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Effects of Aerobic Exercise on Cognitive and Cerebrovascular Function in Hypertensive Adults

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Abstract

The presence of hypertension in middle-age is a major risk factor for later-life development of cognitive and cardiovascular disease. Exercise is widely recommended to combat vascular and brain aging in hypertension. We sought to compare the effects of a single bout of aerobic exercise on 1) arterial stiffness and cerebral hemodynamics and 2) cognitive function in middle-aged adults with controlled-hypertension and without hypertension. Vascular and cognitive measures were assessed pre and post 30-min of aerobic exercise at ≈55% maximal oxygen consumption. Arterial stiffness and cerebral hemodynamics were measured non-invasively. Cognitive function was measured using a computerized testing battery that included executive function and memory tasks. Acute aerobic exercise resulted in similar 1) increases in arterial stiffness and cerebral hemodynamic pulsatility, and 2) accelerated executive function and memory reaction time post-exercise in adults with and without hypertension. Based on these results, we investigated if adults with hypertension had differential vascular contributions to cognitive activity. We measured cerebrovascular hemodynamics non-invasively during cognitive activity as a measure of neurovascular coupling. Adults with and without hypertension exhibit similar increases in large artery stiffness and decreases in extracranial hemodynamic pulsatility during cognitive activity, indicating similar neurovascular coupling between groups. In conclusion, these data indicate that middle-aged adults with controlled-hypertension experience similar 1) vascular responses to acute exercise and cognitive activity, and 2) beneficial changes in cognitive function following acute exercise as their counterparts without hypertension. Our results will be interpreted and explored in the context of hypertension severity and underscore the importance of optimal blood pressure control.

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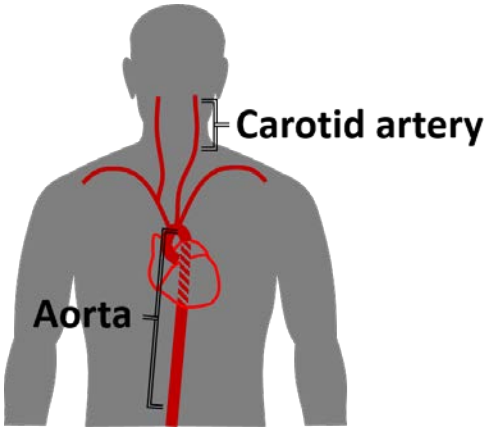
Key Concepts

Hypertension (HTN): A clinical condition characterized by abnormally high pressure inside the blood vessels that carry blood away from the heart. HTN has been identified as a condition that increases the risk of developing further chronic disease (particularly of the heart, kidney, and brain). Controlled HTN refers to medically managed blood pressure via pharmaceutical medication prescribed by a physician alone and/or lifestyle modifications (diet/activity)

Cognitive function: An umbrella term used to describe brain activities that contribute to acquiring and interpreting information and gaining knowledge. Cognitive function is comprised of domains (attention/concentration, language, visuospatial skills, psychomotor skills, executive functions, memory and orientation) that describe specific components required for adequate information acquisition/interpretation. Cognitive function is discussed in this document with a particular focus on the domains of executive function and memory.

Arterial stiffness: A term referring to the material properties of the blood vessels that carry blood away from the heart (i.e. arteries). Arteries are naturally elastic and stretch when the heart ejects blood into the vessel. With aging and disease, the arteries lose elasticity (i.e. increase in stiffness) and this effects how blood flow and is delivered to tissues and organs transmitted throughout the body. This document focuses on large artery stiffness, particularly at the level of the carotid artery and aorta.



Hemodynamics: Derived from *heme*, meaning blood, and *dynamics*, referring to the motion of objects under the action of external forces. Thus, hemodynamics is an encompassing term used to describe the movement of both blood pressure and blood flow throughout the body. Blood pressure and blood flow represent two separate forces. Blood pressure and blood flow travel at

different speeds throughout the body and are altered by different factors. When the heart contracts, the pressure created (energy) is what propels the liquid medium (blood) forward (i.e. downstream). A note for this study – blood pressure and blood flow do not travel in one direction. Blood pressure and blood flow can move backward. In some settings, backward traveling blood pressure and blood flow can be detrimental to health.

Hemodynamic pulsatility: Refers to a specific pattern in which blood flow or pressure is delivered to the body. When the amount blood flow/pressure is somewhat constant from when the heart contracts to when the heart relaxes, it is considered non-pulsatile (i.e. continuous; there is not much difference between maximum and minimum flow/pressure). This continuous, non-pulsatile blood flow is ideal for working organs like the brain and kidney. When the amount of blood flow/pressure is highly variable from heart contraction to relaxation it is considered pulsatile (i.e. discontinuous; high amounts of blood flow/pressure after heart contraction, very low blood flow/pressure after heart relaxation). Discontinuous, pulsatile blood flow can damage fragile tissue and blood vessels in organs like the brain and kidney. See figure 2.3 for visual representation.

Neurovascular coupling (NVC): Describes the increase in blood flow to the brain that is required to support neural activity during cognitive engagement (i.e. thinking). This increase in blood flow is required to deliver oxygen and fuel to, and remove waste from, the working brain cells.

Vascular aging: A broad concept that describes the natural changes in vascular structure and function that accompany natural aging. This concept is often used to describe “accelerated vascular aging” that accompanies certain conditions/diseases (such as hypertension), whereby some individuals exhibit changes associated with “old age” but at a much younger age owing to the biological effects of a condition or chronic disease.

Non-Technical Summary

What is known?

High blood pressure (i.e. hypertension) is a key, treatable risk factor for the development of chronic diseases that impact the heart and brain. High blood pressure damages the brain over time, thereby contributing to cognitive decline (characterized by the loss of higher-order decision making and slowing of processing speed). Changes in artery structure and function can influence the development of hypertension and accelerate cognitive decline. The stiffening of large arteries is one underlying cause of high blood pressure and also contributes to detrimental changes in brain blood flow that impair brain health/function in adults with hypertension.

Exercise is recommended to improve cardiovascular and brain health in adults with hypertension, however the effects of exercise on the arteries and brain in this population is somewhat unclear. Aerobic exercise may affect the stiffness of the arteries differently in adults with hypertension compared to those without. Moreover, it is unknown if aerobic exercise improves cognitive function in adults with hypertension. Thus, this study sought to examine the effect of a single bout of aerobic exercise on artery stiffness and brain blood flow (aim 1), and cognitive function (aim 2) in adults with controlled-hypertension and without hypertension.

What is new and noteworthy from our results?

Aim 1: Arterial stiffness and pulsatile (i.e. discontinuous) blood flow in the brain increased post-exercise in middle-aged adults with, and without, hypertension. We additionally noted that the increases in pulsatile (i.e. discontinuous) blood flow were modest considering the increases in vascular contributors to pulsatile blood flow. That is, we would have theorized much larger increases in pulsatile blood flow in the brain given the changes in blood pressure and arterial stiffness. This may indicate that the brain is somewhat resilient to short-term changes in pulsatile blood flow in middle-aged adults, even in the presence of hypertension.

Aim 2: Cognitive function improved post-exercise in middle-aged adults with, and without, hypertension. Improvements in cognitive function manifested as accelerated processing speeds, where participants were able to respond to executive function and memory tasks significantly faster (measured by reaction time). We are the first to document that a single bout of exercise facilitates processing speed in adults with hypertension. This broadly suggests that the brain's ability to respond to an exercise bout and improve processing speed is undisturbed by the presence of hypertension.

The findings from Aim 1 and 2 indicated that adults with hypertension exhibited similar vascular and cognitive responses to exercise as those without hypertension. The similar responses to exercise may stem from groups having similar health status. Indeed, both adults with, and without hypertension were physically active, had similar age, body fat, sleep quality, and low levels of depression. Additionally, our adults with hypertension had well controlled blood pressure and cholesterol (i.e. no longer markedly elevated on average). Cumulatively, this data indicates that when well-matched for health status, adults with hypertension respond similarly to exercise.

This led us to pursue an exploratory Aim 3 that examined if the vascular contributions to cognitive function differed between adults with hypertension to those without. Increases in brain activity (i.e. while thinking during a cognitive task) depend on complimentary changes in blood flow to deliver nutrients to working brain cells. Thus, the vascular system must deliver adequate blood flow and continuous (i.e. non-pulsatile) to support brain activity. The presence of hypertension may impair the vascular system's ability to deliver adequate, and continuous (i.e. non-pulsatile), blood flow required to support brain activity.

Aim 3: Blood flow and arterial stiffness increased, and pulsatile blood flow decreased, during cognitive activity in both adults with, and without, hypertension. Additionally, both groups

achieved similar oxygen delivery to working areas of the brain during cognitive activity. We noted that reductions in pulsatile blood flow (i.e. making blood flow more continuous) was associated with greater brain oxygenation during cognitive activity. This suggests that the presence of hypertension does not impair the vascular system's ability to increase blood flow to the brain during times of increased brain activity, and that reducing pulsatile blood flow may be an important vascular response to ensure brain oxygenation during cognitive activity.

Implications

Our data largely suggest that proper use of physician-prescribed blood pressure medication and lifestyle factors (such as physical activity) may help attenuate detrimental vascular and cognitive changes that typically accompany hypertension. Moreover, adequate blood pressure control in hypertension may normalize vascular reactivity to perturbations such as acute exercise and cognitive activity such that they become similar to adults without hypertension. These data underscore the importance of hypertension management to slow vascular and cognitive decline in middle-aged adults.

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Chapter I: Introduction

Hypertension (HTN) is among the leading causes of death in the US, affecting one third of adults >20 yrs of age (≈80 million Americans) [1]. HTN is preceded and exacerbated by increases in arterial stiffness [2]. As such, adults with HTN routinely have higher arterial stiffness than their normotensive counterparts [3-7]. Increased arterial stiffness impairs the central vasculature's ability to dampen fluctuations in pressure and flow, which affects blood flow delivery to target organs. Indeed, arterial stiffness affects cerebral blood flow to the brain [8] which ultimately governs cognitive function [9,10]. HTN with concomitant changes in arterial stiffness is recognized as a key risk factor in the vascular pathogenesis of cognitive decline, dementia, and Alzheimer's disease [11]. Additionally, arterial stiffness in mid-life predicts cognitive decline later in life [10] and is a stronger predictor of cognitive decline than blood pressure in HTN [12].

Aerobic exercise *is* recommended by the American College of Sports Medicine and American Heart Association to combat HTN [13,14] and is a potent and safe means to protect against age-related declines in cardiovascular health [15] and cognitive function [16,17]. Aerobic exercise reduces blood pressure, reduces arterial stiffness, improves cerebral perfusion, and enhances cognitive performance both acutely [18-21], and chronically [15,22-27] in most healthy and clinical populations. The favorable effects of exercise on vessel stiffness have been directly linked to improved cerebrovascular function [22,25,27], and protection against age-related cognitive decline [16,17,28-30]. However, upon closer inspection of the literature, it becomes apparent that the hypertensive adult may not experience the same vascular benefits in response to exercise as other populations. A recent meta-analysis of 14 trials in 472 adults found that aerobic exercise training does not reduce arterial stiffness in adults with HTN [31]. That is, aerobic exercise may not be able to de-stiffen the large central arteries in HTN [32-34]. Moreover, hypertensives experience an *increase* in arterial elastance (a proxy of arterial

stiffness) during aerobic exercise [35] owing to underlying endothelial/autonomic dysfunction and an exaggerated pressor response [31]. This begs the question: is aerobic exercise an efficacious therapeutic strategy to improve cerebrovascular and cognitive health in those with HTN?

The effect of exercise on cognitive function in HTN remains largely unexplored. We have also been unable to identify *any* studies investigating the acute effects of aerobic exercise on arterial stiffness, cerebral perfusion, or cognitive function in adults with HTN. Acute responses to exercise predict training responses [36], indicating that a detailed characterization of the acute response may provide insight into what may ultimately govern chronic adaptations.

The specific aims of the proposed study are as follows:

Specific Aim 1: Compare the effects of acute aerobic exercise on central artery stiffness and cerebral perfusion between middle-aged adults with and without hypertension.

Hypothesis 1: Adults with hypertension will experience differential vascular responses to exercise compared to adults without hypertension, manifesting as decreased arterial stiffness and increased cerebral perfusion in adults without hypertension and unaltered arterial stiffness and reduced cerebral perfusion in adults with hypertension following acute aerobic exercise.

Specific Aim 2: Compare the effects of acute aerobic exercise on cognitive function between middle-aged adults with and without hypertension.

Hypothesis 2: Adults with hypertension will experience differential cognitive responses to exercise compared to adults without hypertension, manifesting as increased cognitive function (faster reaction time, higher accuracy on executive function and memory tasks) decreased cognitive function in adults with hypertension following acute aerobic exercise

The results from this study will help elucidate if aerobic exercise is an effective stimulus to improve cerebrovascular and cognitive function in adults with hypertension. If aerobic

exercise does not improve cerebrovascular or cognitive function, other types of exercise (i.e. high-intensity interval) or exercise-lifestyle-pharmacological combinations may be needed to de-stiffen the arteries and improve cerebrovascular/cognitive health in this at-risk population. Thus this initial study will set the groundwork for an important and exciting line of future investigations.

Chapter II: Review of Literature

Hypertension (HTN) is a medical disorder marked by high arterial blood pressure (defined as systolic pressure ≥140 and/or diastolic pressure ≥90 mmHg) that effects roughly 33% of adults >20 years of age [1]. The prevalence of HTN is expected to increase to 42% by the year 2030 and increase total cost of high blood pressure to $274 billion, nearly a 500% increase from the $46 billion spent in 2011 [1]. Aside from the financial burden of this condition, the persistent elevation of blood pressure and its long-term sequelae ultimately increase the risk of chronic diseases. In fact, HTN is one of the most pervasive modifiable-risk factors for cardiovascular disease (CVD) and stroke [37-39], making it a prime target for preventive treatment. Successful treatment of HTN, however, is often complex, owing to its multifaceted etiology.

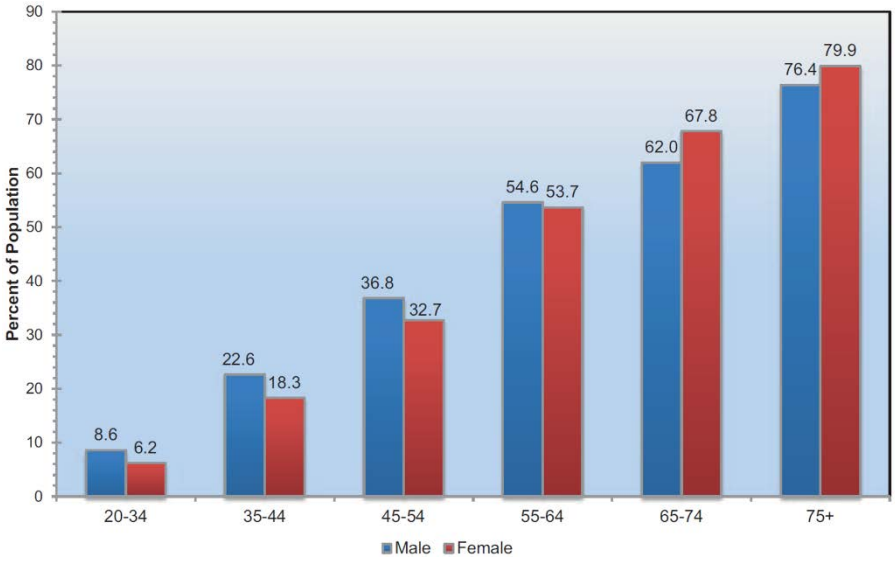

***Figure 2.1**: Prevalence of high blood pressure in adults ≥20 years of age by age and sex (National Health and Nutrition Examination Survey: 2007–2012). HTN defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, if taking anti-HTN medication, or if told >2 occasions that they had HTN. Source: Mozaffarian et al. 2015*

Pathogenesis of HTN

HTN is a complex disease that may develop from multiple mechanisms. For this reason, the initiating factor may not be discernable, particularly as the disease advances and results in additional, compensatory pathological changes [40]. In its simplest model, blood pressure is dependent on the interaction between the heart and vasculature. Specifically, blood pressure is

the product of the amount of blood ejected by the heart (cardiac output, Q) and the resistance to blood flow that originates from the periphery (total peripheral resistance, TPR) [40]. Any alteration in factors impacting this relationship may alter blood pressure. The pathogenesis of HTN is further complicated by numerous contributing factors (i.e. genetics, diet/sodium intake, obesity, insulin resistance etc.) that can interact with one another and influence any of the major pathological pathways leading to HTN. A summary of the main arbiters of HTN is provided in Figure 2.2.

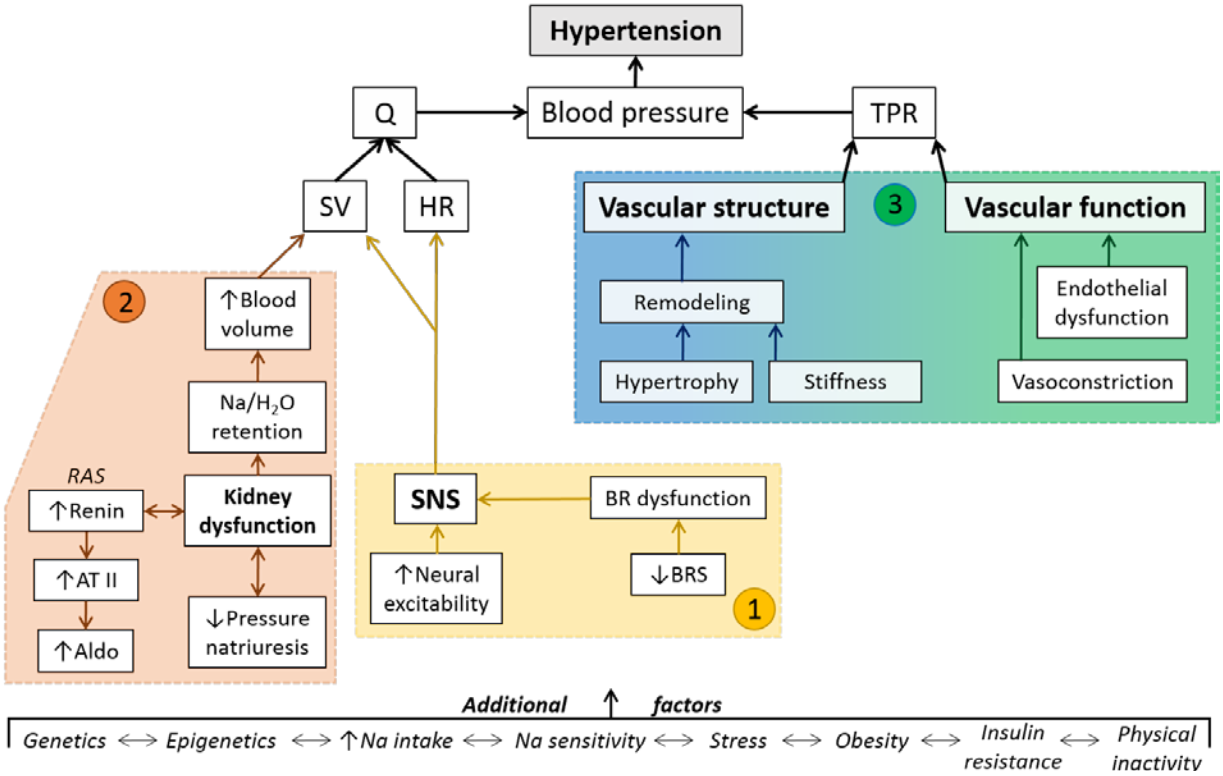

Figure 2.2: *Factors contributing to the pathogenesis of hypertension including: sympathoexcitation (1), kidney dysfunction (2), and systemic vascular structure and function (3).*
Q, cardiac output; TPR, total peripheral resistance; SV, stroke volume; HR, heart rate; Na, sodium; AT II, Angiotensin II; Aldo, aldosterone; SNS, sympathetic nervous system; BR, baroreceptor; BRS,

Sympathoexcitation (1)

Acute increases in blood pressure are typically sensed by stretch receptors located in the carotid and aortic bodies known as baroreceptors (BR). An increase arterial pressure stretches the vessel walls, stimulating the BR and resulting in afferent signals to the cardioregulatory center in the brain [41]. This results in activation of the parasympathetic (and

inhibition of the sympathetic) system, thereby increasing vagal tone, reducing heart rate, vascular resistance, and ultimately restoring blood pressure to normal levels [41]. If the elevation in blood pressure is sustained, however, the BR sensitivity is reset [42], leading to blunted cardio-vagal responses to elevated BP [43] and enhanced sympathoexcitaion. One hypothesis for the pathogensis of HTN is that increased sympathetic outflow (resulting from reduced BR sensitivity) perpetuates HTN through cardiac excitation and hyperkinetic circulation [40,44]. Alternatively, the increase in sympathetic outflow may be of neural origin and mediated through reduced BR sensitivity [45]. Ultimately, hyperkinetic circulation has been identified among pre-hypertensives, suggesting that sympathoexcitation may be an early factor in the development of HTN [44].

Kidney dysfunction (2)

Sympathoexcitation may also effect the kidneys which function as the long term regulators of blood pressure. Renal sympathetic nerves innervate the kidneys and can result in the release of renin, activating the renin-angiotensin-aldosterone system (RAS) [41]. Renin initiates the generation of angiotensin II which acts to increase blood pressure through peripheral vascular vasoconstriction, fluid resorption, and sodium resorption via adrenal aldosterone release [41,46]. Alternatively, kidney dysfunction may occur separate from sympathoexcitation. Disrupted renal hemodynamics may result in isolated ischemic nephrons in the kidney, resulting in chronic low-levels of renin release that activate the RAS pathway [40]. Additionally, impaired pressure natriuresis may play a role in maintaining long term elevations in blood pressure [40,47]. In a normally functioning kidney, pressure natriuresis occurs in response to elevated blood pressure, resulting in sodium and water excretion, thereby reducing blood volume, cardiac output, and blood pressure. Disrupted pressure natriuresis may result in blunted sodium excretion, preventing pressure from returning to normal levels and resulting in

long term elevated blood pressure [40]. Together, changes in kidney function likely play a role in the development and maintenance of HTN.

Systemic vascular structure and function (3)

The peripheral vasculature controls the resistance to blood flow. Any functional or structural factor that increases resistance will result in an equivalent increase in pressure. The vasculature modulates vessel diameter to alter resistance. Any decrease in peripheral vessel diameter will increase TPR and blood pressure since resistance is inversely related to vessel diameter. The ability of the vasculature to increase its diameter (vasodilate) is largely dependent on the endothelium. The endothelium functions to maintain vascular homeostasis and generate vasodilator substances such as nitric oxide [48]. The vascular etiology of HTN may be related to endothelial dysfunction, arising from increases in oxidative stress [49] that disrupts nitric oxide signaling [48]. Impaired nitric oxide generation in HTN [50] would render the vasculature prone to vasoconstriction, increasing TPR and contributing to elevated blood pressure.

Vessel diameter and resistance may also be altered by vascular structure. Vessel remodeling can result in vascular hypertrophy. This type of remodeling is marked by a thickening of the arterial walls which may reduce the internal diameter of the vessel and increase resistance and blood pressure [51]. The Law of Laplace (tension = [pressure x radius]/wall thickness), states that increases in wall thickness can offset increases in pressure to normalize the forces exerted on the artery wall (tension) [52]. This mechanism is considered the primary biological signal governing vascular remodeling in HTN [53]. Importantly, HTN-mediated increases in wall thickness modify the structural and mechanical properties of the arterial wall and results in increased arterial stiffness [54]. Typically, changes in vascular structure (remodeling and increased stiffness) are viewed as consequences, rather than harbingers, of HTN that prevent long term reductions in blood pressure [40]. Recent data however, has begun to highlight a growing role of arterial stiffness in the pathogenesis of HTN.

Arterial stiffness and hypertension

Arterial stiffness refers to the material properties of the artery wall and their functional ability to expand and recoil, dampening the amplitude of fluctuations in pressure and flow [55]. The buffering of the mechanical forces generated by cardiac pulsations is critical in converting pulsatile hemodynamics into continuous blood flow in the capillaries [56]. The stiffness of the vessel varies based on its wall composition which changes throughout the arterial tree. Central arteries (i.e. aorta, carotid) have greater elastic components (less stiff) compared to peripheral/muscular arteries (i.e. brachial) which contain less elastin and more vascular smooth muscle (more stiff) in order control blood flow distribution [57,58]. The elastic, central arteries are instrumental in converting pulsatile blood flow to more continuous, laminar (i.e. smooth) flow, thereby preventing transmission of excess energy into target organs [9]. The increase in pressure generated with each ventricular contraction is buffered by the elastin and collagen components of the arterial walls, with elastin and collagen engaging at low and high distention/pressure, respectively [55]. Elastin is progressively degraded and fragmented with increasing age due to the unrelenting pounding of arterial blood pressure that accumulates over time [59,60]. As elastin degrades, the buffering capacity of vessel shifts to the collagen fibers which is 100-1000 times stiffer than elastin [61]. This reliance on collagen fibers results in a stiffer artery and greater pulsatile hemodynamics (i.e. greater fluctuations in systolic pressure/flow vs diastolic pressure/flow; Figure 2.3) that are transferred downstream into end-organs [62].

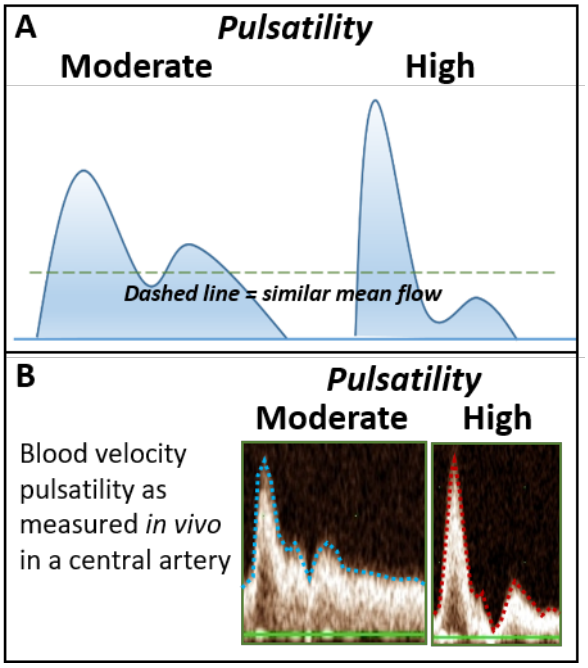

Figure 2.3: *Blood flow pulsatility in theory (A), and in practice (B)*
Adapted from Heffernan KS

Arterial stiffness, and thus hemodynamic pulsatility [56], increases across the life span (Figure 2.4), the progression of which, appears accelerated in those at-risk for, or diagnosed with HTN.

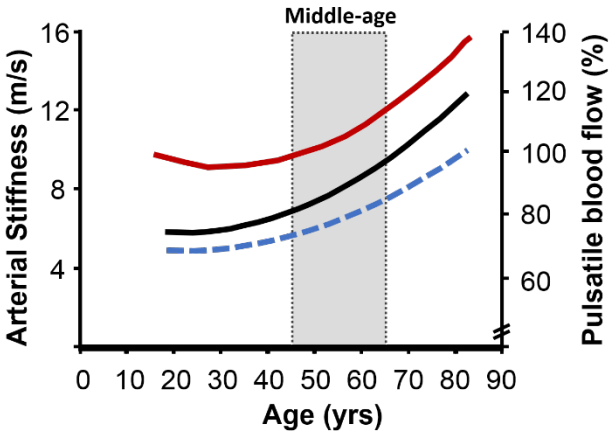

Figure 2.4: *Arterial stiffness and pulsatile blood flow across the life-span. Red solid – pulsatile blood flow in the brain; Black solid – arterial stiffness; Blue dashed – effects of aerobic exercise training.*

Adapted from McEniery et al. 2005, tarumi et al. 2014, and Franklin et al. 2013.

Adults with HTN have been consistently documented to have higher arterial stiffness than their normotensive counterparts [3-7]. The widely held belief is that increased arterial stiffness is merely a manifestation of HTN [2,55,63]. Indeed, elevated arterial pressures alone will shift the pressure load burden to collagen, increasing arterial stiffness [64]. In this manner, HTN can give-way to stiffer central arteries. Recent data, however, challenges the assertion that stiffness is a consequence of HTN; reports now suggest that changes in central artery stiffness precede changes in blood pressure and predict the development of HTN later in life [6,7,65-69]. Thus, increased central artery stiffness has been proposed as a possible *cause* for the development of HTN [2]. Data from large, community-based longitudinal studies has been complimented by data from animal-models documenting changes in arterial stiffness prior to changes in blood pressure and the development of HTN [70-72]. The exact mechanism through which arterial stiffness contributes to the development of HTN has yet to be elucidated but it may occur through alterations in baroreceptor, kidney, and endothelial function.

The role of arterial stiffness in the pathogensis of HTN may occur through multiple pathways (Figure 2.5). Elevated indices of arterial stiffness have been linked to impaired BR sensitivity [73-76] which may give-way to excessive sympathoexcitation and development of

HTN. Increased arterial stiffness is also tightly linked to kidney damage [77-81] and chronic kidney disease [82,83]. Stiffness-mediated increases in pulsatile hemodynamics may disrupt kidney dysfunction by creating pockets of nephron ischemia which have been separately suggested to increase renin release and RAS activation [40]. Arterial stiffness and the concomitant increase in pulsatile hemodynamics is also associated with endothelial dysfunction [84,85]. In this manner, increased arterial stiffness may be the underlying cause of HTN through its effects on the baroreceptors, kidney, and endothelium.

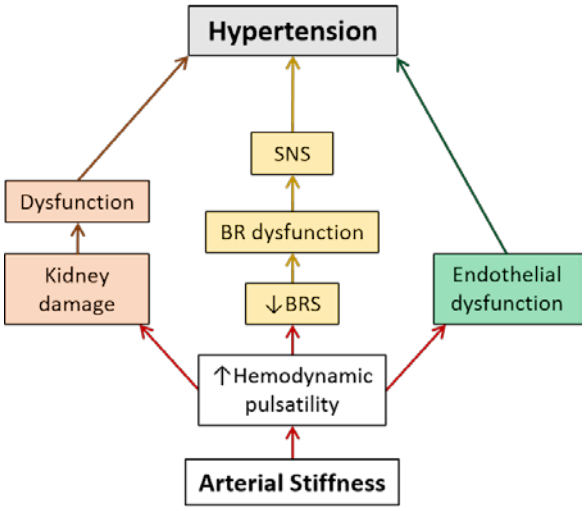

Figure 2.5: *Role of arterial stiffness in the pathogenesis of hypertension.*

Consequences of hypertension

HTN is unequivocally linked to increased cardiovascular disease risk [86] and widespread target organ damage (TOD), including the heart, kidney, and eye [87]. Indeed, elevated blood pressure is associated with left ventricular hypertrophy,[88,89] heart failure [90,91], kidney disease [92], and vascular retinopathy [93,94]. Although elevated blood pressure is unquestionably a major factor contributing to HTN-mediated TOD, evidence suggests other mediators, such as arterial stiffness, are likely involved. Arterial stiffness is strongly associated with left ventricular hypertrophy [95-97], heart failure [98-101], and kidney disease [77,82,83]. Additionally, arterial stiffness and its sequelae appear to play a large mechanistic role in the detrimental effects of HTN on one of the most important target-organs; the brain.

Hypertension and the brain

The brain is a high-flow target organ that is particularly vulnerable to HTN-mediated vascular dysfunction and arterial stiffening that accelerates cerebral aging. Vascular “function” is

a term used to describe if blood vessels have the ability to respond or “react” normally to a given perturbation [26]. In the case of the brain, cerebrovascular function often refers to whether or not the cerebral vessels provide adequate perfusion at rest and during periods of increased demand (such as neural activity). Any reduction in function (i.e dysfunction) may result from damage to the vascular endothelium (via inflammation, oxidative stress, etc.) or from changes in vessel wall structure (i.e. remodeling) [26]. The brain’s natural aging process alters both cerebrovascular structure and function. Reductions in cerebral capillarization and increased tortuosity of white matter vessels reduce resting cerebral blood flow (CBF), attenuate cerebrovascular reserve, and impairs the vessels ability to modulate diameter to prevent hyper- or hypo-perfusion (termed autoregulation) with normal aging [102-104]. The presence of HTN, however, potentiates these age-related changes and reduces the cerebrovascular blood flow response to a hyperemic stimulus [105], and impairs autoregulation [106]. Disturbed autoregulation may weaken the brain’s defenses against excessive arterial pressure and may render the brain more vulnerable to HTN-mediated damage [11].

Chronic exposure to high blood pressure is associated with wide-spread structural damage. HTN is associated with brain atrophy that occurs by both the potentiation of the natural aging processes and by independent, HTN-specific mechanisms [11]. A clear relationship exists between HTN and markers of cerebral damage, including microinfarcts [107] and white matter hyperintensities (WMH) [108,109], a manifestation of cerebral small vessel disease [110,111]. WMH progression is associated with HTN [112] and may mediate the relationship between HTN and cognitive decline [113]. The length of time that the cerebrovasculature is exposed to high blood pressure (BP) may be a key factor in determining the severity of damage [114] which appears strongly linked to arterial stiffness [115]. Increases in arterial stiffness reduce the arterial buffering capacity and alter cerebral hemodynamics. Indeed, increased arterial stiffness results in greater cerebral hemodynamic pulsatility [116,117] and hypoperfusion [8],

consequently altering brain structure and function. Greater arterial stiffness is associated with brain atrophy [118,119] and cerebral small vessel disease [120-124]. Ultimately, HTN and arterial stiffness-mediated cerebrovascular damage has functional consequences for the brain and results in accelerated cognitive decline.

Hypertension and cognition

Cognitive decline is regarded as one of *the most* important determinants of health, function, and quality of life with advancing age [125]. The medical, social and economic burden of cognitive decline is substantial. The worldwide cost of dementia was estimated at $421 billion in 2009 and the number of demented elderly is expected to increase to 63 million by 2030. Cognitive function is generally divided into 7 domains including: attention/concentration, language, visiospatial skills, psychomotor skills, executive functions, memory and orientation [126]. Executive function is an expansive term describing the high-level interrelated cognitive abilities, dependent on lower-level functions, which are necessary to complete goal-directed behavior [127,128]. There is some debate as to the specific components that comprise executive function, but information processing, attentional control, cognitive flexibility, and working memory have all been acknowledged as playing a role [126-128]. Description of the cognitive domains and tests that have been used to target them are displayed in Table 1.

Although cognitive decline is one aspect of natural brain aging, the presence of HTN and its neurocognitive consequences accelerate brain aging [11], resulting in mild cognitive impairment, dementia, and Alzheimer's disease [11], As such, HTN is recognized as an important modifiable risk factor for cognitive decline by AHA [129] and others [130-133] and disease [134,135]. HTN is associated with, and predicts, risk of cognitive impairment [133,134,136-138] and cognitive performance [12,132,139-143], particularly when coupled with additional co-morbidities [144-146]. These associations are detected as early as mid-life, as individuals with elevated mid-life systolic blood pressure have an increased likelihood of

developing mild cognitive impairment and dementia [131,147,148]. The majority of studies on cognition among hypertensives have focused on executive function and memory processing, documenting impaired performance in adults with HTN [3,114,140]. Ultimately, these negative effects of HTN on cognitive function reflect accelerated cerebral aging brought on by the vasculature [11].

Table 2.1: Cognitive domains and their changes with age and hypertension

			Effects on cognitive performance	
Domain	**Description**	**Example test**	**Age**	**Hypertension**
Language	Ability to understand and use oral/written language.	Word search/ fluency	Verbal fluency ↓	
Visuospatial skills	Ability to comprehend shapes/forms and their interpretation	Reproduction of shapes/ images	Simple - Complex ↓	
Memory	Ability to store/retrieve information (short/long term/semantic memory)	free recall	Explicit ↓ Implicit -	↓
Executive function	Ability to conceptualize, evaluate, and complete goal-oriented tasks		↓	↓
	Components			
	Information processing	Reaction time	↓	↓
	Attentional control	Stroop, Flanker	↓	
	Cognitive flexibility	Stroop, Trails B	↓	
	Working memory	N-back	↓	↓

Adapted from *Davis et al. 2013, Logue et al. 2013, Burnett et al. 2013, Olaithe et al. 2013, Harada et al. 2013, Hughes et al. 2015, Hajjar et al. 2016, Shehab et al. 2011*.

Arterial stiffness is associated with cognitive decline [149-152], dementia [149,153], and Alzheimer's disease [154,155]. The effects of arterial stiffness on cognitive function appear to be mediated by cerebrovascular damage [115]. Cerebral pulsatility, stemming from arterial stiffness, is additionally associated with cognitive impairment and predictive of dementia in at risk individuals [156]. The association of arterial stiffening, subclinical brain injury, and cognition has been detected as early as middle-age [157], and independent from stroke or dementia [158], indicating that arterial stiffness may be an ideal target to slow the progression of neurovascular disease and cognitive decline. As such, recent reviews suggest arterial stiffness has the to be a potential indicator for clinicians to identify adults in need of treatment to prevent/delay dementia [152]. This is an area of burgeoning interest, as >20 studies, including meta-analyses, have been published in recent years linking stiffness to cognition

[10,22,30,118,149,151,158-176]. These data suggest that increased central artery stiffness may be one of the harbingers of cognitive decline among hypertensives. In fact, changes in arterial stiffness are a stronger predictor of cognitive decline among hypertensives than changes in blood pressure [12]. Therefore, arterial stiffness could be an important therapeutic target and vital missing link in the successful treatment of HTN and HTN-mediated cognitive decline.

Treatment of hypertension

Due to HTN's complex etiology, there is no single, comprehensive treatment that addresses all causes of HTN. Medications often target the major components of blood pressure, targeting the kidneys (diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors and mineralocorticoid receptor antagonists) and cardiac sympathoexcitation (β-adrenergic blockers, calcium channel blockers) [177]. Many of these anti-hypertensive medications reduce overall blood pressure and improve cardiovascular outcomes, as seen with the 1970s efforts to control HTN, which has been cited as an important contributor to the recent reductions in strokes mortality [1]. Despite some success and recent advances in care, however, the medical community has been challenged by other secondary consequences of HTN, particularly cognitive decline [11].

The length of time that the brain is exposed to elevated blood pressure likely dictates the degree of cognitive decline early and effective treatments are required. Thus, mid-life targeted interventions may serve as a "last chance" to intervene before long term exposure to high blood pressure causes irreversible target organ damage and cognitive impairment [157,178]. Unfortunately, the effect of anti-hypertensive therapy alone on cognitive decline is unclear [11,179,180] and may not consistently reduce the risk of cognitive decline [181-183], suggesting that contributing factors beyond blood pressure alone may be responsible for cognitive decline in this population. Indeed, although many anti-hypertensive drugs target successfully target some contributors to peripheral resistance and cardiac output, few anti-hypertensive drugs have

consistently and directly target central artery stiffness. Indeed, drug treatments that reduce brachial blood pressure in hypertensives do not consistently reduce vessel stiffness [13,14,184]. This may be of particular importance since inability to reduce vascular stiffness beyond the effects on brachial blood pressure predicts clinical outcome [185]. The null effect of HTN treatment on arterial stiffness may explain the inconsistent effectiveness of anti-hypertensive therapy on cognition, particularly since stiffness is more related to cognition than blood pressure among hypertensives [12]. For these reasons finding an additional means to target central artery stiffness, attenuate the burden of HTN, and prevent cognitive decline is of the utmost importance.

Exercise as a preventive intervention

Prevention is a core concept in to reduce the burden of CVD and its co-morbidities like cognitive decline. Governing bodies like the American Heart Association (AHA) recommend that interventional studies beginning as early as midlife are necessary to prevent or postpone the onset of cognitive impairment [16]. Mid-life interventions aimed to prevent late-life cognitive decline and preserve independence are therefore imperative to reduce the burden of cognitive diseases in an ever-growing sect of the US population [11]. Regular aerobic exercise is recognized as the most pluripotent and effective means to maintain cardiovascular health [15] and mental longevity [186-188]. Exercise is as effective, if not more effective, than most drug interventions across a variety of disease treatments (i.e. heart failure, diabetes, stroke) [189], thereby supporting the idea that *exercise is medicine* [190,191]. For these reasons, aerobic exercise *is highly* recommended by the American College of Sports Medicine (ACSM) and AHA to maintain cardiovascular and brain health and prevent vascular-cognitive impairment [192-194].

Exercise and the brain

Numerous investigations have examined the acute effects of aerobic exercise on cognition, across a variety of domains. The findings of any individual study appear variable, likely stemming from methodological differences in cognitive domains examined, tasks used, metrics of cognitive performance (reaction time, accuracy, sum score), exercise duration/intensity, and participant population [20,195]. Interpretation of exercise-cognitive data is further complicated by research design regarding the timing of cognitive testing since cognitive responses to exercise are different if measured during exercise, immediately following, or delayed-following exercise [20,195]. Meta-analytical investigations, however, have found that acute exercise does improve executive function [20,195-198], and may impact memory [20,195], particularly following moderate to vigorous exercise.

With regards to chronic exercise (i.e. training), both epidemiological and experimental studies have consistently shown that physical activity and regular aerobic exercise improves brain health and may act as a primary prevention for cognitive decline [28]. Data from meta-analyses, clinical trials, and cohort-based studies all indicate physical activity reduces the risk of dementia and preserves cognitive function with age [199-202]. Similar patterns are observed with regards to exercise training specifically, rather than global physical activity. Cross-sectionally, higher levels of regular exercise are associated with reduced risk of cognitive decline and Alzheimer's disease [203]. Prospectively, higher cardiorespiratory fitness in early life predicts better cognitive function 25 years later [204]. Cognition is also improved among elderly populations with and without dementia who undergo exercise training interventions [17,205-208].

The exact mechanism behind the beneficial effects of exercise on the brain are yet to be fully understood. Improvements are likely related to changes in neural function, brain structure, and vascular adaptations [26,209,210]. Exercise may improve neural function through direct

modulation of neurotrophic factors such as brain-derived neurotrophic factor, nerve growth factor, and insulin-like growth factor-1 which increase following exercise training [210-214]. These neurotrophic factors have been linked to improved neural plasticity [215], neuroprotection [216], and neuronal growth [213], and likely play a role in improving cognitive function [210,213]. Additionally, exercise alters brain structure, evident by attenuations of age-related brain atrophy. Higher levels of physical activity and aerobic exercise training are associated with greater brain volume [217,218] and lower plaque deposits in the brain (a marker of Alzheimer's disease) [219]. Aerobic exercise training has been shown to reduce risk of age-related atrophy and increase brain volume [220]. Changes in brain volume must be accompanied by improvements in cerebrovascular perfusion if these changes are expected to facilitate function. Thus, while a myriad of adaptations accompany exercise training and may impact the brain [28], there is growing body of literature linking vascular to brain function, suggesting the vasculature may be an emerging moderator of exercise's effects on the brain.

Exercise and arterial stiffness

Although arterial stiffness increases with age [221-223], aerobic exercise consistently elicits beneficial effects on the vasculature, including reductions in both blood pressure and central artery stiffness [18,19,224]. Similar reductions in stiffness and blood pressure are noted following aerobic exercise training [15,24,225-227]. Given the growing connection between the vasculature and brain it would be expected that exercise-mediated reductions in arterial stiffness would elicit improvements in cerebrovascular hemodynamics. Aerobic exercise is cross-sectionally associated with improved cerebral blood flow [25] and cerebrovascular reactivity [25,27]. Moreover endurance-trained adults have lower central artery stiffness, greater cerebral perfusion, and greater cognitive performance compared to their sedentary counterparts [22]. Changes in cerebrovascular hemodynamics likely support changes in brain structure and function. Exercise training increases region-specific cerebral blood volume, which is further

associated with improvements in cognitive performance [228]. Additionally, exercise training increases neural and cerebral hemodynamic (i.e. neurovascular) connectivity at rest [229] and during periods of increased neural activation (i.e. cognitive tasks) [230]. Taken together, these data suggest that exercise-induced improvements in arterial stiffness may favorably impact cerebrovascular hemodynamics at rest, and during neural activity, thereby improving cognition.

Exercise and hypertension

AHA [13] and ACSM [14] recommend aerobic exercise for adults with HTN to lower blood pressure and maintain cognitive health [16]. Despite the established body of literature linking elevated blood pressure to diminished cognitive function, exercise to improved cognitive function, and exercise to reduced blood pressure /stiffness (Figure 2.6), there is a paucity of data on the effect of exercise on cognitive function *in adults with HTN*. In fact, a recent review article on exercise and cognitive function in human HTN relied primarily on rodent-model research [231]. Moreover, this review did not include the only studies conducted in humans on the topic, which noted no beneficial effects of aerobic training on cognition in HTN [232,233]. Other data in adults with type II diabetes reported *reductions* in cognitive performance following an exercise/lifestyle intervention that were only shown in participants with co-morbid HTN [234]. Although limited by a small number of studies, the ineffectiveness of exercise in improving cognition may be related to differential vascular responses to exercise.

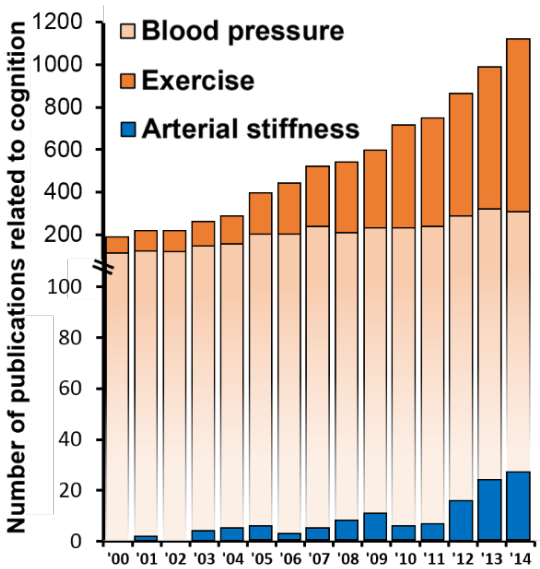

***Figure 2.6**: Publications related to cognitive function indexed by PubMed.*

Unlike normotensive individuals, acute exercise in hypertensives elicits increases in arterial elastance (a proxy measure of arterial stiffness) during exercise [35], and does not alter

arterial stiffness following acute exercise [235]. Chronically, aerobic exercise training does not de-stiffen the arteries of hypertensives, as recently described by a recent meta-analysis of 14 trials in 472 adults [31]. Additionally, cross sectional investigations note that cardiorespiratory fitness is not associated with lower stiffness among hypertensives [236]. It is possible that chronic exposure to high blood pressure may reduce the arteries ability to adapt to exercise training, rendering the vessels unable to de-stiffen [237]. This has particular significance for cognitive function since arterial stiffness is a stronger predictor of cognition than blood pressure among hypertensives [12]. While some of these data are limited by indirect proxies of stiffness (i.e. elastance), which is insensitive to hemodynamic load [238], these data suggest that the effects of aerobic exercise on vascular and cognitive function likely differ for adults with HTN compared to healthy or other clinical populations. Since acute exercise responses predict chronic responses to training [36] we wish to investigate the acute cerebrovascular and cognitive responses to aerobic exercise in adults with HTN.

Proposed study

The aim of the proposed study is to compare the effects of acute aerobic exercise between middle-aged adults with and without HTN on 1) central artery stiffness and cerebral perfusion and 2) cognitive function. It is hypothesized that acute exercise will result in differential vascular and cognitive responses in

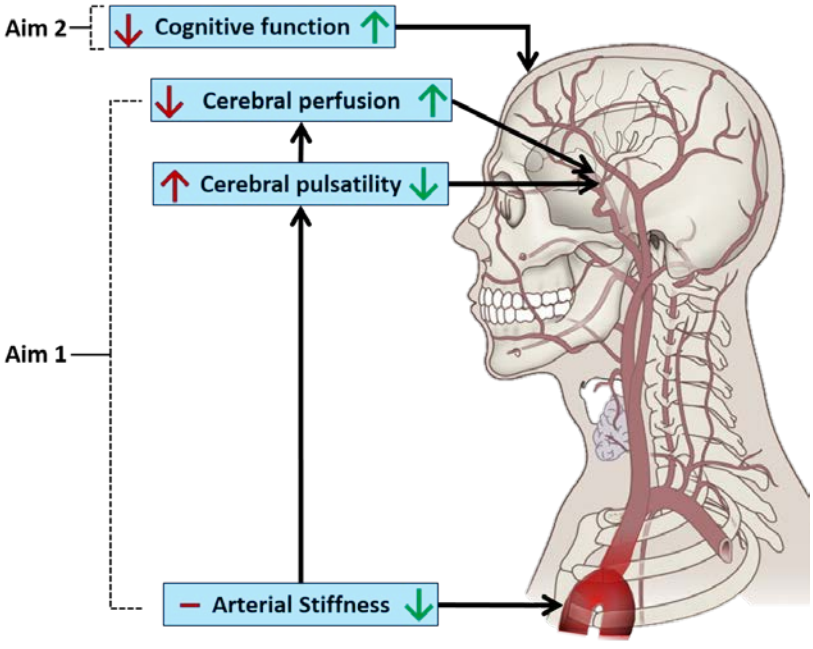

Figure 2.7: *Theoretical model and anticipated responses to acute exercise between adults with hypertension (**red** arrows) and adults without hypertension (**green** arrows).*

adults with compared to without HTN. Specifically, we posit that acute exercise will reduce artery stiffness and increase cerebral perfusion in adults without HTN, while arterial stiffness will be unaltered and cerebral perfusion reduced in adults with HTN. Further, we believe that compared to adults without HTN, adults with HTN will have decreased cognitive function following acute aerobic exercise, manifesting as slower reaction times and reduced accuracy on executive function and memory tasks (Figure 2.7).

Significance/Relevance

Prevention is key if we hope to achieve improve the long-term cardiovascular health of Americans and reduce the burden of cognitive decline. Adults aged $\geq$65 years represent the fastest growing demographic in the US [239] (accounting for >20% of the US population by 2020) [240] and this growing population will change the demographic landscape to that of an aging society where chronic disease prevention is critical. Roughly 70% of middle-age adults already enter their sixth decade with ≥1 chronic condition that will impair overall quality of life, increase healthcare costs, and pose additional burden on society [241,242]. As such, mid-life interventional studies aimed to prevent late-life cognitive decline and preserve independence are imperative to reduce the burden of cognitive diseases in an ever-growing sect of the US population [11]. Aerobic exercise is recommended by governing bodies [13,14] for adults with HTN to lower blood pressure and to maintain cognitive health [16]. Aerobic exercise, however, does not reduce large artery stiffness in hypertensives [34], which is a stronger predictor of cognitive decline than blood pressure in this population [12]. This phenomena, coupled with the virtual dearth of studies investigating the effects of exercise on cognition in adults with HTN, requires further scrutiny. Understanding how acute aerobic exercise effects the large central arteries, cerebrovasculature and subsequently cognitive function in middle-aged adults with HTN may equip us with better tools to prevent stroke, neurovascular disease, and attenuate cognitive decline as these at-risk adults enter their golden years.

Innovation

Traditional investigations of cognition in this field assess function for a given cognitive task by using simple pen-and-paper tasks or by interpreting any combination computerized data, including; 1) accuracy (correct stimuli divided by total stimuli), 2) number of stimuli correct (sum score) or 3) processing speed/RT for correct trials. While these methods provides some insight into cognition, it can lead to mixed conclusions where change in one parameter (i.e. slower RT) may indicate a processing deficit, whereas preservation of accuracy may suggest the contrary. While pen-and-paper tasks do not account for behavioral aspects of decision-making like RT, assessing only accuracy and RT still leaves many questions unanswered. This is because various cognitive processes may contribute to RT and the ability to correctly respond to a task.

Drift-diffusion modeling (DDM) is a descriptive mathematical approach which can be used to decompose observational data (hits, misses, RTs) into latent processes [243-246] (for theoretical basis of mathematical modeling in decision-making and cognitive neuroscience see) [247]. In essence, DDM describes what changes in the underlying decision-making process elicit a given observed response. DDM utilizes *all available behavioral data* (accuracy, correct/error RTs, shape of correct/error RT distributions) rather than focusing solely on RT for correct trials and accuracy in attempts to describe the observed data. This modeling technique can provide insight into whether changes in cognition (observed through accuracy and RT) are due to neurological (i.e. encoding, motor response) or behavioral (i.e. caution, response bias) changes in the underlying decision-making process. Although this technique has not been previously used to interrogate cognition in hypertensives or in the exercise literature at-large, it has been successful in explaining the slowing of RT with advancing age [248,249] and effects of hypoxia on cognition during exercise [250]. Thus, DDM holds significant potential to provide insight into changes in cognition with hypertension and exercise.

Chapter III: Preliminary Data

The student PI has lead multiple projects (as PI) examining racial differences [251], and underlying contributors to arterial stiffness [252]. Additionally, the PI has investigated arterial stiffness, and cognitive/cerebrovascular function at the population level [253] and following a variety of perturbations (including exercise [254,255], environmental stress [256,257], and dietary nitrate supplementation [257,258]). The PI has been involved in research in the Human Performance Laboratory throughout his MS/PhD and is familiar with all physiological and behavioral measures described in the *methodology* and *preliminary data* section. In acquiring these measurement skills the PI has personally collected data in 680 of the estimated 760 participants (age range, 9-89 yrs old) that have participated in HPL studies over the past 6 years.

The vascular response to acute high-intensity (aerobic or resistance) exercise is markedly different than that of aerobic exercise. Vessels stiffness tends to transiently increase following high-intensity exercise and it is debated whether this is a beneficial or detrimental response. We have documented acute increases in arterial stiffness and hemodynamic pulsatility following acute resistance [254,255] (and high intensity cycling exercise) [259] that is buffered prior to reaching cerebral arteries (ophthalmic artery [Figure 3.1], and MCA [Figure 3.2]) in healthy, young adults. Additionally, we found exercise-induced increases in central load

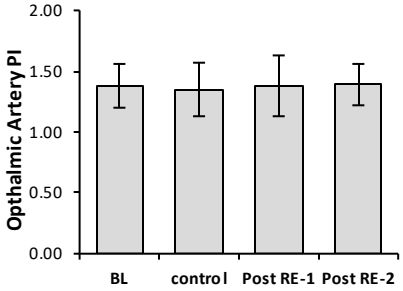

Figure 3.1*: Ophthalmic artery pulsatility at baseline (BL), control, and post resistance exercise. Lefferts et al. 2015*

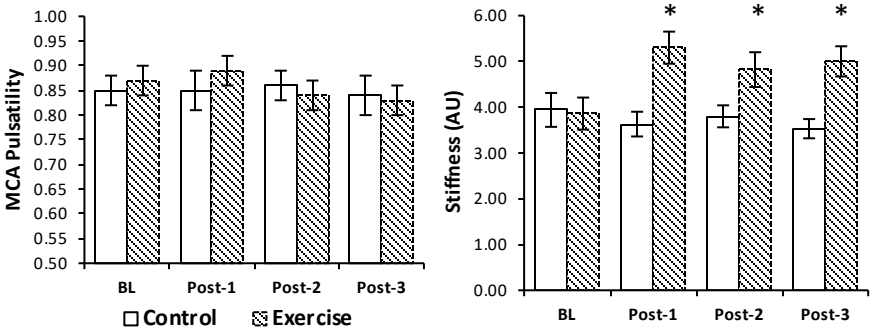

Figure 3.2*: Carotid stiffness and MCA pulsatility at baseline (BL) and post resistance exercise. *p<0.05 vs BL. Lefferts et al. 2014*

(exercise-induced ∆carotid stiffness) was associated with lower resting left ventricular function (assessed as left ventricular fractional shortening, r=-0.437, p=0.045) in healthy men, which was undetected by traditional peripheral hemodynamics (∆brachial systolic pressure vs fractional shortening, r=-0.256, p=0.169) [260].

There is a growing link between vascular hemodynamics and cognitive function. Our laboratory has investigated this relationship under normal physiological conditions [261-263] as well as during acute hypoxia, an environmental stimulus similar to what may occur locally in the brain secondary to HTN and arterial stiffening. We investigated whether nitrate ingestion could improve vascular and cerebral function, and attenuate decrements in cognitive function in hypoxia. We found that hypoxia alone unloaded the heart and was not further effected by nitrate supplementation [258]. With regards to cerebrovascular and cognitive function, acute hypoxia reduced memory performance, but did not alter the change in middle cerebral artery (MCA) blood flow during cognitive activity (i.e. preserved neurovascular coupling; Figure 3.3) [257]. Nitrate ingestion in our study did not further impact the cerebrovascular or cognitive responses to hypoxia.

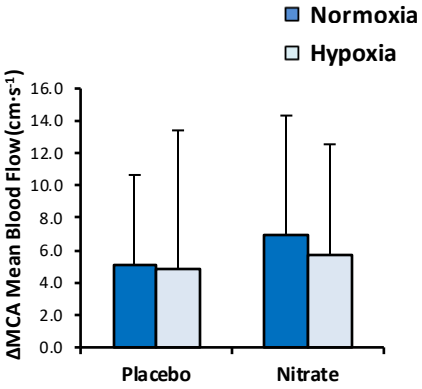

***Figure 3.3**: ∆MCA mV during cognitive activity in normoxia vs hypoxia. Lefferts et al. 2015*

After initial investigations into the relationship between cerebrovascular and cognitive function at rest in hypoxia, my recent doctoral work has expanded to incorporate exercise in such an environment. We then sought to investigate whether changes in cerebral perfusion during cognitive activity were preserved during exercise in hypoxia among 30 healthy men and women [250]. Although MCA flow increased with exercise, there were no further changes with additional cognitive activity (Figure 4). Pfc oxygenation was reduced during hypoxic vs normoxic exercise, but increased during cognitive activity in both conditions (Figure 3.4), indicating

specific increases in oxygenation in areas involved in executive function. Cognitive function was tested using Flanker, N-back and memory recognition tasks (as described previously in *Methods*). No changes in N-back performance or response speed were observed. Cognitive performance (accuracy) was maintained for Flanker and memory tasks during hypoxic exercise despite slower reaction times (RT; memory data depicted in Figure 3.5A,B). We further interrogated our behavioral data using DDM (as described previously). We noted the slowing of RT observed during exercise was related to significant increases in caution in hypoxia compared to normoxia (Figure 3.5D), rather than changes in the other components of RT (such as encoding/motor response, assessed by non-decision time; Figure 3.5C). Taken together, our data support the extracranial vasculature's role in modulating cerebral hemodynamics, which may impact cognitive function.

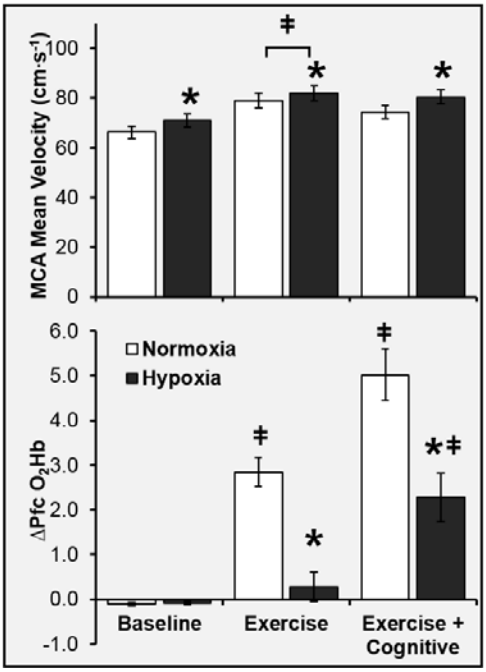

***Figure 3.4**: Cerebral perfusion during normoxic/hypoxic exercise (mean±SE). *p<0.05 vs normoxia; ǂp<0.05 vs previous time-point*

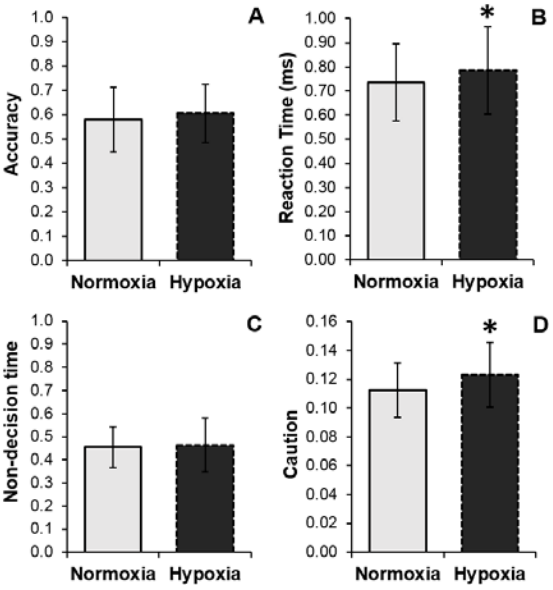

***Figure 3.5**: Memory performance during normoxic and hypoxic aerobic exercise. *p<0.05 vs normoxia*

Chapter IV: Effects of Acute Aerobic Exercise on Arterial Stiffness and Cerebrovascular Pulsatility in Adults With and Without Hypertension

Abstract

Stiffer central arteries, as seen in hypertension (HTN), foster transmission of pulsatile hemodynamics into fragile cerebral vessels. Aerobic exercise is recommended for adults with HTN, but its effects on arterial stiffness and pulsatility in this group are unclear. **Objectives**: This study sought to investigate the effect of acute aerobic exercise on arterial stiffness and cerebrovascular pulsatility in 30 adults with treated HTN and 30 age, sex, and body mass index (BMI)-matched adults without HTN (56±6 yrs, BMI 28.2±2.9 kg/m^2; 28 women). **Methods**: Subjects underwent hemodynamic measures pre/post 30-min cycling (≈55% peak oxygen consumption). Aortic stiffness was measured using carotid-femoral pulse wave velocity (cf PWV) and carotid artery stiffness was assessed with β-stiffness via Ultrasound. Aortic/carotid pulse pressure (PP; aortic via radial generalized transfer function) was measured by tonometry and calibrated to brachial mean (MP) and diastolic pressure. Carotid/middle cerebral artery (MCA) blood velocity pulsatility index (PI) were measured using Doppler. Carotid wave intensity analysis was used to derive forward wave intensity (W_1). **Results**: Exercise impacted hemodynamics similarly in HTN compared to no-HTN. cf PWV, MCA PI, carotid PI, and W_1 increased similarly post exercise in both groups ($p<0.05$). Carotid PP and β-stiffness were unaltered post-exercise. Post-exercise changes in W_1 were positively associated with carotid PI, which was further associated with MCA PI. **Conclusions**: These data suggest adults with treated HTN experience similar increases in aortic stiffness and cerebrovascular hemodynamic pulsatility during early recovery from acute aerobic exercise as their counterparts without HTN.

Introduction

Nearly 20% of the US population is between the ages of 50 and 64; a group considered middle-aged adults by the Center of Disease Control, AARP, and American Medical Association. As recognized by the National Institutes of Health, this growing population will change the demographic landscape to that of an aging society where chronic disease prevention is critical. Roughly 70% of middle-age adults already enter their sixth decade with ≥1 chronic condition that will impair overall quality of life, increase healthcare costs, and pose additional burden on society [241,242]. Hypertension (HTN) is one such chronic condition that represents a leading cause of disability and death in the US, affecting ≈33% of adults >20 yrs of age (≈80 million Americans) [1].

Although the etiology of HTN is multi-factorial, HTN is preceded and exacerbated by increases in arterial stiffness [2,69]. As such, adults with HTN individuals routinely have higher arterial stiffness than their normotensive counterparts [4]. Increased arterial stiffness impairs the central vasculature's ability to dampen fluctuations in pressure and flow, affecting perfusion of target organs [9,55,264]. Indeed, arterial stiffness increases pulsatile hemodynamics in the brain [8] which ultimately damages brain structures. Specifically, cerebrovascular pulsatility is associated with greater prevalence of subcortical infarct [9], and white matter volume [9], integrity [265] and lesions [56]. As such, HTN, with concomitant changes in arterial stiffness and pulsatile hemodynamics, is recognized as a key risk factor in the vascular pathogenesis of dementia and Alzheimer's disease [11].

Aerobic exercise is recommended by the American Heart Association and American College of Sports Medicine to combat hypertension [13,14] and is a potent and safe means to protect against age-related declines in cardiovascular health and brain function. Aerobic exercise reduces blood pressure, reduces arterial stiffness, and improves cerebral perfusion

both acutely [18,19,21], and chronically [22,25,27] in most healthy and clinical populations. The favorable effects of exercise on vessel stiffness have been directly linked to improved cerebrovascular function [22,25,27]. However, upon closer inspection of the literature, it becomes apparent that adults with HTN may not experience the same vascular benefits in response to exercise as other populations. A recent meta-analysis of 14 trials in 472 adults found that aerobic exercise training may not reduce arterial stiffness in adults with HTN independent of substantial changes in blood pressure [31]. That is, aerobic exercise may not be able to de-stiffen the large central arteries in hypertension [32-34]. Indeed, acute aerobic exercise has been shown to have no effect [235] or possibly increase large artery stiffness in HTN [35,266]. How large artery responses to acute exercise impact cerebral hemodynamic pulsatility in HTN is currently unknown. Understanding how modulation of large artery stiffness alters intracranial hemodynamics following an acute stress such as aerobic exercise is important considering that 1) HTN are widely recommended to engage in aerobic exercise [13,14], 2) intracranial pulsatility may be of extracranial origin whereby pulsatile energy originating from the heart is transmitted into downstream cerebrovascular beds [8,9], and 3) recent literature suggests that large extracranial arteries may be resistant to modification by aerobic exercise [34].

The purpose of this study was two-fold: 1) to investigate the effects of acute aerobic exercise on large artery stiffness and cerebrovascular pulsatility in adults with HTN and adults without HTN (no-HTN), and 2) to examine extracranial contributions to intracranial hemodynamic pulsatility following acute aerobic exercise. It was hypothesized that 1) large artery stiffness and pulsatility would respond differently to exercise in adults with versus without HTN, evident by reductions post-exercise in adults without HTN but increases in adults with HTN and 2) exaggerated extracranial pulsatility would contribute to post-exercise intracranial pulsatility regardless of HTN status.

Materials and Methods

Participants

30 middle-aged adults with HTN (56 ± 6 yrs; 14 women) and 30 age-, sex-, and body mass index (BMI)-matched adults without HTN (56 ± 6 yrs; 14 women) were recruited for this study. This age range was selected because large artery stiffness and cerebral pulsatility increases precipitously after ≈50 years of age [221,264], making this age range a prime target for preventive research. Exclusion criteria included self-reported smoking, stroke, dementia, diabetes mellitus, previous cardiovascular events, pulmonary/renal/neurological disease, or recent head trauma (concussion). Additionally, participants were free from dementia (Montreal Cognitive assessment score ≤21), and depression (assessed using the Center for Epidemiologic Studies Depression [CESD] questionnaire). Hyperlipidemic, overweight (BMI 25-30 kg/m^2), and obese (BMI 30-35 kg/m^2) individuals were *not* excluded due to the high prevalence of these risk factors within middle-aged adults (with and without HTN). Menopausal phase (pre-, peri-, post-menopausal) for female participants was documented according to STRAW+10 guidelines [267]. This study was approved by the Syracuse University Institutional Review Board and conformed to the standards outlined in the Declaration of Helsinki. All participants provided written informed consent prior to study initiation.

All participants with HTN were previously diagnosed by a physician *and* undergoing treatment for HTN. Participants did not refrain from anti-HTN medication during testing owing to 1) concern of rebound HTN, and 2) the medicated state is the “natural state” in which most adults with HTN exercise.

Study design

Participants were tested over 3 separate visits: 1) an initial health screening, followed by 7 days of at-home blood pressure measurement, 2) a familiarization visit and aerobic fitness test, and 3) an acute exercise visit.

Health screening

Height and weight were measured using an electronic scale and stadiometer, respectively, and used to derive BMI. Body fat was determined using air displacement plethysmography (Bod Pod, Cosmed, Concord CA). Serum lipoproteins (total cholesterol, triglycerides, low- and high-density lipoproteins) and fasting plasma glucose were assessed using a validated point-of-care device via finger stick (Cholestech, Alere Medical) following an overnight, 12-hour fast and abstinence from caffeine, alcohol, and exercise.

At-home measurements

Participants underwent 7 days of at-home blood pressure measures to confirm blood pressure status, in-line with American Heart Association recommendations [268], using an oscillometric device (BP786N, Omron Healthcare Inc., Lakeforest, IL). Participants were instructed to measure their blood pressure in duplicate twice per day (once in the morning, and once in the evening). Participants were excluded if they were not on blood pressure medication but had an average 7-day blood pressure suggestive of undiagnosed HTN (systolic pressure (SP) ≥135 mmHg and diastolic pressure (DP) ≥85 mmHg) [268].

Familiarization and aerobic fitness test

All participants were familiarized with all vascular measures to be used in the acute exercise visit prior to undergoing a cardiorespiratory fitness assessment. Cardiorespiratory fitness was assessed as peak oxygen intake (VO_2peak) during a progressive exercise test on a cycle ergometer (Excalibur, Lode B.V., Gronigen, Netherlands) to volitional fatigue (cadence <40 RPM, or voluntary exercise cessation). VO_2peak was measured via indirect calorimetry (TrueOne 2400, Parvo Medics) and determined by the highest 15-sec average obtained during exercise. VO_2peak was considered achieved if 2 of the 3 following criterion were achieved: a) heart rate peak >85% age-predicted maximal heart rate (HR; 220-age), b) respiratory exchange ratio (RER) ≥1.10, c) plateau in HR and/or oxygen consumption with increasing intensity.

Acute exercise visit

Participants were instructed to arrive >4-hours fasted, and abstain from non-essential medication (i.e. medication not prescribed for chronic conditions; allergy medication, nutritional supplements, NSAIDS), caffeine, alcohol, and exercise the day of the acute exercise visit. Time of day (morning) was standardized for all acute exercise visits. The acute exercise visit was conducted during the early follicular phase for pre- (n=2) and peri-menopausal (n=6) participants. Measurement periods were not standardized for amenorrheic (no menses for >3 months; n=3) or post-menopausal participants (n=17).

Participants underwent arterial stiffness and cerebrovascular hemodynamic measures pre and post a 30-min bout of moderate aerobic exercise. Pre-exercise cerebrovascular and cognitive testing occurred following 15 min of supine rest. Post-exercise measures were assessed approximately 10 min post in order to allow for instrumentation and avoid immediate recovery from exercise when hemodynamics are subject to rapid changes. This time point was chosen because we wished to understand the effect of exercise on large artery stiffness and pulsatility independent of blood pressure (i.e. after initial hemodynamic recovery but prior to

substantial post-exercise hypotension which may be altered by anti-hypertensive medication) [269]. All pre- and post-measures were assessed in the supine position.

Acute exercise protocol

Acute aerobic exercise consisted of 30 min of moderate-intensity cycling (≈55% VO_2peak). This dose/intensity of exercise is recommended by governing bodies to promote and maintain health in adults <65 years of age [270], and lower blood pressure in HTN [14]. Oxygen consumption was assessed during two separate 5-min increments of the exercise period (min 5-10, 20-25) in order to confirm that the exercise intensity was being optimally maintained.

Measures

Arterial stiffness

Aortic stiffness was assessed using the "gold standard" carotid-femoral (c-f) pulse wave velocity (PWV). Blood pressure waveforms from the carotid and the femoral artery were captured with applanation tonometry (AtCor Medical, Sydney, Australia) over a 10-s epoch along with ECG for simultaneous R-wave gating. PWV was calculated using the time delay between the carotid/femoral waveforms and the transit distance between the carotid and femoral arteries. The time delay was assessed as the time from peak R-wave from simultaneous ECG gating to the foot of the corresponding pressure waveform. Distances from the carotid sampling site to the femoral artery were measured as straight lines with a tape measure to the nearest mm (and properly adjusted for the bi-directional nature of pressure propagation via subtracting the suprasternal notch – carotid distance from the suprasternal notch – femoral distance).

Common carotid artery stiffness was measured using eTracking. The carotid artery was imaged below the carotid bulb using ultrasound (ProSound α7, Aloka, Tokyo, Japan) and a 7.5-

10.0 MHz linear-array probe. The distance from the near wall to far wall lumen-intima interface is continuously traced using eTracking to create a distension waveform analogous to pressure waveforms [271,272]. Carotid distension waveforms were calibrated against carotid systolic and diastolic pressures obtained from applanation tonometry. At least 8 carotid waveforms were averaged to gain a representative average waveform. Regional β-stiffness was calculated as $\ln(P_{Max}/P_{Min})/[(D_{Max} - D_{Min})/D_{Min}]$, where P and D correspond to pressure and diameter respectively, and Max and Min refer to maximum (systolic) and minimum (diastolic) values during the cardiac cycle.

Cerebrovascular pulsatility

Pressure pulsatility

Brachial SP and DP were measured in duplicate via an automatic device on the participant's non-dominant arm (BP786N, Omron Healthcare Inc., Lakeforest, IL). Pressures were taken in duplicate and averaged. If values differed by more than 5 mmHg, a third measure was obtained and the average of the 2 closest measures was used for subsequent analyses. Central pressures (aortic and carotid) were obtained via applanation tonometry. Aortic waveforms (estimated from radial waves using a validated generalized transfer function) and carotid pressure waveforms (obtained during the measurement of PWV, described above) were ensemble averaged to a single waveform for determination of aortic and carotid SP. Central pressure waveforms were calibrated to brachial mean pressure (MP) and DP. MP and pulse pressure (PP) were calculated as 1/3 SP + 2/3 DP and SP – DP, respectively. Augmentation index was calculated from central pressure waveforms as the difference between the early (P1) and late (P2) systolic peaks of the pressure waveforms to the total PP expressed as a percentage (P2 − P1/PP × 100) and standardized to a heart rate of 75 beats per min (AIx75). The rate of systolic pressure rise in the radial pulse (assessed as maximum dP/dt) was used as a surrogate measure of left ventricular contractility.

Blood velocity pulsatility

Carotid artery hemodynamics were assessed using ultrasound and techniques described previously for carotid artery stiffness. Blood velocity pulsatility was measured using Doppler ultrasound with an insonation angle $\leq 60°$ for all measures and sample volume manually adjusted to encompass the entire vessel. Carotid artery mean velocity was calculated with a semi-automated flow tracing software as: $MnV = \int V(t)\, dt/FT$, where $\int V(t)\, dt$ is the velocity-time integral of the velocity waveform and FT is flow time. Carotid artery blood velocity pulsatility index (PI) was calculated as $PI = (V_s - V_d)/ MnV$, where V_s is peak systolic, V_d is diastolic, and MnV is mean velocity. All images were stored for later offline analysis by a single, un-blinded trained investigator.

Middle cerebral artery (MCA) blood velocity was measured using Transcranial Doppler (TCD) using a 2-MHz transcranial probe applied to the left temporal window at a depth of 50-65mm (as is commonly reported for MCA measurements) and secured using a headset in order to ensure optimal insonation angle/position during the testing period. All measurements were taken by a single, trained investigator at the same probe depth and position to ensure recapture of the same cerebral artery. MCA PI and MnV were calculated over a 6-s epoch in the same manner as previously described for the carotid artery PI and by a standard algorithm implemented on the device with use of a fast Fourier transform, respectively MCA hemodynamics were captured as 4 separate 6-s epochs that were subsequently averaged. Cerebrovascular resistance was calculated as MP / MCA MnV. End-tidal CO_2 and respiration rate were assessed via capnography in order to account for the effects of respiration on cerebral hemodynamics.

Contributors to cerebrovascular pulsatility

Additional novel measures of carotid artery hemodynamics were obtained to provide insight into contributors to cerebrovascular pulsatile energetics. Extracranial pulsatile energy transmission was measured via wave-intensity analysis combined with eTracking. Flow waveforms were assessed using range gated color Doppler signals averaged along the Doppler beam and combined with eTracking distension waveforms described previously for carotid artery stiffness. Wave intensity was calculated using time derivatives of blood pressure (P) and velocity (U), such that wave intensity = (dP/dt x dU/dt); the area under the dP/dt x dU/dt curve represents the energy transfer of the wave [273]. W_1 is a forward travelling energy wave generated by the heart during early systole, accelerating flow and increasing pressure; the negative area (NA) occurring immediately following W_1 is a backward travelling compression wave stemming from reflected waves from the periphery that decelerate flow but increase pressure. NA measured in the carotid has been suggested as a measure of cerebrovascular tone [274]. The reflection index was calculated as NA/W_1. Time from ventricular depolarization (R-wave from concurrent ECG-gating) to arrival of W_1 is akin to pre-ejection period and was used as an estimate of cardiac sympathetic modulation.

Statistical analyses

All data are reported as mean ± standard deviation and statistical significance was established *a priori* as $p < 0.05$. Normality of distribution for variables was assessed qualitatively using histograms and Q-Q plots as well as quantitatively using the Shapiro-Wilk test. Non-normally distributed variables were transformed to meet normality assumptions. Descriptive characteristics were compared using independent T-tests for continues variables and χ^2 tests for categorical data. We examined vascular-hemodynamic parameters in no-HTN versus HTN groups across pre- and post-exercise time points using a 2x2 [2 group x 2 time] repeated measures ANOVA. Main effects of HTN status, exercise, and group x time interactions were further explored with Bonferroni corrected post-hoc tests. Repeated measures ANOVA's were

repeated for cf PWV and Carotid/MCA PI while covarying for changes in variables known to effect outcome variables (MAP/heart rate, and ET-CO_2, respectively). Associations between changes in arterial stiffness and hemodynamic pulsatility were examined using Pearson correlation coefficients.

Based on univariate associations, we used path analysis (SPSS, AMOS) to interrogate the theoretical model that changes in carotid diameter and forward wave intensity (W_1) contributed to carotid blood velocity pulsatility, which further contributed to MCA blood velocity pulsatility. Model fit was quantified using the standard metrics of normal fit index (NFI), the comparative fit index (CFI), and the root mean square error of approximation (RMSEA). All analyses were performed using Statistical Package for the Social Sciences (SPSS, Version 24, IBM, Chicago IL).

Results

Group characteristics and baseline hemodynamics

Groups were well-matched for sex, age, anthropometrics, body composition, and lipid profile (Table 4.1). Groups primarily self-identified as white/Caucasian (No-HTN n=29; HTN n=26), with remaining subjects identifying as Black/African (No-HTN n=1; HTN n=4). Mean glucose was higher in HTN vs No-HTN ($p<0.05$), however this difference was not present when accounting for HTN participants on beta-blockers. No-HTN had higher mean cardiorespiratory fitness than the HTN group ($p<0.05$). Non-anti-hypertensive medication use was similar in both groups, with the exception of statin use, which was greater in HTN vs No-HTN ($p<0.05$).

HTN participants had been diagnosed with hypertension for an average of 10.8 ± 8.1 years. The time of day that HTN participants took their anti-hypertensive medication (63.3% AM vs 33.0% PM) was not different within the group ($p=0.095$), with one participant taking

medication at both times of day. Combination therapy was used among 20% of the HTN group (n=7). Anti-hypertensive medication use is reported in Table 4.1. At-home blood pressure monitoring confirmed that 7-day average SP and DP were significantly higher in the HTN vs No-HTN group ($p<0.05$; Table 4.2).

Acute exercise

The mean intensity of the aerobic exercise bout was similar between groups for %VO_2peak (No-HTN 57.6 ± 3.6% vs HTN 56.5 ± 3.5%, $p>0.05$) and %maximum heart rate (No-HTN 69.7 ± 5.5% vs HTN 71.4 ± 7.3%, $p>0.05$). The mean absolute workload, however, was higher for No-HTN vs HTN (No-HTN 82 ± 43W vs HTN 63 ± 22W, $p<0.05$). Participants returned to the supine position to begin recovery within 27 ± 6 and 26 ± 6 sec following cessation from exercise for No-HTN and HTN groups, respectively. Post-exercise measures were initiated (No-HTN 7.16 ± 0.42 min vs HTN 7.12 ± 0.39 min) and completed (No-HTN 12.12 ± 1.25 min vs HTN 11.96 ± 1.10 min) at similar times between groups ($p>0.05$).

Effect of exercise on arterial stiffness

Significant time effects were detected for mean aortic, but not carotid, stiffness post-exercise (Figure 4.1a, 4.1b). Aortic stiffness increased significantly from pre (no-HTN 7.9 ± 1.1 m/s; HTN 8.2 ± 1.3 m/s) to post-exercise in both groups (no-HTN 8.1 ± 0.9 m/s; HTN 8.7 ± 1.5 m/s). Increases in aortic stiffness remained after covarying for changes in MP ($p<0.05$), but were no longer significant after covarying for changes in heart rate. There was no change in carotid artery stiffness from pre (no-HTN 8.4 ± 2.4; HTN 8.4 ± 2.2) to post-exercise in either group (no-HTN 8.4 ± 2.2; HTN 8.9 ± 2.4). No other significant group or interaction effects were detected.

Effect of exercise on cerebrovascular pulsatility

Blood pressure, regardless of measurement site, was not different post-exercise compared to baseline for mean SP, DP, MP (Table 4.3; $p>0.05$). Time effects were detected for mean aortic PP which significantly decreased post-exercise ($p<0.05$) although no such effects were observed for brachial or carotid PP. DP was higher throughout testing in HTN vs no-HTN groups ($p<0.05$). Significant time effects were detected for mean carotid and aortic augmentation indices which decreased post-exercise ($p<0.05$).

MCA Blood velocities were not obtained for 1 individual due to a poor temporal window, thus results for MCA hemodynamics are presented for 30 no-HTN and 29 HTN. Time effects were detected for both mean carotid and MCA blood velocity PI which increased post-exercise in both groups (Figure 1c, 1d; $p<0.05$). Both groups experienced increases in carotid blood velocity PI from pre (no-HTN 1.43 ± 0.34; HTN 1.34 ± 0.26) to post-exercise (no-HTN 1.49 ± 0.34; HTN 1.42 ± 0.26). MCA blood velocity PI increased from pre (no-HTN 0.78 ± 0.12; HTN 0.76 ± 0.11) to post-exercise in both groups (no-HTN 0.82 ± 0.12; HTN 0.78 ± 0.11). Changes in carotid and MCA PI remained after covarying for changes in ET-CO_2 ($p<0.05$).

Significant time effects were detected for mean HR, W_1, NA, carotid mean diameter, ET-CO_2, and respiration rate (Table 4.4). Heart rate, W_1 and NA increased, while carotid mean diameter decreased post-exercise in both groups ($p<0.05$). Minor, but significant, increases in mean respiration rate post-exercise were coupled with similar reductions in ET-CO_2 in both groups ($p<0.05$). A significant interaction effect was observed for MCA MnV however, the minor changes in MnV were not significant after post-hoc Bonferroni adjustment for multiple comparisons. No other significant group or interaction effects were observed.

Associations between arterial stiffness and hemodynamic pulsatility

Correlation matrices for exercise-induced change in hemodynamics are displayed in Table 4.5. Of note, we observed significant positive associations between post-exercise changes in carotid stiffness and both aortic and carotid PP. Exercise-induced changes in PP were positively associated with changes in carotid forward wave intensity (W_1). Post-exercise change in W_1 and aortic/carotid PP were positively associated with change in radial dP/dt, while change in W_1 and carotid PP were positively associated with carotid blood velocity PI. Post-exercise change carotid blood velocity PI was further positively associated with changes in downstream MCA blood velocity PI. We noted significant negative correlations between 1) change in aortic/carotid AIx and change in carotid and MCA blood velocity PI; and 2) change in carotid mean diameter and carotid blood velocity PI.

Path analysis was used to explore the contribution of carotid hemodynamics to extracranial, and in-turn intracranial, pulsatile hemodynamics (Figure 4.2). Changes in carotid diameter and W_1 significantly contributed to carotid blood velocity PI, which further contributed to downstream MCA PI. Our model was significantly better than the saturated model (Chi-square=2.44, p=0.49) and fit the data well (NIF=0.92, CFI=1.00, RMSEA=0.00).

Discussion

This investigation was designed to examine the effects of acute aerobic exercise on large artery stiffness and cerebrovascular pulsatility in middle-aged, adults with and without HTN. Our data suggest that acute moderate-intensity aerobic exercise increases aortic stiffness and cerebrovascular (carotid/MCA) blood velocity pulsatility during early recovery. Additionally, wave-intensity analysis indicates increases in forward wave energy, transmitted from a stiffened aorta into a constricted carotid artery, may be a primary contributor to post-exercise cerebrovascular pulsatility. These observations were not different between adults with and

without HTN, indicating that middle-age adults with HTN respond similarly to acute aerobic exercise as their age-matched counterparts without HTN.

Contrary to our hypothesis, middle-aged, adults with HTN had a similar hemodynamic response following exercise compared to their counterparts without HTN. The similar acute response may be related to similar health status between our groups. Despite a 5 ml/kg/min difference in VO_2peak, groups had comparable traditional cardiovascular disease profiles, and body composition. Moreover, blood pressure of our adults with HTN was well-controlled according to at-home blood pressure values, a notable observation as controlling blood pressure has a favorable effect on the progression of arterial stiffening in the setting of HTN [275]. Our HTN group had a mean cf PWV (8.2 ± 1.3 m/s) comparable to that of normotensive adults in the Framingham Heart Study (mean age 58.2 ± 8.9 yrs, cf PWV 7.9 ± 1.4 m/s) [276]. Additionally, participants did not refrain from use of anti-HTN medication during testing, and this may modify how individuals respond to the physiological stress of acute exercise [269]. Whether vascular responses to acute exercise differ in a less healthy or untreated/uncontrolled cohort of adults with HTN remains unknown and an area of future interest.

We noted increased aortic stiffness during early recovery from acute aerobic exercise in HTN and No-HTN groups. This post-exercise aortic stiffening occurred without any change in distension pressure (i.e. MP) and remained following covariate adjustment for MP. Independent of changes in distension pressure, acute increases in aortic stiffness following submaximal exercise may be related to residual effects of exercise on heart rate. Indeed, the significant increase in aortic stiffness was attenuated when covarying for changes in heart rate post-exercise, indicating that elevations in heart rate contributed to aortic stiffening post-exercise. Heart rate may exert a direct mechanical effect on the vessel wall. Increases in heart rate would shorten diastole, preventing complete wall recoil and thus stiffening the vessel [277]. Separate

from the direct mechanical effects, heart rate is an index of sympathetic activity which may directly modulate aortic stiffness [278].

There were no changes in carotid stiffness following exercise. Our observations of increases in aortic stiffness in the absence of change in carotid stiffness are in-line with previous studies in older adults with controlled HTN [235,266]. The disparate changes in carotid stiffness versus aortic stiffness post-exercise indicates that large arteries may recover from the hemodynamic insult of exercise differently. The exact mechanism underlying this observation is beyond the scope of this study, but may be due to differing wall composition (i.e. elastin, smooth muscle, collagen), or differential effects of sympathetic activation, myogenic tone, or hormonal modulation on the aorta versus carotid artery. Ultimately, differential changes in aortic versus carotid stiffness during early recovery from exercise may have altered pulsatile energy transmission.

Disproportionate increases in aortic compared to carotid stiffness during early recovery from exercise may alter input/characteristic impedance at the aorta-carotid interface, affecting transmission of pulsatile energy into cerebral vessels [9,222]. Using wave-intensity analysis, a novel method of appraising pulse wave dynamics [279], we were able to interrogate potential origins of post-exercise cerebrovascular hemodynamic pulsatility. We documented significant increases in carotid forward wave intensity (W_1) post-exercise. The change in forward wave intensity is likely related to post-exercise elevations in left ventricular contractility [280] as we saw a significant positive relationship between radial dP/dt (a proxy of left ventricular inotropic function) and W_1. Transmission of this forward wave energy may be further amplified in the presence of carotid vasoconstriction [281,282]. Ultimately, left ventricular-generation of forward wave energy [65] has been identified as a primary contributor to hemodynamic pulsatility [283,284]. Indeed, as the forward travelling wave increases in intensity, it augments systolic blood flow velocity [285] and increases blood velocity pulsatility. Indeed, we noted

increased extracranial blood velocity pulsatility at the level of the carotid artery which was likely propagated downstream, increasing MCA pulsatility post-exercise. The contribution of forward wave energy to extra- and intra-cranial pulsatility was corroborated by significant linear associations between the post-exercise change in forward wave intensity (W_1) and carotid blood pressure/blood velocity pulsatility, which was in-turn associated with middle cerebral artery blood velocity pulsatility.

Forward traveling pulse waves are partially reflected by regions of impedance mismatch as they travel downstream. Pressure from wave reflections augment pressure but subtract from flow and may thus play an important role as modulators of hemodynamic pulsatility. Following exercise we noted that reductions in global wave reflections, as assessed via the augmentation index, were inversely associated with carotid and MCA flow pulsatility index. Consistent with previous suggestions by Mitchell, substantial reductions in extracranial pressure from wave reflections may reduce their contribution to PP while concomitantly allowing greater forward wave energy to enter the intracranial circulation and augment flow pulsatility [9,286]. Conversely, we noted increases in regional reflected wave intensity in the carotid artery as indicated by an increase in NA from wave-intensity analysis. Increased carotid wave reflection may stem from downstream changes in cerebrovascular tone [274] and serve to protect the brain from pulsatile hemodynamics. Thus, at any given moment, intracranial flow pulsatility may be influenced by the net balance between regional and global wave reflections.

Regular aerobic exercise is generally known to have beneficial effects on systemic vascular structure and function [15,22]. However, the data presented herein are somewhat counterintuitive. Increases in hemodynamic pulsatility after each bout of exercise would be inferred to harm the cerebral microvascular bed and increase cerebrovascular risk over time. First, we wish to underscore that with only modest increases in intracranial hemodynamic pulsatility following acute exercise, our data may indicate cerebrovascular “resilience” to

pulsatile forces incurred from acute exercise even among HTN, a group typically considered vulnerable to pulsatile burden [287]. Second, habitual exercise training is known to cause vascular remodeling [288,289]. Increased vessel diameter from exercise training may serve to offset impedance mismatches at the aorta-carotid interface, thereby minimizing transmission of pulsatile hemodynamic energy [290].

Limitations and considerations

Our study is the first to examine the effects of acute submaximal exercise, at a dose typically recommended for adults with HTN, on gold-standard measures of arterial stiffness and cerebrovascular pulsatility in adults with well-controlled HTN and well-matched adults without HTN. We purposefully selected adults with controlled-HTN since this is their "free-living" state in which they would typically engage in exercise as a therapeutic intervention. As such, acute responses to submaximal exercise may differ in untreated HTN considering anti-HTN medications' effect on blood pressure (and thus aortic stiffness) and cerebral arterial pulsatility [291,292]. It is possible that higher intensity exercise may elicit different effects although exercise intensity may not elicit greater changes in blood pressure in adults with HTN [293]. A recent meta-analysis suggests that post-exercise hypotension may be attenuated with anti-HTN medication [269] complicating interpretation of post-exercise changes in large artery stiffness between individuals with controlled-HTN and those without HTN. As such, we chose to interrogate the effect of acute exercise on arterial stiffness and hemodynamic pulsatility during early recovery, permitting us to identify potential group differences independent of differential alterations in blood pressure during prolonged recovery. Nonetheless, understanding post-exercise hemodynamic recovery kinetics in HTN is of importance and future research is needed to identify the interactions between anti-HTN medication, post-exercise hypotension, and delayed effects of exercise on large artery stiffness and hemodynamic pulsatility. The contribution of early versus delayed recovery dynamics in governing chronic adaptations is

unclear, and requires additional research to fully elucidate the long-term implications of these acute responses.

In summary, our data indicate that acute, moderate-intensity aerobic exercise increases aortic stiffness and cerebrovascular hemodynamic pulsatility during early recovery from exercise in middle-aged adults with and without HTN. The increases in cerebrovascular pulsatility may be related to increases in forward wave propagation, coupled with carotid vasoconstriction and disparate changes in aortic and carotid stiffness and wave reflections. These data indicate that extracranial hemodynamic responses to a recommended dose/intensity of aerobic exercise contribute to intracranial hemodynamic pulsatility during early recovery from acute exercise. The increase in post-exercise intracranial pulsatility was modest despite exposure to an extracranial hemodynamic milieu that appeared primed to substantially increase intracranial pulsatility, potentially indicative of an apparent cerebrovascular "resilience" to pulsatile hemodynamics in our sample of middle-aged adults with well-controlled HTN and their counterparts without HTN.

Table 4.1: Descriptive characteristics for no-HTN and HTN groups (mean ± SD unless otherwise noted).

	No-HTN	**HTN**	p-value
Sex (male/female)	16/14	16/14	-
Age (yrs)	56 ± 6	56 ± 6	0.93
Anthropometrics			
Height (cm)	169.8 ± 11.3	171.3 ± 9.6	0.57
Weight (kg)	82.0 ± 13.3	82.4 ± 12.5	0.91
Body fat (%)	32.2 ± 8.4	31.4 ± 6.9	0.69
Body mass index (kg/m^2)	28.3 ± 2.6	28.0 ± 3.3	0.71
Medications, %(n)			
Statin	6.7 (2)	40.0 (12)	**0.005**
Birth control	3.3 (1)	0.0 (0)	-
Hormone replacement therapy	3.3 (1)	3.3 (1)	-
Hypothyroid	3.3 (1)	3.3 (1)	-
ACE inhibitor	-	43.3 (13)	-
ARB	-	33.3 (10)	-
Diuretic	-	20 (6)	-
β-Blocker	-	13.3 (4)	-
CCB	-	13.3 (4)	-
Lipid profile			
Hemoglobin (g/dL)	14.2 ± 0.9	13.8 ± 1.3	0.12
Total cholesterol (mg/dL)	202 ± 39	192 ± 36	0.28
HDL (mg/dL)	58 ± 17	56 ± 20	0.56
Triglycerides (mg/dL)	103 ± 61	116 ± 56	0.28
LDL (mg/dL)	128 ± 41	114 ± 30	0.17
Non-HDL (mg/dL)	144 ± 44	136 ± 32	0.43
Total cholesterol:HDL	4 ± 2	4 ± 1	0.89
Glucose (mg/dL)	94 ± 9	102 ± 16	**0.03**
Fitness			
VO_2max (mL/kg/min)	32.4 ± 8.8	27.2 ± 5.6	**0.008**

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VO2max, maximal oxgyen consumption; MVPA, minutes of moderate-vigorous physical activity.

Table 4.2: 7-day average at-home brachial blood pressure measures in No-HTN and HTN groups (mean ± SD).

	No-HTN	**HTN**	p-value
SP (mmHg)	116 ± 9	126 ± 12	**0.001**
DP (mmHg)	73 ± 6	79 ± 8	**0.004**
PP (mmHg)	43 ± 8	47 ± 8	0.06
Heart rate (b/min)	64 ± 8	68 ± 9	0.06

SP, systolic pressure; DP, diastolic pressure; PP, pulse pressure.

Table 4.3: Effect of exercise on blood pressure and wave reflections in no-HTN and HTN groups (mean ± SD).

	No-HTN		HTN				
Measure	**Pre**	**Post**	**Pre**	**Post**	G	T	GxT
Brachial artery							
SP (mmHg)	122 ± 14	123 ± 10	127 ± 13	126 ± 13	0.23	0.54	0.19
DP (mmHg)	76 ± 8	76 ± 6	81 ± 9[†]	81 ± 8	**0.03**	0.72	0.22
MP (mmHg)	91 ± 9	92 ± 7	96 ± 10	95 ± 9	0.053	0.92	0.14
PP (mmHg)	47 ± 11	47 ± 9	46 ± 8	45 ± 8	0.70	0.36	0.51
Aorta							
SP (mmHg)	110 ± 12	110 ± 8	115 ± 12	112 ± 11	0.18	0.07	0.08
PP (mmHg)	33 ± 9	32 ± 7	33 ± 7	30 ± 7	0.18	**0.005**	0.60
AIx (%)	25 ± 12	20 ± 13	27 ± 9	21 ± 11	0.55	**0.001**	0.60
AIx75 (%)	18 ± 12	16 ± 12	21 ± 10	19 ± 10	0.24	**0.001**	0.79
Carotid artery							
SP (mmHg)	113 ± 13	113 ± 9	118 ± 13	116 ± 12	0.17	0.19	0.38
PP (mmHg)	37 ± 10	36 ± 8	37 ± 8	35 ± 8	0.82	0.07	0.89
AIx (%)	15 ± 20	0 ± 19	22 ± 15	5 ± 21	0.17	**0.001**	0.77
AIx75 (%)	7 ± 20	-4 ± 18	15 ± 15	3 ± 21	0.10	**0.001**	0.94

G, group effect; T, time effect; GxT, group-by-time interaction; SP, systolic pressure; DP, diastolic pressure; MP, mean pressure; PP, pulse pressure.

Table 4.4: Effect of exercise on vascular hemodynamics in no-HTN and HTN groups (mean ± SD).

	No-HTN		HTN				
Measure	**Pre**	**Post**	**Pre**	**Post**	G	T	GxT
Heart rate (b/min)	59 ± 10	68 ± 9	61 ± 8	71 ± 11	0.26	**0.001**	0.25
Pre-ejection period (ms)	102 ± 15	99 ± 15	99 ± 11	96 ± 11	0.30	**0.001**	0.76
ET-CO_2 (mmHg)	35 ± 3	34 ± 3	35 ± 3	34 ± 3	0.93	**0.007**	0.76
Respiration rate (br/min)	14 ± 4	16 ± 4	14 ± 3	15 ± 4	0.39	**0.001**	0.89
dP/dt (mmHg/s)	643 ± 230	687 ± 214	630 ± 170	652 ± 182	0.62	0.06	0.51
Carotid artery							
Mean diameter (mm)	5.67 ± 0.54	5.62 ± 0.56	5.55 ± 0.66	5.47 ± 0.65	0.35	**0.008**	0.62
Mean velocity (cm/s)	35.2 ± 5.2	36.1 ± 4.9	37.5 ± 5.8	38.3 ± 7.0	0.11	0.10	0.99
W_1 ($mmHg/m/s^3$)	7.4 ± 6.5	9.2 ± 5.4	6.8 ± 3.0	8.8 ± 4.8	0.68	**0.001**	0.82
NA ($mmHg/m/s^2$)	30.4 ± 26.5	34.5 ± 21.5	23.2 ± 10.4	26.6 ± 14.6	0.28	**0.005**	0.51
NA/W_1 (%)	4.35 ± 2.52	4.18 ± 2.43	3.59 ± 1.35	3.30 ± 1.34	0.17	0.29	0.67
Middle cerebral artery							
Mean velocity (cm/s)	61 ± 15	62 ± 15	63 ± 11	62 ± 11	0.76	0.98	**0.02**
Resistance (mmHg/cm/s)	1.58 ± 0.35	1.56 ± 0.39	1.58 ± 0.36	1.60 ± 0.36	0.71	0.99	0.27

G, group effect; T, time effect; GxT, group-by-time interaction; ET, end-tidal; W_1, forward wave intensity; NA, negative area; NA/W_1; reflection index.

Table 4.5: Linear associations between change in hemodynamics pre to post exercise.

	Δcf PWV	ΔCCA β	ΔAO PP	ΔCCA PP	ΔAO Alx	ΔCCA PI	ΔMCA PI	ΔCCA W_1	ΔCCA NA	ΔCCA NA/W_1	ΔCCA Alx	ΔCCA Diam
ΔCCA β	-0.110											
ΔAO PP	-0.133	**0.386**										
ΔCCA PP	-0.034	**0.554**	**0.777**									
ΔAO Alx	-0.068	0.232	0.066	0.130								
ΔCCA PI	-0.250	0.159	0.238	**0.289**	**-0.294**							
ΔMCA PI	-0.240	0.164	**0.259**	0.171	**-0.442**	**0.494**						
ΔCCA W_1	-0.136	0.008	**0.295**	**0.322**	-0.161	**0.444**	0.202					
ΔCCA NA	0.047	0.032	0.225	**0.330**	-0.013	**0.285**	0.050	**0.550**				
ΔCCA NA/W_1	-0.104	0.049	0.092	**0.063**	-0.013	0.020	0.178	**0.524**	**-0.372**			
ΔCCA Alx	-0.161	0.043	0.198	**0.044**	**0.350**	-0.180	**-0.348**	-0.112	-0.096	-0.246		
ΔCCA Diam	0.045	-0.091	0.071	-0.075	-0.102	**-0.268**	0.008	0.079	-0.082	0.001	0.106	
ΔdP/dt	-0.076	0.210	**0.789**	**0.501**	-0.152	0.128	0.097	**0.292**	0.156	0.149	0.084	0.165

CCA, common carotid artery; AO, aortic; PWV, pulse-wave velocity; PP, pulse pressure; Alx, augmentation index; PI, pulsatility index; W_1, forward wave intensity; NA, negative area; NA/W_1, reflection index; Diam, diameter. Bold denotes $p<0.05$

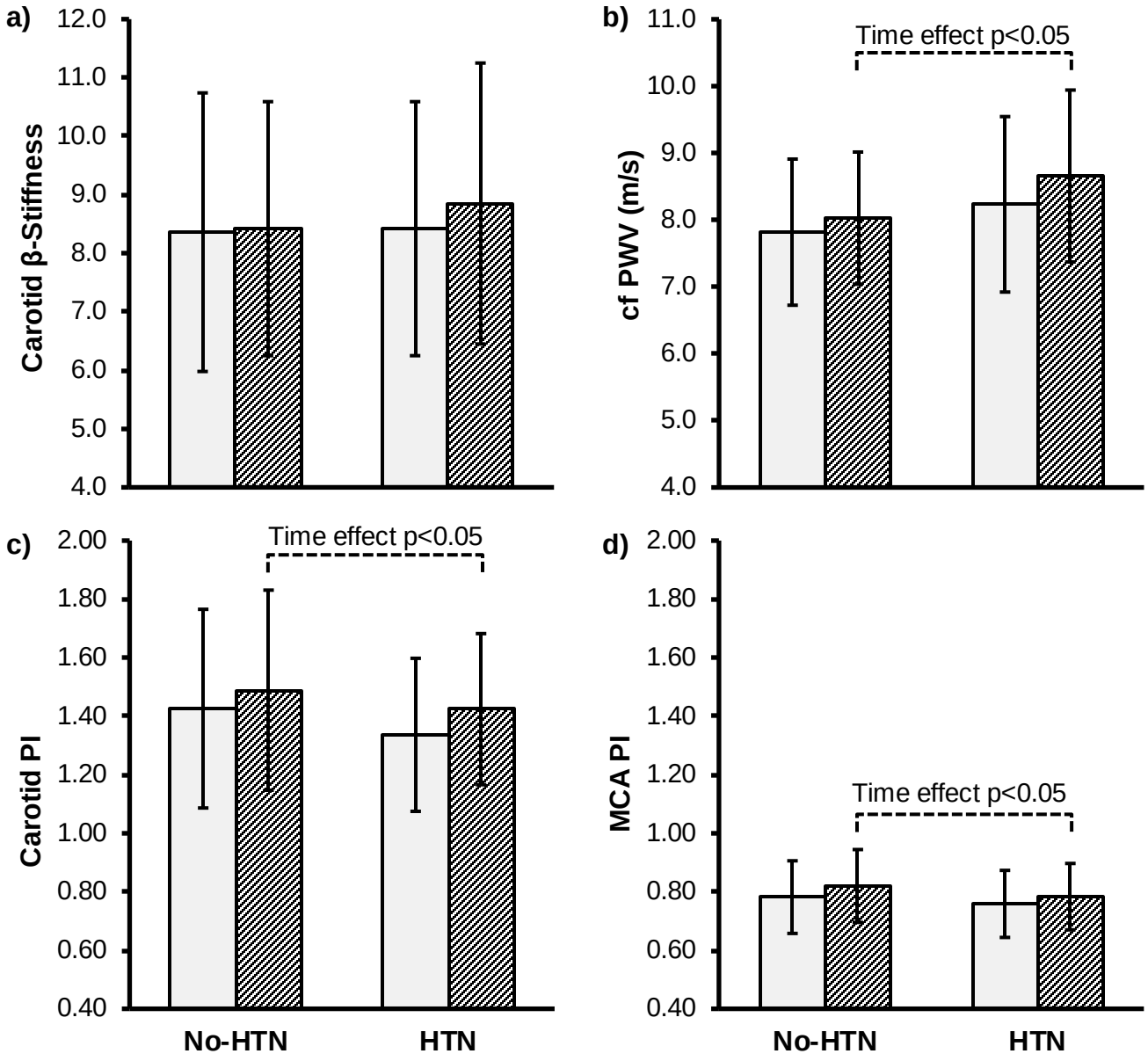

Figure 4.1: Effect of acute exercise on a) Carotid and b) aortic PWV, and c) carotid and d) MCA blood velocity PI in no-HTN and HTN groups. ☐Pre ▨ Post

PWV, pulse wave velocity; MCA, middle cerebral artery; PI, pulsatility index.

a) Group, 0.44; Time, 0.26; Group-by-time, 0.38.

b) Group, 0.08; Time, **0.001**; Group-by-time, 0.22.

c) Group, 0.36; Time, **0.001**; Group-by-time, 0.53.

d) Group, 0.31; Time, **0.003**; Group-by-time, 0.51.

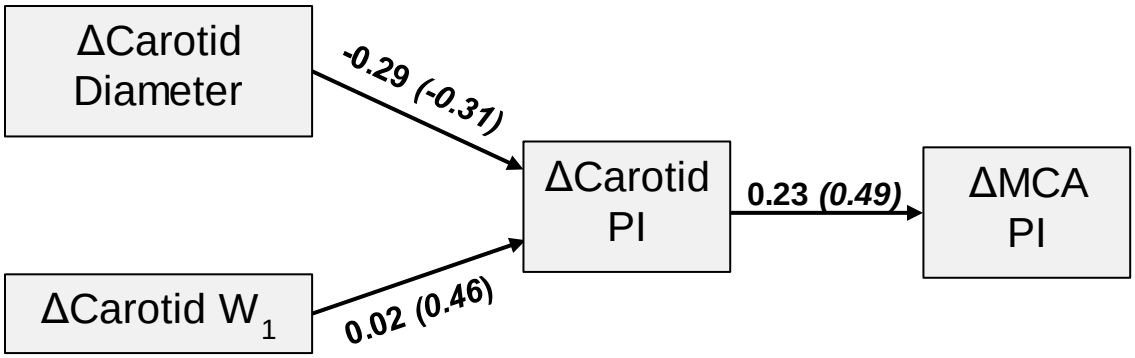

Figure 4.2: Path analysis demonstrating relationships between post-exercise changes in extracranial hemodynamics and intracranial pulsatility.

W_1, forward wave intensity; PI, pulsatility index. Values presented as unstandardized (*standardized*) coefficients, bold denotes $p<0.05$.

Chapter V: Effects of Acute Aerobic Exercise on Cognition and Constructs of Decision-making in Adults with and without Hypertension

Abstract

Hypertension (HTN) is associated with accelerated cognitive decline and dysfunction. Exercise is widely recommended for adults with HTN to slow cognitive decline, yet little data exists on exercise and cognition in HTN. Whether acute exercise improves cognitive function in this at-risk population is unknown. The purpose of this study was to compare the effects of acute aerobic exercise on cognitive function in 30 middle-aged adults with HTN and 30 age, sex, and body mass index (BMI)-matched adults without HTN (no-HTN; 56±6 yrs, BMI 28.2±2.9 kg/m^2; 32 men). Subjects underwent cognitive testing pre/post 30-min cycling (≈55% peak oxygen consumption). Cognition was assessed using standard metrics of accuracy and reaction time (RT) across memory recognition, 2-Back and Flanker tasks. Behavioral data was further analyzed using drift-diffusion modeling to examine underlying components of decision-making (strength of evidence, caution, bias) and RT (non-decision time). Exercise elicited similar changes in cognitive function in both HTN and no-HTN groups ($p>0.05$). Accuracy was unaltered for Flanker and 2-back tasks, while hits and false alarms increased for memory recognition post-exercise ($p<0.05$). Modeling results indicated changes in memory hits/false alarms were due to significant changes in stimulus bias post-exercise. RT decreased for Flanker and memory recognition tasks and was driven by reductions in post-exercise non-decision time ($p<0.05$). Our data indicate acute exercise resulted in unaltered task accuracy and accelerated RT post-exercise in both middle-age adults with and without HTN. Additionally, drift-diffusion modeling revealed that beneficial acceleration of cognitive processing post-exercise (RT) is driven by changes in non-decision components (encoding/motor response) rather than the decision-making process itself.

Introduction

Cognitive decline is regarded as one of the most important determinants of health, function, and quality of life with advancing age [125]. Hypertension (HTN) and its neurocognitive consequences accelerate brain aging [11], resulting in mild cognitive impairment, dementia, and Alzheimer's disease [11]. HTN is associated with, and predicts, risk of cognitive impairment [133,134,136-138] and overall cognitive performance [12,132,139-142]. The cognitive domains of executive function (high-level interrelated cognitive abilities that integrate lower-level functions to complete goal-directed behavior [127,128]) and memory appear to be most vulnerable to HTN [3,114,140]. Associations between high blood pressure and cognitive dysfunction can be detected as early as mid-life, as individuals with elevated mid-life systolic blood pressure have an increased likelihood of developing mild cognitive impairment and dementia [131,147,148]. The length of time that the brain is exposed to elevated blood pressure likely dictates the degree of cognitive decline. Thus, mid-life targeted interventions may serve as a "last chance" to intervene before long term exposure to high blood pressure causes irreversible target organ damage and cognitive impairment [157,178].

Regular aerobic exercise is recognized as the most pluripotent and effective means to maintain brain health and mental longevity [186-188]. As such, aerobic exercise *is highly* recommended by governing bodies [13,14] for adults with HTN to maintain cognitive health [16] and prevent cognitive impairment with advancing age [192-194]. Despite the established body of literature linking HTN to cognitive function, and exercise recommendations to improve cognitive function in HTN, there is a paucity of data on the effect of exercise on cognitive function in adults *with HTN*. Meta-analytical investigations in populations without HTN have shown that acute exercise improves executive function [20,195-197] and may positively impact memory [20,195]. Moderate to vigorous exercise appears to produce the most pronounced, beneficial changes in both executive function and memory [294]. Whether adults with HTN

experience acute improvements in executive function and memory performance following a bout of exercise has not been directly investigated but is of particular interest since these domains are sensitive to the detrimental effects of HTN [3,114,140].

Traditional investigations of cognition and exercise assess function in a given cognitive domain by using simple pen-and-paper tasks or by interpreting a combination of computerized data metrics such as accuracy or processing speed/reaction time (RT) for correct trials. Greater accuracy is believed to reflect better functioning of the cognitive domain of interest (i.e. executive function, memory). Faster RT is posited to indicate improved functioning in the cognitive domain of interest since less time is required for the individual to respond correctly to the stimulus. This traditional analytical approach to studying cognition relies on reverse inference. For example, observing slower RT on an executive function task would be assumed to reflect a change in the cognitive process of interest (i.e. impaired executive function). Reverse inference in this setting is valid only if the changes in behavior (RT) are driven solely by executive function. There is substantial evidence, however, that factors independent of the cognitive process of interest, such as caution and bias, impact both RT and accuracy [295]. As such, observing slower executive function RT may actually reflect changes in caution (i.e. slower responses intended to preserve accuracy), rather than impaired executive function itself.

Drift-diffusion modeling (DDM) is a mathematical approach that helps navigate this obstacle in cognitive testing (the theoretical basis of mathematical modeling in decision-making and cognitive neuroscience is described elsewhere [247]). In brief, DDM decomposes observational data (hits, misses, RT) into latent processes underlying decision-making, including caution, encoding and motor response duration, the strength and quality of evidence presented by the stimulus, and response bias (i.e. implicit or explicit preference for one response over another) [243-246,295]. Thus, DDM attempts to describe what changes in the latent decision-making process are responsible for the observed responses. DDM incorporates

all available behavioral data (accuracy, correct/error RT, shape of RT distributions) rather than solely relying on RT for correct trials and accuracy to describe changes in behavioral data. This modeling technique can provide novel insight into whether changes in cognition stemming from acute exercise (observed through accuracy and RT) are due to neurological (i.e. encoding, motor response) or behavioral changes (i.e. caution, bias) in the latent constructs of decision-making. Although DDM has not been previously used to interrogate cognition in HTN or in the acute exercise literature at-large, it has provided insight into 1) the slowing of RT with advancing age [248,249], and 2) the effect of hypoxia on cognition during exercise [250], and holds significant potential to provide insight into changes in cognition with HTN and exercise.

As such, the purpose of this investigation was to 1) compare the effect of acute aerobic exercise on cognitive function (using memory and executive function tasks) in middle-aged adults with (HTN) and without HTN (no-HTN), and 2) examine the effect of acute exercise on underlying constructs of decision making using DDM. It was hypothesized that acute exercise would differentially effect cognition in adults with versus without HTN, manifesting as improved cognition (manifesting as improved accuracy and accelerated RT post-exercise on executive function and memory tasks) in adults without HTN, while cognition would be unaltered by exercise in HTN.

Methodology

Participants

30 middle-aged adults with HTN (56 ± 6 yrs; 14 women) and 30 age-, sex-, and body mass index (BMI)-matched adults without HTN (56 ± 6 yrs; 14 women) were recruited for this study. We targeted middle-aged adults because 1) cognitive decline can be detected as early as middle-age [296-298], making this age range a prime target for preventive research and 2) recent meta-analyses indicate this is an understudied group regarding acute exercise and

cognition [198]. Exclusion criteria included self-reported smoking, stroke, dementia, diabetes mellitus, obesity (BMI ≥30 kg/m^2), previous cardiovascular events, pulmonary/ renal/neurological disease, or recent head trauma (concussion). Additionally, participants were free from dementia (Montreal Cognitive assessment score ≤21), and depression (assessed using the Center for Epidemiologic Studies Depression (CESD) questionnaire). Hyperlipidemic and overweight participants (BMI 25-30 kg/m^2), were *not* excluded due to the high prevalence of these risk factors within middle-aged adults (with and without HTN). Menopausal phase (pre-, peri-, post-menopausal) was documented according to STRAW+10 guidelines [267]. This study was approved by the Syracuse University Institutional Review Board and all participants provided written informed consent prior to study initiation.

All participants with HTN were diagnosed *and* undergoing treatment for HTN. Participants did not refrain from HTN medication during testing owing to 1) concern of rebound HTN [299], and 2) the medicated state is the "natural state" in which most adults with HTN exercise.

Height and weight were measured using an electronic scale and stadiometer, respectively, and used to derive BMI. Body fat was determined using air displacement plethysmography (Bod Pod, Life Measurement Inc., Concord CA). Serum lipoproteins (total cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein), and fasting plasma glucose were assessed using a validated point-of-care device via finger stick (Cholestech, Alere Medical) following an overnight, 12-hour fast and abstinence from caffeine, alcohol, and exercise.

Cardiorespiratory fitness was assessed as maximal oxygen intake (VO_2max) during a progressive exercise test on a cycle ergometer to volitional fatigue (cadence <40 RPM). VO2max was measured via indirect calorimetry (TrueOne 2400, Parvo Medics) and determined

by the highest 15-sec average obtained during exercise. VO2max was considered achieved if 2 of the 3 the following criterion were achieved: a) heart rate peak >85% age-predicted heart rate (HR) max, b) respiratory exchange ratio (RER) ≥1.10, c) plateau in HR or oxygen consumption with increasing intensity.

Acute Exercise Design:

Participants were instructed to arrive >4-hours fasted, and abstain from non-essential medication, caffeine, alcohol, and exercise the day of the visit. Time of day (morning) was standardized for the all acute exercise visits. Participants underwent cognitive measures pre and post a 30-min bout of aerobic exercise. Pre-exercise cognitive testing occurred following 15-minutes of supine rest. Post-exercise measures were assessed approximately 10-min post because cognition may be negatively affected within the first 10 min post exercise [20]. All pre and post measures were assessed in the supine position.

Acute exercise protocol:

Acute aerobic exercise consisted of 30-min of moderate-intensity cycling (≈55-60% VO_2max). This dose/intensity of exercise is recommended by the American Heart Association and American College of Sports Medicine to promote and maintain health in adults <65 years of age [270], and elicits positive effects on cognition post-exercise [20] in healthy adults. Oxygen consumption was assessed during two separate 5-minute increments of the exercise period (minutes 5-10, 20-25) in order to confirm and titrate the exercise intensity.

Cognitive measures

Cognitive function was assessed using a 15-min, 3-task computerized (Matlab, The MathWorks, Natick, MA; and PsychToolbox) cognitive battery (with a hand-held response clicker) that interrogates the attention (Flanker task) and working memory (N-back task) components of executive function, and memory (word recognition task). This battery of tasks

has been used by our group previously [250]. These domains were selected because they have implications for later-life cognitive function and are effected by HTN and acute exercise [20]. The battery always began with the word study list, followed by the working memory and executive function tasks in a randomized, counter-balanced order, followed by the memory recognition task. Each trial was preceded by verbal instructions and a visual reminder of each task and its respective goals, in addition to brief on-screen instructions prior to beginning each task once testing had begun. This multi-stage instruction process was designed to ensure participants recalled the goal of each task prior to initiation.

Participants were familiarized with all cognitive tasks prior to the acute exercise visit to account for learning effects. Familiarization included point-by-point written and verbal instructions for each task, followed by a complete practice session of the cognitive battery. If participants did not adequately understand a task they were permitted to repeat the task until they were comfortable with the goals and procedures of the task.

Executive function

The attention component of executive function was assessed using the standard Eriksen Flanker task. Participants were presented with 5 arrows (standard Eriksen Flanker task) and instructed to respond to which direction the middle arrow was pointing. This task contained 64 congruent (i.e. all arrows facing the same direction; <<<<<) and 64 incongruent (i.e. flanking arrows facing different direction from middle arrow; <<><<) 1.5-s long trials (totaling approximately 5-minutes). Accuracy was expressed as percent hits and processing speed was assessed as mean hit RT for hit incongruent/congruent trials.

The working memory component of executive function was assessed using a 2-back number task. This task included 160 trials, lasting approximately 4 min. After fixating on 3 crosses, participants were presented with a series of digits (1-9) at a rate of 1/s, with

consecutive numbers separated by 0.25 seconds. They were instructed to press the right response button if the number presented matched the number that was presented 2 numbers before (i.e. 4-7-4; this is the 2-back version of the N-back task) and press the left response button for all non-match stimuli. Accuracy was expressed as percent hits and commission errors (falsely identifying a number as a match), and processing speed was assessed as mean hit RT.

Memory

Memory recognition was assessed by presenting participants with 36 words for memorization and later recognition from memory. The list contained 36 concrete words from the English language that are displayed for 1 s each. Participants then completed two cognitive tasks (flanker and N-back, randomized order) before beginning the memory recognition portion of the test (approximately 10 min later). To assess memory recognition performance, participants were presented with 72 words (36 distracters), at a rate of 1 every 2 s, and instructed to identify the words as "old" if they remembered the word from the study list or "new" if the word being presented was not on the study list. Accuracy was expressed as percent hits (correctly recalled items) and false alarms (old/studied items incorrectly identified as new/distractors). Mean reaction time (RT) for hits was calculated to assess processing speed.

Drift-diffusion modeling

Drift-diffusion modeling (DDM) was conducted post-hoc on all cognitive performance data. This modeling technique can provide insight into whether changes in cognition are due to neurological (i.e. encoding) or behavioral (i.e. caution, bias) changes. DDM has been validated [300] and described in detail previously [243-245]. In short, the model assumes that decisions start at a point (*z*) and noisy evidence is sampled until a boundary (a/0) is reached, initiating a response (Figure 5.1). Wider distances between boundaries (a) indicate slower but more accurate responses (caution). Drift rate (*v*) indicates the strength of evidence (higher drift rate

means stronger evidence), and non-decision time estimates the duration of encoding/motor response. DDM parameters are summarized in Table 5.1.

Statistical Analyses

All data is reported as mean ± standard deviation and statistical significance was established *a priori* as $p < 0.05$. Normality of distribution for variables was assessed qualitatively using histograms and Q-Q plots as well as quantitatively using the Shapiro-Wilk test. Non-normally distributed RT and DDM metrics were transformed to meet normality assumptions. Descriptive characteristics were compared using independent T-tests for continues variables and χ^2 tests for categorical data. We examined cognitive RT and DDM parameters in no-HTN versus HTN groups across pre- and post-exercise time points using a 2x2 [2 group x 2 time] repeated measures ANOVA. Group x time interactions were further explored with Bonferroni corrected post-hoc tests. All accuracy metrics (hit rates) were unable to be successfully transformed to meet assumptions, and were therefore analyzed using Mann-Whitney U-tests run to test the effect of time (pre- vs post-exercise), group (HTN vs no-HTN), and group by time interaction (change in accuracy post-pre for HTN vs no-HTN) with Bonferroni correction for multiple comparisons.

Results

Group characteristics

Groups were well-matched for sex, age, anthropometics, body composition, lipid profile, CESD score, and menstrual status (Table 5.2). Glucose was significantly higher in HTN vs no-HTN ($p<0.05$), however this difference was abolished when accounting for HTN participants on beta-blockers. No-HTN had significantly higher cardiorespiratory fitness, accumulated minutes of MVPA ($p<0.05$), and tended to have greater total number of steps over 6 days ($p=0.058$).

Medication use was similar in both groups, with the exception of statin use which was greater in HTN vs no-HTN ($p<0.05$).

Blood pressure status

Participants with HTN had been diagnosed with HTN for an average of 129 ± 97 months. The time of day that participants with HTN took their BP medication (63.3%, AM vs 33.0%, PM) was not different within the group ($p=0.095$), with one participant taking BP medication at both times of day.

Acute exercise

The intensity of the aerobic exercise bout was similar between groups for %relative VO2max (no-HTN, 57.6 ± 3.6% vs HTN, 56.5 ± 3.5% $p>0.05$) and %maximum heart rate (no-HTN, 69.7 ± 5.5 vs HTN, 71.4 ± 7.3 $p>0.05$). The absolute workload, however, was higher for no-HTN vs HTN (no-HTN, 82 ± 43W vs HTN, 63 ± 22W $p<0.05$).

Post-exercise testing

Participants returned to the supine position within 27 ± 6 and 26 ± 6 seconds following cessation of exercise for no-HTN and HTN groups, respectively. Post-exercise cognitive testing was initiated at similar times between groups (memory study list, no-HTN, 12.12 ± 1.25 min vs HTN, 11.96 ± 1.10 min; Flanker, no-HTN, 16.14 ± 2.67 min vs HTN, 16.78 ± 4.00 min; 2-back, no-HTN, 17.05 ± 3.26 min vs HTN 16.74 ± 3.4 min; Memory, no-HTN, 24.27 ± 1.23 min vs HTN 23.57 ± 2.34 min; $p>0.05$). The higher variability for post-exercise timing of Flanker and 2-back is related to the randomized, counter-balance design.

Effect of exercise on accuracy and RT

Hand-held clicker malfunctions resulted in lost data for 2 no-HTN individuals on the Flanker task and 1 no-HTN individual on the 2-Back. Thus data are presented for n=28 and 29

for Flanker and 2-Back respectively among no-HTN. No significant group, time, or group-by-time effects were detected for accuracy as measured by hit rates on congruent/incongruent Flanker or 2-back ($p>0.05$; Table 5.3). Post-exercise commission errors on the 2-back were not statistically different compared to pre. A significant time effect was detected for memory hit rate, which significantly increased post-exercise in both groups ($p<0.05$; Table 5.4). This was accompanied by a significant time effect for false alarm rate, which also increased post-exercise ($p<0.05$). Significant time effects were detected for Flanker and Memory hit RT, which decreased post-exercise ($p<0.05$). There was a tendency for hit RT to decrease post-exercise on the 2-back although this did not reach statistical significance ($p=0.06$). No statistical effects for discriminability were detected. No group or group by time interactions were observed, indicating that 1) there were no inherent group differences in cognitive performance and 2) the effect of acute exercise on accuracy and processing speed were similar between HTN and no-HTN individuals.

Effect of exercise on constructs of decision-making

Significant time effects were detected for memory stimulus bias, and 2-back and memory non-decision time, all of which decreased post-exercise compared to pre ($p<0.05$). Similar effects were noted for the Flanker non-decision time post-exercise but this did not reach statistical significance ($p=0.066$). No significant group or group by time interactions were detected for DDM metrics, indicating that 1) there were no underlying group differences in latent processes of decision-making, and 2) the effect of acute exercise on latent processes of decision making were similar between HTN and no-HTN groups.

Discussion

The first aim of this study was to compare the effects of acute exercise on cognitive function in middle-aged adults with and without HTN. Acute exercise did not alter accuracy, but

increased processing speed (decreased RT), on executive function and memory tasks post-exercise in both HTN and no-HTN groups. The second aim of this investigation was to interrogate the effects of exercise on underlying constructs of decision-making (encoding and motor response duration [i.e. non-decision time], strength/quality of stimulus evidence, and response bias) via DDM. Our results indicate that non-decision time significantly decreased post-exercise during executive function and memory tasks, and that a significant change in stimulus bias occurred post-exercise during the memory task. Our data cumulatively suggest that middle-age adults with HTN experience similar beneficial increases in executive function and memory processing speed following acute exercise as their counterparts without HTN, and that post-exercise increases in processing speed are driven by changes outside of the decision-making process.

Hypertension and cognition

HTN is associated with accelerated brain aging [11] and impaired cognitive performance [12,132,139-142]. Surprisingly, we noted no differences in baseline cognitive function between adults with and without HTN in our cohort of middle-aged adults. Indeed, task accuracy and processing speeds (RT) were similar across executive function (Flanker, 2-Back) and memory recognition tasks between groups at baseline. The lack of baseline differences in cognitive function contrasts with previous data, indicating lower executive function and memory performance [142], and slower RT in HTN [301]. These conflicting data may relate to our middle-aged sample of adults with HTN since age independently contributes to cognition among hypertension [302]. As such, middle-aged individuals with HTN may not experience notable differences in cognitive function since the duration the brain is exposed to HTN likely contributes to the degree of dysfunction (or lack thereof) [142]. This suggests that our cohort of middle-aged adults with HTN had similar cognitive health as their counterparts without HTN, and were not exhibiting signs of cognitive dysfunction from accelerated brain aging.

The similar cognitive health between our groups may relate to the use of anti-HTN therapy. Indeed, our cohort of adults with HTN relied on anti-HTN medication to control their blood pressure to within normal levels. This is of importance since well-controlled HTN appears to attenuate differences in cognition [302]. Additionally, our HTN group did not refrain from taking their anti-HTN medication during our study which may have influenced our findings. Whether anti-HTN therapy independently impacts cognition is of debate and may depend on age, drug type, and cognitive assessment strategy [11,179,180]. The American Heart Association and American Stroke association have recommended anti-HTN therapy for adults in mid-life and early old age as an effective means to attenuate late-life dementia [16]. Among older adults (>80 years of age), however, the utility of such therapy is unclear and requires additional scrutiny [16]. Additionally, some drug types (angiotensin II receptor blockers [ARB], angiotensin converting enzyme inhibitors [ACE-I], and calcium-channel blockers [CCB]) and combination therapies appear more effective in combating cognitive decline in HTN than other monotherapy drugs [180]. While the long-term implications of anti-HTN therapy delaying/preventing cognitive disease have received the most attention [11,179,180], it is unclear if *acute* ingestion of anti-HTN medication directly impacts cognitive function. Cognition could improve acutely following drug ingestion if the beneficial effects of anti-HTN therapy on the brain results from the direct blood-pressure lowering, or neuroprotective effects of the drug. Indeed, acute doses of an ARB have been reported to enhance prospective memory in young normotensive adults [303], however this remains to be replicated in a clinically relevant population (i.e. HTN). Ultimately, roughly a fifth (20%) of our adults with HTN were on a combination therapy (i.e. >1 anti-hypertensive drug) and 90% used either an ARB, ACE-I, or CCB, which may have contributed to the similar cognitive health between our HTN and no-HTN groups. Taken together, these data indicate that our sample of medicated, well-controlled, middle-aged adults with HTN had similar baseline cognitive function as their counterparts without HTN, which may have contributed to their similar cognitive responses to acute exercise.

Hypertension, exercise, and cognition

To our knowledge, this is the first study to investigate the acute effects of exercise on cognition in adults with HTN, a population at-risk for cognitive decline. Accuracy on executive function tasks was unaltered by acute exercise in both HTN and no-HTN groups. Indeed, hit rates were not significantly different pre compared to post exercise on either Flanker or 2-Back tasks in our sample. With respect to memory recognition, however, we noted a significant effect of exercise on metrics of task performance. Specifically, we observed significant increases in memory recognition hits and false alarms post-exercise in both HTN and no-HTN individuals. Although the number of correctly identified "studied" words (i.e. hits) increased post-exercise, this is not indicative of improved memory recognition performance or accuracy per se since it was accompanied by an increase in the number of false alarms (incorrect responses where distractor words were classified as "studied"). This seems to suggest that acute exercise altered how individuals categorized memory stimuli and will be discussed further below with insight from DDM.

The null effects of acute exercise on cognitive task accuracy observed herein concurs with previous experimental data [294,304,305]. Meta-analytical investigations suggest there may be a small effect on non-time dependent cognitive task performance (i.e. accuracy) [198], although this is not universal [197]. Improvements in cognitive task accuracy post-exercise may be difficult to observe as many studies rely on tasks vulnerable to ceiling effects (i.e. task difficulty is not sufficient that improvements in cognitive processing or decision-making can alter hit rates). Indeed, this may impact our findings with the Flanker task (hit rate ≈99%), although ceiling effects likely did not impact the effect of exercise on 2-back or memory recognition tasks based on the lower mean hit rates (≈70% and ≈53%, respectively). These data indicate that acute aerobic exercise does not improve accuracy on executive function or memory tasks in middle-aged adults with and without HTN.

While task accuracy did not improve following acute aerobic exercise, we noted faster executive function and memory processing speed post-exercise in both adults with and without HTN. Accelerated processing speed post-exercise manifested as significantly reduced RT for Flanker/memory recognition tasks, with trends for 2-back. This facilitation of RT is in-line with recent literature [294,304,305], as well as meta-analyses of the literature at-large that indicate RT is sensitive to changes with acute exercise [195,198]. Previous findings suggest larger benefits of exercise on RT are seen in children and older adults, with attenuated benefits in young healthy adults [198]. While the effect of acute exercise on cognition is under-investigated among middle-aged adults [198], our observation of accelerated RT post-exercise suggests middle-aged adults exhibit similar facilitation of post-exercise RT as children and older adults. Taken together, these data suggest that middle-aged, adults with medicated HTN experience similar facilitation of cognitive processing speed, manifesting as reduced RT, on executive function and memory tasks following acute exercise as their counterparts without HTN.

Exercise, cognition, and insight from drift-diffusion modeling

Previous studies have provided limited insight into psychological factors underlying exercise-induced changes in cognition. A reason for this may be due to reliance on standard metrics of cognitive performance (task accuracy and processing speed (i.e. RT) [198]. Any change in cognitive function could stem from multiple components of the decision-making process including stimulus classification, stimulus evaluation, response selection, and motor execution [306], all of which, influence RT. Mathematical modeling via DDM is a novel means of dissecting the entire decision-making process contained in the behavioral data into its underlying components of visual encoding, evidence accumulation and decision, and motor response. As such, DDM may offer insight into mechanisms behind changes in cognitive performance (hits and false alarms) and mechanisms of accelerated RT following exercise by quantifying the changes in the decision-making process that elicited the observed responses.

We noted no effect of acute exercise on executive function task accuracy, as assessed by hit rate on the Flanker and 2-back. The ability to correctly identify stimuli in a given task is strongly dependent on the strength of evidence extracted from the stimuli itself [295]. An increase in the strength of evidence extracted from the stimuli would be expected to increase the hit rate and potentially decrease RT (since it would take less time to make a decision when interpreting stronger evidence). Seeing as Flanker and 2-Back hit rates were unaltered by exercise, it is not surprising that the strength of evidence (drift rate) did not significantly change post-exercise for either executive function task.

We did, however, observe increases in hit and false alarm rates during the memory recognition task post-exercise. This change in hit and false alarm rates suggests a change in how evidence was extracted from the stimuli (quantified as drift rate by DDM). Indeed, DDM revealed that drift rates for both old/studied and new/distractor words tended to increase post-exercise, although this was not statistically significant. According to the model, more positive drift rate values indicate stronger perceived evidence for stimuli to be an “old/studied” word. In the case of new/distractor word, more positive (i.e. less negative) drift rates indicate weaker perceived evidence as a new/distractor word and thus, stronger evidence for being an old/studied stimuli. The drift rates of old/studied and new/distractor words were summed to create an index of stimulus evaluation bias, which significantly increased post-exercise. An increase in stimulus evaluation bias (and thus, a more positive value) suggests all items seemed to provide more evidence as old/studied even when they were new/distractor stimuli. A change in stimulus evaluation bias signifies a shift in how the stimulus is processed and what evidence is extracted from the stimuli under consideration [244]. This differs from response expectancy bias which alters the amount of evidence required for a given response and would manifest as faster and more probable responses for one response over another [244]. Whether

the post-exercise changes in stimulus evaluation bias are a direct result of exercise or the experimental design itself is unclear and requires further scrutiny.

The significant reductions in post-exercise executive function (Flanker, trend for 2-Back) and memory RT could stem from changes in encoding, the decision process itself, and motor execution. For the first time, DDM was able to provide insight into the components of RT that are altered by acute exercise. Indeed, we noted significant reductions in non-decision time during the 2-Back and memory recognition tasks, with trends for reductions during the Flanker task. As such, DDM proposes that the reductions in executive function and memory recognition RT observed herein were likely related to significant reductions in non-decision time (the sum of encoding and motor response phases that occur immediately prior to, and directly following, the actual decision making process). Previously, it was unclear if changes in RT post-exercise stemmed from alterations in stimulus evaluation (encoding), response selection (decision), or motor execution [305]. Our finding is corroborated by electroencephalographic data that suggest P3 latency (a neuroelectric proxy of stimulus evaluation duration, likely analogous to the decision component of DDM) may not be altered by exercise [307] although this is not universal [308]. This may indicate that improved executive function and memory processing speed post-exercise is largely independent from changes in the decision-making process itself (evidence strength, caution, bias) and is isolated to the encoding and motor response.

While we are unable to directly comment on whether exercise increases cognitive processing speed via accelerated visual encoding, motor response, or a combination of both, there is evidence that each may be altered post-exercise. Limited data suggest there are minor changes in the time required for a motor response post-exercise (approximately 10 ms faster immediately post-exercise) [309]. Even a relatively small reduction in motor response time (i.e. 10 ms) may account for 25%-40% of the mean change in non-decision time (-Δ40-25ms) documented herein for memory and executive function domains respectively. This suggests that

the remaining reductions may stem from accelerated encoding during post-exercise memory recognition and executive function tasks. Residual effects of exercise on sensory cortex excitability [310] may reduce the time required for visual encoding of cognitive stimuli, thereby reducing non-decision time. Alternatively, reductions in non-decision time may be isolated to the motor response component since exercise does not alter the N1 component derived from EEG (potentially reflective of initial sensory extraction from stimulus) [307]. Additional contributors to post-exercise facilitation of non-decision time may include acute elevation of brain-derived neurotrophic factor and acute catecholamine/endorphin-mediated increases in arousal [311,312]. Ultimately, the mechanisms behind the contributions of visual encoding and motor response to post-exercise changes in non-decision time, and in turn to RT, require further research and the use of additional experimental measures.

Implications

Aerobic exercise is recommended as an important lifestyle strategy to attenuate cognitive decline in HTN. To date, however, there is a paucity of data on the effects of aerobic exercise on cognition in HTN. In fact, recent reviews on exercise and cognitive function in human HTN rely primarily on rodent-model research [231]. We examined the effects of acute aerobic exercise on cognitive function and components of decision-making in middle-aged adults with and without HTN, an understudied age group that is ideal for preventive research. We observed similar improvements in executive function and memory processing speeds following acute exercise in no-HTN and HTN groups. Our data cautiously suggest that the brain's ability to respond to an aerobic exercise stimulus and improve processing speed is undisturbed by the presence of HTN, at least in our sample of middle-aged adults with well-controlled HTN. This may provide insight into the brain's ability to reap the touted benefits of chronic exercise and suggest that adults with well-controlled HTN may respond similarly to an exercise training program, however this is speculative at this time. Limited data currently

indicates no beneficial effect of exercise training on cognition in middle-aged adults with untreated HTN [313], older adults with resistant HTN [233], and adults with HTN and co-morbid diabetes mellitus [234]. Whether exercise training results in beneficial changes in cognition among a healthier or well-controlled group of adults with HTN (as studied herein) remains unknown and requires further scrutiny.

Limitations

Our study is the first to examine the effects of acute submaximal exercise, at a dose typically recommended for adults with HTN, on cognitive function and underlying components of decision-making in adults with controlled HTN and well-matched adults without HTN. We purposefully selected controlled-HTN since this is the "free-living" state in which adults with HTN would typically engage in exercise as a lifestyle strategy to improve cognitive health and brain aging. As such, acute cognitive responses to exercise may differ in adults with untreated HTN. Whether responses are different among a group of older adults with HTN is additionally unclear and requires further research. We purposefully chose to interrogate the effect of exercise on cognition from minutes 10-30 post-exercise since we wished to identify if individuals with HTN experienced the same benefits of exercise on cognition as those without HTN and meta-analyses indicate this time period is sensitive to the acute effects of exercise [20]. It is possible that further or differential changes in cognition could occur in these groups during prolonged recovery (i.e. >30 min) from a single bout of exercise.

Conclusions

We sought to investigate the effects of exercise on cognitive function in middle-aged adults with and without HTN, and examine the effect of exercise on underlying processes of decision-making (via DDM). Both individuals with and without HTN had similar cognitive responses following a single exercise bout of a recommended dose/intensity. While acute

exercise did not alter task accuracy, there were significant reductions in post-exercise RT for both executive function and memory domains in both groups. DDM revealed that changes in RT may largely stem from significant reductions in non-decision time which encompasses the early (visual encoding) and late (motor response) portions of the decision-making process.

Table 5.1: Diffusion modeling outcome parameters.

Variable	Description	Interpretation	Tasks
Caution	Metric of speed/ accuracy trade-off	Higher value indicates more cautious (i.e. accuracy over speed), represented as greater distance between criterion boundaries in the latent decision-making processes.	Flanker 2-Back Memory
Non-decision time	(Encoding + motor execution)	Higher value represents slower encoding/motor processing.	Flanker 2-Back Memory
Drift rate	Metric for strength of evidence accumulation for a given response. Calculated for old/new words (memory) and match/non-match (2-Back)	Positive values represent evidence to reject new word/non-match. Greater value indicates stronger evidence. Negative values represent evidence to reject new word/non-match. More negative value indicates stronger evidence. Greater absolute value indicates stronger evidence.	2-Back Memory
Stimulus bias	Memory = (Drift old + drift new) 2-Back = (Drift match + drift non-match)	Value <0 indicates strict criterion for recognizing correct response (i.e. unless very sure, they do not endorse it as a "studied" word/match). Value >0 indicates lenient criterion for recognizing correct response (i.e. endorse "studied" words or matches with less evidence).	2-Back Memory
Response bias	(Stimulus bias / caution)	Value <0.5 indicates bias for "new/non-match." Value >0.5 indicates bias for "old/match."	2-Back Memory
Discriminability	Memory = (Drift new - drift old) 2-Back = (Drift match - drift non-match)	Higher value represents better ability to discriminate between correct (old words/matches) vs incorrect (new words/non-matches) (i.e. better task performance).	2-Back Memory
Perceptual strength	Strength of evidence from displayed arrows	More negative values represent better perceptual ability. Comparable to drift rate from 2-Back, memory tasks.	Flanker
Attention interference	(Attention/selective attention) Metric of selective attention capacity	Indicates duration required to narrow attention completely. Lower values indicative of better selective attention.	Flanker

Table 5.2: Descriptive characteristics for no-HTN and HTN groups (mean ± SD unless otherwise noted).

	No-HTN	**HTN**	p-value
Sex (male/female)	16/14	16/14	-
Age (yrs)	56 ± 6	56 ± 6	0.93
Anthropometrics			
Height (cm)	169.8 ± 11.3	171.3 ± 9.6	0.57
Weight (kg)	82.0 ± 13.3	82.4 ± 12.5	0.91
Body fat (%)	32.2 ± 8.4	31.4 ± 6.9	0.69
Body mass index (kg/m^2)	28.3 ± 2.6	28.0 ± 3.3	0.71
Medications, %(n)			
Statin	6.7 (2)	40.0 (12)	**0.005**
Birth control	3.3 (1)	0.0 (0)	-
Hormone replacement therapy	3.3 (1)	3.3 (1)	-
Hypothyroid	3.3 (1)	3.3 (1)	-
ACE inhibitor	-	43.3 (13)	-
ARB	-	33.3 (10)	-
Diuretic	-	20 (6)	-
β-Blocker	-	13.3 (4)	-
CCB	-	13.3 (4)	-
Lipid profile			
Hemoglobin (g/dL)	14.2 ± 0.9	13.8 ± 1.3	0.12
Total cholesterol (mg/dL)	202 ± 39	192 ± 36	0.28
HDL (mg/dL)	58 ± 17	56 ± 20	0.56
Triglycerides (mg/dL)	103 ± 61	116 ± 56	0.28
LDL (mg/dL)	128 ± 41	114 ± 30	0.17
Non-HDL (mg/dL)	144 ± 44	136 ± 32	0.43
Total cholesterol:HDL	4 ± 2	4 ± 1	0.89
Glucose (mg/dL)	94 ± 9	102 ± 16	**0.03**
Questionnaires			
CESD	6 ± 5	7 ± 4	0.71
Fitness			
VO_2max (mL/kg/min)	32.4 ± 8.8	27.2 ± 5.6	**0.008**

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CESD, Center for Epidemiologic Studies Depression questionnaire; VO_2max, maximal oxygen consumption.

Table 5.3: Executive function parameters pre and post-exercise in HTN and No-HTN individuals (mean ± SD).

		No-HTN		HTN				
Task	**Parameter**	**Pre**	**Post**	**Pre**	**Post**	Group	Time	GxT
Flanker								
	Hits, congruent (%)	99.9 ± 0.3	99.8 ± 0.7	99.9 ± 0.6	99.8 ± 0.6	0.93	0.58	0.94
	Hit RT, congruent (ms)	513 ± 76	493 ± 66	510 ± 64	478 ± 63	0.63	**0.01**	0.15
	Hits, incongruent (%)	97.8 ± 3.0	98.0 ± 2.5	96.8 ± 4.5	95.5 ± 4.9	0.54	0.80	0.83
	Hit RT, incongruent (ms)	606 ± 87	578 ± 82	590 ± 68	562 ± 72	0.46	**0.01**	0.89
DDM	Caution	0.22 ± 0.14	0.21 ± 0.12	0.24 ± 0.24	0.24 ± 0.20	0.77	0.97	0.80
	Non-decision time (ms)	309 ± 121	296 ± 117	320 ± 83	273 ± 112	0.81	0.07	0.28
	Attention interference (ms)	190 ± 171	152 ± 103	198 ±176	158 ± 108	0.55	0.26	0.78
	Perceptual strength	0.53 ± 0.19	0.55 ± 0.17	0.58 ± 0.19	0.59 ± 0.18	0.26	0.35	0.69
2-Back	Hits (%)	67.0 ± 22.2	67.2 ± 21.5	73.5 ± 15.6	74.1 ± 17.0	0.26	0.96	0.69
	Commission errors (%)	6.4 ± 4.9	5.6 ± 5.2	7.3 ± 6.6	6.2 ± 5.5	0.67	0.07	0.98
	Discriminability	0.61 ± 0.22	0.62 ± 0.20	0.66 ± 0.15	0.679 ± 0.168	0.16	0.56	0.86
	Hit RT (ms)	666 ± 106	651 ± 94	633 ± 89	613 ± 88	0.13	0.06	0.83
DDM	Caution	0.14 ± 0.02	0.15 ± 0.02	0.15 ± 0.02	0.14 ± 0.02	0.44	0.28	0.06
	Non-decision time (ms)	402 ± 108	370 ± 95	353 ± 94	344 ± 91	0.11	**0.048**	0.27
	Response bias	0.39 ± 0.11	0.39 ± 0.12	0.40 ± 0.11	0.39 ± 0.10	0.66	0.53	0.52
	Drift rate-match	0.16 ± 0.03	0.17 ± 0.04	0.17 ± 0.04	0.17 ± 0.03	0.23	0.84	0.94
	Drift rate-non-match	-0.13 ± 0.04	-0.13 ± 0.03	-0.13 ± 0.04	-0.14 ± 0.03	0.65	0.36	0.61
	Drift rate-discriminability	0.29 ± 0.06	0.30 ± 0.04	0.31 ± 0.05	0.31 ± 0.03	0.20	0.43	0.90
	Stimulus bias	0.03 ± 0.05	0.03 ± 0.06	0.04 ± 0.60	0.03 ± 0.04	0.70	0.62	0.56

HTN, Hypertension; DDM, Drift-diffusion modeling; GxT, Group-by-time interaction; RT, reaction time.

Table 5.4: Memory recognition parameters pre and post-exercise in HTN and Non-HTN individuals (mean ± SD).

		No-HTN		HTN				
Task	**Parameter**	**Pre**	**Post**	**Pre**	**Post**	Group	Time	GxT
Memory	Hits, studied (%)	51.8 ± 21.0	57.7 ± 20.2	53.5 ± 17.7	57.8 ± 20.7	0.71	**0.02**	0.85
	False alarms (%)	22.6 ± 17.7	27.2 ± 19.9	24.6 ± 17.7	30.2 ± 20.9	0.64	**0.01**	0.88
	Discriminability	0.29 ± 0.18	0.30 ± 0.14	0.29 ± 0.16	0.28 ± 0.19	0.68	0.98	0.55
	Hit RT (ms)	941 ± 181	897 ± 148	894 ± 149	853 ± 145	0.24	**0.02**	0.91
DDM	Caution	0.14 ± 0.02	0.13 ± 0.03	0.12 ± 0.02	0.13 ± 0.02	0.27	0.74	0.07
	Non-decision time (ms)	579 ± 126	531 ± 104	564 ± 101	532 ± 136	0.79	**0.01**	0.53
	Response bias	0.06 ± 0.02	0.07 ± 0.02	0.06 ± 0.01	0.06 ± 0.02	0.45	0.93	0.68
	Drift rate-studied	0.01 ± 0.07	0.04 ± 0.07	0.02 ± 0.06	0.02 ± 0.11	0.95	0.12	0.26
	Drift rate-distractor	-0.11 ± 0.08	-0.09 ± 0.07	-0.10 ± 0.09	-0.08 ± 0.10	0.75	0.11	0.87
	Drift rate-discriminability	0.11 ± 0.08	0.12 ± 0.06	0.11 ± 0.07	0.10 ± 0.07	0.66	0.94	0.24
	Stimulus bias	-0.10 ± 0.12	-0.05 ± 0.12	-0.08 ± 0.133	0.04 ± 0.14	0.44	**0.02**	0.76

HTN, Hypertension; DDM, Drift-diffusion modeling; GxT, Group-by-time interaction; RT, reaction time.

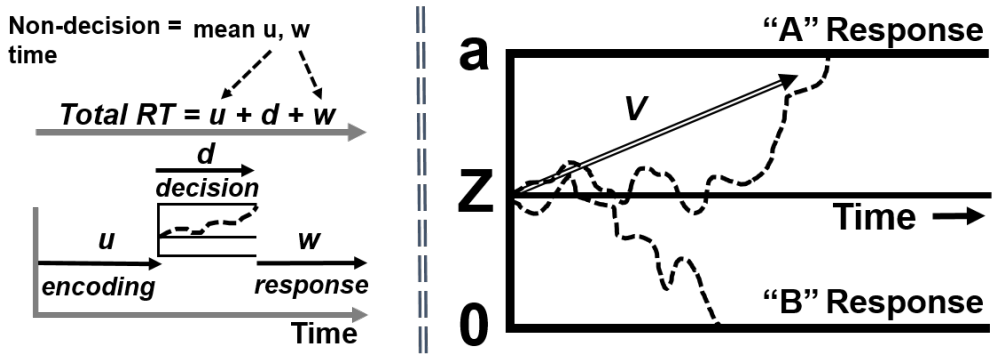

Figure 5.1: Components of the drift diffusion model for a 2-choice decision task. Noisy evidence (dotted line) accumulates over time from the starting point, z, to one of the two boundaries, a or 0. The total response time includes the decision time plus the time taken for non-decision processes like visual encoding and motor response.

Chapter VI: Summary and Exploratory Aim 3

Contrary to our hypotheses, findings from aim 1 and 2 largely indicated our cohort of middle-aged adults with controlled-HTN had similar vascular and cognitive responses to acute exercise as their counterparts without HTN. This contrasts with previous literature and likely stems from the generally healthy nature of our middle-aged adults with well-controlled HTN. Based on our findings from aim 1 and 2 we pursed an exploratory aim 3 that sought to explore if the vascular contributions to cognitive function differed in our cohort of middle-aged adults with HTN to those without HTN.

The vasculature has been recognized as a major contributor to cognitive function, cognitive decline, and dementia [16,314]. The brain is dependent on continuous blood flow that must react acutely to changes in metabolic demand stemming from neural activity. Neuronal activity increases metabolic demand and must be supported by compensatory increases in blood flow to support the active neural circuitry. This process is known as neurovascular coupling (NVC) [315,316]. Optimal NVC determines cognitive performance [179,317] and is a factor in cognitive impairment and dementia [314].

Our lab has previously examined NVC in healthy young/middle-aged adults [261], and in older adults [263]. Our previous findings indicate older adults experience increases in extracranial large artery (i.e. carotid, aorta) stiffness and intracranial pulsatility during cognitive activity, acutely influencing NVC and reducing cognitive performance [263]. Conversely, our observations in younger/middle-age adults indicate they are able to effectively buffer pulsatile hemodynamics by reducing extracranial pulsatility at the level of the carotid artery, leaving intracranial pulsatility unaltered [261]. By including measures of extra-cranial large artery stiffness and hemodynamic pulsatility we can gain further insight into contributors to NVC. Despite the similar resting vascular and cognitive function observed in Aims 1 and 2, it is

possible that examining vascular contributions to cognition *during* cognitive activity (i.e. NVC) will reveal differences not seen at rest or following an exercise bout. As such, it is possible adults with HTN may mimic responses seen in older adults, characterized by excessive transmission of pulsatile cerebrovascular hemodynamics and NVC disruption during cognitive activity.

Exploratory Aim 3: Examine vascular contributions to cognitive function by comparing vascular hemodynamic responses during cognitive activity (i.e. NVC) in middle-aged adults with, and without, HTN.

Hypothesis 3: Adults with HTN will exhibit different vascular responses during cognitive activity. Specifically that compared to adults without HTN, adults with HTN will exhibit impaired NVC, manifesting as insufficient changes in cerebral oxygenation accompanied by disproportionate increases in arterial stiffness and hemodynamic pulsatility.

Innovation

Our lab utilizes an innovative means of assessing the vascular contributions to cognitive engagement described by NVC. We project a computerized-cognitive task horizontally *over the participant* (Figure 6.1). Participants lie supine and perform cognitive tasks while *simultaneous* measures of arterial stiffness and cerebral perfusion (Transcranial Doppler [TCD] and prefrontal cortex (Pfc) tissue oxygenation using functional near-infrared spectroscopy

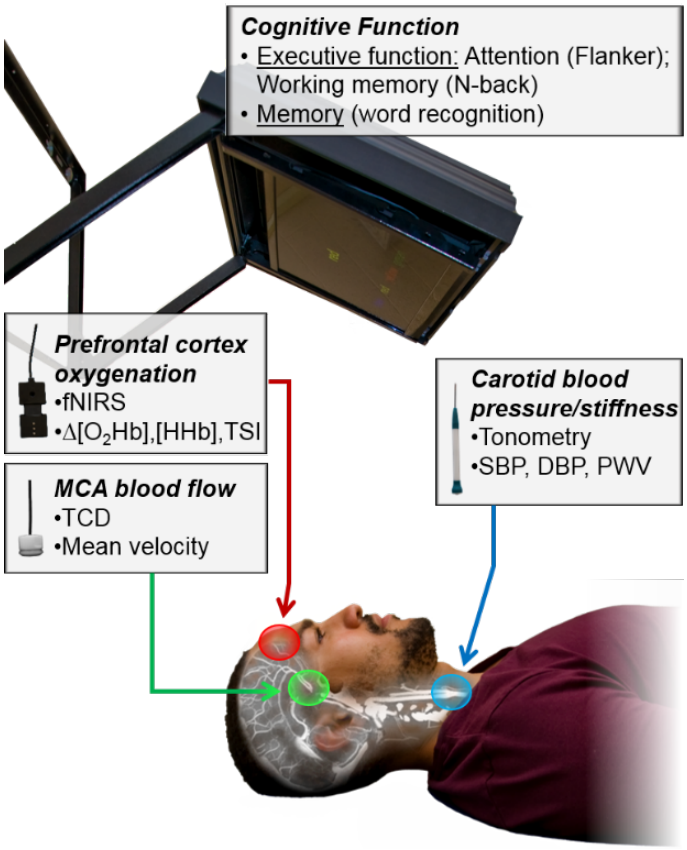

Figure 6.1: *Concurrent vascular & cognitive assessment*

[fNIRS]) are obtained. We will use a cognitive task specific to executive function, a domain mediated by the Pfc, which appear particularly sensitive to HTN-mediated dysfunction [12,318,319]. We can then correlate functional and spatial changes in arterial stiffness and cerebral/Pfc hemodynamics with cognitive performance at the time of measurement. Thus we are targeting cerebral hemodynamics in a susceptible region of the brain relevant to HTN while concurrently activating that region using domain-specific tasks.

Chapter VII: Neurovascular Coupling during Cognitive Activity in Adults With and Without Hypertension

Abstract

Hypertension accelerates vascular aging, which may impair the ability of the cerebrovasculature to increase blood flow to support neural activity (neurovascular coupling [NVC]). Optimal NVC depends on continuous, non-pulsatile flow, which is partially determined by extra- and intra-cranial vessel function. We sought to compare extra- and intra-cranial hemodynamics during cognitive activity (Stroop task) in 30 middle-aged adults with, well-controlled medicated hypertension and 30 age-, sex-, and body mass index (BMI)-matched adults without hypertension (56±6 yrs, BMI 28.2±2.9 kg/m^2; 32 men). Aortic and carotid (single-point) pulse wave velocity (PWV) were assessed via tonometry and ultrasound respectively. Carotid and middle cerebral artery (MCA) blood velocity pulsatility were measured via ultrasound and Doppler. Prefrontal cortex oxy- and deoxy-hemoglobin, and tissue saturation index (TSI) were measured using near-infrared spectroscopy. Accuracy and reaction times were computed to assess cognitive performance. Stroop performance was similar between groups ($p>0.05$). Aortic and carotid PWV increased, carotid pulsatility decreased ($p<0.05$), and MCA pulsatility was unaltered during the Stroop in both groups. Groups achieved similar cortical TSI during Stroop, although hypertensives did so with greater increases in oxyhemoglobin ($p<0.05$). Reduced CCA pulsatility during the Stroop was associated with increased cortical TSI in the combined sample. Our findings suggest that intra- and extra-cranial cerebrovascular reactivity in middle-age adults with medically-controlled hypertension is largely similar to adults without hypertension. Additionally, reductions in extracranial pulsatility during NVC may minimize intracranial pulsatility and enhance downstream cerebral oxygenation in adults with and without hypertension. Our data suggest extracranial hemodynamics may play an important role in optimizing intracranial NVC.

Introduction

Hypertension (HTN) and its neurocognitive consequences potentiate the development of cognitive dysfunction [12] and disease [11]. The link between HTN and cognitive dysfunction may reflect accelerated vascular aging [11] and underlying changes in cerebrovascular structure/function that disrupt cerebral blood flow regulation. Cerebral blood flow is tightly regulated to 1) prevent pressure-mediated hyper- or hypo-perfusion episodes and 2) ensure blood flow reacts appropriately to changes in metabolic demand (assessed as cerebrovascular reactivity) [320]. Cerebrovascular reactivity to carbon dioxide (CO_2) and exogenous vasodilators may be attenuated in adults with HTN compared to without [105,106,321,322]. Of particular concern for HTN, cerebrovascular reactivity is associated with stroke and white-matter hyperintensities [323], lower cognitive function [321], and may precede cognitive dysfunction [316].

The vast majority of investigations into cerebrovascular reactivity in HTN have relied on measuring cerebrovascular responses to changes in CO_2 [105,106,321,324]. The processes governing cerebrovascular reactivity to CO_2, however, likely differs from those dictating cerebrovascular responses during cognitive engagement known as neurovascular coupling (NVC) [320]. The brain is an obligate high-flow target organ that is dependent on acute changes in blood flow to meet metabolic demands. NVC describes the compensatory increases in regional blood flow and oxygen delivery required to support metabolic need during neuronal activation [315,316]. NVC is a significant determinant of cognitive performance [179] and key contributor to cognitive impairment and dementia [314]. Despite extensive insight into molecular factors that contribute to NVC from *in vivo* animal studies, knowledge of contributors to optimal NVC in humans is limited and underexplored [320,325].

Increases in intracranial blood flow necessary for optimal NVC may partially depend on extracranial vessels. Large extracranial vessels are active regulators of intracranial blood flow,

accounting for nearly 25-50% of total cerebrovascular resistance [320]. As such, extracranial changes in diameter may contribute to intracranial flow by modulating blood pressure, a key component of NVC [326]. Moreover, increases in intracranial flow may result in a conducted vasodilation of extracranial feed arteries stemming from regional changes in transluminal pressure and shear stress [327]. Thus, changes in extracranial shear, diameter, and flow may provide greater insight into intracranial NVC.

Optimal NVC is dependent not only on increases in mean blood flow to maintain a steady supply of oxygen, but also on the manner in which that blood flow is delivered. Tissue perfusion at the capillary level relies on continuous blood flow for optimal oxygen extraction, whereas pulsatile blood flow can cause epochs of hypo-perfusion and alter red blood cell transit time, resulting in reduced oxygen extraction, ischemia and microvascular damage, [9,328]. The dampening of hemodynamic pulsatility in the cerebral microvasculature is highly dependent on large extracranial artery elastic function (i.e aorta, carotid) [9]. Acute changes in extracranial vessel stiffness transmits pulsatile hemodynamic energy into downstream vascular beds, possibly influencing NVC and cognitive function [263]. Indeed, during cognitive engagement, older adults experience increases in extracranial large artery stiffness and intracranial pulsatility, acutely impacting NVC and reducing cognitive performance [263]. Conversely, normotensive younger/middle-age adults are able to effectively buffer pulsatile hemodynamics with reductions in extracranial pulsatility and unaltered intracranial pulsatility [261]. As such, incorporating measures of extracranial large artery stiffness and intracranial hemodynamic pulsatility may provide additional insight into contributors to NVC.

Considering HTN is associated with accelerated vascular aging [329], adults with HTN may mimic responses seen in older adults, characterized by pulsatile hemodynamics disrupting NVC. Thus, the first aim of this study was to compare extra- and intra-cranial vascular-hemodynamic reactivity during cognitive activity in middle-aged adults with and without HTN. The second aim was to examine the relationships between extracranial changes in stiffness,

transmission of pulsatile hemodynamics, and cortical oxygenation during cognitive activity in this sample. It was hypothesized that adults with HTN would exhibit different vascular reactivity during cognitive activity versus those without HTN, manifesting as exaggerated increases in extracranial vessel stiffness and hemodynamic pulsatility during cognitive activity compared to their counterparts without HTN. We additionally hypothesized that excessive hemodynamic pulsatility during cognitive activity would be associated with reduced cortical oxygenation and thus impaired NVC.

Methodology

Participants

Thirty middle-aged adults with HTN (56 ± 6 yrs; 16 men) and 30 age-, sex-, and body mass index (BMI)-matched adults without HTN (no-HTN; 56 ± 6 yrs; 16 men) were recruited for this cross-sectional study. Participants were excluded if they reported smoking, stroke, dementia, diabetes mellitus, severe obesity (BMI ≥35 kg/m^2), depression, previous cardiovascular events, pulmonary/renal/neurological disease, or recent head trauma (concussion). Additionally, participants were screened for dementia (Montreal Cognitive assessment score ≤21) and depression (assessed using the Center for Epidemiologic Studies Depression questionnaire). Overweight/obese (BMI 25-35 kg/m^2) and hyperlipidemic individuals were *included* in the sample since these risk factors are highly prevalent within middle-aged adults (regardless of HTN status). Menopausal status (pre-, peri-, post-menopausal) was documented according to STRAW+10 guidelines [267]. This study was approved by the Syracuse University Institutional Review Board and conformed to the standards outlined in the Declaration of Helsinki. All participants provided written informed consent prior to study initiation.

Participants with HTN had been previously diagnosed by a physician *and* were undergoing anti-HTN therapy based on the previous HTN management guidelines [37]. Participants did not abstain from their anti-HTN medication during testing because 1) of concern of rebound HTN, and 2) the medicated state is the "natural state" in which nearly three-quarters of individuals with HTN live.

Study design

Testing was conducted over 3 separate visits: 1) health screening, followed by 7 days of at-home blood pressure measurement and physical activity monitoring, 2) a familiarization visit, and 3) NVC assessment (vascular measures during cognitive engagement).

Health screening

An electronic scale and stadiometer were used to assess height and weight for BMI calculations. Body fat was estimated via air displacement plethysmography (Bod Pod, Cosmed, Concord CA). Fasting plasma glucose and serum lipoproteins (total cholesterol, triglycerides, low- and high-density lipoproteins) were assessed using a validated point-of-care device via finger stick (Cholestech, Alere Medical) following an overnight fast (12-hr) and abstinence from alcohol, caffeine, and exercise. Participants filled out the Pittsburgh Sleep Quality Index, Montreal Cognitive Assessment, and Centers for Epidemiologic Studies Depression questionnaire to assess subjective sleep quality, dementia, and depressive symptomology, respectively.

At-home measures

Blood pressure status was confirmed via 7 days of at-home blood pressure measurement, as recommended by the American Heart Association [268], using an oscillometric blood pressure device (BP786N, Omron Healthcare Inc., Lakeforest, IL).

Participants were asked to take duplicate measures of blood pressure twice per day (morning and evening). Participants not on anti-HTN therapy were excluded if they exhibited an average 7-day blood pressure suggestive of undiagnosed HTN (systolic pressure (SP) ≥135 mmHg and diastolic pressure (DP) ≥85 mmHg) [268].

Physical activity was assessed using a tri-axial accelerometer (activPAL3^{tm}micro, PAL Technologies Ltd, Glasgow, Scotland) secured to the middle of the thigh over a 7-day period. Measures of physical activity included average steps and min of moderate-to-vigorous physical activity (MVPA; number of min with ≥100 steps/min [330]) from 6 full-days of data.

Familiarization

All participants were familiarized with all vascular/cerebral measures and the cognitive task to be used in the NVC protocol. Participants were familiarized with the cognitive task to account for learning effects. Familiarization included point-by-point written and verbal instructions for the task followed by a complete practice session. If participants did not adequately understand the task they were permitted to repeat the task until they were comfortable with the goals of the task.

Neurovascular coupling protocol

Participants were instructed to arrive following a >4-hour fast, and abstinence from non-essential medication (i.e. NSAIDS, nutritional/dietary supplements, allergy medication), alcohol, caffeine, and exercise the day of the NVC assessment. The NVC protocol was standardized to the morning for all participants. NVC was assessed during the early follicular phase for pre- (n=2) and peri-menopausal (n=6) participants. The NVC visit was not standardized for amenorrheic (no menses for >3 months; n=3) or post-menopausal participants (n=17).

The hemodynamic response to cognitive activity (i.e. NVC) was measured as the change in cerebrovascular hemodynamics from rest to each 3-min task. Participants underwent cerebrovascular measures at rest, and during each iteration of the cognitive task (Stroop). NVC testing occurred following 15 min of supine rest. All testing was conducted in the supine position. Cerebrovascular measures included 1) blood pressure; 2) extracranial hemodynamics (common carotid artery [CCA]); and 3) intracranial hemodynamics (middle cerebral artery [MCA] and pre-frontal cortex [PFC] oxygenation). PFC oxygenation was measured continuously, while remaining cerebrovascular measures were initiated after the first 30-seconds of each task to allow adequate time for the hemodynamic lag that follows neural activation.

Cognitive task

Cerebrovascular NVC was assessed during two computerized 3-min modified Stroop color-word tasks (congruent and incongruent tasks, presented in a randomized-counterbalanced order; E-Prime, Psychology Software Tools Inc., Sharpsburg, PA) that participants completed using a hand-held response clicker. The Stroop task interrogates the executive function domain of cognition, which has implications for later-life cognitive function and is affected by HTN [12]. Additionally, the Stroop task has been shown to elicit significant cerebrovascular hemodynamic responses in the PFC [331] and MCA [261,263].

This experimental manipulation and cognitive perturbation has been described in detail previously by our lab [261,263]. In brief, the tasks were displayed above the supine participant using a wall-mounted flat screen television. A target word was displayed in congruous (i.e. the word “red” written in red) or incongruous colors (i.e the word “blue” written in the color red). Participants selected one of the four response items (presented below the target word in similar color scheme [congruous/incongruous] as the target word) that described the color of the target word as quickly and as accurately as possible. Participant’s accuracy was titrated by manipulating the intertrial timing intervals in order to produce similar hemodynamic responses.

The intertrial interval would decrease by 300 ms for every 3 consecutive trials answered correctly and vice versa for incorrect responses (minimum and maximum interval of 400 and 5,000 ms, respectively). If the participant did not respond in time, a large “TOO LATE!” prompt was displayed before the next trial began. Accuracy (hits/[hits+incorrect]) and mean hit reaction times (RT) were recorded for analysis.

Cerebrovascular Measures:

Blood pressure

Brachial SP and DP were taken in duplicate and subsequently averaged using an oscillometric device on the non-dominant arm (BP786N, Omron Healthcare Inc., Lakeforest, IL). If baseline values differed by >5 mmHg, a third measure was obtained and the average of the two closest measures was used for analyses. Carotid pressure waveforms were measured over a 10-s epoch via applanation tonometry (AtCor Medical, Sydney, Australia), ensemble averaged to a single waveform, calibrated to brachial mean pressure (MP) and DP, and used to derive carotid SP. MP and pulse pressure (PP) were calculated as 1/3 SP + 2/3 DP and SP – DP, respectively. Augmentation index (AIx) was derived from central pressure waveforms as the difference between the early (P1) and late (P2) systolic peaks of the pressure waveform to the total PP expressed as a percentage ([P2 − P1]/PP × 100) and standardized to a heart rate of 75 b/min (AIx75).

Extracranial Hemodynamics

Aortic stiffness was measured using “gold standard” carotid-femoral (cf) pulse wave velocity (PWV). Applanation tonometry (described for carotid blood pressure) was used to capture pressure waveforms from the carotid and the femoral artery over a 10-s epoch along with ECG for simultaneous R-wave gating. PWV was calculated using the time delay between the carotid/femoral waveforms and the transit distance between the carotid and femoral arteries.

The time delay was calculated as the time from peak R-wave from simultaneous ECG gating to the foot of the corresponding pressure waveform. The distance between the carotid-femoral pulse sites was measured in mm using a tape measure and adjusted for the bi-directional nature of pressure propagation via subtracting the suprasternal notch – carotid distance from the suprasternal notch – femoral distance.

The left CCA was imaged below the carotid bulb using ultrasound (ProSound α7, Aloka, Tokyo, Japan) and a 7.5-10.0 MHz linear-array probe simultaneously with carotid tonometry performed on the contralateral side. CCA diameters were measured from inside the near-wall intima-media to far-wall intima-media across a 5 mm region of interest via semi-automated digital calipers during systole and diastole (indicated by the T-wave and R-wave from simultaneous ECG gating, respectively). Mean diameter was calculated as (1/3 systolic diameter + 2/3 diastolic diameter). Mean blood velocity (Vm) was measured using Doppler-ultrasound with an insonation angle $\leq 60°$ for all measures and sample volume manually adjusted to encompass the entire vessel. CCA Vm was calculated from an average of 6 ± 1 consecutive waves as: $Vm = \int V(t)\, dt/FT$, where $\int V(t)\, dt$ is the velocity-time integral of the velocity waveform and FT is flow time. CCA pulsatility index (PI) was derived via semi-automated flow tracing software and the following equation: $(Vs\text{-}Vd)/Vm$, where Vs is peak systolic velocity and Vd diastolic velocity. Mean blood flow was calculated as π x (1/3 systolic radius + 2/3 diastolic radius)^2 x Vm x 60. Systolic, diastolic, and mean shear rates were calculated as 4 x velocity/diameter using their respective velocities and diameters. Pulsatile shear rate was calculated in the same manner as blood velocity PI. All images were stored for later offline analysis by a single investigator.

Carotid stiffness was measured using eTracking software that continuously traced the distance from the near wall to far wall lumen-intima interface, creating a distension waveform analogous to pressure waveforms [272]. Distension waveforms were calibrated against CCA

systolic and diastolic pressures estimated via tonometry (described above). Carotid stiffness was calculated using a regional single-point PWV as PWV = $\sqrt{\beta\ x\ P_{Min}/2\rho}$, where β = $\ln(P_{Max}/P_{Min})/[(D_{Max} - D_{Min})/D_{Min}]$ where P and D correspond to pressure and diameter respectively, and Max and Min refer to maximum (systolic) and minimum (diastolic) values during the cardiac cycle.

Wave intensity analysis (WIA) was combined with eTracking to assess novel measures related to genesis of extracranial pulsatile hemodynamics that may influence intracranial NVC. Flow waveforms were measured using range gated color Doppler signals averaged along the Doppler beam. Wave intensity was calculated using time derivatives of blood pressure (P) and velocity (U), where wave intensity = (dP/dt x dU/dt); the area under the dP/dt x dU/dt curve represents the energy transfer of the wave. W_1 is a forward-traveling compression wave produced by the left ventricle during early systole that increases pressure and accelerates flow as it travels downstream. Forward traveling energy waves in the CCA would be expected to increase hemodynamic pulsatility. The negative area (NA) occurring immediately following W_1 is a backward-travelling compression wave caused by downstream wave reflections that increases pressure but decelerates flow. Wave reflections measured in the CCA are of cerebral origin, and as such, NA has been proposed as a measure of cerebrovascular tone [274]. The reflection index (RIx) was calculated as wave reflection intensity relative to forward wave intensity (NA/W_1) and provides insight into pulsatile energy transmission into intracranial circulation. W_2 is a forward travelling expansion wave generated by the cessation of left ventricle contraction and initial untwist and relaxation. This suction wave creates a “braking” force, decreasing pressure while concomitantly decelerating the column of blood from behind [285,332,333] that could alter extracranial (i.e. CCA) pulsatility.

Middle Cerebral Artery Hemodynamics

MCA hemodynamics were measured via Transcranial Doppler (TCD) and a 2-MHz transcranial probe applied to the left temporal window at a depth of 50-65mm and secured using a headset to ensure optimal insonation angle/position throughout testing. The MCA was selected because it is the most commonly interrogated vessel in functional TCD studies, has a substantial body of literature linking it to clinical outcomes (reviewed in [334]), and responds to the Stroop task [263]. MCA hemodynamics were captured across 4 separate 6-second epochs distributed throughout each cognitive task (approximately every 30 s) that were subsequently averaged. The MCA Vm was calculated by a standard algorithm implemented on the device over a 6-s epoch with use of a fast Fourier transform. MCA PI was calculated using the same equation as CCA PI described above via an automated waveform tracking function. MCA conductance and pulsatile dampening factor were calculated as MCA Vm/MP and proximal PI (CCA)/distal PI (MCA), respectively. All measurements were taken by a single, trained investigator.

Prefrontal cortex (PFC) oxygenation

While transcranial Doppler provides a direct measure of blood flow velocity and potential oxygen supply, functional near infrared spectroscopy (NIRS) provides activation-dependent information on cortical hemodynamics related to oxygen extraction and tissue saturation. Thus, the combination of NIRS and TCD provides a more comprehensive appraisal of NVC. A small sensor containing transmitting/receiving optodes (Artinis, Portalite) was placed on the left side of the forehead (Broadman area Fp1 according to the international 10-20 System) with the receiving optode located 2 cm from the midline. The NIRS device was secured in position using a headband and headset to minimize ambient light interference and potential movement artifacts. Changes in oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) were measured via NIRS at 25 Hz using a modified Lambert-Beer law algorithm from the transmitter with the deepest tissue penetration to ensure assessment of brain oxygenation while attempting to avoid

direct influence of changes in skin blood flow. Tissue saturation index (TSI) was calculated (TSI=O_2Hb/tHb) x 100) by the NIRS system (via spatially resolved spectroscopy) from the light attenuation slope between emitting and detection probes. Total hemoglobin (THb) was calculated as the sum of O_2Hb and HHb. An age-dependent path length factor was used to correct for light scattering in the tissue in participants <50 years of age. The path length was assumed constant at 6.61 for all participants >50 years of age. All NIRS data were measured continuously, binned, averaged for each task, and expressed as change from baseline.

Respiration and skin temperature

We assessed end-tidal PCO_2 and respiration rate using capnography and a nasal cannula to account for the effects of respiration on cerebral hemodynamics during NVC. To account for the effects of skin blood flow on the NIRS signal, forehead skin temperature (as a proxy of skin blood flow) was measured on the contralateral aspect of the forehead using a single thermocouple (4600 series, Measurement Specialties, Hampton, VA). Both end-tidal PCO_2, respiration rate, and forehead skin temperature were assessed at the same time as blood pressure measures.

Statistical Analyses

All data are reported as mean ± standard deviation and statistical significance was established *a priori* as $p<0.05$. Normality of distribution for variables was assessed using histograms, Q-Q plots, and Shapiro-Wilk tests. Non-normally distributed variables were transformed to meet normality assumptions prior to analyses. Mean differences in descriptive characteristics and resting hemodynamics were compared using t-tests. Differences in categorical descriptive variables were tested using χ^2 tests. Accuracy and Stroop task RT were analyzed via t-test to assess differences in cognitive performance. The effects of task, HTN status, and interactions between task and HTN status were tested using a 2x3 (2 group [HTN,

no-HTN] x 3 task [baseline, congruent, incongruent]) repeated measures ANOVAs with Bonferroni correction for all cerebrovascular hemodynamics. PFC oxygenation (via NIRS) is expressed as change from baseline to each task. PFC oxygenation analyses were also tested while covarying for mean changes in skin temperature, and when expressed relative to MP (NIRS signal/MP). Pearson correlation coefficients were used to explore associations between cognitive performance, PFC oxygenation, and upstream hemodynamic pulsatility and extra-cranial vessel stiffness.

Results

Group characteristics

Groups were well-matched for sex, age, anthropometics, body composition, lipid profile, depression symptomology, and menstrual status (Table 1). Glucose was significantly higher in HTN vs no-HTN ($p<0.05$); however, this difference was abolished when accounting for HTN participants on beta-blockers. The no-HTN group had higher mean minutes of moderate-to-vigorous physical activity per day compared to HTN ($p<0.05$). Non-HTN medication use was similar in both groups, with the exception of statin use which was greater in HTN vs no-HTN ($p<0.05$).

Blood pressure status and baseline hemodynamics

HTN participants had been diagnosed for an average of 129 ± 97 months. The time of day that HTN participants took their anti-HTN medication (63.3%, AM vs 33.0%, PM) was not different within the group ($p=0.095$), with one participant taking anti-HTN at both times of day. At-home blood pressure measurement confirmed HTN had higher SP (no-HTN 116 ± 9 mmHg; HTN 126 ± 12 mmHg), DP (no-HTN 73 ± 6 mmHg; HTN 79 ± 8 mmHg), and MP (no-HTN 88 ± 6 mmHg; HTN 95 ± 9 mmHg; $p<0.05$) than no-HTN. Group differences in resting hemodynamics as assessed by t-tests are denoted in the baseline column of Tables 2-5. The only differences in

baseline vascular and cerebral hemodynamics between groups were brachial DP and MP which were higher in HTN than no-HTN ($p<0.05$).

Cerebrovascular reactivity to cognitive activity

Task performance

Mean hit RT was similar between groups for congruent (no-HTN 996 ± 143 ms; HTN 971 ± 92 ms) and incongruent tasks (no-HTN 1507 ± 295 ms; HTN 1543 ± 267 ms; $p>0.05$). Accuracy was not different between groups for congruent (no-HTN 95.3 ± 3.6%; HTN 95.5 ± 3.1%) or incongruent (no-HTN 76.7 ± 11.4%; HTN 74.3 ± 10.2%; $p>0.05$).

Heart rate, respiration, and blood pressure

Significant task effects were observed for heart rate, skin temperature, and respiration rate, which each increased from rest to both cognitive tasks (Table 2). Post-hoc analyses within the task effect indicated that heart rate was slightly, albeit significantly, higher during the incongruent compared to congruent tasks. A significant task effect was detected for end-tidal CO_2, which decreased slightly from rest to each cognitive task. Significant task effects were also observed for brachial and carotid SP and PP and augmentation indices (AIx, AIx75) which increased from baseline to each cognitive perturbation ($p<0.05$; Table 3). Significant group and task effects were detected for brachial DP and MP. Brachial DP and MP was higher in the HTN versus no-HTN group and increased similarly from baseline to NVC perturbation ($p<0.05$). Post-hoc analyses indicated brachial SP, DP, and MP were slightly but significantly higher during incongruent compared to congruent tasks. No significant group-by-task interactions were observed, indicating adults with and without HTN responded similarly to the cognitive perturbation.

Extracranial hemodynamics

Significant task effects were observed for Vs, velocity PI, mean diameter, carotid mean blood flow, and systolic, diastolic and pulsatile shear rates ($p<0.05$; Table 4). Carotid mean diameter, and mean blood flow increased, while Vs, and systolic, diastolic and pulsatile shear rates decreased from baseline to both cognitive tasks ($p<0.05$). No significant effects of the NVC perturbation were detected for carotid conductance, MnV, Vd, or mean shear rate. Significant task effects were detected for cf PWV, carotid PWV-β, W1, NA and W2 ($p<0.05$; Table 5). Cf PWV, PWV-β, W1, and NA increased significantly from baseline to each cognitive task. Increases in carotid W2 from baseline were only significant during the congruent task ($p<0.05$). No significant group-by-task interactions were observed, indicating HTN and no-HTN groups had similar extracranial reactivity to the cognitive perturbation.

Intracranial hemodynamics

A significant task effect was revealed for MCA MnV and pulsatile dampening factor, while MCA PI, RI, and conductance were not different during cognitive activity (Table 5). MCA MnV increased in both groups from baseline to cognitive activation ($p<0.05$). The pulsatile dampening factor decreased during the cognitive tasks ($p<0.05$). No significant group-by-task interactions were observed, indicating HTN and no-HTN groups responded similarly to the cognitive perturbation at the level of the MCA.

Significant group differences emerged with respect to prefrontal cortex oxygenation during the NVC perturbation. The change in O_2Hb was greater in HTN vs no-HTN ($p<0.05$; Figure 1), as HTN increased significantly from baseline to each cognitive task, but no-HTN did not. HHb decreased similarly from baseline to NVC perturbation in both HTN and no-HTN ($p<0.05$). Group differences in prefrontal cortex O_2Hb responses to the cognitive tasks remained

significant after covarying for changes in mean skin temperature (as an estimate of change in skin blood flow), and when expressed relative to MP.

Vascular and cognitive associations

Exploratory associations between cerebrovascular hemodynamics and cognitive performance were performed separately for each iteration of the Stroop task (congruent vs incongruent) and are displayed in Tables 6-7. HTN and no-HTN groups were combined for exploratory analyses because of similar extra- and intra-cranial NVC. Of note, during the congruent task changes in PFC TSI were positively associated with Stroop accuracy and negatively associated with CCA PI. Changes in congruent CCA PI and PP were positively associated with MCA PI and CCA PWVβ, respectively. CCA pulsatile shear rate during the congruent task was positively associated with CCA and MCA PI. During the incongruent task, RT was positively associated with changes in PWVβ. Incongruent CCA PI and pulsatile shear rate were positively associated with MCA PI and inversely related to PFC TSI. Incongruent CCA PP was positively associated with MCA PI, mean CCA shear rate, and CCA PWVβ.

Discussion

While select studies have interrogated the effect of HTN on cerebrovascular reactivity in response to CO_2 manipulation, we sought to investigate extra- and intra-cranial cerebrovascular reactivity during a cognitive perturbation (i.e. NVC). Understanding this NVC in response to cognitive activity may have broader implications for cognitive function, particularly in the setting of HTN since this population is at a greater risk of dementia and cognitive decline [11]. Our data indicates that individuals with and without HTN had similar extra- and intra-cranial responses to

sustained neural activity to achieve NVC; however, HTN achieved PFC oxygenation with greater reliance on changes in O_2Hb. A secondary aim of this investigation was to identify the contributions of extracranial stiffness and hemodynamic pulsatility to intracranial hemodynamics during NVC. We noted significant increases in extracranial vessel stiffness and disparate changes in extra- (decreased) vs intra-cranial hemodynamic pulsatility (unaltered) in both groups. Exploratory analyses indicated that extracranial pulsatility was associated with PFC oxygenation in the combined sample, suggesting that extracranial modulation of hemodynamic pulsatility may play a role in ensuring optimal NVC in middle-age adults with and without HTN.

Hypertension, vascular stiffness and neurovascular coupling

Although HTN is typically associated with accelerated vascular aging [329], we observed little evidence of early vascular aging in our cohort of middle-aged HTN. While brachial MP and DP were higher in HTN than no-HTN, average values were controlled to within normal ranges. Additionally, there were no significant group differences in large artery stiffness, a hallmark of vascular aging. These similarities in arterial stiffness are likely related to adequate blood pressure control in HTN, which may help slow the progression of arterial stiffening [275]. Heart rate, a contributor to aortic stiffness [277], was additionally similar between groups. Greater physical activity and less sedentary time is associated with slowing the progression of age-related aortic stiffening [335]. Although no-HTN achieved ≈2,000 more steps/day and averaged ≈10 more MVPA/day compared to HTN individuals, our data indicate both groups on average were physically active and achieved the recommended dose of 150 min/week of MVPA. Our groups also had similar blood lipids [336], body composition [337], subjective sleep quality [338], and depression symptomology [339], all of which can contribute to accelerated vascular aging. Additionally, statin use was higher in our adults with versus without HTN, which may have improved the arterial stiffness profile among our HTN group [340]. Taken together, these data

suggest our cohort of middle-aged adults with HTN was generally healthy, had well-controlled blood pressure and a low vascular risk factor burden.

The use of anti-HTN medication in our HTN sample may have contributed to the similar NVC responses observed herein by influencing vascular health. While the direct effects of anti-HTN medication on brain function is unclear [11,179,180], halting the progression of arterial stiffness (via anti-HTN therapy/blood pressure control) may indirectly benefit the brain by slowing pulsatility-mediated cerebrovascular damage secondary to vascular stiffness [9,158]. Indeed, aortic stiffness may not be associated with cerebral small vessel disease in adults with controlled HTN [123]. With regards to NVC specifically, animal-model research suggests anti-HTN therapy may exert protective effects on the neurovascular unit [341] but may not restore NVC [342]. Overly aggressive blood pressure lowering may impair NVC in HTN [343] since NVC depends on adequate blood/perfusion pressure [326]. However higher MP, and thus perfusion pressure, in adults with HTN may overcome early changes in HTN-mediated intracranial remodeling to ensure adequate absolute flow during NVC. Ultimately it is currently unknown if acute or chronic use of anti-HTN medication can preserve NVC in humans and future research is needed to identify these effects.

Contributions of vascular stiffness and pulsatility to neurovascular coupling

We noted significant increases in carotid and aortic stiffness during the Stroop irrespective of HTN status. This indicates middle-aged adults with and without HTN experience similar increases in large artery stiffness during the Stroop task as older adults, whereas large artery stiffness is unaltered in healthy young/middle-aged adults [261,263]. Increases in vessel stiffness during cognitive activity may stem from changes in blood pressure. Carotid and brachial systolic, diastolic, and MP increased during the Stroop task in both HTN and no-HTN groups. Adequate changes in intracranial flow during NVC is dependent on blood pressure [326]. Increases in pressure during cognitive activity would increase distension pressure within

the vessel and shift the pressure load burden to collagen fibers within the wall, thereby acutely stiffening the vessel [64]. Increases in blood pressure are an integral part of NVC [325] and may reflect the sympathetic response to the cognitive load (i.e. task difficulty/effort required) [344]. Ultimately, concomitant changes in carotid and aortic stiffness herein may help maintain impedance mismatch at the aortic-carotid interface, potentially protecting the cerebrovasculature from excessive transmission of pulsatile energy [9] during cognitive activity. These pressure-mediated changes in extracranial vessel stiffness during cognitive activity may alter the generation and transmission of extracranial pulsatility.

Despite increases in carotid pressure pulsatility (CCA PP), we noted decreases in carotid blood velocity pulsatility (PI) regardless of HTN status. These disparate changes in pulsatile hemodynamics during the Stroop may reflect changes in wave-transmission and reflection during cognitive activity. Carotid WIA is a novel means of appraising pulse wave contributions to extracranial pulsatility [279]. Left ventricular contraction generates a forward traveling compression wave (measured by WIA as W_1) [285] that, when encountering cerebral vessels with increased vasomotor tone, can be reflected toward the heart, creating a backward-traveling expansion wave (measured as NA) [274]. Subsequent left ventricular relaxation creates a forward-traveling expansion wave that decelerates blood flow from behind as it moves downstream [285,332,333]. We observed increases in forward wave energy (W_1) in both HTN and no-HTN during the Stroop task concomitant with equivalent increases in carotid reflected wave energy (NA), resulting in no net change in the amount of forward wave energy penetrating into the downstream cerebrovasculature. Increases in CCA reflected wave energy would be posited to 1) dampen pulsatile blood velocity by braking and slowing forward blood flow, and 2) augment pulsatile pressure (i.e. CCA PP) [345]. Additionally, we noted increases in W_2 during cognitive activity and this is a novel observation. Small increases in this suction wave creates a “braking” force that may additionally contribute to attenuation of CCA blood velocity

pulsatility during cognitive activity. Ultimately, WIA suggests that these hemodynamic forces may work in concert to extinguish flow pulsatility in the large extracranial vessels, potentially minimizing pulsatile transmission into intracranial circulation.

MCA blood velocity PI was not significantly altered during the Stroop task in either HTN or no-HTN groups, similar to observations in healthy younger/middle-age adults [263]. Additionally, we noted reductions in the dampening of hemodynamic pulsatility in the MCA (assessed as pulsatile dampening factor; proximal/distal PI) during the Stroop task, largely driven by reductions in proximal (i.e. CCA) PI. This finding suggests that more pulsatility was buffered in the large extracranial vessels, thereby reducing reliance on intracranial pulsatile dampening during sustained cognitive activity. The exact reason for this response is unknown. Considering CCA and MCA PI were associated, this highlights the importance of reducing pulsatile hemodynamics in the extracranial vessels prior to entering the intracranial circulation where hemodynamic pulsatility could interfere with microvascular oxygenation during NVC.

Contribution of flow to neurovascular coupling

We noted increased CCA diameter during the Stroop tasks in both HTN and no-HTN groups, consistent with our previous observations in healthy young/middle-aged adults [261]. Recent data suggests shear may influence extracranial dilation at the level of the internal but not common carotid artery [327,346,347], and our data support this. We noted no change in CCA mean shear rate during Stroop, accompanied by reductions in systolic, diastolic, and pulsatile shear rate. CCA dilation during stroop was not associated with shear rates (data not shown), which may reflect differing sensitivity to shear in the common versus downstream, internal carotid artery [327]. Increases in mean pressure may also contribute to carotid dilation [327,347] by pushing against the once compliant CCA wall, mechanically distending (increasing diameter) and simultaneously stiffening the vessel during NVC. Although our data may suggest

pressure plays a prominent role in mediating CCA dilation, the importance of shear in this setting should not be completely dismissed. Pressure-mediated stiffening may additionally increase the sensitivity to shear forces [327] as we noted a positive association between CCA stiffness and mean shear during the incongruent Stroop task. This stiffness-mediated change in shear sensitivity may facilitate faster functional changes in blood flow to intracranial circulation, however additional research is required to test this hypothesis. Ultimately, CCA dilation during cognitive activity occurs contrary to mild hypocapnia and any myogenic response from increased pressure that would be expected to constrict the vessel. This may suggest that functional CCA dilation during NVC may override constrictor stimuli, akin to observations during exercise in extracranial vessels [346], to ensure adequate increases in flow.

CCA dilation contributed to increases in CCA mean flow during Stroop, as mean velocity was unchanged. The brunt of this increase in extracranial blood flow can be transmitted intracranially to the ICA and eventually MCA [102]. We noted increases in MCA mean blood velocity during the Stroop task, regardless of HTN status. Increases in pressure partially contributed to this increase in blood flow, as flow expressed relative to pressure (i.e conductance) was unaltered in the CCA and MCA during the Stroop task. Ultimately, increases in both extra- and intra-cranial blood flow would be expected to feed downstream active vascular beds.

We assessed PFC oxygenation during the Stroop task using NIRS. Both no-HTN and HTN achieved similar PFC oxygenation (measured by TSI) during the Stroop tasks, but achieved this by slightly different means. In no-HTN, TSI was driven primarily by reductions in HHb during the Stroop task. TSI in HTN individuals was achieved via similar reductions in HHb, supplemented with increases in O_2Hb during the Stroop task. Increased O_2Hb and decreased HHb at the PFC during cognitive activity likely reflects increased neuronal metabolic demand and neurotransmitter release from active neurons (in this case engaged by the cognitive

task)[348], thereby eliciting local vasodilation [349] and modulating PFC hemodynamics to support cognitive activity. These changes in NIRS signals during the Stroop task remained when expressed relative to MP, indicating this hemodynamic response was not solely dependent on the increases in pressure that contributed to upstream increases in blood flow. Taken together, these data indicate that the functional changes in oxygenation required to support neural activity is largely intact in our middle-aged sample of controlled-HTN compared to their counterparts without HTN.

Neurovascular coupling and task performance

We conducted exploratory analyses on our combined HTN and no-HTN sample to identify associations between extracranial stiffness, cerebrovascular pulsatility, PFC oxygenation, and task performance. Our data suggest that adults who increased their PFC TSI performed better on the congruent task, and that those adults who had greater increases in carotid stiffness responded slower on the incongruent task. Moreover, individuals who were not able to reduce CCA blood velocity pulsatility during the Stroop task had greater decreases in PFC TSI. Interestingly, changes in TSI were not associated with MCA PI, perhaps indicating extracranial vessels play a larger role in optimal NVC than originally thought. Indeed, extracranial vessels are now being recognized as key players in the regulation of brain blood flow [320]. Our data propose that extracranial reductions in blood velocity pulsatility may help maintain brain oxygenation of active neural circuitry within the PFC during cognitive engagement. Taken together, extracranial modulation of hemodynamic pulsatility may be an important part of optimal NVC to support brain oxygenation and ultimately cognitive function.

Limitations and considerations

We tested adults with medicated HTN in order to interrogate cerebrovascular NVC as it would typically be in their “free-living” state. As such, NVC during cognitive activity may differ in

untreated middle-aged adults with HTN. We did not perform an extensive scan for carotid stenosis, however average intima-media thickness (≈0.63 mm) was indicative of minimal stenosis. Cerebrovascular hemodynamics were assessed unilaterally, thus we cannot comment on potential differences in lateralization in HTN. Changes in CCA shear rate were not associated with changes in diameter during cognitive activity. This could reflect differential sensitivity to shear compared to other extracranial vessels [327], or may reflect experimental limitations. We assessed shear at a single time point (potentially missing the peak shear stimulus) during sustained cognitive activity, which may limit the ability to tease out shear-mediated regulation of extracranial flow because of a growing influence of confounding factors (blood pressure, PCO_2 etc.) [347]. Thus, future studies are needed with greater temporal resolution of changes in extracranial shear, stiffness, and flow (including the internal carotid) to understand their complex interplay during cognitive activity. The NIRS signal may respond to changes in skin blood flow. Changes in NIRS signals, however, remained significant when covarying for mean change in forehead skin temperature (a proxy of skin blood flow), thus we do not believe changes in skin blood flow can solely explain the PFC oxygenation responses observed herein.

Conclusion

Our study is the first to investigate NVC during sustained cognitive activity using multi-modal cerebrovascular imaging (Ultrasound, TCD, and NIRS) in middle-aged, medicated HTN. Our data indicates that extra- and intra-cranial cerebrovascular reactivity during cognitive activity was largely maintained in this cohort of generally well-controlled HTN. Individuals with and without HTN exhibited similar 1) increases in blood pressure, blood flow/velocity, and aortic/carotid stiffness during cognitive activity; and similar 2) reductions in CCA blood velocity PI, but not MCA PI, and similar PFC oxygenation during cognitive activity. Additionally, our data suggests that extracranial modulation of hemodynamic pulsatility may have effects on

intracranial oxygenation at the PFC. Together these data suggest that well-controlled middle-aged adults with HTN have similar cerebrovascular NVC as their counterparts without HTN, and that extracranial hemodynamics may play an important role in optimizing the manner in which blood flow is delivered (i.e. non-pulsatile) during NVC.

Table 7.1: Descriptive characteristics for no-HTN and HTN groups (mean ± SD unless otherwise noted).

	No-HTN	**HTN**	p-value
Sex (male/female)	16/14	16/14	-
Age (yrs)	56 ± 6	56 ± 6	0.93
Anthropometrics			
Height (cm)	169.8 ± 11.3	171.3 ± 9.6	0.57
Weight (kg)	82.0 ± 13.3	82.4 ± 12.5	0.91
Body fat (%)	32.2 ± 8.4	31.4 ± 6.9	0.69
Body mass index (kg/m^2)	28.3 ± 2.6	28.0 ± 3.3	0.71
Medications, %(n)			
Statin	6.7 (2)	40.0 (12)	0.005
Birth control	3.3 (1)	0.0 (0)	-
Hormone replacement therapy	3.3 (1)	3.3 (1)	-
Hypothyroid	3.3 (1)	3.3 (1)	-
ACE inhibitor	-	43.3 (13)	-
ARB	-	33.3 (10)	-
Diuretic	-	20 (6)	-
β-Blocker	-	13.3 (4)	-
CCB	-	13.3 (4)	-
Combination therapy (≥2)	-	20.0 (6)	
Atherosclerosis			
Intima-media thickness (mm)	0.61 ± 0.10	0.65 ± 0.12	0.18
Lipid profile			
Hemoglobin (g/dL)	14.2 ± 0.9	13.8 ± 1.3	0.12
Total cholesterol (mg/dL)	202 ± 39	192 ± 36	0.28
HDL (mg/dL)	58 ± 17	56 ± 20	0.56
Triglycerides (mg/dL)	103 ± 61	116 ± 56	0.28
LDL (mg/dL)	128 ± 41	114 ± 30	0.17
Non-HDL (mg/dL)	144 ± 44	136 ± 32	0.43
Total cholesterol:HDL	4 ± 2	4 ± 1	0.89
Glucose (mg/dL)	94 ± 9	102 ± 16	0.03
Questionnaires			
CESD	6 ± 5	7 ± 4	0.71
PSQI	5 ± 3	5 ± 3	0.45
Physical activity			
6-day average steps (count/d)	10913± 4572	8765 ± 3046	0.06
6-day average MVPA (min/d)	40 ± 24	29 ± 20	0.03

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CESD, Center for Epidemiologic Studies Depression questionnaire; PSQI, Pittsburgh Sleep Quality Index; MVPA, moderate-vigorous physical activity.

Table 7.2: Brachial blood pressure, heart rate, end-tidal CO2, skin temperature in response to cognitive activity in adults with and without hypertension (HTN) (mean ± SD).

Measure	Baseline	Congruent Stroop	Incongruent Stroop	G	T	GxT
Heart rate (b/min)						
No-HTN	59 ± 10	66 ± 11*	67 ± 11*#	0.43	0.001	0.70
HTN	61 ± 8	68 ± 9*	69 ± 9*#			
Skin temperature (°C)						
No-HTN	34.00 ± 0.83	34.52 ± 0.64*	34.51 ± 0.65*	0.42	0.001	0.85
HTN	34.12 ± 0.66	34.64 ± 0.49*	34.64 ± 0.49*			
End-tidal CO_2 (mmHg)						
No-HTN	35 ± 3	34 ± 3*	34 ± 3*	0.68	0.001	0.71
HTN	35 ± 3	34 ± 3*	34 ± 3*			
Respiration note (br/min)						
No-HTN	14 ± 4	19 ± 5*	20 ± 4*	0.35	0.001	0.84
HTN	14 ± 3	18 ± 5*	18 ± 5*			

G, group effect; T, time effect; GxT, group by time interaction. †p<0.05 t-test vs No-HTN; †p<0.05 baseline t-test vs No-HTN; *p<0.05 time effect vs baseline; # time effect vs Congruent.

Table 7.3: Brachial and carotid blood pressure responses to cognitive activity in adults with and without hypertension (HTN) (mean ± SD).

Measure	Baseline	Congruent Stroop	Incongruent Stroop	G	T	GxT
Brachial systolic pressure (mmHg)						
No-HTN	122 ± 14	132 ± 16*	134 ± 17*#	0.15	0.001	0.80
HTN	127 ± 13	138 ± 14*	139 ± 14*#			
Brachial diastolic pressure (mmHg)						
No-HTN	76 ± 8	80 ± 9*	81 ± 10*#	0.03	0.001	0.61
HTN	81 ± 9†	85 ± 9*	86 ± 9*#			
Brachial pulse pressure (mmHg)						
No-HTN	47 ± 11	52 ± 12*	52 ± 13*	0.81	0.001	0.54
HTN	46 ± 8	53 ± 10*	53 ± 8*			
Brachial mean pressure (mmHg)						
No-HTN	91 ± 9	98 ± 10*	99 ± 11*#	0.05	0.001	0.91
HTN	96 ± 10†	102 ± 10*	104 ± 10*#			
Systolic pressure (mmHg)						
No-HTN	113 ± 13	121 ± 14*	121 ± 15*	0.08	0.001	0.45
HTN	118 ± 13	126 ± 13*	128 ± 14*			
Pulse pressure (mmHg)						
No-HTN	37 ± 10	41 ± 12*	40 ± 12*	0.73	0.001	0.20
HTN	37 ± 7	41 ± 9*	43 ± 9*			
AIx (%)						
No-HTN	17 ± 19	19 ± 21	22 ± 17	0.42	0.102	0.48
HTN	21 ± 15	24 ± 13	23 ± 13			
AIx75 (%)						
No-HTN	9 ± 19	15 ± 21*	18 ± 17*	0.52	0.001	0.61
HTN	15 ± 15	21 ± 14*	21 ± 13*			

AIx, augmentation index; AIx75, augmentation index at 75 b/min; G, group effect; T, time effect; GxT, group by time interaction. †p<0.05 baseline t-test vs No-HTN; *p<0.05 time effect vs baseline; # time effect vs Congruent.

Table 7.4: Extracranial flow responses to cognitive activity in adults with and without hypertension (HTN) (mean ± SD).

Measure	Baseline	Congruent Stroop	Incongruent Stroop	G	T	GxT
Systolic velocity (cm/s)						
No-HTN	73.9 ± 16.9	70.2 ± 13.8*	70.2 ± 15.7	0.65	0.02	0.70
HTN	74.5 ± 12.4	71.7 ± 11.6*	72.7 ± 14.9			
Diastolic velocity (cm/s)						
No-HTN	21.0 ± 5.5	20.6 ± 4.6	20.0 ± 4.3	0.26	0.65	0.37
HTN	21.7 ± 4.1	21.3 ± 3.7	22.0 ± 5.0			
Mean velocity (cm/s)						
No-HTN	35.3 ± 5.2	35.4 ± 5.5	35.4 ± 5	0.08	0.53	0.71
HTN	37.4 ± 5.8	37.8 ± 5.6	38.6 ± 7			
Velocity PI						
No-HTN	1.525 ± 0.369	1.42 ± 0.30*	1.42 ± 0.40*	0.24	0.001	0.84
HTN	1.418 ± 0.279	1.35 ± 0.26*	1.31 ± 0.20*			
Mean diameter (mm)						
No-HTN	5.67 ± 0.54	5.86 ± 0.58*	5.84 ± 0.57*	0.31	0.001	0.18
HTN	5.55 ± 0.66	5.67 ± 0.65*	5.71 ± 0.69*			
Mean flow (mL/min)						
No-HTN	530 ± 101	571 ± 129*	566 ± 116*	0.85	0.001	0.72
HTN	536 ± 92	563 ± 90*	577 ± 116*			
Conductance (mL/s/mmHg)						
No-HTN	5.89 ± 1.37	5.89 ± 1.37	5.79 ± 1.26	0.41	0.77	0.59
HTN	5.63 ± 1.17	5.55 ± 1.05	5.62 ± 1.32			
Systolic shear rate (/s)						
No-HTN	504.5 ± 131.0	464.3 ± 106.3*	464.7 ± 119.8*	0.35	0.001	0.67
HTN	523.6 ± 117.6	495.3 ± 107.8*	501.4 ± 132.9*			
Diastolic shear rate (/s)						
Non-HTN	154.5 ± 48.5	145.9 ± 39.6*	143.0 ± 39.4*	0.22	0.04	0.45
HTN	164.1 ± 44.2	156.4 ± 38.0*	161.9 ± 47.3*			
Mean shear rate (/s)						
Non-HTN	252.0 ± 51.0	244.8 ± 52.4	245.2 ± 50.9	0.12	0.21	0.87
HTN	277.0 ± 68.0	272.3 ± 64.1	274.6 ± 74.3			
Shear rate PI						
No-HTN	1.40 ± 0.35	1.31 ± 0.28*	1.32 ± 0.38*	0.53	0.001	0.39
HTN	1.32 ± 0.27	1.26 ± 0.25*	1.23 ± 0.20*			

PWV, pulse wave velocity; cf, carotid-femoral; PI, pulsatility index; NA, negative area; RIx, reflection index. G, group effect; T, time effect; GxT, group by time interaction. †p<0.05 baseline t-test vs No-HTN; *p<0.05 time effect vs baseline; # time effect vs Congruent.

Table 7.5: Extracranial vessel stiffness and hemodynamic pulsatility responses to cognitive activity in adults with and without hypertension (HTN) (mean ± SD).

Measure	Baseline	Congruent Stroop	Incongruent Stroop	G	T	GxT
cf PWV (m/s)						
No-HTN	7.8 ± 1.1	8.0 ± 1.1*	8.3 ± 1.3*	0.10	0.005	0.65
HTN	8.3 ± 1.3	8.7 ± 1.6*	8.7 ± 1.4*			
PWVβ (m/s)						
No-HTN	6.3 ± 1.0	6.6 ± 1.0*	6.5 ± 1.0*	0.07	0.001	0.45
HTN	6.6 ± 1.3	7.1 ± 1.3*	7.2 ± 1.2*			
W_1 (mmHg/m/s^3)						
No-HTN	6.3 ± 2.8	9.1 ± 4.2*	8.9 ± 4.7*	0.82	0.001	0.19
HTN	6.8 ± 3.0	8.2 ± 3.6*	9.6 ± 5.6*			
NA (mmHg/m/s^2)						
No-HTN	26.7 ± 19.0	29.8 ± 17.5	29.3 ± 17.9*	0.99	0.03	0.41
HTN	23.4 ± 10.5	27.1 ± 14.2	32.2 ± 20.9*			
RIx (%)						
No-HTN	4.32 ± 2.48	3.37 ± 1.39	3.58 ± 1.85	0.83	0.11	0.46
HTN	3.59 ± 1.35	3.55 ± 1.95	3.64 ± 1.58			
W_2 (mmHg/m/s^3)						
No-HTN	1.8 ± 0.7	2.1 ± 1.2*	2.2 ± 1.1	0.39	0.04	0.64
HTN	1.9 ± 0.7	2.5 ± 1.7*	2.3 ± 1.1			

PWV, pulse wave velocity; cf, carotid-femoral; NA, negative area; RIx, reflection index. G, group effect; T, time effect; GxT, group by time interaction. †p<0.05 baseline t-test vs No-HTN; *p<0.05 time effect vs baseline; # time effect vs Congruent.

Table 7.6: Intracranial (middle cerebral artery) hemodynamic responses to cognitive activity in adults with and without hypertension (HTN) (mean ± SD).

Measure	**Baseline**	**Congruent Stroop**	**Incongruent Stroop**	Group	Time	GxT
Mean velocity (cm/s)						
No-HTN	60 ± 15	64 ± 15	65 ± 15	0.48	0.001	0.54
HTN	63 ± 11	66 ± 12	67 ± 12			
PI						
No-HTN	0.78 ± 0.12	0.77 ± 0.13	0.78 ± 0.13	0.39	0.17	0.85
HTN	0.76 ± 0.11	0.74 ± 0.11	0.74 ± 0.1			
RI						
No-HTN	0.53 ± 0.04	0.53 ± 0.05	0.53 ± 0.05	0.33	0.72	0.66
HTN	0.52 ± 0.05	0.52 ± 0.05	0.52 ± 0.04			
Conductance (cm/s/mmHg)						
No-HTN	0.67 ± 0.18	0.67 ± 0.15	0.67 ± 0.16	0.80	0.44	0.70
HTN	0.66 ± 0.13	0.65 ± 0.14	0.65 ± 0.13			
Pulsatility dampening factor						
No-HTN	1.82 ± 0.29	1.74 ± 0.27	1.71 ± 0.29	0.52	0.001	0.90
HTN	1.77 ± 0.29	1.71 ± 0.24	1.66 ± 0.23			

PI, pulsatility index; RI, resistance index; G, group effect; T, time effect; GxT, group by time interaction. †p<0.05 baseline t-test vs No-HTN; *p<0.05 time effect vs baseline; # time effect vs Congruent.

Table 7.7: Exploratory associations between extra- and intra-cranial hemodynamics and congruent Stroop performance.

	%Hits	RT	ΔPFC TSI	ΔMCA PI	ΔCCA PI	ΔCCA PP	ΔCCA SR-PI	ΔCCA SR	ΔCCA PWVβ
RT	**-0.52**								
ΔTSI	**0.27**	-0.25							
ΔMCA PI	0.01	0.00	-0.15						
ΔCCA PI	-0.18	0.07	**-0.26**	**0.41**					
ΔCCA PP	0.07	-0.20	-0.10	0.11	-0.07				
ΔCCA SR-PI	-0.21	-0.05	-0.18	**0.26**	**0.76**	-0.05			
ΔCCA SR	-0.14	0.06	-0.15	0.01	-0.02	0.03	0.03		
ΔCCA PWVβ	-0.12	-0.06	-0.11	-0.07	-0.05	**0.48**	0.00	0.00	
ΔCF PWV	-0.06	0.20	-0.05	-0.06	0.02	-0.02	0.11	0.03	-0.19

RT, reaction time; PFC, prefrontal cortex; TSI, tissue saturation index; MCA, middle cerebral artery; PI, pulsatility index; CCA, common carotid artery; PP, pulse pressure; SR, shear rate; PWV, pulse wave velocity. Bold $p<0.05$.

Table 7.8: Exploratory associations between extra- and intra-cranial hemodynamics and incongruent Stroop performance.

	%Hits	RT	ΔPFC TSI	ΔMCA PI	ΔCCA PI	ΔCCA PP	ΔCCA SR-PI	ΔCCA SR	ΔCCA PWVβ
RT	**-0.52**								
ΔTSI	0.06	-0.21							
ΔMCA PI	-0.02	0.13	-0.21						
ΔCCA PI	0.05	0.23	**-0.33**	**0.42**					
ΔCCA PP	-0.07	0.12	-0.08	**0.26**	-0.09				
ΔCCA SR-PI	0.02	0.13	**-0.33**	**0.33**	**0.79**	0.04			
ΔCCA SR	-0.07	-0.06	0.06	0.12	-0.13	**0.28**	-0.04		
ΔCCA PWVβ	-0.13	**0.30**	-0.22	0.18	0.09	**0.54**	0.05	**0.26**	
ΔCF PWV	0.18	-0.09	-0.05	-0.15	-0.10	-0.03	-0.06	-0.01	0.01

RT, reaction time; PFC, prefrontal cortex; TSI, tissue saturation index; MCA, middle cerebral artery; PI, pulsatility index; CCA, common carotid artery; PP, pulse pressure; SR, shear rate; PWV, pulse wave velocity. Bold $p<0.05$.

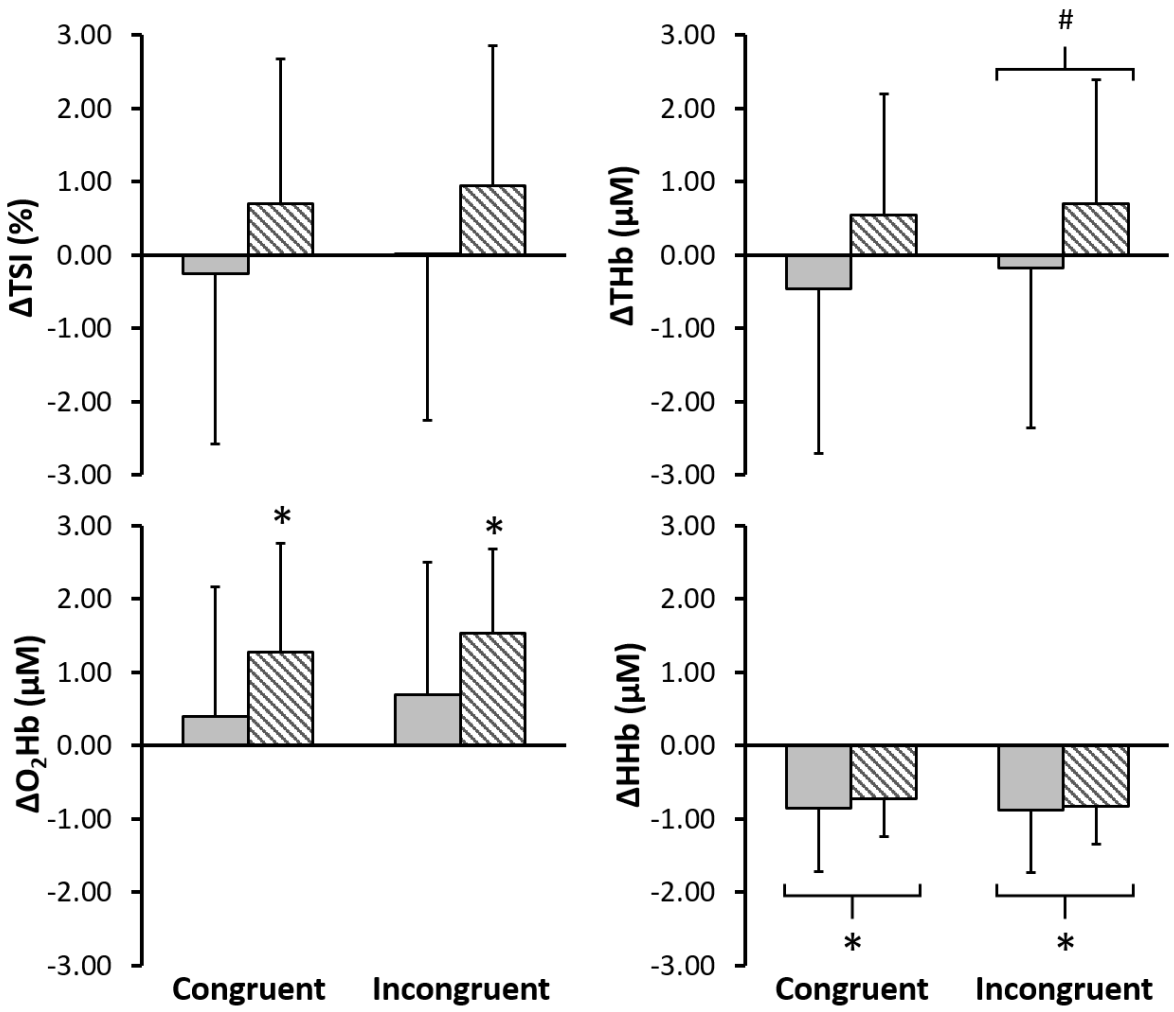

Figure 7.1: Changes in prefrontal cortex oxygenation during congruent and incongruent Stroop tasks adults with and without hypertension (HTN) for a) tissue saturation index (TSI), b) total (THb), c) oxy- (O_2Hb), and d) deoxyhemoglobin (HHb). **No-HTN** **HTN** Effects, ΔTSI (group 0.286; time 0.141; group x time 0.088), ΔTHb (group 0.182; time 0.001; group x time 0.066), ΔO_2Hb (group 0.404; time 0.001; group x time 0.048), ΔHHb (group 0.106; time 0.001; group x time 0.591). *p<0.05 vs baseline, # p<0.05 vs Congruent.

Chapter VIII: Summary, Future Directions, and Conclusions

The presence of hypertension (HTN) in middle-age is important as this population is particularly vulnerable to later-life development of cognitive and cardiovascular disease [11,55]. Identifying means to attenuate the burden of cardiovascular and cognitive diseases in this at risk, middle-aged population is critical to improve quality of life, reduce healthcare costs, and reduce societal burden [241,242]. This study sought to investigate the effects of an acute bout of aerobic exercise of a recommended dose/intensity on arterial stiffness and cognitive function in middle-aged adults with and without HTN.

Our initial hypotheses were largely unsupported by our findings (Figure 8.1). Acute exercise resulted in similar responses in adults with and without HTN, manifesting as increased aortic stiffness and cerebrovascular hemodynamic pulsatility, and accelerated reaction time on executive function and memory tasks in the absence of changes in accuracy. This suggests that

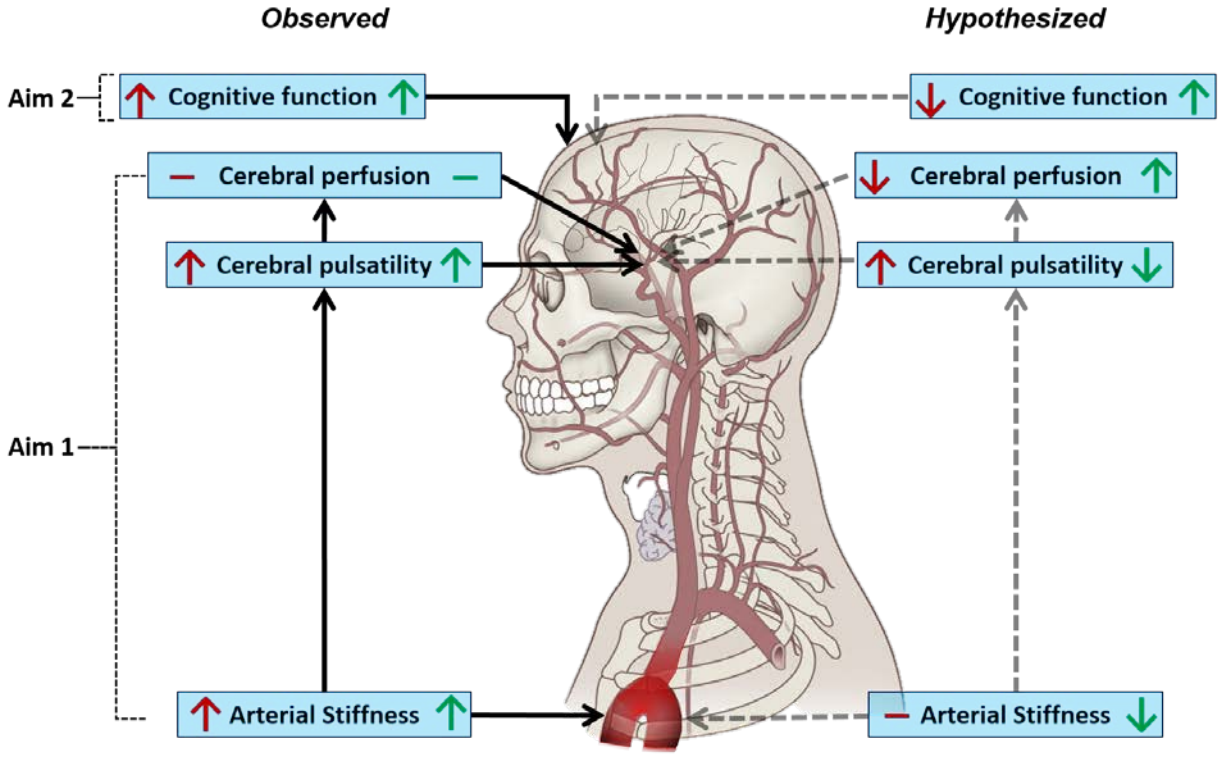

Figure 8.1: *Hypothesized and observed responses to acute exercise between adults with hypertension (**red** arrows) and adults without hypertension (**green** arrows).*

improvements in post-exercise cognitive function occurred immediately following a time of increased arterial stiffness and cerebrovascular pulsatility. This is somewhat contradictory, as greater arterial stiffness and pulsatility are generally associated with reduced cognitive function at rest. These observations indicate that acute changes in vascular hemodynamics post-exercise may not directly influence cognitive function. Rather, improvements in cognitive function, manifesting as accelerated reaction time, may stem from changes in brain-derived neurotrophic factor (BDNF) [350,351]. BDNF release appears dependent on cerebrovascular endothelium-derived nitric oxide [352], which may be released in response to shear stress and/or oxidative stress that occurs with exercise [353]. As such, facilitation of cognitive function post-exercise may be of indirect vascular origin by increasing BDNF release via shear stress.

While were adequately powered to detect significant effects of exercise, we did not observe many HTN effects or HTN-by-exercise effects in our sample. This suggests that either 1) we were not adequately powered to detect such effects, or 2) exercise did not result in meaningful differential responses between our sample of middle-aged adults with well-controlled HTN and those without HTN. Post-hoc power analyses (see Table 8.1) suggest that while an additional 16 subjects may have revealed differential responses to exercise for aortic stiffness between groups, the majority of remaining major outcomes would require a substantially larger sample. Thus, we do not believe we missed capturing any meaningful differences between groups based solely on sample size. As such, our data suggest the exercise responses between our groups were largely similar, giving way to small effect sizes for vascular and cognitive outcomes. It is possible, however, that a less well-matched sample, or group with more severe HTN might increase effects (discussed further below).

Table 8.1: Observed η^2, effect sizes, and required sample size per group to detect significant main effects at a power of 0.8.

	HTN effect			Exercise effect			HTN x exercise interaction		
	η^2	Effect Size f	N/group	η^2	Effect Size f	N/group	η^2	Effect Size f	N/group
cf PWV	0.05	0.24	19	0.20	0.50	6	0.03	0.16	38
Carotid artery									
β-stiffness	0.02	0.14	52	0.02	0.15	47	0.02	0.13	62
Mean diameter	0.01	0.07	197	0.11	0.35	9	0.01	0.07	197
Blood velocity PI	0.02	0.12	66	0.16	0.44	7	0.01	0.09	123
W_1	0.00	0.01	9812	0.28	0.62	4	0.00	0.03	982
Negative area	0.02	0.15	47	0.13	0.39	8	0.01	0.09	123
MCA									
Blood velocity PI	0.02	0.14	55	0.15	0.41	7	0.01	0.09	123
Mean velocity	0.00	0.05	491	0.00	0.01	9812	0.09	0.32	11
Reaction times									
Flanker	0.01	0.07	205	0.34	0.73	4	0.02	0.11	4920
N-Back	0.04	0.21	24	0.05	0.23	20	0.00	0.06	328
Memory	0.02	0.16	41	0.10	0.32	11	0.00	0.01	9812

Based on findings from Aim 1 and 2, we examined an exploratory Aim 3 to probe additional vascular contributions to cognitive function using a novel experimental design by comparing vascular hemodynamic responses *during* cognitive activity (neurovascular coupling [NVC]) in middle-aged adults with and without HTN. Similar to Aims 1 and 2, our hypotheses were largely rejected (Figure 8.2). We noted both adults with and without HTN exhibited similar increases in arterial stiffness and reductions in extracranial (i.e. carotid) pulsatility, and cerebral oxygenation (although adults with HTN appeared to do so with greater reliance on oxy- rather than de-oxygenated hemoglobin) during cognitive activity. Additionally, our data propose that modulation of hemodynamic pulsatility outside of the brain (i.e. extracranially) may impact tissue oxygenation in the brain. In total, the findings from these aims indicate that compared to adults without HTN, well-controlled middle-aged adults with HTN have similar 1) vascular and cognitive responses to acute exercise, and 2) cerebrovascular NVC during cognitive activity.

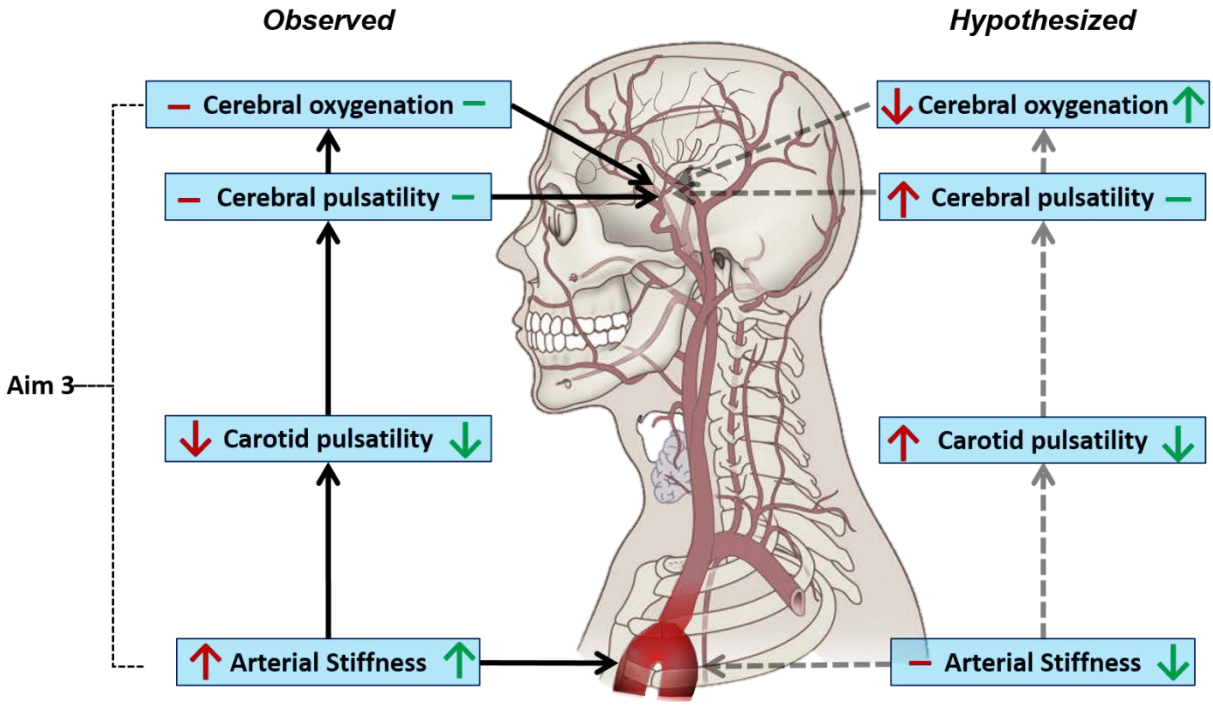

Figure 8.2: *Hypothesized and observed responses during cognitive activity (i.e. NVC) between adults with hypertension (**red** arrows) and adults without hypertension (**green** arrows).*

Implications

A major implication of our data is that middle-aged adults with HTN may not suffer from overt accelerated vascular aging, cognitive dysfunction, or cerebrovascular dysfunction at this stage of life compared to their counterparts free of HTN. Additionally adults with HTN appear to respond similarly to acute perturbations like exercise and cognitive activity. Of note, we believe the similar responses documented herein may largely stem from the general health status of our adults with controlled HTN compared to their counterparts without HTN. Our cohort of adults with controlled HTN had adequately controlled blood pressure and cholesterol, and achieved the recommended levels of physical activity on average. The pleiotropic benefits of certain anti-HTN and cholesterol-lowering medications (such as ACE-inhibitors and statins) may extend beyond lowering blood pressure/cholesterol and helped contribute to preserved vascular function and reactivity in our sample. Ultimately, this combination of lifestyle and pharmaceutical

control of cardiovascular risk factors likely ameliorated detrimental changes in vascular and cognitive function that have previously been observed in middle-aged adults with HTN. As such, our findings highlight the importance of lifestyle and pharmaceutical management and control of HTN. While HTN control and general health status may have helped attenuate differences in vascular and cognitive function between middle-aged adults with and without HTN in our study, it should be underscored adults with controlled-HTN still experience greater cardiovascular disease risk [354,355].

Data indicates that blood pressure control may not ameliorate cardiovascular risk [355-359]. Indeed, middle-aged individuals using anti-HTN medication still have ≈10% lower probability of survival compared to adults without HTN [357] and 46-75% greater risk of cardiovascular disease (cardiovascular death/events, coronary heart disease, and stroke) after adjustment for standard risk factors (i.e. age, blood pressure, cholesterol) [355]. Residual cardiovascular risk in this setting may stem from anti-HTN treatment's inability to reverse underlying cardiovascular structural/functional changes induced by HTN [360]. Some anti-HTN medications may reduce brachial blood pressure without consistently reducing vessel stiffness [13,14,184], giving way to observations of greater vessel stiffness in HTN, regardless of blood pressure control [276]. Additionally, anti-HTN medication may exert differential effects on more clinically relevant central blood pressure compared to brachial (i.e. peripheral) blood pressure [361]. As such, controlled blood pressure in HTN may not necessarily restore vascular structure (vessel stiffness, central blood pressure) and function to normal levels, and thus cardiovascular risk may remain elevated. For this reason, research and lifestyle interventions intended to *prevent* the development of HTN are still critical in reducing the burden of HTN and cardiovascular disease.

Aerobic fitness and physical activity are two important factors that contribute to blood pressure control and cardiovascular disease risk. Our adults without HTN were significantly

more fit (assessed via VO_2peak), had higher levels of physical activity, and had slightly lower average blood pressure at home. This could suggest that this group of middle-aged adults relied on greater amounts of physical activity and aerobic fitness to "control" their blood pressure and prevent the development of HTN. If this was the case, there should be an inverse relationship between fitness/physical activity and blood pressure in our adults without HTN. We noted no such associations between mean pressure and average step count (r=0.076, p=0.69), average minutes of MVPA (r=0.22, p=0.23), or VO_2peak (r=-0.20, p=0.28) in our adults without HTN. This suggests that differences in physical activity/fitness were not the sole determinants of lower blood pressure in our adults without HTN compared to those with HTN. Similar insignificant relationships were documented in our cohort of adults with HTN (mean pressure vs steps [r= -0.11, p=0.55], MVPA [r= -0.08, p=0.67], VO_2peak [r= -0.01, p=0.96]). There was, however, a modest association (r= -0.23) between VO_2peak and mean pressure in the group as a whole, however, that approached statistical significance (p=0.07), suggesting aerobic fitness may play some role in blood pressure control in middle-aged adults regardless of HTN status.

AHA recognizes intervening in mid-life HTN is key for late-life cognitive function [129]. Blood pressure control is associated with slower progression of arterial stiffening [275] reduced cerebral small vessel disease and brain atrophy [123,362], and improved cognitive function [362,363]. While some evidence indicates certain anti-HTN medications are beneficial for cognitive health [180,364,365], AHA and others suggest the direct effects of anti-HTN treatment and cognitive function are unclear and require further scrutiny [11,129,179]. As such, adequate blood pressure control and anti-HTN therapy in middle-aged adults may help slow vascular and brain aging explain why we noted no differences in vascular or cognitive function between our groups. The generally well-controlled HTN seen in our study may have also reflected that we excluded individuals with depression, condition known to reduce adherence to cardiovascular

medication [366]. Thus, differences between adults with and without HTN may emerge with inclusion of this co-morbidity.

Recent literature suggests that HTN severity and length of time exposed to HTN may be the predominant driver of differences between adults with and without HTN. Adults with more severe HTN (i.e. stage II) have higher arterial stiffness, and worse cerebrovascular reactivity and cognitive performance than adults with less severe HTN (i.e. stage I) or no HTN [367]. Similarly, cognitive impairment in this population appears related to HTN severity [302]. Univariate associations within our sample largely echo these observations (see Table 8.2). We noted that individuals with greater exposure to HTN (time since diagnosis) had stiffer arteries, greater pulsatile load and atherosclerotic burden, and lower cognitive performance. Additionally, those adults with more severe HTN (i.e. higher blood pressure) had stiffer arteries and lower memory recognition performance. These data further highlight the importance of early intervention and blood pressure control in slowing the detrimental cumulative effects of HTN.

Table 8.2: Univariate associations between hypertension history, at-home blood pressure, vascular health, cognition, and fitness/activity in middle-aged adults with controlled hypertension (n=30).

	HTN	7-day at home blood pressure					Vascular health			Cognition			Fitness	Activity
	HX	SP	DP	MP	PP	PL	IMT	MCA PI	Cf PWV	WM	ATTN	MEM	VO_2peak	Avg steps
SP	0.25													
DP	0.08	**0.75**												
MP	0.16	**0.91**	**0.96**											
PP	0.30	**0.72**	0.07	**0.36**										
PL	**0.38**	**0.70**	0.30	**0.50**	**0.73**									
IMT	**0.51**	0.16	0.04	0.10	0.20	0.31								
MCA PI	-0.06	-0.08	**-0.46**	-0.32	**0.37**	-0.02	0.01							
Cf PWV	**0.41**	0.26	0.15	0.21	0.23	**0.36**	0.28	-0.03						
WM	**-0.37**	-0.24	-0.19	-0.23	-0.15	-0.22	**-0.47**	0.05	0.01					
ATTN	**-0.48**	-0.06	0.21	0.10	-0.31	-0.28	**-0.47**	-0.09	0.00	**0.59**				
MEM	**-0.47**	**-0.45**	**-0.37**	**-0.43**	-0.28	**-0.40**	-0.03	0.03	-0.07	**0.37**	0.27			
VO_2peak	-0.05	0.10	-0.08	-0.01	0.23	-0.02	**-0.40**	0.08	-0.17	-0.21	-0.17	-0.06		
Avg steps	**0.43**	0.02	-0.20	-0.11	0.24	0.20	0.00	0.14	0.11	**-0.39**	**-0.41**	-0.35	**0.51**	
Avg MVPA	**0.44**	0.02	-0.14	-0.08	0.18	0.10	-0.10	0.18	0.08	-0.31	-0.22	-0.30	**0.51**	**0.86**

HTN HX, self-reported duration of hypertension; SP, systolic pressure; DP, diastolic pressure; MP, mean pressure; PP, pulse pressure; PL, pulsatile load; IMT, intima-media thickness; MCA, middle cerebral artery; PI, pulsatility index; cf PWV, carotid-femoral pulse wave velocity; WM, working memory accuracy (n-back); ATTN, attention accuracy (Flanker); MEM, memory recognition accuracy.

In November of 2017, after conclusion of the current study, AHA and collaborating governing bodies released new guidelines for the diagnosis, treatment, and management of hypertension [368]. The new guidelines now classify individuals with blood pressure >130 mmHg systolic and/or >80 mmHg diastolic, as hypertensive. With this shift, the number of American's with HTN increased from 32% to nearly half of all adults (46%) [369]. The guidelines, however, now take cardiovascular risk scores (Pooling Cohort 10-yr Cardiovasuclar disease risk estimations ≥10%) and age (≥65 yrs) into account prior to initiating pharmaceutical treatment of individuals with stage I HTN (130-139 mmHg systolic, 80-89 mmHg diastolic) [368]. As such, nearly 68.7% of individuals with stage 1 HTN will not qualify for pharmaceutical treatment, but will be treated with non-pharmaceutical therapy (i.e. weight loss, low sodium/high potassium diet, exercise/physical activity, and moderation of alcohol intake) [369]. Within our sample of middle-aged adults, 10 individuals without HTN would be reclassified by the new guidelines as having HTN. All of our "new HTN" individuals were <65 yrs of age, and only 1 would have qualified for pharmaceutical intervention according to the new guidelines (risk score ≥10%). The new guidelines would not have drastically altered our comparison of adults with medically-controlled HTN versus individuals without HTN. Interestingly, under resting conditions, those "new HTN" individuals were more phenotypically similar to the HTN group, exhibiting comparable arterial stiffness and blood pressure (see Table 8.3). This observation echoes the new guidelines that suggest those with blood pressure between 130/80 mmHg and 139/89 mmHg may be at similar risk as those >140/90 mmHg. Ultimately, all groups in our study (regardless of "new" or "old" HTN status) responded similarly to the perturbations of acute exercise and cognitive activity.

Table 8.3 Descriptive characteristics for normotensive (n=20), "≥130/80 HTN" (i.e. new 2017 guidelines; n=10), and "≥140/90 HTN" (i.e. previous 2003 guidelines; n=30).

	Normotensive	"≥130/80" HTN	"≥140/90" HTN	p
Sex (male/female)	9/11	7/3	16/14	0.43
Age (yr)	56 ± 6	56 ± 6	56 ± 6	1.00
Body fat (%)	32.8 ± 9.1	31 ± 7.3	31.4 ± 6.9	0.77
Body mass index (kg/m^2)	28.3 ± 2.3	28.3 ± 3.2	28.0 ± 3.3	0.94
VO_2peak (ml/kg/min)	32.6 ± 9.5	32.1 ± 7.5	27.2 ± 5.6†	**0.03**
Avg steps (#)	10926 ± 4145	10885 ± 5574	8765 ± 3046	0.11
Avg MVPA (min)	38.7 ± 23	44 ± 28	29 ± 20	0.13
At-home blood pressure				
Systolic pressure (mmHg)	111 ± 6	126 ± 5†	126 ± 12†	**0.01**
Diastolic pressure (mmHg)	71 ± 5	78 ± 7	79 ± 8†	**0.01**
Mean pressure (mmHg)	85 ± 4	94 ± 5†	95 ± 9†	**0.01**
Pulse pressure (mmHg)	40 ± 7	48 ± 9†	47 ± 8†	**0.01**
Pulsatile load (mmHg/min)	2509 ± 298	2983 ± 470	3150 ± 602^a	**0.01**
Aortic stiffness				
cf PWV (m/s)	7.6 ± 1.1	8.4 ± 0.9	8.2 ± 1.3	0.09
Middle cerebral artery				
Mean velocity (cm/s)	59 ± 16	63 ± 11	63 ± 11	0.55
Blood velocity PI	0.78 ± 0.11	0.78 ± 0.15	0.76 ± 0.11	0.74
Common carotid artery				
IMT (mm)	0.61 ± 0.09	0.63 ± 0.11	0.65 ± 0.12	0.38
Blood velocity PI	1.399 ± 0.341	1.48 ± 0.347	1.336 ± 0.261	0.42
β-Stiffness	7.7 ± 1.9	9.5 ± 2.8	8.7 ± 3	0.19
Cognition				
Working memory (%)	65.0 ± 20.0	71.0 ± 26.0	73.5 ± 15.6	0.32
Attention (%)	99.0 ± 1.5	98.5 ± 1.7	98.4 ± 2.5	0.60
Memory recognition (%)	49.8 ± 20.7	55.7 ± 22.1	54.5 ± 17.7	0.69

MVPA, moderate-to-vigorous physical activity; cf PWV, carotid-femoral pulse wave velocity; PI, pulsatility index; cognition displayed as %accuracy from working memory (N-back), attention (Flanker), and memory recognition tasks. $^\dagger p<0.05$ vs normotensive.

The new HTN guidelines represent a purposeful attempt to slow the growing burden that results from cumulative exposure to high blood pressure. However, these new guidelines still may not account for a critical component of long-term cardiovascular and cognitive disease risk: arterial stiffness. Arterial stiffness may be an underlying cause of HTN that precedes changes in blood pressure [6,7,65-72]. There is considerable evidence that arterial stiffness and the accompanying pulsatile hemodynamics predicts target organ damage and cardiovascular/ cognitive disease risk [6,66,77,82,83,95-101]. Data suggests arterial stiffness, rather than blood

pressure per se, may account for residual cardiovascular disease risk among adults with and without HTN [276]. Standardization of measurement for arterial stiffness is improving and is used widely in Europe, but has not been adapted in the US despite substantial utility in predicting cardiovascular disease risk [55]. As such, future guidelines should begin to incorporate the growing evidence that arterial stiffness may serve as one of the earliest and most robust indicators of target-organ damage and future disease risk.

Future Directions

Further studies investigating vascular and cognitive function following exercise in the setting of HTN should consider inclusion of additional groups to expand application of their findings to beyond those with well-controlled HTN. Comparing exercise effects in adults without HTN, with uncontrolled HTN, controlled HTN (medication and blood pressure <130/80), and inadequately controlled HTN (medication and blood pressure >130/80). While a substantial undertaking, this expansive group comparison would allow interrogation of multiple important aspects of HTN (severity, length of diagnosis, role of medication use) in all relevant subgroups of HTN (inadequately controlled, controlled, uncontrolled). This design would facilitate an intricate investigation of how HTN (in all of its major clinical forms) effects vascular and cognitive responses to exercise.

We investigated the effects of exercise on cognition using a pre/post design, repeating cognitive testing on a single day. While this reduces variability in responses introduced by testing on separate days, it does introduce the potential for order effects to effect cognitive testing. Despite this possibility, meta-analyses indicate that pre/post designs typically result in smaller effect sizes for changes in cognition, contrary to what would be expected if a large order effect was inherent in such study designs. We attempted to minimize order and learning effects by utilizing a thorough familiarization visit (including practicing each cognitive task in its entirety)

and by randomizing task order to the extent possible (order of Flanker/N-Back, and congruent/incongruent Stroop randomized, counter-balanced). Familiarization appeared successful, as there was a large increase in accuracy on tasks between the practice visit and pre-exercise testing. Additionally, if there was a significant learning effect driving post-exercis changes in cognition, we would expect that learning effect to elicit changes in the decision making process itself (changes in strength of evidence etc.). Of note, all observed changes in post-exercise cognition in this study was isolated to outside of the decision making process (non-decision time component of RT via DDM). None the less, future studies should consider including an additional resting set of cognitive measures, after proper familiarization, to be able to compare to post exercise measures. This would allow researchers to examine the effects of exercise on cognition through two separate comparisons and identify potential differences between the two designs.

Future research is necessary to better understand the intricate and complex relationships between HTN, exercise, and vascular and brain health. More research is recognizing that large conduit arteries may not be responsive to exercise training in HTN [34], however the reason for this remains elusive. To date, there is little data indicating aerobic fitness protects the brain from cognitive decline in HTN. A recent publication, however, from the 1998-2002 NHANES database suggests that older adults with greater self-reported physical activity have better cognitive function [370]. It should be underscored that this is far from a definitive report, based on our experience with the 1998-2002 NHANES sample [253], along with the study's limited sample of older adults, a single cognitive test, and self-reported physical activity. As such, future research is necessary to identify relationships between physical activity, fitness, and cognitive function in HTN through experimental research and stronger, more robust cross sectional analysis than recent publications.

Understanding vascular contributors to NVC in humans is a surprisingly understudied area that could offer insight into vascular contributions to cognitive decline with age and disease [320,325]. While much of the literature has focused on changes in mean blood flow/volume as it pertains to optimal NVC, many have overlooked how changes in hemodynamic pulsatility influence oxygen delivery to working neurons. More detailed characterization of extracranial contributions to intracranial hemodynamics during NVC is necessary. Future investigations should include bilateral assessment of common and internal carotid artery, intracranial, and prefrontal cortex hemodynamics. Including insonation of the anterior cerebral artery may help directly link hemodynamic transmission from the common carotid artery to the level of the prefrontal cortex measured by near-infrared spectroscopy. Utilizing novel experimental manipulations to alter arterial stiffness and pulsatility independent of changes in pressure via lower-body negative pressure could introduce additional insight into the role of extracranial vessel stiffness and pulsatility in NVC. This experimental design would allow for a comprehensive view of pulsatile transmission from the large extracranial vessels to the microvasculature surrounding active neural circuitry. Additional measurement to assess changes in shear stress and circulating BDNF during NVC may help uncover the indirect influence of cerebrovascular hemodynamics on neurotrophic factors and ultimately cognitive function.

Conclusions

The presence of hypertension (HTN) in middle-age is a major risk factor for later-life development of cognitive and cardiovascular disease. Exercise is widely recommended to combat vascular and brain aging in HTN. Acute aerobic exercise results in similar increases in arterial stiffness and hemodynamic pulsatility in adults with and without HTN. Additionally, acute aerobic exercise beneficially effects cognitive function in adults with and without HTN, accelerating executive function and memory processing speeds following exercise. Finally,

adults with and without HTN exhibit similar increases in large artery stiffness and decreases in extracranial hemodynamic pulsatility during cognitive activity, indicating similar NVC between groups. The similar responses to exercise and cognitive perturbations seen between our adults with and without HTN underscores the importance of blood pressure control to attenuate detrimental effects of HTN in middle-aged adults.

Appendix

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INSTITUTIONAL REVIEW
BOARD MEMORANDUM

TO: Kevin Heffernan

DATE: June 14, 2016

SUBJECT: **Expedited Protocol Review - Approval of Human Participants**
IRB #: 16-155

TITLE: *Effects of Aerobic Exercise on Cerebrovascular and Cognitive Function in Hypertensive Adults*

The above referenced protocol was reviewed by the Syracuse University Institutional Review Board for the Protection of Human Subjects (IRB) and has been given **expedited approval.** The protocol has been determined to be of no more than minimal risk and has been evaluated for the following:

1. the rights and welfare of the individual(s) under investigation;
2. appropriate methods to secure informed consent; and
3. risks and potential benefits of the investigation.

The approval period is **June 13, 2016** through **June 12, 2017**. A continuing review of this protocol must be conducted before the end of this approval period. Although you will receive a request for a continuing renewal approximately 60 days before that date, it is your responsibility to submit the information in sufficient time to allow for review before the approval period ends.

Enclosed are the IRB approved date stamped consent and/or assent document/s related to this study that expire on **June 12, 2017**. **The IRB approved date stamped copy must be duplicated and used when enrolling new participants during the approval period** (may not be applicable for electronic consent or research projects conducted solely for data analysis)**.** Federal regulations require that each participant indicate their willingness to participate through the informed consent process and be provided with a copy of the consent form. Regulations also require that you keep a copy of this document for a minimum of three years after your study is closed.

Any changes to the protocol during the approval period cannot be initiated **prior** to IRB review and approval, except when such changes are essential to eliminate apparent immediate harm to the participants. In this instance, changes must be reported to the IRB within five days. Protocol changes must be submitted on an amendment request form available on the IRB web site. Any unanticipated problems involving risks to subjects or others must be reported to the IRB within 10 working days of occurrence.

Thank you for your cooperation in our shared efforts to assure that the rights and welfare of people participating in research are protected.

Katherine
McDonald
IRB Chair

DEPT: Exercise Science, 820 Comstock Ave. – Rm. 207B

STUDENTS: Wesley Lefferts, Jacqueline Augustine, Jacob DeBlois

Electronic Informed Consent

Syracuse University

School of Education

Exercise Science
820 Comstock Avenue
201 Women's Building
Syracuse, NY 13244
(315)-443-2114

Project Title: The effect of exercise on the heart, blood vessels, and brain.

Dr. Kevin Heffernan and Mr. Wesley Lefferts of Syracuse University are collecting information to determine participant eligibility for a research study investigating how exercise affects the heart, blood vessels, and the brain. To determine your eligibility to participate in this study we will need some basic information regarding your health history, current health status and exercise habits. The survey will take no more than 10 minutes to complete and will ask you a series of questions regarding your health and exercise habits.

THE INFORMATION THAT YOU PROVIDE IN THIS SURVEY WILL BE USED TO DETERMINE YOUR ELIGIBILITY FOR THE RESEARCH STUDY ONLY.

You will not receive compensation for providing this information.

If you are eligible for the upcoming exercise research, we will contact you with details. If you are not eligible, we will also contact you to inform you that you do not qualify for this research study.

Willingness to provide information on this survey does not imply willingness to serve as a future research participant. If you are contacted based on eligibility we will provide you with detailed information on that study so that you can make an informed decision with regards to participation.

The information provided here will be held as confidential and protected. In this regard, the Qualtrics survey account is password protected and data from the survey will be stored on password protected computers in secure offices in the Department of Exercise Science, Syracuse University.

Your participation is voluntary, you may withdraw from the survey at any time and you do not need to answer any questions you do not want to.

Whenever one works with e-mail or the internet there is always the risk of compromising privacy, confidentiality and/or anonymity. Your confidentiality will be maintained to the degree permitted by the technology being used. It is important for you to understand that no guarantees can be made regarding the interception of data sent via the internet by third parties.

Risks and discomforts associated with this survey are minimal. There is the risk that confidentiality could be compromised but we have taken steps to minimize this risk as much as possible through password protection and data storage.

Benefits associated with this survey: There are no direct benefits to you from participating in this survey but there are potential benefits if you are eligible for the upcoming research study. Eligible participants for our upcoming exercise study will have the opportunity to receive compensation and information regarding their fitness and health status. Our overarching research goals are to understand how exercise improves heart and brain health and our ability to think. This survey is the first step in identifying participants for this line of research.

If you have any questions, concerns, complaints about this survey, you may contact Dr. Kevin Heffernan (email: ksheffer@syr.edu, telephone: 315-443-9801) or Wesley Lefferts (email: wleffert@syr.edu, telephone: 503-804-4424).

If you have any questions about your rights as a research participant, you have questions, concerns, or complaints that you wish to address to someone other than the investigator, if you cannot reach the investigator, or have experienced research related injuries, contact the Syracuse University Institutional Review Board at 315-443-3013.

PLEASE PRINT A COPY OF THIS INFORMED CONSENT FOR YOUR RECORDS.

By consenting below you indicate that you have read and fully understood this electronic informed consent form. You are fully aware of the purpose and procedures of this survey, as well as the risks, discomforts, and benefits associated with the survey and that you sign this electronic document freely and voluntarily.

___ I am over the age of 18 and I wish to complete the survey in order to be considered for a future exercise and health study.

___ I do not wish to complete the survey and would like to exit this survey.

EXERCISE SCIENCE
820 COMSTOCK AVENUE
201 WOMEN'S BUILDING
SYRACUSE, NY 13210
(315)-443-2114

The Effect of Exercise on Blood Pressure and Cognitive Function

Principal Investigator: Kevin Heffernan, Ph.D.
Telephone: 315-443-9801
Email: ksheffer@syr.edu
IRB Protocol #:

We are inviting you to participate in a research study run by Dr. Kevin Heffernan and Mr. Wesley Lefferts. Involvement in the study is voluntary, so you may choose to participate or not to participate. This sheet will explain the study to you and please feel free to ask questions about the research if you have any. We will be happy to explain anything in more detail if you wish.

Purpose

Blood pressure, which represents the pressure inside the blood vessels when the heart is contracting or relaxing, has direct effects on brain health. High blood pressure, in particular, has negative effects on the brain and blood vessels. High blood pressure is associated with greater risk of developing dementia and Alzheimer's disease. Therefore it has become increasingly important to treat high blood pressure through a combination of medication and lifestyle changes.

Exercise is widely recommended to improve brain health and to treat high blood pressure. Despite exercise's wide recommendations for use, the direct effect of exercise on the brain and blood vessels in adults with high blood pressure is largely unestablished. The purpose of this study is to investigate the effect of acute exercise on the blood vessels, blood pressure, and the brain in adults with normal and high blood pressure. In this study, after determining if exercise is appropriate for you, we will test your blood vessel elasticity, blood pressure, and brain function before and after a 30-minute bout of cycling exercise. This will be done over 3 visits that are described below (visit 1, health screening; visit 2, cardiorespiratory fitness test; visit 3, blood vessel/pressure and brain function testing before/after exercise). Understanding how exercise effects the blood vessels, blood pressure, and the brain in adults with high blood pressure will help us understand the effectiveness of exercise in improving health among this population.

Who can participate?

- Men and women between the ages of 45-64.

Do I have to participate?

- Your participation in this study is voluntary, which means you get to decide whether or not you want to participate
- Make sure that you read this entire form before making a decision and take as much time as you need.
- Feel free to ask as many questions about the study as you want. If you do not understand a term in the form, ask, and a researcher will explain it for you.
- If you decide to participate in the study you will be asked to sign a consent form.
- Do not sign the consent form until all of your questions have been answered and you understand what will happen in the study.
- Your signature means that you agree to participate in this study.
- You can ask for a copy of this form whether or not you agree to take part in the study.
- Your decision not to be in this research study will not result in any loss of benefits to which you are otherwise entitled.

Can I Withdraw From The Study Once It Has Started?

- At any time you may remove yourself from the study without giving any reason.
- If you are a student, withdrawing from the study will not affect your grade in courses in any way.

What Can I Expect From Participating?

For this study, you will need to visit the Human Performance Laboratory, located in the Women's Building at Syracuse University *once* for study health screening and *twice* for the exercise portions of the study. The screening will take about 75 minutes, the first exercise visit will take approximately 50 minutes, and the final exercise visit will take approximately 100 minutes.

Visit 1: Health Screening Visit

- At the ***health screening visit*** we will ask you to arrive >10 hours fasted (i.e. no food, caffeine, or alcohol for the past 10 hours). We ask this so that we can accurately measure your cholesterol and blood sugar (described further below). A light snack will be provided after this visit.
- You will be asked to fill out and sign this consent form, a detailed health history questionnaire, a sleep and physical activity questionnaire, and a depression questionnaire. Additionally, we will measure your height and weight using a stadiometer and electronic scale, in the same manner typically done at the doctor's office.
- We will also have you perform a brief cognitive test to assess basic brain function. We will also have you practice some on the computer in order to become familiar with them.
- We will ask you to give us a small urine sample so that we can check the function of your kidneys. We will provide a small sample container and escort you to the restroom.

- We will then estimate your body composition (percent body fat) using a BodPod and 3-D body scanner that will require you to wear tight fitting, minimal clothing for greatest accuracy in estimations. You will be asked to sit quietly in a chamber that resembles a giant egg for approximately two, 60-second intervals. This machine measures your body volume to estimate body fat. For the 3-D body scanner we will have you stand in the middle of the scanner in the same outfit you wear for the BodPod and 3 laser-guided cameras will scan down your body from head to toe. These lasers are not dangerous and will not damage your eyes, if your eyes are sensitive however we will invite you to close your eyes for the scan. The scan takes approximately 10 seconds for the cameras to move from your head to your toes.
- We will measure your blood pressure in both arms. We will place a blood pressure cuff around both your left and right upper arms (bicep) and they will inflate and deflate slowly. This is the same measurement that is often done at the Doctors office during a routine visit. We will take this measurement both while you are sitting, and while you are lying down.
- We will also measure your hemoglobin/hematocrit, cholesterol, glucose, and whole-body inflammation by obtaining a few small drops of blood from your fingertip (finger prick). These tests require that you arrive >10 hours fasted.
- As you leave the screening visit we will send you home with a small physical activity monitor and at-home blood pressure monitor. The physical activity monitor is less than 2 inches in length and will measure how much you move throughout the week. You will be instructed to attach it to the middle of your thigh using a special tape that we provide. We ask that you wear the monitor for a full 7 days, only removing it when involved in water activities such as showering/bathing and swimming. We will also ask you to measure your blood pressure twice a day, once in the morning, and once at night over the same 7 day span.
- Depending on your health status determined from the answers you provide on health questionnaires along with your home blood pressure measurements, we may ask you to contact your physician and receive permission to continue with the exercise portion of the study on subsequent visits.
- In total, the screening visit will take approximately 75 minutes.

Visit 2: Cardiorespiratory Fitness (exercise) Test

- For the first ***exercise visit*** we will ask you to arrive not having eaten within the past 3 hours. Intense exercise may upset your stomach if you have recently eaten. Therefore, we will please ask you to refrain from exercising or consuming alcohol or caffeine (including caffeinated coffee, tea, soda or energy drinks) on the day that you will come into the lab.
- We will have you practice some brain/cognitive tasks on the computer that we will have you perform in the third visit (described further under Visit 3). We have you practice them at the second visit so that you can become familiar with them.
- We will then prepare you for the cardiorespiratory fitness test. We will have you sit on a cycle ergometer (stationary bicycle) and rest for 5 minutes while we measure your blood pressure. During this time we will explain the exercise protocol to you.
- The cardiorespiratory fitness test will consist of cycling exercise, starting at a very low intensity for warm-up, and increasing exercise intensity with time. We will increase the intensity of exercise by increasing the resistance that you are pedaling against (i.e. making it harder to pedal). The goal of this test is to measure how much oxygen your body can consume during exercise. The more oxygen you can take in, the more fit you are. We will instruct you to continue exercising as long as you can. The test will end whenever you believe you cannot exercise any

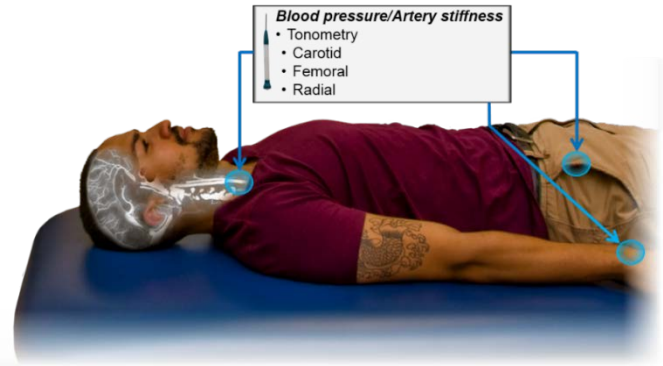
harder. If you are ever uncomfortable or concerned you may end the test at any time. If your cycling speed decreases too much we may also stop the test. The exercise test will usually last somewhere between 6-12 minutes.

- During the exercise test we will measure the following…

  - o Your blood pressure on the upper arm.
  - o The oxygen delivery to your calf muscle using a small sensor enclosed in a compressive stocking.
  - o Your heart rate using a thin strap that will be placed directly on the skin around your chest.
  - o The amount of oxygen you are consuming using a small device that is worn like a small backpack with a facemask (see image on the left).
  - o How hard you think you are working using a scale ranging from 6 (no work) to 20 (working as hard as I can).
  - After ending the test we will have you cool down and recover briefly by exercising at a very low intensity for 3-5 minutes before dismissing you.
- The cardiorespiratory fitness test visit will take approximately 50 minutes.

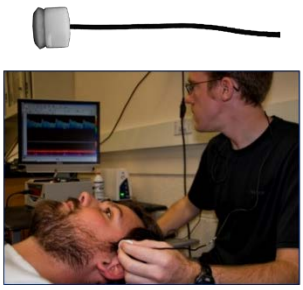
Visit 3: Acute exercise

- For the ***second exercise visit*** we will ask you to arrive >4 hours fasted (i.e. no food, caffeine, or alcohol for the past 4 hours) and to wear shorts and a T-shirt. At this visit we will measure your blood vessels, blood pressure, and brain function both before, and after, 30-minutes of moderate-intensity cycling exercise.
- First we will measure your blood pressure in the same manner as the previous visits. This is the same measurement that is often done at the Doctors office during a routine visit. We will take this measurement both while you are sitting, and while you are lying down.
- Next we will measure blood pressure at specific blood vessels in the body. To do so, we will take a small tonometer (a small pen-like device that senses pressure) and press it gently against the carotid artery (neck), radial artery (wrist), and femoral artery (upper leg/hip). We will do this while simultaneously measuring your heart rate from electrodes placed on your ribs and shoulder. We can use these pressure waves to calculate how stiff your blood vessels are.

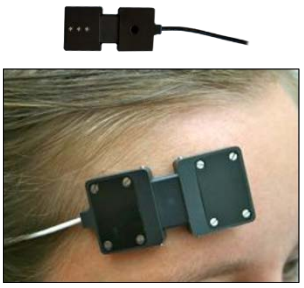


- Next we will measure your neck blood flow and brain blood flow using two non-invasive (no needles, no blood) techniques, Doppler ultrasound and blood flow sensors. Ultrasound probes will be placed on your neck and on the side of your face (near your temple, between your eye and ear) to assess neck artery stiffness and blood flow and brain blood flow. Additionally a blood flow sensors will be placed on the forehead and secured with a headband to assess brain blood flow.

Ultrasound probes



Blood flow sensor



- We will also measure the amount of carbon dioxide you exhale with each breath. This is done by placing small sampling lines directly under your nostrils and having you relax and breathe normally through your nose.
- After completion of the resting measures, you will begin a series of cognitive tasks that will be projected from a laptop to a screen above you. You will use a hand clicker to respond to questions on the monitor for ≈15 minutes. During these cognitive tasks we will continue to measure brain blood flow using the ultrasound probes and blood flow sensors previously described. This test will give us information about how the arteries in your brain react to the thinking required to answer the cognitive test. These cognitive tasks will be the same ones that you practiced at visit 2 and are designed to test your attention, reflexes, and memory.
- Once you have completed the cognitive tests we will remove our instruments and you will begin the 30-minute cycling exercise bout. The cycling intensity will be set at a workload to approximate 50-60% of your peak oxygen consumption (determined from visit 2).
- During the 30-minute cycling exercise bout we will measure blood pressure, heart rate, how hard you think you are working, and how much oxygen you are breathing in using the same techniques from the cardiorespiratory fitness test.
- After completing the exercise bout we will have you return to the testing table and let you recover for approximately 10 minutes while we set our instruments back up. After that we will repeat the same measures from before exercise (blood pressure, blood flow, cognitive function).
- Once the cognitive tasks are complete, we will remove our instruments and you will be permitted to leave.
- This exercise visits will take approximately 100 minutes to complete (25 minutes pre-testing, 30 minutes exercise, 35 minutes post-exercise).
- If you wish to withdraw from the study at any time you are free to do so.

Table 3 (Summary): Estimate timeline for participants across the 3 laboratory visits

Visit 1 *(≈1.25 hr)*		Visit 2 *(≈0.83 hr)*		Visit 3 *(≈1.66 hr)*	
Item	**Time (min)**	**Item**	**Time (min)**	**Item**	**Time (min)**
Consent	15	Cognitive task practice	15	Rest/instrumentation	10
Height/weight	5	Instrumentation	5	Blood pressure	
Blood lipids	5	Warm-up	5	Artery stiffness	10
Body composition	10	cardiorespiratory fitness test	15	Blood flow	
Kidney function	5	Cool-down	5	Cognitive testing	15
Blood pressure	15	Post-exercise monitoring	5	Acute exercise	30
Questionnaires	10			Rest/instrumentation	10
Dementia/depression	10			Blood pressure	
				Artery stiffness	10
				Blood flow	
				Cognitive testing	15
Total	75 min		50 min		100

Total time burden ≈ 3.75 hr

Can I be excluded from participation for any reason?

- Exercise is not appropriate for all individuals based on their health status. This study has a multi-stage process where we may exclude you from participating in the exercise portions of the study. An online eligibility survey is the first step, which you have already completed, followed by the health screening visit and at-home blood pressure measurements. Throughout this process, you may be excluded from the study based on answers to the eligibility survey, the questionnaires administered in the screening visit, if you have low kidney function (determined from the urine test), very low cognitive function (determined from the basic cognitive function test on visit 1), high depressive symptomology (determined from a questionnaire), and very high cholesterol or blood sugar (determined from blood tests). We may also exclude you if…
  - We find that you regularly experience any signs or symptoms that suggest you may have a medical condition and your health care provider is not aware that you are experiencing these symptoms. We will exclude you from the study and ask that you contact your health care provider.
  - You have recently sustained a concussion.
  - You have high blood pressure (systolic pressure >140, diastolic pressure >90 mmHg) and are not undergoing medical treatment for it. We will exclude you and ask that you follow up with your health care provider.
  - You have an abnormal blood pressure response to exercise during visit 2.
  - You have >2 cardiovascular risk factors and your physician does not give you, or you do not obtain, clearance to exercise.
- If you are experiencing any signs or symptoms of a serious/significant health condition *at the time of consent* (i.e. severe chest pain, leg pain, dizziness, feelings of heart palpitations) we will

contact emergency medical services immediately and you will not be able to participate in the study.

What Benefits Can I Expect From Participating?

- You may feel good about helping others with their research study by participating in this research study.
- You will receive information on your blood pressure, cholesterol levels, body composition, aerobic fitness, and cognitive function.
- ***These tests are not being used to diagnose a problem (NOT for medical/clinical purposes). These tests are for research purposes only.*** If you have high blood pressure we will inform you to go the university health center or go see your health care provider.

Are There Any Potential Risks From Participating In This Study?

- There are some risks associated with portions of this study.
- We will use a small amount of gel to help us measure your brain blood flow. There is minimal risk of gel getting into your eye when we measure brain blood flow due to the small amount of gel used in this technique. None the less, we will remind you to remain still as we take these measures to ensure that the gel does not come into contact with your eye. The gel is water-based and is designed for eye exams so in the event some comes in contact with your eye the discomfort should be minimal and temporary and can be rinsed out easily. We will escort you quickly to a sink to rinse out your eye if discomfort occurs.
- You may experience discomfort from the finger stick to test your blood lipids, hematocrit and hemoglobin. This will only be done two or three times and no more than that. We will use different fingers each time to reduce discomfort. If desired we can also place ice on the finger prior to the finger stick to reduce discomfort from the pinch.
- There is a small risk of infection associated with the finger stick. However, we will reduce this risk by ensuring that equipment is clean and sterile and the finger stick technician will wear lab coat, gloves, will clean the finger with alcohol swabs and will clean the area with a disinfectant wipe afterwards.
- There are inherent risks associated with exercise.
    - o There is a small risk of losing consciousness following intense exercise. We will minimize this risk by having you “cool-down” following the cardiorespiratory fitness test at visit 2. This will prevent the blood from staying down in your legs and will reduce the risk of light-headedness or dizziness after exercise. Additionally we will ask you communicate directly with us if you feel any light-headedness so that we can take appropriate precautions.
    - o Any type of exercise may, in rare instances, lead to heart attack, stroke or death; however, this is unusual, especially in adults free of known cardiovascular disease, free of any signs or symptoms of cardiovascular disease, and with few major risk factors of cardiovascular disease. Thus, risks associated with exercise are low in healthy, middle-aged adults. Our multi-stage screening process will help us ensure that exercise is appropriate and saafe for you. The multi-stage screening process will let us identify any pre-existing conditions or abnormalities that might limit exercise. By design, our exclusion criteria and extensive health screening priot to the exercise visits (visit 2 and 3) will remove you from participating if you are a high-risk individual.
    - o Based on our criteria however, you may be a moderate-risk individuals (i.e. you have >2

cardiovascular risk factors). The odds are, if you have high blood pressure you will fall into this moderate-risk group. As mentioned previously, we will require you to obtain clearance from your physician to participate in the exercise portion of the study if you are in this moderate-risk group (>2 cardiovascular risk factors). If you are unable to obtain clearance from your physician you will not be allowed to participate in the exercise visits.

- o It should be noted that exercise is widely recommeneded by health organizations as a lifestyle modification to reduce the negative effects of cardiovascular disease, even in moderate-risk populations with high blood pressure. Our multi-stage screening process and physican clearance steps will ensure that you will only engage in exercise if it is appropriate and safe for you, thus these risks should be minimal should you be cleared for the exercise portions of the study.

- Communicating with the researcher throughout the protocol will reduce risks.
- If at any point you are uncomfortable or feel pain anywhere, please tell us immediately.
- In the event of illness or physical injury resulting from taking part in this research study, medical treatment will not be compensated for. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by Syracuse University. You have not waived any of your legal rights by signing this form.

Are There Any Costs?

- There will be no costs to you for participating in this study.

Is There Any Compensation?

- Yes, you may receive monetary compensation for your time. You may receive $5 for completing the health screening visit, $5 for completing the physical activity and at-home blood pressure monitoring, $15 for completing the cardiorespiratory fitness test, and $20 for completing the final exercise visit. If you remove yourself, or are excluded, from the study prior to completing all visits, you will only be compensated for the trials that were completed. If you withdraw or are excluded from the study at visit 2 or 3 your compensation will be pro-rated depending on what stage of the visit you had completed. For visit 2, you will receive $5 for completing the cognitive practice tests, and $10 for undergoing the cardiorespiratory fitness test. For visit 3, you will be compensated with $5 for completing the resting measures, $5 for completing the 30-min exercise bout, and $10 for completing the post-measures.

Who Can See Information About This Study?

- ***The research records from this study will be confidential.*** Confidentiality means that it is our responsibility to keep any information you provide private and safe. Although we have taken steps in order to maximize and maintain confidentiality, it is important to understand that confidentiality cannot be guaranteed in lab settings.
- Only members of the trained research staff for this study with training in research ethics may look over your research records.
- The paperwork, results and records will be kept in a locked filing cabinet that only the researchers with training in research ethics will have access to.
- You will be given a study identification number (coded numbers, known only by primary researchers) and this will be entered into all research computers used to collect your blood pressure and blood flow. Your name will not appear anywhere on these computers or the data output from these computers.

- All information stored on computers requires a password access it. Only members of the research team with training in research ethics will have this password.
- The data and research record will be stored for up to 10 years.
- ***Your individual results will not be used in any way (we will average all results and display group averages only when presenting findings in papers and presentations)***

What Are My Rights In This Study?

- If at any point you wish to withdraw yourself from the study you may.
- You do not give up any of your legal rights by participating in this study.

Who Can I Contact For Questions Or More Information?

- If there are research related injuries or if you have any questions, concerns, or complaints about this study at any time, please feel free to contact:
  - Dr. Kevin Heffernan at ksheffer@syr.edu or call his office at 315-443-9801.
- If you have any questions about your rights as a research participant, you have questions, concerns, or complaints that you wish to address to someone other than the investigator, if you cannot reach the investigator, or have experienced research related injuries, contact the Syracuse University Institutional Review Board at 315-443-3013.

By signing below you indicate that you have read and fully understood this informed consent form. You are fully aware of the purpose and procedures of this study as well as the risks, discomforts, and benefits associated with the experimental protocol and that you sign this document freely and voluntarily.

All of my questions have been answered, I am 18 years of age or older, and I wish to participate in this research study. I have received a copy of this consent form.

_____ _____

Signature of participant Date

_____

Printed name of participant

_____ _____

Signature of researcher Date

_____

Printed name of researcher

Human Performance Lab Health Screening Form

Date_____

Age _____

Gender _____

Study ID:_____

Please answer the following questions as honestly as you can. Your patterns of responses will determine whether you may participate in the study.

Known Diseases (Medical Conditions)

1. List the medications and dietary supplements you take on a regular basis. (Include prescription and non-prescription, aspirin, vitamins/minerals, nutrition supplements [Ensure, Boost, etc.])

   _____

   _____

   _____

   _____

2. Has your health care provider ever told you have diabetes? No Yes
3. Do you have acute or terminal illness (if so, please explain below)? No Yes

   _____

4. Have you ever had a stroke, heart attack or heart trouble? No Yes
5. Has your health care provider ever told you that you have a heart murmur? No Yes
6. Have you had a head injury in the past 3 months? No Yes
7. Do you have asthma /take asthma medication? No Yes
8. Has your health care provider ever told you that you have kidney or liver disease? No Yes
9. Has your health care provider ever told you that you have chronic pulmonary or respiratory disease? No Yes
10. Has your health care provider ever told you that you have peripheral artery disease? No Yes
11. Has your health care provider ever told you that you have high blood pressure? No Yes
12. Has your health care provider ever told you that you have high cholesterol? No Yes
13. Do you smoke cigarettes on a daily basis? No Yes

If yes to #13, how many packs per day _____

If yes to #13, how long have you been smoking _____

14. Have you lost or gained weight in the previous 6 months? No Yes

If yes, how much weight? _____

15. Has a first degree relative (e.g. father, mother, sister, brother, or child) suffered from a heart attack or diagnosed cardiovascular disease? No Yes

Relative	Age	Did they pass away?

16. Do you often have pains in your heart, chest, neck, jaw, arms or other areas especially during exercise? No Yes

17. Do you regularly get pains in you calves or lower legs during exercise which are not due to soreness or stiffness? No Yes

18. Do you experience swelling or accumulation of fluid in or around your ankles? No Yes

19. Do you often feel faint or have spells of severe dizziness during exercise? No Yes

20. Do you often get the feeling that your heart is beating faster, racing, or skipping beats, either at rest or during exercise? No Yes

21. If you answered YES to question(s) 17-21, does your health care provider know that you have this/these symptom(s)? No Yes

22. If you answered YES to question(s) 16-20, are you currently experiencing this/these symptom(s) RIGHT NOW? No Yes

23. With which hand do you write? Left Right

24. How do you define your race/ethnicity? _____

25. What is the highest grade/level of schooling/education completed?

8th Grade Some HS HS some college college graduate school

26. Have you ever lost consciousness before during any daily activity? No Yes
If you answered YES to question 31, please explain below.

27. On a scale of 1-5 (1= not anxious at all; 5= very anxious) how anxious do you feel during a typical Doctor's office visit? 1 2 3 4 5

28. Additional:

Please circle all that apply

Allergies	Fibromyalgia	Polio	Flu
Anemia	Attention Deficit Hyperactivity Disorder	Reflux or Ulcers	Seizures
Anxiety	Glaucoma	Liver Disease	Concussion
Arthritis	Lupus	Bone Disease	Eczema
Asthma	Meningitis	Leg/foot Ulcers	Epilepsy
Cataracts	Chronic Lyme Disease	Diverticulitis	Headaches/Migraine
Chronic Bronchitis	Gout	Infection	Urinary Tract Infection
Lung Disease	Thyroid (underactive/overactive)	Cold	Kidney Stones

Continued on back.

Blood pressure history

3. Have you ever been told you have high blood pressure (i.e. hypertension)? No Yes

4. Have you ever been diagnosed with high blood pressure by your physician? No Yes

   If yes, how long have you been living with high blood pressure? _____

5. Are you currently taking prescription medication to treat/control your blood pressure? No Yes

   If yes, what kind of medication are you taking? _____

   What dose? _____

   Approximately how long have you been taking this medication? _____

   Has your medication or your dose changed in the past 4-6 weeks? No Yes

6. Have you had trouble medically controlling your blood pressure (i.e. been on multiple medications)?
   No Yes

Exercise history

1. Do you currently exercise on a regular basis? No Yes

2. Please rate your exercise level on a scale of 1 to 5 (5 indicating very strenuous) for each age range to your present age:

   15-20 _____ 21-30 _____ 31- 40 _____ 41-50 _____ 50 & older _____

3. Were you a high school and/or college athlete?

   If yes, please specify: _____

4. Approximately how much time per week do you engage in exercise? No Yes

   Minutes/day: _____ Days/week: _____

5. Are you currently involved in regular endurance (cardiovascular) exercise? No Yes

   If yes, specify the type of exercise(s): _____

   Days/week: _____ Minutes/day: _____

   Rate your perception of the exertion during your endurance/cardiovascular exercise (circle the number):

   (1) Light (2) Fairly Light (3) Somewhat Hard (4) Hard

6. Are you currently involved in regular strength building (weight lifting) exercise?

   If yes, specify the type of exercise(s): _____

   Days/week: _____ Minutes/day: _____

   Rate your perception of the exertion during your strength building exercise (circle the number):

   (1) Light (2) Fairly Light (3) Somewhat Hard (4) Hard

7. How long have you been exercising regularly? _____ months _____ years

8. Do you participate in any sport, or recreational activities?

   If yes, please specify the sports/activities

   _____

   _____

Menstrual Status (answer these questions only if you are a female)

1. Do you currently experience a regular menstrual cycle (i.e. period)? No Yes
   If no, approximately how many years ago did you have a regular menstrual cycle (10-12 a year)?_____

   If yes, approximately how many periods in a year do you have? _____

   Approximately how many days between periods? _____

   What was the approximate date of your last menstrual period?_____

2. Has the time between your menstrual cycles changed at all recently? No Yes
   Has the length differed by >7 days? No Yes

   Has the length between cycles been >60 days (2 months)? No Yes

3. Have you ever experienced menstrual irregularity? No Yes

   Please describe (i.e. number of skipped menses, or prolonged menses): _____

   Approximately how long did this occur? Are you experiencing this currently?_____

4. Are you currently ammenhoreic? No Yes

5. Have you gone through menopause (defined as no menstrual cycle/period for more than 12 months without any other possible causes)? No Yes

6. Do you currently experience any of the following? Circle all that apply No Yes

7. Hot flashes	8. Irregular menstrual cycles	9. Night sweats	10. Sleep problems
11. Mood changes	12. Frequent urination	13. Urinary tract infections	14. Uncomfortable genital dryness

15. Do you use oral contraceptives? No Yes
    If yes, for how long have you been using? _____
    Which kind? _____
    What dose?_____
    Do you take the withdrawal/Placebo pills?_____

16. Do you use Depo-Provera for birth control? No Yes
    If yes, for how long have you used this method?_____

17. Do you use hormone replacement therapy? No Yes
    If yes, for how long have you been using? _____

    Which kind? _____

    What dose?_____

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.
Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

f) Feel too cold

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

g) Feel too hot

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

h) Had bad dreams

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

i) Have pain

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

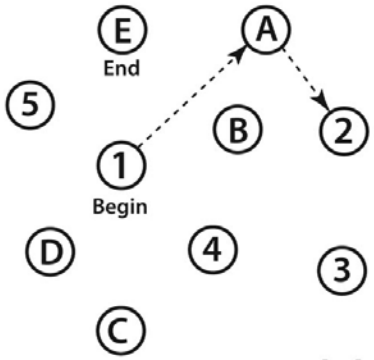
Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



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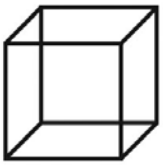


[ ] [ ]

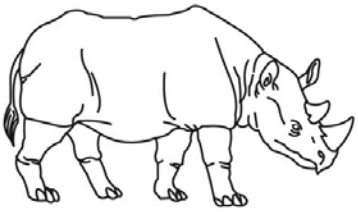
Draw CLOCK (Ten past eleven)
(3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

NAMING

[ ]



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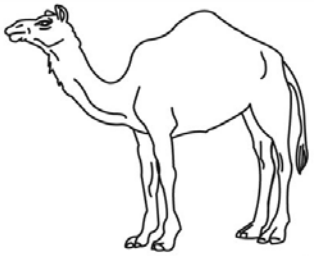


[ ] ___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL

	FACE	VELVET	CHURCH	DAISY	RED	
Has to recall words **WITH NO CUE**	[ ]	[ ]	[ ]	[ ]	[ ]	Points for UNCUED recall only
Optional Category cue						
Optional Multiple choice cue						

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
(August 2002)

SHORT LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is supported to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information
More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**
   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

   _____ **hours per day**
   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

CES-D Depression Inventory

INSTRUCTIONS: For each statement, please circle the number in the column that best describes how you have been feeling *in the past week*.

		Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)
1.	I was bothered by things that usually don't bother me.	0	1	2	3
2.	I did not feel like eating; my appetite was poor.	0	1	2	3
3.	I felt that I could not shake off the blues, even with the help from family or friends.	0	1	2	3
4.	I felt that I was just as good as other people.	3	2	1	0
5.	I had trouble keeping my mind on what I was doing.	0	1	2	3
6.	I felt depressed.	0	1	2	3
7.	I felt that everything I did was an effort.	0	1	2	3
8.	I felt hopeful about the future.	3	2	1	0
9.	I thought my life had been a failure.	0	1	2	3
10.	I felt fearful.	0	1	2	3
11.	My sleep was restless.	0	1	2	3
12.	I was happy.	3	2	1	0
13.	I talked less than usual.	0	1	2	3
14.	I felt lonely.	0	1	2	3
15.	People were unfriendly.	0	1	2	3
16.	I enjoyed life.	3	2	1	0
17.	I had crying spells.	0	1	2	3
18.	I felt sad.	0	1	2	3
19.	I felt that people dislike me.	0	1	2	3
20.	I could not get "going".	0	1	2	3

Anyone with suicidal urges should seek immediate consultation with a qualified psychiatrist or psychologist.

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	**1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	**2. Do you feel pain in your chest when you do physical activity?**
☐	☐	**3. In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	**4. Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	**5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	**6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	**7. Do you know of any other reason why you should not do physical activity?**

If you answered YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→ **DELAY BECOMING MUCH MORE ACTIVE:**

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

CSEP | SCPE

Tri-fold recruiting pamphlet

HUMAN PERFORMANCE LABORATORY

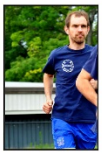
Interested in participating in our *research study* or learning more?

E-mail Syracuse University researcher Wes Lefferts at wleffert@syr.edu

Blood pressure and the brain!

- **Blood pressure has been linked to...**
  - Decline in cognitive function with age
  - Risk of dementia and Alzheimer's disease.

- **Exercise has been linked to...**
  - Improved blood pressure and brain function as we age.



- **Exercise may serve as a way to improve our blood pressure and make sure our brains age gracefully.**

Our Research

We at the Human Performance Lab (HPL) at Syracuse University are investigating how exercise affects blood pressure and the brain in middle-age adults with medically controlled blood pressure compared to normal blood pressure.

Who can participate?

- **Middle-age adults (45-64 years old) who use medication to control their blood pressure, or have normal blood pressure.**

Am I eligible to participate?

- Eligibility is determined by an online health survey that we use to assess if exercise is appropriate for you.

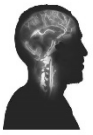
What does the study entail?

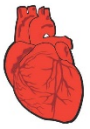
- Fill out the online eligibility survey. We will contact you if you qualify!
- This study includes 3 visits to the HPL (room 306, Women's bldg, SU).
- Visit 1: (75 min) Comprehensive health screening

- Take home a blood pressure and activity monitor for a week
- Visit 2: (60 min) Perform an cycling exercise test to determine your fitness
- Visit 3: (120 min) We will measure your blood pressure and brain function before and after cycling exercise.

Do you take medication to control your blood pressure?

Are you interested in the health of your brain and blood vessels?





Syracuse University researchers are investigating how exercise affects the brain and blood vessels in adults who take medication to help control their blood pressure.

Want to participate?

We are recruiting middle-aged adults (45-64 years old) who have normal blood pressure or are taking medication to help control their blood pressure.

You will receive up to $45 for participating.

HUMAN PERFORMANCE LABORATORY

What do you get out of it?

- **Have your health assessed using our state-of-the-art technology! We will measure...**
  - How much muscle you have using our BodPod and 3D-body scanner!

  - The health of your blood vessels!

  - Your brain function, cholesterol, and aerobic fitness!

- **Receive up to $45 for completing the study!**

Interested in participating?

- **Please email wleffert@syr.edu.**
- **We will send you the eligibility survey.**
- **Once we have received your health survey information we will contact you if you qualify!**

Please email wleffert@syr.edu if you want to participate in our research study or have any questions.

At home blood pressure monitoring log

		Reading 1		Reading 2		
		SYS 1	**DIA 1**	**SYS 2**	**DIA 2**	**Notes/comments**
Monday	AM	119	72	124	70	
example	PM	138	80	136	78	Had stressful day at work and forgot to sit for 5 min before measuring
Monday	AM					
	PM					
Tuesday	AM					
	PM					
Wednesday	AM					
	PM					
Thursday	AM					
	PM					
Friday	AM					
	PM					
Saturday	AM					
	PM					
Sunday	AM					
	PM					

Please wear the physical activity monitor taped to the middle part of your thigh. Please wear this monitor during all waking and sleeping hours. **Remove the monitor before any water activity** (i.e. swimming, bathing, showering) **and document the time and duration that it was off of your body**.

EXAMPLE DAILY LOG

Monday **Woke up at*: 6:30AM*** **Went to bed at: *10:30PM***

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	
6:45-7:00AM - shower	-
5:30-5:40PM - shower after exercise	-
-	-
-	-
-	-

Monday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Tuesday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Wednesday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Thursday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Friday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Saturday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Sunday **Woke up at:** **Went to bed at:**

Please indicate time interval when monitor was not worn (i.e. "8:05-8:25AM - shower)	

Other notes:

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015; 131 (4):e29-322.
2. Mitchell GF. Arterial stiffness and hypertension. Hypertension 2014; 64 (1):13-18.
3. Gurunathrao PS, Manjunatha A, Kanti DK. Evaluation of arterial stiffness in elderly with prehypertension. Indian journal of physiology and pharmacology 2015; 59 (1):16-22.
4. Liu CY, Chen D, Bluemke DA, Wu CO, Teixido-Tura G, Chugh A, et al. Evolution of aortic wall thickness and stiffness with atherosclerosis: long-term follow up from the multi-ethnic study of atherosclerosis. Hypertension 2015; 65 (5):1015-1019.
5. Barbaro NR, Fontana V, Modolo R, De Faria AP, Sabbatini AR, Fonseca FH, et al. Increased arterial stiffness in resistant hypertension is associated with inflammatory biomarkers. Blood pressure 2015; 24 (1):7-13.
6. Najjar SS, Scuteri A, Shetty V, Wright JG, Muller DC, Fleg JL, et al. Pulse wave velocity is an independent predictor of the longitudinal increase in systolic blood pressure and of incident hypertension in the Baltimore Longitudinal Study of Aging. Journal of the American College of Cardiology 2008; 51 (14):1377-1383.
7. Liao D, Arnett DK, Tyroler HA, Riley WA, Chambless LE, Szklo M, et al. Arterial stiffness and the development of hypertension. The ARIC study. Hypertension 1999; 34 (2):201-206.
8. Tarumi T, Shah F, Tanaka H, Haley AP. Association between central elastic artery stiffness and cerebral perfusion in deep subcortical gray and white matter. American journal of hypertension 2011; 24 (10):1108-1113.
9. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. Brain : a journal of neurology 2011; 134 (Pt 11):3398-3407.
10. Waldstein SR, Rice SC, Thayer JF, Najjar SS, Scuteri A, Zonderman AB. Pulse pressure and pulse wave velocity are related to cognitive decline in the Baltimore Longitudinal Study of Aging. Hypertension 2008; 51 (1):99-104.
11. Gasecki D, Kwarciany M, Nyka W, Narkiewicz K. Hypertension, brain damage and cognitive decline. Current hypertension reports 2013; 15 (6):547-558.
12. Hajjar I, Goldstein FC, Martin GS, Quyyumi AA. Roles of Arterial Stiffness and Blood Pressure in Hypertension-Associated Cognitive Decline in Healthy Adults. Hypertension 2015.
13. Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, et al. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the american heart association. Hypertension 2013; 61 (6):1360-1383.
14. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Medicine and science in sports and exercise 2004; 36 (3):533-553.
15. Seals DR. Edward F. Adolph Distinguished Lecture: The remarkable anti-aging effects of aerobic exercise on systemic arteries. Journal of applied physiology (Bethesda, Md : 1985) 2014; 117 (5):425-439.
16. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. Stroke; a journal of cerebral circulation 2011; 42 (9):2672-2713.
17. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychological science 2003; 14 (2):125-130.

18. Cameron JD, Dart AM. Exercise training increases total systemic arterial compliance in humans. The American journal of physiology 1994; 266 (2 Pt 2):H693-701.
19. Heffernan KS, Collier SR, Kelly EE, Jae SY, Fernhall B. Arterial stiffness and baroreflex sensitivity following bouts of aerobic and resistance exercise. International journal of sports medicine 2007; 28 (3):197-203.
20. Chang YK, Labban JD, Gapin JI, Etnier JL. The effects of acute exercise on cognitive performance: a meta-analysis. Brain research 2012; 1453:87-101.
21. Lucas SJ, Ainslie PN, Murrell CJ, Thomas KN, Franz EA, Cotter JD. Effect of age on exercise-induced alterations in cognitive executive function: relationship to cerebral perfusion. Experimental gerontology 2012; 47 (8):541-551.
22. Tarumi T, Gonzales MM, Fallow B, Nualnim N, Pyron M, Tanaka H, et al. Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. Journal of hypertension 2013; 31 (12):2400-2409.
23. Hawkins HL, Kramer AF, Capaldi D. Aging, exercise, and attention. Psychology and aging 1992; 7 (4):643-653.
24. Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR. Aging, habitual exercise, and dynamic arterial compliance. Circulation 2000; 102 (11):1270-1275.
25. Bailey DM, Marley CJ, Brugniaux JV, Hodson D, New KJ, Ogoh S, et al. Elevated aerobic fitness sustained throughout the adult lifespan is associated with improved cerebral hemodynamics. Stroke; a journal of cerebral circulation 2013; 44 (11):3235-3238.
26. Barnes JN. Exercise, cognitive function, and aging. Advances in physiology education 2015; 39 (2):55-62.
27. Barnes JN, Taylor JL, Kluck BN, Johnson CP, Joyner MJ. Cerebrovascular reactivity is associated with maximal aerobic capacity in healthy older adults. Journal of applied physiology (Bethesda, Md : 1985) 2013; 114 (10):1383-1387.
28. Lista I, Sorrentino G. Biological mechanisms of physical activity in preventing cognitive decline. Cellular and molecular neurobiology 2010; 30 (4):493-503.
29. Deary IJ, Whalley LJ, Batty GD, Starr JM. Physical fitness and lifetime cognitive change. Neurology 2006; 67 (7):1195-1200.
30. Lee YH, Yoon ES, Park SH, Heffernan KS, Lee C, Jae SY. Associations of arterial stiffness and cognitive function with physical fitness in patients with chronic stroke. Journal of rehabilitation medicine 2014; 46 (5):413-417.
31. Montero D, Roche E, Martinez-Rodriguez A. The impact of aerobic exercise training on arterial stiffness in pre- and hypertensive subjects: a systematic review and meta-analysis. International journal of cardiology 2014; 173 (3):361-368.
32. Miura H, Takahashi Y, Maki Y, Sugino M. Effects of exercise training on arterial stiffness in older hypertensive females. European journal of applied physiology 2015; 115 (9):1847-1854.
33. Ferrier KE, Waddell TK, Gatzka CD, Cameron JD, Dart AM, Kingwell BA. Aerobic exercise training does not modify large-artery compliance in isolated systolic hypertension. Hypertension 2001; 38 (2):222-226.
34. Pierce GL. Aortic Stiffness in Aging and Hypertension: Prevention and Treatment with Habitual Aerobic Exercise. Current hypertension reports 2017; 19 (11):90.
35. Park S, Ha JW, Shim CY, Choi EY, Kim JM, Ahn JA, et al. Gender-related difference in arterial elastance during exercise in patients with hypertension. Hypertension 2008; 51 (4):1163-1169.
36. Liu S, Goodman J, Nolan R, Lacombe S, Thomas SG. Blood pressure responses to acute and chronic exercise are related in prehypertension. Medicine and science in sports and exercise 2012; 44 (9):1644-1652.

37. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42 (6):1206-1252.
38. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet (London, England) 2002; 360 (9349):1903-1913.
39. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. The New England journal of medicine 2001; 345 (18):1291-1297.
40. Kaplan NM. Clinical Hypertension. Baltimore, MD: Williams & Wilkins; 1998.
41. Fernandez G, Lee JA, Liu LC, Gassler JP. The Baroreflex in Hypertension. Current hypertension reports 2015; 17 (3):19.
42. Chapleau MW, Cunningham JT, Sullivan MJ, Wachtel RE, Abboud FM. Structural versus functional modulation of the arterial baroreflex. Hypertension 1995; 26 (2):341-347.
43. Grassi G, Cattaneo BM, Seravalle G, Lanfranchi A, Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 1998; 31 (1):68-72.
44. Julius S, Schork N, Schork A. Sympathetic hyperactivity in early stages of hypertension: the Ann Arbor data set. Journal of cardiovascular pharmacology 1988; 12 Suppl 3:S121-129.
45. Abboud FM. The sympathetic system in hypertension. State-of-the-art review. Hypertension 1982; 4 (3 Pt 2):208-225.
46. Johns EJ. Renal Sympathetic Nerves and Extracellular Fluid Volume Regulation. In: Izzo JL, Jr., Black HR, Sica DA, editors. Hypertension Primer. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
47. Omvik P, Tarazi RC, Bravo EL. Regulation of sodium balance in hypertension. Hypertension 1980; 2 (4):515-523.
48. Gkaliagkousi E, Gavriilaki E, Triantafyllou A, Douma S. Clinical Significance of Endothelial Dysfunction in Essential Hypertension. Current hypertension reports 2015; 17 (11):85.
49. Dikalov SI, Dikalova AE. Contribution of mitochondrial oxidative stress to hypertension. Current opinion in nephrology and hypertension 2016; 25 (2):73-80.
50. Panza JA, Casino PR, Kilcoyne CM, Quyyumi AA. Role of endothelium-derived nitric oxide in the abnormal endothelium-dependent vascular relaxation of patients with essential hypertension. Circulation 1993; 87 (5):1468-1474.
51. Baumbach GL. Mechanisms of Vascular Remodeling. In: Izzo JL, Jr., Black HR, Sica DA, editors. Hypertension Primer. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
52. Ibrahim J, Berk BC. Flow-mediated vascular remodeling in hypertension: relation to hemodyamics. Stroke; a journal of cerebral circulation 2009; 40 (2):582-590.
53. Mulvany MJ, Baumbach GL, Aalkjaer C, Heagerty AM, Korsgaard N, Schiffrin EL, et al. Vascular remodeling. Hypertension 1996; 28 (3):505-506.
54. Intengan HD, Schiffrin EL. Structure and mechanical properties of resistance arteries in hypertension: role of adhesion molecules and extracellular matrix determinants. Hypertension 2000; 36 (3):312-318.
55. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, et al. Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness: A Scientific Statement From the American Heart Association. Hypertension 2015; 66 (3):698-722.
56. Tarumi T, Ayaz Khan M, Liu J, Tseng BY, Parker R, Riley J, et al. Cerebral hemodynamics in normal aging: central artery stiffness, wave reflection, and pressure pulsatility. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2014; 34 (6):971-978.
57. Nichols WW, O'Rourke MF. McDonald's blood flow in arteries. Theoretical, experimental and clinical principles. London: Hodder Arnold; 2005.

58. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. Circulation 2003; 107 (22):2864-2869.
59. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. Journal of the American College of Cardiology 2007; 50 (1):1-13.
60. Sun Z. Aging, arterial stiffness, and hypertension. Hypertension 2015; 65 (2):252-256.
61. Kovacic JC, Moreno P, Nabel EG, Hachinski V, Fuster V. Cellular senescence, vascular disease, and aging: part 2 of a 2-part review: clinical vascular disease in the elderly. Circulation 2011; 123 (17):1900-1910.
62. Zarrinkoob L, Ambarki K, Wahlin A, Birgander R, Carlberg B, Eklund A, et al. Aging alters the dampening of pulsatile blood flow in cerebral arteries. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2016.
63. Mitchell GF. Arterial stiffness and hypertension: chicken or egg? Hypertension 2014; 64 (2):210-214.
64. Smulyan H, Mookherjee S, Safar ME. The two faces of hypertension: role of aortic stiffness. Journal of the American Society of Hypertension : JASH 2016; 10 (2):175-183.
65. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Aortic stiffness, blood pressure progression, and incident hypertension. JAMA : the journal of the American Medical Association 2012; 308 (9):875-881.
66. Dernellis J, Panaretou M. Aortic stiffness is an independent predictor of progression to hypertension in nonhypertensive subjects. Hypertension 2005; 45 (3):426-431.
67. Takase H, Dohi Y, Toriyama T, Okado T, Tanaka S, Sonoda H, et al. Brachial-ankle pulse wave velocity predicts increase in blood pressure and onset of hypertension. American journal of hypertension 2011; 24 (6):667-673.
68. Laurent S, Boutouyrie P. The structural factor of hypertension: large and small artery alterations. Circulation research 2015; 116 (6):1007-1021.
69. Koivistoinen T, Lyytikainen LP, Aatola H, Luukkaala T, Juonala M, Viikari J, et al. Pulse Wave Velocity Predicts the Progression of Blood Pressure and Development of Hypertension in Young Adults. Hypertension 2018.
70. Le VP, Knutsen RH, Mecham RP, Wagenseil JE. Decreased aortic diameter and compliance precedes blood pressure increases in postnatal development of elastin-insufficient mice. American journal of physiology Heart and circulatory physiology 2011; 301 (1):H221-229.
71. Niederhoffer N, Lartaud-Idjouadiene I, Giummelly P, Duvivier C, Peslin R, Atkinson J. Calcification of medial elastic fibers and aortic elasticity. Hypertension 1997; 29 (4):999-1006.
72. Weisbrod RM, Shiang T, Al Sayah L, Fry JL, Bajpai S, Reinhart-King CA, et al. Arterial stiffening precedes systolic hypertension in diet-induced obesity. Hypertension 2013; 62 (6):1105-1110.
73. Mattace-Raso FU, van den Meiracker AH, Bos WJ, van der Cammen TJ, Westerhof BE, Elias-Smale S, et al. Arterial stiffness, cardiovagal baroreflex sensitivity and postural blood pressure changes in older adults: the Rotterdam Study. Journal of hypertension 2007; 25 (7):1421-1426.
74. Kingwell BA, Cameron JD, Gillies KJ, Jennings GL, Dart AM. Arterial compliance may influence baroreflex function in athletes and hypertensives. The American journal of physiology 1995; 268 (1 Pt 2):H411-418.
75. Virtanen R, Jula A, Huikuri H, Kuusela T, Helenius H, Ylitalo A, et al. Increased pulse pressure is associated with reduced baroreflex sensitivity. Journal of human hypertension 2004; 18 (4):247-252.
76. Okada Y, Galbreath MM, Shibata S, Jarvis SS, VanGundy TB, Meier RL, et al. Relationship between sympathetic baroreflex sensitivity and arterial stiffness in elderly men and women. Hypertension 2012; 59 (1):98-104.
77. Safar ME, Plante GE, Mimran A. Arterial stiffness, pulse pressure, and the kidney. American journal of hypertension 2015; 28 (5):561-569.

78. Ishimura E, Taniwaki H, Tsuchida T, Obatake N, Emoto M, Shoji T, et al. Urinary albumin excretion associated with arterial wall stiffness rather than thickness in type 2 diabetic patients. Journal of nephrology 2007; 20 (2):204-211.
79. Smith A, Karalliedde J, De Angelis L, Goldsmith D, Viberti G. Aortic pulse wave velocity and albuminuria in patients with type 2 diabetes. Journal of the American Society of Nephrology : JASN 2005; 16 (4):1069-1075.
80. Yokoyama H, Aoki T, Imahori M, Kuramitsu M. Subclinical atherosclerosis is increased in type 2 diabetic patients with microalbuminuria evaluated by intima-media thickness and pulse wave velocity. Kidney international 2004; 66 (1):448-454.
81. Cirillo M, Stellato D, Laurenzi M, Panarelli W, Zanchetti A, De Santo NG. Pulse pressure and isolated systolic hypertension: association with microalbuminuria. The GUBBIO Study Collaborative Research Group. Kidney international 2000; 58 (3):1211-1218.
82. Ford ML, Tomlinson LA, Chapman TP, Rajkumar C, Holt SG. Aortic stiffness is independently associated with rate of renal function decline in chronic kidney disease stages 3 and 4. Hypertension 2010; 55 (5):1110-1115.
83. Madero M, Peralta C, Katz R, Canada R, Fried L, Najjar S, et al. Association of arterial rigidity with incident kidney disease and kidney function decline: the Health ABC study. Clinical journal of the American Society of Nephrology : CJASN 2013; 8 (3):424-433.
84. Ceravolo R, Maio R, Pujia A, Sciacqua A, Ventura G, Costa MC, et al. Pulse pressure and endothelial dysfunction in never-treated hypertensive patients. Journal of the American College of Cardiology 2003; 41 (10):1753-1758.
85. Figueiredo VN, Yugar-Toledo JC, Martins LC, Martins LB, de Faria AP, de Haro Moraes C, et al. Vascular stiffness and endothelial dysfunction: Correlations at different levels of blood pressure. Blood pressure 2012; 21 (1):31-38.
86. Thompson PD, Franklin BA, Balady GJ, Blair SN, Corrado D, Estes NA, 3rd, et al. Exercise and acute cardiovascular events placing the risks into perspective: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism and the Council on Clinical Cardiology. Circulation 2007; 115 (17):2358-2368.
87. Karpha M, Lip GV. The pathophysiology of target organ damage in hypertension. Minerva cardioangiologica 2006; 54 (4):417-429.
88. Ozel E, Tastan A, Ozturk A, Ozcan EE. Relationship between Sympathetic Overactivity and Left Ventricular Hypertrophy in Resistant Hypertension. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 2015; 56 (6):501-506.
89. Kollias A, Lagou S, Zeniodi ME, Boubouchairopoulou N, Stergiou GS. Association of Central Versus Brachial Blood Pressure With Target-Organ Damage: Systematic Review and Meta-Analysis. Hypertension 2016; 67 (1):183-190.
90. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA : the journal of the American Medical Association 1996; 275 (20):1557-1562.
91. Haider AW, Larson MG, Franklin SS, Levy D. Systolic blood pressure, diastolic blood pressure, and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Annals of internal medicine 2003; 138 (1):10-16.
92. Gargiulo R, Suhail F, Lerma EV. Hypertension and chronic kidney disease. Disease-a-month : DM 2015; 61 (9):387-395.
93. Frank RN. The Eye in Hypertension. In: Izzo JL, Jr., Black HR, Sica DA, editors. Hypertension Primer. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
94. Varghese M, Adhyapak SM, Thomas T, Sunder M, Varghese K. The association of severity of retinal vascular changes and cardiac remodelling in systemic hypertension. Therapeutic advances in cardiovascular disease 2016.

95. Tan J, Pei Y, Hua Q, Xing X, Wen J. Aortic pulse wave velocity is associated with measures of subclinical target organ damage in patients with mild hypertension. Cell biochemistry and biophysics 2014; 70 (1):167-171.
96. Dellegrottaglie S, Sands RL, Gillespie BW, Gnanasekaran G, Zannad F, Sengstock D, et al. Association between markers of collagen turnover, arterial stiffness and left ventricular hypertrophy in chronic kidney disease (CKD): the Renal Research Institute (RRI)-CKD study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2011; 26 (9):2891-2898.
97. Nitta K, Akiba T, Uchida K, Otsubo S, Otsubo Y, Takei T, et al. Left ventricular hypertrophy is associated with arterial stiffness and vascular calcification in hemodialysis patients. Hypertension research : official journal of the Japanese Society of Hypertension 2004; 27 (1):47-52.
98. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 2003; 107 (5):714-720.
99. Desai AS, Mitchell GF, Fang JC, Creager MA. Central aortic stiffness is increased in patients with heart failure and preserved ejection fraction. Journal of cardiac failure 2009; 15 (8):658-664.
100. Kim DB, Baek SH, Jang SW, Her SH, Shin DI, Park CS, et al. Improvement of arterial stiffness in the transition from acute decompensated heart failure to chronic compensated heart failure. Clinical cardiology 2013; 36 (6):358-362.
101. Agoston-Coldea L, Mocan T, Bobar C. Arterial stiffness and left ventricular diastolic function in the patients with hypertension. Romanian journal of internal medicine = Revue roumaine de medecine interne 2008; 46 (4):313-321.
102. Farkas E, Luiten PG. Cerebral microvascular pathology in aging and Alzheimer's disease. Progress in neurobiology 2001; 64 (6):575-611.
103. Kalaria RN. Linking cerebrovascular defense mechanisms in brain ageing and Alzheimer's disease. Neurobiology of aging 2009; 30 (9):1512-1514.
104. Park L, Anrather J, Girouard H, Zhou P, Iadecola C. Nox2-derived reactive oxygen species mediate neurovascular dysregulation in the aging mouse brain. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2007; 27 (12):1908-1918.
105. Hajjar I, Zhao P, Alsop D, Novak V. Hypertension and cerebral vasoreactivity: a continuous arterial spin labeling magnetic resonance imaging study. Hypertension 2010; 56 (5):859-864.
106. Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V. Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. Stroke; a journal of cerebral circulation 2000; 31 (8):1897-1903.
107. Wang LY, Larson EB, Sonnen JA, Shofer JB, McCormick W, Bowen JD, et al. Blood pressure and brain injury in older adults: findings from a community-based autopsy study. Journal of the American Geriatrics Society 2009; 57 (11):1975-1981.
108. Skoog I. A review on blood pressure and ischaemic white matter lesions. Dementia and geriatric cognitive disorders 1998; 9 Suppl 1:13-19.
109. Longstreth WT, Jr., Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke; a journal of cerebral circulation 1996; 27 (8):1274-1282.
110. Xiong YY, Mok V. Age-related white matter changes. Journal of aging research 2011; 2011:617927.
111. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology 2010; 9 (7):689-701.

112. Verhaaren BF, Vernooij MW, de Boer R, Hofman A, Niessen WJ, van der Lugt A, et al. High blood pressure and cerebral white matter lesion progression in the general population. Hypertension 2013; 61 (6):1354-1359.
113. Murray AD, Staff RT, McNeil CJ, Salarirad S, Starr JM, Deary IJ, et al. Brain lesions, hypertension and cognitive ageing in the 1921 and 1936 Aberdeen birth cohorts. Age (Dordrecht, Netherlands) 2012; 34 (2):451-459.
114. Hughes TM, Sink KM. Hypertension and Its Role in Cognitive Function: Current Evidence and Challenges for the Future. American journal of hypertension 2015.
115. Cooper LL, Woodard T, Sigurdsson S, van Buchem MA, Torjesen AA, Inker LA, et al. Cerebrovascular Damage Mediates Relations Between Aortic Stiffness and Memory. Hypertension 2015.
116. Kwater A, Gasowski J, Gryglewska B, Wizner B, Grodzicki T. Is blood flow in the middle cerebral artery determined by systemic arterial stiffness? Blood pressure 2009; 18 (3):130-134.
117. Webb AJ, Simoni M, Mazzucco S, Kuker W, Schulz U, Rothwell PM. Increased cerebral arterial pulsatility in patients with leukoaraiosis: arterial stiffness enhances transmission of aortic pulsatility. Stroke; a journal of cerebral circulation 2012; 43 (10):2631-2636.
118. Tsao CW, Seshadri S, Beiser AS, Westwood AJ, Decarli C, Au R, et al. Relations of arterial stiffness and endothelial function to brain aging in the community. Neurology 2013; 81 (11):984-991.
119. Katulska K, Wykretowicz M, Minczykowski A, Krauze T, Milewska A, Piskorski J, et al. Gray matter volume in relation to cardio-vascular stiffness. Journal of the neurological sciences 2014; 343 (1-2):100-104.
120. Bateman GA, Levi CR, Schofield P, Wang Y, Lovett EC. The venous manifestations of pulse wave encephalopathy: windkessel dysfunction in normal aging and senile dementia. Neuroradiology 2008; 50 (6):491-497.
121. Henry Feugeas MC, De Marco G, Peretti, II, Godon-Hardy S, Fredy D, Claeys ES. Age-related cerebral white matter changes and pulse-wave encephalopathy: observations with three-dimensional MRI. Magnetic resonance imaging 2005; 23 (9):929-937.
122. Henry-Feugeas MC, Roy C, Baron G, Schouman-Claeys E. Leukoaraiosis and pulse-wave encephalopathy: Observations with phase-contrast MRI in mild cognitive impairment. Journal of Neuroradiology 2009; 36 (4):212-218.
123. Poels MM, Zaccai K, Verwoert GC, Vernooij MW, Hofman A, van der Lugt A, et al. Arterial stiffness and cerebral small vessel disease: the Rotterdam Scan Study. Stroke; a journal of cerebral circulation 2012; 43 (10):2637-2642.
124. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, et al. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. Hypertension 2008; 52 (6):1120-1126.
125. Wilson RS, Boyle PA, Segawa E, Yu L, Begeny CT, Anagnos SE, et al. The influence of cognitive decline on well-being in old age. Psychology and aging 2013; 28 (2):304-313.
126. Davis KK, Allen JK. Identifying cognitive impairment in heart failure: a review of screening measures. Heart & lung : the journal of critical care 2013; 42 (2):92-97.
127. Logue SF, Gould TJ. The neural and genetic basis of executive function: Attention, cognitive flexibility, and response inhibition. Pharmacology, biochemistry, and behavior 2013.
128. Burnett AC, Scratch SE, Anderson PJ. Executive function outcome in preterm adolescents. Early human development 2013; 89 (4):215-220.
129. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, et al. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. Hypertension 2016; 68 (6):e67-e94.
130. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001; 56 (1):42-48.

131. Kivipelto M, Helkala EL, Hanninen T, Laakso MP, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology 2001; 56 (12):1683-1689.
132. Reitz C, Tang MX, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. Archives of neurology 2007; 64 (12):1734-1740.
133. Goldstein FC, Levey AI, Steenland NK. High blood pressure and cognitive decline in mild cognitive impairment. Journal of the American Geriatrics Society 2013; 61 (1):67-73.
134. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiology of aging 2000; 21 (1):49-55.
135. Yamada M, Mimori Y, Kasagi F, Miyachi T, Ohshita T, Sasaki H. Incidence and risks of dementia in Japanese women: Radiation Effects Research Foundation Adult Health Study. Journal of the neurological sciences 2009; 283 (1-2):57-61.
136. Tsivgoulis G, Alexandrov AV, Wadley VG, Unverzagt FW, Go RC, Moy CS, et al. Association of higher diastolic blood pressure levels with cognitive impairment. Neurology 2009; 73 (8):589-595.
137. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology 2005; 64 (2):277-281.
138. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. The Lancet Neurology 2005; 4 (8):487-499.
139. Singh-Manoux A, Marmot M. High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. Journal of clinical epidemiology 2005; 58 (12):1308-1315.
140. Shehab A, Abdulle A. Cognitive and autonomic dysfunction measures in normal controls, white coat and borderline hypertension. BMC cardiovascular disorders 2011; 11:3.
141. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA : the journal of the American Medical Association 1995; 274 (23):1846-1851.
142. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. American journal of epidemiology 1993; 138 (6):353-364.
143. Kritz-Silverstein D, Laughlin GA, McEvoy LK, Barrett-Connor E. Sex and Age Differences in the Association of Blood Pressure and Hypertension with Cognitive Function in the Elderly: The Rancho Bernardo Study. The journal of prevention of Alzheimer's disease 2017; 4 (3):165-173.
144. Wadley VG, McClure LA, Howard VJ, Unverzagt FW, Go RC, Moy CS, et al. Cognitive status, stroke symptom reports, and modifiable risk factors among individuals with no diagnosis of stroke or transient ischemic attack in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Stroke; a journal of cerebral circulation 2007; 38 (4):1143-1147.
145. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Current Alzheimer research 2007; 4 (2):111-116.
146. Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimer's & dementia : the journal of the Alzheimer's Association 2009; 5 (3):207-214.
147. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Archives of neurology 2005; 62 (10):1556-1560.
148. Tervo S, Kivipelto M, Hanninen T, Vanhanen M, Hallikainen M, Mannermaa A, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dementia and geriatric cognitive disorders 2004; 17 (3):196-203.

149. Pase MP, Herbert A, Grima NA, Pipingas A, O'Rourke MF. Arterial stiffness as a cause of cognitive decline and dementia: a systematic review and meta-analysis. Internal medicine journal 2012; 42 (7):808-815.
150. Rabkin SW, Jarvie G. Comparison of vascular stiffness in vascular dementia, Alzheimer dementia and cognitive impairment. Blood pressure 2011; 20 (5):274-283.
151. Zhong W, Cruickshanks KJ, Schubert CR, Carlsson CM, Chappell RJ, Klein BE, et al. Pulse wave velocity and cognitive function in older adults. Alzheimer disease and associated disorders 2014; 28 (1):44-49.
152. Li X, Lyu P, Ren Y, An J, Dong Y. Arterial stiffness and cognitive impairment. Journal of the neurological sciences 2017; 380:1-10.
153. Rabkin SW. Arterial stiffness: detection and consequences in cognitive impairment and dementia of the elderly. Journal of Alzheimer's disease : JAD 2012; 32 (3):541-549.
154. Hughes TM, Kuller LH, Barinas-Mitchell EJ, Mackey RH, McDade EM, Klunk WE, et al. Pulse wave velocity is associated with beta-amyloid deposition in the brains of very elderly adults. Neurology 2013; 81 (19):1711-1718.
155. Hughes TM, Kuller LH, Barinas-Mitchell EJ, McDade EM, Klunk WE, Cohen AD, et al. Arterial stiffness and beta-amyloid progression in nondemented elderly adults. JAMA neurology 2014; 71 (5):562-568.
156. Chung CP, Lee HY, Lin PC, Wang PN. Cerebral Artery Pulsatility is Associated with Cognitive Impairment and Predicts Dementia in Individuals with Subjective Memory Decline or Mild Cognitive Impairment. Journal of Alzheimer's disease : JAD 2017; 60 (2):625-632.
157. Pase MP, Himali JJ, Mitchell GF, Beiser A, Maillard P, Tsao C, et al. Association of Aortic Stiffness With Cognition and Brain Aging in Young and Middle-Aged Adults: The Framingham Third Generation Cohort Study. Hypertension 2016.
158. Tsao CW, Himali JJ, Beiser AS, Larson MG, DeCarli C, Vasan RS, et al. Association of arterial stiffness with progression of subclinical brain and cognitive disease. Neurology 2016.
159. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin JM, et al. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. Stroke; a journal of cerebral circulation 2009; 40 (4):1229-1236.
160. Yaffe K, Falvey C, Hamilton N, Schwartz AV, Simonsick EM, Satterfield S, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. Archives of neurology 2012; 69 (9):1170-1175.
161. Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, et al. Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. Hypertension 2013; 61 (1):160-165.
162. Elias MF, Robbins MA, Budge MM, Abhayaratna WP, Dore GA, Elias PK. Arterial pulse wave velocity and cognition with advancing age. Hypertension 2009; 53 (4):668-673.
163. Poels MM, van Oijen M, Mattace-Raso FU, Hofman A, Koudstaal PJ, Witteman JC, et al. Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study. Stroke; a journal of cerebral circulation 2007; 38 (3):888-892.
164. Tarumi T, de Jong DL, Zhu DC, Tseng BY, Liu J, Hill C, et al. Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. NeuroImage 2015.
165. Gutierrez J, Marshall RS, Lazar RM. Indirect Measures of Arterial Stiffness and Cognitive Performance in Individuals Without Traditional Vascular Risk Factors or Disease. JAMA neurology 2015.
166. Nilsson ED, Elmstahl S, Minthon L, Nilsson PM, Pihlsgard M, Tufvesson E, et al. Nonlinear association between pulse wave velocity and cognitive function: a population-based study. Journal of hypertension 2014; 32 (11):2152-2157; discussion 2157.

167. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di Daniele N. Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. International journal of cardiology 2013; 169 (5):371-377.
168. Yukutake T, Yamada M, Fukutani N, Nishiguchi S, Kayama H, Tanigawa T, et al. Arterial stiffness determined according to the cardio-ankle vascular index(CAVI) is associated with mild cognitive decline in community-dwelling elderly subjects. Journal of atherosclerosis and thrombosis 2014; 21 (1):49-55.
169. Singer J, Trollor JN, Crawford J, O'Rourke MF, Baune BT, Brodaty H, et al. The association between pulse wave velocity and cognitive function: the Sydney Memory and Ageing Study. PloS one 2013; 8 (4):e61855.
170. Zeki Al Hazzouri A, Newman AB, Simonsick E, Sink KM, Sutton Tyrrell K, Watson N, et al. Pulse wave velocity and cognitive decline in elders: the Health, Aging, and Body Composition study. Stroke; a journal of cerebral circulation 2013; 44 (2):388-393.
171. Chrysohoou C, Psaltopoulou T, Panagiotakos D, Pitsavos C, Lazaros G, Skoumas J, et al. Aortic elastic properties and cognitive function in elderly individuals: the Ikaria Study. Maturitas 2013; 74 (3):241-245.
172. Watson NL, Sutton-Tyrrell K, Rosano C, Boudreau RM, Hardy SE, Simonsick EM, et al. Arterial stiffness and cognitive decline in well-functioning older adults. The journals of gerontology Series A, Biological sciences and medical sciences 2011; 66 (12):1336-1342.
173. Benetos A, Watfa G, Hanon O, Salvi P, Fantin F, Toulza O, et al. Pulse wave velocity is associated with 1-year cognitive decline in the elderly older than 80 years: the PARTAGE study. Journal of the American Medical Directors Association 2012; 13 (3):239-243.
174. Pase MP, Pipingas A, Kras M, Nolidin K, Gibbs AL, Wesnes KA, et al. Healthy middle-aged individuals are vulnerable to cognitive deficits as a result of increased arterial stiffness. Journal of hypertension 2010; 28 (8):1724-1729.
175. van Sloten TT, Mitchell GF, Sigurdsson S, van Buchem MA, Jonsson PV, Garcia ME, et al. Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: cross-sectional findings from the AGES-Reykjavik Study. Journal of psychiatry & neuroscience : JPN 2015; 41 (1):140334.
176. Muela HCS, Costa-Hong VA, Yassuda MS, Moraes NC, Memoria CM, Machado MF, et al. Higher arterial stiffness is associated with lower cognitive performance in patients with hypertension. Journal of clinical hypertension (Greenwich, Conn) 2017.
177. Dudenbostel T, Glasser SP. Effects of antihypertensive drugs on arterial stiffness. Cardiology in review 2012; 20 (5):259-263.
178. Launer LJ, Hughes T, Yu B, Masaki K, Petrovitch H, Ross GW, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. Hypertension 2010; 55 (6):1352-1359.
179. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nature reviews Cardiology 2010; 7 (12):686-698.
180. Kherada N, Heimowitz T, Rosendorff C. Antihypertensive Therapies and Cognitive Function: a Review. Current hypertension reports 2015; 17 (10):79.
181. Peters R, Beckett N, Forette F, Tuomilehto J, Ritchie C, Walton I, et al. Vascular risk factors and cognitive function among 3763 participants in the Hypertension in the Very Elderly Trial (HYVET): a cross-sectional analysis. International psychogeriatrics / IPA 2009; 21 (2):359-368.
182. Anderson C, Teo K, Gao P, Arima H, Dans A, Unger T, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. The Lancet Neurology 2011; 10 (1):43-53.
183. Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH. Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. Hypertension 2011; 57 (2):e6-7.

184. Lu DY, You LK, Sung SH, Cheng HM, Lin SJ, Chiang FT, et al. Abnormal Pulsatile Hemodynamics in Hypertensive Patients With Normalized 24-Hour Ambulatory Blood Pressure by Combination Therapy of Three or More Antihypertensive Agents. Journal of clinical hypertension (Greenwich, Conn) 2015.
185. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006; 113 (9):1213-1225.
186. Ballesteros S, Kraft E, Santana S, Tziraki C. Maintaining older brain functionality: A targeted review. Neuroscience and biobehavioral reviews 2015; 55:453-477.
187. Prakash RS, Voss MW, Erickson KI, Kramer AF. Physical activity and cognitive vitality. Annual review of psychology 2015; 66:769-797.
188. Behrman S, Ebmeier KP. Can exercise prevent cognitive decline? The Practitioner 2014; 258 (1767):17-21, 12-13.
189. Naci H, Ioannidis JP. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. BMJ (Clinical research ed) 2013; 347:f5577.
190. Lobelo F, Stoutenberg M, Hutber A. The Exercise is Medicine Global Health Initiative: a 2014 update. British journal of sports medicine 2014; 48 (22):1627-1633.
191. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. Scandinavian journal of medicine & science in sports 2015; 25 Suppl 3:1-72.
192. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. Stroke; a journal of cerebral circulation 2006; 37 (6):1583-1633.
193. Pedersen BK, Saltin B. Evidence for prescribing exercise as therapy in chronic disease. Scandinavian journal of medicine & science in sports 2006; 16 Suppl 1:3-63.
194. Lange-Asschenfeldt C, Kojda G. Alzheimer's disease, cerebrovascular dysfunction and the benefits of exercise: from vessels to neurons. Experimental gerontology 2008; 43 (6):499-504.
195. Tomporowski PD. Effects of acute bouts of exercise on cognition. Acta psychologica 2003; 112 (3):297-324.
196. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nature reviews Neuroscience 2008; 9 (1):58-65.
197. McMorris T, Hale BJ. Differential effects of differing intensities of acute exercise on speed and accuracy of cognition: a meta-analytical investigation. Brain and cognition 2012; 80 (3):338-351.
198. Ludyga S, Gerber M, Brand S, Holsboer-Trachsler E, Puhse U. Acute effects of moderate aerobic exercise on specific aspects of executive function in different age and fitness groups: A meta-analysis. Psychophysiology 2016; 53 (11):1611-1626.
199. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychological medicine 2009; 39 (1):3-11.
200. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. The New England journal of medicine 2003; 348 (25):2508-2516.
201. Middleton L, Kirkland S, Rockwood K. Prevention of CIND by physical activity: different impact on VCI-ND compared with MCI. Journal of the neurological sciences 2008; 269 (1-2):80-84.
202. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA : the journal of the American Medical Association 2008; 300 (9):1027-1037.

203. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. Journal of internal medicine 2011; 269 (1):107-117.
204. Zhu N, Jacobs DR, Jr., Schreiner PJ, Yaffe K, Bryan N, Launer LJ, et al. Cardiorespiratory fitness and cognitive function in middle age: the CARDIA study. Neurology 2014; 82 (15):1339-1346.
205. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Ageing, fitness and neurocognitive function. Nature 1999; 400 (6743):418-419.
206. Williamson JD, Espeland M, Kritchevsky SB, Newman AB, King AC, Pahor M, et al. Changes in cognitive function in a randomized trial of physical activity: results of the lifestyle interventions and independence for elders pilot study. The journals of gerontology Series A, Biological sciences and medical sciences 2009; 64 (6):688-694.
207. van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W. The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine 2008; 18 (6):486-500.
208. Law LL, Barnett F, Yau MK, Gray MA. Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: a systematic review. Ageing research reviews 2014; 15:61-75.
209. Hayes SM, Alosco ML, Forman DE. The Effects of Aerobic Exercise on Cognitive and Neural Decline in Aging and Cardiovascular Disease. Current geriatrics reports 2014; 3 (4):282-290.
210. Kirk-Sanchez NJ, McGough EL. Physical exercise and cognitive performance in the elderly: current perspectives. Clinical interventions in aging 2014; 9:51-62.
211. Rasmussen P, Brassard P, Adser H, Pedersen MV, Leick L, Hart E, et al. Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. Experimental physiology 2009; 94 (10):1062-1069.
212. Seifert T, Brassard P, Wissenberg M, Rasmussen P, Nordby P, Stallknecht B, et al. Endurance training enhances BDNF release from the human brain. American journal of physiology Regulatory, integrative and comparative physiology 2010; 298 (2):R372-377.
213. Cotman CW, Berchtold NC. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends in neurosciences 2002; 25 (6):295-301.
214. Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S, et al. The impact of resistance exercise on the cognitive function of the elderly. Medicine and science in sports and exercise 2007; 39 (8):1401-1407.
215. Vaynman S, Gomez-Pinilla F. License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. Neurorehabilitation and neural repair 2005; 19 (4):283-295.
216. Carro E, Trejo JL, Busiguina S, Torres-Aleman I. Circulating insulin-like growth factor I mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. The Journal of neuroscience : the official journal of the Society for Neuroscience 2001; 21 (15):5678-5684.
217. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences of the United States of America 2011; 108 (7):3017-3022.
218. Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. The journals of gerontology Series A, Biological sciences and medical sciences 2003; 58 (2):176-180.
219. Head D, Bugg JM, Goate AM, Fagan AM, Mintun MA, Benzinger T, et al. Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. Archives of neurology 2012; 69 (5):636-643.

220. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. The journals of gerontology Series A, Biological sciences and medical sciences 2006; 61 (11):1166-1170.
221. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). Journal of the American College of Cardiology 2005; 46 (9):1753-1760.
222. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 2004; 43 (6):1239-1245.
223. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, et al. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. Circulation 2010; 122 (14):1379-1386.
224. Milatz F, Ketelhut S, Ketelhut S, Ketelhut RG. Favorable effect of aerobic exercise on arterial pressure and aortic pulse wave velocity during stress testing. VASA Zeitschrift fur Gefasskrankheiten 2015; 44 (4):271-276.
225. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. Journal of the American Heart Association 2013; 2 (1):e004473.
226. Heffernan KS, Vieira VJ, Valentine RJ. Microvascular function and ageing L-arginine, tetrahydrobiopterin and the search for the fountain of vascular youth. The Journal of physiology 2008; 586 (8):2041-2042.
227. Nualnim N, Barnes JN, Tarumi T, Renzi CP, Tanaka H. Comparison of central artery elasticity in swimmers, runners, and the sedentary. The American journal of cardiology 2011; 107 (5):783-787.
228. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proceedings of the National Academy of Sciences of the United States of America 2007; 104 (13):5638-5643.
229. Voss MW, Erickson KI, Prakash RS, Chaddock L, Malkowski E, Alves H, et al. Functional connectivity: a source of variance in the association between cardiorespiratory fitness and cognition? Neuropsychologia 2010; 48 (5):1394-1406.
230. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Proceedings of the National Academy of Sciences of the United States of America 2004; 101 (9):3316-3321.
231. Peri-Okonny P, Fu Q, Zhang R, Vongpatanasin W. Exercise, the Brain, and Hypertension. Current hypertension reports 2015; 17 (10):82.
232. Pierce TW, Madden DJ, Siegel WC, Blumenthal JA. Effects of aerobic exercise on cognitive and psychosocial functioning in patients with mild hypertension. Health psychology : official journal of the Division of Health Psychology, American Psychological Association 1993; 12 (4):286-291.
233. Teixeira RB, Marins JC, de Sa Junior AR, de Carvalho CJ, da Silva Moura TA, Lade CG, et al. Improved cognitive, affective and anxiety measures in patients with chronic systemic disorders following structured physical activity. Diabetes & vascular disease research 2015; 12 (6):445-454.
234. Fiocco AJ, Scarcello S, Marzolini S, Chan A, Oh P, Proulx G, et al. The effects of an exercise and lifestyle intervention program on cardiovascular, metabolic factors and cognitive performance in middle-aged adults with type II diabetes: a pilot study. Canadian journal of diabetes 2013; 37 (4):214-219.
235. Aizawa K, Petrella RJ. Acute and chronic impact of dynamic exercise on arterial stiffness in older hypertensives. The open cardiovascular medicine journal 2008; 2:3-8.
236. Kraft KA, Arena R, Arrowood JA, Fei DY. High aerobic capacity does not attenuate aortic stiffness in hypertensive subjects. American heart journal 2007; 154 (5):976-982.

237. Tanaka H, Safar ME. Influence of lifestyle modification on arterial stiffness and wave reflections. American journal of hypertension 2005; 18 (1):137-144.
238. Chirinos JA, Rietzschel ER, Shiva-Kumar P, De Buyzere ML, Zamani P, Claessens T, et al. Effective arterial elastance is insensitive to pulsatile arterial load. Hypertension 2014; 64 (5):1022-1031.
239. Wiener JM, Tilly J. Population ageing in the United States of America: implications for public programmes. International journal of epidemiology 2002; 31 (4):776-781.
240. Velkoff V. The next four decades: the older population in the United States: 2010-2050. Curr Population Rep 2010; 2010:1-14.
241. Multack M. Use of Preventive Services and Prevalence of Health Risk Factors among Adults Aged 50-64: National and State-Level Racial/Ethnic Socioeconomic, and Health Insurance Coverage Status Dispairities. Washington D. C.: AARP Public Policy Institute; 2013.
242. Centers for Disease Control and Prevention A, American Medical Association. Promoting Preventive Services for Adults 50-64: Community and Clinical Partnerships. Atlanta, GA: National Association of Chronic Disease Directors; 2009.
243. White CN, Congdon E, Mumford JA, Karlsgodt KH, Sabb FW, Freimer NB, et al. Decomposing decision components in the stop-signal task: a model-based approach to individual differences in inhibitory control. Journal of cognitive neuroscience 2014; 26 (8):1601-1614.
244. White CN, Poldrack RA. Decomposing bias in different types of simple decisions. Journal of experimental psychology Learning, memory, and cognition 2014; 40 (2):385-398.
245. White CN, Ratcliff R, Starns JJ. Diffusion models of the flanker task: discrete versus gradual attentional selection. Cognitive psychology 2011; 63 (4):210-238.
246. White CN, Ratcliff R, Vasey MW, McKoon G. Using diffusion models to understand clinical disorders. Journal of mathematical psychology 2010; 54 (1):39-52.
247. Forstmann BU, Wagenmakers EJ. Model-Based Cognitive Neuroscience: A Conceptual Introduction. In: Forstmann BU, Wagenmakers EJ, editors. An Introduction to Model-Based Cognitive Neuroscience. New York: Springer; 2015. pp. 139-156.
248. Ratcliff R, Thapar A, McKoon G. Aging and individual differences in rapid two-choice decisions. Psychonomic bulletin & review 2006; 13 (4):626-635.
249. Starns JJ, Ratcliff R. The effects of aging on the speed-accuracy compromise: Boundary optimality in the diffusion model. Psychology and aging 2010; 25 (2):377-390.
250. Lefferts WK, Babcock MC, Tiss MJ, Ives SJ, White CN, Brutsaert TD, et al. Effect of hypoxia on cerebrovascular and cognitive function during moderate intensity exercise. Physiology & behavior 2016; 165:108-118.
251. Lefferts WK, Augustine JA, Spartano NL, Atallah-Yunes NH, Heffernan KS, Gump BB. Racial Differences in Aortic Stiffness in Children. The Journal of pediatrics 2017; 180:62-67.
252. Lefferts WK, Sperry SD, Jorgensen RS, Kasprowicz AG, Skilton MR, Figueroa A, et al. Carotid stiffness, extra-media thickness and visceral adiposity in young adults. Atherosclerosis 2017; 265:140-146.
253. Lefferts WK, Heffernan KS, Barreira TV. Association between pulsatile blood pressure and cognitive performance among older adults: Insight from the National Health and Nutrition Examination Survey 1999-2002. International journal of cardiology 2016; 223:981-984.
254. Lefferts WK, Augustine JA, Heffernan KS. Effect of acute resistance exercise on carotid artery stiffness and cerebral blood flow pulsatility. Frontiers in physiology 2014; 5:101.
255. Lefferts WK, Hughes WE, Heffernan KS. Effect of acute high-intensity resistance exercise on optic nerve sheath diameter and ophthalmic artery blood flow pulsatility. Journal of human hypertension 2015.

256. Lefferts WK, Heffernan KS, Hultquist EM, Fehling PC, Smith DL. Vascular and central hemodynamic changes following exercise-induced heat stress. Vascular medicine (London, England) 2015; 20 (3):222-229.
257. Lefferts WK, Hughes WE, White CN, Brutsaert TD, Heffernan KS. Effect of Acute Nitrate Supplementation on Neurovascular Coupling and Cognitive Performance in Hypoxia. Applied Physiology, Nutrition, and Metabolism 2015.
258. Lefferts WK, Hughes WE, Heffernan KS. Effect of acute nitrate ingestion on central hemodynamic load in hypoxia. Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society 2016; 52:49-55.
259. Babcock MC, Lefferts WK, Hughes WE, Fitzgerald KL, Leyer BK, Redmond JG, et al. Acute effect of high-intensity cycling exercise on carotid artery hemodynamic pulsatility. European journal of applied physiology 2015; 115 (5):1037-1045.
260. Babcock MC, Lefferts WK, Heffernan KS. Relation between exercise central haemodynamic response and resting cardiac structure and function in young healthy men. Clinical physiology and functional imaging 2015.
261. Heffernan KS, Spartano NL, Augustine JA, Lefferts WK, Hughes WE, Mitchell GF, et al. Carotid artery stiffness and hemodynamic pulsatility during cognitive engagement in healthy adults: a pilot investigation. American journal of hypertension 2015; 28 (5):615-622.
262. Spartano NL, Augustine JA, Lefferts WK, Gump BB, Heffernan KS. The relationship between carotid blood pressure reactivity to mental stress and carotid intima-media thickness. Atherosclerosis 2014; 236 (2):227-229.
263. Heffernan KS, Augustine JA, Lefferts WK, Spartano NL, Hughes WE, Jorgensen RS, et al. Arterial stiffness and cerebral hemodynamic pulsatility during cognitive engagement in younger and older adults. Experimental gerontology 2017; 101:54-62.
264. Tarumi T, Ayaz Khan M, Liu J, Tseng BM, Parker R, Riley J, et al. Cerebral hemodynamics in normal aging: central artery stiffness, wave reflection, and pressure pulsatility. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2014; 34 (6):971-978.
265. Jolly TA, Bateman GA, Levi CR, Parsons MW, Michie PT, Karayanidis F. Early detection of microstructural white matter changes associated with arterial pulsatility. Frontiers in human neuroscience 2013; 7:782.
266. Gkaliagkousi E, Gavriilaki E, Nikolaidou B, Triantafyllou G, Douma S. Exercise-induced pulse wave velocity changes in untreated patients with essential hypertension: the effect of an angiotensin receptor antagonist. Journal of clinical hypertension (Greenwich, Conn) 2014; 16 (7):482-487.
267. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. Climacteric : the journal of the International Menopause Society 2012; 15 (2):105-114.
268. Pickering TG, Miller NH, Ogedegbe G, Krakoff LR, Artinian NT, Goff D. Call to action on use and reimbursement for home blood pressure monitoring: a joint scientific statement from the American Heart Association, American Society of Hypertension, and Preventive Cardiovascular Nurses Association. The Journal of cardiovascular nursing 2008; 23 (4):299-323.
269. Carpio-Rivera E, Moncada-Jimenez J, Salazar-Rojas W, Solera-Herrera A. Acute Effects of Exercise on Blood Pressure: A Meta-Analytic Investigation. Arquivos brasileiros de cardiologia 2016; 106 (5):422-433.
270. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Medicine and science in sports and exercise 2007; 39 (8):1423-1434.

271. Niki K, Sugawara M, Chang D, Harada A, Okada T, Sakai R, et al. A new noninvasive measurement system for wave intensity: evaluation of carotid arterial wave intensity and reproducibility. Heart and vessels 2002; 17 (1):12-21.
272. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, Vanmolkot FH, Staessen JA, Kragten JA, et al. Non-invasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. Journal of hypertension 2001; 19 (6):1037-1044.
273. Sugawara M, Niki K, Ohte N, Okada T, Harada A. Clinical usefulness of wave intensity analysis. Medical & biological engineering & computing 2009; 47 (2):197-206.
274. Bleasdale RA, Mumford CE, Campbell RI, Fraser AG, Jones CJ, Frenneaux MP. Wave intensity analysis from the common carotid artery: a new noninvasive index of cerebral vasomotor tone. Heart and vessels 2003; 18 (4):202-206.
275. Gepner AD, Tedla Y, Colangelo LA, Tattersall MC, Korcarz CE, Kaufman JD, et al. Progression of Carotid Arterial Stiffness With Treatment of Hypertension Over 10 Years: The Multi-Ethnic Study of Atherosclerosis. Hypertension 2017; 69 (1):87-95.
276. Niiranen TJ, Kalesan B, Hamburg NM, Benjamin EJ, Mitchell GF, Vasan RS. Relative Contributions of Arterial Stiffness and Hypertension to Cardiovascular Disease: The Framingham Heart Study. Journal of the American Heart Association 2016; 5 (11).
277. Mangoni AA, Mircoli L, Giannattasio C, Ferrari AU, Mancia G. Heart rate-dependence of arterial distensibility in vivo. Journal of hypertension 1996; 14 (7):897-901.
278. Swierblewska E, Hering D, Kara T, Kunicka K, Kruszewski P, Bieniaszewski L, et al. An independent relationship between muscle sympathetic nerve activity and pulse wave velocity in normal humans. Journal of hypertension 2010; 28 (5):979-984.
279. Segers P, O'Rourke MF, Parker K, Westerhof N, Hughes A. Towards a consensus on the understanding and analysis of the pulse waveform: Results from the 2016 Workshop on Arterial Hemodynamics: Past, present and future. Artery research 2017; 18:75-80.
280. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. American journal of hypertension 2005; 18 (1 Pt 2):3S-10S.
281. Studinger P, Lenard Z, Kovats Z, Kocsis L, Kollai M. Static and dynamic changes in carotid artery diameter in humans during and after strenuous exercise. The Journal of physiology 2003; 550 (Pt 2):575-583.
282. Gaddum NR, Keehn L, Guilcher A, Gomez A, Brett S, Beerbaum P, et al. Altered dependence of aortic pulse wave velocity on transmural pressure in hypertension revealing structural change in the aortic wall. Hypertension 2015; 65 (2):362-369.
283. Fok H, Guilcher A, Brett S, Jiang B, Li Y, Epstein S, et al. Dominance of the forward compression wave in determining pulsatile components of blood pressure: similarities between inotropic stimulation and essential hypertension. Hypertension 2014; 64 (5):1116-1123.
284. Li Y, Gu H, Fok H, Alastruey J, Chowienczyk P. Forward and Backward Pressure Waveform Morphology in Hypertension. Hypertension 2017; 69 (2):375-381.
285. Jones CJ, Sugawara M, Kondoh Y, Uchida K, Parker KH. Compression and expansion wavefront travel in canine ascending aortic flow: wave intensity analysis. Heart and vessels 2002; 16 (3):91-98.
286. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. Journal of applied physiology (Bethesda, Md : 1985) 2008; 105 (5):1652-1660.
287. Sierra C, de la Sierra A, Chamorro A, Larrousse M, Domenech M, Coca A. Cerebral hemodynamics and silent cerebral white matter lesions in middle-aged essential hypertensive patients. Blood pressure 2004; 13 (5):304-309.

288. Zeppilli P, Vannicelli R, Santini C, Dello Russo A, Picani C, Palmieri V, et al. Echocardiographic size of conductance vessels in athletes and sedentary people. International journal of sports medicine 1995; 16 (1):38-44.
289. Liu HB, Yuan WX, Qin KR, Hou J. Acute effect of cycling intervention on carotid arterial hemodynamics: basketball athletes versus sedentary controls. Biomedical engineering online 2015; 14 Suppl 1:S17.
290. Yano Y, Stamler J, Garside DB, Daviglus ML, Franklin SS, Carnethon MR, et al. Isolated systolic hypertension in young and middle-aged adults and 31-year risk for cardiovascular mortality: the Chicago Heart Association Detection Project in Industry study. Journal of the American College of Cardiology 2015; 65 (4):327-335.
291. Pieniazek W, Dimitrow PP, Jasinski T. Comparison of the effect of perindopril and acebutolol on cerebral hemodynamics in hypertensive patients. Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 2001; 15 (1):63-67.
292. Koumaras C, Tzimou M, Stavrinou E, Griva T, Gossios TD, Katsiki N, et al. Role of antihypertensive drugs in arterial 'de-stiffening' and central pulsatile hemodynamics. American journal of cardiovascular drugs : drugs, devices, and other interventions 2012; 12 (3):143-156.
293. Boutcher YN, Boutcher SH. Exercise intensity and hypertension: what's new? Journal of human hypertension 2017; 31 (3):157-164.
294. Tsukamoto H, Takenaka S, Suga T, Tanaka D, Takeuchi T, Hamaoka T, et al. Effect of Exercise Intensity and Duration on Postexercise Executive Function. Medicine and science in sports and exercise 2017; 49 (4):774-784.
295. White CN, Curl RA, Sloane JF. Using Decision Models to Enhance Investigations of Individual Differences in Cognitive Neuroscience. Frontiers in psychology 2016; 7:81.
296. Nyberg L, Lovden M, Riklund K, Lindenberger U, Backman L. Memory aging and brain maintenance. Trends in cognitive sciences 2012; 16 (5):292-305.
297. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, et al. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ (Clinical research ed) 2012; 344:d7622.
298. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nature reviews Cardiology 2015; 12 (5):267-277.
299. Mehta JL, Lopez LM. Rebound hypertension following abrupt cessation of clonidine and metoprolol. Treatment with labetalol. Archives of internal medicine 1987; 147 (2):389-390.
300. Voss A, Rothermund K, Voss J. Interpreting the parameters of the diffusion model: an empirical validation. Memory & cognition 2004; 32 (7):1206-1220.
301. Li X, Wang W, Wang A, Li P, Zhang J, Tao W, et al. Vulnerability of the frontal and parietal regions in hypertensive patients during working memory task. Journal of hypertension 2017; 35 (5):1044-1051.
302. Muela HC, Costa-Hong VA, Yassuda MS, Moraes NC, Memoria CM, Machado MF, et al. Hypertension Severity Is Associated With Impaired Cognitive Performance. Journal of the American Heart Association 2017; 6 (1).
303. Mechaeil R, Gard P, Jackson A, Rusted J. Cognitive enhancement following acute losartan in normotensive young adults. Psychopharmacology 2011; 217 (1):51-60.
304. Ji LY, Li XL, Liu Y, Sun XW, Wang HF, Chen L, et al. Time-Dependent Effects of Acute Exercise on University Students' Cognitive Performance in Temperate and Cold Environments. Front Psychol 2017; 8:1192.
305. Tsai CL, Chen FC, Pan CY, Wang CH, Huang TH, Chen TC. Impact of acute aerobic exercise and cardiorespiratory fitness on visuospatial attention performance and serum BDNF levels. Psychoneuroendocrinology 2014; 41:121-131.

306. Doucet C, Stelmack RM. The effect of response execution on P3 latency, reaction time, and movement time. Psychophysiology 1999; 36 (3):351-363.
307. Chu C-H, Alderman BL, Wei G-X, Chang Y-K. Effects of acute aerobic exercise on motor response inhibition: An ERP study using the stop-signal task. Journal of Sport and Health Science 2015; 4 (1):73-81.
308. Kamijo K, Hayashi Y, Sakai T, Yahiro T, Tanaka K, Nishihira Y. Acute effects of aerobic exercise on cognitive function in older adults. The journals of gerontology Series B, Psychological sciences and social sciences 2009; 64 (3):356-363.
309. Ando S, Yamada Y, Tanaka T, Oda S, Kokubu M. Reaction time to peripheral visual stimuli during exercise under normoxia and hyperoxia. Eur J Appl Physiol 2009; 106 (1):61-69.
310. Bullock T, Elliott JC, Serences JT, Giesbrecht B. Acute Exercise Modulates Feature-selective Responses in Human Cortex. Journal of cognitive neuroscience 2017; 29 (4):605-618.
311. McMorris T, Collard K, Corbett J, Dicks M, Swain JP. A test of the catecholamines hypothesis for an acute exercise-cognition interaction. Pharmacol Biochem Behav 2008; 89 (1):106-115.
312. Dishman RK, O'Connor P. Lessons in exercise neurobiology: The case of endorphins. Mental Health and Physical Activity 2009; 2 (1):4-9.
313. Madden DJ, Blumenthal JA, Ekelund LG. Effects of beta-blockade and exercise on cardiovascular and cognitive functioning. Hypertension 1988; 11 (5):470-476.
314. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. American journal of physiology Heart and circulatory physiology 2017; 312 (1):H1-H20.
315. Vingerhoets G, Stroobant N. Lateralization of cerebral blood flow velocity changes during cognitive tasks. A simultaneous bilateral transcranial Doppler study. Stroke; a journal of cerebral circulation 1999; 30 (10):2152-2158.
316. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nature reviews Neuroscience 2004; 5 (5):347-360.
317. Nealon RS, Howe PR, Jansen L, Garg M, Wong RH. Impaired cerebrovascular responsiveness and cognitive performance in adults with type 2 diabetes. Journal of diabetes and its complications 2017; 31 (2):462-467.
318. Raz N, Rodrigue KM, Haacke EM. Brain aging and its modifiers: insights from in vivo neuromorphometry and susceptibility weighted imaging. Annals of the New York Academy of Sciences 2007; 1097:84-93.
319. Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. Neuropsychology 2007; 21 (2):149-157.
320. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. The Journal of physiology 2014; 592 (5):841-859.
321. Hajjar I, Marmerelis V, Shin DC, Chui H. Assessment of cerebrovascular reactivity during resting state breathing and its correlation with cognitive function in hypertension. Cerebrovascular diseases (Basel, Switzerland) 2014; 38 (1):10-16.
322. Ficzere A, Valikovics A, Fulesdi B, Juhasz A, Czuriga I, Csiba L. Cerebrovascular reactivity in hypertensive patients: a transcranial Doppler study. Journal of clinical ultrasound : JCU 1997; 25 (7):383-389.
323. Zhao P, Alsop DC, Abduljalil A, Selim M, Lipsitz L, Novak P, et al. Vasoreactivity and peri-infarct hyperintensities in stroke. Neurology 2009; 72 (7):643-649.
324. Grant H, Bhambhani Y, Singhal A, Haennel R, Warren S. Reliability and reactivity of the prefrontal hemodynamic responses in essential hypertension: a functional near infrared spectroscopy study. Journal of the American Society of Hypertension : JASH 2015; 9 (10):811-820.

325. Phillips AA, Chan FH, Zheng MM, Krassioukov AV, Ainslie PN. Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2016; 36 (4):647-664.
326. Phillips AA, Warburton DE, Ainslie PN, Krassioukov AV. Regional neurovascular coupling and cognitive performance in those with low blood pressure secondary to high-level spinal cord injury: improved by alpha-1 agonist midodrine hydrochloride. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2014; 34 (5):794-801.
327. Carter HH, Atkinson CL, Heinonen IH, Haynes A, Robey E, Smith KJ, et al. Evidence for Shear Stress-Mediated Dilation of the Internal Carotid Artery in Humans. Hypertension 2016; 68 (5):1217-1224.
328. Rasmussen PM, Jespersen SN, Ostergaard L. The effects of transit time heterogeneity on brain oxygenation during rest and functional activation. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2015; 35 (3):432-442.
329. Harvey A, Montezano AC, Touyz RM. Vascular biology of ageing-Implications in hypertension. Journal of molecular and cellular cardiology 2015; 83:112-121.
330. Marshall SJ, Levy SS, Tudor-Locke CE, Kolkhorst FW, Wooten KM, Ji M, et al. Translating physical activity recommendations into a pedometer-based step goal: 3000 steps in 30 minutes. American journal of preventive medicine 2009; 36 (5):410-415.
331. Takeda T, Kawakami Y, Konno M, Matsuda Y, Nishino M, Suzuki Y, et al. PFC Blood Oxygenation Changes in Four Different Cognitive Tasks. Advances in experimental medicine and biology 2017; 977:199-204.
332. Parker KH, Jones CJ, Dawson JR, Gibson DG. What stops the flow of blood from the heart? Heart and vessels 1988; 4 (4):241-245.
333. Sugawara M, Uchida K, Kondoh Y, Magosaki N, Niki K, Jones CJ, et al. Aortic blood momentum--the more the better for the ejecting heart in vivo? Cardiovascular research 1997; 33 (2):433-446.
334. Willie CK, Colino FL, Bailey DM, Tzeng YC, Binsted G, Jones LW, et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. Journal of neuroscience methods 2011; 196 (2):221-237.
335. Ahmadi-Abhari S, Sabia S, Shipley MJ, Kivimaki M, Singh-Manoux A, Tabak A, et al. Physical Activity, Sedentary Behavior, and Long-Term Changes in Aortic Stiffness: The Whitehall II Study. Journal of the American Heart Association 2017; 6 (8).
336. Wang X, Ye P, Cao R, Yang X, Xiao W, Zhang Y, et al. Triglycerides are a predictive factor for arterial stiffness: a community-based 4.8-year prospective study. Lipids in health and disease 2016; 15:97.
337. Brunner EJ, Shipley MJ, Ahmadi-Abhari S, Tabak AG, McEniery CM, Wilkinson IB, et al. Adiposity, obesity, and arterial aging: longitudinal study of aortic stiffness in the Whitehall II cohort. Hypertension 2015; 66 (2):294-300.
338. Kim CW, Chang Y, Zhao D, Cainzos-Achirica M, Ryu S, Jung HS, et al. Sleep Duration, Sleep Quality, and Markers of Subclinical Arterial Disease in Healthy Men and Women. Arteriosclerosis, thrombosis, and vascular biology 2015; 35 (10):2238-2245.
339. Baune BT, Stuart M, Gilmour A, Wersching H, Heindel W, Arolt V, et al. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. Translational psychiatry 2012; 2:e92.
340. Ichihara A, Hayashi M, Koura Y, Tada Y, Kaneshiro Y, Saruta T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. Journal of human hypertension 2005; 19 (2):103-109.
341. Liu W, Yamashita T, Kurata T, Kono S, Hishikawa N, Deguchi K, et al. Protective effect of telmisartan on neurovascular unit and inflammasome in stroke-resistant spontaneously hypertensive rats. Neurological research 2015; 37 (6):491-501.

342. Calcinaghi N, Wyss MT, Jolivet R, Singh A, Keller AL, Winnik S, et al. Multimodal imaging in rats reveals impaired neurovascular coupling in sustained hypertension. Stroke; a journal of cerebral circulation 2013; 44 (7):1957-1964.
343. Alrawi YA, Panerai RB, Myint PK, Potter JF. Pharmacological blood pressure lowering in the older hypertensive patients may lead to cognitive impairment by altering neurovascular coupling. Medical hypotheses 2013; 80 (3):303-307.
344. Hess TM, Ennis GE. Age differences in the effort and costs associated with cognitive activity. The journals of gerontology Series B, Psychological sciences and social sciences 2012; 67 (4):447-455.
345. Laskey WK, Kussmaul WG. Arterial wave reflection in heart failure. Circulation 1987; 75 (4):711-722.
346. Smith KJ, Hoiland RL, Grove R, McKirdy H, Naylor L, Ainslie PN, et al. Matched increases in cerebral artery shear stress, irrespective of stimulus, induce similar changes in extra-cranial arterial diameter in humans. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism 2017:271678x17739220.
347. Hoiland RL, Smith KJ, Carter HH, Lewis NCS, Tymko MM, Wildfong KW, et al. Shear-mediated dilation of the internal carotid artery occurs independent of hypercapnia. American journal of physiology Heart and circulatory physiology 2017; 313 (1):H24-h31.
348. Agbangla NF, Audiffren M, Albinet CT. Use of near-infrared spectroscopy in the investigation of brain activation during cognitive aging: A systematic review of an emerging area of research. Ageing research reviews 2017; 38:52-66.
349. Andresen J, Shafi NI, Bryan RM, Jr. Endothelial influences on cerebrovascular tone. Journal of applied physiology (Bethesda, Md : 1985) 2006; 100 (1):318-327.
350. Dinoff A, Herrmann N, Swardfager W, Lanctot KL. The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. The European journal of neuroscience 2017; 46 (1):1635-1646.
351. de Assis GG, de Almondes KM. Exercise-dependent BDNF as a Modulatory Factor for the Executive Processing of Individuals in Course of Cognitive Decline. A Systematic Review. Frontiers in psychology 2017; 8:584.
352. Banoujaafar H, Monnier A, Pernet N, Quirie A, Garnier P, Prigent-Tessier A, et al. Brain BDNF levels are dependent on cerebrovascular endothelium-derived nitric oxide. The European journal of neuroscience 2016; 44 (5):2226-2235.
353. Borror A. Brain-derived neurotrophic factor mediates cognitive improvements following acute exercise. Medical hypotheses 2017; 106:1-5.
354. Struthers AD. A new approach to residual risk in treated hypertension--3P screening. Hypertension 2013; 62 (2):236-239.
355. Blacher J, Evans A, Arveiler D, Amouyel P, Ferrieres J, Bingham A, et al. Residual cardiovascular risk in treated hypertension and hyperlipidaemia: the PRIME Study. Journal of human hypertension 2010; 24 (1):19-26.
356. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008; 117 (6):743-753.
357. Andersson OK, Almgren T, Persson B, Samuelsson O, Hedner T, Wilhelmsen L. Survival in treated hypertension: follow up study after two decades. BMJ (Clinical research ed) 1998; 317 (7152):167-171.
358. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ (Clinical research ed) 2007; 335 (7611):136.
359. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. The New England journal of medicine 2008; 358 (20):2107-2116.

360. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Journal of hypertension 2007; 25 (6):1105-1187.
361. Agabiti-Rosei E, Mancia G, O'Rourke MF, Roman MJ, Safar ME, Smulyan H, et al. Central blood pressure measurements and antihypertensive therapy: a consensus document. Hypertension 2007; 50 (1):154-160.
362. Kern KC, Wright CB, Bergfield KL, Fitzhugh MC, Chen K, Moeller JR, et al. Blood Pressure Control in Aging Predicts Cerebral Atrophy Related to Small-Vessel White Matter Lesions. Frontiers in aging neuroscience 2017; 9:132.
363. Lamar M, Wu D, Durazo-Arvizu RA, Brickman AM, Gonzalez HM, Tarraf W, et al. Cognitive Associates of Current and More Intensive Control of Hypertension: Findings From the Hispanic Community Health Study/Study of Latinos. American journal of hypertension 2017; 30 (6):624-631.
364. van Middelaar T, van Vught LA, van Charante EPM, Eurelings LSM, Ligthart SA, van Dalen JW, et al. Lower dementia risk with different classes of antihypertensive medication in older patients. Journal of hypertension 2017; 35 (10):2095-2101.
365. Stuhec M, Keuschler J, Serra-Mestres J, Isetta M. Effects of different antihypertensive medication groups on cognitive function in older patients: A systematic review. European psychiatry : the journal of the Association of European Psychiatrists 2017; 46:1-15.
366. Hennein R, Hwang SJ, Au R, Levy D, Muntner P, Fox CS, et al. Barriers to Medication Adherence and Links to Cardiovascular Disease Risk Factor Control: The Framingham Heart Study. Internal medicine journal 2017.
367. Muela HCS, Costa-Hong VA, Yassuda MS, Machado MF, Nogueira RC, Moraes NC, et al. Impact of hypertension severity on arterial stiffness, cerebral vasoreactivity, and cognitive performance. Dementia & neuropsychologia 2017; 11 (4):389-397.
368. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017.
369. Flack JM, Calhoun D, Schiffrin EL. The New ACC/AHA Hypertension Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. American journal of hypertension 2018; 31 (2):133-135.
370. Loprinzi PD, Frith E. Association Between Perceived Physical Activity and Cognitive Function in Older Adults. Psychological reports 2018:33294117750632.

CURRICULUM VITAE
Wesley Lefferts
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Syracuse, NY 13244
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Education

2014-2018 Syracuse University, Syracuse, New York
Doctor of Philosophy in Science Education
Exercise Science Concentration
Dissertation: Effect of Aerobic Exercise on Cognitive and Cerebrovascular Function in Hypertensive Adults

2012-2014 Syracuse University, Syracuse, New York
Masters of Science in Exercise Science
Thesis: Effects of Nitrate Supplementation on Cognitive and Cerebrovascular Function at Simulated High Altitude

2007 – 2011 Skidmore College, Saratoga Springs, New York
Bachelor of Science in Health and Exercise Sciences; Magna Cum Laude
Thesis: Effects of Altered Core Temperature on Cardiovascular Strain, Thermal Strain and Performance

Academic/Professional Experience

07/2016 – 05/2018 American Heart Association Pre-Doctoral Fellow, Founder's Affiliate.

06/2017 Course Instructor, Syracuse University, Undergraduate Trauma Research Training program (NSF REU), Syracuse, NY.
Stress Physiology

01/2014 – 05/2016 Course instructor/lecturer, Syracuse University, Department of Exercise Science, School of Education, Syracuse, NY.
PPE 500 Environmental Physiology, PPE 497 Exercise Physiology

08/2012 – 05/2016 Laboratory instructor, Syracuse University, Department of Exercise Science, School of Education, Syracuse, NY.
PPE 497 Exercise Physiology, PPE 500 Environmental Physiology

09/2011 – 08/2012 Full-time Research Assistant, Skidmore College, Department of Health and Exercise Sciences, Saratoga Springs, NY.

07/2011 – 08/2011 Research Assistant, Zephyr Technology Ltd, Mt. Wellington, New Zealand

05/2010 – 07/2011 Student Research Assistant, Skidmore College, Department of Health and Exercise Sciences, Saratoga Springs, NY.

01/2010 – 05/2011 Teaching Assistant, Skidmore College, Department of Health and Exercise Sciences, Saratoga Springs, NY.
EX-311 Exercise Physiology, EX-242 Exercise Testing and Prescription, EX-361 Cardiovascular Physiology

Publications

1. **Lefferts WK**, DeBlois JP, Receno CN, Barreira TV, Brutsaert TD, Carhart CR, Heffernan KS. Effects of acute aerobic exercise on arterial stiffness and cerebrovascular pulsatility in adults with and without hypertension. *Journal of Hypertension*; in press.

2. Heffernan KS, Augustine JA, **Lefferts WK**, Spartano NL, Hughes WE, Jorgensen RS, Gump BB. Arterial stiffness and cerebral hemodynamic pulsatilty during cognitive engagement in younger and older adults. *Experimental Gerontology* 2018; 101: 54-62.

3. Heffernan KS, **Lefferts WK**, Yoon ES, Park SH, Lee YH, Jae SY. Carotid artery reactivity following acute resistance exercise in healthy young adults. *Clinical Autonomic Research* 2017; 27(6): 417-421.

4. **Lefferts WK**, Sperry SD, Jorgensen RS, Kasprowicz AG, Skilton MR, Figueroa A, Heffernan KS. Carotid stiffness, extra-media thickness, and visceral adiposity in young adults. *Atherosclerosis* 2017; 265: 140-146.

5. DeBlois JD, **Lefferts WK**, Heffernan KS. Maybe the fountain of youth was actually a treadmill: role of exercise in reversing microvascular and diastolic dysfunction. *Journal of Physiology* 2017; 595(17): 5755-5756.

6. **Lefferts WK**, Augustine JA, Spartano NS, Atallah-Yunes NH, Heffernan KS, Gump BG. Racial differences in aortic stiffness in children. *Journal of Pediatrics* 2017; 180: 62-67.

7. Ives SJ, **Lefferts WK**, Wharton M, Fehling PC, Smith DL. Exercise-induced heat stress disrupts the shear-dilatory relationship. *Experimental Physiology* 2016; 101(12): 1541-1551.

8. **Lefferts WK**, Heffernan KS, Barreira TV. Association between pulsatile blood pressure and cognitive performance among older adults: insight from the National Health and Nutrition Examination Survey 1999-2002. *International Journal of Cardiology* 2016; 223: 981-984.

9. **Lefferts WK**, Babcock MC, Tiss M, Ives SJ, White CN, Brutsaert TD, Heffernan KS. Effect of hypoxia on cerebrovascular and cognitive function during moderate intensity exercise. *Physiology & Behavior* 2016; 165: 108-118.

10. **Lefferts WK**, Hughes WE, Heffernan KS. Effect of acute nitrate ingestion on central hemodynamic load in hypoxia. *Nitric Oxide* 2016; 52: 49-55.

11. Augustine JA, **Lefferts WK**, Dowthwaite J, Brann L, Brutsaert TD, Heffernan, KS. Subclinical atherosclerotic risk in endurance-trained premenopausal amenorrheic women. *Atherosclerosis* 2016; 244: 157-164.

12. **Lefferts WK**, Hughes WE, White CN, Brutsaert TD, Heffernan KS. Effect of acute nitrate supplementation on neurovascular coupling and cognitive function in hypoxia. *Applied Physiology, Nutrition, & Metabolism* 2016; 41(2): 133-141.

13. Babcock MC, **Lefferts WK**, Heffernan KS. Relation between exercise central hemodynamic response and resting cardiac structure and function in young healthy men. *Clinical Physiology and Functional Imaging* 2017; 37(4): 372-378.

14. **Lefferts WK**, Hughes WE, Heffernan KS. Effect of acute high intensity resistance exercise on optic nerve sheath diameter and ophthalmic artery blood flow pulsatility. *Journal of Human Hypertension* 2015; 29(12): 744-748.

15. **Lefferts WK**, Heffernan KS, Hultquist EM, Fehling PC, Smith DL. Vascular and central hemodynamic changes following exercise-induced heat stress. *Vascular Medicine* 2015; 20(3): 222-229.

16. Babcock MC, **Lefferts WK**, Hughes WE, Fitzgerald KL, Leyer BK, Redmond JG, Heffernan KS. Acute effect of high-intensity cycling exercise on carotid artery hemodynamic pulsatility. *European Journal of Applied Physiology* 2015; 115(5): 1037-45.

17. Fehling PC, Haller J, **Lefferts WK**, Hultquist EM, Wharton M, Rowland T, Smith DL. Effect of exercise, heat stress, and dehydration on myocardial performance. *Occupational Medicine* 2015; 65(4): 317-323.

18. Heffernan KS, Spartano NL, Augustine JA, **Lefferts WK**, Hughes WE, Mitchell GF, Jorgensen RS, Gump BB. Carotid artery stiffness and hemodynamic pulsatility during cognitive engagement in healthy adults: a pilot investigation. *American Journal of Hypertension* 2015; 28(5): 615-622.

19. Hughes WE, Spartano NL, **Lefferts WK**, Augustine JA, Heffernan KS. Sex differences in noninvasive estimates of left ventricular pressure energetics but not myocardial oxygen demand in young adults. *Artery Research* 2014; 8(4): 197-204.

20. Spartano NL, Augustine JA, **Lefferts WK**, Gump BB, Heffernan KS. The relationship between carotid blood pressure reactivity to mental stress and carotid intima-media thickness. *Atherosclerosis* 2014; 236(2): 227-229.

21. **Lefferts WK**, Augustine JA, Heffernan KS. Effect of acute resistance exercise on carotid artery stiffness and cerebral blood flow pulsatility. *Frontiers in Physiology* 2014; 5(101): 1-10.

22. Spartano NL, Augustine JA, **Lefferts WK**, Hughes WE, Redmond JG, Martin ED, Kuvin JT, Gump BB, Heffernan KS. Arterial stiffness as a non-invasive tissue biomarker of cardiac target organ damage. *Current Biomarker Findings* 2014; 2014(4): 23-34.

23. Heffernan KS, **Lefferts WK**, Augustine JA. Hemodynamic correlates of late systolic flow velocity augmentation in the carotid artery. *International Journal of Hypertension* 2013; 2013: 1-7.

24. Heffernan KS, **Lefferts WK**. A new exercise central hemodynamics paradigm: time for reflection or expansion? *Hypertension* 2013; **62**(5)**:** e35.

25. Heffernan KS, **Lefferts WK**, Kasprowicz AG, Tarzia BJ, Thijssen DH, Brutsaert TD. Manipulation of arterial stiffness, wave reflections, and retrograde shear rate in the femoral artery using lower limb external compression. *Physiological Reports* 2013; 1(2): e00022

26. Heffernan KS, Tarzia BJ, Kasprowicz AG, **Lefferts WK**, Hatanaka M, Jae SY. Self-reported sitting time is associated with higher pressure from wave reflections independent of physical activity levels in healthy young adults. *American Journal of Hypertension* 2013; 26(8)**:** 1017-1023.

27. Smith DL, Arena L, Deblois JP, Haller JM, Hultquist EM, **Lefferts WK**, Russell T, Wu A, Fehling PC. Effect of base layer materials on physiological and perceptual responses to exercise in personal protective equipment. *Applied Ergonomics* 2014; 45(3): 428-436.

28. Smith DL, Fehling PC, Hultquist EM, Arena L, **Lefferts WK**, Haller JM, Storer TW, Cooper CB. The effect of precooling on cardiovascular and metabolic strain during incremental exercise. *Applied Physiology, Nutrition, & Metabolism* 2013; 38(9)**:** 935-940.

29. Smith DL, Fehling PC, Hultquist EM, **Lefferts WK**, Barr DA, Storer TW, Cooper CB. Firefighter's personal protective equipment and the chronotropic index. *Ergonomics* 2012; 55(10)**:** 1243-1251.

30. Smith DL, Haller JM, Hultquist EM, **Lefferts WK**, Fehling PC. Effect of clothing layers in combination with fire fighting personal protective clothing on physiological and perceptual responses to intermittent work and on materials performance test results. *Journal of Occupational and Environmental Hygiene* 2013; 10(5)**:** 259-269.

Manuscripts in Progress

1. Sperry SD, **Lefferts WK**, Jorgensen RS, Spink G, Kasprowicz A, Heffernan KS. Sleep duration and cardiovascular health in young men. *Sleep*; in review.

2. **Lefferts WK**, DeBlois JP, Heffernan KS. Neurovascular coupling during cognitive activity in adults with and without hypertension. *Journal of Applied Physiology*; in review.

3. **Lefferts WK**, DeBlois JP, White CN, Heffernan KS. Effects of acute aerobic exercise on cognition and constructs of decision-making in adults with and without hypertension. *Frontiers in Neuroscience*; in review.

4. **Lefferts WK**, Heffernan KS. Cerebral pulse pressure and intracranial aneurysms: Reflecting on things to come. *Interventional Neuroadiology*; in review.

5. Palmiere S, Wade M, DeBlois JD, **Lefferts WK**, Heffernan KS. Aortic stiffness, central pulse pressure and cognitive function following acute resistance exercise. *European Journal of Applied Physiology*; in review.

National Presentations **Slide presentation, ǂInvited symposium, †Award recipient*

1. **Lefferts WK**, DeBlois JP, Mammolito GL, Dressel EA, Receno CN, Heffernan KS. "Effect of Aerobic Exercise on Artery Stiffness and Cerebrovascular Pulsatility in Hypertensive and Non-Hypertensive Adults. Accepted for presentation at the American College of Sports Medicine 64th Annual Meeting, Minneapolis, MN, May 29-June 2, 2018.

2. **Lefferts WK**, DeBlois JP, Mammolito GL, Dressel EA, Receno CN, Heffernan KS. "Cerebrovascular Reactivity and Cognitive Function in Hypertensive and Non-Hypertensive Adults." Accepted for presentation at Experimental Biology, San Diego, CA, April 21-25, 2018.

3. *† **Lefferts WK**, DeBlois JP, Gump BB, Heffernan KS. "Extracranial Vascular Contributions to Intracranial Hemodynamic Pulsatility in Children." Presentated at the Okanagan Cardiovascular & Respiratory Symposium, Okanagan, BC, Canada, March 15-17, 20178.

4. **Lefferts WK**, Babcock MC, Tiss M, Brutsaert TD, Heffernan KS. "No sex differences in the cardiac response to acute normobaric hypoxia." Presented at the American College of Sports Medicine 64th Annual Meeting, Denver, CO, May 30-June 3, 2017.

5. DeBlois JP, **Lefferts WK**, Augustine JA, Nunemacher KN, Heffernan KS. "Effect of Sitting Time on Measures of Subclinical Atherosclerosis in Older Adults." Presented at the American College of Sports Medicine 64th Annual Meeting, Denver, CO, May 30-June 3, 2017.

6. **Lefferts WK**, Figueroa A, Sperry SD, Jorgensen RS, Skilton MR, Heffernan KS. "Carotid Stiffness, Extra-Media Thickness, and Central Adiposity in Young Adults." Presented at the at the North American Artery Society 7th Annual Meeting, Chicago, IL, May 19-20, 2017.

7. † **Lefferts WK**, Augustine JA, Atallah-Yunes NH, Gump BG, Heffernan KS. "Differential Vascular Contributors to Racial Differences in Aortic Pressure among Children." Presented at Experimental Biology, Chicago, IL, April 22-26, 2017.

8. **Lefferts WK**, Augustine JA, Nunemacher K, Heffernan KS. "No Sex Differences in the Cardiovascular Response to Mental-Stress in Older Adults." Presented at the at the North American Artery Society 6th Annual Meeting, Chicago, IL, September 9-10, 2016.

9. **Lefferts WK**, Babcock MC, Tiss M, White CN, Brutsaert TD, Heffernan KS. "Effect of Hypoxia on Cognition and Neurovascular Coupling During Exercise." Presented at the American College of Sports Medicine 63rd Annual Meeting, Boston, MA, May 31-June 4, 2016.

10. Nunemacher K, Augustine JA, **Lefferts WK**, Barreira T, Heffernan KS. "Physical Activity Mediates the Relationship Between Sleep Quality and Vascular Health in Older Adults Presented at the American College of Sports Medicine 63rd Annual Meeting, Boston, MA, May 31-June 4, 2016.

11. Wade M, **Lefferts WK**, Heffernan KS. "The Effects of Acute Resistance Exercise on Vascular and Cognitive Function." Presented at the American College of Sports Medicine 63rd Annual Meeting, Boston, MA, May 31-June 4, 2016.

12. *† **Lefferts WK**, Hughes WE, Heffernan KS. "Effect of Nitrate Ingestion on Central Hemodynamics in Hypoxia" Presented at the North American Artery Society 5th Annual Meeting, Chicago, IL, September 11-12, 2015.

13. † **Lefferts WK**, Hughes WE, White CN, Brutsaert TD, Heffernan KS. "Effect of Nitrate Supplementation on Cognitive Function and Neurovascular Coupling at High Altitude."

Presented at the American College of Sports Medicine's 62nd Annual Meeting, San Diego, CA, May 26-May 30, 2015.

14. Ives SJ, **Lefferts WK**, Wharton M, Fehling PC, Smith DL. "Exercise-induced heat stress disrupts the shear-dilatory relationship in the brachial artery." Presented at Experimental Biology, Boston, MA, March 28-April 1, 2015.

15. Heffernan KS, Spartano NL, **Lefferts WK**, Augustine JA, Hughes WE, Gump BB. "Buffering of carotid artery pressure and flow pulsatility during cognitive engagement in healthy adults." Presented at the North American Artery Society 4th Annual Meeting, Chicago, IL, September 5-6, 2014.

16. **Lefferts WK**, Augustine JA, Heffernan KS. "Acute Resistance Exercise and the Cerebrovasculature: Differential Effects on Pressure and Flow Pulsatility." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014.

17. Fitzgerald KL, Babcock WC, Hughes WE, **Lefferts WK**, Leyer BK, Redmond JG, Heffernan KS. "Aortic Wave Reflections Are Associated With Anaerobic Power Production In Young Adults." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014.

18. Heffernan KS, Spartano NL, **Lefferts WK**, Augustine JA, Hughes WE, Gump BB. "Arterial Stiffness and Pressure from Wave Reflections during Cognitive Challenge in Children and Adults." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014.

19. Redmond JG, Babcock WC, Leyer BK, Fitzgerald KL, **Lefferts WK**, Hughes WE, Heffernan KS. "Effect of Body Composition on Anaerobic Power in Division I Women's Ice Hockey Players." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014

20. Babcock WC, Leyer BK, Fitzgerald KL, **Lefferts WK**, Hughes WE, Redmond JG, Heffernan KS. "No Sex Differences in Carotid Artery Stiffness and Blood Flow Pulsatility Following High Intensity Exercise." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014

21. Martin ED, Augustine JA, Spartano NL, **Lefferts WK**, Heffernan KS. "No Association Between Body Fat And Arterial Stiffness In Non-obese Women." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014

22. Spartano NL, Augustine JA, **Lefferts WK**, Hughes WE, Morse BG, Martin ED, Gump BB, Heffernan KS. "Physical Activity is Associated with Attenuated Carotid Blood Pressure Response to Mental Stress." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014

23. Hughes WE, Spartano NL, **Lefferts WK**, Augustine JA, Heffernan KS. "Sex Differences in Arterial Stiffness and Left Ventricular Pressure Energetics." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014

24. Augustine JA, **Lefferts WK**, Martin ED, Spartano NL, Heffernan KS. "Vascular Function in Exercise-Trained Females." Presented at the American College of Sports Medicine's 61st Annual Meeting, Orlando, FL, May 27-May 31, 2014

25. † Heffernan K, **Lefferts WK**, Augustine J. "Resistance exercise-induced increases in carotid artery stiffness do not affect cerebral blood flow pulsatility." Presented at the North American Artery Society 3rd Annual Meeting, Chicago, IL, September 6-7, 2013.

26. Heffernan KS, **Lefferts WK**, Tarzia BJ, Kasprowicz AG. "Arterial Stiffness and Shear Rate Patterns in the Femoral Artery During Lower Limb Reductions in Transmural Pressure." Presented at the American College of Sports Medicine's 60th Annual Meeting, Indianapolis, ID, May 28-June 1, 2013.

27. Tarzia BJ, Kasprowicz AG, **Lefferts WK**, Heffernan KS. "Physical Activity, Sedentary Behavior and Blood Pressure in Young Adults." Presented at the American College of Sports Medicine's 60th Annual Meeting, Indianapolis, ID, May 28-June 1, 2013.

28. **Lefferts WK,** Hultquist E, Heffernan K, Fehling P, Smith D. "Vascular changes following exercise-induced hyperthermia." Presented at the American College of Sports Medicine's 60th Annual Meeting, Indianapolis, ID, May 28-June 1, 2013.

29. † **Lefferts WK,** Hultquist EM, Barr DA, Storer TW, Cooper CB, Fehling PC, Smith DL. "Cardiovascular and metabolic responses during Maximal Incremental Exercise in Firefighter's Personal Protective Equipment." Presented at the American College of Sports Medicine's 59th Annual Meeting, San Francisco, CA, May 29-June 2, 2012.

30. Smith DL, Barr DA, Hultquist EM, **Lefferts WK**, Haller JM, Fehling PC, Storer TW, Cooper CB. Does "Exercise Mode or Protocol Alter the Chronotropic Index?" Presented at the American College of Sports Medicine's 59th Annual Meeting, San Francisco, CA, May 29-June 2, 2012.

31. Haller JM, Hultquist EM, **Lefferts WK**, Smith DL, Fehling PC. "Influence of Clothing Layers Under Firefighting Protective Clothing on Physiological/Perceptual Responses to Intermittent Work." Presented at the American College of Sports Medicine's 59th Annual Meeting, San Francisco, CA, May 29-June 2, 2012.

32. Hultquist EM, Arena L, **Lefferts WK**, Storer TW, Cooper CB, Fehling PC, Smith DL. "The Effect of Pre-cooling on Cardiovascular and Metabolic Strain During Incremental Exercise." Presented at the American College of Sports Medicine's 59th Annual Meeting, San Francisco, CA, May 29-June 2, 2012.

33. Smith DL, Hultquist E, Arena L, **Lefferts WK**, Fehling PC "Effect of Heat Acclimation on Cardiac and Vascular Function, Oxygen Consumption, and Body Fluids." Presented at the American College of Sports Medicine's 58th Annual Meeting, Denver, CO, May 31-June 4, 2011.

Regional Presentations **Slide presentation, ǂInvited symposium, †Award recipient*

1. ***Lefferts WK**, DeBlois JP, Mammolito GL, Dressel EA, Receno CN, Heffernan KS. "Effect of Aerobic Exercise on Artery Stiffness and Cerebrovascular Pulsatility in Hypertensive and Non-Hypertensive Adults. Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 3-4, 2017.

2. DeBlois JP, **Lefferts WK**, Heffernan KS. "Influence of High-Intensity Exercise on Aortic Stiffness and Femoral Artery Shear Patterns. Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 3-4, 2017.

3. Keller AP, **Lefferts WK**, Augustine JA, DeBlois JD, Heffernan KS. "Muscular Strength is Inversely Associated with Central Hemodynamic Load in Young Women." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 3-4, 2017.

4. Augustine JA, **Lefferts WK**, DeBlois JP, Barreira TV, Liu K, Taylor B, Heffernan KS. "Sex Differences in Aortic Stiffness, 24-hour Aortic Blood Pressure and Cardiac Deformation in Marathon Runners." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 3-4, 2017.

5. Pagan P, Palamar AJ, DeBlois JP, **Lefferts WK**, Heffernan KS. "Retrograde Shear in the Superficial Femoral Artery in Recreationally Active and Exercise-Trained Men." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 3-4, 2017.

6. *ǂ **Lefferts WK**. "The Consequences of Increased Pulsatility on the Brain and Cognitive Function." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 4-5, 2016.

7. DeBlois JP, **Lefferts WK**, Augustine JA, Nunemacher KN, Heffernan KS. "Effect of Sitting Time on Measures of Subclinical Atherosclerosis in Older Adults." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 4-5, 2016.

8. ***Lefferts WK**, Babcock MC, Tiss M, White CN, Brutsaert TD, Heffernan KS. "Effect of Hypoxia on Cerebrovascular and Cognitive Function During Exercise." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 6-7, 2015.

9. Nunemacher K, Augustine JA, **Lefferts WK**, Barreira T, Heffernan KS. "Physical Activity Mediates the Relationship Between Sleep Quality and Vascular Health in Older Adults." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 6-7, 2015.

10. Wade M, **Lefferts WK**, Heffernan KS. "The Effects of Acute Resistance Exercise on Vascular and Cognitive Function." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 6-7, 2015.

11. Babcock MC, **Lefferts WK**, Heffernan KS. "Acute Effects of High-Intensity Exercise on Femoral Artery Stiffness and Shear Patterns." Presented at for the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 6-7, 2015.

12. *† **Lefferts WK**, Hughes WE, White CN, Brutsaert TD, Heffernan KS. "Effect of Nitrate on Cognitive Function and Neurovascular Coupling at High Altitude" Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, October 31-November 1, 2014.

13. Babcock MC, **Lefferts WK**, Heffernan KS. "Relation Between Exercise Central Hemodynamic Load and Resting Cardiac Structure and Function in Young Men" Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, October 31-November 1, 2014.

14. Augustine JA, **Lefferts WK**, Spartano NL, Hughes WE, Gump BB, Heffernan KS. "Physical Function, Cognitive Function, and Aortic Stiffness in Older Adults" Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, October 31-November 1, 2014.

15. Martin E, Augustine JA, Spartano NL, **Lefferts WK**, Heffernan KS. "No Association between Body Fat and Arterial Stiffness in Non-obese Women" Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 1-2, 2013.

16. Augustine JA, **Lefferts WK**, Martin E, Spartano NL, Heffernan KS. "Vascular Function in Exercise-Trained Women." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 1-2, 2013.

17. Spartano NL, Augustine JA, **Lefferts WK**, Hughes W, Morse B, Martin E, Bill K, Gump B, Heffernan KS. "Carotid blood pressure reactivity is associated with carotid intima-media thickness independent of central adiposity." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 1-2, 2013.

18. Hughes WE, Spartano NL, **Lefferts WK**, Augustine JA, Heffernan KS. "Sex differences in arterial stiffness and left ventricular pressure energetics." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 1-2, 2013.

19. ***Lefferts WK**, Augustine J, Heffernan K. "Resistance exercise, carotid artery stiffness, and cerebral blood flow pulsatility" Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 1-2, 2013.

20. ***Lefferts WK,** Hultquist E, Heffernan K, Fehling P, Smith D. "Vascular changes following exercise-induced hyperthermia." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 2-3, 2012.

21. Tarzia BJ, Kasprowicz AG, **Lefferts WK**, Heffernan KS. "Physical Activity, Sedentary Behavior and Blood Pressure in Young Adults." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 2-3, 2012.

22. *† **Lefferts WK**, Hultquist E, Arena L, DeBlois J, Fehling PC, Smith DL. "Effect of Base Layers on Physiological and Perceptual Strain during Exercise in Personal Protective Equipment." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 5-6, 2010.

23. Hultquist E, Arena L, DeBlois J, **Lefferts WK**, Fehling PC, Smith DL. "Effect of Heat Acclimation on Cardiac and Vascular Function, Oxygen Consumption, and Body Fluids." Presented at the Mid-Atlantic Regional Conference American College of Sports Medicine, Harrisburgh, PA, November 5-6, 2010.

Other Publications and Reports

- DeBlois JP, **Lefferts WK**, Heffernan KS. Don't Let the Pressure Get to You. *New York State Association for Health, Physical Education, Recreation and Dance Winter Newsletter* 2017.

- Smith DL, Haller JM, **Lefferts WK**, Hultquist EM, Fehling PC. Heat Stress, Dehydration, Cardiac Strain and Personal Protective Equipment. *Fire Engineering* 2015.

- Smith DL, DeBlois JP, Haller JM, **Lefferts WK**, Fehling PC. Effect of Heat Stress and Dehydration on Cardiovascular Function. First Responder Health and Safety Laboratory, Health and Exercise Sciences, Skidmore College 2014.

- Smith DL, Haller JM, Hultquist EM, **Lefferts WK**, Fehling PC. The Station Uniform Shirt: Does it Play a Role Beyond Appearance? *Firehouse* 2013; 38(1):74, 76-78.

Grants/Support

Funded

1. American Heart Association Pre-Doctoral Fellowship ($51,900) – *Effects of aerobic exercise on cerebrovascular and cognitive function in hypertensive adults* (2016). PI-Lefferts; Sponsor-Heffernan
2. American College of Sports Medicine Foundation Research Grant ($4,998.37) – *Effects of aerobic exercise on cerebrovascular and cognitive function in hypertensive adults* (2016). PI-Lefferts; Sponsor-Heffernan
3. Joan N. Burstyn Endowed Fund for Collaborative Research ($2,470) – *Effects of Exercise on Markers of Brain Function at High Altitude* (2015). PI-Lefferts; Sponsor-Heffernan
4. American College of Sports Medicine Foundation Research Grant ($4,983.93) – *The effect of Dietary Nitrate on Cognitive and Cerebrovascular Function in Hypoxia* (2014). PI-Lefferts; Sponsor-Heffernan
5. Syracuse University Department of Neuroscience Travel Grant – ($500, 2016)
6. Syracuse University School of Education Travel Grant – ($400, 2014, 2017; $348, 2015)
7. Syracuse University Graduate School Organization Travel Grant ($200, 2014; $250, 2015; $450, 2017)

Unfunded

1. American Heart Association Pre-Doctoral Fellowship ($46,000) – PI
   The effect of high-intensity interval exercise on cerebrovascular and cognitive function in middle-aged adults (2015)

Professional Organizations

American College of Sports Medicine (ACSM), 2010 – present.
Mid-Atlantic Regional Chapter (MARC) of ACSM, 2010 – present.
American Heart Association (AHA), 2015 – present.
North American Artery (NAA), 2015 – present.
American Physiological Society (APS), 2016 – present.

Service Activities

Internal Service

- Syracuse University Vice President for Research Search Committee, 2017
- Skidmore College's Science/Math Open House, Alumni Panel, 2016
- School of Education graduate student Q&A panel, 2016
- Planning Committee for the Syracuse University Exercise Science Games, 2016-2018
- Syracuse University Learning Community information session on research in Exercise Science, 2013-2017
- Prospective Exercise Science student information sessions on laboratory skills and research, 2012-2017
- Fitness testing/consulting for Syracuse University D-I Women's field hockey (2013-2016), soccer (2018)

External Service

- East Syracuse Minoa Central Schools PEAK program, 2012-2018
- Central blood pressure assessment, Loving Myself Loving My Sisters, Heart Month event organized by the Syracuse American Heart Association, 2017
- Heart-to-Heart panel member, community talk sponsored by the Syracuse Downtown YMCA, 2017
- Reviewer for MS/PhD student research awards, MARC-ACSM conference, 2016

Invited Lectures

- **Lefferts WK**, Schroeder EC. *How Does Your Body Respond to Exercise?* Presented to 4th grade students, University Preparatory School, Denver, CO, May 30, 2017.

- **Lefferts WK**, *Cardiovascular Disease, Arterial Stiffness, and the Brain*. Presented to EX 361: Clinical Aspects of Cardiovascular Disease, Skidmore College, Saratoga Springs, NY, April 8, 2016.

- **Lefferts WK**, *Principles and Measures of Assessing Body Composition*. Presented to HES 1823: Scientific Principles of Health and Disease, Oklahoma University, Norman, OK, November 23, 2015.

- **Lefferts WK**, *Perspectives on Atherosclerosis*. Presented to HES 1823: Scientific Principles of Health and Disease, Oklahoma University, Norman, OK, September 4, 2015.

- **Lefferts WK**, *Novel Measures of Body Composition*. Presented to PPE 500: Obesity and Body Composition, Syracuse University, Syracuse, NY, April 22, 2014.

Invited Talks

- **Lefferts WK**, Heffernan KS. "Premature vascular aging." Presented at the Aging Studies Institute, Syracuse University, April 20, 2018.

- **Lefferts WK**, Spartano N, Augustine J. "Cardiovascular function and health implications: research and application." Presented to the Syracuse University School of Education Board of Visitors, Syracuse, NY, September 21, 2013.

- **Lefferts WK** "Summer Collaborative Research Experience." Presented at the Skidmore College Board of Trustees Reception and Dinner, Saratoga Springs, NY, February 24, 2011.

Local Presentations **Slide presentation, †Award recipient*

- **†* **Lefferts WK**, DeBlois JD, White CN, Heffernan KS. "Effects of Acute Aerobic Exercise on Cognition and Constructs of Decision-Making in Adults with and without Hypertension." Presented at Neuroscience Research Day, Syracuse, NY, April 6, 2018.

- ***Lefferts WK**, Figueroa A, Sperry SD, Jorgensen RS, Heffernan KS. "Relationships between Carotid Stiffness, Extra-Medial Thickness, and Central Adiposity in Young Adults" Presented at Neuroscience Research Day, Syracuse, NY, April 7, 2017.

- **Lefferts WK**, Babcock MC, Tiss M, White CN, Brutsaert TD, Heffernan KS. "Effect of Hypoxia on Cognition and Neurovascular Coupling during Exercise." Presented at Neuroscience Research Day, Syracuse, NY, April 15, 2016.

- **Lefferts WK**, Hughes WE, White CN, Brutsaert TD, Heffernan KS. "Effect of Nitrate Supplementation on Cognitive Function and Neurovascular Coupling in Hypoxia" Presented at Neuroscience Research Day, Syracuse, NY, April 3, 2015.

- ***Lefferts WK**, Hultquist E, Arena L, Fehling, PC, Smith, DL. Effects of Altered Core Temperature on Cardiovascular Strain, Thermal Strain and Performance. Presented at Undergraduate Research Conference, Saratoga Springs, NY, October 1, 2011.

- ***Lefferts WK**, Hultquist E, Arena L, Fehling PC, Smith, DL. Effects of Altered Core Temperature on Cardiovascular Strain, Thermal Strain and Performance. Presented at Skidmore College Academic Festival, Saratoga Springs, NY, May 4, 2011.

- ***Lefferts WK**, Hultquist E, Arena L, DeBlois J, Fehling PC, Smith DL. Effect of Base Layers on Physiological and Perceptual Strain during Exercise in Personal Protective Equipment. Presented at Skidmore College Celebration Weekend Spotlight on Collaborative Research, Saratoga Springs, NY, October 15, 2010.

- ***Lefferts WK**, Hultquist E, Arena L, DeBlois J, Fehling PC, Smith DL. Effect of Base Layers on Physiological and Perceptual Strain during Exercise in Personal Protective Equipment. Presented at Summer Collaborative Research Meeting, Saratoga Springs, NY, August 6, 2010.

Honors/Awards

- Syracuse University Neuroscience Research Day, Graduate Research Award, 2018
- Okanagan Cardiovascular & Respiratory Symposium, The Dr. Chris Willie Graduate Research Award, 2018
- The American Physiology Society, Caroline tum Suden/Frances Hellebrandt Professional Opportunity Award, Experimental Biology, 2017
- North American Artery, Program Committee's Choice, Best Abstract Award, 2015
- American College of Sports Medicine Environmental and Occupational Physiology Interest Group MS Research Award, 2015
- Mid-Atlantic Regional Chapter, American College of Sports Medicine, MS Research Award, 2014
- American College of Sports Medicine Environmental and Occupational Physiology Interest Group BS Research Award, 2012
- Graduated Magna Cum Laude, Skidmore College, Health and Exercise Sciences, 2011
- Margaret Paulding Award in Exercise Science, Skidmore College, 2011
- Mid-Atlantic Regional Chapter, American College of Sports Medicine, Matthew Kerner Undergraduate Research Award, 2010

Invited Journal Reviewer

Journal of Physiology
American Journal of Physiology: Heart and Circulatory Physiology
Biological Psychology
Physiology & Behavior
Journal of Human Hypertension
Vascular Medicine
Nutrients
Physiological Reports
International Journal of Chronic Obstructive Pulmonary Disease
International Journal of Sports Medicine