were observed in SAs. Both groups showed a modest association between number of daily steps and lower CVR (CA: $r = -0.49, p = 0.033$; SA: $r = -0.44, p = 0.050$). No significant relationship between physical activity and PI was observed in either groups. SA group also did not show any relationship with RI. On the other hand,

in CA group, a negative association was observed between RI and AEE and daily steps ($r = -0.45$, $p = 0.038$; $r = -0.45$, $p = 0.038$, respectively). Inverse relationships between SWA-measured physical activity variables and cerebrovascular reactivity to CO_2 under hypercapnic and hypocapnic conditions were observed in CA group. Similarly, trends were observed under hypercapnic conditions in SA group, but in contrast to CA group, positive relationships between SWA-measured physical activity variables and cerebrovascular reactivity to hypocapnic conditions were noted in SA group. Relationships between blood markers and SWA data were also examined in CA and SA group. SWA-measurements of physical activity were correlated with lower HbA_{1c} levels in SA group (TEE: $r = -0.47$, $p = 0.028$; AEE: $r = -0.55$, $p = 0.013$; PAEE: $r = -0.45$, $p = 0.045$; duration of physical activity: $r = -0.46$, $p = 0.044$), and a trend was noted in CA group between duration of physical activity and lower HbA_{1c} ($r = -0.37$, $p = 0.091$). Also, in CA group, greater energy expenditure and duration of physical activity were associated with lower CRP levels (AEE: $r = -0.49$, $p = 0.021$; PAEE and duration of physical activity: $r = -0.55$, $p = 0.008$). A similar trend in lower CRP levels was noted in SA group with greater number of steps per day ($r = -0.42$, $p = 0.068$). Lower LDL levels were also correlated with greater energy expenditures in CA group (TEE: $r = -0.60$, $p = 0.003$; AEE: $r = -0.51$, $p = 0.016$; $r = -0.51$, $p = 0.017$; duration of physical activity: $r = -0.46$, $p = 0.031$), but these relationships were not significant in SA group.

Table 1. Participant Characteristics

Characteristics	CA (n=22)	SA (n=22)	p-value †
Demographics			
Age, years	71 ± 5	71 ± 5	---
Gender, n M/F	11/11	11/11	---
Immigrant, % (n)	27 (6)	100 (22)	<0.001
Body Measurements			
Height, cm	171 ± 10	164 ± 9	0.027
Weight, kg	79 ± 12	73 ± 13	0.138
BMI, kg/m ²	27 ± 4	27 ± 5	0.922
Waist Circumference, cm	94 ± 10	104 ± 1	0.006
Hip Circumference, cm	105 ± 10	108 ± 10	0.367
WHR ^a	0.90 ± 0.08	0.96 ± 0.04	0.003
Body Surface Area, m ²	1.90 ± 0.18	1.79 ± 0.17	0.033
Marital Status			
Married, % (n)	64 (14)	68 (15)	1.000
Divorced, % (n)	27 (6)	0 (0)	0.028
Widowed, % (n)	5 (1)	32 (7)	0.051
Highest Educational Attainment			
Less than High School Edu, % (n)	9 (2)	46 (10)	0.018
High School Edu, % (n)	14 (3)	27 (6)	0.455
Post-Secondary Edu or Higher, % (n)	77 (17)	27 (6)	0.003
Total Years of Education, years	16 ± 4	8 ± 6	<0.001
Other Health Risk Factors			
Current Smoker, % (n)	36 (8)	0 (0)	0.006
Frequent Alcohol Intake (current), % (n)	91 (20)	18 (4)	<0.001
Hypertension, % (n)	41 (9)	36 (8)	1.000
Hyperlipidemia, % (n)	23 (5)	41 (9)	0.332
Diabetes Mellitus, % (n)	0 (0)	9 (2)	0.469
Metabolic Syndrome, % (n)	27 (6)	18 (4)	0.719
Plaque, % (n)	5 (1)	36 (8)	0.025
Arrhythmia, % (n)	18 (4)	73 (16)	<0.001
Family History of CVD, % (n)	23 (5)	50 (11)	0.117
Family History of Stroke, % (n)	14 (3)	27 (6)	0.455
Family History of Hypertension % (n)	27 (6)	50 (11)	0.216

Data are presented as mean ± SD for continuous variables. Categorical variables are presented as proportions with the count shown in parentheses. BMI, body mass index; WHR, waist hip ratio; Edu, education; CVD, cardiovascular diseases.

† Significant difference between CA and SA group using two-tailed unpaired t-test for continuous variables and z-test for proportions. $p \leq 0.05$ was considered statistically significant difference (bolded values).

^a Variable failed to meet the assumption of equal variance for parametric statistics; however, the outcome of significance was the same when a non-parametric test was applied. For consistency, the parametric test results were shown in the table.

Table 2. Biochemical Characteristics

Blood Biomarkers	CA (n=22)	SA (n=22)	p-value†
Glucose, mM	5.4 ± 0.5	5.0 ± 0.7	0.031
HbA _{1c} , %	5.3 ± 0.4	5.9 ± 0.6	<0.001
Average Hematocrit, %	42 ± 3*	43 ± 3	0.505
TG, mM	1.4 ± 0.8	1.4 ± 0.4	0.912
Total Cholesterol, mM	5.1 ± 1.1	5.5 ± 1.0	0.198
HDL, mM	1.3 ± 0.3	1.6 ± 0.3	0.006
LDL, mM	3.1 ± 0.9	3.9 ± 1.0	0.013
TC/HDL	3.9 ± 0.9	3.5 ± 0.9	0.128
CRP, mg/L §	2.0 ± 2.2	3.9 ± 5.8	0.152
Glycated Albumin, ng/mL §	---	53 ± 40	---
Insulin, µU/mL	---	10.8 ± 5.5	---
HOMA-IR index, mM/ µU/mL	---	2.4 ± 1.4	---

Data are presented as mean ± SD. HbA_{1c}, glycosylated hemoglobin; TG, triglycerides; HDL, high-density lipoproteins; LDL, low-density lipoproteins; TC/HDL, total cholesterol to high-density lipoprotein ratio; CRP, C-reactive protein; HOMA-IR: homeostasis model assessment of insulin resistance. The sample size (n) for each measure was indicated in the table.

† Two-tailed unpaired t-test comparing CA group and SA group; $p \leq 0.05$ was considered statistically significant difference (bolded values).

§ CRP and glycated albumin were natural log transformed.

* Sample size was n=21.

Table 3. Participant Medications

Characteristics	CA (n=22)	SA (n=22)	p-value †
Medications			
Antihypertensive, % (n)	41 (9)	41 (9)	1.000
ACEi, % (n)	14 (3)	9 (2)	1.000
ARB, % (n)	18 (4)	9 (2)	0.660
CCB, % (n)	5 (1)	23 (5)	0.188
Beta-blocker, % (n)	5 (1)	18 (4)	0.342
ASA, % (n)	18 (4)	23 (5)	1.000
Antithrombotic, % (n)	14 (3)	18 (4)	1.000
Statin, % (n)	32 (7)	46 (10)	0.536
Anti-diabetic, % (n)	0 (0)	9 (2)	0.469
Supplements			
Calcium, % (n)	46 (10)	27 (6)	0.347
Vitamin D, % (n)	59 (13)	23 (5)	0.032

Data are presented as proportions with the count shown in parentheses. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ASA, acetylsalicylic acid.

† z-test comparing proportions between CA group and SA group; $p \leq 0.05$ was considered statistically significant difference (bolded value).

Table 4. Qualitative and Quantitative Measures of Physical Activity

Physical Activity	CA (n=18)	SA (n=22)	p-value†
Self-Reported			
Inactive Lifestyle, % (n)	0 (0)	59 (13)	<0.001
Active Lifestyle, % (n)	33 (6)	36 (8)	0.894
Highly Active Lifestyle, % (n)	67 (12)	5 (1)	<0.001
	CA (n=22)	SA (n=20)	
SenseWear™ Armband-Measurements			
Daily METs	1.3 ± 0.2	1.3 ± 0.3	0.854
TEE, kcal/day	2324 ± 398	2106 ± 430	0.096
AEE, kcal/day	553 ± 271	498 ± 351	0.574
PAEE, kcal/day §	359 ± 231	300 ± 354	0.282
Duration of PA, hour/day §	1.3 ± 0.8	1.3 ± 1.3	0.538
Steps, count/day	8095 ± 2719	5623 ± 2730	0.006

Data are presented as mean ± SD for continuous variables. Categorical variables are presented as proportions with the count shown in parentheses. METs, metabolic equivalent units; TEE, total energy expenditure; AEE, activity-related energy expenditure; PAEE, physical activity-related energy expenditure; PA, physical activity.

† Statistical significance from CA using two-tailed unpaired t-test for continuous variables and z-test for proportions. $p \leq 0.05$ was considered statistically significant difference (bolded values), and a statistical trend towards significance was defined by $0.05 \leq p \leq 0.10$.

§ Duration of daily PA and PAEE were square root transformed.

Table 5. Participant Performance on Simple and Choice Reaction Time Cognitive Tasks

Reaction Time Tasks	CA (n=18)	SA (n=22)	p-value†
Log10 Right Simple RT, ms ^a	2.45 ± 0.04	2.69 ± 0.15	<0.001
CV _{log10 Right Simple RT} , %	0.02 ± 0.01	0.02 ± 0.01	0.815
Log10 Left Simple RT, ms ^a	2.47 ± 0.06	2.69 ± 0.16	<0.001
CV _{log10 Left Simple RT} , %	0.01 ± 0.01	0.02 ± 0.01	0.555
Log10 Right Choice RT, ms	2.70 ± 0.06	2.82 ± 0.09	<0.001
CV _{log10 Right Choice RT} , %	0.012 ± 0.006	0.013 ± 0.008	0.846
Log10 Left Choice RT, ms	2.71 ± 0.05	2.81 ± 0.10	<0.001
CV _{log10 Left Choice RT} , %	0.011 ± 0.005	0.021 ± 0.046	0.293

Data are presented as log transformed mean ± SD. Transformation was made to normalize the data. RT, reaction time; ms, milliseconds; CV, coefficient of variance.

† Two-tailed unpaired t-test comparing CA group and SA group; $p \leq 0.05$ was considered statistically significant difference (bolded values).

^a Variables failed to meet the assumption of equal variance for parametric statistics; however, non-parametric statistics gave the same p-value. For consistency, the parametric test results were shown in the table.

Table 6. Measurements of Arterial Structure and Function and Cerebral Blood Flow in the Supine Rest Position

Measurements	CA	SA	p-value†
Arterial Structure and Function			
PP _{car} , mmHg ^a	46 ± 10***	59 ± 18	0.005
baPWV, m/s	11 ± 2	12 ± 2***	0.080
Mean IMT, mm	0.74 ± 0.14	0.68 ± 0.09	0.073
Maximum IMT, mm ^a	0.85 ± 0.17	0.68 ± 0.07	<0.001
DC, 10 ⁻³ /kPa [§]	29 ± 16***	22 ± 11	0.109
CC, mm ² /MPa	789 ± 323***	601 ± 282	0.048
ICA Diameter and Velocity			
<i>Right ICA</i>			
Diameter, cm [§]	0.53 ± 0.12**	0.52 ± 0.09	0.913
MFV, cm/s [§]	22 ± 7**	27 ± 9	0.046
<i>Left ICA</i>			
Diameter, cm [§]	0.50 ± 0.08***	0.50 ± 0.08	0.803
MFV, cm/s	23 ± 6**	26 ± 6	0.140
Supine CBF			
Right ICA, mL/min [§]	268 ± 76**	349 ± 153	0.062
Left ICA, mL/min [§]	265 ± 91**	311 ± 130	0.204
Anterior, mL/min [§]	536 ± 134*	660 ± 233	0.065

Data are presented as mean ± SD. baPWV, brachial-ankle pulse wave velocity; PP_{car}, carotid pulse pressure; IMT, intima-media thickness; DC, distensibility coefficient; CC, compliance coefficient; ICA, internal carotid artery; MFV, mean flow velocity. The sample size (n) for each measure was indicated in the table. Anterior CBF refers to the sum of the right and left ICA blood flow.

† Two-tailed unpaired t-test comparing CA group and SA group; p ≤ 0.05 was considered statistically significant difference (bolded values), and a statistical trend towards significance was defined by 0.05 ≤ p ≤ 0.10.

^a Variables failed to meet the assumption of equal variance for parametric statistics; however, the outcome of significance was the same when a non-parametric test was applied. For consistency, the results of the parametric test were presented in the table.

[§] DC, right ICA diameter, right ICA MFV, right ICA CBF, left ICA diameter, left ICA CBF, and anterior CBF were natural log transformed.

* Sample size was n=19, ** n=20, and *** n=21.

Table 7. Cerebrovascular and Cardiovascular Variables in Supine and Seated Rest Positions

TCD Measurements	Supine			Seated		
	CA (n=22)	SA (n=15)	p- value†	CA (n=22)	SA (n=16)	p- value†
SFV, cm/s	79 ± 18	93 ± 26	0.063	76 ± 17	91 ± 22	0.030
DFV, cm/s	34 ± 8	39 ± 15	0.259	31 ± 7	35 ± 11	0.286
MFV, cm/s	53 ± 12	61 ± 19	0.145	50 ± 11	57 ± 15	0.091
CVR, mmHg/mL/min	0.19 ± 0.05*	0.16 ± 0.05	0.063	0.19 ± 0.06*	0.16 ± 0.05	0.075
CVRi, mmHg/cm/s	1.87 ± 0.51	1.64 ± 0.43	0.161	1.38 ± 0.43	1.29 ± 0.35	0.520
RI	0.58 ± 0.08	0.59 ± 0.06	0.654	0.61 ± 0.11	0.62 ± 0.06	0.656
PI	0.83 ± 0.13	0.91 ± 0.16	0.085	0.92 ± 0.15	1.00 ± 0.16	0.107
Cardiovascular Variables	CA (n=22)	SA (n=22)		CA (n=22)	SA (n=22)	
HR, bpm	64 ± 10	67 ± 10	0.336	64 ± 9	66 ± 12	0.516
SBP, mmHg	133 ± 11	139 ± 18	0.226	134 ± 13	138 ± 20	0.524
DBP, mmHg	74 ± 7	68 ± 9	0.017	73 ± 10	69 ± 10	0.205
MAP, mmHg	94 ± 8	94 ± 11	0.981	94 ± 11	94 ± 14	0.968
TPR, mmHg/L/min	18 ± 5**	15 ± 5	0.035	19 ± 7**	17 ± 5	0.264
Qi, L/min/m ²	3.0 ± 0.8**	3.8 ± 0.8	0.003	3.0 ± 0.8**	3.4 ± 0.7	0.093
P _{ET} CO ₂ , mmHg	37 ± 3	41 ± 3**	<0.001	36 ± 4	40 ± 4**	0.005

Data are presented as mean ± SD. SFV, systolic flow velocity; DFV, diastolic flow velocity; MFV, mean flow velocity; CVR, cerebrovascular resistance (MAP/aCBF); CVRi, cerebrovascular resistance index (MAP/MFV); RI, resistive index; PI, pulsatility index; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; TPR, total peripheral resistance; Qi, cardiac index; P_{ET}CO₂, end-tidal carbon dioxide. The sample size (n) for the measurements were indicated in the table.

† Two-tailed unpaired t-test comparing SA group and CA group. $p \leq 0.05$ was considered statistically significant difference (bolded values), and $0.05 \leq p \leq 0.10$ was considered as statistical trends towards significance.

* Sample size was n=19 and ** n=21.

Table 8. Cerebrovascular Reactivity to Carbon Dioxide under Hypercapnic and Hypocapnic Conditions

Cerebrovascular Reactivity	CA (n=22)	SA (n=16)	p-value†
HICO ₂ , $\Delta\text{cm/s}/\Delta\text{mmHg}$ §	1.8 ± 0.7	2.4 ± 1.8	0.330
LOWCO ₂ , $\Delta\text{cm/s}/\Delta\text{mmHg}$	1.5 ± 0.5	1.4 ± 0.8	0.466
HICO ₂ , $\%/ \Delta\text{mmHg}$ §	3.6 ± 1.2	4.1 ± 2.4	0.658
LOWCO ₂ , $\%/ \Delta\text{mmHg}$	4.1 ± 1.5	3.2 ± 1.7	0.096

Data are presented as mean ± SD. HICO₂, hypercapnia; LOWCO₂, hypocapnia.

† Two-tailed unpaired t-test comparing SA group and CA group; $p \leq 0.05$ was considered statistically significant difference, and $0.05 \leq p \leq 0.10$ was considered as statistical trends towards significance.

§ Absolute ($\Delta\text{cm/s}/\Delta\text{mmHg}$) and relative ($\%/ \Delta\text{mmHg}$) HICO₂ cerebrovascular reactivity were natural log transformed.

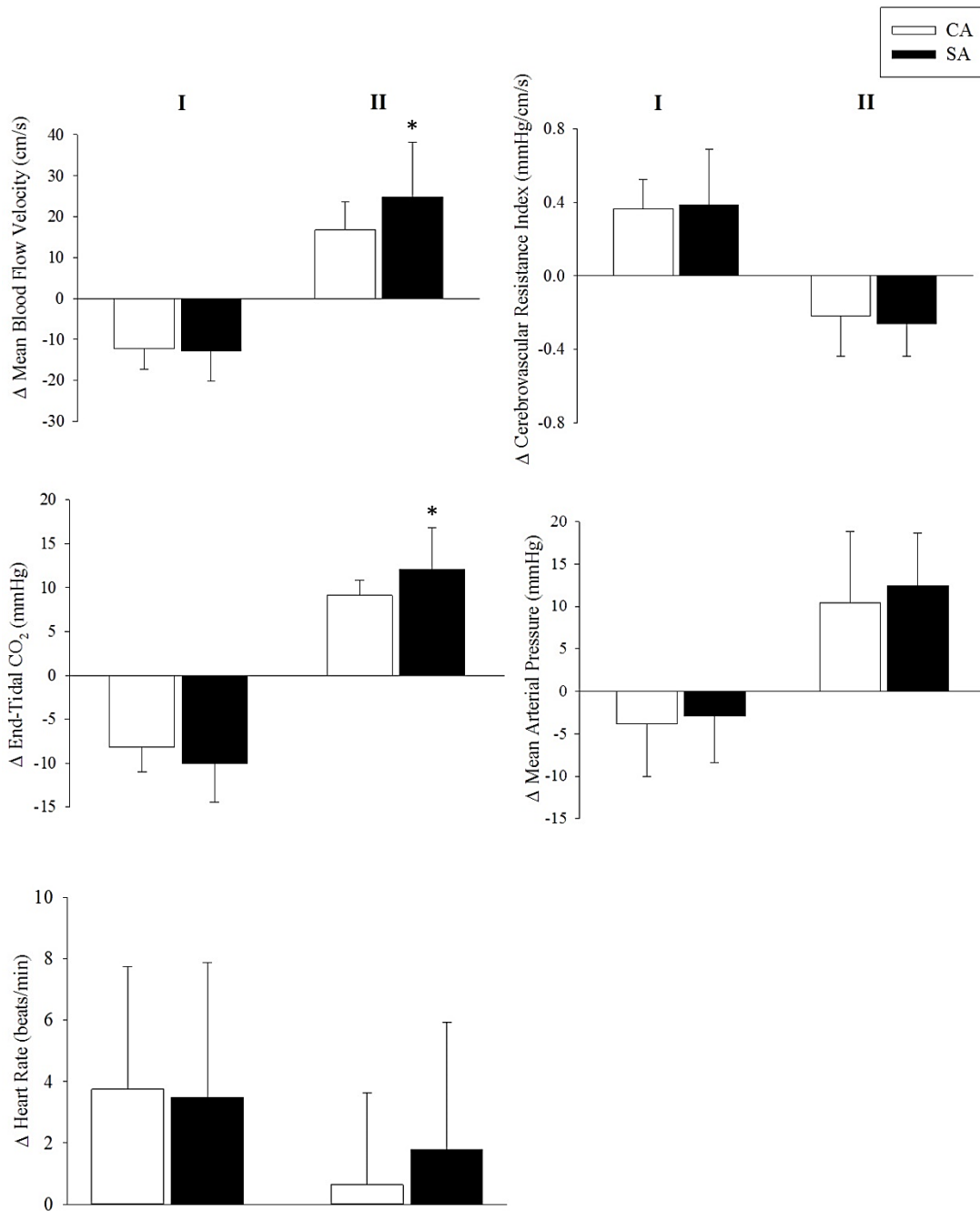


Figure 2. Cardiovascular and Cerebrovascular Responses to Hypocapnia and Hypercapnia in White Caucasian and South Asian Older Adults

Absolute (delta) change from **I**: baseline to hypocapnia and **II**: baseline to hypercapnia. Open bars represented CA group and closed bars represented SA group. * indicates significant difference between groups at $p \leq 0.05$.

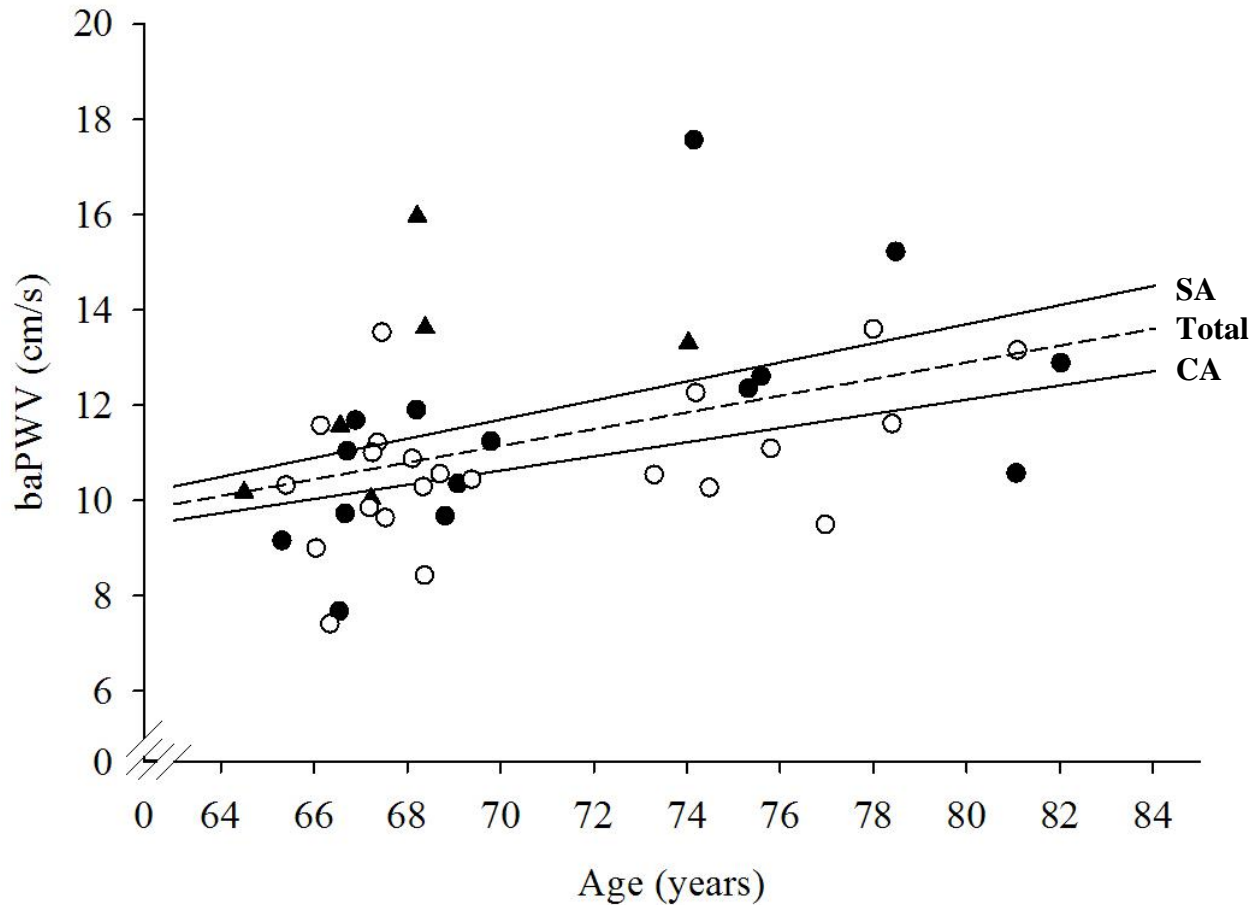


Figure 3. Age-Associated Increase in Arterial Stiffness in CA and SA Older Adults

Brachial-ankle pulse wave velocity (baPWV) was plotted against age in CA group (○) and SA group (●). ▲ represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. Age-related increase in baPWV was observed in CA group ($r=0.47$, $p=0.029$, $n=22$) and SA group ($r=0.44$, $p=0.045$, $n=21$). The middle dashed line represented the relationship for the total sample ($r=0.43$, $p=0.004$). Ethnicity did not have a significant effect on this relationship (adjusted $R^2=0.20$, $\beta=0.05$, $p=0.654$).

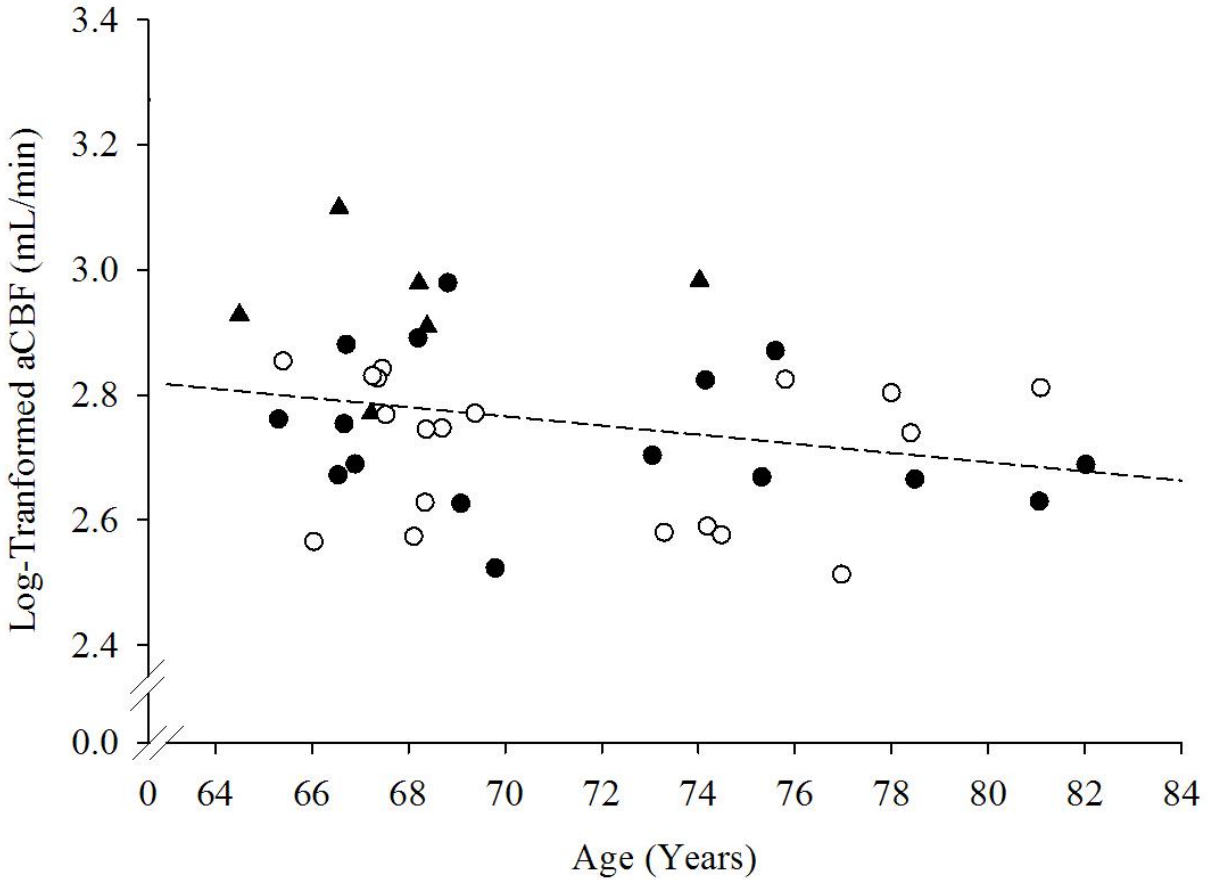


Figure 4. Relationship between Age and Anterior Cerebral Blood Flow in SA and CA Older Adults

Log-transformed anterior cerebral blood flow (aCBF) was plotted against age in CA group (○), SA group (●). ▲ represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A linear trend was noted in the total study sample (dashed line: $r = -0.26$, $p = 0.098$), but no relationship found when ethnic groups were analyzed separately (CA: $r = -0.12$, $p = 0.626$, $n = 19$; SA: $r = -0.34$, $p = 0.118$, $n = 22$).

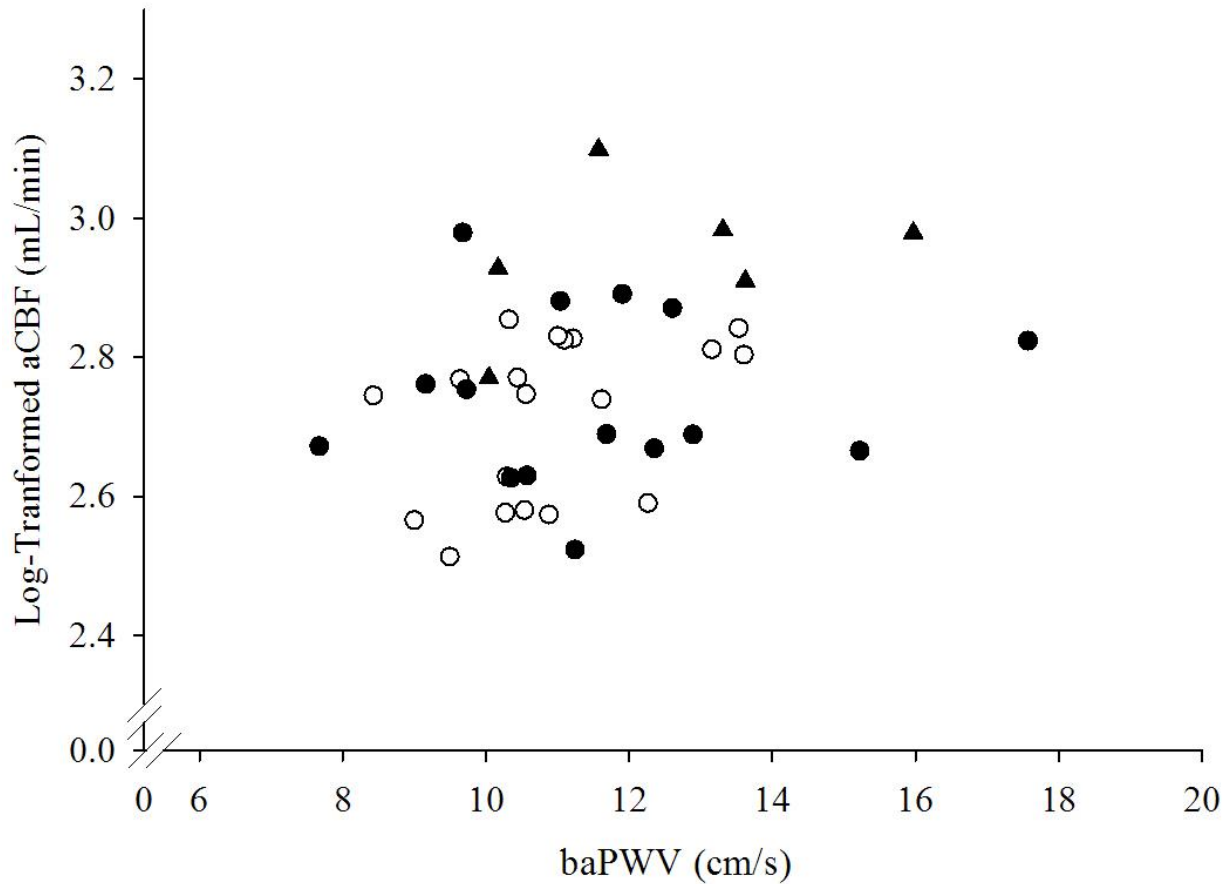


Figure 5. Relationship between Arterial Stiffness and Anterior Cerebral Blood Flow in CA and SA Older Adults

Log-transformed anterior cerebral blood flow (aCBF) was plotted against brachial-ankle pulse wave velocity (baPWV) in CA group (○) and SA group (●). ▲ represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. Middle dashed line represented the total study sample. No significant relationship was found in either ethnic group. Ethnicity had no effect on this relationship (adjusted $R^2=0.10$, $\beta= -0.02$, $p= 0.433$).

Table 9. Correlations between Arterial Structure and Function and Cerebrovascular Properties in CA and SA Older Adults

	CA					SA				
	baPWV	PP _{car}	DC [§]	CC	IMT	baPWV	PP _{car}	DC [§]	CC	IMT
aCBF[§]	0.40	0.23	-0.09	-0.26	-0.30	0.20	0.07	0.18	0.31	-0.25
MFV	-0.74**	0.14	0.11	0.04	0.28	-0.04	0.05	0.28	0.30	-0.42
CVRi	0.75**	-0.10	-0.17	-0.21	-0.25	0.21	0.28	-0.58*	-0.57*	0.39
CVR	-0.33	-0.20	0.07	0.13	0.37	-0.09	0.11	-0.30	-0.41*	0.30
PI	0.33	0.057	0.01	0.07	0.46*	0.14	0.22	-0.20	-0.22	0.83**
RI	0.21	0.28	-0.04	0.11	-0.07	0.12	0.15	-0.13	-0.17	0.81**
HICO₂, Δcm/s/mmHg[§]	-0.46*	0.07	0.15	0.09	0.35	-0.37	-0.10	0.18	0.15	-0.04
LOCO₂, Δcm/s/mmHg	-0.55*	-0.07	0.15	0.09	0.20	-0.03	0.21	-0.21	-0.25	0.24

Data are presented as the Pearson product coefficient. baPWV, brachial-ankle pulse wave velocity; PP_{car}, carotid pulse pressure; DC, distensibility coefficient; CC, compliance coefficient; IMT, intima-media thickness; aCBF, anterior cerebral blood flow; MFV, mean flow velocity; CVRi, cerebrovascular resistance index (MAP/MFV); CVR, cerebrovascular resistance (MAP/aCBF); PI, pulsatility index; RI, resistive index; HICO₂, cerebrovascular reactivity to hypercapnia; LOWCO₂, cerebrovascular reactivity to hypocapnia.

* p < 0.05 and ** p < 0.001 were considered statistically significant.

§ DC, aCBF and HICO₂ were natural log transformed.

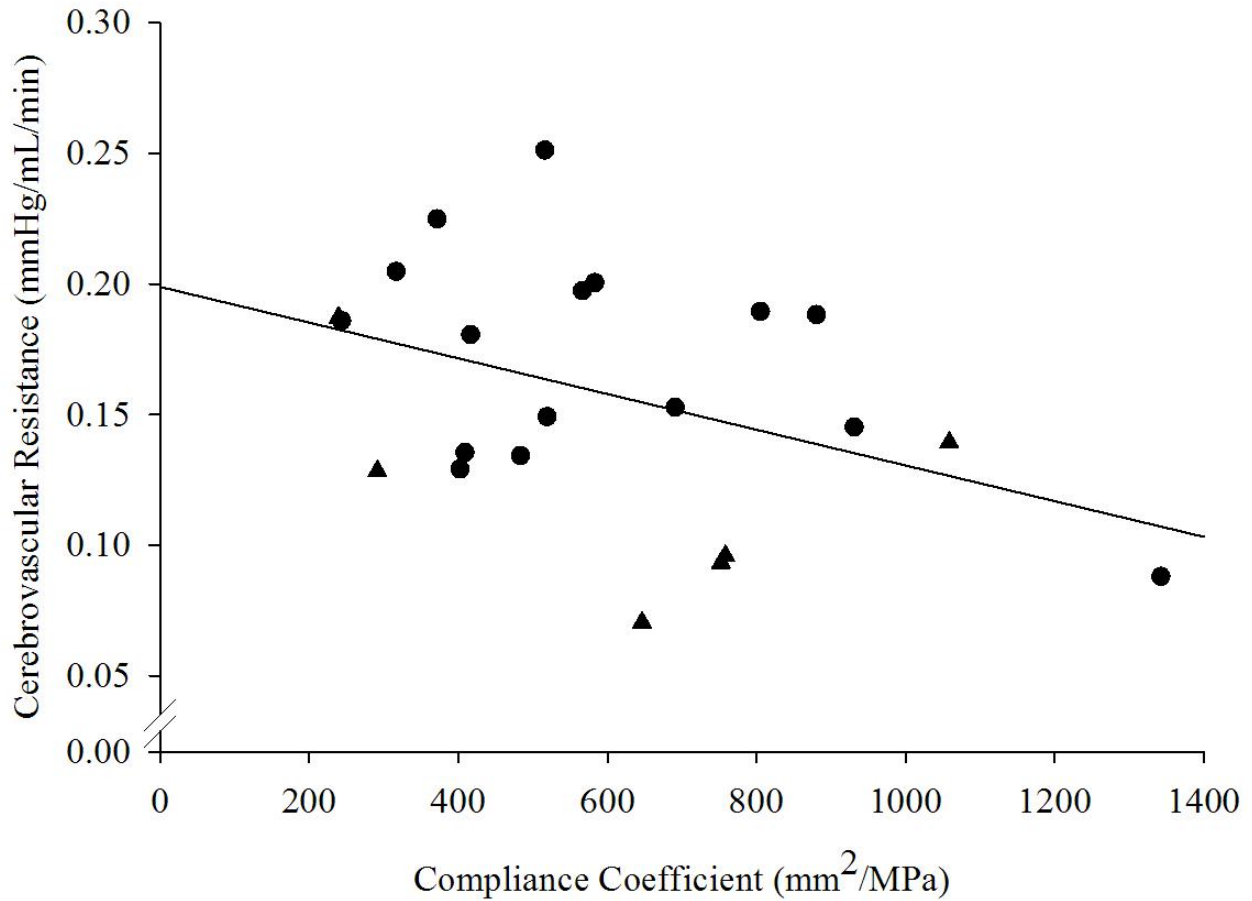


Figure 6. Relationship between Carotid Artery Compliance and Cerebrovascular Resistance in SA Older Adults

Cerebrovascular resistance (CVR=MAP/aCBF) was plotted against carotid compliance coefficient in SA group (●). ▲ represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A significant relationship was found in SA group ($r = -0.41$, $p = 0.059$, $n = 22$).

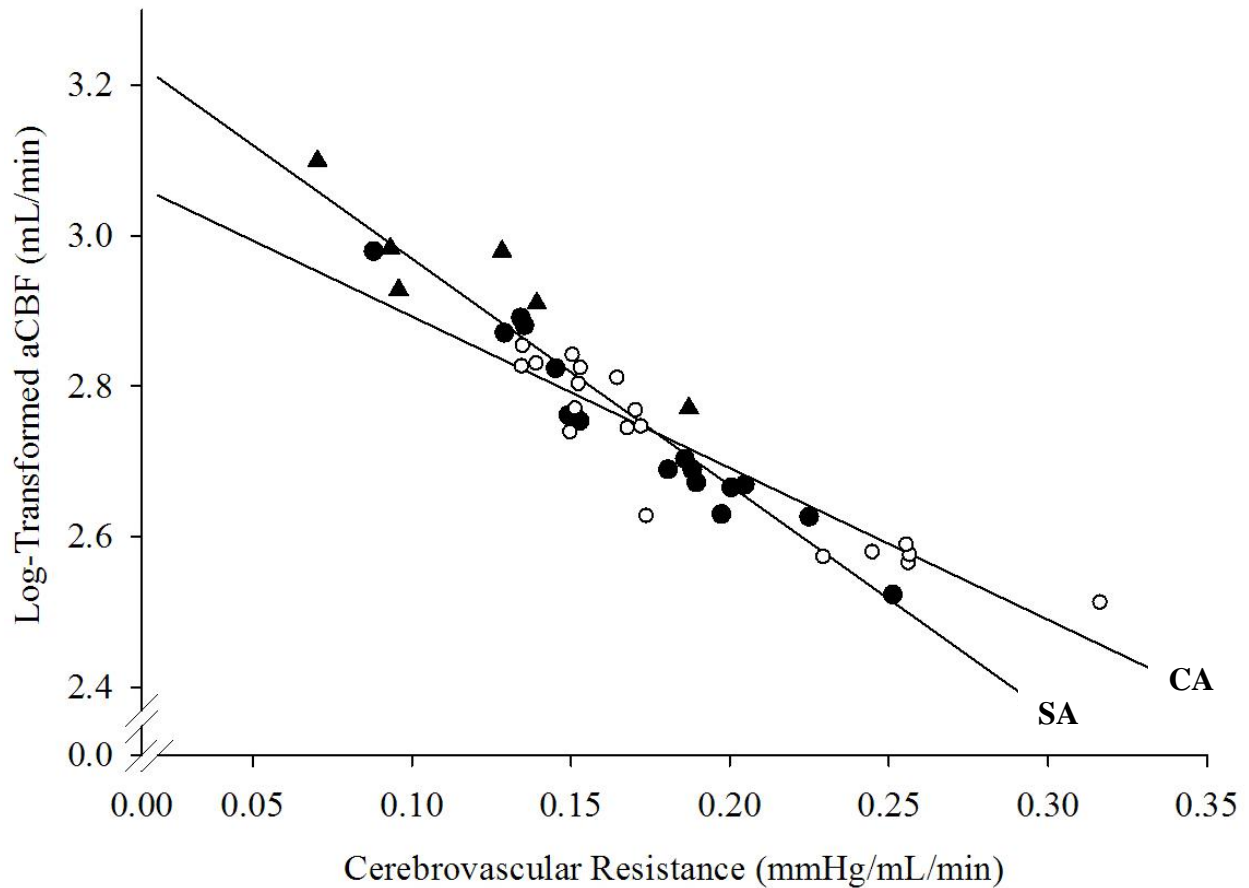


Figure 7. Relationship between Cerebral Blood Flow and Cerebrovascular Resistance in SA Older Adults

Cerebral blood flow (aCBF) was plotted against cerebrovascular resistance ($CVR=MAP/aCBF$) in CA group (\circ) and SA group (\bullet). \blacktriangle represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A significant relationship was found in CA group ($r= -0.93$, $p<0.001$, $n=19$) and SA group ($r= -0.96$, $p<0.001$, $n=22$). Ethnicity had a significant effect on this relationship (adjusted $R^2=0.90$, $\beta= -1.00$, $p<0.001$).

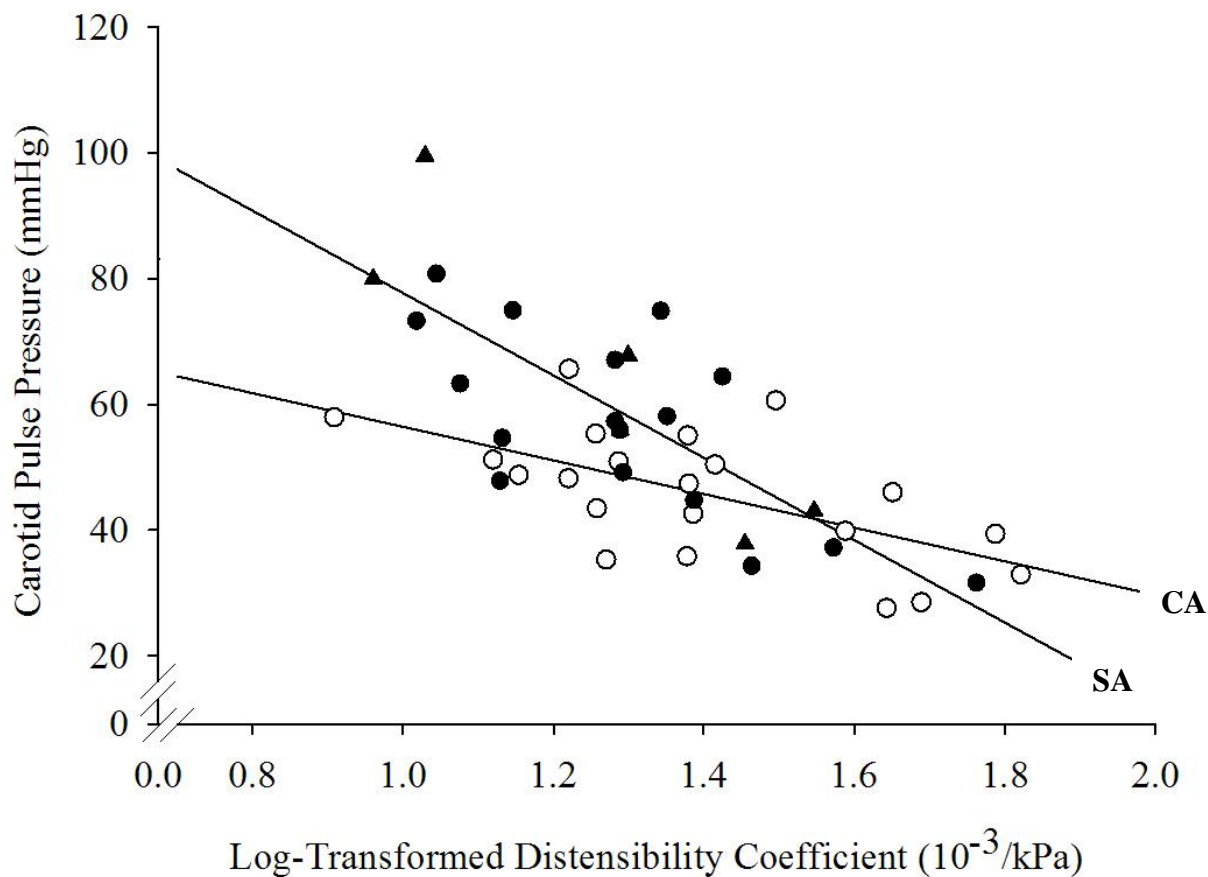


Figure 8. Relationship between Carotid Artery Distensibility and Pulse Pressure in CA and SA Older Adults

Carotid artery pulse pressure, PP_{car} , was plotted against log-transformed carotid distensibility coefficient in CA group (\circ) and SA group (\bullet). \blacktriangle represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A significant relationship was found in CA group ($r = -0.61$, $p = 0.004$, $n = 21$) and SA group ($r = -0.77$, $p < 0.001$, $n = 22$). Ethnicity had a significant effect on this relationship (adjusted $R^2 = 0.59$, $\beta = -38.8$, $p = 0.01$).

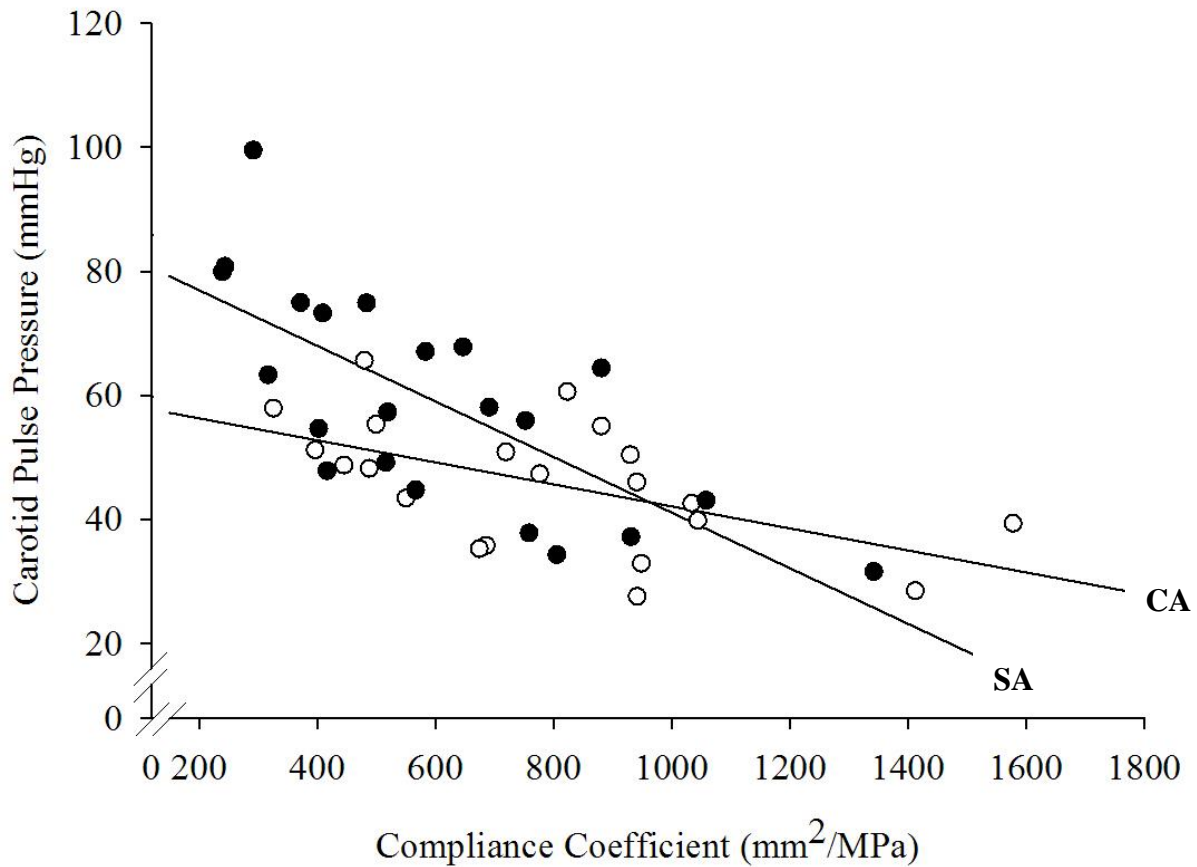


Figure 9. Relationship between Carotid Artery Compliance and Pulse Pressure in CA and SA Older Adults

Carotid artery pulse pressure, PP_{car} , was plotted against carotid compliance coefficient in CA group (\circ) and SA group (\bullet). \blacktriangle represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A significant relationship was found in CA group ($r = -0.56$, $p = 0.009$, $n = 21$) and SA group ($r = -0.72$, $p < 0.001$, $n = 22$). Ethnicity had a significant effect on this relationship (adjusted $R^2 = 0.53$, $\beta = -0.03$, $p = 0.02$).

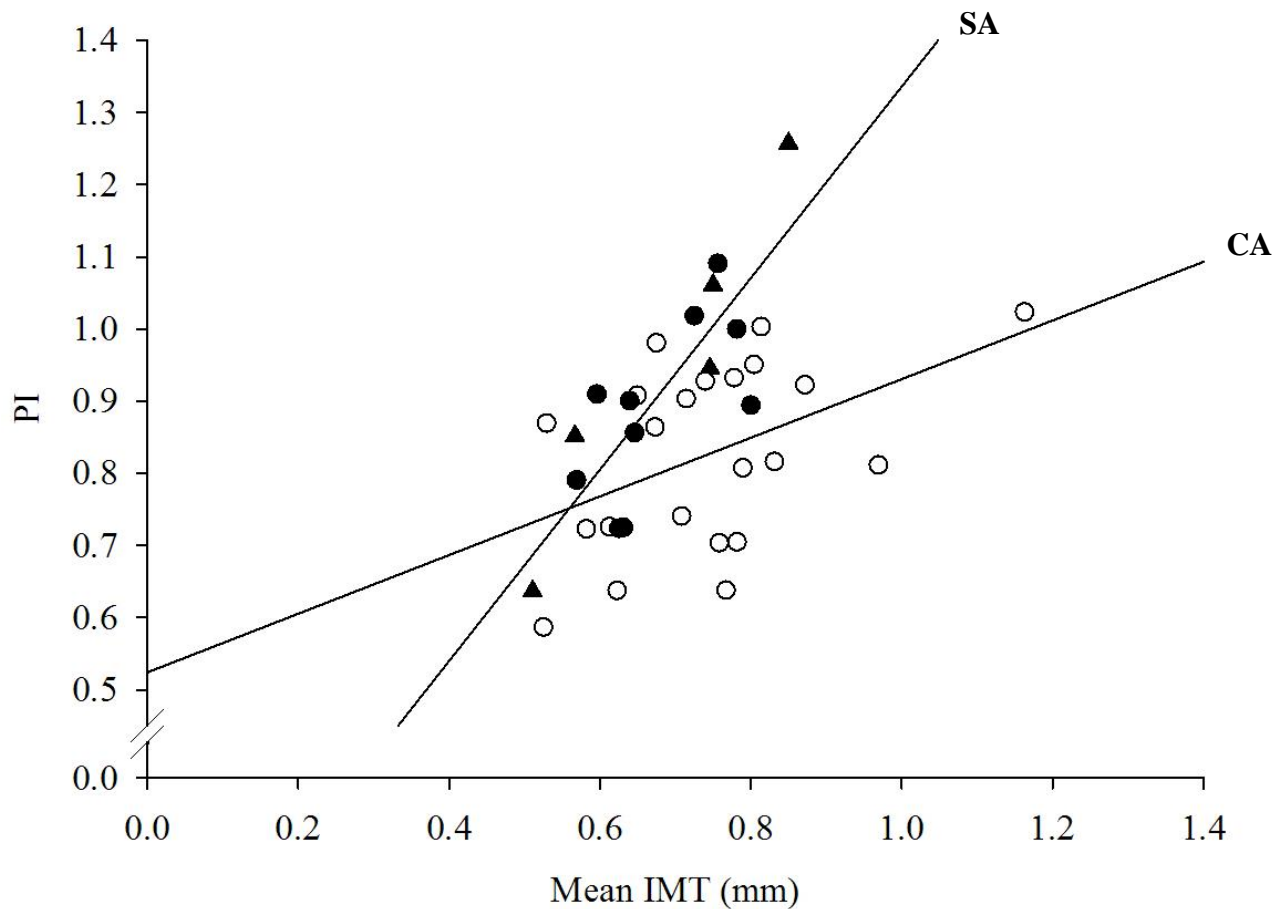


Figure 10. Relationship between Common Carotid Artery Intima-Media Thickness and Middle Cerebral Artery Pulsatility Index in CA and SA Older Adults

Carotid artery intima-media thickness, IMT, was plotted against pulsatility index (in supine), PI, at the middle cerebral artery in CA group (○) and SA group (●). ▲ represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A significant relationship was found in CA group ($r=0.46$, $p=0.032$, $n=22$) and SA group ($r=0.83$, $p<0.001$, $n=15$). Ethnicity had a significant effect on this relationship (adjusted $R^2=0.45$, $\beta=0.92$, $p=0.009$).

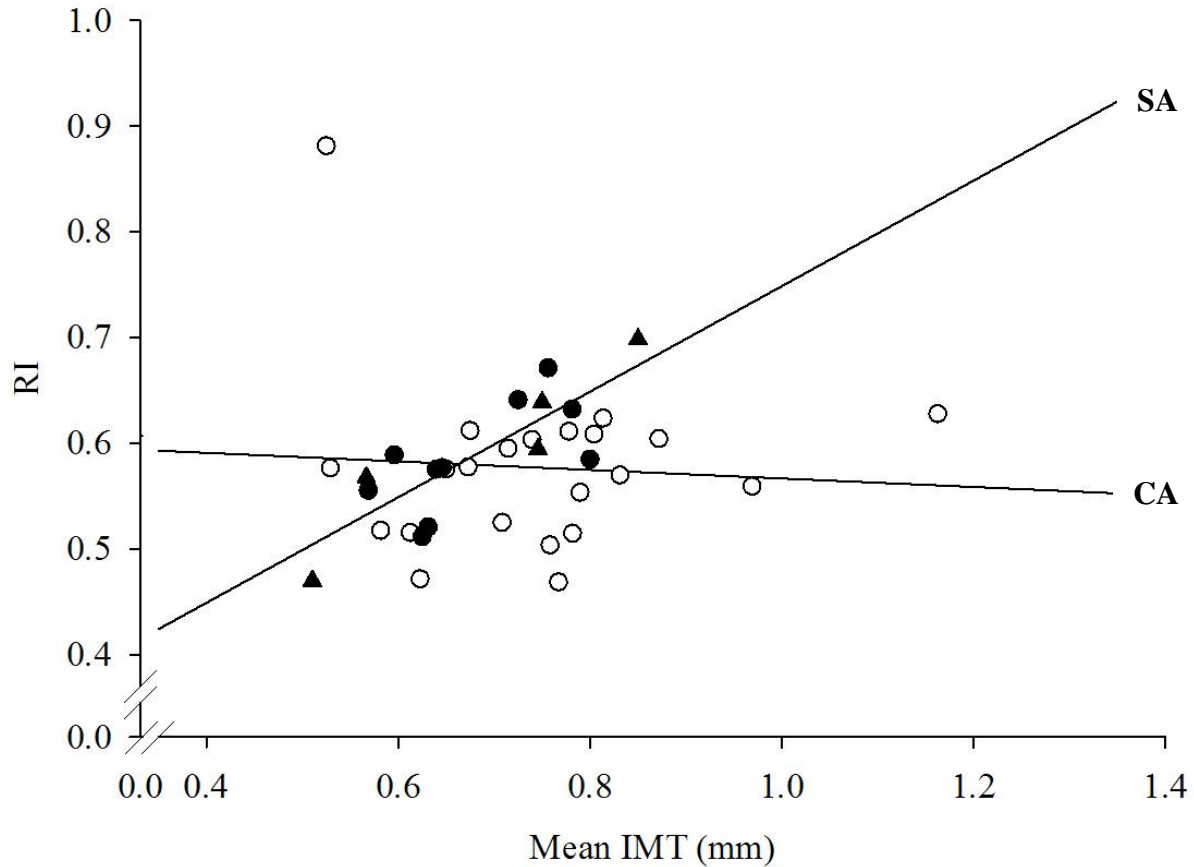


Figure 11. Relationship between Common Carotid Artery Intima-Media Thickness and Middle Cerebral Artery Resistive Index in CA and SA Older Adults

Carotid artery intima-media thickness, IMT, was plotted against resistive index (in supine), RI, at the middle cerebral artery in CA group (○) and SA group (●). ▲ represents participants in SA group who were identified during the study to have untreated hypertension or signs of ipsilateral ICA stenosis. A significant relationship was found in SA group ($r=0.81$, $p<0.001$, $n=15$) but not in CA group ($r=-0.07$, $p=0.76$, $n=22$). Ethnicity had a significant effect on this relationship (adjusted $R^2=0.11$, $\beta=0.54$, $p=0.017$).

Table 10. Correlations between Arterial Stiffness, Anthropometric Measurements and Blood Biomarkers in CA and SA Older Adults

	CA			SA		
	baPWV	PP _{car}	CC	baPWV	PP _{car}	CC
Anthropometric Measurements						
Height	0.35	0.15	0.184	0.46*	-0.21	0.44*
BMI	-0.25	-0.139	0.09	-0.44*	-0.25	0.16
Waist	0.26	-0.004	-0.10	-0.37	-0.16	0.05
WHR	0.44*	0.001	-0.27	0.02	0.07	-0.15
Blood Biomarkers						
Glucose	-0.16	-0.08	0.14	0.012	-0.16	-0.01
HbA1c	-0.06	0.10	-0.24	-0.15	0.22	-0.24
CRP §	-0.22	0.05	-0.37	0.17	0.14	-0.06
TCHOL	-0.29	-0.01	-0.16	-0.18	0.16	0.03
HDL	-0.14	-0.03	0.02	0.06	-0.10	0.12
LDL	-0.33	-0.04	-0.08	-0.18	0.18	-0.01
TC/HDL	-0.04	0.13	-0.21	0.26	-0.07	-0.10
TG	0.08	0.11	-0.32	0.05	-0.13	0.07
G-Alb §	---	---	---	-0.14	0.13	-0.15
Insulin	---	---	---	-0.18	-0.33	0.35
HOMA-IR	---	---	---	-0.17	-0.34	0.34

Data are presented as the Pearson product coefficient. baPWV, brachial-ankle pulse wave velocity; PP_{car}, carotid pulse pressure; CC, compliance coefficient; WHR, waist to hip ratio; HbA_{1c}, glycosylated hemoglobin; CRP, C-reactive protein; TCHOL, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC/HDL, total cholesterol to high-density lipoprotein ratio; TG, triglycerides; G-Alb, glycated albumin; HOMA-IR, homeostasis model assessment of insulin resistance.

§ CRP and G-Alb were natural log transformed.

* $p \leq 0.05$ was considered statistically significant.

Table 11. Pearson Correlations between Quantitative Measures of Physical Activity, Arterial Structure and Function, Cerebrovascular Hemodynamic Properties, and Blood Biomarkers in CA and SA Older Adults

	CA					SA				
	Daily Energy Expenditure			Duration of PA [‡]	Daily Steps	Daily Energy Expenditure			Duration of PA [‡]	Daily Steps
	TEE	AEE	PAEE [‡]			TEE	AEE	PAEE [‡]		
Anthropometric Measurements										
BMI	-0.13	-0.43*	-0.46*	-0.54*	-0.23	0.25	0.01	-0.29	-0.42 [#]	-0.41 [#]
Waist Circumference	0.37 [#]	-0.10	0.002	-0.12	-0.17	0.14	-0.08	-0.43 [#]	-0.56*	-0.48*
WHR	0.46*	0.29	0.42*	0.36 [#]	0.24	-0.19	-0.25	-0.57*	-0.62*	-0.24
Arterial Structure and Function										
baPWV	0.43*	0.38 [#]	0.50*	0.50*	0.20	0.024	0.04	0.20	0.21	0.45*
PP _{car}	0.06	0.05	0.02	0.03	-0.08	-0.34	-0.15	-0.16	-0.08	-0.01
DC	0.11	0.04	0.05	-0.003	0.12	0.40 [#]	0.26	0.25	0.17	0.05
CC	0.12	0.04	0.02	-0.02	-0.08	0.43 [#]	0.21	0.31	0.21	0.09
IMT	-0.19	-0.01	-0.10	-0.10	-0.03	0.14	0.13	0.10	0.04	0.05
Cerebrovascular Variables										
aCBF [§]	0.35	0.49*	0.55*	0.56*	0.52*	0.19	0.09	0.23	0.18	0.46*
MFV	-0.43*	-0.43*	-0.49*	-0.51*	-0.31	0.18	0.18	0.06	0.06	0.48 [#]
CVR	-0.43 [#]	-0.51*	-0.55*	-0.55*	-0.49*	-0.28	-0.18	-0.34	-0.29	-0.44
PI	-0.01	0.04	0.18	0.14	-0.21	0.04	0.20	0.12	0.10	-0.26
RI	-0.15	-0.45*	-0.33	-0.38 [#]	-0.45*	0.09	0.27	0.19	0.18	-0.29
HICO ₂ , Δcm/s/mmHg [§]	-0.28	-0.35	-0.39[#]	-0.44*	-0.14	0.08	0.04	-0.46 [#]	-0.48 [#]	-0.15
LOWCO ₂ , Δcm/s/mmHg	-0.35	-0.42*	-0.47*	-0.53*	-0.33	0.57*	0.68*	0.67*	0.66*	0.278
Blood Markers										
HbA _{1c}	-0.12	-0.27	-0.32	-0.37 [#]	-0.12	-0.47*	-0.55*	-0.45*	-0.46*	-0.21
CRP [§]	-0.37 [#]	-0.49*	-0.55*	-0.55*	-0.12	-0.06	0.11	-0.02	-0.04	-0.42 [#]
LDL	-0.60*	-0.51*	-0.51*	-0.46*	-0.21	0.13	0.23	0.09	0.09	-0.21

Data are presented as the Pearson product coefficient. TEE, total energy expenditure; AEE, activity-related energy expenditure; PAEE, physical activity-related energy expenditure; PA, physical activity; baPWV, brachial-ankle pulse wave velocity; PP_{car}, carotid pulse pressure; DC, distensibility coefficient; CC, compliance coefficient; IMT, intima-media thickness; BMI, body mass index; WHR, waist to hip ratio; aCBF, anterior cerebral blood flow; MFV, mean flow velocity; CVR, cerebrovascular resistance (MAP/aCBF); PI, pulsatility index; RI, resistive index; HICO₂, cerebrovascular reactivity to hypercapnia; LOWCO₂, cerebrovascular reactivity to hypocapnia; HbA_{1c}, glycosylated hemoglobin; CRP, C-reactive protein; LDL, low-density lipoprotein.

* p < 0.05 and ** p < 0.001 were considered statistically significant; # 0.05 ≤ p ≤ 0.10 was considered as statistical trends towards significance.

‡ PAEE and duration of PA were square root transformed.

§ aCBF, HICO₂ and CRP were natural log transformed.

7 Discussion

The primary objectives of the present study were to investigate ethnic differences in: i) structural and functional vascular properties and cerebral hemodynamics and ii) the relationship between arterial stiffness and resting cerebral blood flow (aCBF) in CA and SA older adults. Specifically, the ethnic groups were compared for differences in baPWV, carotid artery pulse pressure (PP_{car}), distensibility, compliance, and wall thickness (IMT) as well as aCBF, cerebrovascular resistance (CVR) and cerebrovascular reactivity to CO_2 . The first hypothesis that SA older adults had greater arterial stiffness compared to age- and gender-matched CAs was confirmed by the findings that SAs tended to have faster baPWV, reduced carotid arterial compliance, and higher pulse pressure. A difference in arterial structure was also observed between CAs and SAs, where SAs displayed a trend for less IMT compared to CAs. Contrary to the second hypothesis, SAs appeared to have trends for greater aCBF compared to CAs. Furthermore, a trend was observed for lower CVR in SAs compared to CAs, whereas cerebral blood flow velocity (MFV), RI and PI were comparable between the two groups. Contrary to the third hypothesis, cerebrovascular reactivity to CO_2 was not different between CAs and SAs. Finally, the fourth hypothesis that increased arterial stiffness in SAs would be associated with a reduction in aCBF was confirmed by the finding that reduced central arterial compliance, an indicator of regionally-specific arterial stiffness, was associated with greater CVR, and this was in turn associated with a greater reduction in aCBF.

The secondary objectives of this study were to examine: i) the relationship between structural and functional vascular properties and cerebral hemodynamics in each ethnic group; ii) ethnic differences in health factors, including blood biomarkers and physical activity; and iii) ethnic differences in cognitive function, along with exploring the relationship between central

arterial and cerebrovascular health and cognitive performance. The study findings suggest that carotid artery wall thickness (IMT) was associated with greater increase in MCA PI and RI in SAs in comparison to CAs. Results from fasting blood samples revealed that SAs had higher HbA_{1c}, HDL, and LDL levels, but lower fasting glucose levels compared to CAs. Furthermore, the amount of free-living physical activity, estimated by the number of daily steps, was less in SAs compared to CAs. Of note, additional correlation analyses revealed that greater physical activity in both ethnic groups demonstrated beneficial effects on aCBF and lowering blood biomarkers associated with the risk of cardiovascular diseases, including HbA_{1c}, CRP and LDL. Finally, SA older adults performed slower on the cognitive tasks than CAs, but no meaningful relationships were observed between cognitive performance and structural and functional vascular properties or cerebrovascular hemodynamics.

7.1 Ethnic Disparities in Arterial Stiffness and Arterial Structure and Function

7.1.1 Arterial Stiffness and Arterial Function

In the present study, baPWV was examined as a surrogate for central arterial stiffness along with regionally-specific central artery stiffness indicators of carotid artery pulse pressure, distensibility, and compliance in CA and SA older adults. Consistent with previous studies (Din *et al.*, 2006; Gunarathne *et al.*, 2009; Webb *et al.*, 2012) the present study confirmed that SAs had increased central arterial stiffness compared to age- and gender-matched CAs. It was observed that baPWV tended to be higher in SAs compared to CAs ($p=0.08$). Furthermore, this study observed for the first time in a SA population that carotid artery compliance was lower and pulse pressure was greater compared to CAs (**Table 6**). Taken together, these findings suggest increased arterial stiffness in SAs. Increased central arterial stiffness is a well-established predictor of cardio- and

cerebrovascular morbidity and mortality independent of other risk factors (Sutton-Tyrrell *et al.*, 2005; Mattace-Raso *et al.*, 2006; Vlachopoulos *et al.*, 2012; Gepner *et al.*, 2014). Excess mortality from these diseases among SAs is well documented (Balarajan *et al.* 1984; Balarajan 1991; Wild & Mckeigue 1997; Gunarathne *et al.*, 2009); however, the role of arterial stiffness in these diseases has not been thoroughly examined in this population.

Low arterial compliance and greater central pulse pressure observed in SAs are characteristic of stiff arteries. The common carotid arteries have elastic (compliant) properties and are involved in dissipating the pressure waves generated by each heartbeat and transforming the pulsatile characteristics of flow to steady peripheral flow. The central arteries are the first line of defense to minimize large changes in pressure to extend in the microcirculation of peripheral organs and tissues, such as the brain. Compliance is defined as the change in volume per unit change in pressure ($\Delta V/\Delta P$). For a given change in blood volume, the change in pressure (pulse pressure) is determined by arterial compliance. Normal compliant arteries are able to expand during systole and recoil during diastole and accommodate large volume of blood with little effect on the blood pressure. On the other hand, in less compliant (stiff) arteries, the ability to expand and recoil is greatly reduced, and as a consequence, this results in greater pulse pressure for a given change in volume. In this study, less compliant (and distensible) arteries in SAs was associated with a greater increase in pulse pressure compared to CAs (**Figure 8 & 9**). It seems logical that greater pulse pressures is a consequence of less compliant arteries, but due to the experimental design of the study, a cause and effect relationship between central pulse pressures and compliance cannot be established. Theoretically, with advancing age central arteries are exposed to a lifetime of pressure that can lead to fatigue and breakdown of the vessel's structure. When the structural composition of the central arteries become compromised, the vessels' ability to cushion the

pressure waves is diminished and the arteries become stiffer. As a consequence, the pulse wave transit time is smaller, and therefore, the reflected waves travel to and from the reflection points sooner, thereby augmenting the systolic phase and reducing the diastolic phase of the pressure waveform (O'Rourke *et al.*, 2010) (**Figure 1**). The stiffening of arteries and faster pulse waves are responsible for larger central pulse pressures. Over time, these pulse pressures accelerate arterial damage and reduce arterial function even further; thus, this process becomes a vicious cycle of vessel wall degradation. Elevated central pulse pressures associated with arterial stiffness can extend into the brain and cause irreversible structural changes and microvascular damage (Henskens *et al.*, 2008; Aribisala *et al.*, 2014). Increased arterial stiffness is associated with silent cerebral infarcts and white matter hyperintensities (Saji *et al.*, 2011; Saji *et al.*, 2012; Poels *et al.*, 2012; Tsao *et al.*, 2013). The results from this study indicate that asymptomatic SA older adults display greater central arterial stiffness that is associated with greater resistance to brain blood flow. This information provides insight into the mechanisms that might contribute to the pathogenesis of cerebrovascular diseases and could, in part, explain the higher prevalence of such diseases in SA communities. These findings should be strengthened by additional studies that explore the relationship between arterial stiffness and brain lesions in SA communities.

Pulse pressure is the difference between systolic (SBP) and diastolic blood pressures (DBP). High pulse pressures result from elevated SBP and/or a reduction in DBP. The SA older adults in this study had similar SBP values as the CA older adults, but the SAs had significantly lower DBP values during the supine assessment, resulting in widened pulse pressures (**Table 7**). This observation is consistent with other studies that have reported low DBP values in the SA populations compared with CA populations (Lyrtzopoulos *et al.*, 2005; McElduff *et al.*, 2005). Some studies have observed the opposite (Williams, 1993; Cappuccio *et al.*, 1997); however, these

studies examined young SAs, and therefore, it is difficult to directly compare their BP values with that of the SA older adults in the present study. With advancing age, DBP rises until 50 years of age, after which it levels off or declines in all ethnic groups (including SAs) (Landahl & Bengtsson, 1986; Burt *et al.*, 1995; Franklin *et al.*, 1997; Hakala & Tilvis, 1998; McElduff *et al.*, 2005). Low DBP values in SA older adults observed in this study could be a consequence of greater arterial stiffness (less compliant arteries and greater baPWV). A low DBP is reportedly associated with greater risk of ischemic stroke and white matter lesions (Reshef *et al.*, 2011). High pulse pressure signifies that greater volume of blood has gone through the central vessels to the periphery during systole and insufficient flow during diastole, which renders the brain vulnerable to ischemic events during diastolic phase. Low DBP among SA older adults in this study indicates that they may be at high risk for cerebrovascular ischemic events compared to CA older adults; this calls for further work with larger sample size studies to confirm this speculation.

7.1.2 Potential Explanations for Elevated Arterial Stiffness in South Asians

Age-related changes in vascular structure and function increase arterial stiffness (Nichols *et al.*, 2011). In the present study, age was associated with increased arterial stiffness (baPWV) in both CAs and SAs (Figure 2). Although there was a significant difference in arterial stiffness between the two ethnic groups, the age-related increase in arterial stiffness appeared to be similar. It can be postulated that changes in arterial stiffness in old age may be similar between CAs and SAs, but it remains uncertain whether ethnic differences exist in the progression of arterial stiffness with aging during the early years of life. Moreover, the potential mechanisms underlying increased arterial stiffness in the SA population are still unclear. Oxidative stress (Wang *et al.*, 2012), inflammation (Yasmin *et al.*, 2004; Vlachopoulos *et al.*, 2005), and reduced nitric oxide bioavailability (Kinlay *et al.*, 2001; Wilkinson, 2002) are associated with increased arterial

stiffness and have been studied in SAs, (Murphy *et al.*, 2007; Dotesenko *et al.*, 2007), but whether these are related to arterial stiffness in SAs remains elusive. Also, elevated arterial stiffness has been reported with certain chronic diseases (cardio- and cerebrovascular diseases, end-stage renal disease) (London *et al.*, 1990; Giannattasio *et al.*, 2004; Meguro *et al.*, 2009; De Silva *et al.*, 2009) as well as cardiometabolic risk factors, including diabetes (Salomaa *et al.*, 1995; Schram *et al.*, 2002; Schram *et al.*, 2004), hypertension (Benetos, 2002), hyperlipidemia (Wilkinson *et al.*, 2002), and obesity (Zebekakis, PE *et al.*, 1846; Toto-Moukouo *et al.*, 1986). SAs in the present study had no clinically overt signs of chronic diseases. Two SA participants were diabetic, and the prevalence of hypertension and hyperlipidemia were similar across the two ethnic groups, implying that these conditions may not explain the increased arterial stiffness in SAs in this study. In fact, correlation analyses revealed no significant relationships between the blood markers of glycemic control and arterial stiffness in SAs (**Table 10**). However, considering the small sample size of this study, caution must be taken when interpreting these results and speculations.

Some studies suggests that the presence of diabetes and/or hypertension in SA populations is associated with increased arterial stiffness and can explain the higher risk for cardio- and cerebrovascular diseases and mortality (McKeigue *et al.*, 1993; Wilkinson *et al.*, 1996; Wild & Mckeigue, 1997; Gunarathne *et al.*, 2008*b*, 2009*b*). In the current study, when the two SA participants with diabetes were removed from the analyses, differences in arterial stiffness between CAs and SAs and the relationship between decreased arterial compliance and CVR in SAs remained significant at the same or similar strength. This information implies that the presence of diabetes does not necessarily account for the ethnic differences in arterial stiffness between CAs and SAs. Indeed, high prevalence of diabetes in SAs is well documented in the literature, and diabetes can further augment arterial stiffness (Aoun & Blacher, 2001; Schram *et al.*, 2002);

however, it did not explain elevated arterial stiffness among SAs in the present study. Furthermore, apart from aging, hypertension is a major factor associated with accelerated arterial stiffness and risk of stroke (Shekelle *et al.*, 1974; Antikainen *et al.*, 1998). The World Health Organization has identified hypertension as one of the leading and preventable causes of premature death worldwide (Organization, 2012). In an Ontario survey from 2008, the prevalence of hypertension was highest among SAs (Leenen *et al.*, 2008), and similar findings have been reported in other countries (Primatesta *et al.*, 2000; Agyemang *et al.*, 2005). Moreover, hypertension contributes to high incidence of stroke in the SA population (Cappuccio *et al.*, 1997; Banerjee *et al.*, 2001; Bhattacharya *et al.*, 2005). A number of studies reported that hypertension was the most common factor in SA ischemic stroke patients (Banerjee *et al.*, 2001; Kaul *et al.*, 2002; Bhattacharya *et al.*, 2005; De Silva *et al.*, 2009; Vibha & Prasad, 2012). The present study had comparable prevalence rates of hypertensive older adults in each ethnic group. Interestingly, two SA participants had untreated hypertension, which is common in this ethnic group. SAs are often unaware of the health risks associated with high blood pressure, and therefore, treatment for high blood pressure is inadequately pursued (Gupta *et al.*, 2012, 2013; Anchala *et al.*, 2014). Gupta and colleagues (2013) evaluated the prevalence of hypertension among middle-class SAs in India and found that half of the individuals with hypertension were aware of their condition, but more than half of these individuals were not receiving treatment. This implies that poorly treated hypertension is likely a distinct characteristic in the SA population, and thus, higher prevalence of hypertension could be a major contributing factor to increased susceptibility to cardio- and cerebrovascular diseases in this ethnic population. Hypertension is a manageable health condition that can be controlled by medical intervention, exercise and diet. Therefore, public awareness efforts as well as disease

management and prevention projects need to be considered to help fill the gaps in communication and understanding within SA communities in efforts to promote overall cardiovascular health.

7.1.3 Ethnic Disparities in Vascular Structure

SA older adults had trends for lower mean IMT, whereas the maximum IMT was significantly lower in SA compared to CA older adults (**Table 6**). This finding is consistent with a previous report by Anand and colleagues (2000) who also reported lower maximum IMT in SAs compared to CAs after adjusting for age and gender. Anand and colleagues (2000) found that the prevalence of cardiovascular diseases was greater in SAs even with reduced carotid IMT. In the present study, the mean IMT value of the SA group was comparable to a recent multiethnic study that reported non-diabetic SAs had a mean IMT of 0.6 ± 0.1 mm (Kanaya *et al.*, 2010). Carotid IMT is a well-established subclinical marker for atherosclerosis (pathological process of plaque buildup and hardening of the arterial lining). IMT is used to identify asymptomatic individuals at high risk of cardiovascular disease in the early stages of the disease process. Prospective and longitudinal studies have shown that IMT is associated with future risk of myocardial infarctions and stroke in general adult populations (Chambless *et al.*, 1997, 2000; Iglesias del Sol *et al.*, 2002), older adult populations (Bots *et al.*, 1997; O'Leary *et al.*, 1999), and multi-ethnic cohorts in the absence of major risk factors or clinical diseases (Polak *et al.*, 2013). IMT is also independently associated with cardiovascular diseases in SAs (Jadhav & Kadam, 2001; Hansa *et al.*, 2003; Meenakshisundaram *et al.*, 2011). In the current study, IMT was used as an indicator of structural changes within the arterial system. It has been well-documented in the literature that SAs have an increased risk and prevalence of cardio- and cerebrovascular diseases (Anand *et al.*, 2000; Lee *et al.*, 2001; Gunarathne *et al.*, 2009a; Palaniappan *et al.*, 2010; Boparai *et al.*, 2011; Tillin *et al.*, 2013; Hajra *et al.*, 2013). Based on this information, it was anticipated that SA older adults would

have greater mean and maximum IMT compared to CA older adults, but this was not the case for maximum IMT values. Ethnic differences in IMT measurements observed in this study could potentially be explained by the differences in other risk factors that are associated with increased IMT, such as smoking status (Poredos *et al.*, 1999; van den Bergmortel *et al.*, 2000; Recio-Rodriguez *et al.*, 2013). The pathophysiological mechanisms that explain this association between current smoking status and increased IMT are related to changes in endothelial function (Tappia *et al.*, 1995; Zeiher *et al.*, 1995; Ichiki *et al.*, 1996) and the elevation of inflammatory markers (Tracy *et al.*, 1997) that promote atherosclerosis (Bazzano, 2003). The present investigation found that more CA participants were smokers, whereas the SA participants were neither current nor past smokers. Therefore, it is reasonable to speculate that the trend for greater mean IMT values and statistically greater maximum IMT observed in CA participants may have been related to their smoking behavior, but this argument cannot be confirmed from the present study.

7.2 Ethnic Disparities in Cerebrovascular Hemodynamics

7.2.1 Cerebral Blood Flow

Contrary to the second hypothesis, lower aCBF was not observed in SAs; rather, SAs appeared to have trends for greater aCBF compared to CAs. Corresponding to this finding was that a trend for lower CVR and significantly higher $P_{ET}CO_2$ values were observed in SAs compared to CAs. CO_2 is a primary regulator of CBF, playing a particular role in mediating cerebrovascular tone. A multiple linear regression analysis revealed that 18% of the variance in aCBF was accounted for by the high $P_{ET}CO_2$ levels in the SA group (**APPENDIX D, Supplementary Table 3**). Although not measured in this study, decreased alveolar ventilation (CO_2 elimination) may be a possible explanation for the observation of elevated $P_{ET}CO_2$ in SAs (Munson *et al.*, 1966).

Alveolar ventilation is defined as the volume of gas that enters the alveoli in the lungs for gas exchange and is expired out per minute (minute ventilation) corrected for physiologic dead space (Miller & Pardo, 2011). The alveolar ventilation equation ($P_{ACO_2} = (\dot{V}CO_2 / \dot{V}_A \cdot 0.863)$), where P_{ACO_2} is alveolar PCO_2 , $\dot{V}CO_2$ is CO_2 output, \dot{V}_A is alveolar ventilation, and 0.863 is a constant that converts different standard units for \dot{V}_A (L/min, BTPS) and $\dot{V}CO_2$ (mL/min, STPD) to mmHg shows that for a constant $\dot{V}CO_2$, P_{ACO_2} would be elevated if \dot{V}_A is lower. In healthy human lungs, the alveolar PCO_2 is approximately equivalent to arterial PCO_2 . In this regard, the elevated P_{ETCO_2} observed in SAs relative to CAs might reflect a corresponding elevation in alveolar PCO_2 , and hence, and an elevation in arterial PCO_2 (Jones *et al.*, 1979). If indeed arterial PCO_2 was elevated in the SAs, then it can be speculated that \dot{V}_A was lower in SAs. Lower ventilation allows CO_2 to build up in the blood. Accordingly, it can be postulated that CAs and SAs have different arterial chemosensitivity to CO_2 . Central (located in the medulla) and peripheral (in the carotid arteries and aorta) arterial chemoreceptors are involved in the maintenance of arterial blood gases within homeostatic range. They stimulate the respiratory control center of the brain to change ventilation in response to changes in arterial PCO_2 , PO_2 , and pH (Sherwood, 2012). To test chemosensitivity to CO_2 , the ventilatory response to inhaled CO_2 can be assessed. \dot{V}_A rises in response to increased arterial PCO_2 . Chemosensitivity to CO_2 has not been investigated in the SA population; however, comparative studies between other ethnic populations have revealed significant differences in the ventilatory response to CO_2 stimulus (Beral & Read, 1971; Willcox & Benatar, 1990). Beral & Read (1971) reported that New Guinea natives (an island north of Australia) had significantly lower ventilation when inhaling increased levels of CO_2 compared to CAs. Another study found that compared to CAs, other ethnic groups have significantly lower ventilatory response to CO_2 (Willcox & Benatar, 1990). Furthermore, higher resting P_{ETCO_2} levels than CAs have also been

reported in other ethnic groups, such as African Americans (Anderson *et al.*, 2001). Taken together, these studies support the notion that ethnic disparities in the tolerance or sensitivity to CO₂ exist. Accordingly, the ethnic groups in the present study may have differences in CO₂ sensitivity, and thus, this could explain the trends observed for ethnic differences in resting CVR and aCBF.

Furthermore, morphological and morphometric studies of the lungs have suggested that CAs have larger total lung capacity compared to SAs, likely attributed to greater inspiratory and expiratory muscle pressure and greater height in CAs (Whittaker *et al.*, 2005). Chest dimension, height, and ethnicity have shown to explain 86% of the variation in total lung capacity among CA, SA and Chinese ethnic groups (Donnelly *et al.*, 1991). Lung volumes tend to be larger in tall individuals than in short individuals. In the present study, there were obvious differences in body size between the SA and CA group; CA participants were taller and had significantly greater body surface area compared to SA group. Although the chest walls were not measured, it was postulated that CA participants in the study had physically larger chests; therefore, this could imply that CAs were able to distend their lungs more and have a higher ventilatory capacity to breathe more CO₂ out than SAs. The mechanisms underlying the differences in lung volumes are largely unknown. A recent study suggested that cultural, socioeconomic or environmental conditions do not explain the differences in lung volumes between CAs and SAs (Strippoli *et al.*, 2013). Rather, the underlying basis for these ethnic differences could potentially be explained by genetic variation, differences in respiratory muscle strength, or elastic recoiling of the lung (Whittaker *et al.*, 2005; Hirsch *et al.*, 2013). However, data from the present study cannot confirm these speculations, and literature that examine these speculations are currently lacking. For this reason, more work in the SA population is required to confirm.

7.2.2 Cerebrovascular Function

In contrast to the previous work by Bathula and colleagues (2011), the present study did not find significant differences in resting TCD-derived cerebrovascular hemodynamic variables between CAs and SAs; the ethnic groups had comparable resting supine values for MFV, RI and PI (**Table 7**). A trend was observed for greater resting supine SFV in SAs ($p=0.063$), which became significant in the seated position ($p=0.030$). Bathula and colleagues (2011) reported that SAs had greater cerebrovascular resistance (RI and PI) and MFV compared to CAs. Most importantly, they included participants with existing comorbidities in their study which might have confounded the results. For instance, there was a disproportionately greater number of diabetic patients in the SA group compared to the CA group. A study has shown that cerebral blood flow velocity and cerebrovascular resistance is significantly elevated in diabetic patients compared to healthy patients (Lee *et al.*, 2000; Dikanovic *et al.*, 2005). Accordingly, it can be speculated that the differences in cerebral hemodynamic measures between CAs and SAs in Bathula and colleagues (2011) study could be explained by the greater proportion of diabetic patients with abnormal cerebrovascular hemodynamics in the SA group. Conversely, the present study was designed to only include participants with no overt signs of chronic diseases to minimize the influence of such confounding factors. SA older adults in this study did not display significant differences to CA older adults in resting cerebral blood flow measurements obtained from the TCD.

In addition, no differences in CO₂ reactivity were detected between CAs and SAs (**Table 8**). Although this finding did not confirm the third hypothesis of this study, an interesting finding was that absolute changes in P_{ET}CO₂ and TCD-derived MFV were significantly larger in the SAs compared to CAs during hypercapnic conditions (**Figure 2**). The large increase in MFV was likely a consequence of higher and larger increase in P_{ET}CO₂ observed in SAs. Even though the SAs and

CAs began the assessment at a similar $P_{ET}CO_2$ level and inhaled the same concentration of CO_2 during hypercapnia, there was a significant difference in the change in $P_{ET}CO_2$ during hypercapnia. Again, it appears that ethnic differences in ventilatory chemosensitivity might explain these results. It is possible that low ventilatory response to CO_2 in SAs resulted in a significant increase in $P_{ET}CO_2$ during hypercapnia, and therefore, this could contribute to the decrease in cerebrovascular resistance and subsequent increase in MFV. The present study was the first to examine ethnic differences in cerebrovascular reactivity between CAs and SAs. Considering the small sample size of this study and the success rate for successful TCD recordings in SAs was only 72% (16/22), caution must be taken before drawing conclusions or making generalizations about the results. A technical consideration is that TCD is unable to measure MCA diameter. TCD is commonly used in the literature as a surrogate of estimating CBF under the assumption MCA diameter remains constant. Relative changes in MFV reflect proportional changes in CBF. However, the assumption of a constant MCA may be invalid under exposure to extreme hypoxic and hypercapnic conditions (Valdúeza *et al.*, 1999; Willie *et al.*, 2012). Therefore, TCD may have underestimated measurements of CBF if changes in MCA diameter did occur. Importantly, SAs had greater $P_{ET}CO_2$ change during hypercapnia compared to CAs, which may have caused the MCA to dilate in SAs. If this was the case, then for a given volume of blood flow, MCA dilation would decrease the resistance to flow and decrease MFV. As a consequence, MFV would underestimate true CBF. However, greater increase in MFV was observed in SAs in parallel with greater increase in $P_{ET}CO_2$ during hypercapnia. Moreover, in the absence of supporting literature for ethnic differences in the effect of CO_2 on arterial diameter, it is unknown whether the changes in MCA diameter may have impacted the results. The study findings clearly warrant further investigation using TCD to confirm these speculations. TCD is a valuable non-invasive technique

that enables the detection of flow abnormalities and may be promising tool to identify asymptomatic patients at high risk for development of cerebrovascular disease (Mok *et al.*, 2012).

7.3 Ethnic Disparities in the Effects of Arterial Stiffness on Cerebral Blood Flow

Reduced carotid artery compliance, an indicator of regionally-specific arterial stiffness, in SA older adults was associated with greater cerebrovascular resistance (CVR) (**Figure 6**), and this was in turn associated with a greater reduction in aCBF compared to CAs (**Figure 7**). These findings supported the fourth hypothesis that elevated arterial stiffness in SAs would be associated with a greater reduction in aCBF relative to CAs. Increased CVR could reflect a compensatory mechanism by which the brain attempts to protect the microvessels from excessive pressure waves and pulsatile flow that were not being effectively managed by the central arteries. The transmission of poorly cushioned, high pulsatile flow is a hemodynamic stress that may damage arterial lining of cerebral vessels and induce chronic vascular structural alterations that increase myogenic vasoconstriction (Baumbach, 1996; Jacobsen *et al.*, 2008; Mitchell *et al.*, 2008; Takashi *et al.*, 2014). As a consequence, greater CVR causes a reduction in CBF, potentially compromising cerebral perfusion and increasing the risk for ischemic events. Common carotid arterial stiffness is an independent risk factor for ischemic stroke (Tsivgoulis *et al.*, 2005).

This study did not detect a direct association between arterial stiffness (baPWV, PP_{car}, compliance or distensibility measures) and aCBF. Specifically, a relationship between baPWV and aCBF was not detected (**Figure 5**), and as a result, no ethnic differences in this relationship were detected between CAs and SAs. baPWV may not be a sensitive marker in detecting ethnic differences in arterial stiffness and its effect on aCBF. In addition, the lack of relationship between the two variables could be due to higher P_{ET}CO₂ levels and a trend for higher aCBF observed in

SAs. Higher P_{ETCO_2} corresponds to higher arterial PCO_2 . It appears that SAs allowed their arterial PCO_2 to be increased, which in turn, caused cerebrovascular dilation and increased aCBF.

The link between the structural characteristics of central arteries and the hemodynamic properties of blood flow in the cerebral microcirculation was also explored. Although SAs appeared to have smaller IMT compared to CAs, there were still significant relationships with indicators cerebral hemodynamics, and that stronger relationships were observed in SAs. Mean carotid IMT was independently associated with both PI and RI in the MCA in SAs. The relationship between IMT and PI was also noted in CAs; however, increased IMT in SAs was associated with an even greater increase in PI and RI compared to CAs. PI and RI were cerebral hemodynamic indices derived from the TCD flow velocity waveforms that reflect intracranial resistance and compliance of small cerebral vessels downstream from the MCA. PI is the ratio of the amplitude of pulsation to the time average value of the blood flow velocity (SFV-DFV/MFV), and RI is the ratio of the amplitude of pulsation to the peak systolic blood flow velocity (SFV-DFV/SFV). Independently, the SFV, DFV and MFV measurements used to calculate PI and RI were not significantly different between CAs and SAs (**Table 7**). As a result, no differences in PI and RI between the two ethnic groups were observed during baseline assessments. However, differences between the groups emerged when these indices were associated with IMT measurements. In spite of having less pronounced (maximum) IMT, SAs had greater PI and RI for a given IMT compared to CAs (**Figure 10 & 11**). The findings suggest that structural alterations of the carotid artery (arteriosclerosis) were linked to more pulsatile blood flow patterns and resistance in the cerebral circulation, and that these relationships were more pronounced in SAs than in CAs. SAs may have had more advanced arteriosclerosis (hardening of arteries) as a consequence of increased arterial stiffness, and thus, it is speculated that arterial stiffness may

mediate the relationship between IMT and cerebral hemodynamics properties. Elevated pulsatile blood flow is associated with cerebrovascular damage (Webb *et al.*, 2012a; Jolly *et al.*, 2013). Thus, the finding from the present study provides valuable insight into the possible role of arteriosclerosis in the development of cerebral pathologies in the SA population. The changes in PI and RI may reflect changes in cerebral blood flow patterns that could be interpreted as a consequence of increased resistance in the cerebral microvessels due to prior damage, or may be caused by the direct transmission of high pulsatile pressure and flow from central arteries into the cerebral circulation (Mitchell *et al.*, 2011; Aribisala *et al.*, 2014). It is postulated that increased central arterial stiffness and reduced cushioning effect of pressure and flow by central arteries in SAs over time results in increased resistance in the cerebral microcirculation, and as a consequence, PI and RI are increased. However, no direct relationships between CVR (or CVRi) and PI or RI were found in this study, nor a significant association between central arterial stiffness and PI or RI. As a result, conclusive cause and effect relationships are difficult to determine. Thus, longitudinal studies are needed to elucidate the temporal relationship between arterial stiffness and hemodynamic changes in the cerebral microcirculation.

7.4 Potential Ethnic Disparities in Plaque Burden

Although this study was not designed to specifically look for plaque in the carotid arteries, plaque was seen in more SA participants than in CA participants during the imaging assessments. Atherosclerotic plaque buildup is a physical barrier in the arteries that can interrupt and interfere with the blood flow to the brain. The burden of plaque has been reported to be associated with increased risk of stroke in older adults free of CVD (Polak *et al.*, 1998) and provides additive value in predicting the risk of future cardiovascular events in addition to IMT measurements (Nambi *et*

al., 2010, 2012; Polak *et al.*, 2013). A recent study on SA patients with acute ischemic stroke reported that higher values of IMT, PI and RI were observed in these patients compared to healthy individuals, and that the degree of plaque was related to higher PI (Das *et al.*, 2011). This implies that plaque buildup contributes to altered blood flow properties in the brain. Furthermore, seeing that IMT appears to be less in SAs compared to CAs, it was unclear whether the progression of plaque appears before the changes in IMT in SAs; in other words, plaque development could be an accelerated process in SAs, and thus, it could contribute to the increased risk of stroke reported in this population. A large prospective study has shown that the presence of carotid plaque relates to subsequent ischemic stroke (Chambless *et al.*, 2000). Ischemic stroke is the most common type of stroke among SAs, followed by hemorrhagic stroke, as documented in both South Asian countries and in Western countries (Banerjee *et al.*, 2001; Das *et al.*, 2007; Dalal *et al.*, 2008; Gunarathne *et al.*, 2008a, 2009a; Kulshreshtha *et al.*, 2012). It can be speculated that the burden of plaque in SAs is an important precursor contributing to the increased risk of cerebrovascular diseases. Some studies suggest that the progression of atherosclerosis in SA populations is associated with abnormal lipid profile (high LDL and low HDL cholesterol levels), diabetes (high glucose levels), higher systolic blood pressure, greater WHR, and high levels of thrombosis-promoting factors like fibrinogen and plasminogen activator inhibitor-1 (PAI-1) (Anand *et al.*, 2008; Chow *et al.*, 2008). In the current study, higher levels of HDL, LDL, and HbA_{1c}, and greater WHR were observed in SAs relative to CAs. Therefore, ethnic differences in these factors might have contributed to greater plaque formation and buildup detected in SAs. Again, the primary purpose of this study was not to investigate plaque. Plaque burden in SAs was an incidental finding, and therefore, additional research is recommended to confirm this observation.

7.5 Ethnic Disparities in Health Factors

7.5.1 Blood Biomarkers

SAs in this study were primarily non-diabetic, yet they had higher levels of HbA_{1c} compared to non-diabetic CAs, consistent with other studies (Mostafa, 2012; Mebazaa *et al.*, 2013). On the other hand, fasting glucose levels were lower in SAs. Fasting glucose levels indicate the current level at the time the blood samples were taken, which can fluctuate throughout the day and with consumption of food (Lang *et al.*, 1979; Jenkins, 1982, 1984; Read *et al.*, 1986). All participants were required to fast overnight for at least 8 hours for morning blood draw. There is a possibility that some participants may not have had a meal the night before, and as a consequence, they may have had lower blood glucose levels in the morning (a condition known as fasting hypoglycemia) (Santiago, 1982; Yang *et al.*, 1991). Another possibility could be that participants may have experienced the “dawn phenomenon”, which is a condition that refers to the rise in glucose levels in the early hours of the morning (Schmidt *et al.*, 1981; Bolli *et al.*, 1984). This condition is related to the changes in the overnight release of glucose-regulating hormones which can affect the morning blood glucose levels (Van Cauter, 1990; Edge *et al.*, 1990; Qin *et al.*, 2003). As a result, fasting glucose levels might not be a stable marker that accurately measures glycemic control. On the other hand, HbA_{1c} is considered a better indicator of glycemic control, reflecting the average blood glucose levels over the previous three months (Gonen *et al.*, 1977; Nathan *et al.*, 1984). Previous studies have found that fasting glucose and HbA_{1c} levels are independently related to accelerated stiffening of arteries (van Popele *et al.*, 2006; Rahman *et al.*, 2008; Liang *et al.*, 2012). In the present study, SAs displayed both elevated levels of HbA_{1c} and arterial stiffness compared to CAs. However, correlation analyses employed in each ethnic group did not reveal

significant relationships between HbA_{1c} and indicators of arterial stiffness. These findings should be interpreted with caution in light of the small sample size.

Furthermore, additional markers of glycemic status (glycated albumin, insulin, and HOMA-IR) were chosen for examination in SAs, though data on these markers were unavailable in CAs because the decision had been made after the completion of data collection in CAs. As a consequence, the lack of a comparison group meant that comparison analyses between the two ethnic groups could not be performed. The rationale to include the aforementioned glycemic markers in this study was because glycated albumin has gained considerable clinical interest as a short-term measure of glycemic changes and has been proposed as a more accurate and useful measure of glycemic status than HbA_{1c} (Silver *et al.*, 1964; Schleicher *et al.*, 1993; Ohkubo *et al.*, 1995; Juraschek *et al.*, 2012). Also, several studies suggest that abnormal insulin sensitivity and glucose intolerance in individuals in the absence of diabetes are associated with increased arterial stiffness (Salomaa *et al.*, 1995b; Sengstock *et al.*, 2005; Seo *et al.*, 2005; Sliem & Nasr, 2010; Paik *et al.*, 2012; Meng *et al.*, 2013; Shen *et al.*, 2013). However, glycated albumin, insulin, and HOMA-IR did not show significant correlations with the indicators of arterial stiffness in SAs (**Table 10**). Despite these negative findings, comparable data on these markers and their potential role in arterial stiffness in the SA population are lacking. In light of the emerging evidence that suggests a role of impaired glycemic control and insulin resistance in increasing arterial stiffness, glycated albumin, insulin, and HOMA-IR may be promising markers for future investigations to evaluate glycemic control in the SAs and other populations with elevated arterial stiffness.

7.5.2 *Physical Activity*

SAs were physically inactive compared to CA older adults according to the self-reported physical activity. In addition, objectively measured physical activity data revealed that SAs took

fewer steps per day compared to CAs, implying that more time was spent in sedentary behavior. The recent Canadian Health Measures Survey reported that individuals aged 60 to 79 years averaged 7,900 steps a day for men and 7,000 steps a day for women (Colley *et al.*, 2011). CA participants were well above the national average (CA males 9032 ± 2338 steps/day, CA females 7158 ± 2851 steps/day), whereas SA participants were below the national average (SA males $6,467 \pm 2687$ steps/day, SA females $4,593 \pm 2548$ steps/day). Physical inactivity among Canadian older adults is reported to be higher among visible minorities and immigrants (Azagba & Sharaf, 2014). In Canada, the largest visible minority group is the SA population, and indeed, SAs are less active than the rest of the population (Tremblay *et al.*, 2006; Liu *et al.*, 2010). Physical inactivity is reported as a major health concern among SAs, which may account for this population's greater prevalence of cardiometabolic risk (including diabetes, abdominal obesity, hypertension and hyperlipidemia) as compared to their CA counterparts (Fischbacher *et al.*, 2004; Razak *et al.*, 2005; Williams *et al.*, 2010, 2011; Ranasinghe *et al.*, 2013).

7.5.3 *Benefits of Physical Activity*

In spite of having lower levels of physical activity than CA older adults, SA older adults in this study displayed several health benefits to physical activity. For instance, greater physical activity was associated with lower HbA_{1c} (**Table 11**). Elevated levels of HbA_{1c} is an early indicator for the risk of developing future type-2 diabetes (Perry *et al.*, 2001; Lee *et al.*, 2002; Edelman *et al.*, 2004; Hamilton & Jeyarajah, 2007; Inoue *et al.*, 2007; Sato *et al.*, 2009). Evidence suggests that a sedentary lifestyle (i.e. any waking behavior that has low levels of energy expended done in a sitting or reclining posture) (de Rezende *et al.*, 2014) is strongly associated with greater risk of diabetes, cardiovascular diseases, and all-cause mortality (Katzmarzyk *et al.*, 2009; Patel *et al.*, 2010; Hawkes *et al.*, 2011). In addition, human bed-rest studies show that physical inactivity can

disrupt normal metabolic function and can consequently lead to insulin resistance, hyperlipidemia, and have deleterious effects on the vasculature (Bleeker *et al.*, 2005; Hamburg *et al.*, 2007; Alibegovic *et al.*, 2009). Sedentary behavior has been shown to be associated with greater glycemic indices in SAs (Gill *et al.*, 2011). More importantly, living a sedentary lifestyle in combination with a genetic susceptibility can substantially increase the risk of type-2 diabetes (Alibegovic *et al.*, 2010). A genetic basis for the susceptibility of diabetes in SA population is evident with the variants of the transcription factor 7-like 2 gene (TCF7L2) (Chandak *et al.*, 2007; Rees *et al.*, 2008; Sanghera *et al.*, 2008). The expression of this gene is involved in regulating glucose metabolism, and variants of this gene have been associated with impaired insulin secretion, glucose production and tolerance (Lyssenko & Lupi, 2007). Non-diabetic individuals who carry variants of this gene (such as SAs) display elevated levels of HbA_{1c} and early signs of impaired glucose regulation (Gjesing *et al.*, 2011; Gautier *et al.*, 2011), and thus, these individuals are at a high genetic risk of developing type-2 diabetes. Fortunately, this study found that greater free-living physical activity was associated with lower HbA_{1c} in SAs, suggesting that physical activity could potentially attenuate the genetic predisposition to diabetes in SAs.

Furthermore, physical activity measures in SA older adults were associated with lower waist circumference, WHR and lower levels of CRP. These associations have been confirmed previous studies that investigated physical activity interventions in SAs and found that SAs showed improvements in weight loss (Rush *et al.*, 2007; Bhopal *et al.*, 2014). Other studies have also seen physical activity in SAs to improve blood pressure and blood lipid profiles (Mathews *et al.*, 2007). However, perceived barriers exist among SA older adults that hinder them from adhering to physical activity. For instance, pain is the most common reported complaint in SA older adults that makes them reluctant to exercise (Horne *et al.*, 2013). Other factors including sweating,

increased heart rate, and breathlessness experienced with physical activity are negatively perceived as symptoms of illness rather than normal physiological responses to exercise (Hayes *et al.*, 2002; Lawton *et al.*, 2006). The fear of having these symptoms discourages the SAs to exercise. Therefore, it is imperative to investigate how to overcome these barriers and promote the benefits of undertaking regular physical activity.

There is compelling evidence in the literature that physical activity is related to reduced arterial stiffness (Vaitkevicius *et al.*, 1993; Gando *et al.*, 2010; Miyazaki *et al.*, 2011; O'Donovan *et al.*, 2014). For that reason, a positive relationship between physical activity and arterial stiffness (baPWV) was an unexpected finding in the present study. This finding could be a statistical artifact as a result of intercorrelations with other variables; physical activity measures and baPWV were interrelated with WHR in CA older adults and with height in SA older adults. Despite the negative findings, positive correlations between physical activity and CBF were observed in both ethnic groups, further supporting the benefits of physical activity. There is growing evidence that supports the notion that physical activity attenuates age-related decline in CBF (Rogers *et al.*, 1990; Ainslie *et al.*, 2008). Chronic reduction in CBF in older adults with increased risk of cardiovascular diseases is associated with higher risk of cardiovascular mortality and stroke (Markus, 2004; Sabayan *et al.*, 2013). In this way, physical activity protects against the incidence of ischemic stroke. Some evidence suggests that the relationship between physical activity and CBF is mediated by an improvement in cerebral microvascular function (Barnes *et al.*, 2013; Murrell *et al.*, 2013; Bailey *et al.*, 2013), although relationships between physical activity and cerebrovascular reactivity to CO₂ were not observed in this study. Nonetheless, the beneficial effects of physical activity are multifaceted, and thus, emphasis should be placed on implementing

lifestyle interventions for high-risk ethnic minority populations that are culturally-targeted to reduce cardio- and cerebrovascular risk.

7.6 Ethnic Disparities in Cognitive Performance

The current study found that SA older adults were slower in performing reaction time cognitive tasks compared with CA older adults. These differences were not explained by differences in education. A growing body of literature suggests that greater central arterial stiffness is associated with accelerated brain aging (Waldstein *et al.*, 2008; Sugawara *et al.*, 2010; Mitchell *et al.*, 2011; Zeki Al Hazzouri *et al.*, 2013; Tsao *et al.*, 2013; Singer, 2014). These studies observed negative relationships between cognitive test scores and arterial stiffness using various cognitive tasks (rather than the reaction time tasks) to assess different cognitive domains, such as executive functioning, verbal learning, nonverbal memory, and visual-spatial processing. These tasks have not been validated for all linguistic and cultural groups, and therefore, they cannot be used cross-culturally to reliably represent an individual's true abilities or characteristics fairly without introducing bias (Rait *et al.*, 2000; Kristjansson *et al.*, 2003). For this reason, it was appropriate to choose simple and nonlinguistic processing speed tasks (sRT and cRT) for the present study to reduce language and cultural bias. No relationships were observed in the current study between cognitive performance and arterial stiffness or brain blood flow. The reason for the lack of relationship might be because reaction time tasks were not sensitive to measure subtle changes in cognitive function associated with vascular aging in this small study sample. Although the findings differ from other studies, the present study presented a preliminary exploration of cognitive function and arterial aging among ethnic groups, and hence, future investigations are warranted.

8 Limitations

The study findings must be interpreted in light of the following limitations: i) the cross-sectional design precludes causal inferences; ii) the small study sample limits the generalizability of results; iii) certain methodological limitations exist; and iv) data on nutrition or dietary status are lacking.

- i) The cross-sectional design of the study allowed comparisons to be made between ethnic groups and demonstrated several meaningful associations, but was not sufficient to establish causal or temporal relationships.
- ii) The study samples were small and selected at ease of participant availability, thereby limiting generalizability of the results. The CA participants were from a convenient sample of community-living older adults whose health status was maintained for university research, and the SA participants were exclusively Punjabi Sikh in origin, representing only one subgroup of the SA community. While the subgroups of the SA population are heterogeneous in regards to culture, lifestyle, religion, and socioeconomic status (Williams *et al.*, 2010), nonetheless they all share an elevated risk of cardio- and cerebrovascular diseases.

Another major issue with relatively small sample sizes is that significant differences between the groups may have been detected, but there is the risk of finding differences due to chance. Also, there is the possibility of missing real differences. As a result, it becomes difficult to interpret the implications of these results. Furthermore, the employment of extensive multiple comparison procedures and linear regressions would impose a statistical cost of loss of power. For this reason, a conservative approach was employed to maintain adequate statistical power to test the primary hypotheses of interest. The extent of linear regression analyses were restricted to preserve statistical power. While acknowledging these limitations, several

meaningful differences and relationships were identified that are consistent with the current literature. Most importantly, the study findings did confirm the primary hypotheses of this study in that i) arterial stiffness was elevated in SAs compared to age- and gender-matched CAs, and ii) greater arterial stiffness in SAs was associated with increased cerebrovascular resistance and corresponding decrease in aCBF. To verify the major outcomes of this study, future work should consider larger sample sizes which would be more representative of the general CA and SA populations (various SA subgroups included).

iii) The first methodological limitation was that data were not collected by a single investigator, which may have introduced an interpretation bias for differences between the two groups. Ideal to have one investigator collect and analyze data for both groups, unfortunately not feasible in this study. Possible interpretation bias was dealt with by standardization of data collection and analysis techniques across the two groups to preserve comparability. Furthermore, a major challenge for interpreting is to determine to what extent the observed differences are due to ethnicity *per se* versus to differences in exposure to cardiovascular risk factors accumulated with aging, particularly in studies involving older adult populations. Certainly, ethnic disparities in health outcomes between CA and SA populations are evident, yet the underlying mechanisms are not fully elucidated. Findings from this study do provide unique insight into physiological differences between CA and SA ethnic groups that call for future work to investigate causal pathways and mechanisms to explain these differences and associations.

Second, different capnography devices were used to monitor $ETCO_2$ in the CA and SA group, which might explain some of the differences observed in $P_{ET}CO_2$ levels between the two groups. Due to technical issues, the capnography device used for the CA group (Pilot 9200, Colin Medical Instruments, San Antonio TX, USA) had to be substituted with a different

device for the SA group (Ohmeda 5200 spectroscopy CO₂ Monitor, Madison WI, USA). There is a possibility that these devices had different pump speeds/sampling rates of the gas and different length and size of the sampling line that may have led to different ET_{CO}₂ readings. A slower sampling rate delays the response time of the initial rise of the signal, thereby slowing the time to reach the true peak (end-tidal) CO₂ value for every breath. This, in turn, can result in underestimation of the P_{ET}CO₂ values, and consequently, an underestimation of arterial PCO₂. Furthermore, long or wide sampling lines can slow the response time, allowing the air in the tube or particulate matter to mix with the inhaled gas, which can cause erroneous readings of the CO₂ values. Irrespective of these issues, both devices were consistent in the use of infrared absorption spectroscopy to continuously measure CO₂. Both devices were also calibrated by the same concentration of gas (5% CO₂) to ensure accurate CO₂ measurements. Most importantly, this study found that the absolute change in P_{ET}CO₂ when inhaling 5% CO₂ during hypercapnia was larger in SAs, which corresponded to a larger response in the change in MFV values. These results support the proposition that P_{ET}CO₂ (and arterial PCO₂) were indeed higher in SAs. Nevertheless, the differences in the capnography devices should be systematically examined in order to mitigate any issues that they may have influenced results.

Third, the posterior CBF through the vertebral arteries was not measured in this study. Vertebral arteries supply the brain a small portion (~20%) of the total CBF, whereas the majority (80%) of the total CBF is supplied by the (internal) carotid arteries (anterior CBF). Therefore, this study examined anterior CBF as a proxy measure of total CBF for the purpose to explore potential ethnic disparities in brain blood flow. In the future, measurements of both the posterior and anterior CBF will allow for the determination of total CBF.

Fourth, the direct body surface measurements of the distance between the brachial and ankle arterial sites might have underestimated the true arterial path length, thereby introducing a potential source of error in baPWV measurements. Differences in body contour and height might have introduced measurement errors (Bossuyt *et al.*, 2013; Sugawara *et al.*, 2014). Formulas that account for body height have been proposed but not yet validated in populations with different anthropomorphic characteristics (Van Bortel *et al.*, 2012; Levi-Marpillat *et al.*, 2013). Furthermore, there is no consensus in the literature regarding the optimal method to estimate pulse transit time. The present study estimated the pulse transit times by manually identifying the upstroke of each pressure wave, which is a time consuming process. Recently, Vardoulis and colleagues (2013) developed a computational algorithm (called diastolic patching) that determined the lowest point of the foot of the pressure waves based on the regional characteristic of that point. They proposed this method could accurately and precisely estimate the pulse transit time, but it has not yet been validated. Moreover, high resting HR can increase PWV measurements (Lantelme *et al.*, 2002; Erik *et al.*, 2004). Although the present study recorded pressure waveforms at the brachial and ankle arterial sites sequentially as opposed to simultaneously in the SA participants, resting HR did not significantly change between each measurement, indicating that HR variability in participants was minimal during the PWV assessment.

The fifth methodological limitation was that the Modelflow algorithm from the Finometer device may not have provided reliable estimates of model-derived cardiac output (Q) and total peripheral resistance (TPR) due to assumptions inherent in the algorithm. The algorithm is based on a three-element Windkessel model that represents the three major properties of the arterial system: aortic impedance, arterial compliance, and systemic (peripheral) vascular

resistance. Aortic impedance and compliance of the model depend on the elastic properties of the aorta and are estimated from the nonlinear aortic pressure-area relationship, which was originally derived from a *post mortem* study (Langewouters et al., 1986). Langewouters and colleagues (1986) found that the aortic cross-sectional area is a function of pressure and a function of the individual's age, gender, height and weight. However, this relationship does not capture aortic stiffening as a function of pressure. As arteries stiffen, they do not exhibit large changes in cross-sectional area in response to change in pressure. As a consequence, the Modelflow algorithm may not provide accurate estimates for individuals with stiff arteries. In addition, the algorithms used were not ethnic-specific, and thus, results should be interpreted with caution.

Sixth, the order of the cerebrovascular reactivity to CO₂ in hypocapnic and hypercapnic conditions was not randomized. Hypocapnia was conducted prior to hypercapnia so that the CA and SA group protocol was consistent. To mitigate potential lingering effects of an individual's response in the first condition influencing the response in the second condition, each participant was given 3 minutes between conditions, which was considered more than the ample time, to recover. Another generic methodological obstacle during cerebrovascular reactivity assessments is the use of P_{ET}CO₂ as an estimate of arterial PCO₂ (Robbins *et al.*, 1990). P_{ET}CO₂ tends to overestimate arterial PCO₂ in hypercapnic conditions, and consequently may lead to inaccurate estimates of cerebrovascular reactivity in hypercapnia (Peebles *et al.*, 2007; Willie *et al.*, 2012). The method to overcome this obstacle is to implement invasive arterial blood sampling of CO₂; indirect estimation from expired gases is a method that encumbers all studies.

Seventh, the major assumption of the TCD was that the MCA diameter did not change during experimental assessments; therefore, any change in cerebral blood flow velocity directly represented a change in cerebral blood flow (CBF). This assumption was based on previous studies that demonstrated minimal change in the MCA diameter in response to manipulations of $ETCO_2$ (Bishop *et al.*, 1986; Nuttall *et al.*, 1996; Valdueza *et al.*, 1997; Serrador *et al.*, 2000; Peebles *et al.*, 2007). Although widely adopted, this assumption has received legitimate criticism. Studies have found that the MCA diameter increases in hypercapnia (Valdueza *et al.*, 1999; Coverdale *et al.*, 2014). However, in the absence of magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging techniques that directly measure CBF (Calamante *et al.*, 1999; Zande *et al.*, 2005; Vernooij *et al.*, 2008), TCD was an alternative method to measure changes in CBF under the assumption that the manipulation of P_{ETCO_2} was within the range that did not result in significant changes in the MCA diameter.

Furthermore, the indices of cerebrovascular resistance (RI, PI, CVRi and CVR) were based on assumptions that must be considered when interpreting the findings. RI and PI were derived from the velocity spectral tracings to provide quantitative measures of flow patterns and resistance of the downstream cerebrovascular beds. PI has been used to describe the pulsatile characteristics of CBF and to reflect distal cerebrovascular resistance (Giller *et al.*, 1990; Lim *et al.*, 2009). However, PI does not solely represent the downstream resistance in the cerebral microcirculation; rather, PI is viewed as a complex function of several hemodynamic factors in addition to resistance, including cerebral perfusion pressure, compliance of cerebral arterial bed, and heart rate (de Riva, 2012). Another drawback of RI and PI is that these indices do not account for the role of arterial pressure in CBF regulation. For this reason, CVRi (and

CVR), which does account for arterial pressure in the formula, was another index of cerebrovascular resistance used in this study. CVR_i (and CVR) was estimated by the ratio of perfusion pressure, which was estimated by MAP corrected for the hydrostatic pressure difference at the level of the MCA, to the mean CBF velocity (and CBF). This relationship assumes that CBF ceases when the pressure is zero. However, it has been theoretically described that CBF stops when the cerebral vessels collapse below a critical threshold pressure (Burton, 1951; Dewey *et al.*, 1974; Panerai *et al.*, 1999; Aaslid *et al.*, 2003), thereby affecting the interpretation of CVR_i (and CVR). Alternative resistance indices that have been recommended by others are critical closing pressure and resistance area product. The critical closing pressure refers to the theoretical pressure at which CBF is zero. Direct measurements of the critical closing pressure are unethical in humans because it would require lowering arterial pressure to reach zero flow in the brain. Therefore, the critical closing pressure can be estimated by extrapolation from a linear model of the instantaneous relationship between cerebral blood flow velocity and blood pressure. The resistance area product represents the passive resistance between flow velocity and pressure. These measures have shown promising results in understanding the subtle changes in cerebrovascular tone (Robertson *et al.*, 2014), and could be pursued in future studies to examine potential differences between ethnic populations. Clearly, several indices exist that aid in understanding the complex cerebrovascular system. Each of these indices provide unique information about hemodynamics in the cerebral vessels (Weyland *et al.*, 2000; Kidwell *et al.*, 2001; Gouveia *et al.*, 2014; Varsos *et al.*, 2014).

Lastly, the non-invasive, continuous monitoring of daily physical activity by the arm-band device (SWA) might have overestimated the resting metabolic rate (RMR) when compared to

the gold standard indirect calorimetry method (Heiermann *et al.*, 2011), resulting in inaccurate estimates of the energy expended doing daily activities (AEE). Heiermann and colleagues (2011) have postulated that this could be due to age-related changes in skin conductance and temperature. Older adults have thinner, dryer skin, and sweating rates are lower (Silver *et al.*, 1964), which can affect the sensitivity of the SWA sensors, and therefore, impact the accuracy of the SWA algorithm estimations. For the purpose of this study, the SWA was an appropriate tool to assess physical activity and activity of daily living in older adults within a free-living setting with little disruption to their activity. The SWA data were also used to supplement the self-reported physical activity data, which are subject to recall bias and translation bias.

- iv) The present study did not examine the differences in dietary intake between the CAs and SAs. The justification of this decision was that there are no standardized dietary assessment tools that account for culture-specific foods. The dietary assessment tools currently used in research have been developed and validated in general populations (Beer-Borst & Amadò, 1995; Klipstein-Grobusch *et al.*, 1998; Hu & Rimm, 1999; Jain *et al.*, 2003). Some multi-ethnic cohort studies have evaluated the validity of diet records, but they have raised concerns about measurement errors in the design, analysis, and interpretation that likely result in underestimations of the actual food intake (Kristal & Feng, 1997; Kelemen *et al.*, 2003; Mai *et al.*, 2007). The food typical of SA diets is not commonly included in the food lists, and often times the diet is composed of complex dishes for which it is difficult to quantify individual amounts of recipe ingredients. There is a need for culture-specific diet assessment methods that are accurate and can be comparable between groups. As well, the rather small sample size of the present study would likely be subject to a high degree of variability in food intake between participants. As a result, meaningful interpretations of the results or reaching

definitive conclusions become difficult to achieve. Furthermore, dietary intake was not collected in the comparison group (CA group). Taken together, it was considered impractical to collect data on the diet of SA participants. In this regard, potential dietary effects cannot be discounted as studies have shown that certain diets can alter the degree of arterial stiffness (Avolio *et al.*, 1986; Gates *et al.*, 2004; Aatola *et al.*, 2010; Chan *et al.*, 2014).

9 Future Directions

In light of the small, cross-sectional design of this study, larger sample size studies are needed to confirm the findings. Furthermore, based on the study findings that SA older adults have stiffer central arteries than CA older adults, it's possible that SAs have *accelerated* vascular aging. Increased arterial stiffness has been reported in young, healthy SAs in comparison to age- and gender-matched CAs (Din *et al.*, 2006), implying that the vascular structure and function changes occur early in life for SAs. The well-described phenomenon of arterial stiffness and decline in CBF with aging may be enhanced in SAs at an early age. Future work should consider comparing young and old SAs and also follow them, along with CAs, prospectively to evaluate racial differences in the longitudinal change in arterial stiffness and its role in the differential development of cardio- and cerebrovascular diseases between these ethnic groups. These studies would determine whether arterial stiffness is accelerated with advancing age in SAs compared to CAs at younger age, or if it is accelerated in SAs later in life. The indicators of increased arterial stiffness, including faster PWV, decreased compliance, and elevated central pulse pressure, that were observed in SAs in this study all have clinical relevance in predicting cardio- and cerebrovascular disease events and mortality in the general population (Shokawa *et al.*, 2005; Sutton-Tyrrell *et al.*, 2005; Mattace-Raso *et al.*, 2006; Tsivgoulis *et al.*, 2006; Mitchell *et al.*, 2010). In this regard, assessment of the prognostic value of arterial stiffness in high-risk populations like the SAs warrant further investigation. In addition, longitudinal studies are required to delineate the temporal relationship between central arterial stiffness and hemodynamic changes in the cerebral circulation that may associated with increased risk of cerebrovascular damage (Henskens *et al.*, 2008; Mitchell *et al.*, 2011; Poels *et al.*, 2012a).

Indeed, increased arterial stiffness in SAs may be a complex integration of the effects of genetics (Lacolley *et al.*, 2009) and cumulative damage of cardiovascular risk factors on the vasculature over time, but this progression of arterial stiffness can be slowed down with lifestyle interventions, such as regular physical activity (Tanaka *et al.*, 2000), medications (Ferrier *et al.*, 2002; Ichihara *et al.*, 2005; Kanaki *et al.*, 2013; Oh *et al.*, 2014), and with modifying other cardiovascular risk factors (e.g., hypertension, diabetes, and hyperlipidemia). It is unknown the extent to which these factors attenuate arterial stiffening in SA populations, and therefore, future work should consider examining the intensity level of physical activity and dose of medication that may be needed to reduce arterial stiffness in high-risk populations, such as SAs, who have elevated arterial stiffness compared to the rest of the population. Also, these studies must consider the cultural barriers towards interventions that may pose particular challenge when studying the SA ethnic population. Furthermore, it may be beneficial to target the SA population at a young age to help to reduce the risk for early development of future cardiovascular events (van de Laar *et al.*, 2010).

Atherosclerosis may also contribute directly to the acceleration of vascular aging in SA populations. A follow up investigation is required to determine plaque prevalence in SAs and to examine whether plaque and IMT progression in SAs is similar to or greater than that of other ethnic groups. It would be valuable to evaluate the factors that contribute to the progression of subclinical atherosclerosis in this population to understand the underlying mechanisms contributing to the ethnic disparities in disease risk and prevalence. Genetic factors are currently being studied in SAs to understand the genetic link to cardio- and cerebrovascular diseases. Some studies have found strong genetic predisposition to diabetes (Kooner *et al.*, 2011) and coronary artery disease (Kooner *et al.*, 2011), but it is unclear whether there is a genetic contribution (i.e.

change in gene expression or gene polymorphism) to vascular remodeling and increased age-related arterial stiffening in SAs (Medley *et al.*, 2003, 2004; Mitchell *et al.*, 2005). Understanding the genetic basis is essential to identify the molecular pathways that might be involved in ethnic differences in susceptibility and pathology of diseases.

10 Conclusion

The major findings of the present investigation were that SA older adults had larger pulse pressures, lower diastolic pressure, and reduced central arterial compliance – all indicators of arterial stiffening – compared to age- and gender-matched white Caucasian older adults. This study supports a link between increased central arterial stiffness, specifically reduced arterial compliance, and increased cerebrovascular resistance which in turn is associated with reduction in CBF in SAs. Furthermore, the extent of atherosclerosis as measured by IMT appeared to be less pronounced in SAs compared to CAs, but greater IMT in SAs was associated with even greater increase in pulsatile and resistant blood flow in the cerebral vessels. Taken together, these findings suggest that cerebrovascular hemodynamic changes may be influenced by the structural and functional alterations of central arteries, and that this appears to be more pronounced in SAs. It seems reasonable to speculate that SAs are vulnerable to the harmful effects of arterial stiffening, particularly in old age. Increased arterial stiffness may underlie the disproportionate burden of cardio- and cerebrovascular diseases, such as myocardial infarction and stroke, in SAs. A greater understanding of the determinants of increased arterial stiffness in this high risk ethnic population is required to inform intervention efforts to slow the process of arterial stiffness with aging and its effects on organs, such as the brain.

The study findings provide unique and meaningful insight into physiological differences between CAs and SAs before the onset of overt cardio- and cerebrovascular diseases. Given that SAs have greater susceptibility and prevalence of these diseases, follow up investigations are required to determine whether differences in arterial stiffness and cerebrovascular hemodynamic properties are early indicators of cardio- and cerebrovascular disease processes, thereby being useful predictors of future disease development. The key to managing potentially preventable and

treatable diseases in high risk populations lies in understanding the underlying mechanisms that contribute to the ethnic disparities in health outcomes. This study reveals highly relevant ethnic disparities that could aid in understanding differences in disease risk.

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APPENDIX A – INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

- Male and female participants of South Asian origin (immigrant or Canadian-born) greater or equal to 65 years of age and older

Exclusion Criteria

- History of stroke (cerebrovascular disease);
- Carotid endarterectomy or stent;
- Atrial fibrillation or heart failure;
- Heart attack/angina;
- Open heart surgery;
- Chronic inflammatory diseases, such as arthritis;
- Neurological disorders, such as Parkinson's disease;
- Diagnosed with dementia or cognitive disorders;
- Signs of cognitive deficits demonstrated by the inability to understand and provide informed written consent for participation in the study;
- Significant hearing and vision problems identified by self-report;
- Metastatic or current cancer;
- Chronic kidney disease;
- Unstable health (overnight hospitalization with the past 12 months);
- Previous allergic, sensitivities or other reactions to gels or adhesives that may be used for the heart rate electrode

APPENDIX B – AGING HEALTH QUESTIONNAIRE

Health History

1. Your Background

1. What is your birthdate?
_____ (MM/DD/YYYY) (____ years old)

2. People living in Canada come from many different cultural and racial backgrounds.
Are you? (Check (✓) all that apply)
 Aboriginal 1st Nation Inuit Métis
 White Black Southeast Asian (*i.e.*, Vietnamese)
 Filipino Chinese South Asian (*i.e.*, East/South Indian, Pakistani)
 Latin American Other: _____

3. What is your primary language? _____
4. What language did **you** first learn to speak as a child? _____

5. In what languages can **you** conduct a conversation? _____

6. What is **your** birthplace?
City/Town _____ Province _____
If born outside Canada, Country _____ Years in Canada: _____

7. What is **your mother's** birthplace?
City/Town _____ Province _____
If born outside Canada, Country _____

8. What is **your father's** birthplace?
City/Town _____ Province _____
If born outside Canada, Country _____

2. Your Marital Status

- never married
- married or living with a partner
- widowed, not currently married
- divorced, not currently married
- separated

3. Your Education

1. What are your total years of formal education (includes grades 1 and higher):
_____years

2. What diplomas, certificates or degrees have you obtained?

(Check (√) all that apply)

- | | |
|--|---|
| <input type="checkbox"/> None | <input type="checkbox"/> High School |
| <input type="checkbox"/> Trade certificate/diploma | <input type="checkbox"/> Community college diploma |
| <input type="checkbox"/> University undergraduate degree | <input type="checkbox"/> University graduate degree |

4. Your Occupation

1. What kind of work did you do for most of your life?

2. If you did not work for pay, what did your spouse do for most of their life?

3. Are you working for pay now?

- If yes, please check (√):
- casual
 - part time
 - full time

If no, year last worked _____ or never worked

5. Your Related Chronic Health Checklist (Check (✓) all that apply to you)

<input type="checkbox"/> Hypertension (high blood pressure) (<i>Go to Question 1a</i>) <input type="checkbox"/> Hyperlipidemia (high cholesterol) (<i>Go to Question 1b</i>) <input type="checkbox"/> Diabetes mellitus (<i>Go to Question 1c</i>) <input type="checkbox"/> Insulin Dependent	<u>Cardiovascular (heart) risk factors:</u> <input type="checkbox"/> Hypertension (high blood pressure) (<i>Go to Question 1a</i>) <input type="checkbox"/> Hyperlipidemia (high cholesterol) (<i>Go to Question 1b</i>) <input type="checkbox"/> Diabetes mellitus (<i>Go to Question 1c</i>) <input type="checkbox"/> Insulin Dependent	<input type="checkbox"/> Irritable bowel syndrome <input type="checkbox"/> Heart burn/esophageal reflux disease (GERD) <input type="checkbox"/> Peptic ulcer disease <input type="checkbox"/> Gall bladder <input type="checkbox"/> Other: _____ <input type="checkbox"/>	<u>Gastrointestinal (stomach/intestine):</u> <input type="checkbox"/> Irritable bowel syndrome <input type="checkbox"/> Heart burn/esophageal reflux disease (GERD) <input type="checkbox"/> Peptic ulcer disease <input type="checkbox"/> Gall bladder <input type="checkbox"/> Other: _____ <input type="checkbox"/>
<input type="checkbox"/> Chronic bronchitis <input type="checkbox"/> Emphysema <input type="checkbox"/> Asthma <input type="checkbox"/> Other lung disease: _____ <input type="checkbox"/> Sleep apnea <input type="checkbox"/> Other sleep disorders: _____ <input type="checkbox"/>	<u>Pulmonary (lung):</u> <input type="checkbox"/> Chronic bronchitis <input type="checkbox"/> Emphysema <input type="checkbox"/> Asthma <input type="checkbox"/> Other lung disease: _____ <input type="checkbox"/> Sleep apnea <input type="checkbox"/> Other sleep disorders: _____ <input type="checkbox"/>	<input type="checkbox"/> Osteoporosis <input type="checkbox"/> Low intensity trauma fracture <input type="checkbox"/> Hip <input type="checkbox"/> Vertebral <input type="checkbox"/> Wrist <input type="checkbox"/> Osteoarthritis <input type="checkbox"/> Other: _____	<u>Musculoskeletal(muscles/bones):</u> <input type="checkbox"/> Osteoporosis <input type="checkbox"/> Low intensity trauma fracture <input type="checkbox"/> Hip <input type="checkbox"/> Vertebral <input type="checkbox"/> Wrist <input type="checkbox"/> Osteoarthritis <input type="checkbox"/> Other: _____
<input type="checkbox"/> Seizure disorder <input type="checkbox"/> Migraine <input type="checkbox"/> Depression <input type="checkbox"/> Schizophrenia <input type="checkbox"/> Manic depression/bipolar <input type="checkbox"/> Anxiety disorder (generalized, panic, phobia, etc.) <input type="checkbox"/>	<u>Neurological (Brain)/Psychiatric (Mood):</u> <input type="checkbox"/> Seizure disorder <input type="checkbox"/> Migraine <input type="checkbox"/> Depression <input type="checkbox"/> Schizophrenia <input type="checkbox"/> Manic depression/bipolar <input type="checkbox"/> Anxiety disorder (generalized, panic, phobia, etc.) <input type="checkbox"/>	<input type="checkbox"/> Sickle cell anemia <input type="checkbox"/> Hypercoaguable (blood clotting) states or related conditions: <input type="checkbox"/> DVT - deep vein thrombosis <input type="checkbox"/> Pulmonary emboli - blood clot in the lung	<u>Anemia (blood disorders):</u> <input type="checkbox"/> Sickle cell anemia <input type="checkbox"/> Hypercoaguable (blood clotting) states or related conditions: <input type="checkbox"/> DVT - deep vein thrombosis <input type="checkbox"/> Pulmonary emboli - blood clot in the lung
<input type="checkbox"/> _____ Specify type and location:	<u>Cancer:</u> Specify type and location: _____	<input type="checkbox"/>	<u>Color blind</u>

1. How long have you had:
- a) Hypertension? _____ years.
- b) Hyperlipidemia? _____ years.
- c) Diabetes? _____ years.

6. Your Surgeries

Date (month and year)	Surgery (type of surgery, area of body)

7. Your Medications (including supplements) taken within the last week.

Medication Name (Prescription: Y/N)	Strength (mg)	Route: (e.g. by mouth, on skin, inhaled)	Frequency: (e.g., 1x/day, 4x/day)	Duration: (How long have you been taking the medication, in years?)

1. Do you take any herbal medications?

Yes

No

2. What is the purpose of taking the herbal medicine?

8. Medication Adherence

Thinking of the medications PRESCRIBED to you by your doctor(s), please **circle** the most appropriate response for each question.

1. Do you ever forget to take your medications?

Never

Rarely

Sometimes

Often

Always

2. Are you careless at times about taking your medications?

Never

Rarely

Sometimes

Often

Always

3. When you feel better, do you sometimes stop taking your medications?

Never

Rarely

Sometimes

Often

Always

4. Sometimes if you feel worse when you take your medications, do you stop taking them?

Never

Rarely

Sometimes

Often

Always

5. Many people have trouble taking their medications exactly as prescribed by their doctor. Thinking back to the last time you didn't take your medication(s) as prescribed, can you describe why?

9. Your Family Health History

Please make a **checkmark** (✓) for family members (**blood relations only**) who have any of these conditions or has passed away from them.

CONDITION	Mother	Father	Brothers	Sisters	Sons	Daughters
Heart Attack						
Angina						
High Blood Pressure						
Peripheral Vascular Disease						
Stroke						
Dementia						

10. Alcohol Use

The next 6 questions are about drinking alcoholic beverages.

Included are liquor (such as whiskey or gin), beer, wine, wine coolers and any other type of alcoholic beverage.

1 drink = 12 oz. of beer
 = 5 oz. of wine
 = 1 ½ oz. of liquor

- In **any one year**, have you had at least 12 drinks of any type of alcoholic beverage?
 - Yes (*go to Question 3*)
 - No (*Continue to Question 2*)

2. In your **entire life**, have you had at least 12 drinks of any type of alcoholic beverage?

Yes

No (*end of alcohol questions* → *Go to **12. Tobacco Use** section.*)

3. In the **past 12 months**, how **often** did you drink any type of alcoholic beverage?
(That is, how many days per week, per month or per year did you drink?)

Number of days: _____ per (*check one*) week
 month
 year

4. In the **past 12 months**, on those days that you drank alcoholic beverages, on average, **how many drinks** did you have?

Number of drinks: _____

5. In the **past 12 months**, on how many days per week, per month or per year did you have **5 or more drinks** of any alcoholic beverage in a single day?

Number of days: _____ per (*check one*) week
 month
 year

6. Was there **ever a time or times in your life** when you drank **5 or more drinks** of any kind of alcoholic beverage **almost every day**?

Yes

No

11. Tobacco Use

Section A is about cigarette smoking.

Section B is about cigar, pipe and other tobacco use.

Section A

1. Have you smoked at least 100 **cigarettes** in your **entire life**?

- Yes
- No (*go to Section B – Question 1*)

2. How **old** were you when you **first started** to smoke cigarettes fairly regularly?

_____ age (in years)

- never smoked cigarettes fairly regularly

3. Do you **now** smoke cigarettes? (check one)

- every day (*go to Question 6*)
- some days (*go to Question 6*)
- not at all (*Continue to Question 4*)

4. a) How **old** were you when you **last smoked** cigarettes fairly regularly?

_____ age (in years)

b) If you quit smoking regularly in this past year, how many weeks has it been?

_____ weeks

5. At **that time**, how many cigarettes did you **usually** smoke per day?

1 pack = 20 cigarettes

Number of cigarettes/day _____

or

Number of packs/day_____

*(If you no longer smoke, skip **Questions 6 & 7** → go to **Section B**)*

Current Smoking status:

6. During the **past 30 days**, on how many days did you smoke cigarettes?

Number of days_____

7. During the **past 30 days**, on the days that you smoked, how many cigarettes did you smoke per day?

1 pack = 20 cigarettes

Number of cigarettes/day_____

or

Number of packs/day_____

Section B

Cigars include cheroots and cigarillos.
Smokeless tobacco includes chewing tobacco or snuff.

1. Have you **ever** smoked a pipe, smoked a cigar or used smokeless tobacco?

Pipe No Yes

Cigar No Yes

Smokeless tobacco No Yes

*(If 'No' to all→ go to **12. Physical Activity** section).*

2. How **old** were you when you first started to smoke a pipe/cigar/smokeless tobacco regularly?

_____ Age (in years)

never smoked regularly

3. Do you **currently** smoke a pipe, smoke a cigar or use smokeless tobacco?

Pipe	<input type="checkbox"/> No	} <i>go to Question 4</i>	<input type="checkbox"/> Yes	} <i>go to Question 5</i>
Cigar	<input type="checkbox"/> No		<input type="checkbox"/> Yes	
Smokeless tobacco	<input type="checkbox"/> No		<input type="checkbox"/> Yes	

4. a) How **old** were you when you **last smoked** a pipe/cigar/smokeless tobacco regularly?

_____ age (in years)

a) If you quit smoking regularly in this past year, how many weeks has it been?

_____ weeks.

*Go to **12. Physical Activity** section.*

5. On average, how **many times a week** do you smoke a pipe, smoke a cigar or use smokeless tobacco?

Pipe _____ (times per week)

Cigar _____ (times per week)

Smokeless tobacco _____ (times per week)

6. On **average**:

How many pipes full of tobacco do you smoke each week? _____

How many cigars do you smoke each week? _____

How much smokeless tobacco do you use each week? _____

12. PHYSICAL ACTIVITY

Physical activity is any form of body movement that requires effort, but does not include routine activities of daily living such as self-care and cooking. Physical activity can be required for work or transportation, or for pleasure.

The **intensity** of physical activity refers to the amount of effort you put into the activity. It can be judged on a 10-point scale, where '0' is sitting and '10' is all out effort, or it can be described in terms of how much you are sweating and breathing. To help us group activities together, we split intensity into 3 categories: **LIGHT**, **MODERATE** and **HARD**.

LIGHT: 2-4 on a scale from 0-10.
No sweating, but faster breathing.
(e.g., walking)

MODERATE: 5-6 on a scale from 0-10.
Some sweating and deeper breathing,
but still able to talk comfortably.
(e.g., brisk walking or biking)

HARD: 7-8 on a scale from 0-10.
Heavy sweating and heavy breathing
with difficulty talking.
(e.g., running or swimming)

1. This question asks you to list specific activities that you have regularly performed **during the past 4 months**. List any regular activity from gardening to running. Circle the appropriate **Frequency** and **Duration** for each **Activity** you list. **Intensity** might vary within the activity. Please indicate the percentage of time you spend at each **Intensity** for all the **Activities** you list. An example listing has been completed in the first row.

Activity Description	Frequency (# of sessions per week)	Duration (minutes per session)	Intensity (described above)
e.g. Cycling	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard <u>50%</u> <u>50%</u> <u>0%</u>
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ____% ____% ____%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ____% ____% ____%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ____% ____% ____%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ____% ____% ____%
	1-2 3-4 5+	up to 20 20-30 30-60 60+	Light Moderate Hard ____% ____% ____%

2. This question asks you about the amount of regular physical activity you perform. Only consider activities you perform for **at least 20 continuous minutes** at a time.

Please check one box in each intensity category that describes the frequency of your average physical activity habits **during the past year.**

a) I have engaged in **LIGHT** physical activity:

- No days per week
- 1 to 4 days per week
- At least 5 days per week

b) I have engaged in **MODERATE** physical activity:

- No days per week
- 1 or 2 days per week
- 3 or 4 days per week
- At least 5 days per week

c) I have engaged in **HARD** physical activity:

- No days per week
- 1 or 2 days per week
- 3 days per week
- At least 4 days per week

3. Next, we would like to know about your average Physical Activity level at specific periods in your **entire adult life**. For each time period, please indicate the how often you participated in LIGHT, MODERATE and HARD physical activity.

Your age, in years	Physical Activity		
	Light (Check one)	Moderate (Check one)	Hard (Check one)
64 years to present (minus the year you already answered in Question 2)	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 to 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 or 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 days per week <input type="checkbox"/> At least 4 days per week
51-64 years	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 to 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 or 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 days per week <input type="checkbox"/> At least 4 days per week
31 – 50 years	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 to 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 or 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 days per week <input type="checkbox"/> At least 4 days per week
18-30 years	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 to 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 or 4 days per week <input type="checkbox"/> At least 5 days per week	<input type="checkbox"/> No days per week <input type="checkbox"/> 1 or 2 days per week <input type="checkbox"/> 3 days per week <input type="checkbox"/> At least 4 days per week

4. These next questions are about strength training (weight lifting).

a) In the **last year**, I have been lifting weights, on average (*check one*):

Twice or more a week Once a week Less than once a week

Never

b) In my **entire adult life**, I have been lifting weights, on average (*check one*):

Twice or more a week Once a week Less than once a week

Never

Additional Comments:

Fitness Centers/Clubs

1. Do you belong to a fitness group or club (*i.e.*, in your building or in and around your neighborhood)?

__Yes

__No

End of Questionnaire.

**APPENDIX C – SELF-REPORTED PHYSICAL ACTIVITY SCORING
GUIDELINE**

a) I have engaged in **LIGHT** physical activity:

- | | |
|----------|---|
| 0 | <input type="checkbox"/> No days per week |
| 1 | <input type="checkbox"/> 1 to 4 days per week |
| 2 | <input type="checkbox"/> At least 5 days per week |

b) I have engaged in **MODERATE** physical activity:

- | | |
|----------|---|
| 0 | <input type="checkbox"/> No days per week |
| 2 | <input type="checkbox"/> 1 or 2 days per week |
| 3 | <input type="checkbox"/> 3 or 4 days per week |
| 5 | <input type="checkbox"/> At least 5 days per week |

c) I have engaged in **HARD** physical activity:

- | | |
|----------|---|
| 0 | <input type="checkbox"/> No days per week |
| 3 | <input type="checkbox"/> 1 or 2 days per week |
| 7 | <input type="checkbox"/> 3 days per week |
| 9 | <input type="checkbox"/> At least 4 days per week |

Add the scores for a, b and c:

Inactive: 0-2 points

Active Lifestyle: 3-6 points

Highly Active: >7 points

APPENDIX D – SUPPLEMENTARY ANALYSES

Supplementary Table 1. Physical Activity Measurements in Participants with Two-Day and Three-Day Data Collection

	CA			SA		
	2 days (n=2)	3 days (n=20)	p- value†	2 days (n=7)	3 days (n=13)	p- value†
TEE, kcal/day	1974 ± 278	2359 ± 396	0.198	1946 ± 456	2193 ± 408	0.231
Steps, count/day	8530 ± 4622	8052 ± 2651	0.819	5601 ± 3065	5636 ± 2665	0.979

Data were presented as mean ± SD. TEE, total energy expenditure.

† Statistical significance using two-tailed unpaired t-test. $p \leq 0.05$ was considered statistically significant.

Supplementary Table 2. Physical Activity Data Collection during the Weekdays Only and Including Weekends

	CA			SA		
	Weekdays only (n=10)	Includes Weekends (n=12)	p-value†	Weekdays only (n=13)	Includes Weekends (n=7)	p-value†
PAEE, kcal/day §	17 ± 7	18 ± 7	0.798	15 ± 10	16 ± 5	0.902
Duration of PA, hour/day §	1.1 ± 0.4	1.1 ± 0.4	0.809	1.0 ± 0.6	1.0 ± 0.3	0.880

Data were presented as mean ± SD. TEE, total energy expenditure; PAEE, physical activity-related energy expenditure; PA, physical activity.

§ Duration of daily PA and PAEE were square root transformed.

† Statistical significance using two-tailed unpaired t-test. $p \leq 0.05$ was considered statistically significant.

Supplementary Table 3. Multiple Linear Regression Model of Ethnicity and End-Tidal Carbon Dioxide with Anterior Cerebral Blood Flow

Dependent Variable	Ethnicity	Models	β	p-value[†]	Model Adjusted R²
aCBF	CA (n=19)	P _{ET} CO ₂	-0.004	0.62	0.00
	SA (n=21)	P _{ET} CO ₂	0.024	0.02	0.21
	Both (n=41)	P _{ET} CO ₂	0.012	0.03	0.09
		P _{ET} CO ₂	0.009	0.16	0.09
		Ethnicity	0.046	0.35	
		P _{ET} CO ₂	0.004	0.64	0.18
		Ethnicity	-1.047	0.04	
P _{ET} CO ₂ * Ethnicity	-0.028	0.03			

aCBF, anterior cerebral blood flow; CA, white Caucasians; SA, South Asians; P_{ET}CO₂, end-tidal carbon dioxide.

Data were presented as parameter estimates (β) for P_{ET}CO₂, ethnicity and the interaction term between ethnicity and P_{ET}CO₂, significance of parameter estimate (p-value), and explained variance R² of the model.

[†] Statistical significance using two-tailed unpaired t-test. $p \leq 0.05$ was considered statistically significant.