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Impacts of Systemic Hemodynamic Factors on Cerebral and Peripheral Perfusion

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Impacts of Systemic Hemodynamic Factors on Cerebral and Peripheral Perfusion

by

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Dedication

To my beloved aunt, Assoc. Prof. Pradab Prasatkeaw, who inspired me and helped me fall in love with cardiovascular physiology.

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Impacts of Systemic Hemodynamic Factors on Cerebral and Peripheral Perfusion

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Changes in physiological factors involving modulation of hemodynamics such as baroreflex sensitivity (BRS), heart rate, and/or blood pressure influence blood flow to downstream tissues leading to changes in response and/or function of tissues. For example, a sufficient increase in heart rate elicits greater accumulative shear stimuli on a per minute basis leading to a greater vasodilatory response of endothelial cells and providing greater perfusion to skeletal muscle. The high-flow and low-impedance nature of the cerebral circulation leads to increased susceptibility to damage from considerable blood pressure fluctuations. For this reason, the cerebrovasculature holds a very narrow range of operation of cerebral autoregulation in response to changes in perfusion pressure.[1] In a nondemented elderly population[2] and patients with Alzheimer's disease, impaired BRS has been linked with poor cognitive function[3] and a link between high pulsatile components of blood pressure (i.e., pulse pressure) and impaired cognitive function has also been reported.[4]

Three research investigations were included in this dissertation study. The first study was to determine the association between heart rate at rest and endothelium-dependent vasodilation as assessed by flow-mediated dilation (FMD) of the brachial artery. The primary findings from study 1 revealed an indirect association between heart

rate and FMD through shear stimuli. The studies 2 and 3 sought to determine the association of regional cerebral perfusion with cardiovagal BRS and blood pressure components. A link between cardiovagal BRS and regional cerebral perfusion of the hippocampus was demonstrated in the study 2. This finding may add mechanistic insight to the relationship between impaired BRS and cognitive dysfunction. The primary finding from the study 3 revealed a significant relationship between peripheral pulsatile blood pressure components and regional cerebral perfusion of the hippocampus as well as anterior white matter. This finding highlights the importance of pulsatile pressure on cerebral vascular beds. Taken together, the overall findings from this dissertation study indicate the potential impacts of systemic hemodynamic factors on cerebral and peripheral perfusion. Future longitudinal studies in nondemented elderly and individuals with Alzheimer's disease are warranted to reveal the causality of these associations.

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Chapter 1: General Introduction

The tight regulation of the circulatory system is essential for ensuring proper blood flow to downstream tissues. Changes in physiological factors that regulate hemodynamics, such as baroreflex sensitivity (BRS), heart rate, and/or blood pressure, influence vasoactive states and perfusion function. For instance, sufficient increases in heart rate elicit higher accumulative shear stimuli on a per minute basis, which could induce greater vascular endothelial responses. Understanding the association between heart rate and endothelial function may provide further mechanistic insight into the beneficial effects of exercise training on vascular function.

Exercise training provides benefits not only to the vascular beds that are involved during the session, but also to those in nonworking sites or limbs.[5-7] This phenomenon could be explained by increased shear stimuli in nonworking limbs during an exercise bout.[8] Changes in systemic hemodynamic factors influence not only peripheral blood flow but also cerebral blood flow. The brain is a vital organ with high-flow and low-impedance vascular beds. Therefore, it is one of the regions most susceptible to dramatic blood pressure fluctuations. Hypoperfusion to the brain from a failure to control steady perfusion pressure could potentially cause damage to brain tissues[9] resulting in impaired cognitive function. The importance of an extra-cranial mechanism to ensure proper cerebral blood flow was suggested by a recent study showing a very narrow range of operation of cerebral autoregulation in response to changes in blood pressure.[1] High pulsatile components of blood pressure (i.e., pulse pressure) were demonstrated to be

linked with poorer cognitive function.[4] Greater pulse pressure, a surrogate marker of arterial stiffness[10], may cause accumulated damages in the microvasculature of the brain due to excessive pulsatile stress.

Taken together, this background lends support to the importance of systemic hemodynamic factors on cerebral and peripheral circulations. Understanding the associations between these hemodynamic factors and cerebral and peripheral perfusion may allow for greater insight into both physiological impacts (e.g., exercise training) and pathological impacts (e.g., hypoperfusion and impaired cognitive function) of systemic hemodynamic control.

PURPOSES AND HYPOTHESES

This dissertation study aims to further understand the effects of systemic hemodynamic factors on cerebral and peripheral perfusions. Three specific aims were addressed, each of which focused on different components of systemic hemodynamic factors and their relationship to either cerebral blood perfusion or peripheral vascular function.

Study #1: The aim of study 1 was to determine whether heart rate at rest influences endothelium-dependent vasodilation via shear stimuli. We hypothesized that the association between heart rate at rest and flow-mediated dilation was mediated by shear stimuli.

Study #2: The aim of study 2 was to determine the association between BRS and regional cerebral perfusion. We hypothesized that cardiovagal BRS was inversely related to cerebral perfusion in regions of the brain.

Study #3: The aim of study 3 was to determine the associations between blood pressure components (i.e., steady state and pulsatile blood pressure components) and regional cerebral perfusion. We hypothesized that the pulsatile blood pressure component was more strongly related to regional cerebral perfusion in brain regions than steady state blood pressure component.

Chapter 2: Study 1- The Influence of Heart Rate on Peripheral Endothelium-Dependent Vasodilation

ABSTRACT

Heart rate is a hemodynamic factor that can modulate vascular response to blood flow as it influences the frequency of shear stimuli acting on the arterial wall. An elevated heart rate has been recognized as a risk factor for cardiovascular disease. However, from a physiological perspective, it is feasible that a high heart rate could have the opposite effect on vascular response. We aimed to determine the association between heart rate at rest and endothelium-dependent vasodilation assessed by flow-mediated dilation (FMD) at the brachial artery in 98 apparently healthy adults (18-63 years). The findings revealed a link between heart rate at rest and FMD through shear stimuli in a positive fashion. The indirect effect of heart rate at rest on FMD that mediated through shear stimuli was confirmed by a bias-corrected bootstrap 95% CIs (0.0157-0.1056). We concluded that heart rate at rest was indirectly associated with endothelium-dependent vasodilation through shear stimuli.

Laosiripisan J, Parkhurst KL, Tanaka H. Associations of resting heart rate with endothelium-dependent vasodilation and shear rate. *Clinical and Experimental Hypertension* 2017; **39**(2): 150-154.

Parkhurst KL: provided data, Tanaka H: supervised project

INTRODUCTION

Vascular endothelial cells maintain vascular tone by adjusting vascular diameter in response to changes in shear stimuli. Increased shear stimuli within the vascular wall causes endothelial cells to release endothelium-derived relaxing factors (e.g., NO). The response of endothelial cells to shear stimuli is modulated by magnitude, rate of change, and frequency of the shear stimuli.[11,12] Heart rate is a hemodynamic parameter that can affect the frequency of blood flow and shear stimuli that is exposed to the vessel wall. A recent study assessing endothelial function using FMD in young healthy subjects found an inverse association between resting heart rate and endothelial function.[13] This finding is consistent with epidemiological findings of a relationship between elevated heart rate and increased risk of atherosclerosis.[14] However, if we consider from a physiological standpoint instead of a pathological standpoint, the opposite association could be feasible as well. For instance, endothelial cells that were exposed to increased frequency of flow demonstrated graded vascular relaxation responses. This could lend support to the possibility of a positive association between heart rate and endothelium-dependent vasodilation.[12] Theoretically, if the flow pattern does not change, elevated heart rate should provide greater cumulative shear stimuli per unit time eliciting a greater endothelium-dependent vasodilation response. Indeed, results from the Framingham Heart Study showed a positive association between heart rate and FMD.[15] However, the results from this study may be difficult to interpret because it recruited older participants with chronic diseases as well as those who had been taking cardiovascular acting

medications. The physiological perspective of the association between heart rate and endothelial function may provide an explanation for the beneficial effects of exercise training in non-exercising muscular beds.[5-7] Indeed, shear stimuli in non-exercising limbs has been reported to be increased during an incremental exercise session.[8]

Accordingly, we aimed to determine the association between resting heart rate and FMD, particularly from the physiological standpoint. Apparently healthy adults taking no cardiovascular acting medication were recruited for the study in order to eliminate the influences of chronic diseases and medications. We hypothesized that heart rate at rest was indirectly associated with FMD through shear stimuli.

METHODS

Human Subject: Apparently healthy adults ages 18 to 70 years were recruited for the study. Individuals with a history of cardiovascular disease (e.g., coronary artery disease, myocardial infarction, and heart failure) or related signs and symptoms (e.g., angina pectoris), and metabolic disorders (i.e., diabetes, thyroid disorder) were excluded. Additional exclusion criteria included overt neurological diseases (e.g., stroke, Parkinson disease, clinically significant traumatic brain injury), major psychiatric illnesses (e.g., bipolar disorder, schizophrenia), and smoking (within the last 2 years). A medical history was assessed using a health status questionnaire.

Study Design: All of the measurements described below were conducted after at least 4 hours of fasting and abstinence from caffeine and 24 hours of no strenuous physical exercise or alcohol consumption. Premenopausal women participated in the

study during the early follicular phase of the menstrual cycle to minimize the potential effects of circulating estrogen on vascular function (i.e., FMD).[16] Subjects rested quietly for at least 15 minutes in a supine position before the measurements to ensure the resting state.

Statistical Analysis: The distributions of all variables were examined using the Shapiro-Wilk test of normality. Pearson correlations analyses were conducted to assess associations of interest. Partial correlational analyses were performed to account for the influence of potential confounding factors (e.g., age, sex, baseline diameter, brachial systolic blood pressure, physical activity level). All data were presented as mean ± SD. Data were analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). A two-tailed α-level of 0.05 was set *a priori* as the criterion for statistical significance.

Two sets of analyses were conducted to determine direct and indirect effects of heart rate on FMD. First, structural equation modeling was conducted using AMOS 22 (IBM, Armonk, NY, USA) to determine direct effects as well as indirect effects of heart rate on FMD through shear rate. The significant paths from heart rate to shear rate and from shear rate to FMD is required in order to further analyze the indirect effect of heart rate on FMD through shear rate. However, analyses of indirect effects of heart rate on FMD through shear rate do not require significant associations between heart rate (i.e., independent variable) and FMD (i.e., outcome).[17] In the second analysis, indirect effect was further analyzed using SPSS macro, PROCESS. The bias-corrected bootstrap analyses were performed based on 5,000 bootstrap samples. Significant indirect effect was confirmed with the 95% confidence intervals (CI) that do not include zero.[17]

Detailed Methods:

Flow-mediated dilation (FMD)

Brachial FMD measurements have been previously described in detail.[18-20] Briefly, an ultrasound machine (iE33; Phillips, Bothel, WA, USA) equipped with a high-resolution linear array transducer was used to measure brachial artery diameter. The transducer was placed 5-10 cm proximal to the antecubital fossa. The baseline measurements of brachial artery diameter and blood velocity were performed before brachial artery occlusion. The brachial artery was occluded using a blood pressure cuff connected to a rapid cuff inflator (E20; Hokanson, Bellevue, WA, USA) that was placed 3-5 cm distal to the antecubital fossa. During the occlusion period, the cuff was inflated to 100 mmHg above systolic blood pressure for 5 minutes. Blood velocity data was obtained at 10 seconds before cuff deflation and continued until 20 seconds after cuff release. The area under the curve method was used to analyze blood velocity (i.e., during the first 15 seconds after the cuff deflation).[21,22] B-mode image recording was used to obtain images of brachial artery diameter from the 20th second to the 3rd minute after cuff deflation.[19] The digital images from ultrasound machine were transferred for offline analysis using image analysis software (Brachial Analyzer; Medical Imaging Applications, Coralville, IA, USA).

FMD (%) was calculated as the difference in the maximum diameter after cuff release and diameter at baseline using the following equation: [(maximum diameter – baseline diameter)/baseline diameter] x 100.[23] Allometrically-scaled FMD was also

calculated in order to adjust for the influence of baseline diameter on FMD.[24] Shear rate was calculated using the equation: blood velocity/brachial artery diameter.

Heart rate at rest

A three-lead ECG measured heart rate while participants were in the supine position.

Physical activity level

A modified Godin physical activity questionnaire was used to assess physical activity levels.[25]

RESULTS

Selected subject characteristics including demographic and vascular measures are shown in Table 2.1. Results from simple correlations shows a mild and positive association between heart rate and FMD (Figure 2.1 A, r=0.26, p<0.01). However, this association was no longer significant after controlling for age, sex, BMI, SBP, and physical activity level (β=0.15, p=0.21) or age, baseline diameter, BMI, SBP, and physical activity level (β=0.12, p = 0.29).

The lack of association between heart rate and allometrically-scaled FMD (accounting for baseline brachial diameter) is shown in Figure 2.2 A. Shear rate was related to heart rate (Figure 2.1 B, r=0.41, p<0.001) The association between shear rate and heart rate remained significant after accounting for age, baseline diameter, and brachial systolic blood pressure (β= 0.20, p< 0.05). The allometrically-scaled FMD was not significantly related to shear rate (Figure 2.2 B).

The path analysis revealed two significant paths (i.e., heart rate to shear rate and shear rate to FMD, Figure 2.3) that were sufficient to allow for further analysis of the indirect effect of heart rate on FMD through shear rate. The indirect effect of heart rate on FMD via shear rate was confirmed by a bias-corrected bootstrap 95% CIs (95% CI = 0.0157-0.1056) based on 5,000 bootstrap samples.

Table 2.1 Selected subject characteristics

Variable	Mean ± SD
Men/ women (n)	52/46
Age (years)	34 ±12
Height (cm)	168 ±9
Body mass (kg)	69.4 ±13.7
BMI (kg/m^2)	24.4 ±4.4
Systolic BP (mmHg)	114 ±10
Diastolic BP (mmHg)	66 ±8
Heart rate (bpm)	59 ±10
Baseline brachial diameter (mm)	3.7 ±0.7
Peak brachial diameter (mm)	3.9 ±0.7
FMD (%)	6 ±3.2
Allometrically-scaled FMD (%)	14.5 ±3.5
FMD/SR (%)	9.3 ±7.0
Physical activity score (U)	32 ±26

BMI, body mass index; BP, blood pressure; FMD, flow-mediated dilation; SR, shear rate.

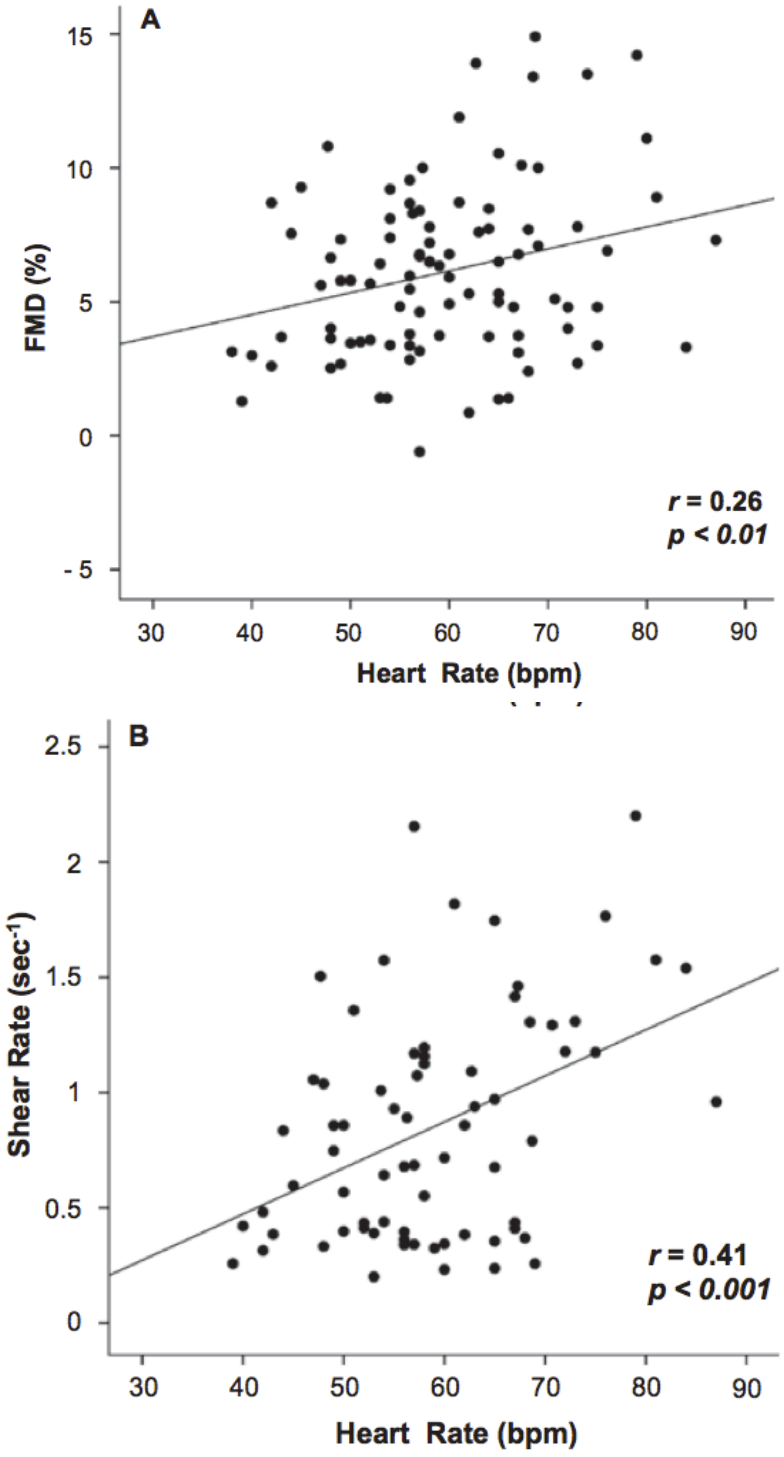


Figure 2.1 Associations between flow-mediated dilation (FMD) and heart rate (A), and between shear rate and heart rate (B).

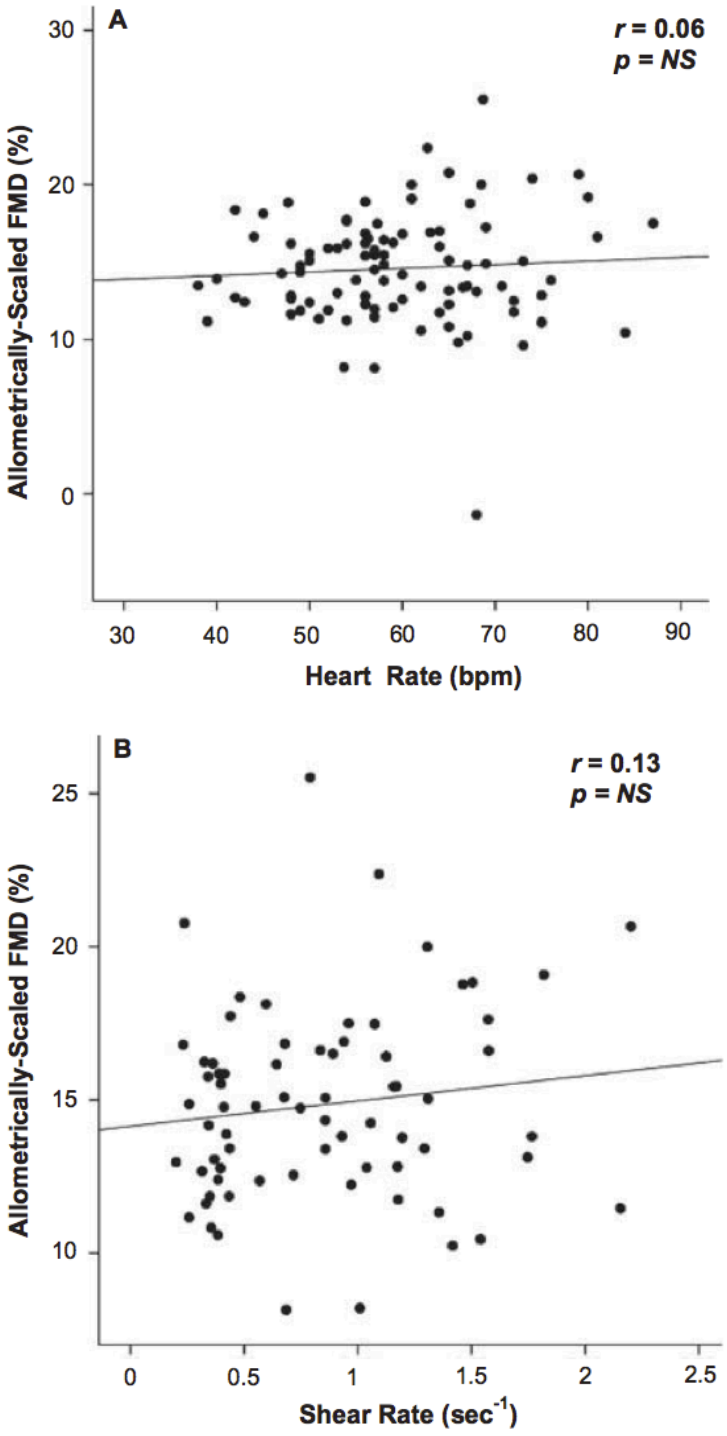


Figure 2.2 Associations of allometrically-scaled flow-mediated dilation (FMD) with heart rate (A), and shear rate (B)

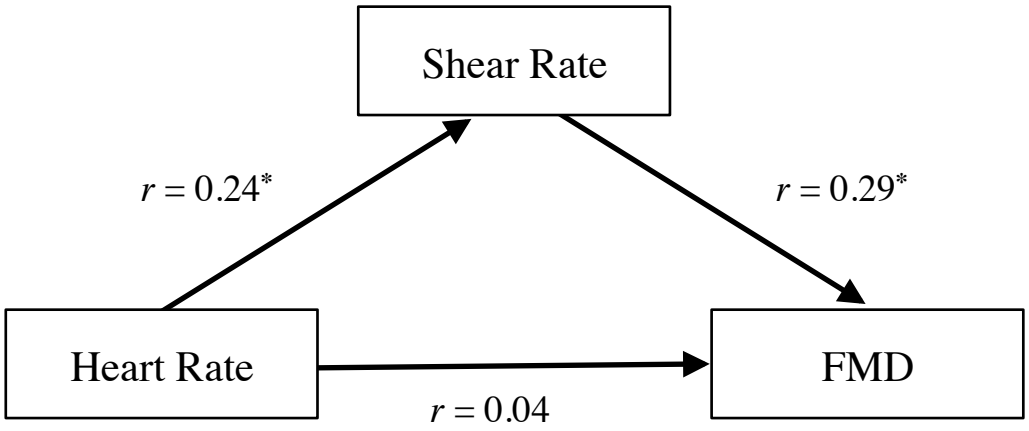


Figure 2.3 The results of the path analyses showing indirect effects of heart rate through shear rate on flow-mediated dilation (FMD).

* $P < 0.05$

DISCUSSION

This study determined the association between heart rate and endothelium-dependent vasodilation as assessed by FMD in apparently healthy, non-medicated adults. The effect of heart rate on FMD appears to be indirectly mediated by shear stimuli. The results from two sets of analyses confirmed this conclusion. The initial step using structural equation modeling reveals two significant paths (i.e., heart rate to shear rate and from shear rate to FMD). Further analysis using SPSS macro PROCESS found a significant indirect effect of heart rate on FMD as determined by 95% confidence intervals (CI) that did not include zero (95% CI = 0.0157 – 0.1056).

The positive-indirect effect of heart rate on FMD from the present study is in marked contrast to a recent study showing an inverse association between FMD and heart rate at rest in young healthy adults.[13] The results from the previous study make sense from an epidemiological perspective, as there are epidemiological studies that have reported increased cardiovascular morbidity and mortality with elevated heart rate.[26-30] However, a high risk of impaired vascular function with elevated heart rate is not convincing based on the available literature. For instance, an in-vitro flow-chamber experiment using cultured porcine aortic cells revealed that the frequency-induced higher risk for atherosclerotic lesion development was limited. This study observed a limited number of genes expressed with potentially atherogenic role.[31] Even though there is evidence showing an anti-atherogenic effect of heart rate lowering drugs[32,33], the full

extent of this anti-atherogenic effect cannot be completely ascribed to lower heart rates as these drugs also exert inotropic and/or antihypertensive effect.[34]

The overall finding of the present study was an indirect effect of heart rate on FMD. The positive-indirect association was mediated by shear stimuli. A number of available literature provide support for an effect of frequency of shear stimuli on the endothelium response.[11,12] The shear-mediated vasodilatory response of endothelium cells is modulated not only by magnitude, but also by the rate and frequency of shear stimuli. Greater vasodilatory responses in isolated rat artery preparations were induced by faster increases in shear stimuli.[11] Production of endothelium-derived vasodilator substance (e.g., NO) induced by an increase blood flow and shear stimuli involves a G-protein-dependent cascade.[35] A higher expression of G-protein in human endothelial cells was demonstrated after the vessel wall was exposed to a faster strain rate.[36] A frequency-sensitive phenomenon of endothelial cell response to shear stimuli was also revealed in a study using rabbit aortic segments. In this animal study flow-induced production of endothelium-derived relaxing factors (e.g., NO) was augmented after endothelial cells were exposed to a higher frequency of flow.[12] Taken together, these experimental studies could lend support to the present finding that an increase in frequency of shear stimuli (i.e., due to higher heart rate) could mediate a greater endothelium-dependent vasodilation response.

The study design that involves a manipulation of heart rate, such as bradycardic pharmacological agents, could increase the impact of the present study's findings. However, a pharmacological manipulation of heart rate could also affect autonomic

nervous system activity that could likely affect vascular response. Therefore, using a pharmacological approach could confound the interpretation if the effect of heart rate on vascular response was not isolated. Therefore, the present study used a series of statistical approaches to determine a link between heart rate and endothelium-dependent vasodilation via shear stimuli.

There are a number of limitations of the present study that should be mentioned. First, a cross-sectional study design could not definitively infer the causal relationship between the variables of interest. Second, only apparently healthy subjects were included to minimize the confounding effects of disease and medication which could limit the generalizability of the findings. Third, none of the subjects included in the present study have resting heart rate greater than 100 bpm, which is recognized as the tachycardia threshold of adverse cardiovascular outcomes.[26,37]

In conclusion, this study indicated that heart rate at rest is indirectly associated with FMD and this association appears to be mediated by shear stimuli. These findings are inconsistent with previous epidemiological-oriented findings that have reported a link between elevated heart rate and atherosclerosis through impaired endothelium function.

Chapter 3: Study 2-Association between Baroreflex Sensitivity and Regional Cerebral Blood Flow

ABSTRACT

Impaired baroreflex sensitivity (BRS) could potentially disturb normal control of the blood perfusion to the brain. A failure to control perfusion to the brain could lead to chronic brain hypoperfusion and, eventually, cognitive impairment. The primary aim of this study was to determine whether cardiovagal BRS was associated with regional cerebral perfusion using arterial spin labeling (ASL) MRI technique. Fifty-two middle-aged normotensive adults with normal global cognitive function were recruited for this study. Baroreflex sensitivity was assessed using the Valsalva maneuver technique. Cerebral perfusions in 10 pre-determined brain regions of interest were measured using ASL MRI technique. The results show a significant association between cardiovagal BRS and hippocampal perfusion ($R^2 = 0.17$, $P = 0.01$). The association remained significant after age, sex, BMI, and mean blood pressure were taken into account. When participants were divided into tertiles based on their BRS, regional cerebral perfusion of the hippocampus of individuals in high BRS group (60.5 ± 8.4 ml/100 g/min) was significantly greater than that of the individuals in low BRS group (39.1 ± 4.3 ml/100 g/min).

Laosiripisan J, Tarumi T, Gonzales MM, Haley AP, Tanaka H. Association between cardiovagal baroreflex sensitivity and baseline cerebral perfusion of the hippocampus. *Clinical Autonomic Research* 2015; **25**(4): 213-218.

Tarumi T and Gonzales MM: provided data, Haley AP and Tanaka H: supervised project

INTRODUCTION

Cerebral blood flow is a critical determinant of normal brain function. A failure to control steady perfusion pressure to the brain could potentially cause damage to the brain tissue resulting in impaired cognitive function.[9] Control of human brain blood flow needs integrative regulation including cardiovascular system. The importance of extra-cranial mechanisms to maintain stable cerebral blood flow was suggested by a recent study that demonstrated a very narrow range of pressure (~10 mmHg) in which cerebral autoregulation is capable of maintaining a stable mean cerebral blood flow.[1] Cardiovagal BRS is considered a key mechanism for the maintenance of circulatory homeostasis in humans. Impaired BRS may cause a failure to control proper perfusion pressure leading to chronic brain hypoperfusion and ultimately impaired cognitive function.[38-40] Indeed, the link between cardiovagal BRS dysregulation and poorer memory in apparently healthy elderly has been demonstrated.[2] In addition, reduced baroreflex function was shown in patients with Alzheimer's disease.[3] Taken together, this extensive literature could lend support to the importance of cardiovagal BRS for cognitive function. However, the mechanism underlying the association between cardiovagal BRS and cognitive function is currently unknown.

Accordingly, we aimed to determine whether cardiovagal BRS is associated with regional cerebral blood flow. We hypothesized that lower cardiovagal BRS was associated with lower cerebral perfusion in regions of the brain that closely link to memory, such as the hippocampus.

METHODS

Human Subject: Middle age adults (40-60 years) around the Austin, Texas area were recruited through local newspaper and online advertisements. Individuals with a history of cardiovascular disease (e.g., coronary artery disease, myocardial infarction, and heart failure) or related signs and symptoms (e.g., angina pectoris), and/ or metabolic disorders (i.e., diabetes, thyroid disorder) were excluded. Additional exclusion criteria included overt neurological disease (e.g., stroke, Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g., bipolar disorder, schizophrenia), smoking (within the last 2 years), or MRI contraindications. A medical history was assessed using a health status questionnaire. Global cognitive function was assessed using the Mini-Mental State Exam (MMSE).[41]

Study Design: All of the measurements described below were conducted after at least 4 hours of fasting and abstinence from caffeine and 24 hours of no strenuous physical exercise and alcohol consumption. Vascular function measurements (i.e., blood pressure and baroreflex sensitivity) and regional cerebral perfusion were assessed on two separate days. Subjects rested quietly at least 15 minutes in a supine position before measurements to ensure the resting state.

Statistical Analysis: The normality of all variable distributions was examined using the Shapiro-Wilk test of normality. Simple correlation or zero-order correlation determined the association between the cardiovagal BRS and the regional cerebral perfusion of ten brain regions. The regional cerebral perfusion of the area that had

significant correlation to cardiovagal BRS was then analyzed using partial correlations analyses to verify the unique effect of cardiovagal BRS on regional cerebral perfusion after controlling for covariates. The covariates that were entered to the partial correlation analyses were selected from their significant correlation with either predictor (i.e., cardiovagal BRS) or outcome of interest (i.e., regional cerebral perfusion). Additionally, all subjects were divided into tertiles based on their cardiovagal BRS and differences in cerebral perfusion were examined. All data were presented as means ± SEM. Data were analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). A two-tailed α-level of 0.05 was set *a priori* as the criterion for statistical significance.

Detailed Methods:

Blood Pressure

Brachial blood pressure was measured using a semi-automated blood pressure device (Press-Mate 7800, Colin Medical Instruments, San Antonio, TX) with the arm at heart level.

Regional Cerebral perfusion

Regional cerebral perfusion in 10 *a priori* regions of interest (hippocampus, anterior white matter, central insula, thalamus, caudate, posterior insula, central white matter, posterior white matter, posterior cingulate, and occipitoparietal area) that have been shown to be related to memory and are susceptible to cerebrovascular disease[42,43] was measured using the ASL MRI technique, as previously described in detail.[44-46] Briefly, MRI images were acquired using 3T GE Signa Excite scanner (GE Healthcare, Waukesha, WI). Brain structural landmarks for subsequent ASL analyses were obtained

from imaging slices of whole-brain T1-weighted images (spoiled gradient echo sequence, 256 x 256 matrix, field of view = 24 x 24 cm^2, 1 mm slice thickness, 0 gap). ASL Perfusion imaging includes a single-shot spiral readout, a cerebrospinal fluid reference scan, and a minimum contrast scan.[47,48] Cerebral blood flow was calculated from the difference between the control and tagged images (CBFv3.2, Function Biomedical Informatics Research Network). The minimum contrast scan was used for correction of the inhomogeneous fields in the images. Physiological units (ml/100 mg/min) was obtained from conversion of the information from image using the reference signals.[47,48] The Analysis of Functional NeuroImages (AFNI) software[49] was used to create the 5 mm of spherical at regional of interest according to the Talairach and Tournoux atlas.[50]

Cardiovagal baroreflex sensitivity (BRS)

Cardiovagal BRS was assessed using the Valsalva maneuver technique, as previously described.[51,52] Briefly, after deep inspiration, the participant performed forced expiration through a mouthpiece with a 1-inch diameter. The participant was asked to maintain expiratory mouth pressure at 40 mmHg for 10 seconds. Participant received visual feedback of the expiratory pressure via computer screen (Windaq, Dataq Instruments). R-R interval (via ECG) and beat-to-beat arterial blood pressure (Finapres Ohmeda) were continuously recorded during the testing period. The measurement was performed twice with a 5-minute rest between trials. Cardiovagal BRS was analyzed using phase IV of the Valsalva maneuver.[53] The R-R interval was regressed on the systolic blood pressure; the slope of this association (ms/mmHg) represents the cardiovagal BRS if the linear regression coefficient (r) is greater than 0.80.

RESULTS

Table 3.1 provides the demographic and vascular characteristics of the middle-age subjects who participated in the study. As shown in Table 3.1, none of the subjects were classified as hypertensive based on their brachial blood pressure. Based on the average BMI subjects were classified as overweight.

The average values for the right and left side of regional cerebral perfusion of the 10 brain regions of interest examined in this study are illustrated in Table 3.2. Zero-order correlation between the cardiovagal BRS and regional cerebral perfusion of the 10 brain regions of interest are shown in Table 3.3. As shown in Table 3.3, the hippocampus is the only region in which the regional cerebral perfusion was positively correlated with cardiovagal BRS (Figure 3.1, $R^2 = 0.17$, $P = 0.01$). The significant independent contribution of cardiovagal BRS to regional cerebral perfusion was demonstrated after potential confounding factors were taken into account (age, sex, BMI, and mean blood pressure). Results from partial correlational analyses revealed that cardiovagal BRS explained 11% of the variability ($r = 0.33$) in the regional cerebral perfusion of the hippocampus ($P < 0.05$)

As shown in Figure 3.2 when the subjects were divided into tertiles based on cardiovagal BRS, the mean of the regional cerebral perfusion of the hippocampus of the individuals in high BRS group (11.8 ± 1.9 ms/mmHg) was significantly greater than that of the individuals in low BRS group (3.5 ± 0.1 ms/mmHg).

Table 3.1 Selected subject characteristics

Variable	Mean ± SEM
Male/female, n	27/25
Age, years	48.6 ± 0.9
Height, cm	169 ± 1
Body mass, kg	85.4 ± 2.6
Body mass index, kg/m^2	29.7 ± 0.8
Education, years	14.8 ± 0.6
Systolic BP, mmHg	128 ± 2
Diastolic BP, mmHg	78 ± 1
Heart rate, bpm	65 ± 1
BRS, ms/mmHg	7.8 ± 0.6

BP, blood pressure; BRS, cardiovagal baroreflex sensitivity

Table 3.2 Regional cerebral perfusion in various brain regions

Brain region	Regional cerebral perfusion (ml/ 100 g/min)
Hippocampus	52.1 ± 3.8
Anterior white matter	38.0 ± 2.9
Central insula	55.6 ± 3.0
Thalamus	42.1 ± 4.1
Caudate	35.7 ± 3.1
Posterior insula	54.8 ± 2.5
Central white matter	37.2 ± 5.0
Posterior white matter	43.9 ± 3.7
Posterior cingulate	74.5 ± 3.3
Occipitoparietal area	69.6 ± 3.0

Data are mean ± SEM

Table 3.3 Correlation coefficients between cardiovagal baroreflex sensitivity and regional cerebral perfusion

Brain region	R^2 (P value)
Hippocampus	0.17 (0.01)
Anterior white matter	0.04 (0.25)
Central insula	0.07 (0.09)
Thalamus	0.02 (0.37)
Caudate	0.05 (0.19)
Posterior insula	0.001 (0.86)
Central white matter	0.005 (0.70)
Posterior white matter	0.06 (0.13)
Posterior cingulate	0.005 (0.64)
Occipitoparietal area	0.03 (0.23)

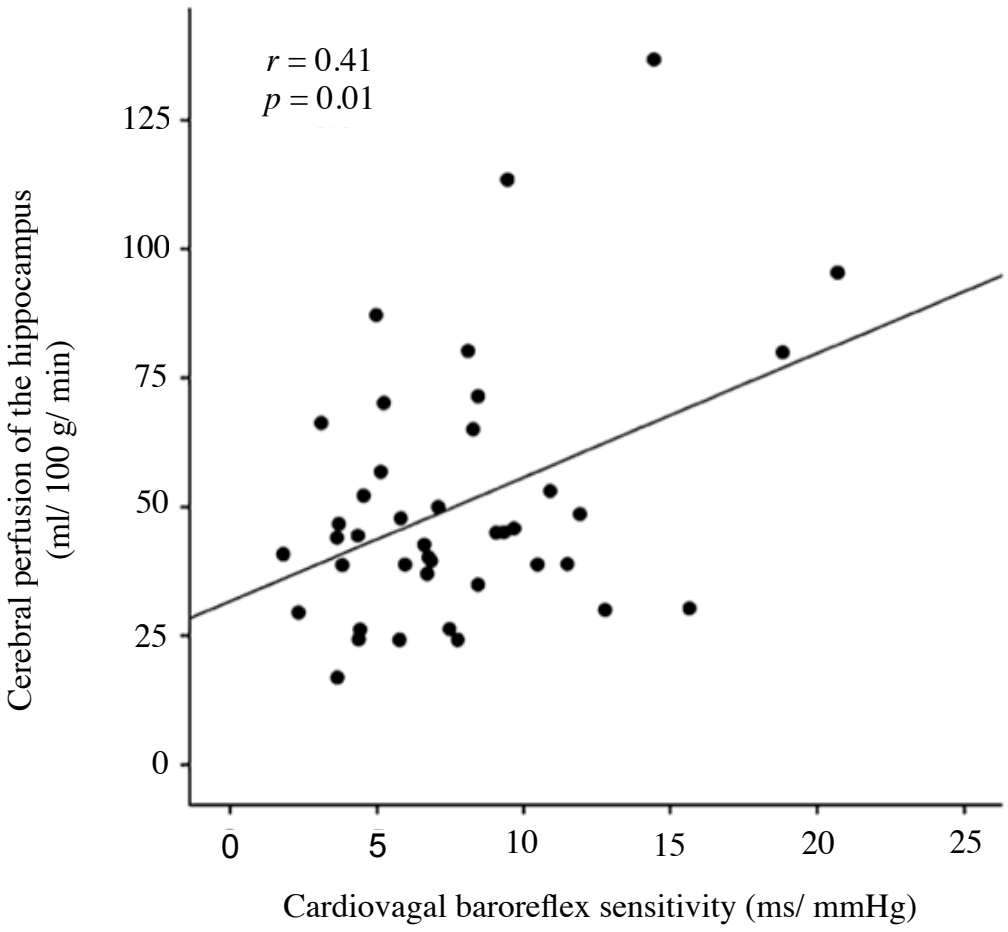


Figure 3.1 Association between regional cerebral perfusion of the hippocampus and cardiovagal baroreflex sensitivity (BRS)

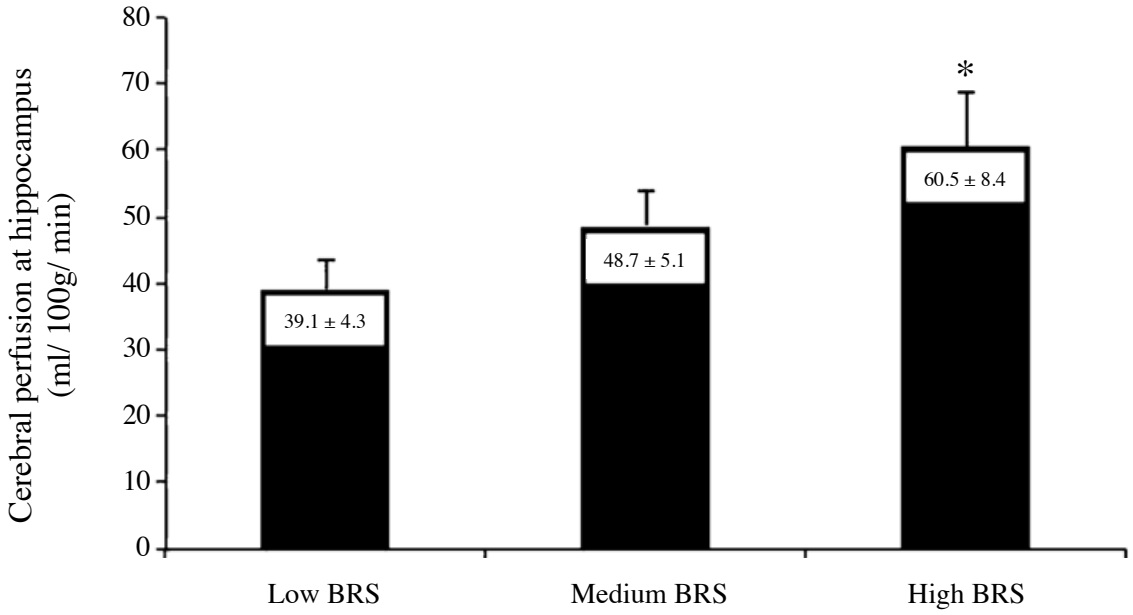


Figure 3.2 Comparison of regional cerebral perfusion of the hippocampus in low, medium, and high tertiles of cardiovagal baroreflex sensitivity (BRS)

* $P < 0.05$ vs. Low BRS

DISCUSSION

The major finding of the present study is a significant positive association between cardiovagal BRS and regional cerebral perfusion of the hippocampus. The direct association between cardiovagal BRS and regional cerebral blood perfusion of the hippocampus remained significant after potential confounding variables were controlled (i.e., age, sex, BMI, and mean blood pressure). Results from partial correlational analyses revealed that cardiovagal BRS explained 11% of the variability in the regional cerebral perfusion of the hippocampus. The regional cerebral perfusion of the hippocampus was substantially greater in subjects who were in the high BRS group compared with subjects who were in the low BRS group. Taken together, these findings indicate the potential contribution of cardiovagal BRS on cerebral hypoperfusion even in apparently healthy middle-aged adults with normal global cognitive function.

There is a wealth of available evidence indicating impaired baroreflex sensitivity in patients with Alzheimer's disease.[3,54] The close relationship between impaired cognitive function and abnormal cardiovagal BRS is supported by findings of impaired cognitive function in populations that typically demonstrate impaired cardiovagal BRS, such as patients with hypertension[55,56] and orthostatic hypotension[57,58]. Reductions in blood flow to the brain could be a mechanism linking reduced BRS to poor cognitive function. Support for this hypothesis was found in reduced mean cerebral blood flow velocity measured by transcranial Doppler (TCD) technique with decreased baroreflex sensitivity during head-up tilt test.[59] Consistent with this finding, the present study

demonstrated a direct association between cardiovagal BRS and cerebral perfusion of the hippocampus. This finding indicates that even within our sample of normotensive, cognitively normal middle-aged adults, a depressed cardiovagal BRS is associated with impaired regional blood perfusion of the hippocampus.

Among the 10 *a priori* brain regions of interest, cardiovagal BRS was significantly associated with regional cerebral perfusion of the hippocampus. Theoretically, a hemodynamic perturbation caused by impaired cardiovagal BRS should manifest as a global reduction in blood flow in all brain regions. However, particular brain regions are more vulnerable to changes in blood perfusion, such as the temporal lobe where the hippocampus is located.[60] Diminished cerebral blood flow has been reported to relate to a reduction in volume and thickness of the temporal lobe.[60] Moreover, a high susceptibility to hypoperfusion insult of the hippocampus could be partly explained by poor vascularized patterns in that region.[61] The hippocampus is a region of the brain that plays an important role in the memory domain of cognitive function. Hippocampal atrophy has been reported to be related to impaired cognitive function as assessed by the Mini-Mental State Examination (MMSE).[62] Moreover, impaired cognitive function in individuals with subcortical ischemic vascular disease, a common cause of vascular dementia, is associated with hippocampal atrophy.[63,64] Therefore, the link between cardiovagal BRS and hippocampal regional blood flow illustrated in this study suggests a potential role of cardiovagal BRS as a cardiovascular regulatory mechanism that could influence regional cerebral perfusion and subsequent cognitive function. However, we cannot exclude the possible involvement of

neurodegenerative changes in both cognitive-related brain regions and the central autonomic pathway.

Cardiovagal BRS has been reported to decline with advancing age in humans.[65] Stiffening of the large elastic arteries is one of the factors that contributes to declines in BRS.[52] Habitual exercise has been shown to elicit improvements in arterial distensibility. Exercise-associated destiffening of arteries is associated with a corresponding increase in cardiovagal BRS.[66,67] To the best of our knowledge, it is unknown whether habitual exercise could improve regional cerebral blood flow. However, a recent study demonstrated an association between lower central arterial stiffness as measured by pulse wave velocity and greater regional cerebral perfusion of the occipitoparietal area in endurance-trained individuals.[68] The finding of this study may have an important implication for preventing impaired BRS, subsequent cerebral hypoperfusion and cognitive dysfunction. The chronic effect of exercise training on regional cerebral perfusion (i.e., restoration and/or prevention) and cognitive function would be an important research agenda for future interventions.

There are a number of limitations of the present study that should be mentioned. First, based on study design (i.e., cross-sectional study design), the causal relation between cardiovagal BRS and brain hypoperfusion could not be determined. Second, there is some limitation regarding ASL technique including errors due to the transit delays of magnetically-labeled blood between the labeling region and the imaging site.[69] Third, cardiovagal BRS and cerebral perfusion were assessed in different conditions. Cardiovagal BRS was assessed using a blood pressure-perturbing maneuver (i.e.,

Valsalva maneuver) which may have been influenced by acute baroreflex resetting and/or sympathetic nerve activity of the SA node during the beginning of the maneuver.[70]

In conclusion, the results of this study indicate a significant association between reduced cardiovagal BRS and reductions in hippocampal regional blood perfusion in apparently healthy middle-age adults with normal global cognitive function. Future longitudinal studies are warranted to determine the causal relationship between impaired cardiovagal BRS and cognitive dysfunction.

Chapter 4: Study 3-The Impact of Steady Blood Pressure Component, and Pulsatile Blood Pressure Component on Cerebral Perfusion

ABSTRACT

Arterial blood pressure can be divided into two primary components: steady component (determined by mean arterial pressure) and pulsatile component (expressed as either systolic blood pressure or pulse pressure). We aimed to determine the relationships between blood pressure components and regional cerebral perfusion. A total of 52 apparently healthy middle-age adults with normal global cognitive function were recruited for this study. Regional cerebral perfusion in 10 *a priori* regions of interest was measured using perfusion MRI technique. There were 5 regions of the brain with regional perfusion values significantly associated with either pulsatile blood pressure component (i.e., hippocampus, posterior insula, and central white matter) or both steady and pulsatile components (i.e., anterior white matter, and occipitoparietal area). After potential confounding variables (i.e., body mass index, education, age, and sex) were taken into account, associations between pulsatile blood pressure components and regional cerebral perfusion remained significant in two regions: the hippocampus and anterior white matter. A significant contribution of peripheral pulsatile blood pressure component on the variability of hippocampal perfusion was demonstrated. Brachial systolic blood pressure and pulse pressure explained 11% and 12% of the variability in hippocampal perfusion, respectively, independent of covariates.

Laosiripisan J, Haley AP, Tanaka H. Steady State vs. Pulsatile Blood Pressure Component and Regional Cerebral Perfusion. *American journal of hypertension* 2017; **30**(11)**:** 1100-1105.

Haley AP: supervised project, and provided data, Tanaka H: supervised project

INTRODUCTION

Elevated blood pressure is a vascular risk factor that could contribute to cognitive impairment during later life.[71] Indeed, the trajectories of cognitive function in individuals with hypertension have demonstrated faster declines in memory and information processing speed.[72] One of the possible mechanisms related to elevated blood pressure and cognitive impairment is the interruption of cerebral blood flow especially in regions that are susceptible to cerebrovascular disease.[42,43] Arterial blood pressure is composed of two major components: steady state and pulsatile components.[73,74] These two components of arterial blood pressure are influenced by different vascular-related parameters. For instance, the steady state component is represented by mean arterial pressure and is affected by small resistance artery function. The pulsatile component is influenced primarily by large artery stiffness.[74] Therefore, separating blood pressure into steady and pulsatile components may provide a better understanding of high blood pressure-related cognitive decline.

Accordingly, we determined the association between pulsatile or steady state components of blood pressure and regional cerebral perfusion in the regions that exhibit susceptibility to cerebrovascular disease. Based on existing literature of cardiovascular risks[73,75], we hypothesized that pulsatile component of blood pressure was associated with regional cerebral perfusion to a greater extent compared with the steady state component.

METHODS

Human Subject: Middle age adults (40-60 years) around the Austin, Texas area were recruited through local newspaper and online advertisements. Individuals with a history of cardiovascular disease (e.g., coronary artery disease, myocardial infarction, and heart failure) or related signs and symptoms (e.g., angina pectoris), and metabolic disorders (i.e., diabetes, thyroid disorder) were excluded. Additional exclusion criteria included overt neurological disease (e.g., stroke, Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g., bipolar disorder, schizophrenia), smoking (within the last 2 years), or MRI contraindications. A medical history was assessed using a health status questionnaire. Participants were cognitively normal as assessed by the Mini-Mental State Exam and had an average score greater than 28.[41]

Study Design: All of the measurements described below were conducted after at least 4 hours of fasting and abstinence from caffeine and 24 hours of no strenuous physical exercise and alcohol consumption. Vascular function measurement (i.e., blood pressure) and regional cerebral perfusion were assessed on two separate days. Subjects rested quietly at least 15 minutes in a supine position before measurements to ensure the resting state.

Statistical Analysis: Shapiro-Wilk test of normality was first performed to test the distributions of all variables. Associations of interest (i.e., blood pressure components and regional cerebral perfusion) were examined using Pearson correlations analyses.

Significant zero-order correlations were further analyzed using sequential multiple regressions to test the distribution of predictor of interest (i.e., blood pressure components) on outcome variables (regional cerebral perfusion) after accounting for related covariates. The covariates in multiple regressions were selected from their significant correlations with either predictors or outcomes of interest. Significant R^2 change from the sequential multiple regression analyses were used to confirm the significant contribution of the predictor on the outcome. A two-tailed α level of 0.05 was used as the criterion for significance for all analyses. All data were presented as means ± SEM. Data were analyzed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA).

Detailed Methods:

Blood Pressure

Brachial blood pressure, including systolic, mean, and diastolic pressure, were measured using an oscillometric automated sphygmomanometer (VP-1000 plus, Omron Healthcare, Kyoto, Japan). Carotid artery pressure waveforms were obtained using arterial applanation tonometry incorporating an array of 15-micropiezoresistive transducers (VP-1000 plus, Omron Healthcare, Kyoto, Japan) placed on the common carotid artery. The hold-down force of the sensor on the carotid artery was corrected by equating the carotid mean arterial and diastolic blood pressure to the brachial mean arterial and diastolic blood pressure, as described previously.[4] All blood pressure measurements were performed at least three times while subjects were in the supine position. The average of the three measurements were used for data analyses.

Regional cerebral perfusion

Regional cerebral perfusion was measured using the ASL MRI technique, as described previously.[44-46] Based on the existing literature related to areas in the brain that are susceptible to cerebrovascular disease, regional cerebral perfusion was determined in ten *a priori* regions of interest (hippocampus, anterior white matter, central insula, thalamus, caudate, posterior insula, central white matter, posterior white matter, posterior cingulate, and occipitoparietal area).[42,43]

RESULTS

The subjects were middle-age (50 ± 1 year) normotensive individuals. Selected subject characteristics are shown in Table 4.1. The average body mass index was 30 ± 1 kg/m^2. Normal global cognitive performance of all subjects was confirmed by a Mini-Mental State Exam score greater than 28. The results from simple correlation analyses revealed significant associations between regional cerebral perfusion of 5 brain regions with either pulsatile blood pressure components (i.e., hippocampus, posterior insula, and central white matter) or both steady and pulsatile components (i.e., anterior white matter and occipitoparietal area) (Table 4.2). In general, the pulsatile component of blood pressure (i.e., systolic blood pressure and pulse pressure) was more strongly associated with cerebral perfusion than the steady component of blood pressure (i.e., MAP). Brachial blood pressure was found to have a greater number of correlations with cerebral perfusion compared with carotid blood pressure.

After body mass index, education, age, and sex were taken into account, associations between pulsatile blood pressure components and regional cerebral perfusion remained significant in hippocampus and anterior white matter regions. The significant independent contribution of blood pressure components on hippocampus perfusion (Table 4.3) and anterior white matter perfusion (Table 4.4) were confirmed by significant R^2 changes from sequential multiple regression analyses. As shown in Table 4.3, results from sequential multiple regression analyses revealed a significant contribution of brachial systolic blood pressure that explained 11% of the variability in hippocampus

perfusion ($\Delta R^2 = 0.11$, p=0.03, model 2) independent of the entered covariates. Another peripheral pulsatile blood pressure component (i.e., brachial pulse pressure) also shows a significant contribution to the variability in hippocampus perfusion ($\Delta R^2 = 0.12$, p=0.02) independent of the entered covariates (Table 4.3, model 4). The significant contribution of brachial systolic blood pressure and brachial MAP to anterior white matter perfusion was illustrated (Table 4.4). As shown in Table 4.4 brachial systolic BP explained 12% ($\Delta R^2 = 0.12$, p=0.03, model 2) of the variability in anterior white matter perfusion independent of the entered covariates. Brachial MAP also revealed a significant independent contribution to the variability in anterior white matter perfusion ($\Delta R^2 = 0.11$, p=0.04), independent of the entered covariates (Table 4.4, model 4).

Table 4.1 Selected subject characteristics

Variable	Mean ± SEM
Male/ female, n	27/25
Age, years	50 ± 1
Height, cm	169 ± 1
Body mass, kg	86.3 ± 1.8
Body mass index, kg/m^2	30 ± 1
Education, years	14.9 ± 0.2
Brachial systolic BP, mmHg	126 ± 1
Brachial diastolic BP, mmHg	76 ± 1
Brachial PP, mmHg	50 ± 1
Brachial mean BP, mmHg	94 ± 1
Carotid systolic BP, mmHg	117 ± 1
Carotid PP, mmHg	41 ± 1
Total cholesterol, mg/dl	200 ± 4
LDL cholesterol, mg/dl	119 ± 3
HDL cholesterol, mg/dl	46 ± 1
Blood glucose, mg/dl	116 ± 4
HbA1C, %	4.9 ± 0.1
Mini Mental Status Exam (MMSE) score	28.2 ± 0.1

BP blood pressure, *PP* pulse pressure, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein

Table 4.2 Simple correlation coefficients (with P-values) between blood pressure components and regional cerebral perfusion in 10 regions of interest

Variable	Hippocampus	Anterior white matter	Central insula	Thalamus	Caudate	Posterior insula	Central white matter	Posterior white matter	Posterior cingulate	Occipitoparietal area
Brachial										
SBP	**- 0.325**	**- 0.350**	- 0.126	- 0.272	- 0.149	**- 0.366**	**- 0.341**	- 0.179	- 0.145	**- 0.403**
	(0.03)	**(0.02)**	(0.39)	(0.07)	(0.37)	**(0.01)**	**(0.04)**	(0.24)	(0.31)	**(0.004)**
PP	**- 0.367**	**- 0.343**	- 0.043	- 0.237	- 0.012	- 0.255	**- 0.406**	- 0.252	- 0.102	**- 0.363**
	(0.01)	**(0.02)**	(0.77)	(0.12)	(0.94)	(0.09)	**(0.01)**	(0.09)	(0.47)	**(0.01)**
MAP	- 0.302	**- 0.327**	- 0.187	- 0.295	- 0.026	- 0.274	- 0.024	0.006	- 0.157	**- 0.355**
	(0.07)	**(0.04)**	(0.25)	(0.10)	(0.89)	(0.11)	(0.90)	(0.97)	(0.30)	**(0.027)**
Carotid										
SBP	- 0.308	- 0.316	0.003	- 0.202	- 0.097	- 0.185	- 0.168	- 0.167	- 0.112	**- 0.378**
	(0.05)	(0.05)	(0.98)	(0.21)	(0.58)	(0.24)	(0.35)	(0.30)	(0.45)	**(0.01)**
PP	- 0.235	- 0.260	0.106	- 0.146	- 0.013	- 0.001	- 0.138	- 0.204	- 0.039	**- 0.324**
	(0.14)	(0.11)	(0.48)	(0.37)	(0.94)	(0.99)	(0.45)	(0.20)	(0.79)	**(0.03)**

Data are Pearson r (p-value). Significant correlations ($P<0.05$) are highlighted in bold.

SBP=systolic blood pressure, PP=pulse pressure, MAP=mean arterial pressure

Table 4.3 Multiple regression analyses depicting independent correlates of hippocampus perfusion

Model	ΔR^2 (*P* value)	Variable	β	*P* value	95% CI	
					Lower	Upper
Dependent variable: hippocampus perfusion						
1	0.05	BMI	-0.12	0.51	-1.72	0.86
	(0.70)	Edu	-0.19	0.85	-3.04	2.52
		Age	-0.19	0.22	-1.54	0.37
		Sex	-0.06	0.71	-15.93	10.91
2	0.11	bSBP	**-0.35**	**0.03**	-0.81	-0.03
	(0.03)	BMI	-0.04	0.82	-1.41	1.12
		Edu	-0.02	0.92	-2.79	2.53
		Age	-0.20	0.19	-1.51	0.31
		Sex	0.01	0.95	-12.70	13.46
Dependent variable: hippocampus perfusion						
3	0.05	BMI	-0.12	0.51	-1.72	0.86
	(0.70)	Edu	-0.03	0.85	-3.04	2.52
		Age	-0.19	0.22	-1.54	0.37
		Sex	-0.06	0.70	-15.93	10.91
4	0.12	bPP	**-0.36**	**0.02**	-1.55	-0.12
	(0.02)	BMI	-0.03	0.86	-1.36	1.14
		Edu	-0.03	0.86	-2.86	2.40
		Age	-0.18	0.25	-1.43	0.38
		Sex	-0.04	0.79	-14.36	11.06

BMI body mass index, *Edu* years of education, *bSBP* brachial systolic blood pressure, *bPP* brachial pulse pressure

Significant correlations (P<0.05) are highlighted in bold.

Table 4.4 Multiple regression analyses depicting independent correlates of anterior white matter

Model	ΔR^2 (*P* value)	Variable	β	*P* value	95% CI	
					Lower	Upper
Dependent variable: anterior white matter perfusion						
1	0.07	BMI	-0.16	0.38	-1.61	0.63
	(0.62)	Edu	0.11	0.51	-1.89	3.72
		Age	-0.17	0.33	-1.31	0.45
		Sex	-0.05	0.79	-14.09	10.81
2	0.12	bSBP	**-0.37**	**0.03**	-0.78	-0.04
	(0.03)	BMI	-0.06	0.74	-1.27	0.92
		Edu	0.13	0.42	-1.59	3.74
		Age	-0.18	0.27	-1.30	0.37
		Sex	0.02	0.91	-11.29	12.66
Dependent variable: anterior white matter perfusion						
3	0.07	BMI	-0.16	0.38	-1.61	0.63
	(0.62)	Edu	0.11	0.51	-1.89	3.72
		Age	-0.17	0.33	-1.31	0.45
		Sex	-0.05	0.79	-14.09	10.81
4	0.11	bMAP	**-0.35**	**0.04**	-0.98	-0.02
	(0.04)	BMI	-0.07	0.69	-1.32	0.88
		Edu	0.14	0.39	-1.54	3.84
		Age	-0.14	0.39	-1.21	0.48
		Sex	0.02	0.92	-11.49	12.63

BMI body mass index, *Edu* years of education, *bSBP* brachial systolic blood pressure, *bMAP* brachial mean arterial pressure

Significant correlations (P<0.05) are highlighted in bold.

DISCUSSION

In the present study, we found that in a sample of middle-age adults with normal global cognitive function both components of blood pressure were inversely related to regional cerebral perfusions in 5 of 10 regions of interest. In general, for the significant associations, the pulsatile component of blood pressure was more strongly associated with regional cerebral perfusion than the steady component.

These findings are consistent with a previous study in older adults that found a greater association between pulse pressure and cognitive function compared with MAP.[75] A longitudinal study in nondemented individuals demonstrated a higher decline of cognitive function in individuals with greater baseline pulse pressure compared with their peers.[4] The exact causes or physiological mechanisms linking pulsatile pressure and impaired cerebral perfusion are not known. However, the plausible mechanism is that excessive pulsatile force into the cerebral microcirculation due to greater fluctuations in blood pressure (i.e., higher pulse pressure) could cause damage to the brain's microvasculature. Regional hypoperfusion and cognitive dysfunction could be insults from excessive pulsatile force-induced cerebral microvascular damage.[76,77] The results from present study are consistent with this hypothesis. An alternative explanation could be an adaptive change in the cerebral vasculature. A strong positive association between cerebral pulse pressure and cross-sectional area of pial arterioles was reported in animal models.[78] In this situation the pial arterioles underwent hypertrophy after exposure to

chronically high cerebral pulse pressure aiming to protect the brain tissues from high pressure. However, this could also, in turn, cause reductions in cerebral perfusion.

MAP is a major factor that determines the perfusion pressure to various organs. From a physiological perspective, MAP should be more strongly associated with regional cerebral perfusion. However, in this study we found a weak association between MAP and regional cerebral perfusion. One possibility that may partly explain this finding is that cerebral autoregulation may closely control the steady component of blood pressure (i.e., MAP) that eventually attenuates its adverse effects. Alternatively, a high driving force (i.e., MAP) could be a protective adaptation to maintain proper blood perfusion to the brain. In support of this notion, a recent study in individuals with hypertension found a higher prevalence of congenital narrow vertebral arteries and incomplete posterior circle of Willis.[79] The causality analysis in the previous study reveals an elevated cerebral vascular resistance before the development of hypertension.[79]

Considering the superior ability to predict cardiovascular disease outcomes of central (i.e., carotid) over peripheral (i.e., brachial) blood pressure[73], we hypothesized that central blood pressure would be more closely associated with cerebral perfusion than peripheral blood pressure. However, the findings were opposite to our initial hypothesis. The reason for these findings is unclear. The nature of blood perfusion in the brain is very unique as the brain's tissues are continuously perfused at high flow rate due to low vascular resistance.[80] Therefore, it is possible that the response of the brain may differ from other vascular beds. The other reason that may explain a closer relationship between peripheral, compared with central, blood pressure and cerebral perfusion could partly due

to differences in arterial properties between peripheral (i.e., brachial artery) and central (i.e. carotid artery) arteries. For instance, brachial artery is more muscular compared with carotid artery. Arterial stiffness, which is one of the factors that determine pulsatility of arterial pressure that passes through cerebral circulation, can be modified by functional factors (e.g., changes in vascular tone due to contraction/relaxation of vascular smooth muscle cells) and structural factors (e.g., changes in elastic and/or collagen proportion).[81] The functional changes (i.e., changes in vascular tone) that lead to changes in arterial stiffness and ultimately arterial pressure pulsatility would be expected to occur earlier than structural changes in the arterial wall. As the participants in this study were healthy middle age adults, it is possible that that functional changes of the artery may have been more dominant than structural changes.

The major limitation of the present study was the cross-section design that cannot determine the causality of interest (i.e., blood pressure components and regional cerebral perfusion). However, we could infer the cause and effect between blood pressure components and regional cerebral perfusion based on existing literature showing a faster decline in cognitive performance in individuals with hypertension.[72]

In conclusion, the present study adds clinically important information to the existing evidence by demonstrating a stronger association between the pulsatile blood pressure component and regional cerebral perfusion than steady state component. Future longitudinal studies with a large number of sample size is warranted to determine the causality between pulsatile blood pressure component and cognitive dysfunction.

Chapter 5: Review of Literature

ENDOTHELIAL FUNCTION

Blood flow through arteries generates mechanical forces on the vessel wall. In order to maintain vascular homeostasis, endothelial cells in the vessel wall sense these mechanical forces and transduce these stimuli into intracellular signals.[82] Initiation of cellular events in response to shear stimuli involves multiple molecular elements, such as integrin, vascular endothelial growth factor (VEGF) receptor-2, G-protein-coupled receptors (GPCRs), and trimetric G-proteins.

- *Shear stimuli-mediated endothelial signaling*

Changes in shear stimuli could trigger acute responses (i.e., increases in vascular diameter) as well as slow or chronic structural remodeling. Shear stress-induced nitric oxide (NO) production is one of the most important physiological responses attributed to endothelial cells. Endothelial cells sense an increase in shear stimuli that initiates a mechanotransduction cascade resulting in the production of vasodilators (e.g., NO).[83]

The shear stress-induced NO production is a G-protein-dependent process.[35] Structural deformation of endothelial cells by shear force activates GPCRs[84] and leads to hydrolysis of PIP2 (phosphatidylinositol 4,5-biphosphate) to IP3 (inositol triphosphate).[85] IP3 triggers the release of calcium, which increases the concentration of cytosolic calcium ($[Ca^{2+}]$). The increase in Ca^{2+}-calmodulin (CaM) complexes ultimately target the recruitment and activation of endothelium nitric oxide synthase (eNOS), the enzyme that is responsible for NO production.[85]

Factors modulating release of endothelium-derived relaxing factor

The release of endothelium-derived relaxing factors (e.g., NO) is affected not only by the magnitude of the mechanical force (i.e., shear stimuli) but also by the rate and frequency of shear stimuli exposed to endothelial cells. Exposing isolated arteries to faster increases in shear stimuli resulted in greater vasodilatory responses.[11] The frequency-sensitive phenomenon of flow-induced production of endothelium-derived relaxing factors (e.g., NO) has also been shown in isolated rabbit aortic segments, as the percentage of vascular relaxation was directly proportional to the frequency of flow to which endothelial cells were exposed.[12] In addition, a study in human endothelial cells demonstrated the higher expression of G protein, one of the major mechanotransduction molecules that involved in shear stimuli-induced NO production, after exposure to a faster strain rate.[36]

- *Assessment of endothelium function*

Endothelial cells are not just a passive interface between blood and the arterial wall, but are considered large paracrine tissues that secrete a number of factors regulating vascular tone, vascular growth, and vasoprotection. Among these factors, NO is an important vasodilator molecule that also plays other key roles in the inhibition of atherosclerosis, including inhibitions of platelet adhesion and aggregation, leukocyte adhesion and migration, and smooth muscle cell proliferation.

The endothelium is a key element for the mechanotransduction cascade that is needed to maintain vascular homeostasis. The response of endothelial cells to increases in blood flow-associated shear stress is termed endothelium-dependent flow-mediated

dilation (FMD)[86-88] and has become a common measurement that provides information on the function of the endothelium in humans.

FMD of the brachial artery is a noninvasive approach that has become the most widely used technique to assess endothelial function. Brachial artery FMD assesses the endothelial function through the ability of an artery to respond to acute reactive hyperemia. The changes in arterial diameter after acute reactive hyperemia (induced by releasing blood pressure cuff after 5-minute occlusion on brachial artery) are obtained from ultrasound images of arterial diameter before and after cuff occlusion. To obtain an assessment that primarily reflects NO-dependent FMD, there are at least two major conditions that should be considered.

1. Occlusion cuff placement. An occluding cuff should be placed distal to the site that obtains the arterial diameter. Placing an occluding cuff proximal to the imaged artery leads to a FMD that comprises a substantial component related to tissue ischemia rather than NO-mediated component.[89]

2. Occlusion duration. A 5-minute occlusion protocol is typically well tolerated and often used. Prolonged duration (i.e., greater than 5 minutes) has been demonstrated to evoke a non-NO-mediated vasodilation.[90]

IMPACTS OF HEART RATE ON VASCULAR FUNCTION

Heart rate is one of many hemodynamic factors that influence vascular function. Measurement of large artery stiffness, such as carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx), is dependent on heart rate. As cfPWV is known

to be a pressure dependent variable and an increase heart rate is commonly accompanied by increased blood pressure. A recent study isolated the true effect of heart rate on cfPWV using in situ cardiac pacemakers or cardioverter defilbrillators to determine the effect of intrinsic heart rate without the effects of sympathovagal-dependent changes in heart rate and blood pressure.[91] The results from this study demonstrated a mean heart rate dependency in the range of 0.16 to 0.20 m/s per 10 bpm independent of blood pressure changes. This result may show minimal physiologically relevant changes of cfPWV with small changes in heart rate; however, there are some circumstances that could induce large differences in heart rate after the intervention. In the event of such circumstances, heart rate should be considered a factor that contributes to significant differences in cfPWV. No studies to date have shown the mechanisms involved in this heart rate dependency. However, the viscoelasticity of the arterial wall[92,93] and reduced time for the artery to recoil[94,95] at higher heart rates have been offered as potential mechanisms behind the impact of heart rate on cfPWV.

AIx is an indicator of systemic arterial stiffness that is derived from pulse wave analysis. Heart rate is one of the factors that influence this arterial stiffness index, specifically AIx is inversely related to heart rate.[93,96] An increase in heart rate will decrease the absolute duration of systole resulting in shifting of the reflected wave into diastole.[93,96] Individuals with permanent cardiac pacemakers and those who underwent routine cardiac catheterization demonstrated declines in AIx ranging from 3.9% to 5.6% for each 10 bpm increment of heart rate.[93,96]

The influence of heart rate on vascular function has also been demonstrated in a study that determined endothelial responses to heart rate. Blood flow across the arterial wall generates shear stimuli that induces vascular signaling response via the function of endothelial cells. Mechanotransduction by endothelial cells induces endothelial gene expression. Vascular phenotypes (i.e., atherosclerosis susceptibility or atherosclerosis protection) are determined based on the nature of shear stimuli that interact with the arterial wall. Amplitude, pattern, and frequency of shear stimuli all influence endothelial response. For example, the induction of eNOS is activated by high shear stress.[97] A study using aortic endothelial cells demonstrates different endothelial responses to a "physiologic" and "pathologic" frequency of shear stimuli.[31] In this study, the endothelium cells respond to a physiologic frequency (i.e., 1 Hz) of shear stimuli by inducing a number of atheroprotective transcriptions and repressing inflammatory transcripts. In contrast, the responses of endothelium cells to a frequency of shear stimuli that is higher than physiologic frequency involves induction of a proinflammatory phenotype, such as monocyte chemoattractant protein-1 and intercellular adhesion molecule-1. However, clinical data regarding the influence of heart rate on endothelial function are inconclusive. A positive association between heart rate and brachial FMD, an index of endothelial function, has been reported in a large cohort of the Framingham Heart Study.[15] Yet an inverse relationship between heart rate and FMD was found in a study with a small number of subjects.[13]

IMPACTS OF CARDIOVASCULAR SYSTEM ON CEREBRAL PERFUSION

The brain is a vital organ with a high metabolic demand and receives 15% of total cardiac output, despite the fact that it weighs only 2% of total body weight.[98,99] Even though the brain has its own autoregulatory mechanism to control cerebral perfusion, a recent study has analyzed the relationship between cerebral blood flow and mean arterial pressure using projection pursuit regression to circumvent the linear limitations of this relationship. This study found that in young healthy subjects, when blood pressure was oscillated at 0.03 Hz, a cerebral autoregulatory operation range was shown to be very narrow (~10 mmHg).[1] This finding suggests the importance of intact cardiovascular hemodynamic function in providing normal blood perfusion to the brain. Hypoperfusion to the brain may lead to ischemia and damage to brain tissues that could eventually result in impaired cognitive function. Indeed, brain perfusion and cognitive performance are significantly related.[60]

- *Impacts of cardiovascular dysfunction on impaired cerebral perfusion and declined cognitive function*

The high incidents of cognitive dysfunction in patients with severe cardiovascular disease presumably reflect the impact of impaired cardiovascular function on the aging brain.[100-102] Reduced cardiac output and impaired systemic vascular structure and function have been shown to be related to cognitive dysfunction and structural abnormalities of the brain.[102-108] Reduced systemic blood flow due to impaired cardiac output shows a significant association with white matter hyperintensities (WMH), an

important index that is related to cognitive decline in later life in those with cardiovascular disease.[108]

Available literature have reported strong relationships between indices of vascular aging (i.e., atherosclerosis and arteriosclerosis) and cognitive impairment. A significant inverse association between carotid intima-media thickness (IMT) and cognitive function has been observed in both cross-sectional and longitudinal studies.[109-113] A thicker carotid arterial wall was shown to be related to lower cognitive performance even after the age, education, and/or the presence of cardiovascular risk factors were taken into account.[109,113] Poorer cognitive function has also been shown to be related to arterial stiffness which is an independent risk factor for impaired cognitive funciton with advancing age.[114,115] A number of longitudinal studies have demonstrated a prospective association between higher PWV at baseline measurement and poorer cognitive function in later years.[4,116]

The effects of cardiovascular function on cognitive function may also be attributed to endothelium function. An impaired peripheral endothelium function as measured by brachial FMD in elderly individuals with cardiovascular disease has been reported to related to increased WMH.[107] A study of eldery individuals with subjective memory complaints reported an association between the severity of WMH and von Willerbrand Factor (i.e., a biomarker of endothelial dysfunction).[117]

There are a number of studies showing that changes in cerebral blood flow[118] and/ or structure[119] precede cognitive decline. In an animal model using a 2-vessel occlusion (i.e., both common carotid arteries) technique to induce brain hypoperfusion, capillary

degeneration in the CA1 section of the hippocampus and neuronal damage was found after the animals experienced cerebral hypoperfusion for 12 months.[120] Moreover, the same animal study also demonstrated a significant direct association between cognitive performance decline and severity of capillary damage in the hippocampal CA1 area. Therefore, despite lacking direct evidence showing a relationship between the cardiovascular system and cerebral blood flow, as based on the available literature which has reported the close relationship between cardiovascular system and cognitive function could lend support to the plausible role of cardiovascular system on cerebral blood flow.

- *Brain areas susceptible to hypoperfusion*

A failure to regulate cardiovascular function could lead to global cerebral hypoperfusion. The specific adverse effects of cerebral hypoperfusion on memory performance[60] suggests that the hippocampus, a brain region critical for memory, could be a region that is more sensitive to ischemic insults. The pattern of cerebrovascular anatomy that supplies the hippocampal region may be a primary determinant in raising susceptibility of hypoperfusion insults.

A study of the anatomical patterns of cerebral microcirculation revealed the susceptibility of certain areas to hypoperfusion, including the hippocampus.[61] In contrast to the areas that have high resistance to hypoperfusion (e.g., cerebral cortex, the subcortical arcuate fibers, and the corpus callosum) that are irrigated by short-penetrating arteries, the hippocampus is poorly irrigated, especially in the CA1 sector.[121] Systemic hypoperfusion with hypoxia-ischemia is postulated as a cause of hippocampal sclerosis, a

localized form of ischemia and atrophy, in very old subjects with dementia and cardiac disease.[122]

- *Assessments of cerebral blood flow*

Cerebral blood flow can be assessed by a number of techniques. A simple technique such as transcranial Doppler (TCD) ultrasound has been used to assess global cerebral blood flow.[123] However, TCD has some limitations as only mean blood velocity, not blood flow, can be assessed using this technique. TCD also has a limitation in the analysis of blood flow in specific brain regions. The arterial spin labeling (ASL), or perfusion functional MRI technique, provides a non-invasive, quantitative measure of cerebral blood flow in specific brain regions. ASL has been used as the approach for examining cerebral blood flow in regions of interest linked to cognitive dysfunction and dementia.[44-46] The ASL MRI technique uses arterial blood water that is magnetically labeled using radiofrequency irradiation as an endogenous tracer. Water molecules of flowing blood toward a region of interest (ROI) are labeled or tagged by radiofrequency irradiation. The tagged or magnetized blood travels into the imaging slices, which can be measured with a standard MRI imaging sequence. Cerebral blood flow in a ROI is calculated from the difference between the control (unlabeled) and tagged images.[44-46]

BAROREFLEX AND ITS POTENTIAL IMPACT ON THE BRAIN

The arterial baroreflex is the major mechanism that works to control moment-to-moment fluctuations of arterial blood pressure. The baroreflex controls blood pressure through two hemodynamic parameters that determine blood pressure, including cardiac

output and total peripheral resistance.[124] The arterial baroreceptors located in the adventitial layer of the carotid sinuses and aortic arch are composed of mechanosensitive afferent nerves. A negative feedback loop controlling blood pressure from the function of baroreflex involve a complex network of brain stem units such as the nucleus of the solitary tract (NTS), the nucleus ambiguous (NA), and the rostral ventrolateral medulla (RVLM). This complex network within the brain stem subserve cardiovascular response through modulation of the autonomic system (i.e., sympathetic, and parasympathetic). Changes in arterial pressure cause mechanical deformation of the arterial wall, which then generate mechanotransduction-excitatory input to neurons located in the NTS.[125,126] A direct input from barosensitive NTS neurons to a group of vagal preganglionic neurons located in the ventrolateral portion of the nucleus ambiguous provide a beat-to-beat control of the heart rate[127], one of the hemodynamic factors that determines cardiac output. Total peripheral resistance, another determinant of arterial pressure, is primarily controlled by the sympathotinhibitory pathway that involves a connection between the NTS and sympathoexcitatory neurons located in the RVLM. These RVLM neurons are responsible for the activation of the sympathetic vasoconstrictor output to vessels in skeletal muscle, mesenteric, and renal regions.[128,129]

- *Assessments of cardiovagal BRS*

Baroreflex sensitivity can be assessed using the slope of the R-R interval-systolic blood pressure relation obtained from various protocols.[53] The protocols generate an acute change in arterial pressure to trigger the response of the arterial baroreflex. Change

in the R-R interval (or heart rate) per unit change in systolic blood pressure is represented as cardiovagal BRS.

The Valsalva's maneuver, a simple, reproducible, and noninvasive procedure, is one of the protocols that have been used for BRS assessment. During the Valsalva's maneuver, abrupt transient elevations in intra-thoracic and intra-abdominal pressures are provoked by straining (i.e., performing forced expiration against a closed glottis). Adequate stimulus during the period of Valsalva straining is monitored as mouth pressure (an estimated intrapleural pressure) and is commonly raised to 40 mmHg for 10 seconds. The responses to the Valsalva's maneuver are composed of 4 phases.

Phase 1. Immediately after the onset of Valsalva straining, there is a brief rise in arterial pressure and a reduction in heart rate. However, an elevated arterial pressure during phase 1 of the Valsalva's maneuver does not appear to be mediated by sympathetic autonomic nervous system as it is not preceded by an increase in burst amplitude of muscle sympathetic nerve activity.[53]

Phase 2. The elevated arterial pressure during phase 1 is followed by a decrease in arterial pressure to the baseline level in phase 2. In this phase, pressures in all baroreceptors are reduced.

Phase 3. After expiratory pressure (i.e., a straining) is released, there is a very brief further reduction in arterial pressure and an increase in heart rate.

Phase 4: In this phase, a sustained elevated arterial blood pressure above baseline levels then stimulates arterial baroreflex-mediated prolongation of R-R interval. The response

of the R-R interval and systolic blood pressure during phase 4 of the Valsalva's maneuver is used to determine BRS.

- *BRS and its potential impact on the brain*

A depressed BRS may lead to impaired cardiovascular control, which could affect perfusion pressure to the downstream tissues. Impaired BRS could cause serious consequences especially in organs that have high metabolic demands with a limited capacity to store nutrients and oxygen, such as the brain. Despite the fact that the brain has its own autoregulation to maintain steady cerebral blood perfusion, a recent study has revealed a very narrow range of operation (~10 mmHg) of cerebral autoregulation in young healthy subjects.[1] This finding highlights the importance of extra-cranial mechanisms in maintaining stable cerebral blood flow even if cerebral autoregulation is intact. Moreover, a study of healthy young adults reported an important role of cardiac baroreflex in cerebral autoregulation by demonstrating attenuated dynamic cerebral autoregulation function during cardiac autonomic blockade (i.e., inhibited cardiac baroreflex response).[130]

Cardiovagal BRS in humans has been reported to decline with advancing age[65], and this change is attributed to hardening of the large, elastic arteries.[51] The potential impact of BRS on the brain has been shown in a number of studies. Higher incidence of memory impairment has been shown in an elderly population with impaired BRS compared with age-matched peers with normal BRS.[2] Additionally, depressed BRS has been reported in patients with Alzheimer's and Parkinson's diseases.[54] A recent study in older adults further suggests a close relation between BRS and the brain. In this recent

study, higher executive function was associated with better white matter integrity in areas of the brain that have significant correlations with BRS and central artery stiffness (i.e., carotid-femoral pulse wave velocity).[131]

In addition to changes in the peripheral component of baroreflex (i.e., stiffening of large elastic arteries where baroreceptors are located), changes in the central component of baroreflex and its efferent pathway could also contribute to impaired BRS. The baroreflex involves modulation of the autonomic nervous system through a complex network of neurons in brain stem; thus, degeneration of these neurons (e.g., NTS, RVLM) could lead to impaired baroreflex response to fluctuating blood pressure.

The autonomic nervous system is one of the mechanisms that regulates cerebral blood flow. There are extensive innervations of adrenergic and cholinergic fibers throughout the entire cerebrovasculartur.[132-135] Activation of α-adrenoeptors causes vasoconstriction in the cerebrovascular bed.[136] Vasodilation of the vessels in the brain is primarily caused by activation of **β**-adrenoceptor. Activation of parasympathetic nerve activity via cholinergic fibers has been shown to increase cortical cerebral blood flow (i.e., the cerebral neocortex and hippocampus) in animal models.[137,138] Therefore, changes in the balance between sympathetic and parasympathetic activation could affect not only the function of baroreceptor but cerebral blood flow as well.

In addition to an acute regulation of blood pressure, baroreflex is also involved in chronic blood pressure control. Clinical trials have reported an anti-hypertensive response to electrical stimulation of the carotid baroreflex in patients with resistant hypertension.[139-144] Results from these studies show that electrical baroreflex activation

not only provides global inhibition of sympathetic activity, but also suppresses renal sympathetic nerve activity (RSNA), a major mechanism mediating chronic blood pressure regulation. This finding lends support to the important role of baroreflex on blood pressure control and brain blood flow.

BLOOD PRESSURE AND BRAIN FUNCTION

The role of systolic and diastolic blood pressures in cardiovascular disease was compared in the Framingham Heart Study in 1971.[145] This longitudinal study showed that the risk stratification of cardiovascular disease based on systolic and diastolic blood pressure is modified by aged. In younger individuals, diastolic blood pressure is the stronger predictor of coronary heart disease. In contrast, systolic blood pressure is the predominant predictor of coronary heart disease in older individuals. Age-related changes in systolic blood pressure, diastolic blood pressure, pulse pressure, and mean arterial pressure were demonstrated in a longitudinal study that performed biannual evaluation over a 30-year follow-up period.[146] In this epidemiological study, systolic blood pressure increases disproportionally with diastolic blood pressure after 50 years of age with a marked drop in diastolic blood pressure after the age of 60, resulting in a further widening of pulse pressure. The age-related stiffness of the large elastic artery (i.e., aorta) could be a major factor contributing to increases in systolic blood pressure and declines in diastolic blood pressure as a reduced capacity of the elastic reservoir that lead to a greater peripheral runoff of stroke volume during systole.

- *Steady state vs. pulsatile blood pressure component and cognitive function*

Among a number of vascular risk factors, chronic hypertension is an important factor that contributes to impaired cognitive function.[147] Indeed, chronically elevated blood pressure has been shown to induce detrimental impacts on brain structures.[148]

Arterial blood pressure is comprised of two major components: steady state and pulsatile components. The steady state component is assessed as mean arterial pressure and is largely influenced by cardiac output and small resistance artery function. On the other hand, the pulsatile component is represented by pulse pressure and systolic blood pressure, and is driven primarily by large artery stiffness.[74] As the two components of arterial blood pressure are influenced by different factors, deconstructing blood pressure into the steady and pulsatile components may offer a better understanding of the pathophysiology of high blood pressure on impaired cognitive performance. Indeed, there is extensive literature on the superiority of pulsatile blood pressure in predicting end-organ damage[149], cognitive performance[75], and Alzheimer-related biomarkers[150].

A longitudinal study in elderly individuals revealed a prospective decline in cognitive performance, including verbal learning, nonverbal memory, working memory, and cognitive screening measure in older adults with greater pulse pressure.[4] The plausible mechanisms underlying the impact of pulse pressure on cognitive performance may include the fact that the brain is a vital organ that has high flow and low impedance. Therefore, it is susceptible to an increase in pulsatile nature of blood flow. Greater pulse pressure, a surrogate marker of arterial stiffness[10], may place microvessels in the brain at high risk for damage. Higher pulse pressure may induce microvascular damage by

transmission of excessive pulsatile stress into the cerebral microvasculature which could lead to regional hypoperfusion. Indeed, an association between pulse pressure and increased risk for impaired brain structure and function has been demonstrated even in elderly individuals without a history of dementia.[77]

- *Central vs. peripheral blood pressure and cognitive function*

An increase in both central and peripheral blood pressure has been reported to be related to poorer cognitive function.[151] Higher peripheral pressure (i.e., brachial blood pressure) was related to poorer Stroop processing and spatial working memory in middle-aged individuals.[151] However, a stronger association between central blood pressure and cognitive performance, compared with peripheral blood pressure, was reported in a study that recruited a sample of a wide age range (28 to 82 years).[151] An increase in aortic stiffening and central blood pressure are related to arterial aging.[152] Given that blood flow to the brain is delivered through the central large arteries, stiffening of the large elastic arteries with advancing age could reduce the ability of the arterial wall to dampen blood pressure before reaching the brain. Therefore, sustained high central blood pressure may cause accumulative damage of vascular beds in the brain and could eventually lead to impaired cognitive function in later life.

- *Possible Adverse effect of blood pressure lowering medication on cognitive function*

Although high blood pressure, especially during midlife, is related to cognitive decline in later life, treating hypertension with anti-hypertensive medication may cause an adverse effect on cerebral blood flow. The cerebral autoregulatory curve of MAP and cerebral blood flow undergoes a shift-to-the-right to maintain cerebral blood flow at a

higher blood pressure level in individuals with hypertension.[153,154] Despite an intact function of cerebral autoregulation in individuals with hypertension[155], the lower limit of this mechanism operates at a higher pressure than normotensive individual. The changes in the lower limit of cerebral autoregulation in individuals with hypertension may cause a problem when blood pressure is decreased by blood pressure lowering medication.

Chapter 6: Summary and Future Directions

SUMMARY

The overall findings from this dissertation study highlight the potential impacts of systemic hemodynamic factors on cerebral and peripheral perfusion. The physiological impact of systemic hemodynamic factors was demonstrated in the study 1 as the results indicate an indirect effect of heart rate on endothelium-dependent vasodilation. As frequency of blood flow through the arterial wall could be modified by heart rate. The finding from study 1 could provide the support for the systemic effect of regular exercise on vascular beds in non-exercising muscles.

Findings from the studies 2 and 3 provide insights into the potential impacts of systemic hemodynamic factors (i.e., BRS and blood pressure) on blood flow to the brain region that play an important role on memory domain of cognitive function (i.e., hippocampus region). A direct association between BRS and regional blood perfusion in hippocampal region may partly explain the previous findings that demonstrated an impaired cognitive function in individuals with impaired BRS.[3,54] In particular, findings from the study 2 suggest that individuals with lower BRS would have lower hippocampus perfusion. A reduction in blood flow to the brain especially in the regions that are susceptible to cerebrovascular disease could cause an impaired brain function. A simple test such as tilt table test could help the clinician to early diagnostic individuals who may at risk of developing an impaired cognitive function due to an impaired baroreflex function.

Last, an inverse association between pulsatile component of blood pressure and regional cerebral perfusion at hippocampus and anterior white matter regions in study 3 suggest a negative effect of high blood pressure pulsatility on blood perfusion to the

brain. These findings support the utility of pulsatile blood pressure components (i.e., systolic blood pressure and pulse pressure) as risk factors to predict an impaired cognitive function in the future.

FUTURE DIRECTIONS

The cause and effect relationship between systemic hemodynamic function and perfusion in cerebral and/or peripheral vascular beds needs further investigation, using a longitudinal study design. Future studies that include nondemented elderly, individuals with mild cognitive impairment, and individuals with dementia may further our understanding about the effects of systemic hemodynamic factors and/or mechanisms on cerebral perfusion and cognitive function.

Longitudinal studies that include exercise interventions are another interesting future research direction. Habitual aerobic exercise has been reported to attenuate the age-related decline in cardiovagal BRS.[66] The age-related decline in BRS is attributed to stiffening of the large elastic arteries.[51] The link between destiffening of the arteries with habitual exercise has been reported, and such greater arterial compliance is associated with a corresponding higher in cardiovagal BRS.[66,67] The potential of exercise training to act as an effective preventive or therapeutic strategy to prevent or restore impaired regional cerebral perfusion and potentially impaired cognitive function in advancing age needs to be investigated in future longitudinal studies.

Appendices

Appendix A: Abbreviations and Acronyms

AIx = augmentation index

ASL = arterial spin labeling

BMI = body mass index

BP = blood pressure

BRS = baroreflex sensitivity

cfPWV = carotid-femoral pulse wave velocity

CI = confidence interval

eNOS = endothelium nitric oxide synthase

FMD = flow-mediated dilation

GPCRs = G-protein-coupled receptors

IMT = intima-media thickness

MMSE = the Mini-Mental State Exam

MRI = magnetic resonance imaging

NA = the nucleus ambiguous

NO = nitric oxide

NTS = the nucleus tractus solitarii

RVLM = the rostral ventrolateral medulla

SBP = systolic blood pressure

SR = shear rate

TCD = transcranial Doppler

VEGF = vascular endothelial growth factor

WMH = white matter hyperintensities

Appendix B: Research Health Questionnaire

Cardiovascular Aging Research Laboratory

Personal Information

Date_____Subject ID_____

Date of Birth_____Age_____ Sex ☐ Male

☐ Female: Date of Last Menstrual Period:_____

Please circle the highest grade in school you have completed:

Elementary school	1	2	3	4	5	6	7	8
High school	9	10	11	12				
College/ Post Grad	13	14	15	16	17	18	19	20+

What is your marital status? ☐ Never Married ☐ Married ☐ Widowed ☐ Divorced; Separated

Ethnic Background: Hispanic or Latino Not Hispaic or Latino

Race:

☐ White ☐ American Indian/ Alaskan Native ☐ Pacific Islander

☐ Black or African American ☐ Asian ☐ Other:_____

Symptoms or Signs Suggestive of Disease

Check appropriate box:

Yes	No	
☐	☐	1. Have you experienced unusual pain or discomfort in your cheek, neck, jaw, arms or other areas that may be due to heart problems?
☐	☐	2. Have you experienced unusual fatigue or shortness of breath at rest, during usual activities, or during mild-to-moderate exercise (e.g., climbing stairs, carrying groceries, brisk walking, cycling)?
☐	☐	3. When you stand up, or sometimes during the night while you are sleeping, do you have difficulty breathing?
☐	☐	4. Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5. Do you suffer from swelling of the ankles (ankle edema)?
☐	☐	6. Have you experience an unusual and rapid throbbing or fluttering of the heart?
☐	☐	7. Have you experience severe pain in your leg muscles during walking?
☐	☐	8. Has a doctor told you that you have a heart murmur?

Chronic Disease Risk Factors

Check appropriate box:

Yes	No	
☐	☐	9 a. Are you a male over age 45 years or a female over age 55 years?
☐	☐	b. Are you a female who has experienced premature menopause?
☐	☐	c. If you answered "yes" to 9b, are you on estrogen replacement therapy?
☐	☐	10. Has your father or brother had a heart attack or died suddenly of heart disease before age of 55; has your mother or sister experienced these heart problems before the age of 65?
☐	☐	11. Are you a current cigarette smoker? If quit smoking, when? Date:_____
☐	☐	12. Has a doctor told you that you have high blood pressure (more than 140/90 mmHg) or a heart condition?
☐	☐	13. Is your total serum cholesterol greater than 200 mg/dl, or has a doctor told you that your cholesterol is at a high risk-level?
☐	☐	14. Do you have diabetes mellitus?
☐	☐	15. Are you physically inactive and sedentary? (little physical activity on the job or during leisure time)?
☐	☐	16. Do you have a bone or joint problem that could be made worse by a change in your physical activity?
☐	☐	17. During the past year, would you say that you have experienced enough stress, strain, and pressure to have a significant effect on your health?
☐	☐	18. Do you eat foods nearly every day that are high in fat and cholesterol such as fatty meats, cheese, fried foods, butter, whole milk, or eggs?
☐	☐	19. Do you weigh 30 or more pounds than you should?
☐	☐	20. Do you know of any other reason you should not do physical activity?

Medical History

21. *Please check which of the following conditions you have had or now have. Also check medical conditions in your family (father, mother, brother(s), or sister(s)). Check as many as apply.*

Self	Family	Medical Condition	Self	Family	Medical Condition
☐	☐	Coronary heart disease, heart attack; by-pass surgery	☐	☐	Major injury/ fracture to foot, leg,knee
☐	☐	Arrhythmias	☐	☐	Major injury to back or neck
☐	☐	Angina	☐	☐	Major injury/ fracture to hip or shoulder
☐	☐	Marfan's syndrome	☐	☐	
☐	☐	High blood pressure	☐	☐	Recent leg trauma/ injury
☐	☐	Peripheral vascular disease	☐	☐	Rheumatoid arthritis
☐	☐	Phlebitis or emboli	☐	☐	Osteoarthritis
☐	☐	Other heart problems	☐	☐	Osteoporosis
☐	☐	Stroke	☐	☐	Fibromyalgia
☐	☐	Asthma	☐	☐	Chronic fatigue syndrome
☐	☐	Bronchitis	☐	☐	Systemic lupus erythematosus
☐	☐	C.O.P.D. (emphysema)	☐	☐	Anemia (low iron)
☐	☐	Pulmonary embolism (blood clots in the lungs)	☐	☐	Thyroid problems
☐	☐	Deep vein thrombosis (blood clots in legs)	☐	☐	Gout
☐	☐	Antithrombin III deficiency	☐	☐	Kidney disease
☐	☐	Inherited hypercoaguability	☐	☐	Nephrotic syndrome
☐	☐	Acquired hypercoaguability	☐	☐	Gallstones/ gallbladder disease
☐	☐	Factor V leiden mutations	☐	☐	Liver disease (cirrhosis)

Self	Family	Medical Condition	Self	Family	Medical Condition
☐	☐	Protein C deficiency	☐	☐	Hepatitis
☐	☐	Protein S defiencey	☐	☐	Diabetes mellitus
☐	☐	Stomach/ duodenal ulcer	☐	☐	Raynaud's disease
☐	☐	Rectal growth or bleeding	☐	☐	Crohn's disease
☐	☐	Irritable bowel syndrome	☐	☐	Hysterectomy
☐	☐	Lung cancer	☐	☐	Problems with menstruation
☐	☐	Breast cancer	☐	☐	Post-menopausal Date:
☐	☐	Prostate cancer	☐	☐	Allergies
☐	☐	Skin cancer	☐	☐	Depression
☐	☐	Colorectal cancer	☐	☐	Anxiety, phobias
☐	☐	Other cancer Specify:	☐	☐	Eating disorders
☐	☐	Hearing loss	☐	☐	Substance abuse problems (alcohol, other drugs, etc.)
☐	☐	Cataracts	☐	☐	Sleeping problems
☐	☐	Glaucoma	☐	☐	Other Specify:

Please specify and include information on any recent illnesses, hospitalizations, surgical procedures, or other health problems.

_____

_____

22. a. Are you currently pregnant, think you may be pregnant, or are currently trying to get pregnant?

☐ Yes ☐ No ☐ Not sure ☐ Not applicable (male or post-menopausal)

b. If you answered "yes" or "not sure" to 22a, do you need a pregnancy test? ☐ Yes ☐ No

23. In the past two weeks, have you had a barium test, a nuclear medicine scan, or x-rays with a dye injection?

☐ Yes ☐ No

24. *Please check any of the following medications you take regularly and give the name and dose of the medication.*

Medication	**Name of Medication**
☐ Heart medicine	_____
☐ Blood pressure medicine	_____
☐ Blood cholesterol medicine	_____
☐ Thromboembolic disease medicine	_____
☐ Hypercoaguability medicine	_____
☐ Steroids	_____
☐ Hormone/HRT	_____
☐ Medicine for breathing/lungs	_____
☐ Insulin	_____
☐ Other medicine for diabetes	_____
☐ Arthritis medicine	_____
☐ Medicine for depression	_____
☐ Medicine for anxiety	_____
☐ Thyroid medicine	_____
☐ Medicine for ulcers	_____
☐ Painkiller medicine	_____
☐ Allergy medicine	_____
☐ Dietary supplements (herbs, vitamins, etc)	_____
☐ Other (please specify)	_____

25. Do you have any known drug allergies?

_____

Body Weight

26. What is the most you have ever weighed? _____

27. Are you now trying to:

☐ Lose weight ☐ Gain weight ☐ Stay about the same ☐ Not trying to do anything

Stress

28. During the past month, how would you rate your overall level of stress?

☐ Very high ☐ High ☐ Moderate ☐ Low

29. In the past year, how much effect has stress had on your health?

☐ A lot ☐ Some ☐ Hardly any or none

30. On average, how many hours of sleep do you get in a 24-hour period?

☐ Less than 5 ☐ 5-6 ☐ 7-6 ☐ More than 9

Substance Use

31. How would you describe your cigarette smoking habits?

☐ Never smoked

☐ Used to smoked. How many years has it been since you smoked? _____ years

☐ Still smoke. How many cigarettes a day do you smoke on average _____ cigarettes/day

32. How many alcoholic drinks do you consume? (A "drink" is a glass of wine, a wine cooler, a 16 oz bottle/ 12 oz can of beer, a shot glass of liquor, or a mixed drink).

☐ Never use alcohol ☐ Less than 1 per week ☐ 1-6 per week

☐ 1 per day ☐ 2-3 per day ☐ More than 3 per day

33. In one sitting, how many drinks do you typically consume? _____

34. How many cups (8 ounces) of coffee do you drink per day? _____

35. How many ounces of sodas containing caffeine do you drink per day? _____

Physical Fitness, Physical Activity/ Exercise

36. Considering a **7-day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your **free time** (write on each line the appropriate number).

Times Per Week

a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY)

_____

(i.e., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE (NOT EXHAUSTING)

_____

(i.e., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE (MINIMAL EFFORT)

_____

(i.e., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

37. Considering a 7-day period (a week), during your leisure-time, how often do you engage in

any regular activity long enough to work up a sweat (heart beats rapidly)?

☐ Often ☐ Sometimes ☐ Never/Rarely

38. How long have you exercised or played sports regularly?

☐ I do not exercise regularly ☐ Less than 1 year ☐ 1-2 years

☐ 2-5 years ☐ 5-10 years ☐ More than 10 years

Physical Fitness, Physical Activity/ Exercise

36. Considering a **7-day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your **free time** (write on each line the appropriate number).

Times Per Week

a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY)

_____

(i.e., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE (NOT EXHAUSTING)

_____

(i.e., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE (MINIMAL EFFORT)

_____

(i.e., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

37. Considering a 7-day period (a week), during your leisure-time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

☐ Often ☐ Sometimes ☐ Never/Rarely

38. How long have you exercised or played sports regularly?

☐ I do not exercise regularly ☐ Less than 1 year ☐ 1-2 years
☐ 2-5 years ☐ 5-10 years ☐ More than 10 years

Appendix C: Mini-mental state examination

"I will be asking you to do a number of things todays, some will be easy, others more difficult. Please remember that not everyone answers every question, or solves every problem. All we ask is that you give us your best effort."

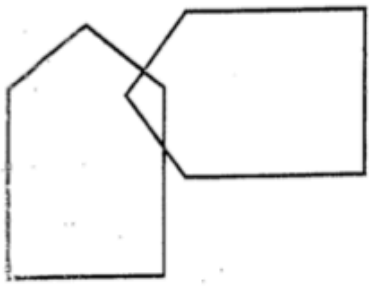
MINI-MENTAL STATE EXAMINATION

1. What day is today_____, month_____, day of the month_____, year_____, season_____ ( ) 5
2. What is the name of the building we are in_____, town_____, county_____, state_____, country_____ (___) 5
3. Remember these words: peach, truth, chair. Repeat them now (*Practice until subject is able to repeat them, recording number of repetitions required_____)* (___) 3
4. Subtract 7 from 100 and continue subtracting 7 from the remainder until I say stop. _____(*give one point for each correct subtraction even if the starting number was incorrect). If unable, have the subject spell the word "WORLD" backwards*_____(DLROW) (___) 5
5. What were those words I asked you to remember? _____ (___) 3
6. What is this (*show the subject a pen/ pencil and a watch)*_____ (___) 2
7. Repeat after me: "NO IFS, ANDS, OR BUTS."_____ (___) 1
8. Do this: (*show subject the phrase Close Your Eyes written in large print* ( ) 1
9. Take this paper in your right hand, fold it in half, and put it on the floor. (___) 3
10. Write a complete sentence here: (___) 1

_____

_____

11. Copy this drawing (___) 1



_____

_____/30

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