Effect of Aerobic Exercise on Cerebral Blood Flow and Cognitive Function in Persons with Down Syndrome

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THESIS

Submitted as partial fulfillment of the requirements

For the degree of Doctor of Philosophy in Rehabilitation Science

In the Graduate College of the

University of Illinois at Chicago, 2017

Chicago, Illinois

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ACKNOWLEDGEMENTS

I would like to send my sincerest thanks to my family. Your understanding and support have carried me through this process. Very special thanks to my mom, dad, and sister. I could not have done this without you and your endless belief and support.

Thank you to my remarkable lab-mates: Mandy, AJ, Elizabeth, and Georgios. Especially, I would like to thank Elizabeth and Garett for your countless proofreads. All of you made this journey possible and memorable.

I would truly like to thank my mentor and advisor, Dr. Bo Fernhall, for your amazing guidance and patience. Also, I am very grateful for your advice and encouragement to go through this journey. I also appreciate the guidance provided by my committee: Dr. Tracy Baynard, Dr. Shane Phillips, Dr. David X. Marquez, and Dr. Thessa Hilgenkamp. I am extremely fortunate to have had your input and expertise not only for this journey but also in future endeavors.

I would like to extend a special thanks to “Ups for Downs” and those who participated in the project. Without your participation, this project could not have happened.

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ABBREVIATIONS

DS	Down syndrome
AD	Alzheimer's disease
CBF	Cerebral blood flow
CHD	Congenital heart disease
VO2	Oxygen consumption
VO_{2peak}	Peak oxygen consumption
CO	Cardiac output
HR_{peak}	Peak heart rate
a-vO_{2diff}	Arterial-venous oxygen content difference
SV	Stroke volume
BP	Blood pressure
NTS	Nucleus tractus solitarius
PA	Physical activity
HRV	Heart rate variability
BPV	Blood pressure variability
BRS	Baroreceptor sensitivity
LVF	Very low frequency
LF	Low frequency
HF	High frequency
LF/HF	Low frequency/high frequency
NE	Norepinephrine

PWV	Pulse wave velocity
AIx	Augmentation index
AIx@75	Heart rate normalized augmentation index
IMT	intima-media thickness
AC	Arterial compliance
Ep	elastic modulus
APP	Amyloid precursor protein
β-amyloid	Beta amyloid
APP	Amyloid precursor protein
MRI	Magnetic resonance imaging
mMCAv	Mean middle cerebral artery blood flow velocity
fNIRS	Functional near-infrared spectroscopy
HR_{max}	Maximum heart rate
HR	Heart rate
CO_2	Carbon dioxide
$ETCO_2$	End tidal carbon dioxide
TVR	Total vascular resistance
PI	Pulsatility index
RI	Resistance index
cPI	Carotid pulsatility index
cRI	Carotid resistance index
BMI	Body mass index
ABI	Ankle/brachial index

CAVI	Cardio/Ankle vascular index
AQT	A Quick Test of Cognitive Speed
β-stiffness	Beta stiffness
ANOVA	Analysis of variance
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
MAP	Mean arterial pressure
bSBP	Brachial systolic blood pressure
bDBP	Brachial diastolic blood pressure
bMAP	Brachial mean arterial pressure
aSBP	Aortic systolic blood pressure
aDBP	Aortic diastolic blood pressure
aMAP	Aortic mean arterial pressure
cSBP	Carotid systolic blood pressure
cDBP	Carotid diastolic blood pressure
cMAP	Carotid mean arterial pressure
cBF	Carotid blood flow
CVC	Cerebral vascular conductance
RT	Reaction time

Chapter I: Introduction

Down syndrome (DS) is the most common genetic cause of intellectual disability in North America and is caused by a genetic chromosomal disorder.[1, 2] Individuals with DS commonly experience multiple secondary health conditions, such as diabetes mellitus, dyslipidemia, congenital heart defects, leukemia, thyroid disease, cognitive decline and Alzheimer's disease (AD),[3, 4] all of which contribute to a shorter lifespan in this population. Individuals with DS also have altered autonomic function with reduced sympathetic activity and sustained parasympathetic activity leading to chronotropic incompetence and reduced aerobic capacity.[5] Reduced aerobic capacity is related to higher mortality and morbidity in the general population.[6] Furthermore, reduced aerobic capacity is related to cognitive decline in an aging population.[7] Thus, these abnormal health conditions including, autonomic dysfunction, reduced aerobic capacity, and AD may play a significant role in premature death in individuals with DS.

Cognitive impairment related to AD and dementia is a very common issue in individuals with DS.[8] Up to 70% of people with DS will develop dementia and AD by 60 years of age.[9] This cognitive impairment is largely due to cerebral vascular damage from the accumulation of harmful substances, such as β-amyloid and tau protein.[10] This damage in the cerebral vasculature may lead to a reduction in cerebral metabolism and circulation, which results in cognitive impairment. Studies in individuals without DS have shown that reduced cerebral blood flow (CBF) is related to the cerebral vascular damage and cognitive decline.[11-13] However, there are limited data on CBF in individuals with DS. Thus, due to the lack of literature in this population, it is unknown whether individuals with DS have different levels of CBF compared to individuals without DS. In addition, it is unknown if any alterations in CBF by exercise is related to cognitive function improvement in DS. Aerobic exercise has beneficial effects on mild

cognitive impairment in the general population.[14, 15] In addition, evidence shows that both acute and chronic aerobic exercise elicits improvement in cognitive function with increased brain activity in populations without DS.[16, 17] However, it is unknown whether acute aerobic exercise elicits similar improvements in cognitive function in people with DS, which may be related to changes in CBF.

Therefore, the main objective of this thesis was to test the hypothesis that a single bout of aerobic exercise improves cognitive function and cerebral blood flow in individuals with and without DS.

Chapter II Literature Review

i. Down syndrome, causes, prevalence and health issues

Down syndrome (DS) is the most common genetic cause of intellectual disability in North America and is caused by a genetic chromosomal disorder.[1, 2] An abnormal chromosomal pair or location on the 21st chromosomal pair causes DS.[18] There are three major causes of DS: an extra chromosome, Robertsonian translocation, and mosaicism. The most common cause of DS is the genetic mutation of an extra chromosome on the twenty-first chromosomal pair in each cell of the body. This is referred to as trisomy and occurs in approximately 95% of individuals diagnosed with DS. This extra chromosome causes several characteristics of DS, such as shorter height, reduced muscle tone, reduced cognitive function, language and speech impairment, and a shorter attention span.[19, 20] The other 2 chromosomal abnormalities that cause DS are Robertsonian translocation (2% – 4%) and mosaicism (1% - 3%).[21] Robertsonian translocation is the mis-location of the long chromosome of the 21st pair, usually to the 14th chromosome.[21] Lastly, mosaic DS is due to the random occurrence of trisomy in chromosomes other than the 21st chromosome pair.[22] Mosaic DS is diagnosed when there is a mixture of the normal cells with 46 chromosomes and some cells with 47 with extra chromosome on the 21st pair.[22] The rate of cells with an extra chromosome defines the percentage of Mosaic DS. All types of DS share similar characteristics (as listed above), but depending on the percentage of mutations, the individuals with Mosaic DS may have fewer or more characteristics typically associated with DS.[22]

The current estimate of individuals with DS in United States (US) differs based on the estimation method. Birth prevalence data, the most commonly used method, estimates there are

approximately 300,000 to 400,000 individuals with DS in the US, which is about 8.27 out of every 10,000 births, or, 1 in every 700 births.[23, 24]

The life expectancy of individuals with DS is significantly shorter than that of individuals without DS.[25] Approximately 50% of individuals with DS are born with a congenital heart defect, which leads to a 5-fold higher death rate within one year of birth.[26] Until the early 1960s, the life expectancy of individuals with DS was only 10 years. However, since 1970, the life expectancy has drastically improved due to improvements in medical care. As of 2010, individuals with DS have an increased life expectancy to around their mid-50s.[27] Even though the lifespan of individuals with DS has increased dramatically, most people with DS experience numerous secondary health conditions such as obesity, leukemia, thyroid dysfunction, sleep disorders, hypotonia, impaired vision and hearing, cognitive dysfunction, memory and learning impairment, dementia and AD.[3, 4] These secondary health conditions often hinder the well-being of people with DS. Later in life, cognitive decline becomes a very common and serious health issue due to the risk of developing dementia or AD.[28, 29] In individuals without DS, 20–25% of individuals over the age of 75 years are at risk for developing dementia, whereas this number increases significantly to 55% in those with DS by the age of 55.[30]

ii. Aerobic capacity and autonomic function in individuals with and without DS

Working muscles require a constant supply of oxygen and nutrients to generate energy to perform muscular contraction. The heart is continuously pumping oxygen-rich blood to the periphery to supply the required oxygen to the working muscles and to remove waste products.[31] Oxygen consumption (VO_2) represents the amount of oxygen consumed by muscle tissue, which allows us to measure cardiovascular capacity that creates energy to produce works, which is proportional to the workload. Furthermore, peak oxygen consumption (VO_{2peak})

measures the body's peak ability to deliver and utilize oxygen to perform work.[32, 33]

According to the Fick principle, oxygen uptake is a function of oxygen supplied, by cardiac output (CO), and oxygen extracted in the periphery, which is explained by the arterial-venous oxygen content difference (a-vO_{2diff}).[34] CO plays a very important role in supplying oxygenated blood to working muscle tissues. Thus, understanding the regulation of CO is important in the regulation of aerobic capacity. CO is a function of heart rate (HR) and stroke volume (SV). Thus, changes in HR and/or SV affect CO, which determines the oxygenated blood volume that is delivered to the body. One of the most important regulatory systems responsible for regulating HR and SV is the autonomic nervous system.

The autonomic nervous system includes two major efferent pathways, the sympathetic and parasympathetic pathways.[31] The sympathetic and parasympathetic nervous systems are controlled by the cardioacceleratory and cardioinhibitory centers in the medulla, specifically the nucleus tractus solitarius (NTS), and control the acceleration and deceleration of heart rate and cardiac contraction.[31] Sympathetic and parasympathetic nerves innervate the atria and ventricles of the heart.[31] The main parasympathetic nerve is the Vagus nerve (10th cranial nerve), which innervates the atria of the heart and its activation inhibits cardioacceleratory effect and reduces HR, SV, and CO. On the other hand, sympathetic activation causes an increase in HR and ventricular contraction, which increase SV and CO. (Figure 1) Thus, abnormal autonomic function, or autonomic dysfunction, will cause alterations in HR, SV, CO and VO_2 at a given workload.[31]

Another important aspect controlling VO_{2peak} is oxygen extraction (a-vO_{2diff}). Oxygen extraction is tightly related to blood flow, which is regulated by changes in vascular tone.[35] As mentioned earlier, working muscle tissue requires oxygen and nutrients in order to perform

adequate muscle contraction and this is supplied by blood flow. Blood vessels, especially arterioles, control blood flow largely by changing in diameter, which is caused by vascular smooth muscle contraction and dilation.[36] This diameter change is partially regulated by the autonomic nervous system, especially the sympathetic nervous system.[31] The direct effect of increased sympathetic activity on blood vessels is vasoconstriction. Sympatho-excitatory stimulation send sympathetic afferent signals to central nervous system and increase sympathetic efferent signals. The increased sympathetic efferent outflow causes release of neurotransmitters, particularly norepinephrine, from the sympathetic nerve endings and leads to smooth muscle contraction in the arteries.[31, 35] This vasoconstriction reduces blood flow. These changes in vascular tone regulate blood flow to active and inactive organs and muscles.[36] During exercise, sympathetic activity causes vasoconstriction of arterioles in inactive organs to redistribute CO to working muscles, where local factors from active muscles cause vasodilation to enhance blood flow to meet metabolic needs.[35, 36] Even though increased CO is mainly redistributed to working muscle, vital organs such as the brain and kidneys still continuously utilize blood flow at a constant percentage of CO.[37] Thus, exercise increases blood flow to the brain and kidneys.

Furthermore, vascular tone plays an important role in BP regulation. Proper BP regulation is necessary for the maintenance of proper perfusion to our body. BP is a function of CO and total peripheral resistance (TPR); BP = CO X TPR.[36] Thus, vasoconstriction caused by increased sympathetic activity increases TPR, which elicits a BP elevation. During exercise, CO increases up to 5 times compared to resting conditions, due to increased venous return, leading to increased SV, coupled with increased HR. This increased CO, and adequately regulated BP, enhances circulation to the body and increases oxygen uptake.[35]

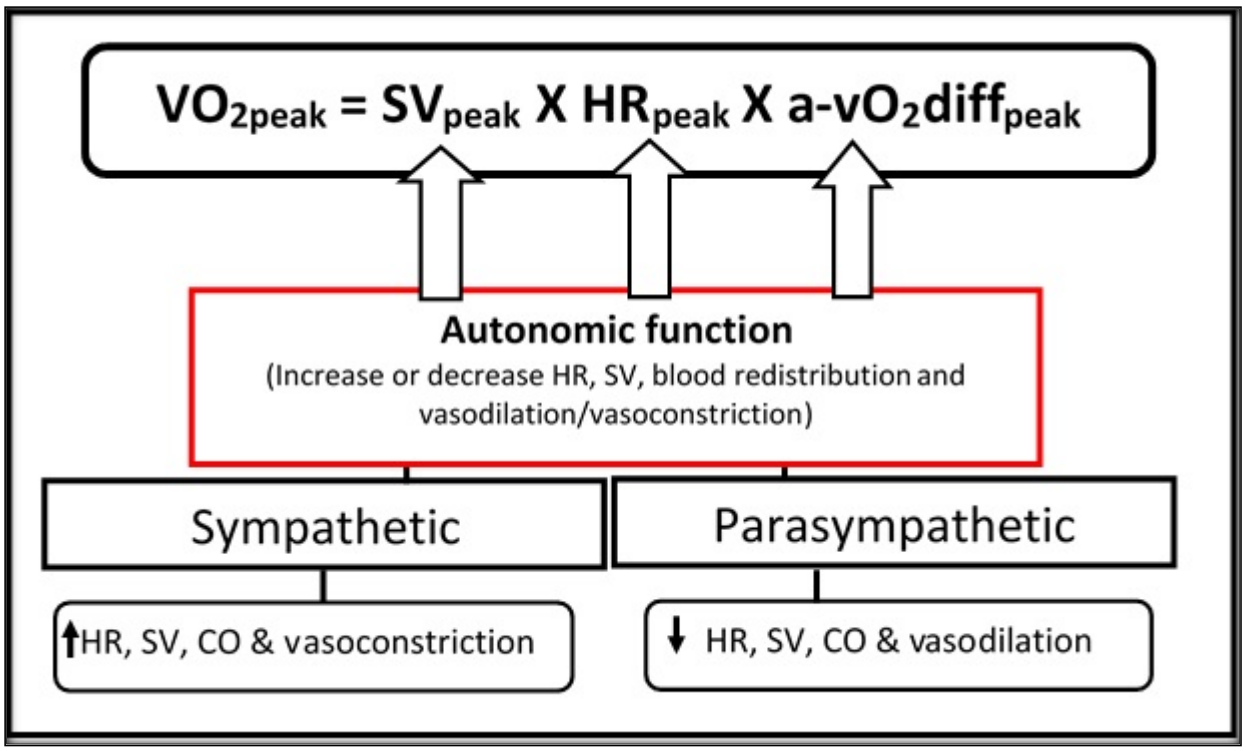

Figure 1. Autonomic regulation of oxygen consumption.

Physical activity (PA) levels in individuals with DS are significantly lower than in individuals without DS.[38, 39] In the healthy non-DS population, increased PA leads to a lower risk of developing cardiovascular disease, high blood pressure, dyslipidemia and overweight/obesity.[40] Furthermore, increased PA is related to increased aerobic capacity, which is a marker of cardiovascular fitness.[41] Increasing aerobic capacity in healthy individuals without DS has an inverse relationship with all-cause mortality, and the rate of cardiovascular morbidity and mortality.[42] Thus, increasing PA levels and aerobic capacity is important for improving the quality of life in people with and without various health conditions.

Individuals with DS exhibit reduced aerobic capacity, which is related to altered autonomic regulation that may explain the lower level of physical activity and higher health risk in this population.[1, 43, 44] In addition, individuals with DS exhibit chronotropic incompetence, an inability to raise HR during excitatory stimulations, which contributes to their lower VO_{2peak}.[44-48] The low level of aerobic capacity in DS, about 30 - 35% lower than that of individuals without DS, may contribute to their sedentary lifestyle, and a sedentary lifestyle is associated with obesity and a higher risk of morbidity and mortality.[47, 49, 50] Even though modern medicine has significantly improved longevity for individuals with DS, low levels of aerobic capacity remain detrimental to the health and well-being among individuals with DS.[5, 51] A retrospective study from our group showed that individuals with DS exhibit significantly lower peak oxygen consumption (VO_{2peak}) and peak heart rate (HR_{peak}) when compared to that of individuals without DS.[5] This difference in VO_{2peak} no longer existed when normalized to HR_{peak}, showing that HR_{peak} is a major contributor to the lower VO_{2peak} in DS. Thus, evaluating HR regulation at rest and during different tasks of sympathoexcitation can help determine the cause of reduced aerobic capacity, sedentary behavior and reduced work capacity. A complete

understanding of the autonomic dysfunction in DS would prove helpful in understanding the exercise intolerance in DS and lead to better exercise prescription to improve health and quality of life in this population.

Sympathoexcitation methods have been utilized to examine autonomic function. The most common methods used are passive upright tilt, cold pressor test, isometric handgrip test, or a maximal exercise test. Heart rate variability (HRV), blood pressure variability (BPV), and baroreceptor sensitivity (BRS) measurements are commonly used methods to examine in-depth function of individuals' autonomic regulation.[43, 44, 47, 52] HRV is a measurement that can examine autonomic regulation of the heart. Spectral analysis of the R-R interval of cardiac electrical activity from a short-term recording of 2 to 5 minutes provides information about sympathetic and parasympathetic modulation of the heart. In brief, spectral analysis can be analyzed in different ranges of frequencies including very low frequency (LVF, 0.003-0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15-0.4 Hz). Each indicates a different area of autonomic function: HF represents vagal activity, LF includes both sympathetic and parasympathetic modulation and LF/HF ratio represents sympatho-vagal dominance.[53, 54]

BPV is also used to examine autonomic function. BPV is known to represent the autonomic regulation of vasomotor function, which regulates cardiovascular functions including vascular tone, BP, HR and respiration.[55] The literature shows that increased BPV is related to cardiovascular mortality, hypertension, and stroke.[56-58] Short-term (i.e., 3 to 5 minute) spectral analysis of beat-to-beat blood pressure waveforms provides important information regarding autonomic regulation. LF power (0.04–0.15 Hz) is known to indicate sympathetic regulation of the vasculature.[59]

Homeostasis in our body is tightly regulated. Short-term blood pressure regulation is accomplished by the baroreceptors, which are mechanoreceptors located in the carotid sinus and the aortic arc. These receptors are sensitive to pressure changes and send afferent nerve signals to the higher brain in order to regulate and maintain appropriate pressure.[31] The resulting efferent nervous outflow from the brain has both central (SV and HR) and peripheral effects, impacting vascular resistance via vasomotor modulation.[60] For example, when the baroreceptors sense stretch from an increase in blood pressure, afferent signals are sent to the higher brain to inhibit sympathetic efferent outflow and increase parasympathetic efferent signals.[31] This lowers HR and increases peripheral vasodilation, which lowers BP. The responsiveness and ability of the baroreceptor to respond to changes in pressure is referred to as baroreceptor sensitivity, which is the major factor in short term regulation of BP.[61] Thus, sensitivity of the baroreceptors has an important role in regulating HR, vasomotor function and BP. Baroreceptor sensitivity is measured by a model-based method using spectral analysis of BP and R-R intervals of HR, [61, 62] Baroreceptor sensitivity is also indicative of one's autonomic function. The time domain of BRS provides information regarding vagal modulation.[60]

Passive upright tilt uses gravity to test autonomic function. At the beginning of the tilt, blood is shifted toward the legs due to the effects of gravity, which reduces venous return and CO. This leads to a baroreceptor response, which stimulates the sympathetic nervous system to increase HR and CO [44, 45], as well as to vasoconstrict vessels in the periphery to maintain appropriate BP for perfusion.[63, 64] Autonomic dysfunction in individuals with DS has been exhibited in several studies during passive upright tilt. This has been shown by blunted HR and BP responses in comparison to control subjects, as well as different changes in vagal and sympathetic cardiovascular autonomic modulation measured with HRV and BPV.[44, 45] This

indicates that individuals with DS may have reduced sympathetic activation resulting in inability to appropriately increase their HR that may be a function of altered baroreceptor sensitivity (BRS). BP changes to orthostatic stress by upright tilt has also been examined and showed significantly reduced BP response to upright tilt in individuals with DS.[45] This evidence showed that individuals with DS exhibit altered sympathetic activation to sympathoexcitation. Further investigation of vagal and sympathetic cardiovascular autonomic modulation (HRV and BPV) during upright tilt test also confirmed that individuals with DS exhibit altered autonomic function. Individuals with DS have blunted vagal withdrawal indicated by reduced LF, HF, LF/HF ratio in HRV, as well as LF of BPV and reduced sympathetic activation. Also, individuals with DS show smaller changes in baroreceptor sensitivity.[45]

Studies from our laboratory have confirmed the autonomic dysfunction in DS by investigating the HR and BP response to isometric handgrip exercise and a cold pressor test. Both methods should elicit an increase in sympathetic activity, which then increases HR and BP. However, individuals with DS showed a blunted, or lack of, HR and BP response following these tests compared to controls.[46, 65] HRV analysis during submaximal isometric handgrip exercise showed that individuals with DS exhibit significantly blunted vagal withdraw, sustained parasympathetic activity, and less sensitive HR, BP, HRV recovery.[46, 65]

The cold pressor test evaluates the effect of sympathetic activity on the autonomic control of HR, CO and BP. Increased sympathetic activity causes increased HR and vasoconstriction, which results in elevated BP due to the increased CO and peripheral resistance. However, Undeschini et al.(1985) showed that individuals with DS do not exhibit any change in HR despite a lower BP during a cold pressor test.[66] In addition, results from our laboratory also showed reduced HR and BP response during cold pressor testing.[65] These results indirectly

suggest that individuals with DS exhibit autonomic dysfunction via reduced sympathetic activation and blunted vagal withdrawal to sympatho-excitatory stimulations.

Sympathetic nervous system activation can also be detected by measuring plasma hormone levels. Catecholamines (epinephrine and norepinephrine) are produced from the adrenal medulla and postganglionic sympathetic nerve endings during increased sympathetic activity.[31] Lower levels of catecholamine levels following maximal intensity exercise in individuals with DS indicates autonomic dysfunction in this population, as it is indicative of an ability to activate the sympathetic nervous system appropriately.[48]

Obesity negatively influences autonomic function, causing higher sympathetic activation and lower parasympathetic activation, and is inversely related to aerobic capacity in a non-DS population.[67, 68] Importantly, given the phenotype of individuals with DS, all of these findings about autonomic dysfunction with reduced sympathetic activity and blunted parasympathetic withdrawal that causes lower level of HR_{peak} and VO_{2peak} in individuals with DS are independent of obesity.[46, 65]

Autonomic dysfunction in DS is negatively related to aerobic capacity and work capacity in this population, mainly from the reduction in HR and CO [1, 5] (Figure 2) and further affects blood flow to the system.[43, 46, 69] This reduced CO decreases oxygen delivery to the organs, such as the brain, and working muscles, which reduces aerobic capacity. In addition to reduced CO, blood flow to working muscle tissues is an important aspect of aerobic capacity regulation. Sympathetic nerves not only innervate the heart, but are also tightly connected to α-adrenergic receptors in the smooth muscle of blood vessels. Activation of these nerves causes sympathetic presynaptic ganglion to release neurotransmitters, specifically norepinephrine (NE). This results in vasoconstriction by smooth muscle cell contraction throughout the activated region to control

blood flow.[31] This vasoconstriction by sympathetic activity is necessary to maintain perfusion to working muscle tissues.

Contraction of blood vessels by sympathetic activation reduces blood flow at the onset of muscle contraction. However, local metabolites from muscle contraction cause vasodilation to help meet the metabolic and oxygen needs of the tissue. This phenomenon is called functional sympatholysis.[70] Thus, altered autonomic function leads to inappropriate blood pressure that causes abnormal blood flow to working muscle, which limits oxygen delivery.

Vascular function and blood flow are most commonly measured by using ultrasonography to record blood flow and the diameter of the brachial artery during handgrip exercise or a standing test. During a short bout of low-intensity rhythmic handgrip exercise, healthy young individuals showed a reduction in brachial artery diameter, indicating increased sympathetic activation.[71] Blood flow is also affected by sympathetic activation. During a simple test of positional change from supine to standing elicited reduction in forearm blood flow measured by ultrasonography.[72] This changes indicate the effect of autonomic function on vascular and blood flow regulation. Unfortunately, data about regulation of blood flow in DS are scarce.

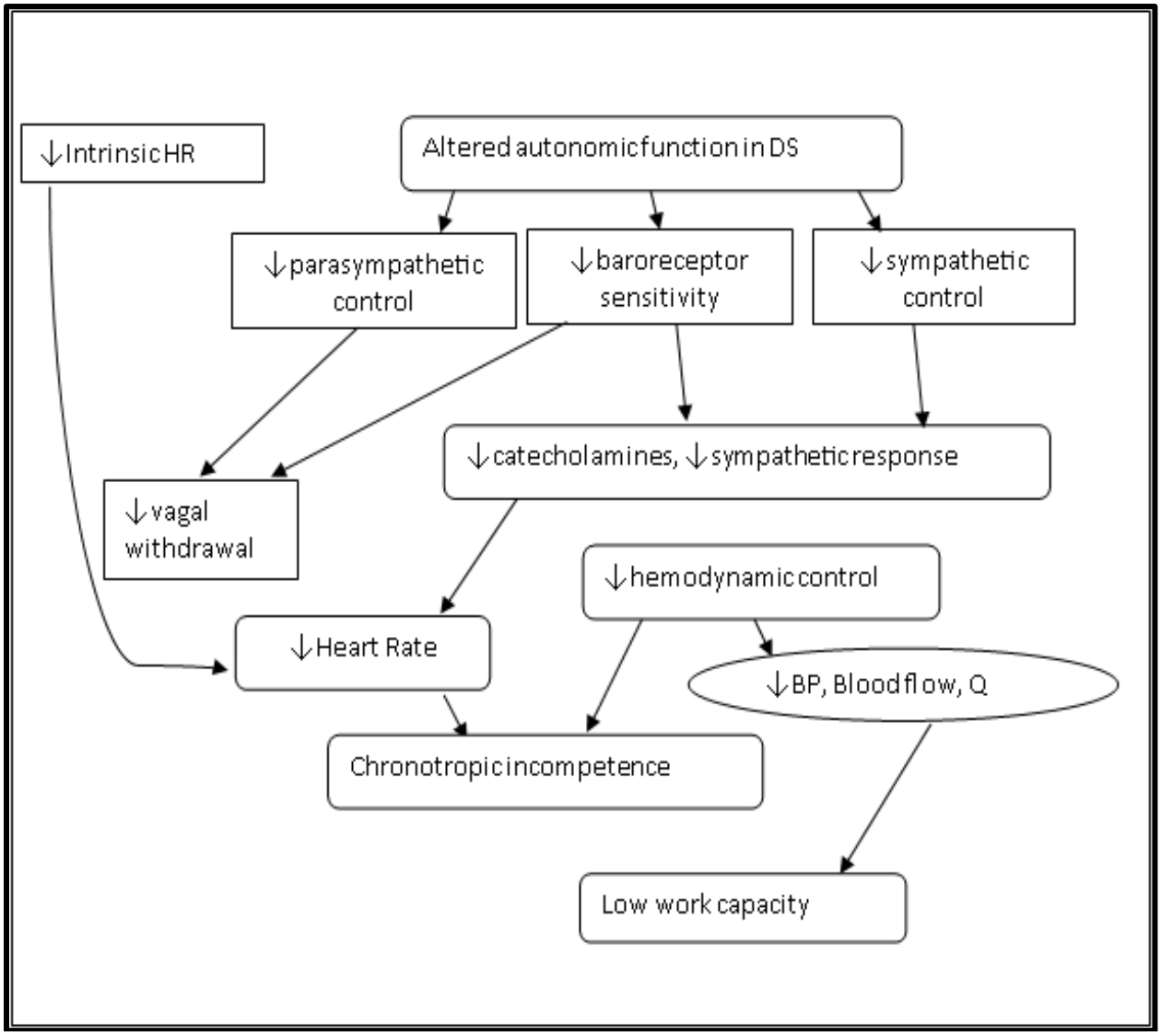

Figure 2. Autonomic dysfunction and low work capacity in DS.
Recreated from Bo Fernhall, Goncalo V. Mendonca, and Tracy Baynard, 2013 MSSE [1]

iii. Vascular Function, Blood Flow, and Exercise

Another aspect that is affected by autonomic function and has an important role in blood flow and aerobic capacity is vascular function. Arterial stiffness has been used to measure aspects of vascular function. Arterial stiffness, especially central artery stiffness, is an independent predictor of all-cause mortality and cardiovascular mortality.[73] Furthermore, it is an independent risk factor for future cardiovascular events and other health issues including hypertension, myocardial infarction, cerebrovascular events and abnormal cognitive function.[74, 75] With increasing age, arteries change their structural conformation by losing flexibility (reductions in elastin) and gaining stiffness (increases in collagen). This detrimental structural change causes functional changes, resulting in higher pulse pressure and more pulsatile blood flow to end organs [76], such as the kidneys and brain. This end-organ pulsatile flow may damage the microvasculature [36, 77], which may further influence the function of the organs, such as cognitive function or kidney function.[75, 78]

In addition, aging is inversely related to brain activity and cerebral blood flow, as well as brain atrophy.[79, 80] Putting this information together, increased arterial stiffness with aging may be related to reduced cerebral blood flow. A study has shown a significant relationship between carotid-femoral PWV and regional cerebral blood flow.[81] DS has also been recognized as ‘premature aging’ since individuals with DS exhibit numerous similar physiological characteristics of an aging population, such as reduced mobility and work capacity, decreased cognitive function and higher obesity rate.[82] However, the literature on arterial stiffness in individuals with DS is very limited. Interestingly, the literature shows a lack of arterial stiffness or atherosclerosis in individuals with DS.[83-86] Despite the lacked evidence, two studies reported no difference in arterial stiffness indices found between individuals with

and without DS at rest including: heart rate normalized augmentation index (AIx@75), intima-media thickness (IMT), beta-stiffness index, arterial compliance (AC) or elastic modulus (Ep).[87, 88] This suggests that individuals with DS do not exhibit arterial stiffness.

Changes in arterial stiffness indices with stimulation, especially with exercise, provides valuable information regarding vascular function. In individuals without DS, arterial stiffness increases with acute exercise due to the increased sympathetic activation.[89-91] A study from our group showed a significant increase in arterial stiffness measured by pulse wave velocity, AIx@75, Ep and beta-stiffness after a single bout of high intensity exercise in individuals without DS, whereas individuals with DS showed no changes in these arterial stiffness indices after exercise.[87] In healthy males without DS, short term aerobic exercise training (6 days) results in improvements in central and peripheral PWV.[92] Studies with longer exercise training exhibit similar beneficial effects on arterial stiffness indices.[93, 94] However, the effects of exercise training on arterial stiffness and blood flow in individuals with DS is unknown.

iv. Cognitive Impairment, Chromosomal Abnormality, and Altered Brain Anatomy in DS

Most individuals with DS experience mild to moderate cognitive impairment, reduced motor and memory function, and language impairment.[8, 95, 96] Cognitive function in DS may deteriorate further with aging and lead to the development of AD and dementia.[97] However, declines in cognitive function may also occur at an earlier age in DS, even before AD or dementia develops.[97, 98] Executive function, including memory and task management, are common aspects of cognitive function that decline with aging in individuals with DS and AD.[99]

A major cause of cognitive impairment and development of dementia and AD is amyloid-beta deposition in the brain.[100, 101] Most aging individuals with DS, even without dementia

or AD, exhibit significant amounts of amyloid-beta plaque in the brain.[102] An abnormal deposition is also commonly seen in AD.[103] Individuals with DS have a similar abnormal deposition of amyloid beta and tau protein in the brain as AD, as well as a smaller brain volume and reduced neural connectivity, which could help explain the cognitive impairment commonly seen.[104-106] Additionally, the 21st chromosome contains amyloid precursor protein (APP) that is responsible for amyloid beta production.[103] Due to individuals with DS having an additional 21st chromosome, individuals with DS exhibit overexpression of APP, which causes additional deposition of amyloid-beta plaque in the brain. Accumulation of amyloid beta plaque and neurofibrillary tau tangles is very common in individuals with DS after 40 years of age. Evidence also shows that the accumulation of amyloid plaque may cause damage in the cerebral vasculature and brain cells, which is related to cognitive impairment in DS.[107-109] In addition, up to 77% of people with DS develop dementia and AD with advancement of their age.[29, 110, 111]

Even though both DS and AD are characterized by cognitive impairment, the development and pathological degeneration of the brain in DS is different due to the smaller brain volumes, confirmed by autopsy. These deficits are seen in the frontal lobe, hippocampus and the cerebellum.[112] These are critical as the frontal lobe is responsible for motor function, problem solving, memory and language; and temporal lobes are responsible for auditory and visual function, memory and social function.[113-115] A magnetic resonance imaging (MRI) study also supports the autopsy study results as individuals with DS have an approximately 20% smaller brain compared to non-DS brains.[116]

Not only is the volume of specific brain regions different in individuals with DS, but also the number of neurons and ability to generate new neurons, neurogenesis, is different in persons

with DS. Individuals with DS have 20 to 50 % fewer neurons in the brain and display decreased neurogenesis at an early age.[117] In addition, it takes significantly longer to generate new neurons, and they experience early and more rapid neuronal cell death during childhood and adult life.[118] Thus, these pathological changes in the brain of individuals with DS results in abnormal neuronal connectivity that may limit their information processing ability.[119] These neuronal and anatomical abnormalities may also be related to impaired cognitive function, executive function, language, working memory and emotional issues, which are commonly observed in individuals with DS.[117]

v. Cerebral Blood Flow in DS

The brain requires constant blood flow to deliver oxygen and nutrients to function.[120] Cerebral blood flow (CBF) is reduced with aging [121] and inadequate cerebral blood supply and cerebral reactivity is closely related to cognitive impairment in the aging population.[122] In addition, aging individuals with cognitive decline, dementia or AD also exhibit significantly reduced CBF.[123, 124] Since most individuals with DS exhibit cognitive impairment [102], reduced CO due to autonomic dysfunction[1] and DS is recognized as a condition with accelerated aging [125], reduced CBF in DS would be expected. However, the literature on CBF in individuals with DS is very limited. Studies with small sample sizes show reduced overall CBF at rest in individuals with DS compared to age matched controls without DS.[126] More importantly, another study also showed a reduction in regional CBF in persons with DS, with a similar decrease in magnitude and pattern as that observed in Alzheimer patients.[127] Not only the level of CBF, but also the CBF response during cognitive stimulation was reduced in DS.[128] Individuals with DS have impaired cognitive function (determined using the Wisconsin card sorting test) and reduced regional CBF in response to that test compared to non-DS

individuals.[128] Another study showed significant cognitive decline and reduced regional CBF in individuals with DS age over 40.[129] Thus, both cognitive function and cerebral perfusion are reduced with aging in persons with DS. Therefore, it is important to investigate if there is difference in CBF between individuals with and without DS at a young age.

vi. Cognitive Function, Cerebral Blood Flow and Aerobic Exercise

Cognitive impairment and its further decline with age are serious issues in individuals with DS, as well as in older individuals without DS. Significant correlations between resting CBF and cognitive function have been identified in an aging study looking at individuals with different brain conditions, such as AD or dementia.[130] However, others have shown no relationship between CBF and cognitive function in aging individuals.[131, 132] Thus, further investigation of relationship between CBF and cognitive function is necessary.

Exercise has been known to have numerous health benefits. In studies of populations without DS, regular aerobic exercise has shown beneficial effects on cognitive function.[133] Furthermore, a meta-analysis showed that exercise training significantly improved cognitive function and behavior in people with dementia and related cognitive impairment.[134] Improvement in cognitive function following aerobic exercise training was also seen in animals with AD, 3xTg-AD mice, related cognitive impairment.[135] Furthermore, the beneficial effects of a single bout of aerobic exercise on cognitive function have been well studied. A single bout of submaximal cycle ergometer exercise improved brain activity and cognitive function in healthy individuals.[136] Benefits of both moderate and vigorous intensity aerobic exercise on executive function were also seen in older women.[137] This improvement in cognitive function following a single bout of exercise may be a result of improved cerebral perfusion.[138, 139] Orlandi and Murri showed improved middle cerebral artery blood flow velocity with voluntary

physical activity in young and older people.[140] In addition, a study in young females showed that 20 minutes of moderate intensity aerobic exercise improved executive function with increased brain activation.[141] This brain activation may lead to changes in brain blood flow to meet the metabolic needs. However, if the improvement in cognitive function is related to the changes in CBF is still controversial.

Even though there are controversial results in the relationship between cognitive improvements with CBF change, a study with functional near-infrared spectroscopy (fNIRS) showed significant correlation between cognitive function improvements with increased CBF in young individuals.[142] The study investigated changes in cognitive function by the color-word stroop test after 10 minutes of low intensity exercise with brain arousal measured by fNIRS. Short bouts of exercise significantly improved reaction time as well as brain activation and arousal of brain regions and these changes were strongly correlated with each other. This evidence indicates that changes in cerebral blood flow by exercise can improve cognitive function.[142] On the other hand, exercise does not or very minimally effects cognitive function in individuals with AD. Regular exercise, including aerobic exercise, strength exercise, and balance exercise, did not benefit cognitive function in individuals who already developed AD.[143] This lack of improvement in cognitive function following exercise in individuals with AD may be due to the lack of task understanding or the low level of exercise adherence, which have been commonly observed in studies in this population.

However, the effect of exercise on cognitive improvement in individuals with DS has rarely been investigated. Limited evidence showS that exercise improves cognitive function in individuals with DS. A study investigated different intensities of exercise on cognitive function in DS. Interestingly, moderate intensity treadmill exercise, 50 – 75% of predicted HR_{max}, showed

significant improvement in information processing speed and executive function, whereas high intensity exercise, 75 – 85% of predicted HR_{max}, did not improve cognitive function among those with DS.[144] Another study also investigated the effect of a single 30 minute bout of assisted cycling exercise on cognitive function in individuals with DS. The results show significant improvement in cognitive function, including reaction time, cognitive planning, and motor function.[145] The same group evaluated the effect of 8 weeks of aerobic training, 3 times/week, 30 minutes per session. They compared the effect of assisted exercise to voluntary exercise and control groups on executive function and cognitive planning ability.[146] The study results showed significant improvement in executive function in the assisted cycling exercise group compared to the voluntary exercise and control groups.[146] This evidence indicates that exercise can improve cognitive function in individuals with DS. However, it is unknown if the cognitive improvements are due to the changes in CBF in individuals with DS.

vii. Summary

Individuals with Down syndrome (DS) experience numerous health issues including thyroid abnormality, leukemia, dyslipidemia, dementia, and Alzheimer's disease (AD).[4] Among these health issues, cognitive decline is a major health issue, which affects the quality of life and hinders normal activities of daily living.[147, 148] Autopsy and imaging studies show that individuals with DS have smaller brain volume, less activation of brain regions and lower blood flow to the brain.[114, 149] In addition, the lower level of cerebral blood flow is similar to that of individuals with AD.[126]

Studies in individuals without DS indicate cognitive decline and dysfunction may be related to cerebral blood flow (CBF) in normal aging as well as pathological conditions including

stroke, depression, dementia and Alzheimer's disease.[150-153] However, this relationship has not been studied in individuals with DS.

Physical activity and exercise improve cognitive function in individuals with and without DS.[144, 145, 154-157] Also, evidence shows that exercise elicits increases in CBF, which may be related to the improvement in cognitive function. Changes in CBF are dependent on exercise intensity, in which moderate intensity exercise elicits increases in CBF, whereas high intensity decreases CBF.[158, 159]

Putting this information together, a proper exercise bout may produce beneficial changes in CBF, which may improve cognitive function in individuals with DS. We aimed to examine the effects of moderate intensity treadmill walking on cognitive function and cerebral blood flow characteristics in individuals with and without DS. Furthermore, we examined the relationship between CBF and cognitive function in both individuals with and without DS.

viii. Specific Aims and Hypothesis

The overall aim of our study was to test the hypothesis that moderate intensity exercise improves cognitive function and cerebral blood flow in individuals with and without DS.

Specific Aim 1) To investigate the effect of aerobic exercise on cerebral blood flow in individuals with DS.

We hypothesized cerebral blood flow would increase with a bout of aerobic exercise in both individuals with and without DS compared to their baseline level.

Specific Aim 2) To investigate the differences in cerebral blood flow prior to and after aerobic exercise in individuals with and without DS.

We hypothesized individuals with DS have reduced cerebral blood flow indices at rest and reduced responses with a bout of moderate intensity treadmill exercise compared to individuals without DS.

Specific Aim 3) To investigate the changes in cognitive function prior to and after aerobic exercise in individuals with and without DS.

We hypothesized cognitive function in both individuals with and without DS would improve with treadmill exercise.

Specific Aim 4) To investigate the relationship between cerebral blood flow and cognitive function in individuals with and without DS.

We hypothesized that cerebral blood flow is related to cognitive function in both individuals with and without DS

Chapter III. Effect of Aerobic Exercise on Cerebral Blood Flow and Cognitive Function in Individuals with Down Syndrome

i. Introduction

Individuals with DS commonly experience mild to moderate cognitive decline.[102] With aging, these individuals are at an even higher risk of further cognitive decline leading to a high prevalence of dementia and AD.[8, 160, 161] This not only hinders their quality of life, but is a leading cause of death in this population.[96, 97] Additionally, individuals with DS commonly exhibit autonomic dysfunction, with altered sympathetic and parasympathetic control of heart rate and blood pressure. This autonomic dysfunction may cause significantly reduced aerobic capacity mainly due to the inability to increase heart rate, which may partially explain the sedentary lifestyle and obesity commonly seen in this population.[1, 5] However, our previous work showed that obesity was not a major factor that contributes to the reduced aerobic capacity in individuals with DS.[162] Altered autonomic function in individuals with DS also affects cardiovascular regulation, including HR and BP, which is essential for blood flow regulation to active muscles and organs.[45, 48, 163-165] This altered blood flow regulation may affect cerebral blood flow and be associated with brain function in individuals with DS.[166] Furthermore, reduced cerebral blood flow is related to impaired cognitive function in pathological populations including stroke, dementia, and AD.[123, 127, 167] However, evidence is lacking regarding a potential CBF difference or similarities between individuals with and without DS.

The carotid artery is the main artery that supplies blood flow to the brain and therefore its function is important for the affects it may have on CBF characteristics.[81] Carotid arterial stiffness is an independent CV disease risk factor[168] and higher carotid stiffness may transmit

pulsatile blood flow to the brain, which would have detrimental effects on the brain microvasculature.[75] Thus, investigating carotid vascular function and carotid blood flow characteristics is important. Furthermore, examining the carotid artery vascular response and carotid BF (cBF) characteristics among individuals with DS following acute aerobic exercise may provide valuable information to understanding the vascular regulation of CBF.

Regular exercise has numerous health benefits including regulating BP, managing body weight, blood glucose, vascular function, and more.[169-171] Acute aerobic exercise also has beneficial effects on cognitive function in different populations, including individuals with DS.[139, 145, 154, 172] In addition, exercise may improve CBF and elicit activation of different areas in the brain.[138, 158, 173] However, it is unknown whether or not acute aerobic exercise can improve CBF in individuals with DS and, further, if the change in CBF is related to cognitive function. Thus, the overall aim of this study was to examine the differences in CBF between individuals with and without DS, on CBF, cognitive function, and the relationship between CBF and cognitive function in individuals with and without DS. Furthermore, we examined the effects of acute aerobic exercise carotid artery function and blood flow. We hypothesized that individuals with DS have significantly lower CBF and altered carotid artery function at rest, and exercise would improve both CBF and cognitive function. Additionally, we hypothesized that cognitive function would be closely related to CBF in individuals with and without DS.

ii. Methods

Subjects

A total of 40 apparently healthy volunteers, who were not physically active or participating in competitive sports, with and without DS, between 18 - 40 years, participated in

the study. Twenty volunteers with DS (male = 11) and twenty volunteers without intellectual disability (male = 10) completed the required visits. Subjects were recruited by flyers, emails to local DS communities, intra-campus e-mail announcements, social media posts and word of mouth in the Chicago area.

All participants were in general good health. Exclusion criteria for the study were individuals with cardiovascular disease, diabetes mellitus (fasting glucose > 110 mg/dl), high BP (BP > 140/90 mmHg), current smokers or uncorrected congenital heart disease. Participants who caught a common cold were directed to wait at least 2 weeks until the cold was completely resolved before their visit. All participants provided written informed consent. Parent of participant with DS also provided separate written informed consent. The study was approved by the Institutional Review Board at the University of Illinois at Chicago.

Study Design and Procedure

Once participants were qualified for the study, participants were invited to the laboratory for a total of 2 visits, including a familiarization visit and a testing visit. The familiarization visit included familiarization with equipment, cognitive function testing, laboratory environment and graded exercise testing to obtain VO_{2peak} for each participant. Average duration of familiarization visit was between 1.5 - 2 hours. The experimental visit included 20 minute of moderate intensity treadmill walking exercise and data collection before and after exercise. Prior to the experimental day, participants were given instructions to abstain from caffeine, alcohol, multivitamins and exercise for at least 12 hours prior to the experimental testing. Participants with DS who were taking thyroid medication were allowed to take their regular prescribed medication dosage. Participants were asked to be fasted a minimum of 4 hours prior to the testing.

Visit one: Familiarization, cognitive function testing, vascular function measurement, and maximal exercise testing: Upon qualifying for study participation, the participants and their parent or caregiver were asked to provide informed consent.

Prior to study initiation, research personnel provided laboratory familiarization to help the participants with DS become comfortable with the laboratory environment and equipment. Familiarization included: BP measurements, wearing a mask for oxygen consumption and respiratory gas measurement, walking on a treadmill at different speeds and inclines for the maximal exercise test, cognitive function test trials, and a transcranial Doppler trial for cerebral blood flow measurement. Participants wore a mask in order to measure oxygen consumption during the graded exercise test during the familiarization visit and to measure end tidal O_2 and CO_2 throughout the testing visit. Once participants felt comfortable with the testing environment and equipment, the baseline cognitive function test (A Quick Test for Cognitive Speed, Pearson Education, UK) was performed. Prior to the baseline cognitive function test, practice trials were performed for the participants' understanding of the test. Participants with DS were asked to wear a face mask during the cognitive function test familiarization trials to help them become familiar with the test condition. Once the participants were accustomed to the test conditions, the baseline cognitive function test was administered. After the cognitive function test, anthropometric data, including height, weight, and waist circumference were measured. Body mass index (BMI) was calculated using the standard calculation (kg/m^2). Following anthropometric data collection, vascular function was measured (VS-1500 AU, Fukuda Denshi) in the supine position using blood pressure cuffs applied to all four limbs. After the vascular function measurements, proper treadmill walking speed, consisting of a brisk but comfortable pace, was assessed for the maximal exercise test. At the end of the familiarization visit,

participants performed the maximal exercise test on a motorized treadmill in order to measure their aerobic capacity. Detailed procedures for the above-mentioned tests are described in subsequent sections.

Visit 2: Cognitive function, cerebral blood flow before and after moderate intensity exercise: Participants were asked to come back to the laboratory at least 48 hours after the familiarization visit. In addition, participants were asked to follow the same diet, exercise, and caffeine consumption rules as Visit 1. When participants arrived at the laboratory, 3 electrodes were placed on their chest to obtain a continuous electrocardiographic recording to calculate HR (ECG100C, Biopac System, Inc., USA). Participants were asked to wear an additional HR monitor to measure their HR during treadmill exercise. There was a total of 3 time points of data collection/recording, including carotid ultrasound vascular measurement, hemodynamic assessment, and cognitive function testing: (1) before exercise, (2) immediately post exercise, and (3) 30 minutes post-exercise.

After the preparation setup, participants were guided to sit in a chair and the transcranial ultrasound Doppler (Neurovision, Multigon Industry Inc., USA) probe was placed on the right side of participants' heads to measure the cerebral blood flow in the middle cerebral artery. Participants were asked to wear a mask (Hans Rudolph Inc, Shawnee, Kansas) for respiratory gas collection to measure the end tidal carbon dioxide (CO2100C, Biopac System Inc, USA) throughout the visit. End-tidal CO_2 and cerebral blood flow were recorded continuously throughout the remainder of the procedure. Once the transcranial Doppler and the mask were placed, a 2-minute baseline cerebral blood flow (CBF) measurement was recorded followed by the cognitive function test (A Quick Test of Cognitive Speed, Pearson Educ LTD, UK). BP was measured at the last minute of CBF measurement using an ambulatory BP monitor (Mobil-O-

graph, I.E.M., GmbH, Deutschland). HR, CO and total vascular resistance (TVR) were derived from the ambulatory BP measurement during the CBF measurement recording. HR, CO and TVR that were derived from an ambulatory BP monitor were validated and low variability from ultrasound driven values.[174]

Once the cognitive function test and BP measurements were completed, carotid artery vascular function, including β-stiffness and blood flow characteristics, carotid blood flow were measured using ultrasonography echo tracking and b-mode with high fidelity ultrasound (Hitachi Aloka Alpha 7, Japan). Carotid pulsatility index (cPI) and resistance index (cRI) were derived from carotid blood flow measurement. After baseline measurements, participants were guided to a treadmill to perform a moderate intensity walking exercise. The exercise session consisted of 20 minutes of moderate intensity exercise on a treadmill at an intensity of 55 - 60% of the previously determined VO_{2peak}. A target heart rate range of 55 – 60 % of VO_{2peak} was matched to the HR calculated from the maximal exercise test results. HR was checked every 5 minutes to ensure that the participants were exercising at proper intensity. If the HR was not within the range, either the speed or the incline of treadmill was adjusted. After completion of the exercise session, participants were guided back to the chair for post-exercise measurements. Once participants sat down comfortably, post-exercise data collection was performed immediately post and 30 minute post exercise. The same data collection procedures were performed at each time point.

Measurements

Anthropometric. Participants' height and weight were measured by stadiometer and digital scale, respectively. Body mass index (BMI) was calculated by weight in kilograms divided by squared

height in meters: BMI = Weight (kg)/height (m^2). Waist circumference was measured at a narrowest portion of the torso, above the level of the umbilicus, based on American College of Medicine measurement guidelines.[175]

Ankle/Brachial Index (ABI). ABI is a measurement examining peripheral vascular occlusion and arterial stiffness. Four BP cuffs were applied to the ankles and brachial arteries to measure ABI using an automated instrument (VaSera VS 1500AU, Fukuda Denshi, Japan). ABI is derived from the ratio of ankle systolic blood pressure to arm systolic blood pressure.[176] Right and left ABI are calculated separately by the automated system. e.g.; Right ABI = the highest systolic pressure in the right ankle/the highest systolic pressure in both arms.[177] An ABI greater than 1.0 is considered normal, whereas an ABI less than 1.0 is considered an indicator of arterial disease in an adult population.[177]

Cardio/Ankle Vascular Index (CAVI). CAVI is the measurement of systemic arterial stiffness and arteriosclerosis (VaSera VS 1500AU, Fukuda Denshi, Japan). It is assessed by measuring the changes in pulse wave from a central point (aortic valve level, brachial) to target sites (ankles) and pulse wave velocity between the two sites (the brachial and ankle).[178] CAVI between the heart and ankle arteries is assessed using measurements of time between the second heart sound and plethysmograms taken at the brachial and ankle arteries. The instrument measures both right (R-CAVI) and left CAVI (L-CAVI). This measurement is independent of BP.

Augmentation Index (AIx) and Heart Rate Normalized Augmentation Index (AIx@75). Augmentation index (AIx) is a measure of arterial stiffness and wave reflection, which is derived

from the aortic pressure wave form. It is calculated as: AIx= augmented pressure / aortic pulse pressure.[179] Since AIx is strongly affected by HR, it is common to use HR normalized at 75 AIx (AIx@75).[180, 181] AIx was derived from an ambulatory blood pressure monitor (Mobil-O-graph, I.E.M., GmbH, Deutschland).

Carotid Blood Pressure. Carotid artery pressure waveforms were obtained from the neck on the subjects' right side in the seated position using applanation tonometry and a high-fidelity strain gauge transducer (Millar Instruments, Houston, TX). A probe with a high-fidelity strain gauge transducer was applied to the surface of carotid artery and the stabilized pressure from the carotid artery was measured over a period of time.[182] This technique has been validated and reproducibility of measures is high.[183, 184] The pressure was calibrated with brachial diastolic BP and mean arterial pressure.[184]

Carotid Blood Flow Characteristics: Carotid Blood Flow (cBF), Pulsatility Index (cPI), and Resistance Index (cRI). The right common carotid artery was imaged longitudinally approximately 1-2 centimeters proximal to the carotid bifurcation via ultrasonography with a 7 - 15 MHz linear-array probe (Hitachi Aloka Alpha 7, Japan). cBF was measured using B-mode and spectral Doppler.[185] The gate was placed approximately 1-2 cm distal to the carotid bulb. In order to obtain cBF, the diameter of common carotid artery was measured from the near wall to the far wall. At least 5 cardiac cycles of carotid blood flow were recorded to obtain quality flow waves. Flow waves were obtained by range-gated spectral Doppler signals averaged with the Doppler beam. Insonation angle was kept less than 60 degrees and the sample volume was adjusted for a high quality flow image.[186] cPI and cRI were derived from the flow waveform.

PI represents the characteristics of blood flow, where RI represent the resistance to the blood flow. PI is the difference in carotid systolic flow velocity and carotid diastolic flow velocity divided by carotid mean flow velocity; cPI = (carotid systolic flow velocity – carotid diastolic flow velocity) / carotid mean flow velocity. cRI is the difference of carotid systolic flow velocity and carotid diastolic flow velocity divided by carotid systolic flow velocity; cRI = (carotid systolic flow velocity – carotid diastolic flow velocity) / carotid systolic flow velocity.

Carotid β-stiffness. Carotid β-stiffness is a marker of central stiffness, which is one of the most commonly used clinical markers[187] and it is an independent risk factor for future cardiovascular events.[188] β-stiffness was measured using b-mode and echo tracking with high fidelity ultrasound (Hitachi Aloka Alpha 7, Japan)[189] to detect the displacement of the carotid artery walls. It was calculated as the log of changes in carotid pressure (SphygmoCor, AtCor Medical, USA) divided by changes in carotid artery compliance: (log P1/P0)/(D1-D0/D0); where P1 is the systolic and P0 is diastolic carotid pressures and D1 and D0 are the maximum (systolic) and minimum (diastolic) diameters, respectively.[190]

Aerobic Capacity. Participants were asked to perform a maximal exercise test to obtain maximal aerobic capacity (VO_{2peak}) and peak HR. Respiratory gas exchange was measured by open-circuit spirometry (Parvo-Medics Inc., Sandy, UT). The treadmill test was individualized to the ability of the participants. The treadmill test protocol started with a comfortable walking speed for 3 minutes followed by 2 minutes of pre-assessed fast walking speed (speed between 1.5 to 3.7 mph). This treadmill speed was kept constant throughout the test and grade was increased 2.5% every 2 minutes until 12.5% grade was achieved. From this point, grade was kept constant,

whereas speed was increased 1 mph every minute until voluntary exhaustion. Participants were allowed to minimally hold the handrail for balance as needed. Tests were terminated based on participants' fatigue and ability to keep up with the treadmill speed. This protocol has been shown to be both valid and reliable for testing individuals with and without Down syndrome.[5, 191] Upon cessation of the treadmill test, recovery recordings of HR and BP were collected at minute 1, 3 and 5.

Cognitive Function Test. A Quick Test of Cognitive Speed (AQT, Pearson Education Ltd, UK) was used to examine participants' information processing time and accuracy. The test consisted of three different tasks; naming colors, shapes, and the combination of both color and shape. During each task, task completion time and error rate were recorded. The main factor that determined the participants' cognitive function was the task completion time. This test has been validated to detect early cognitive decline related to impaired parietal lobe function in studies with AD, cognitive dysfunction and cognitively normal population.[192-194] Test results were analyzed based on participants' performance and categorized in to three levels; normal, slower than normal, and pathologically slow.

Modified Flanker Test. Participants without DS were also asked to complete the modified Flanker test on a computer immediately following AQT in order to avoid the potential ceiling effect of AQT. The Modified Flanker test is designed to evaluate inhibitory control of the test subject. The test involves a set of 5 flanking arrows of congruent (<<<<<) and incongruent (>><>>) orientation. Participants were asked to correctly identify the direction of the central

target arrow. The test consists of one block of 200 stimuli (100 congruent and 100 incongruent), or flanking tasks. Total time to take the test was about 6 minutes.

Cerebral blood flow (CBF). CBF was measured using a 2-MHz transcranial Doppler ultrasound probe (MultiDop T, DWL Electronics, Sipplingen, Germany) attached to a headpiece to stabilize it on the right side of the participants' head. This probe was fixed at an angle to insonate the right middle cerebral artery over the temporal window. The sample volume and the depth of the penetration of Doppler signal were optimized for each participant to obtain the best quality signal. Systolic velocity, diastolic velocity, mean blood flow velocity, pulsatility index (PI), and resistance index (RI) were recorded at 500 kHz and stored off-line for analysis. PI is the difference of systolic flow velocity and diastolic flow velocity divided by mean flow velocity; PI = (systolic flow velocity – diastolic flow velocity) / mean flow velocity. RI is the difference of systolic flow velocity and diastolic flow velocity divided by systolic flow velocity; RI = (systolic flow velocity – diastolic flow velocity) / systolic flow velocity. One minute average values for the CBF velocity and its characteristics were calculated. Data were analyzed at rest, immediately post-exercise, and 30 minutes post exercise.

End-Tidal CO_2 ($ETCO_2$). $ETCO_2$ was measured throughout the second visit by gas collection tubes attached to a mask (Hans Rudolph Inc, Shawnee, Kansas) on the participants' face over the mouth and nose. $ETCO_2$ was recorded on-line (CO2100C, Biopac System Inc, USA) and analyzed for baseline, immediately post, and 30 minutes post-exercise time points.

Statistical Analyses. Shapiro-Wilk tests were used to test the normality of each study variable. A 2 x 3 (group x time) repeated measure of analysis of variance (ANOVA) was used to investigate the differences in group and pre-/post-exercise time points. Tukey's *post-hoc* tests were performed when the initial significance was found using the repeated measure of ANOVA. Pearson's correlational analyses were performed to test the relationships between the all study variables. Results are presented as mean ± SEM with a significance level set at $p<0.05$. SPSS version 24 (IBM SPSS Statistics, Armonk, NY) was used for statistical analysis. Sample size was calculated in order to provide the study with 80% power to detect an exercise effect on cognitive function in individuals with DS using an effect size of 0.45 determined from a previous study investigating the effect of acute treadmill walking on cognitive function in individuals with DS to show an exercise effect on cognitive function.[144] The power analysis approximated a sample size of 10 in each group to obtain statistical power at *p*-value of <0.05 in this study.

iii. Results

Descriptive Characteristics.

Participant descriptive, baseline hemodynamics, and vascular function data are shown in Table 1. Both the DS and the control group consisted of 20 participants each. The average age of both groups was 25 yrs ($p>0.05$). The DS group exhibited shorter height, higher BMI, lower VO_{2peak} and HR_{peak} than the control group ($p<0.05$ for all). Body weight was not different between groups ($p>0.05$).

There was no statistical difference in baseline brachial and aortic systolic, diastolic, and mean arterial pressure between DS and control group ($p>0.05$ for all). In addition, HR, CO, and TVR also were similar between both group ($p>0.05$ for all). AIx@75 was higher in the control group but this was not statistically significant ($p>0.05$). R-CAVI and L-CAVI, indices of arterial

stiffness, were significantly higher in the control group ($p<0.05$), whereas R-ABI and L-ABI, indices of arteriosclerosis, also were not different in between groups ($p>0.05$).

Table 1. Descriptive Characteristics

	DS	Control	*p*-value
Age (yrs)	25 ± 0.9	25 ± 0.8	0.94
Height (cm)	156.5 ± 0.02	171.7 ± 0.02	0.00 §
Weight (kg)	71.3 ± 3.1	74.5 ± 5.0	0.65
BMI (kg/m^2)	29.4 ± 1.4	24.9 ± 1.3	0.02 §
Waist Girth (cm)	93.0 ± 3.0	84.1 ± 3.8	0.08
VO_{2peak} (mL/kg/min)	28.25 ± 1.56	40.86 ± 1.32	0.00 §
HR_{peak} (bpm)	167 ± 3	195 ± 2	0.00 §
SBP (mmHg)	120 ± 3	120 ± 2	0.63
DBP (mmHg)	69 ± 2	72 ± 1	0.31
MAP (mmHg)	93 ± 2	94 ± 2	0.85
HR (bpm)	62 ± 2	63 ± 2	0.97
CO (L/min)	5.30 ± 0.20	5.07 ± 0.21	0.44
TVR (dyn*s/cm5)	1.08 ± 0.05	1.15 ± 0.05	0.38
aorSBP (mmHg)	109 ± 3	111 ± 2	0.47
aorDBP (mmHg)	71 ± 2	73 ± 1	0.47
AIx@75	10.2 ± 3.0	16.6 ± 3.5	0.17
R-CAVI	5.2 ± 0.2	5.9 ± 0.2	0.00 §
L-CAVI	5.3 ± 0.2	5.9 ± 0.2	0.02 §
R-ABI	1.01 ± 0.02	1.04 ± 0.02	0.38
L-AVI	1.01 ± 0.02	1.06 ± 0.02	0.14

BMI=Body mass index, VO_{2peak}= Peak oxygen consumption, HR_{peak}=Peak heart rate, SBP=Brachial systolic blood pressure, DBP=Brachial diastolic blood pressure, MAP=Brachial mean arterial pressure, HR=Heart rate, CO=Cardiac output, TVR=total vascular resistance, aorSBP=Aortic systolic blood pressure, aorDBP=Aortic diastolic blood pressure, AIx@75= Augmentation index normalized at a heart rate of 75 beats per minute, R-CAVI=Right cardio ankle vascular index, L-CAVI=Left cardio ankle vascular index, R-ABI=Right ankle brachial index, L-ABI=Left ankle brachial index, Mean ± SEM, § indicates significant group difference, Alpha level set at $p<0.05$.

Brachial Blood Pressures, Aortic Blood Pressures, Hemodynamic variables

Data for hemodynamic changes following exercise are presented in Table 2. There were no group differences in brachial SBP, DBP, and MAP ($p>0.05$). Brachial SBP ($p<0.05$, F=7.526), DBP ($p<0.05$, F=27.551) and MAP ($p<0.05$, F=23.985) were elevated immediately post-exercise in the overall cohort, without an interaction ($p>0.05$, $\eta^2=0.066$).

HR was higher both immediately post-exercise and 30 minutes post-exercise in the overall group ($p<0.05$, F=245.236), but with no differences between groups nor any significant interactions ($p>0.05$, $\eta^2=0.031$).

Aortic BP responded to exercise similarly to brachial BP. Aortic SBP (aorSBP) and aortic DBP (aorDBP) were higher immediately post-exercise ($p<0.05$) without any group differences ($p>0.05$) or any interactions ($p>0.05$, $\eta^2=0.037$ [aorSBP], $\eta^2=0.043$ [aorDBP], respectively). There was an exercise effect ($p<0.05$, F=23.121) for aorMAP, without an interaction ($p>0.05$, F=1.607, $\eta^2=0.051$). *Post hoc* analysis showed that aorMAP was elevated immediately following exercise compared to other time points ($p<0.05$). There were no group differences ($p>0.05$) or exercise effects on CO ($p>0.05$, F=0.228). TVR also elicited an exercise effect ($p<0.05$, F=3.428), with no group difference (p>0.05). TVR was elevated at immediate post exercise ($p=0.052$) and reduced at 30 minute post exercise time point from immediate post-exercise ($p<0.05$).

Table2. Pre- and Post-Exercise Hemodynamic Data

	DS			Control		
	Baseline	Immediate post exercise	30minute post-exercise	Baseline	Immediate post exercise	30minute post-exercise
SBP (mmHg)	122 ± 3	126 ± 3	122 ± 3	112 ± 3	130 ± 3†	121 ± 3
DBP (mmHg)	69 ± 2	75 ± 2†	71 ± 2	72 ± 2	81 ± 2†	74 ± 2
MAP (mmHg)	93 ± 2	98 ± 2†	94 ± 2	94 ± 2	104 ± 2†	96 ± 2
HR (bpm)	63 ± 2†	89 ± 2	73 ± 2	63 ± 2†	93 ± 2	77 ± 2
aorSBP (mmHg)	109 ± 3	111 ± 3	110 ± 3	111 ± 3	118 ± 3†	110 ± 3
aorDBP (mmHg)	72 ± 2	77 ± 2†	73 ± 2	74 ± 2	83 ± 2†	76 ± 2
aorMAP (mmHg)	84 ± 2	89 ± 2†	85 ± 2	86 ± 2	95 ± 2†	88 ± 2
CO (L/min)	5.30 ± 0.21	5.10 ± 0.10	5.03 ± 0.17	5.07 ± 0.21	5.25 ± 0.10	5.50 ± 0.17
TVR	1.08 ± 0.05	1.17 ± 0.02	1.14 ± 0.05	1.15 ± 0.05	1.19 ± 0.02	1.07 ± 0.05‡

SBP=Brachial systolic blood pressure, DBP=Brachial diastolic blood pressure, MAP=Brachial mean arterial pressure, HR=Heart rate, aorSBP=Aortic systolic blood pressure, aorDBP=Aortic diastolic blood pressure, CO=Cardiac output, TVR=total vascular resistance, † indicates the significant difference from other time points, ‡ indicates the significant difference from immediate post exercise time point, Mean ± SEM, Significance level set at $p<0.05$.

Carotid Arterial Stiffness and Arterial compliance. (Figure 3)

β-stiffness was increased in the overall cohort immediately post-exercise, with no interaction ($p>0.05$, $F=0.319$, $\eta^2=0.006$) or group differences ($p>0.05$). β-stiffness returned closer to baseline at 30 minutes post-exercise, however, it was not different from immediate post exercise ($p>0.05$) or baseline ($p>0.05$). In addition, there was a reduction in arterial compliance (AC) ($p<0.05$, $F=6.665$) immediately and 30 minutes post-exercise ($p<0.05$) compared to baseline, with no interaction ($p>0.05$, $\eta^2=0.036$), or group differences ($p>0.05$).

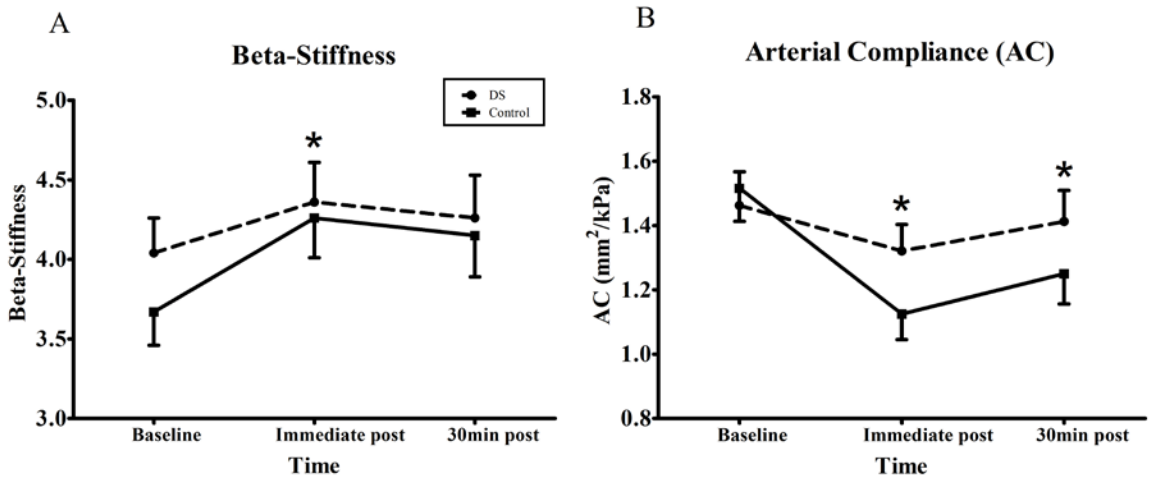

Figure 3. Changes in Arterial Stiffness Following Exercise. A. Beta-stiffness=carotid arterial stiffness, B. AC= arterial compliance. * indicates a significant difference from unmarked time points. Significance level set at $p<0.05$.

Carotid Blood Pressure, Carotid Blood Flow, Pulsatility Index, and Resistance Index. (Figure 4)

There was an exercise effect ($p<0.05$, F=5.941) on cSBP with elevated pressure immediately post-exercise ($p<0.05$), with no interaction ($p>0.05$, F=2.499, $\eta^2=0.065$). In addition, there was no group difference ($p>0.05$).

cDBP exhibited an interaction ($p<0.05$, F=3.540). *Post hoc* analysis showed that the control group exhibited an increase in cDBP at immediately post-exercise time point ($p<0.05$).

There was an exercise effect ($p<0.05$, F=5.860) in cMAP with an interaction ($p<0.05$, F=5.666). *Post hoc* analyses showed that the control group exhibited an increase in cMAP at immediately post-exercise ($p<0.05$), whereas the DS group did not exhibit any changes at this time point ($p>0.05$).

There were neither group differences ($p>0.05$) nor exercise effects ($p>0.05$, F=0.490) or an interaction ($p>0.05$, F=0.038, $\eta^2=0.001$) in carotid blood flow (cBF).

There was an exercise effect with higher carotid pulsatility index (cPI) ($p<0.05$, F=3.974) at immediate post ($p<0.05$) and 30-minute post-exercise ($p<0.05$) time points, but there was no interaction ($p>0.05$, F=0.606, $\eta^2=0.015$). Furthermore, the DS group exhibited higher overall PI (significant group effect; $p<0.05$).

There was a exercise effect on carotid resistance index (cRI) ($p<0.05$, F=9.304) with higher cRI at immediate post ($p<0.05$) and 30 minute post-exercise ($p<0.05$) time points, with no interaction ($p>0.05$, F=2.186, $\eta^2=0.051$), and no group difference ($p>0.05$).

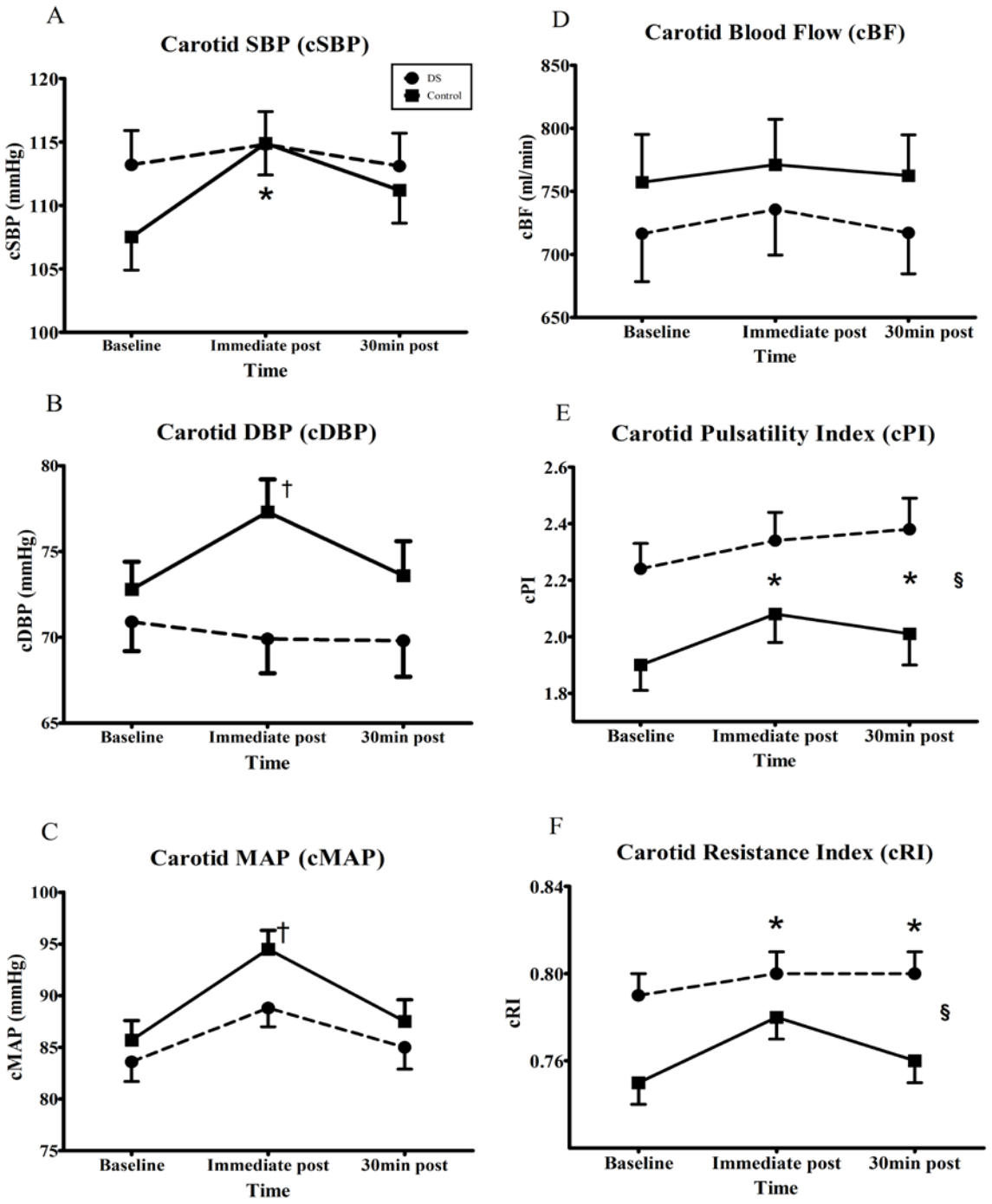

Figure 4. Changes in Carotid Pressure and Blood Flow Characteristics Following Exercise. A. cSBP=carotid systolic blood pressure, B. cDBP=carotid diastolic blood pressure, C. cMAP=carotid mean arterial pressure, D. cBF=carotid blood flow, E. cPI=carotid pusatility index, F. cRI=carotid resistance index, * indicates a significant difference from unmarked time point as a group, † indicates a significant difference at the time within the group, Significance level set at $p<0.05$.

Cerebral Artery Blood Velocity (mMCAv), End Tidal Carbon Dioxide ($ETCO_2$), Pulsatility Index (PI), and Resistance Index (RI). (Figure 5)

There was no exercise effect ($p>0.05$, $F=1.005$, $\eta^2=0.027$), interaction ($p>0.05$, $F=0.038$, $\eta^2=0.033$), or group difference ($p>0.05$) for mMCAv.

Lower values for $ETCO_2$ were observed for $ETCO_2$ ($p<0.05$, $F=3.396$) with at 30 minutes post-exercise ($p<0.05$), without an interaction ($p>0.05$, $F=1.089$, $\eta^2=0.03$), or group difference ($p>0.05$).

PI and RI exhibited a group differences ($p< 0.05$ for both), with a higher level of PI and RI in the DS group. There was no exercise effect ($p>0.05$), or interaction for either PI or RI ($p>0.05$ for both, $\eta^2=0.045$ [PI], $\eta^2=0.019$ [RI]).

There was an exercise effect on cerebral vascular conductance (CVC) ($p<0.05$, $F=11.422$) with reduced CVC both immediately post and 30 minute post-exercise ($p<0.05$ for both groups), without an interaction ($p>0.05$, $F=1.089$, $\eta^2=0.045$) or group difference ($p>0.05$).

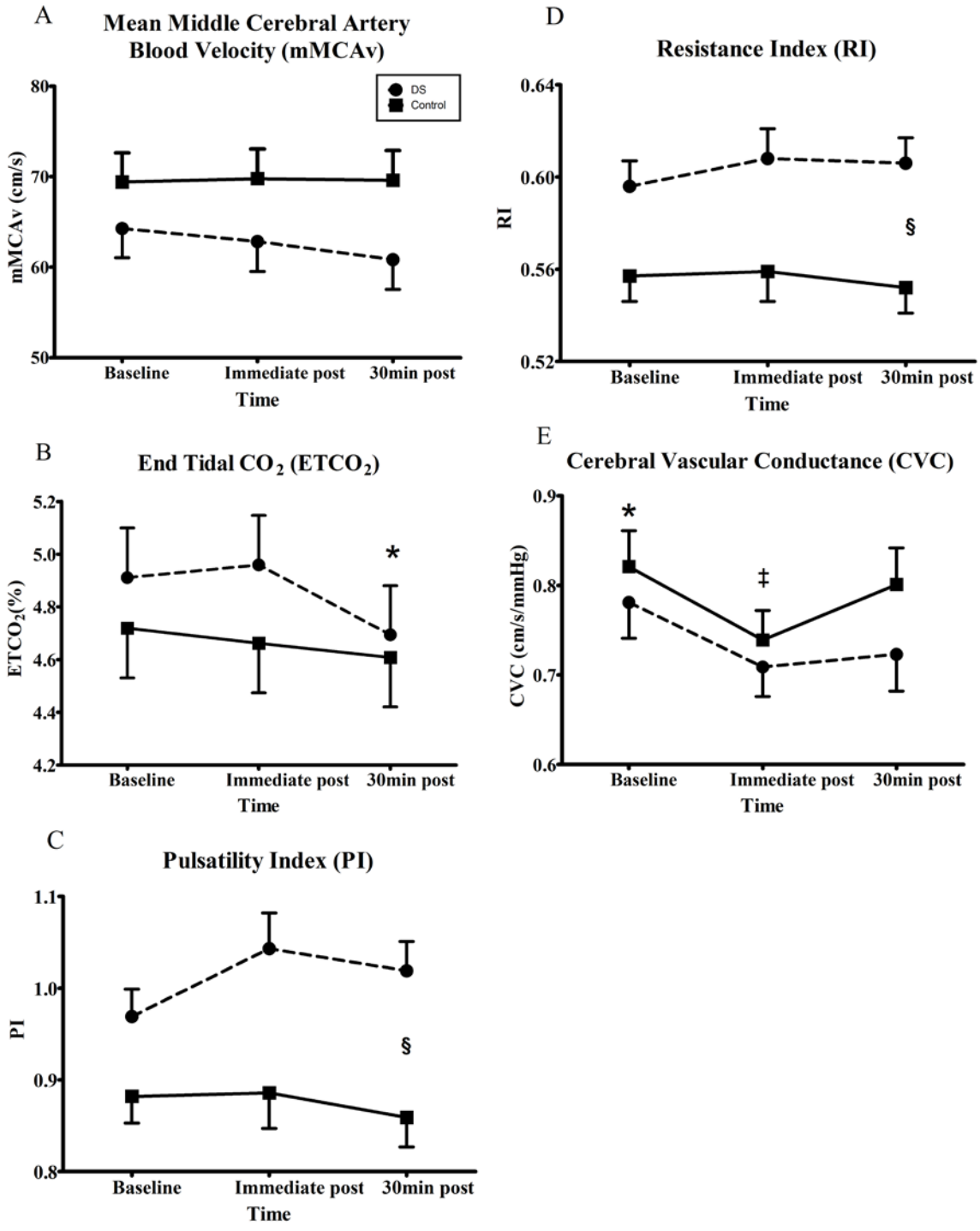

Figure 5. Changes in Cerebral Blood Flow Characteristics following Exercise.
A. mMCAv=middle cerebral artery blood velocity, B. $ETCO_2$=end tidal carbon dioxide, C. PI=pulsatility index, D. RI=resistance index, E. CVC=cerebral vascular conductance, * indicates a significant difference from other time points, § indicates a significant group difference, ‡ indicates significant difference form other time points. Significance level set at $p<0.05$.

Cognitive Function Test: AQT and Modified Flanker

A Quick Test for Cognitive Speed. (Table 3)

There was no exercise effect ($p>0.05$, F=1.449), or interaction effect on AQT time ($p>0.05$, F=0.958, $\eta^2=0.029$). However, there was a group difference with the control group finishing the task faster than the DS group ($p<0.05$). The error rate for AQT was similar to AQT time data. There was no exercise effect on ($p>0.05$, F=0.70), or interaction on the AQT error rate ($p>0.05$, F=0.429, $\eta^2=0.017$). However, there was a group difference, with a lower error rate in the control group ($p<0.05$).

Modified Flanker Test. (Table 4)

Only the control group completed the Modified Flanker Test.

Overall Reaction Time (RT). There was an exercise effect on overall RT ($p<0.05$, F=19.474) with faster reaction time at immediate post and 30 minute post-exercise time points ($p<0.05$ for both)

Overall Accuracy. There was no exercise effect on overall accuracy ($p>0.05$, F=1.151)

Congruent and incongruent reaction time (RT). There were exercise effects on congruent RT ($p<0.05$, F=18.182) and incongruent RT ($p<0.05$, F=16.878), with faster reaction time at immediate post and 30 minute post-exercise time points ($p<0.05$ for both).

Table 3. Pre- and Post-Exercise Cognitive Function Test (AQT)

	DS			Control		
	Baseline	Immediate post exercise	30 minute post exercise	Baseline	Immediate post exercise	30 minute post exercise
AQT Time §	90.3 ± 5.5	85.1 ± 4.5	92.1 ± 6.5	47.2 ± 5.6	44.7 ± 4.6	44.8 ± 6.6
AQT Error §	1.5 ± 0.3	2.1 ± 0.4	2.0 ± 0.4	0.4 ± 0.3	0.5 ± 0.4	0.3 ± 0.4

AQT Time=A quick test for cognitive speed time, AQT Error=A quick test for cognitive speed error, § indicates significant group difference, Mean ± SEM, Significance level set at $p<0.05$.

Table 4. Pre- and Post-Exercise Modified Flanker Test

	Control		
	Baseline	Immediate post exercise	30 minute post exercise
Overall RT	508.16 ± 8.76	*491.87 ± 8.67	*491.21 ± 8.71
Overall Accuracy	91.66 ± 3.44	93.97 ± 1.53	93.55 ± 1.65
Congruent RT	471.89 ± 7.82	*455.87 ± 7.57	*456.92 ± 7.91
Congruent Accuracy	95.37 ± 2.90	97.79 ± 0.79	97.90 ± 0.56
Incongruent RT	548.61 ± 9.28	*530.88 ± 9.99	*528.91 ± 9.30
Incongruent Accuracy	87.95 ± 4.08	90.16 ± 2.38	89.21 ± 2.83

Overall RT=overall reaction time, Overall Accuracy=overall accuracy, Congruent RT=congruent reaction time, Congruent Accuracy= Congruent Accuracy, Incongruent RT=incongruent reaction time, Incongruent Accuracy= Incongruent Accuracy, * indicates a significant difference from the baseline, Mean ± SEM, Significance level set at $p<0.05$.

Correlations

There were inverse relationships between VO_{2peak} and AQT Time ($p<0.05$, r=-0.411), HR_{peak} and AQT Time ($p<0.05$, r=-0.620), VO_{2peak} and PI ($p<0.05$, r=-0.318), and VO2peak and PI ($p<0.05$, r=-0.385). However, there was no relationship between mMCAv and AQT Time ($p>0.05$, r=-0.085) or mMCAv and AQT error ($p>0.05$, r=-0.068). (Table 5)

However, these significant correlations disappeared ($p>0.05$ in all) when the correlation analyses were performed in the DS and control groups separately (Table 6 and Table 7).

Table 5. Correlations in overall group

		VO_{2peak}	HRpeak	AQT Time	AQT Error	mMCAv	PI	RI
VO_{2peak}	Pearson r	1	0.626♦	-0.411♦	-0.268	0.169	-0.318♦	-0.385♦
	p-value		0.000	0.009	0.104	0.303	0.017	0.016
HR_{peak}	Pearson r	0.626♦	1	-0.620♦	-0.304	0.044	-0.323♦	-0.340♦
	p-value	0.000		0.000	0.063	0.792	0.045	0.034
AQT Time	Pearson r	-0.411♦	-0.620♦	1	0.557♦	-0.085	0.150	0.151
	p-value	0.009	0.000		0.000	0.608	0.361	0.358
AQT Error	Pearson r	-0.268	-0.304	0.557♦	1	-0.068	0.165	0.149
	p-value	0.104	0.063	0.000		0.686	0.323	0.370
mMCAv	Pearson r	0.169	0.044	-0.085	-0.068	1	-0.339♦	-0.298
	p-value	0.303	0.792	0.608	0.686		0.035	0.065
PI	Pearson r	-0.318♦	-0.323♦	0.150	0.165	-0.339♦	1	0.981♦
	p-value	0.017	0.045	0.361	0.323	0.035		0.000
RI	Pearson r	-0.385♦	-0.323♦	0.151	0.149	-0.298	0.981♦	1
	p-value	0.016	0.045	0.358	0.370	0.065	0.000	

Table Legend. VO_{2peak}=maximal aerobic fitness capacity (Peak oxygen consumption), HR_{peak}=Peak heart rate, AQT Time=A Quick Test for Cognitive Speed Time, AQT Error=A Quick Test for Cognitive Speed Number of Error, PI=Pulsatility index, RI=Resistance index, ♦ indicates the significant correlation, Significance level set at $p<0.05$.

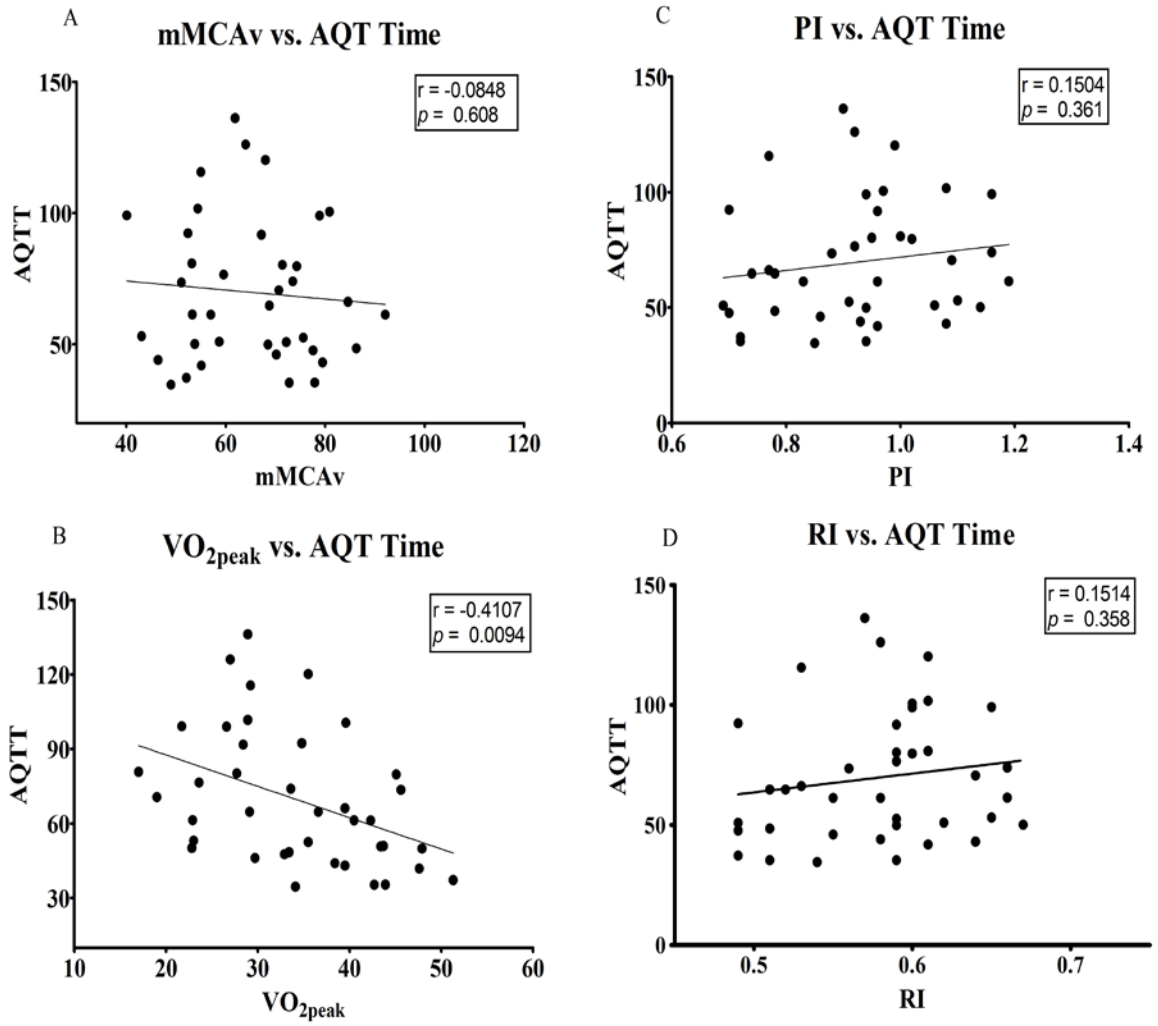

Figure 6. Correlations Between mMCAv and AQT Time (A), VO2peak and AQT Time (B), PI and AQT Time (C), and RI and AQT Time (D) in overall cohort. VO_{2peak}= Peak oxygen consumption, HR_{peak}=Peak heart rate, AQT Time=A Quick Test for Cognitive Speed Time, AQT Error=A Quick Test for Cognitive Speed Number of Error, PI=Pulsatility index, RI=Resistance index.

Table 6. Correlations in DS group

		VO_{2peak}	HR_{peak}	AQT Time	AQT Error	mMCAv	PI	RI
VO_{2peak}	Pearson r	1	0.290	0.256	-0.013	0.206	-0.405	-0.435
	p-value		0.214	0.275	0.958	0.382	0.077	0.055
HR_{peak}	Pearson r	0.290	1	-0.078	0.051	-0.310	0.183	0.213
	p-value	0.214		0.744	0.837	0.184	0.440	0.367
AQT Time	Pearson r	0.256	-0.078	1	0.448	0.012	-0.349	-0.366
	p-value	0.275	0.744		0.055	0.959	0.131	0.112
AQT Error	Pearson r	-0.268	-0.304	0.448	1	0.053	-0.058	-0.074
	p-value	0.104	0.063	0.055		0.831	0.814	0.762
mMCAv	Pearson r	0.169	0.044	-0.085	0.053	1	-0.343	-0.312
	p-value	0.303	0.792	0.608	0.831		0.139	0.181
PI	Pearson r	-0.405	0.183	0.150	-0.058	-0.343	1	0.980♦
	p-value	0.077	0.440	0.361	0.814	0.139		0.000
RI	Pearson r	-0.435	0.213	0.367	-0.074	-0.312	0.980♦	1
	p-value	0.055	0.367	-0.366	0.762	0.181	0.000	

Table Legend. VO_{2peak}=maximal aerobic fitness capacity (Peak oxygen consumption), HR_{peak}=Peak heart rate, AQT Time=A Quick Test for Cognitive Speed Time, AQT Error=A Quick Test for Cognitive Speed Number of Error, PI=Pulsatility index, RI=Resistance index, ♦ indicates the significant correlation, Significance level set at $p<0.05$.

Table 7. Correlations in control group

		VO_{2peak}	HR_{peak}	AQT Time	AQT Error	mMCAv	PI	RI
VO_{2peak}	Pearson r	1	-0.295	-0.010	0.057	-0.260	0.195	0.216
	p-value		0.207	0.969	0.816	0.283	0.423	0.375
HR_{peak}	Pearson r	-0.295	1	-0.040	-0.118	-0.150	-0.360	-0.430
	p-value	0.207		0.870	0.631	0.539	0.130	0.066
AQT Time	Pearson r	-0.010	-0.040	1	0.444	0.353	0.137	0.097
	p-value	0.969	0.870		0.057	0.138	0.577	0.693
AQT Error	Pearson r	0.057	-0.118	0.444	1	-0.171	0.241	0.170
	p-value	0.816	0.631	0.057		0.483	0.320	0.487
mMCAv	Pearson r	-0.260	-0.150	0.353	-0.171	1	-0.191	-0.133
	p-value	0.283	0.539	0.138	0.483		0.433	0.587
PI	Pearson r	0.195	-0.360	0.137	0.241	-0.191	1	0.977♦
	p-value	0.423	0.130	0.577	0.320	0.433		0.000
RI	Pearson r	0.216	-0.430	0.097	-0.074	-0.133	0.977♦	1
	p-value	0.375	0.066	0.693	0.762	0.587	0.000	

Table Legend. VO_{2peak}=maximal aerobic fitness capacity (Peak oxygen consumption), HR_{peak}=Peak heart rate, AQT Time=A Quick Test for Cognitive Speed Time, AQT Error=A Quick Test for Cognitive Speed Number of Error, PI=Pulsatility index, RI=Resistance index, ♦ indicates the significant correlation, Significance level set at $p<0.05$.

iv. Discussion

An important and unique finding of our study was that cognitive function (AQT) was not affected by exercise in individuals with DS, whereas controls improved reaction time following exercise (Flanker test). Interestingly, our study showed no difference in mean CBF velocity between individuals with DS and controls at rest. Furthermore, mean CBF velocity did not change from rest to following exercise in either group. This was a unique finding, as most of the literature in individuals without DS have shown increased mean CBF velocity with exercise.[158, 172, 195-197] In addition, no relationship between CBF velocity and cognitive function were found in either individuals with and without DS. The most significant finding of this study was that individuals with DS exhibit significantly different CBF characteristics compared to controls, with higher PI and RI at rest and after aerobic exercise. To our knowledge, this is the first study to investigate the differences in CBF characteristics and cognitive function, and their relationship, in individuals with DS at rest and following a single bout of moderate intensity aerobic exercise.

Peripheral and Central Blood Pressure & Hemodynamics at Rest and Post-Exercise

Our results show no difference in brachial or aortic BP between individuals with DS and controls at rest, which agrees with the recent literature.[45, 86] Following exercise, there were no changes in brachial, aortic or carotid BP in the overall cohort. However, the DS group showed an attenuated SBP and MAP response to exercise, although these changes were not significantly different from the control group. These findings were similar for brachial, aortic and carotid BPs. An attenuated BP response in individuals with DS has been shown in our previous work, and it may be due to autonomic dysfunction in individuals with DS as a result of lower sympathetic

activity and blunted parasympathetic withdrawal.[45, 46, 87, 164] The fact that we did not observe a significant attenuation in BP in persons with DS, may be a function of the current data being collected during recovery from exercise, while previous data were collected during exercise.

Interestingly, our current results do not show any post exercise hypotension, which is commonly seen after exercise.[198-200] There is little information about post exercise BP regulation in individuals with DS. Studies with similar exercise intensity in individuals without DS show reduced SBP up until 60 minutes to 12 hours following exercise.[201] Pescatello et al. reported that a single 40 minute bout of either low (40%) or moderate (70%) intensity exercise reduced arterial blood pressure for at least 8 hours, which was measured by an ambulatory BP monitor.[201] Another study also saw BP reductions after 45 minutes of moderate to high intensity exercise.[202] Both studies measured BP with an ambulatory BP monitor in a seated position. These studies had longer durations of exercise, lasting between 30 to 60 minutes, whereas our study only used 20 minutes of exercise. Thus, the duration of exercise may play an important role in post exercise BP changes and this may be one important reason we did not observe any reduction in post exercise BP in our study.

There were also no baseline differences in CO or TVR between individuals with DS and controls, similar to findings from previous work.[69] TVR did not change at any time point in individuals with DS, whereas individuals without DS exhibited reduced TVR at 30 minutes post exercise. This reduction in TVR may be due to peripheral vasodilation.[198, 199] The lack of TVR response to exercise in individuals with DS may be due to the autonomic dysfunction and abnormal vascular function in this population. TVR increases with sympathetic activation, such as exercise, which causes vasoconstriction in the periphery. Conversely, local factors in

contracting muscles cause peripheral vasodilation, causing vasodilation even with a greater sympathetic stimulus, termed sympatholysis.[199, 202] This physiological response to sympathoexcitation may be altered in individuals with DS. One potential cause of this differential TVR response to exercise between individuals with DS and controls may be due to the altered local vasodilatory function, such as endothelial function or the production of local vasodilatory factors, which are supposed to cause vasodilation in the working muscles in response to exercise.[70] This reduced vascular function may cause the lack of TVR changes. Data from our laboratory show a lack of change in brachial blood flow and vascular conductance in response to sympathoexcitation induced by lower body negative pressure in individuals with DS, whereas controls showed a significant reduction in vascular conductance and blood flow.[165] Thus, this different TVR response to exercise may be due to a combination of autonomic dysfunction and altered peripheral vascular regulation, such as endothelial function or local factors. There is only one study investigating endothelial function in DS using the acetylcholine infusion technique, in which they showed robust endothelial dysfunction in DS.[203] This data may also explain the lack of change in TVR in individuals with DS, due to the lack of endothelial dependent vasodilation. However, studies investigating vascular function, such as reactive hyperemia, in individuals with DS are lacking and more studies in this area are necessary to understand vascular function in this population.

Carotid Blood Flow, Carotid Pulsatility Index (cPI), Carotid Resistance Index (cRI) at Rest and Post-Exercise

There was no difference in common carotid artery blood flow between DS and controls. In addition, carotid blood flow did not change following moderate intensity treadmill walking

exercise in either group. We expected carotid blood flow to increase following exercise, but, a previous study has reported common carotid artery blood flow recovers quickly after moderate to high intensity treadmill exercise.[204] Because this was not our primary outcome, the timing of the measurement may have reduced our chance of finding a difference. Our immediate post exercise carotid blood flow measurement timing was approximately 15 minutes after completion of exercise due to the measurement procedure. Thus, by the time we conducted the measurements, carotid blood flow may have already returned to the pre-exercise level. Others have shown changes in carotid blood flow with similar exercise stimulation during exercise.[205] Jiang et al. (1995) investigated changes in common carotid artery blood velocity during incremental exercise in healthy young males. There was a significant increase in common carotid artery blood flow velocity during exercise, which was proportional to exercise intensity.[205] Unlike these aforementioned studies, we were unable to measure carotid artery blood flow during the exercise. As earlier, carotid artery blood flow may have been elevated during exercise and already returned to the baseline level when the measurement took place in our study. Thus, timing of the data collection may affect the results.

cPI and cRI were higher in the DS group and stayed elevated immediate and 30 minutes post exercise. Higher cPI is related to cardiovascular risk,[206] and higher cRI reflects atherosclerotic conditions, which hinders blood flow in the brain.[207] A correlation study showed that cPI is related to arterial stiffness, measured by pulse wave velocity (PWV). Since PWV is an independent risk factor for future cardiovascular event, cPI may also be considered to be related to cardiovascular risk.[206] PI can be elevated when the artery becomes narrower or stiffer by numerous different mechanisms, such as high pulse pressure, high oxidative stress, high reactive oxygen species, diabetes, hypertension and other health issues.[208] The high PI

indicates a transferring of higher pulsatile blood flow to the end organs, such as the brain or the kidneys.[209] Since these organs require continuous blood flow, high pulsatile blood flow may damage the microvasculature in the organs. In addition, high RI is closely related to incidence of atherosclerosis and downstream blood flow resistance.[207] Thus, our data suggest that individuals with DS may be exposed to the higher cardiovascular risk and atherosclerotic conditions.

Difference in Cerebral Blood Flow (CBF) Characteristics Between Individuals with DS and Controls at Rest and Following Exercise

We hypothesized individuals with DS would have lower cerebral blood flow velocity (mCBFv) at rest. However, our results did not show a difference in mCBFv between persons with DS and controls at rest. Similar results were also previously reported by Shapiro et al.,[128] but others have shown significantly reduced CBF in individuals with DS.[126] Melamed et al. examined regional CBF by MRI in older individuals with and without DS as well as age-matched AD patients. This study found that individuals with DS exhibit reduced regional CBF, of similar levels to that of AD patients.[126] The major difference between this study and ours is the age of the study participants. Based on the participant information and study results, we suggest that age may be an important factor influencing resting CBF levels in individuals with DS. Furthermore, individuals with DS start experiencing symptoms of dementia and AD as early as 40 years of age.[210] Thus, CBF may not decline until the symptoms of dementia or AD become evident.

One related factor of reduced CBF in individuals with DS may be attenuated metabolism in the brain due to the changes in brain anatomy, coupled with excessive production of amyloid

precursor protein (APP), membrane protein that is responsible for production of β-amyloid, in DS genes and β-amyloid deposition. Most individuals with DS possess an extra chromosome on their 21st chromosomal pair. The 21st chromosome contains an essential growth protein, APP, which produces β-amyloid. Due to the extra chromosome, individuals with DS produce excessive amounts of β-amyloid, leading to an abnormal accumulation of β-amyloid plaque, which causes detrimental changes in brain volume, and metabolism with age in individuals with DS.[211] Thus, these abnormal changes in aging individuals with DS may contribute to changes in CBF. Thus, the young age of our participants could potentially explain why we did not see any resting CBF differences in our study (mean age: 25 yrs).

DS may cause premature aging due to the abnormal physiological changes.[212] Since individuals with DS exhibit similar physiological characteristics as an aging population, we compared our mMCAv to data from studies with older populations without DS. Studies with healthy older participants show mMCAv between 30 cm/s to 50 cm/s, whereas our DS group's mean mMCAv was 62 cm/s.[213] Based on these data, our DS group appears to have a higher mMCAv compared to a healthy older population, and is similar to that of young individuals without DS (40~90 cm/s). This suggests that in young, generally healthy individuals with DS, a normal mMCAv is maintained.

Importantly, our results show that individuals with DS have higher PI and RI compared to individuals without DS. The brain requires constant blood flow for a continuous supply of oxygen and nutrients due to its high metabolic rate.[214] In order to meet these demands, the brain has a large number of microvessels with low resistance. Commonly, PI increases with aging due to detrimental changes, such as narrowing or stiffening of arteries in cerebral arteries and different health conditions.[215] This increase in PI with aging is due to the increased late

systolic blood flow velocity, which increases flow wave augmentation. This augmented flow wave can transfer higher pulsatile blood flow to the brain microvasculature and cause damage.[214] In addition, high PI (PI >1.19) and RI (RI >0.8) indicate elevated cerebral vascular resistance, which hinders proper blood flow and increases the risk of microvascular damage due to pulsatile flow.[75, 216, 217] Individuals with DS produce higher levels of β-amyloid, which has detrimental effects not only to the neurons, but also to the volume of the brain, which can decrease the amount of cerebral arteries.[10] These detrimental changes in the brain anatomy with a smaller vessel bed may induce higher resistance in the brain, and cause greater pulsatile flow waves.[214] This is an important finding that may explain the early cognitive decline in individuals with DS.

We hypothesized that individuals with DS have a reduced cerebral blood flow response to a bout of moderate intensity treadmill exercise compared to individuals without DS. However, our results show no changes in CBF and $ETCO_2$ following 20 minutes of moderate intensity treadmill exercise in either individuals with or without DS. This finding is supported by findings from Ogoh et al. (2014), which investigated the effects of a 50 minute cycling bout on cerebral blood flow and cognitive function. The study found that CBF velocity increased immediately with exercise.[172] However, CBF velocity decreased to close to baseline levels after 10 minutes of continuous moderate intensity exercise.[172] This rapid return of mMCAv to baseline values may indicate that moderate intensity exercise has a limited effect on mMCAv. Another study also showed similar post exercise CBF return as our findings.[218] The study suggested that the rapid post exercise CBF decrease to baseline is due to the reduction in neuronal activation that reduces cerebral metabolism.[218] This data may explain the lack of change in post-exercise mMCAv. However, others show increased mMCAv during similar exercise intensities.[158, 219]

Moderate intensity supine cycling exercise induced significant mMCAv elevation in a healthy population during exercise.[158] Ide et al. (1999) also demonstrated a significant increase in CBF and cerebral metabolism during bouts of exercise equal to 30% and 60% of maximal capacity cycle exercise.[173] However, these changes in CBF was measured during exercise, not following exercise. Thus, this may explain why we saw no changes in CBF in our study. Further studies are needed to measure CBF during exercise in individuals with DS.

Even though there was no CBF velocity difference between individuals with and without DS in this study, individuals with DS exhibit higher PI throughout the recovery, with no changes from exercise. This higher PI indicates higher cerebral vascular resistance and more inconsistent blood flow, which may create the periods of hypoperfusion.[75, 220] All these conditions may be detrimental to cerebral vasculature and brain function.[75] PI increases with aging and different health conditions. Aging is related to a decrease in CBF velocity and increased PI.[75, 221] However, our data only partially support above mentioned changes in cerebrovascular function. The CBF velocity in individuals with DS in our study was not different from that of controls. This different finding may be due to the age and participants' health status in our study. Our study included young, relatively healthy participants. Thus, if we include those who are older and present with further cognitive decline, CBF velocity may in fact be different from that of controls. However, it is not surprising that individuals with DS, who may exhibit premature aging, exhibited higher PI than controls. Again, this high PI may contribute to cerebral vascular damage and accelerated cognitive decline in this population. However, our correlation data could not support this relationship, since there was no correlation found between PI and cognitive function in this study.

Cognitive Function at Rest and Changes Following Exercise

Individuals with DS had reduced cognitive function compared to controls. Based on the scoring of the AQT, individuals with DS consistently exhibited a pathological level of task completion time deficit throughout the protocol. The AQT task completion time (color and shape naming) tests brain function, specifically of the parietal lobe and prefrontal cortex activity,[192] suggesting this may be an area of decline in those with DS. Validation studies showed that parietal lobe function and prefrontal cortex activity are closely related to memory function, working memory, information processing ability and perceptual processing ability.[222-224] Thus, the longer task completion time in individuals with DS in this study corresponds to areas of cognitive abnormalities often seen as early symptoms of dementia.[225, 226]

In this study, moderate intensity exercise did not alter cognitive function in either individuals with DS. These results are against our hypothesis stating that moderate intensity exercise will improve cognitive function. Previously, exercise has shown improvements in cognitive function following moderate intensity exercise. But, our study is not the first to see no effect. Chen et al. (2014) also reported no improvement in choice-response time and attention shift following 20 minutes of moderate intensity (50 – 80% of calculated HR_{peak}) treadmill walking in individuals with DS.[154] Of note, these cognitive outcomes are similar to those measured with the AQT.

However, a large body of literature showed that moderate intensity exercise improves cognitive function, especially executive function, attention span, information processing speed and working memory in populations with and without DS.[145, 154, 227-229] A study from Ringenbach et al. (2014) showed significant improvements in reaction time after 30 minutes of moderate intensity assistive cycling in individuals with DS, whereas voluntary cycling did not

show any improvement.[145] This difference may be due to the intensity of exercise provided by assistive cycling in the study. Those who performed voluntary cycling did not have to maintain a high exercise intensity (80 rpm), whereas those on assistive cycling did maintain 80 rpm. Thus, higher intensity exercise may be necessary to improve cognitive function or cognitive function may have been improved due to motor activity occurring without having to actively think about the required motions. Another study from same group also investigated the changes in cognitive function following 8 weeks of assistive exercise training and reported improvement in executive function in individuals with DS.[230] Furthermore, Hillman et al. examined the effects of a 30-minute bout of moderate intensity treadmill walking on cognitive function in children without DS using a very similar protocol to the one implemented in our study. They elicited improvements in cognitive function, especially attention after exercise.[231] However, these studies used a longer duration of exercise, 30 minutes of voluntary or assistive exercise, compared to our 20 minutes. Thus, the duration of the exercise may be an important aspect of cognitive function change. Another potential cause of different findings in our study is the mode of exercise. Individuals with DS have been shown to improve cognitive function were assistive exercise studies,[145, 230] whereas our study used voluntary walking exercise. Assistive mode exercise might produce a higher workload, which may have elicited more brain perfusion and cognitive function improvement.

In our study, individuals without DS performed an additional cognitive function test, the Flanker test. The purpose of the Flanker test was to avoid the potential ceiling effect of AQT in control subjects and to evaluate the effect of exercise on the similar cognitive aspects that is tested by AQT. Interestingly, our results show that exercise significantly improved overall, and both congruent and incongruent, reaction time in individuals without DS. The Flanker differs

from the AQT in that it measures spontaneous reaction time and overall task completion time. Thus, AQT may not be sensitive enough to detect the cognitive improvement from our exercise stimulus. Other studies in young, healthy individuals have shown that moderate intensity exercise leads to improvements in working memory, reaction time, and information processing time, supporting our findings.[232] This may indicate that there are different areas of cognitive function that can be improved by a single bout of moderate intensity exercise. In addition, the cognitive function test that was used by Ringenbach et al. and Chen et al. was a comprehensive cognitive function test, evaluating different areas of cognitive function including reaction time, information processing ability, working memory, and executive function.[144, 145, 230, 233] The AQT only measures information processing time, which evaluates parietal lobe function. We chose AQT to test our hypothesis, since it is a validated test to examine brain function related to early signs of dementia and AD. In addition, the testing duration of the AQT is significantly shorter than that of other tests that were used in previous studies. The short test duration allowed us to examine the effects of acute exercise on cognitive function at multiple post exercise time points. However, AQT did not detect any changes in cognitive function following acute exercise. Thus, a more comprehensive and more sensitive cognitive function test may be needed to detect the acute benefits of exercise on cognitive function.

Correlations

We hypothesized that there is relationship between cerebral blood flow and cognitive function in individuals with and without DS. We did not find any significant relationship between CBF and cognitive function in either group. This agrees with the findings from Ogoh et al. (2014) showing no relationship between CBF and cognitive function improvement. Although

they saw improvement in cognitive function, whereas we did not see in individuals with DS, they indicate the improvement in cognitive function following exercise may be due to neural activation from exercise instead of CBF changes.[172] However, we still question the separation between neural activation and CBF changes from this study. If there is neural activation induced by exercise, this will increase oxygen uptake of the brain, which should increase CBF.[214] Thus, even though we did not see any changes in CBF velocity in our study, we observed an improvement in cognitive function in controls suggesting that the exercise induced cognitive function improvement was elicited by cerebral activation that was not detected by our CBF measurement. However, this area of study is still controversial and requires further exploration.

Limitations

There are some limitations in our study. The CBF characteristics measured only measures blood flow velocity. Transcranial Doppler does not measure the diameter of the MCA or blood volume, which help fully describe flow through a vessel, in addition to blood velocity. Furthermore, we were unable to detect which areas of the brain were activated by the exercise stimulation. In order to obtain diameter of the cerebral artery and information about activation of the brain, scans such as MRI or PET are required. However, the cost of these scan is very high. Another limitation of our study is that individuals with DS had a large variance in cognitive function level. Individuals with different cognitive function levels may react differently to exercise. Lastly, the cognitive function test, AQT, that we chose may be too specific to one area of the brain to detect the overall effects of exercise on cognitive function changes. Thus, further studies with participants with similar cognition levels, a more inclusive cognitive function test, and different brain activity and blood flow measurement techniques are needed.

Conclusions.

We found CBF velocity is not different between young individuals with and without DS. However, we found that individuals with DS are more exposed to pulsatile blood flow, which is detrimental to cerebral microvascular health. This high pulsatile blood flow may contribute to reductions in brain health and may cause further cognitive decline in this population. Cognitive function was lower in individuals with DS. Furthermore, cognitive function, measured by AQT, and CBF velocity were not affected by moderate intensity treadmill exercise among individuals with DS. This lack of change in CBF velocity and cognitive function may be due to the variation in our participants' physiological conditions or the sensitivity of the cognitive function test. Lastly, we did not find any relationship between CBF characteristics and cognitive function in either group. However, our results suggest that improving aerobic capacity may improve CBF characteristics, RI and PI, which may improve brain perfusion and reduce pulsatile blood flow.

Chapter IV. Summary of Results and Significance

Individuals with DS exhibit impaired cognitive function compared to individuals without DS. However, mean CBF velocity in individuals with DS was not different from that of controls. Interestingly, cognitive function was not related to mean CBF velocity. We believe that young, relatively healthy individuals with DS do not exhibit reduced CBF velocity, but still have reduced cognitive function. However, we found that individuals with DS exhibit significantly higher PI and RI, which are detrimental to the brain microvasculature. This elevated PI and RI may cause further damage in the brain, which may cause further cognitive decline in this population.

We found that cognitive function was not related to CBF velocity in either individuals with and without DS. This finding may suggest that cognitive function may be related to other factors such as brain volume or neuronal connectivity instead of just cerebral perfusion. Another potential factor that may affect the lack of relationship in our study is that the AQT may be a too specific test, focusing on parietal lobe function, to evaluate the relationship between cognitive function and CBF.

Exercise did not improve cognitive function or CBF velocity in individuals with DS, whereas individuals without DS showed significant improvement in cognitive function. However, we need to consider the sensitivity of AQT, whether it was sensitive enough to detect the effect of exercise induced CBF change on cognitive function.

This research may be important for the researchers because our study suggests that different intensity or duration or a different exercise mode may be needed to improve CBF and cognitive function improvement in individuals with DS, since 20 minute of moderate intensity exercise did not show any changes in cognitive function or mean CBF blood flow. Furthermore,

our study results may be used to encourage individuals with DS or a DS society to engage in a more active lifestyle, even though our results did not show changes in CBF or cognitive function. However, improving aerobic fitness may improve those CBF characteristics which are detrimental to the brain function. In addition, there are other health benefits provided by regular exercise.

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EDUCATION

University of Illinois at Chicago, Chicago, IL **2012 – 2017**
Doctor of Philosophy, Rehabilitation Science
Advisor: Dr. Bo Fernhall
Dissertation: Effects of Aerobic Exercise on Cerebral Blood Flow and Cognitive Function in Individuals with Down Syndrome

California State University Northridge, Northridge, CA **2010 - 2012**
Master of Science, Applied Physical Activity.
Advisor: Dr. Konstantinos Vronginostinos/Dr. Taeyou Jung
Thesis: Cardiorespiratory Response to Continuous Passive Exercise in People with Spinal Cord Injury

Auburn University, Auburn, AL
Master of Education, Exercise Science **2001 - 2004**
Advisor: Dr. Peter W. Grandjean
Emphasis: Health Promotion and Lipid Metabolism

Korea University, Seoul, South Korea **1992 - 2000**
Bachelor of Science, Sports and Leisure Studies

EXPERIENCES

1. Research Assistant **2012 - 2017**
*Skills Acquired: Ultrasound Vascular & Cardiac measurements, Phlebotomy, Graded Exercise Testing with Respiratory Analysis, ECG*Integrative Physiology Laboratory, University of Illinois at Chicago

2. Teaching Experiences

Laboratory Instructor **2013 - 2017**
Lecture & Laboratory
Courses:
Advanced Exercise Assessment (Graduate students)
Electrocardiograph (Undergraduate students)
Exercise Physiology (Undergraduate students)
University of Illinois at Chicago

Land-based and Aquatic-based Therapy Supervising Instructor **2010 - 2012**
Skills Acquired: Physical fitness Assessment & Exercise Prescription, Individuals Therapy Techniques
Aquatic group exercise therapy(elderly population based classes)
Center of Achievement, California State University Northridge

Physical Activity Class Instructor **2010 - 2011**
Tennis, Swimming, Weight Training
California State University Northridge

Laboratory Instructor **2002 - 2006**
Skills Acquired: Graded Exercise Testing with Respiratory Analysis, ECG, Body Composition Assessment, Blood Analysis
Fitness Assessment & Programming,
Exercise Technology Laboratory, Auburn University

3. Other Professional Experiences

Laboratory Technician/Phlebotomist **2004 - 2007**
Exercise Technology Laboratory, Auburn University

Hospital Rotation Internship: Diabetes Care Center, Cardiac Rehab **2004**
East Alabama Medical Center Cardiac Rehabilitation Center

Teaching Assistant **2000 - 2001**
Korea University, Korea, Department of Sport and Leisure Studies

Military service **1994 - 1996**
Republic of Korea Air Force White House Military Band

AWARDS

Research Award: Korea United States Applied Physiology Society **2016**
Title: Hemodynamic and Peripheral Vascular Conductance in Individuals with Down Syndrome Following Hypovolemic Pressure Challenge

Conference Presenter Awards **2013 - 2016**
Graduate College Presenter Award
Graduate Student Council Presenter Award
Health Professional Student Council Travel Grant
University of Illinois at Chicago

CERTIFICATIONS

Arthritis Foundation Land Exercise Instructor	**2011**
Phlebotomist from Auburn University Nursing school	**2006**
Korea Ski Association Certified Ski Instructor	**1999**
Red Cross Lifeguard	**1998**
Korea Scuba Diving Advanced License	**1993**
Korea Recreation Association Certified Instructor	**1993**

PUBLICATIONS AND PRESENTATIONS

Peer-reviewed Journal Articles

Wee SO, Pitetti KH, Goulopoulou S, Collier SR, Guerra M, Baynard T. Impact of obesity and Down syndrome on peak heart rate and aerobic capacity in youth and adults. *Research in developmental disabilities.* Oct 24 2014;36C:198-206.

Lee YH, Park SH, Yoon ES, Lee CD, **Wee S.O.**, Fernhall B, & Jae SY. Effects of Combined Aerobic and Resistance Exercise on Central Arterial Stiffness and Gait Velocity in Patients with Chronic Poststroke Hemiparesis. *Am J Phys Med Rehabil*. 2014

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Mestek, M.L., Garner, J.C., Plaisance, E.P., Hilson, B.D., Alhassan, S., Taylor, J.K., **Wee, S.O.**, & Grandjean, W. P. Blood lipid responses after continuous & accumulated aerobic exercise. *International Journal of Sport Nutrition & Exercise Metabolism*, 16 (3): 245-254.2006.

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ORAL PRESENTATION

Presentation at North American Federation of Adapted Physical Activity: *Effect of Acute Aerobic Exercise on Cerebral Blood Flow and Cognitive function in Individuals with Down Syndrome.* Edmonton, Canada, 2016

Research Award Presentation at American College of Sports Medicine Annual meeting: *Hemodynamic and Peripheral Vascular Conductance in Individuals with Down Syndrome Following Hypovolemic Pressure Challenge*: Boston, MA, 2016

Presentation at Midwest American College of Sports Medicine Annual meeting: *Hemodynamic and Peripheral Vascular Conductance in Individuals with Down Syndrome Following Hypovolemic Pressure Challenge*: Ft. Wayne, IN. 2015

Presentation at Midwest American College of Sports Medicine Annual meeting: *Sex Differences in Hemodynamic Responses Following 8 Weeks of Aerobic Exercise Training: Wave Separation Analysis*: Merriville, IN, 2013

Presentation at 27th Annual International Technology and Persons with Disabilities Conference: *Cardiorespiratory Response to Continuous Passive Exercise in People with Spinal Cord Injury*: San Diego, CA, 2012

Invited Presentation: *Adapted Physical Activity for Children with Disability*: Korean Educators and Parents Seminar, California State University Northridge, CA. 2011

International Congress Presentation: *Effect of Smoking in Blood Clotting Elements:* XIII Simposio Internacional en Ciencias del Deporte, el Ejercicio y la Salud, Universidad de Costa Rica, San José, Costa Rica. 2006.

CO-AUTHOR ABSTRACTED PRESENTATIONS

Wee SO, Rosenberg AJ, Bunsawat K, Griffith GJ, Baynard T, Fernhall B. *Responses in Arterial Distensibility and Compliance Following Lower Body Negative Pressure Challenge in Individuals with and without Down Syndrome.* American College of Sports Medicine Annual meeting, Denver, CO, Abstracted: 2017

Bunsawat K, Grigoriadis G, **Wee SO,** Griffith G, Brown MD, Phillips SA, Fadel PJ, Clifford PS, Fernhall B, Baynard T. *No Evidence of Impaired Functional Sympatholysis in Young Obese Adults. FASEB J.* April 2017; 31: 836.24.

Rosenberg AJ, **Wee SO**, Schroeder EC, Grigoriadis G, Bunsawat K, Hilgenkamp TIM, Griffith GJ, Baynard T..The Effects of Acute Exercise on Cerebral Blood Flow and Cognition in Persons with Multiple Sclerosis. *FASEB J.* April 2017; 31: 842.4.

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Wee S. O., Rosenberg A., Bunsawat K., Griffith G., Baynard T., Fernhall B. *Higher Carotid Strain in Individuals with Down Syndrome at rest and during Hypovolemic Pressure Challenge.* Artery. 2016. Annual Meeting, Copenhagen, Denmark. Abstracted: 2016.

Wee S. O., Rosenberg A., Bunsawat K., Griffith G., Baynard T., Fernhall B. *Vascular Function in individuals with Down Syndrome.* North American Artery. 6th Annual Meeting, Chicago, IL. Abstracted: 2016.

Wee S. O., Rosenberg A., Bunsawat K., Griffith G., Baynard T., Fernhall B., FACSM. *Hemodynamic and Peripheral Vascular Conductance in Individuals with Down Syndrome Following Hypovolemic Pressure Challenge*: American College of Sports Medicine Annual meeting, Boston, MA, Abstracted: 2016

Wee S. O., Rosenberg A., Bunsawat K., Griffith G., Baynard T., Fernhall B., FACSM, *Vascular Responses to Hypovolemic Pressure Challenge in Individuals with Down Syndrome:* Experimental Biology, San Diego, CA, Abstracted 2016

Wee S. O., Rosenberg A., Bunsawat K., Griffith G., Baynard T., Fernhall B., FACSM. *Vascular Responses to Hypovolemic Pressure Challenge in Individuals with Down Syndrome:* Midwest American College of Sports Medicine Annual meeting, Ft Wayne, IN. Oct, Abstracted: 2015

Wee S. O., Griffith G., Klaren E. R., Motl W. R., Baynard T., Fernhall B., FACSM. *Hemodynamic Responses Following 12 Weeks of Home-Based Exercise in Individuals with Multiple Sclerosis: Wave Separation Analysis.* North American Artery. 5th Annual Meeting, Chicago, IL. Abstracted: 2015.

Bunsawat K., Kappus M. R, Rosenberg J. A., Shafer B., **Wee S. O.,** Baynard T., FACSM Brown D. M., FACSM, Haus M. J, Phillips A. S., Fernhall B., FACSM. *Autonomic Function during Exercise in Older Adults: The Influence of Antioxidant Supplementation.* American College of Sports Medicine Annual Meeting, San Diego, CA. Abstracted: 2015.

Rosenberg J. A., Bunsawat K., Kappus M. R, Shafer B., **Wee S. O**., Baynard T., FACSM Brown D. M., FACSM, Haus M. J, Phillips A. S., Fernhall B., FACSM. *Racial Differences in HRV in Response to AN Acute Bout of Forearm Exercise.* American College of Sports Medicine Annual Meeting, San Diego, CA. Abstracted: 2015.

Griffith G., **Wee S. O.,** Klaren E. R., Thur L., Kappus M. R., Shafer B., Bunsawat K., Motl R., Baynard T., Fernhall B., FACSM. *HOME-BASED EXERCISE IN PERSONS WITH MULTIPLE SCLEROSIS: FITNESS AND WALKING MOBILITY PRELIMINARY RESULTS.* American College of Sports Medicine Annual Meeting, San Diego, CA. Abstracted: 2015.

Wee S. O., Ranadive M. S., Kappus M. R., Cook M., Yan H., Lane D. A., Fernhall B., FACSM, *Hemodynamic Responses Following Acute Inflammation in Older adults: Wave Separation Analysis.* American College of Sports Medicine Annual Meeting, San Diego, CA. Abstracted: 2015.

Kappus M. R, Shafer B, **Wee S. O.**, Baynard T, Haus M. J, Phillips A. S, Brown D. M., Fernhall B. *Racial Differences in Macrovascular and Microvascular Function Following Acute Antioxidant Supplementation.* Experimental Biology, San Diego, CA, Abstracted 2015.

Wee S. O., Lane A, Bunsawat K, Rosenberg A, Fernhall B. *Sex Differences in Hemodynamic Responses Following acute inflammation: Wave Separation Analysis.* North American Artery. 4th Annual Meeting, Chicago, IL. Abstracted: 2014.

Wee S. O., Rosenberg, A.J., Lane, A., Kappus, R.M., Yan H., Ranadive, S., & Fernhall, B. *Sex Differences in Hemodynamic Responses Following 8 Weeks of Aerobic Exercise Training: Wave Separation Analysis.* American College of Sports Medicine Annual Meeting, Orlando, FL. Abstracted: 2014.

Wee S. O., Rosenberg, AJ, Ranadive, S, Lane A, Kappus RM, Fernhall, B. *Sex Differences in Post Exercise Hypotension.* North American Artery. 3rd Annual Meeting, Chicago, IL. Abstracted: 2013.

Wee S. O., Rosenberg, AJ, Ranadive, S, Lane A, Kappus RM, Fernhall, B. *Sex Differences in Hemodynamic Responses Following 8 Weeks of Aerobic Exercise Training: Wave Separation Analysis*: Midwest American College of Sports Medicine Annual meeting, Merriville, IN. Abstracted: 2013

Wee S. O., Pitett K, Guerra, I M, Baynard, T & Fernhall, B. *Impact of Obesity and Down Syndrome on Maximal Heart Rate and Work Capacity in Youth and Adults with Intellectual Disability*. American College of Sports Medicine Annual Meeting, Indianapolis, IN. Abstracted: 2013.

Wee S. O., Konstantinos K. D., Jung T., & Stacyk S. *Cardiorespiratory Response to Continuous Passive Motion Exercise in People with Spinal Cord Injury.* American College of Sports Medicine Annual Meeting, San Francisco, CA. Abstracted: 2012.

Mestek M.L., E.P. Plaisance, L. Ratcliff, J.K. Taylor, **Wee S. O.**, & P.W. Grandjean (FACSM). *Investigating aerobic exercise characteristics on postprandial lipemia in men with metabolic syndrome.* American College of Sports Medicine Annual Meeting, Indianapolis, IN. Abstracted: *Medicine and Science in Sports and Exercise.*Vol.40 (5) No. 1748, 2008.

Wee S-O., A. Reisi, E.P. Plaisance, M.L. Mestek, J.K. Taylor, F. Araya- Ramírez and P.W. Grandjean.*Immediate cardiovascular changes after cigarette smoking and moderate-intensity aerobic exercise.* American College of Sports Medicine Annual Meeting, New Orleans, LA.Abstracted: *Medicine and Science in Sports and Exercise*.Vol.39 (5) No. 1555, 2007.

Araya- Ramírez F., **Wee S-O.**, A.J. Mahurin, E.P. Plaisance, M.L. Mestek, D. Dean and P.W. Grandjean. *Aerobic fitness, waist girth and markers of metabolic syndrome in women.* American College of Sports Medicine Annual Meeting, New Orleans, LA. Abstracted: *Medicine and Science in Sports and Exercise*.Vol.39 (5) No. 1547, 2007.

Alhassan S., Reese.A. K, Plaisance P. E., Hilson.D. B, Garner C. J., **Wee S-O.** and Grandjean W. P. *Effects of dietary plant stanol ester margarine and aerobic exercise training on blood lipid concentrations.* American College of Sports Medicine Annual Meeting, Nashville, TN. Abstracted*: Medicine and Science in Sports and Exercise. Vol*.37 (5), No. 1973, 2005

Garner J.C., Mestek L. M., Plaisance P. E, Hilson.D. B, Alhassan S., Taylor K. J, **Wee S-O.** and P.W. Grandjean. *Blood lipid responses after continuous and accumulated aerobic exercise:* American College of Sports Medicine Annual Meeting, Nashville, TN. Abstracted: *Medicine and Science in Sports and Exercise*. Vol.37 (5), No. 1969, 2005.

Grandjean P.W., A.B. Grandjean, S. Alhasson, E.P. Plaisance, K.A. Reese, B.D. Hilson, J.C. Garner & **Wee S-O.** The influence of fitness status on cardiorespiratory responses to continuously graded & ramped treadmill protocols. American College of Sports Medicine Annual Meeting, St. Louis, Missouri. Medicine and Science in Sports and Exercise. 36: S114, 05/2004.

Professional Memberships

2008- American College of Sports Medicine (ACSM) member

2014-2016 American Heart Association (AHA) member