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Relationship Among Neurogenic Orthostatic Hypotension, Cerebral Hemodynamics, and Cognitive Functioning

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Graduate Program in Kinesiology
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Abstract

Neurogenic orthostatic hypotension (NOH) is characterized by a drop in systolic blood pressure ≥20mmHg or diastolic blood pressure ≥10mmHg within three minutes of upright posture. A large drop in blood pressure can trigger cerebral hypoperfusion, which has been linked to deficits in cognitive function. The current thesis aimed to measure cerebral hemodynamics and cognitive function in 20 NOH patients and 20 controls in the supine and head-up tilt (HUT) positions. Information processing speed (IPS) was assessed using the Symbol-Digit Modalities Test and attention was measured using the Stroop Test. NOH patients had significantly slower IPS in both the supine($p<0.001$) and HUT($p<0.001$) positions and had worse attention during HUT($p=0.029$) compared to controls. During HUT, NOH patients had significantly reduced cerebral blood flow velocity($p=0.003$) and cerebral oxygen saturation($p=0.025$) from baseline, whereas controls revealed no significant changes. Decreased cerebral hemodynamics in NOH patients could be linked to their impairment in IPS and attention.

Keywords: neurogenic orthostatic hypotension, cognitive function, information processing speed, attention, regional cerebral oxygen saturation, cerebral blood flow velocity

Summary for Lay Audience

Neurogenic orthostatic hypotension (NOH) is characterized by a drop in in systolic blood pressure ≥ 20mmHg or diastolic blood pressure ≥ 10mmHg within three minutes of upright posture. A severe drop in blood pressure can cause symptoms such as lightheadedness, dizziness, weakness, and fatigue. This thesis objected to determine if patients with NOH experienced alterations in cognitive function with a positional change from lying to standing. Cognitive function was assessed using the Symbol-Digit Modalities Test to measure information processing speed and the Stroop Test to measure attention. Recent research proposed that reductions in cerebral blood supply can accelerate the natural process of cognitive decline. Therefore, this thesis also aimed to measure cerebral blood flow using transcranial doppler and near infrared spectroscopy to determine if there were any differences between NOH patients and healthy control subjects. It was found that NOH patients had significantly slower information processing speed in both the lying and standing positions compared to controls, as well NOH patients had significantly reduced attention in the standing position compared to controls. Patients with NOH experienced a significant reduction in cerebral blood flow in the standing position compared to the lying position. Repeated exposure to reduced cerebral blood flow as a result of autonomic dysfunction is likely a contributing factor to our finding of impaired information processing speed and attention in NOH patients. This thesis sheds new light on cognitive function and cerebral blood flow in NOH patients.

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List of Abbreviations

AD	Alzheimer's disease
AF	Autonomic failure
ANS	Autonomic nervous system
ARS	Autonomic reflex screen
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CBFv	Cerebral blood flow velocity
CON	Control subject
DBP	Diastolic blood pressure
HR	Heart rate
HRDB	Heart rate deep breathing
IPS	Information processing speed
HUT	Head-up tilt
LBD	Lewy body dementia
MAP	Mean arterial pressure
MCI	Mild cognitive impairment
mmHg	Milliliters of mercury

MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
MS	Multiple sclerosis
MSA	Multiple system atrophy
NIRS	Near infrared spectroscopy
NOH	Neurogenic orthostatic hypotension
OH	Orthostatic hypotension
PAF	Pure autonomic failure
PD	Parkinson’s disease
PFC	Prefrontal cortex
PNS	Parasympathetic nervous system
QSART	Quantitative sudomotor axon reflex test
rSO_2	Regional cerebral oxygen saturation
SBP	Systolic blood pressure
SDMT	Symbol digit modalities test
SNS	Sympathetic nervous system
TCD	Transcranial doppler
VM	Valsalva maneuver
VR	Valsalva ratio

Chapter 1

1 Introduction

It is common knowledge that cognitive decline is a natural process of aging [1]. Aging causes a decrease in many cognitive domains including memory, spatial visualization, information processing speed (IPS), attention, executive functioning, and conceptual reasoning[1,2]. Reduced IPS can be especially problematic since it is a predictor of the ability to perform simple daily activities and an indicator of independence [3,4]. Cognitive decline can occur at an accelerated rate in neurodegenerative conditions like Alzheimer's disease (AD), Lewy-body dementia (LBD), Parkinson's disease (PD), and multiple sclerosis (MS) [5,6]. There is limited literature on a neurological condition referred to as neurogenic orthostatic hypotension (NOH) and its relationship to cognitive decline. NOH is a cardinal feature of many neurodegenerative diseases such as Multiple System Atrophy (MSA), PD, LBD, and pure autonomic failure (PAF), therefore it could also be linked to accelerated cognitive decline.

NOH is characterized by a drop in systolic blood pressure (SBP) ≥ 20mmHg or diastolic blood pressure (DBP) ≥ 10mmHg in the absence of a compensatory increase in heart rate (HR) within three minutes of upright posture or head-up tilt (HUT). Autonomic nervous system damage can cause inadequate release of norepinephrine, from the sympathetic nerves therefore insufficient vasoconstriction occurs and results in a postural blood pressure (BP) drop. The severe drop in BP causes symptoms such as lightheadedness, dizziness, weakness, and fatigue. These symptoms make simple daily activities difficult to perform and can increase the risk of falls [7].

Prior research has stated that this large drop in BP can provoke a reduction in cerebral blood flow [8,9]. This is problematic because cerebral hypoperfusion has been linked to cognitive decline [7,10]. There is a variety of literature related to this topic but there is very little research specifically

related to NOH patients and cognitive decline. Determining if alterations in cerebral blood supply affect cognitive functioning in NOH patients will be an important addition to the current literature. Therefore, this thesis will provide general information about the autonomic nervous system and conditions and diseases related to autonomic dysfunction with an emphasis on NOH. Epidemiology, diagnostic testing, and treatment of NOH will be addressed in great detail. This thesis will also discuss how alterations in cerebral hemodynamics affect cognitive functioning, specifically IPS and attention.

The first research study presented in this thesis aimed to investigate the potential changes in cognitive function experienced by individuals with NOH in both the supine and HUT positions. The study also aimed to describe the relationship between cognitive function and the change in SBP in NOH patients. The second study presented in this thesis assessed cerebral hemodynamics parameters including cerebral blood flow velocity (CBFv) and regional cerebral oxygen saturation (rSO_2) in NOH patients in the supine and HUT positions. This study also aimed to determine the effects of cerebral hypoperfusion on IPS and attention.

Accordingly, the following hypotheses were made:

1. NOH patients will experience a decline in IPS and attention in the HUT position compared to the supine position due to the associated reduction in postural BP. Controls will experience an increase in IPS and attention in the HUT position compared to supine.

2. The magnitude of the postural SBP drop will correspond with a worsening in IPS and attention. Therefore, the larger the drop in SBP, the worse the NOH patients will perform on the cognitive tests.

3. NOH patients will have a reduction in CBFv and rSO_2 in the HUT position compared to the supine position, whereas controls will experience no changes in CBFv and rSO_2 with the change in position.

4. The reduced measures of CBFv and rSO_2 may be related to a decline in IPS and attention.

Chapter 2

2 Literature Review

2.1 Autonomic Nervous System

The autonomic nervous system (ANS) unconsciously provides neural control to regulate bodily functions such as heart rate, blood pressure, sweating, respiration, gastrointestinal motility, urinary and bowel excretion, and reproduction. The ANS maintains homeostasis through the coordinated control of all bodily functions [11]. This system is composed of three main divisions; the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS), and the enteric nervous system. This thesis will only focus on the SNS and PNS, which are displayed in Figure 1. The SNS and PNS have antagonistic effects; the SNS works to increase bodily functions such as HR, breathing, sweating, and constricts blood vessels, whereas the PNS is used to slow these high energy functions during times of rest and digestion. Therefore, these systems work together to ensure the balance of homeostasis.

The SNS originates in the spinal cord, specifically in the lateral grey column of T1 to L1-2 [11]. A preganglionic efferent neuron exits the spinal column, synapses at a ganglion, and then continues as a postganglionic neuron. Postganglionic neurons innervate target organs such as the eyes, heart, lungs, stomach, intestines, bladder, sweat glands, reproductive organs, and kidneys. In the SNS the preganglionic neurons are relatively short and are cholinergic releasing acetylcholine whereas the postganglionic fibers are fairly long and are noradrenergic releasing norepinephrine. The primary neurotransmitter of the SNS is norepinephrine and when released it stimulates the body during times of increased activity [12,13].

The PNS originates in two primary areas. Firstly, the cranial nerves III, VII, and IX which arise in the cranium and then synapse with a ganglia before going to their target tissues, as well as the vagus nerve (cranial nerve X) which originates in the medulla oblongata and controls the heart, lungs and the digestive tract [11]. Secondly, cell bodies in the lateral grey horn of the spinal cord at the level of T12-L1, which then exit the spinal cord at S2-S4. The preganglionic neurons release acetylcholine at both the ganglion synapses and the postsynaptic terminals [12]. Postganglionic fibres in the PNS are shorter than in the SNS. This system acts to slow bodily functions and is primarily used during times of rest and digestion.

The SNS and PNS function primarily through autonomic reflexes. The baroreflex is extremely important in the control of regulating arterial BP [11]. The receptors responsible for measuring changes in BP are found in the aortic arch and the carotid sinus. These receptors relay information to the central nervous system. When BP decreases the baroreceptors are activated and cause an increase in excitatory input to the preganglionic sympathetic neurons, which in turn produces an increase in BP. This type of reflex is activated anytime BP drops, for example when an individual stands up. Together these two systems function to control most involuntary mechanisms and work to maintain homeostasis of the body [11].

Multiple studies have demonstrated that the PNS and the SNS are involved in cognitive functioning [14,15]. The PNS is responsible for regulating high frequency heart rate variability which was associated with greater inhibitory cognitive control during the Eriksen flanker task in a study of 56 participants [15]. A study found that individuals with greater hear rate variability had better executive function than individuals with low heart rate variability. A link has been found between the performance of a cognitive task and an increase in SNS activation [14]. Therefore, damage to the PNS or the SNS may result in altered cognitive functioning.

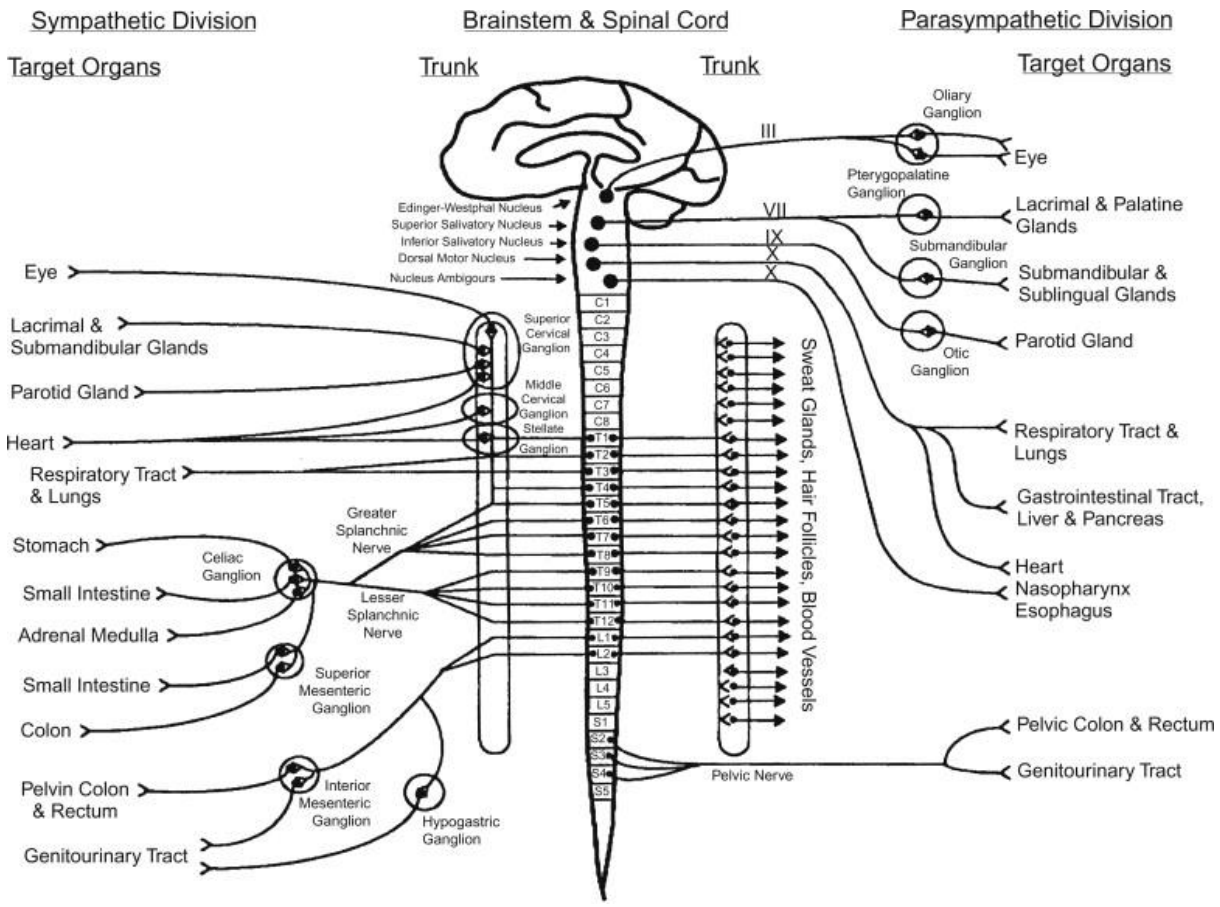

Figure 1. The Autonomic Nervous System [13]

This diagram displays both the sympathetic and parasympathetic divisions of the ANS. The SNS originates at T1-L2 and the PNS originates at CN III, VII, IX, and X and S2-S4. Each division innervates specific target organs.

2.2 Autonomic Dysfunction

Any main system of the human body can suffer from dysfunction including the ANS. Damage to the ANS can occur from an autoimmune disease, diabetes, an infection, a side effect of medication, an abnormal protein buildup, or an inherited disorder [16]. Nerve damage interferes with the signals communicating between the brain and the effector organ. Consequently, severe symptoms can arise in the presence of autonomic dysfunction since the ANS controls many vital bodily functions. Autonomic dysfunction can present with a variety of symptoms, including irregularities with sweating, inability to regulate heart rate, lightheadedness, dizziness, weakness, fatigue, urinary problems, sexual dysfunction, and digestive issues. A common and debilitating symptom referred to as orthostatic hypotension (OH) can occur in individuals with autonomic dysfunction. OH is characterized by a profound drop in systolic blood pressure (SBP) of $\geq$ 20mmHg or diastolic blood pressure (DBP) of $\geq$ 10mmHg within three minutes of upright posture. OH can be triggered by either a nonneurogenic or a neurogenic cause. Nonneurogenic OH can be caused by hypovolemia, cardiac pump failure, venous pooling and some medications [17]. Nonneurogenic OH can sometimes be resolved by increasing fluid intake, increasing salt intake, wearing compression stockings or an abdominal binder. Neurogenic orthostatic hypotension usually has no cure and often results from permanent damage to the ANS.

A large array of diseases and disorders are related to autonomic dysfunction. Some common conditions include Parkinson's disease (PD), lewy body dementia (LBD), pure autonomic failure (PAF), multiple systems atrophy (MSA), primary amyloidosis and diabetic neuropathy. These diseases present with different clinical features, for example PD can present with a tremor, LBD can present with cognitive problems, but most will also present with the symptom of OH. Autonomic dysfunction develops early in patients with MSA, PAF and LBD thus OH is normally the most prominent clinical feature. Parkinson's disease can also present with autonomic dysfunction, but it normally presents later in the disease. Up to 58% of PD patients will experience autonomic failure [18] .

2.3 Neurogenic Orthostatic Hypotension (NOH)

Neurogenic orthostatic hypotension (NOH) is a hallmark feature of autonomic failure [19]. NOH occurs secondary to either neuropathy of the peripheral nervous system or to a central nervous system lesion [20]. It is most commonly found in the elderly population [21]. NOH is characterized by a severe drop in systolic blood pressure (SBP) ≥ 20mmHg or diastolic blood pressure (DBP) ≥ 10mmHg within three minutes of standing up or HUT [22].

NOH is associated with autonomic degenerative disorders such as PD, MSA, LBD, and PAF. It is also associated with peripheral neuropathies such as Guillain Barre syndrome, diabetic neuropathy, hereditary amyloidosis, and familial dysautonomia [21]. NOH is a common symptom related to these diseases since BP regulation is often affected when the ANS is damaged.

When a healthy individual changes position from sitting to standing, the effect of gravity causes a shift of approximately 500-1000ml of blood into the lower extremities [23]. Pooling of blood in the lower body results in decreased venous return, which causes decreased cardiac output and a reduction in postural BP. The baroreflex response then acts to increase peripheral resistance, venous return to the heart and cardiac output [23]. Consequently, there is very little change in systemic BP since the baroreflex activation is immediate. Individuals with NOH have an impaired BP and HR response to standing due to baroreflex failure. The sympathetic vasomotor neurons do not release an adequate amount of norepinephrine to produce suitable peripheral vasoconstriction. Without vasoconstriction blood pools in the lower extremities resulting in a BP drop [21].

NOH patients experience a variety of symptoms during an orthostatic challenge; the most common being lightheadedness, dizziness, weakness, fatigue, and difficulty thinking. Symptoms tend to worsen with specific stressors. These stressors include; standing up in the morning after being supine for a long duration, hot weather/ hot shower or bath which cause cutaneous vasodilatation, after eating a large meal which causes splanchnic vasodilatation, during prolonged standing which

can cause BP to continually decease, coughing since it increases intrathoracic pressure which further decreases venous return to heart [24]. Symptomatic NOH can be severely disabling, increase the risk for injurious falls, and decrease quality of life [25].

2.4 Diagnostic Tests for NOH

When diagnosing NOH, a clinician will take into consideration a medical history, neurological examination and a standardized autonomic reflect screen (ARS). The ARS is a validated tool that consists of four tests which assess the integrity of the ANS [26]. The function of both the sympathetic and parasympathetic nervous system can be evaluated using the ARS. Each test is described in depth below.

2.4.1 Quantitative Sudomotor Axon Reflex Test (QSART)

The human sweat glands are regulated by postganglionic sympathetic sudomotor axons [27]. When acetylcholine is released from the axon terminals it causes a sweat response to occur. QSART assesses the sweat function of four postganglionic nerves; ulnar, peroneal, saphenous and sural. A multicompartmental sweat cell is placed over each one of the four nerves and secured in place with a rubber strap. Ground electrodes are positioned beside each sweat cell. The placement of each sweat cell is as follows; forearm between the ulnar epicondyle and the pisiform bone, proximal leg 5 cm distal to the fibular head, distal leg 5 cm proximal to the medial malleolus, and dorsum of the foot over the extensor digitorum brevis muscle [28]. The sweat cell has an outer ring where the acetylcholine gel is located and an inner compartment from which the sweat response is recorded. Five minutes of constant anodal current iontophoresis of 10% acetylcholine at an intensity of 2mA is used to stimulate the sudomotor axons. The 2mA current causes the release of the acetylcholine from the multicompartmental sweat cell, which activates the sweat response. After the stimulation is turned off an additional five minutes is recorded. Sweat volumes are recorded for the total duration of the test.

A normal test (Figure 2A) displays sweat volumes above the lower limit which is as follows 0.122, 0.160, 0.079, and 0.102uL for forearm, proximal leg, distal leg, and foot respectively. Whereas, irregular tests (Figure 2B) can show significantly reduced (i.e. hypohidrosis) or increased (i.e. hyperhidrosis) sweat volumes. Individuals with peripheral neuropathy are likely to have a length dependent reduction in sweat volumes, thus the most reduced volumes are located the most distally. Irregular test results can indicate damage to the postganglionic axons in the SNS [26].

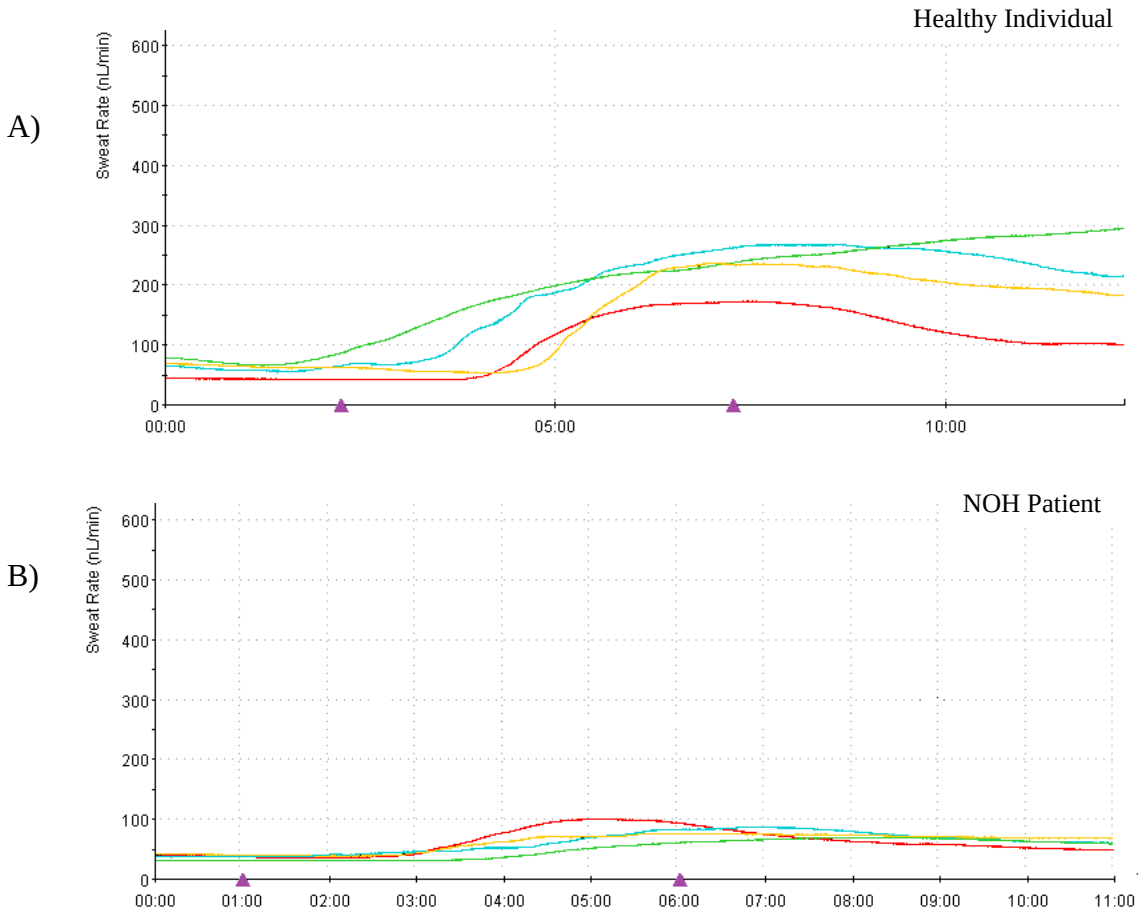

Figure 2. QSART in A) Healthy Individual and B) NOH Patient

Each line represents one of the 4 sites tested. Red line: forearm, blue line: proximal leg, green line: distal leg, and yellow line: foot. The purple arrows indicate when the electrical stimulation started and ended. Graph A shows a normal response to QSART, whereas graph B shows reduced sweat volumes in a patient with NOH.

2.4.2 Heart Rate Variability to Deep Breathing

A deep breathing exercise can be used to assess cardiovagal function [26]. A breathing frequency of five seconds inspiration and five seconds expiration is used for eight consecutive cycles. To accurately achieve this breathing frequency slow deep breaths are completed following a column of green light, breathing in as the light goes up the column and breathing out as the green light is going down the column. HR is recorded during this test to measure HR variability which analyzes parasympathetic function.

In a healthy individual HR should increase during inspiration and decrease during expiration, therefore large fluctuations in HR should occur with deep breathing, this can be seen in Figure 3A. The lower limit for HR difference during deep breathing is 4.8bpm for males and 6.2bpm for females. Impaired cardiovagal function is indicated by a HR variability below the lower limit. NOH patients are a group of individuals who show very little HR variability during this test, suggesting cardiovagal impairment, which can be seen in Figure 3B.

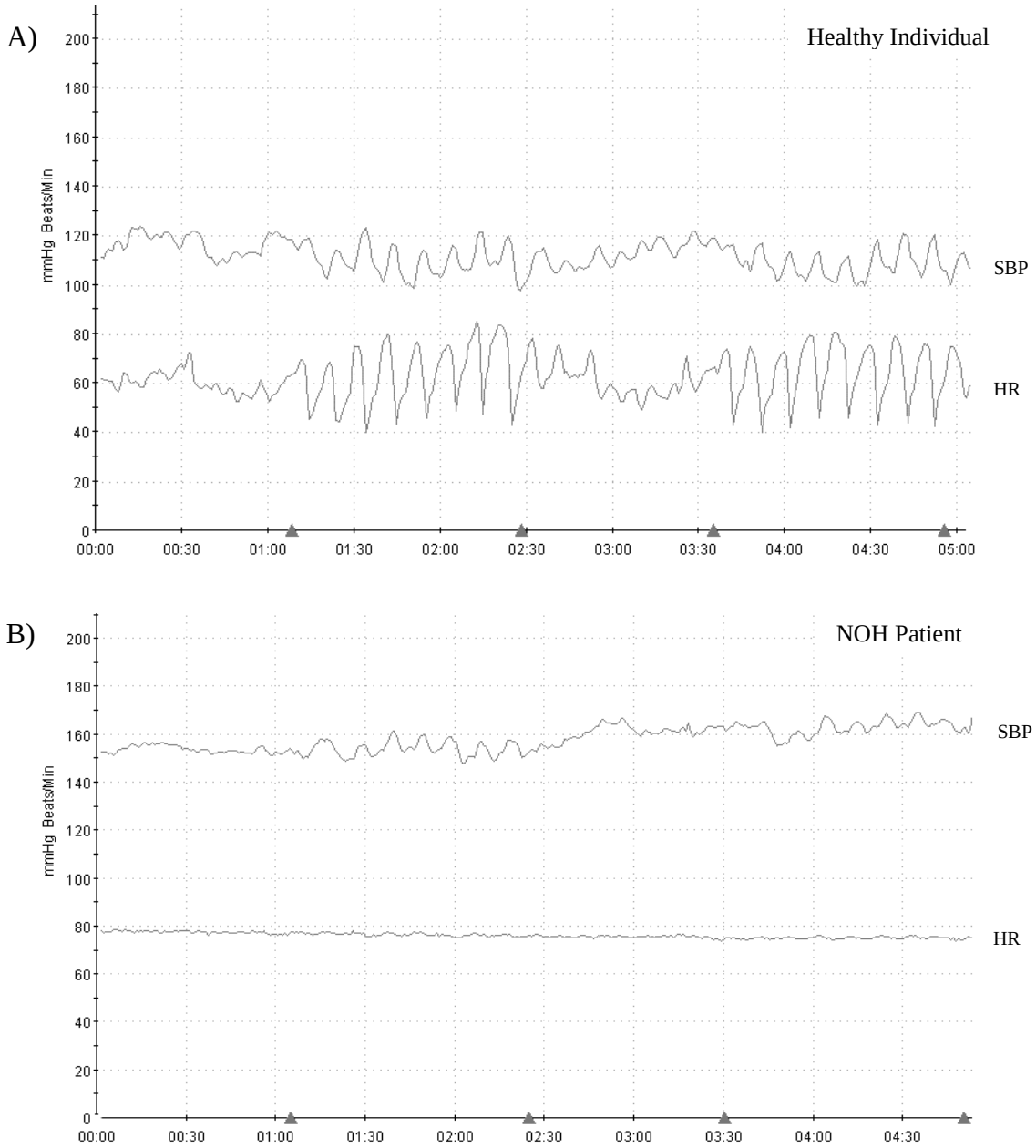

Figure 3. Deep Breathing Task in A) Healthy Individual and B) NOH Patient

The deep breathing task is performed two times with a one-minute rest period between trials, the start and end of each trial are indicated by the markers at the bottom of the graph. Graph A shows large fluctuations in HR during deep breathing, whereas graph B shows almost no change in HR during deep breathing.

2.4.3 Valsalva Maneuver

The Valsalva maneuver (VM) is used to calculate a Valsalva ratio (VR) which is the maximum HR achieved during the VM divided by the minimum HR occurring within 30 seconds of the maximum HR. The maneuver requires the participant to blow into a mouthpiece to a pressure of 40mmHg and hold it at this pressure for 15 seconds. The maneuver produces a cascade of events; there is a change in intrathoracic pressure which decreases venous return, there is a drop in BP, activation of baroreflex, reflex tachycardia, and peripheral vasoconstriction [13]. Monitoring beat-to-beat BP changes during the maneuver allows for evaluation of the baroreflex function. The lower limit of normal for the VR in males is 1.31 and in females is 1.3. If the VR is below this limit, it can indicate impairment of cardiovagal function.

In a healthy individual the beat-to-beat BP response to this maneuver shows four distinct phases, which are as follows: Phase I demonstrates an increase in BP due to increased intrathoracic and intra-abdominal pressure which causes compression on the aorta, which reduces venous return. Early Phase II shows a drop in BP due to the reduced venous return. This drop in BP activates baroreflexes. Late Phase II shows an increase in BP back towards baseline BP (alpha-adrenergic). Phase III occurs due to decreased in intrathoracic pressure, therefore BP decreases causing a burst of sympathetic activity. Phase IV is represented by an overshoot in BP (beta-adrenergic) [13]. Following this maneuver, the time it takes for both BP and HR return to resting values is measured. This response is displayed in Figure 4A.

Individuals with NOH show a different beat-to-beat BP response to this maneuver, which is displayed in Figure 4B. The beat-to-beat BP recording displays absent late phase II indicating an impaired baroreflex response, therefore BP continues to drop. Phase IV overshoot is also absent because there is no burst in sympathetic activity to cause a rapid increase in BP. Since NOH patients experience very little change in HR during the VM a low VR will result.

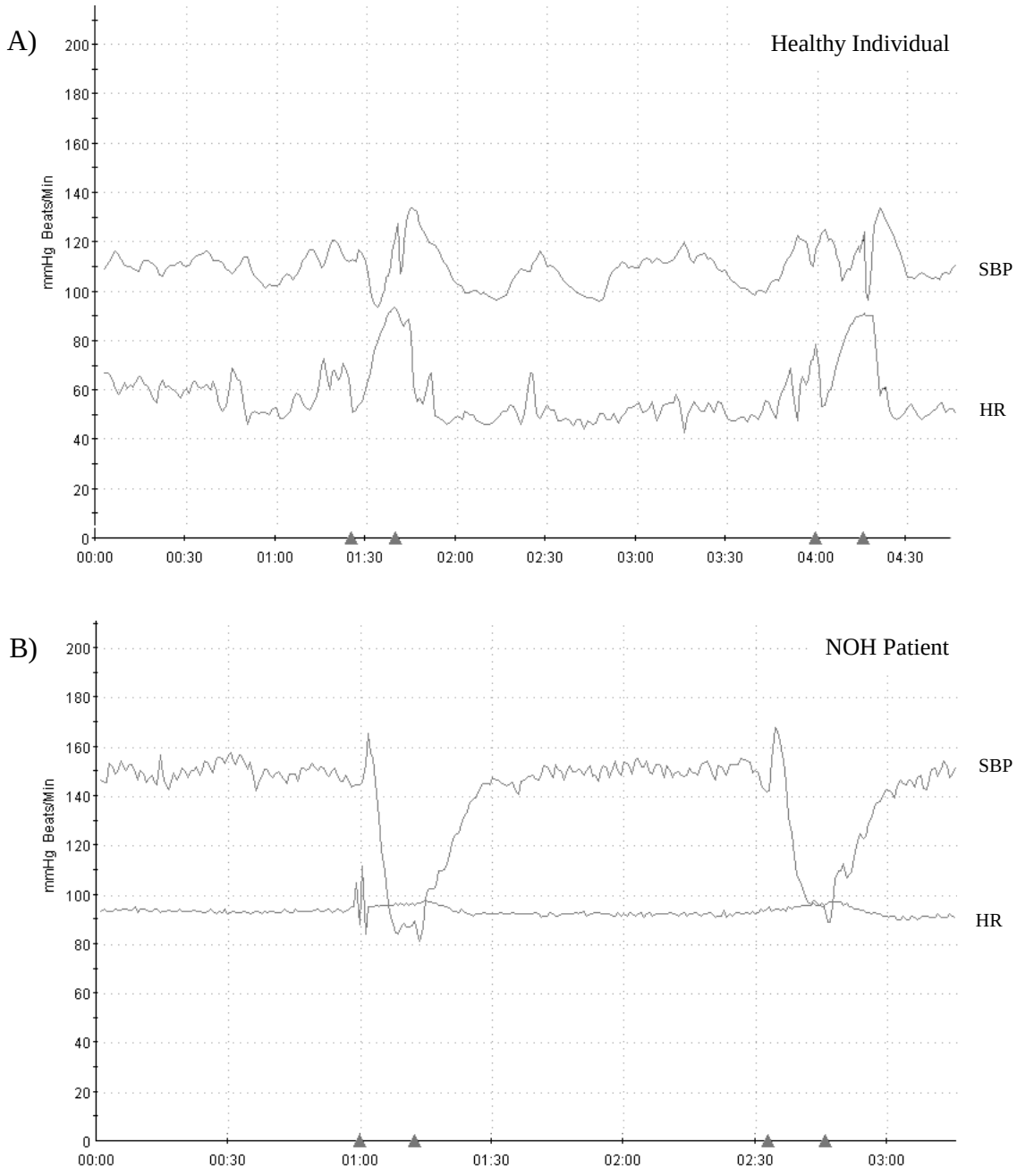

Figure 4. Valsalva Maneuver in A) Healthy Individual and B) NOH Patient

The Valsalva maneuver (VM) is performed two times, indicated by the markers at the bottom of the graph. Graph A shows all 4 distinct phases of the VM and a large increase in HR, whereas graph B shows an absent late phase II and phase IV overshoot and very little change in HR.

2.4.4 Head-Up Tilt

Head-up tilt (HUT) is one of the most important tests when diagnosing NOH. HUT assesses adrenergic function during an orthostatic challenge. The patient is positioned on a tilt table in the supine position with their feet flat against a footboard. HR is measured using an electrocardiography device and BP is measured with a beat-to-beat BP monitor. These measures are recorded in the supine position for one minute to determine resting HR and BP. Following one-minute baseline, the bed is tilted to 70 degrees upright and remains in this position for five minutes, the table is then tilted back down to the supine position and an additional five minutes of recovery is recorded [26].

This test simulates standing and allows the natural force of gravity to act on the body which causes a shift of blood volume into the lower limbs. A healthy individual will have very little change in BP and HR during HUT since the ANS activates a response to increase vasoconstriction which maintains BP at a normal level, which can be seen in Figure 5A. If a slight drop in BP occurs during HUT HR will increase slightly to compensate for the BP decrease.

Individuals with NOH experience a significant drop in BP within 2-3 minutes of HUT (Figure 5B). BP will drop at least 20/10mmHg with little to no change in baseline HR. This large drop in BP with no compensatory postural tachycardia indicates autonomic dysfunction. Damage to the sympathetic nerves causes insufficient vasoconstriction therefore, blood continues to pool in the lower extremities. Consequently, BP remains reduced for the whole duration of an orthostatic challenge. When standing, some patients feel severe symptoms of lightheadedness, dizziness, weakness, and/or fatigue, whereas some patients are asymptomatic. Symptoms are often dependent upon how large the drop in BP is and if the patient's body has adapted to this drop. When the tilt table is returned to the supine position BP will increase back to baseline.

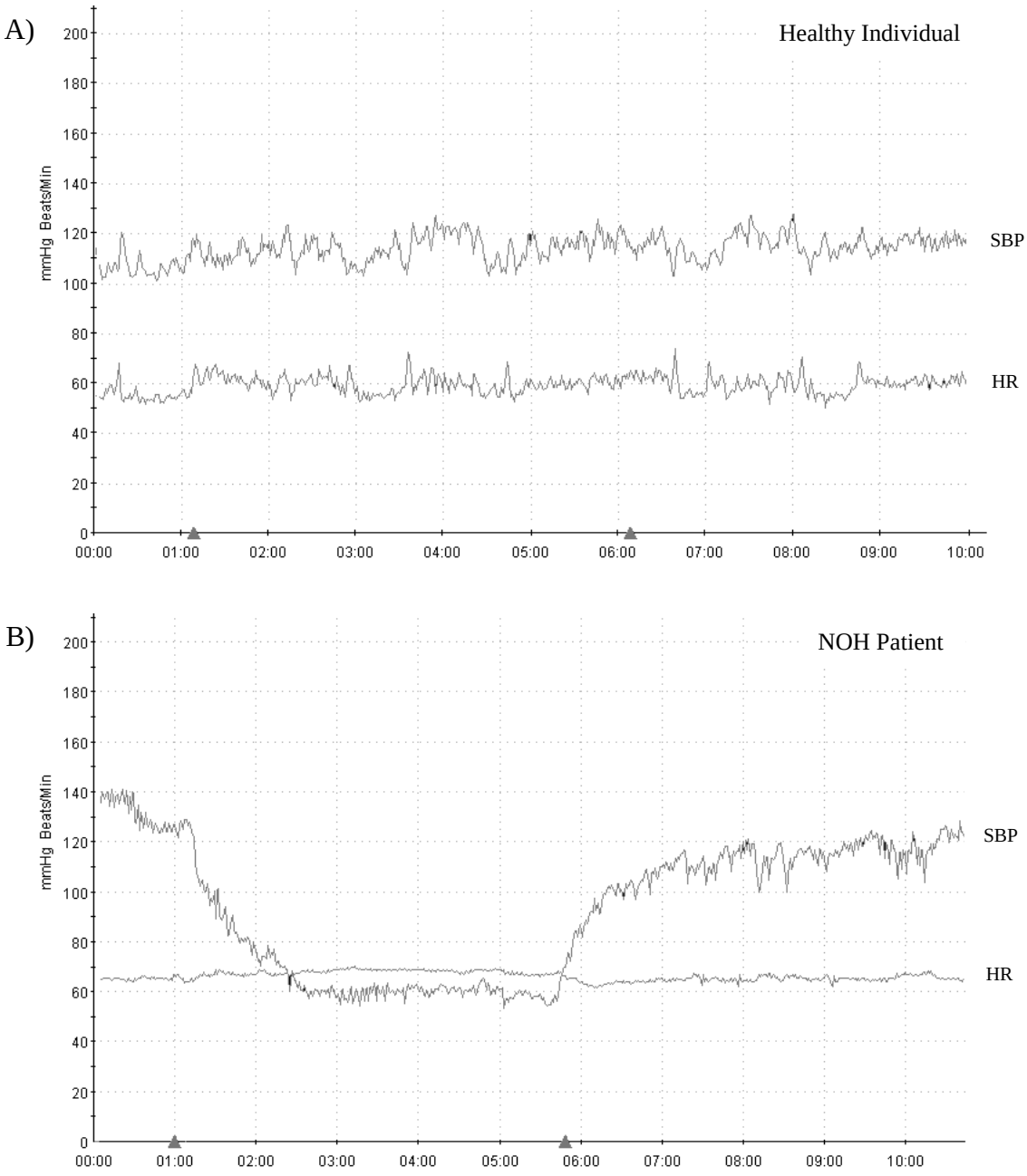

Figure 5. Head-up Tilt in A) Healthy Individual and B) NOH Patient

Initiation of head-up tilt occurs at the first marker at the bottom of the graph and the table is returned to the supine position at the second marker. Graph A shows very little change in SBP and a slight increase in HR during HUT, whereas graph B shows a severe drop in SBP and a very small change in HR during HUT.

2.5 Treatment of NOH

There is currently no cure for NOH, therefore treatment can be used to reduce the associated symptoms. Decreasing the occurrence of symptoms improves the quality of life of the patients. Both non-pharmacological and pharmacological interventions can be used to help treat symptoms.

2.5.1 Non-pharmacological Treatment

Non-pharmacological interventions can be used to reduce the occurrence and severity of symptoms associated with low BP. Both increased fluid intake and increased salt intake can help raise overall BP. It has been advised that NOH patients should consume 2 to 2.5 L of water per day [17]. During activities in the upright position wearing an abdominal binder can assist in increasing venous return which may reduce the drop in BP. Patients should be instructed to consume small meals since large meals containing a high carbohydrate content cause splanchnic vasodilatation. Activities that raise core body temperature should be avoided such as exercising on hot days, hot showers/baths, and saunas since they cause skin vasodilatation and NOH patients have impaired vasoconstriction. If safe, patients should be instructed to complete lower body strength training, this will help maintain lower limb muscle pumps to push blood back to the heart it will also prevent deconditioning. Patients should be instructed to avoid straining and coughing since these maneuvers cause a drop in BP. To ensure BP is not too high when lying down the head of the bed should be tilted up when sleeping. These simple strategies can help reduce the burden of symptoms [29]. If these non-pharmacological measures do not improve symptoms pharmacological measures can be implemented.

2.5.2 Pharmacological Treatment

Pharmacological treatments are implemented to increase BP during times of low BP. Florocortisone is used at a dose of 0.05 to 0.2 mg daily to help retain sodium and water [24]. Midodrine is an α1 agonist used at a dose of 2.5 to 5 mg once to twice daily to induce vasoconstriction [23]. Pyridostigmine can be used with a dose of 60 mg twice to three times per day or long acting forms 180 mg daily [28]. Pyridostigmine inhibits acetylcholinesterase in preganglionic

sympathetic neurons therefore increasing sympathetic traffic [24]. It also has a much milder affect on BP than midodrine and fludrocortisone.

2.6 Cerebral Hemodynamics

Monitoring cerebral hemodynamics in healthy individuals gives insight about natural cerebral blood flow changes that occur with aging. Between the ages of 20-70 there is a continual decline in cerebral blood flow velocity (CBFv) in the basal arteries [30]. Aging affects both cerebral blood flow and cerebral vasculature [31]. Cerebral autoregulation is a mechanism used to ensure the brain is receiving adequate blood supply despite changes in systemic BP [32]. This mechanism works by rapidly adjusting cerebrovascular resistance and compensating for fluctuations in cerebral perfusion pressure [33]. It is a protective mechanism and prevents against brain ischemia when BP is low and capillary damage when BP is high [34]. Severe changes in BP can cause disruption to cerebral blood flow if SBP is outside of the autoregulation range (approximately ~80-160mmHg in healthy individuals) [35]. NOH patients experience significant fluctuations in SBP, therefore it is important to identify if they have alterations in cerebral blood supply. Common techniques used to measure cerebral blood supply are transcranial doppler and near infrared spectroscopy.

2.7 Transcranial Doppler

Transcranial Doppler (TCD) is a non-invasive ultrasound technique used to measure real-time cerebral blood flow velocity (CBFv). TCD emits ultrasound waves from a probe at a frequency of 2MHz which penetrate through the skull and are reflected by moving red blood cells [36]. A term referred to as the Doppler shift frequency is the difference in frequency between the emitted and reflected waves, which is proportional to the speed of moving red blood cells [36]. The middle cerebral artery (MCA) is commonly used to measure CBFv since it is found near a thin region of the skull referred to as the transtemporal window where the ultrasound waves can easily penetrate through the skull. The MCA can be found with the probe set to a depth between 45 to 55mm. TCD also measures pulsatility index, which provides information about the downstream cerebral vascular resistance [37]. The pulsatility index is normally between 0.5 to 1.19 [37]. A limitation of

TCD is that measures can not be obtained in about 10-15% of people. This occurs when individuals have an inadequate transtemporal window due to the thickness and porosity of the bone near the window [36]. The following formula describes the relationship between flow velocity (reflector speed) and Doppler shift frequency [36]: $Reflector\ speed\ \left(\frac{cm}{s}\right) = \frac{(doppler\ shift) X\ propagation\ speed}{2\ X\ incident\ frequency\ X\ cos\theta}$

The doppler shift is the change in frequency of a wave in relation to an observer who is moving relative to the wave source. The propagation speed is the speed of ultrasound in the tissue. The incident frequency is the original frequency of the ultrasound. Theta (θ) is the angle of the emitted wave relative to the direction of blood flow in the vessel [36].

The application of TCD can be used to monitor a variety of conditions such as vasospasm in sickle cell disease, raised intracranial pressure, head injuries, subarachnoid hemorrhage, intra- and extracranial arterial stenosis and occlusion, and intraoperative monitoring [37]. Monitoring CBFv can provide important information about the clinical conditions listed. Alterations in CBFv also occur when there are drastic changes in systemic BP [9]. Accordingly, it is beneficial to measure CBFv in NOH patients since they are a population who experience large fluctuations in BP.

2.8 Near Infrared Spectroscopy

Near infrared spectroscopy (NIRS) is a non-invasive technique used to measure regional cerebral oxygen saturation (rSO_2) using light wavelengths between 700-1000nm. NIRS is placed bilaterally on the forehead to measure rSO_2 in the frontal lobes. The wavelengths are able to pass through the skull to reach the cortical tissue [38]. Oxygen uptake is calculated by the difference in oxyhemoglobin and deoxyhemoglobin. rSO_2 provides insight about the oxygen supply the brain is receiving. Normal rSO_2 values range from 60-80% [39].

rSO_2 will vary depending on how much oxygen the brain requires. rSO_2 increases when the metabolic activity of neurons rises so that the metabolic demands can be met [40]. For example, when a brain region is functionally activated there will be an increased metabolic demand. A decrease in systemic BP has been linked to a decrease in rSO_2. A decrease in blood flow can affect oxygen delivery to the brain tissues being measured [39]. Therefore, rSO_2 should be monitored in patients with NOH.

2.9 Cerebral Hemodynamics &Autonomic Dysfunction

Adequate cerebral blood supply is important for physical and cognitive functioning. Monitoring cerebral hemodynamics in patients with autonomic dysfunction is beneficial to determine if the brain is receiving an adequate blood supply since this population can suffer from cerebral hypoperfusion. Substantial evidence suggests that cerebral hypoperfusion contributes to cognitive dysfunction [41]. Multiple studies have assessed cerebral hemodynamics in patients with autonomic dysfunction but the mechanisms altering cerebral perfusion are not completely understood [42].

As mentioned individuals with autonomic dysfunction lack the ability to control vascular tone when standing, therefore they are unable to increase systemic vascular resistance [43]. Consequently, blood supply to the brain may be reduced in the upright position. Multiple studies have assessed cerebral hemodynamics in both the supine and standing positions in patients with autonomic dysfunction [32,43,44]. A prior study assessed 8 patients with PAF and 1 patient with MSA who experienced a significant decrease in BP upon standing. Findings demonstrated that supine CBFv was higher in patients than controls and upon standing CBFv decreased significantly in the patient group. In the standing position rSO_2 also decreased more in the patient group than the controls [43]. A separate study assessing cerebral hemodynamics in 7 MSA patients and 9 controls found that during HUT, MSA patients had a greater decrease in mean arterial pressure (MAP) at the level of the skull than controls. During HUT, there was also a reduction in cerebral oxygenation in MSA patients and controls, but no significant difference between groups [32]. Cerebral oxygenation was investigated in 18 patients with autonomic failure (AF) and 10 healthy controls in both the supine

and HUT positions. Results demonstrated that during HUT, MAP increased in the controls by 12.3mmHg and decreased in the patients by -46.7mmHg. During HUT, the control group had a small reduction in rSO_2 by -0.5% whereas the patient group had a significant decrease by -8.5% [44]. These studies revealed that an orthostatic stress can cause a reduction in CBFv and rSO_2 in patients with autonomic dysfunction.

When assessing rSO_2 in 19 MSA patients and 10 healthy controls it was found that during HUT presyncopal patients experienced a significantly larger decrease in rSO_2 (-3.1 ± 1.7%) than non pre-syncopal patients (-0.9 ± 0.5%) and controls (-1.1 ± 1.0%). These results demonstrated that the reduction in rSO_2 was related to orthostatic symptoms. During HUT most of the presyncopal MSA patients had SBP readings below 80mmHg and had rSO2 values below 70%. Accordingly, when SBP is extremely low, cerebral autoregulation may not be as effective [8]. Patients are more likely to experience symptoms when they are outside the autoregulated range of 80-160mmHg [35]. When BP drops individuals with PAF exhibited symptoms of cerebral hypoperfusion. These individuals had reduced rSO_2 measures compared to controls [45]. Cerebral blood flow was investigated in 7 women with OH. During HUT, there was a decrease in mean hemispheric blood flow compared to supine. During HUT, there was also a redistribution of blood flow, with an increase in the postcentral areas and a decrease in the frontal area [46]. It is evident that changes in both CBFv and rSO_2 occur in patients with autonomic dysfunction during an orthostatic challenge due to a postural reduction in systemic BP. Even in healthy individuals a drop in cerebral perfusion has been identified upon standing since cerebral autoregulation is unable to immediately compensate for the initial drop in BP that results from the gravitational blood pooling upon standing [47]. This decrease in rSO_2 is extremely short lived and lasts for only seconds in healthy individuals. Whereas, NOH patients can have a reduction in rSO_2 that lasts the entire duration of standing.

Literature specifically related to NOH patients and changes in cerebral blood flow is limited. A study revealed that in the standing position NOH patients had transient cerebral hypoperfusion and upon returning to the supine position cerebral blood flow returned to normal [48]. Consequently,

continuous exposure to repeated cerebral hypoperfusion may endure brain changes that could lead to accelerated cognitive decline [48,49]. Prior research has speculated a link between cerebral hypoperfusion and deficits in short-term memory, abstract thinking, visual memory, and attention [50]. There are few studies specifically related to patients who experience cerebral hypoperfusion and how it could be related to changes in cognitive function, therefore further investigation on this topic is necessary.

2.10 Normal Aging and Cognitive Decline

The process of natural aging causes changes in brain structure including a reduction in total brain volume [31], cortical thinning, white-matter degradation [51], and alterations in synaptic connectivity [52]. Brain volume decreases by about 5% per decade after the age of 50 [53], particularly the frontal lobes [31]. A review examining MRI scans found that prefrontal cortex (PFC) volume had the greatest atrophy in older adults [53]. The PFC is also affected by molecular changes which correlate with aging [54]. MRI can be used to measure the thickness of the cerebral cortex to investigate cortical thinning. Studies have found that cortical thinning occurs by middle age and affects a widespread cortical area that continues to thin with aging [55]. White matter loss also occurs with aging. The development of white matter hyperintensities and hippocampal volume loss are a natural process of aging [56]. A study investigating rhesus monkeys found that aging causes a significant overall loss of synapses in prefrontal area 46 [57]. These alterations in brain structure have been related to an increased rate of cognitive decline. The aging brain has differences in both structure and function which are associated with cognitive decline [51].

These structural changes related to aging come with severe consequences to cognitive function. Aging is associated with a decline in memory, spatial visualization, information processing speed, attention, executive functioning, and conceptual reasoning [1,2]. As previously mentioned, aging causes PFC atrophy. The PFC is one of the most important areas involved in cognitive control and is responsible for executive functioning [58]. The PFC is heavily relied upon to accurately perform cognitive tasks such as the Stroop test which involves selective attention [59].

2.11 Cognitive Decline Associated with Disease

Some diseases and conditions are associated with decreased cognitive functioning. Alzheimer's disease (AD) and LBD accelerate the progression of brain atrophy and cognitive decline [60]. Individuals with AD experience the fastest rate of decline in attention, visuo-spatial and executive functions compared to other cognitive functions [6]. A stroke can also result in changes in cognitive function. A study investigating IPS post-stroke and its effect on cognitive function found that stroke patients performed significantly worse in all cognitive domains compared to healthy controls. Processing speed was significantly reduced in 90% of stroke patients demonstrated by poor Symbol Digit Modalities Test scores [61]. Total white matter hyper-intensity volume is also significantly related to slower IPS [56]. Traumatic brain injury can also result in decreased cognitive functioning. Patients who suffered from a traumatic brain injury had reduced IPS and attentional difficulties [62]. A review found that long-term cognitive impairment occurred in about 50% of individuals with a single traumatic brain injury [63]. A multitude of reasons can contribute to the accelerated rate of cognitive decline therefore, investigation is needed to determine exactly what is triggering the decline in cognitive functioning. It is important to be able to distinguish between normal cognitive decline and accelerated cognitive decline as a result of disease.

Neurological diseases can affect important cognitive domains such as IPS and attention. IPS is a measure of the time between receiving a stimulus and responding to a stimulus [64]. This type of processing is an essential component of cognitive functioning [2, 65]. A decline in IPS can affect many cognitive domains, such as verbal fluency, attention, visuospatial function, memory, and executive function. Multiple sclerosis (MS) is a neurological disease that often presents with a decline in IPS. This decline is one of the first cognitive deficits to surface in MS patients [66]. A study used neuropsychological tests to assess IPS in MS patients during times of relapse and recovery. Results showed that during time of relapse MS patients had significantly worse SDMT scores indicating slower IPS [67]. This finding is common among other studies investigating cognitive function in MS patients [68]. If, IPS is reduced early in disease progression in MS patients, it may also be reduced early in other neurodegenerative conditions.

Cognitive performance has been assessed in individuals with mild cognitive impairment (MCI) and those with MCI and OH. The individuals with OH had reduced processing speed and visual working memory compared to the group without OH. It was found that a higher prevalence of OH was correlated with the severity of cognitive status [7]. A cohort of 4690 participants aged 50 plus were examined to determine the relationship between supine hypertension, OH, and cognitive performance. Results revealed that individuals with supine hypertension combined with OH had poorer global cognition and executive function than individuals with only supine hypertension [69]. A relationship between cognitive impairment and OH has also been established in patients with α-synucleinopathies which includes PD, LBD and MSA. It is believed that the presence of α-synuclein could be contributing to both OH and cognitive impairment or the hypoperfusion resulting from OH is impairing cognition [5].

2.12 Cognitive Function and its Relationship to NOH

The prevalence of NOH increases with age and is commonly diagnosed in the elderly population which is also the population at risk for normal cognitive decline [21]. Consequently, there may be a relationship between NOH and changes in cognitive function. NOH patients can suffer from ANS damage, hypotension, cerebral hypoperfusion and fatigue [70]. These symptoms could be factors influencing the decline in cognitive functioning. Prior research has stated that NOH and cognitive decline could be related since the brain regions involved in both are responsible for cardiovascular autonomic processes and cognitive control [49]. NOH patients frequently complain about difficulty concentrating and thinking [71]. Consequently, cognitive function in NOH patients has been investigated in a variety of ways, including assessing cognitive function in the supine, sitting, and standing positions, as well as comparing cognitive function to healthy controls.

Baseline cognitive function is evaluated in the seated position to ensure cognitive performance is not affected by a positional change in BP. Fourteen patients with PAF with a postural SBP drop of at least 20mmHg underwent neuropsychological assessment in the seated position. Patients presented with significant deficits in speed, attention and executive functioning. These deficits

were found in both patients with and without white matter lesions, therefore the lesion was not the only cause of cognitive impairment [72]. In a sample of 5,963 individuals aged 50 plus, 6.3% had OH. Participants with OH had significantly worse global cognitive function, processing speed, sustained attention, and memory compared to participants without OH [73]. Therefore, OH may be contributing to changes in cognitive functioning.

Previous literature has demonstrated that OH causes an increased risk of developing cognitive impairment. At a 4 year follow up the incidence of cognitive impairment was significantly greater in OH individuals (23.7%) than a control group (9.2%) [74]. OH patients who had a significant drop in SBP while standing had worse verbal memory, global cognition and scanning and tracking scores than those without OH [75]. A study found that the prevalence of OH correlated with the severity of cognitive deficits. The group of individuals with OH and MCI presented with significantly reduced processing speed, working memory and executive functions [7].

When assessing cognitive function during an orthostatic challenge such as HUT it was found that NOH patients experienced a significant drop in SBP of at least 20 mmHg and had significantly worse global and executive cognitive performances [76]. A study assessed cognitive function in a variety of different positions in 12 patients with PAF or autoimmune autonomic neuropathy and 12 control subjects. Findings revealed that in the seated position global cognitive function was preserved but during HUT the patients had a significant decrease in immediate memory, working memory, abstract thinking, and sustained attention compared to controls [77]. Neuropsychological assessment was used to evaluate cognitive function in both the supine and HUT positions in 10 NOH patients. During HUT, NOH patients experienced a significant worsening in executive functioning, including a decrease in global cognitive functioning and specific tasks compared to the supine position [78]. Overall, a significant difference in cognitive function between the supine and HUT positions has found been found in patients who experience NOH.

2.13 Cognitive Tests

There are many neuropsychological assessments available to evaluate cognitive function. When selecting which cognitive assessments to administer it is important to consider the population being assessed, length and ease of administration, established norms, and reliability of the assessment. Prior research has stated that a decline in IPS is one of the first cognitive deficits to surface in MS patients [66], therefore a reduction in IPS may arise early in other neurological conditions such as NOH. Individuals with NOH struggle to remain in the standing position for an extended period of time since BP drops in this position. Therefore, when selecting tests to assess cognitive function in this population it is important to ensure the tests are short in duration if assessing patients in the upright position.

2.13.1 Symbol Digit Modalities Test

The symbol digit modalities test (SDMT) is a paper based neuropsychological test used primarily to assess IPS. A sheet of paper has a key at the top with the numbers 1 to 9, each number has a corresponding symbol above. Beneath the key there are eight rows of symbols with each row consisting of 15 symbols [79]. In the oral version, the participant has 90 seconds to say out loud what number correctly corresponds with each symbol. The number of correct responses and the number of errors are recorded.

The SDMT is a validated test and is widely accepted as an accurate measure of IPS [80]. The SDMT was originally administered in a written format where the participant would write down the corresponding number that matched with the symbol. The oral version of the SDMT is beneficial because it does not require motor movement, which is necessary for the written version. The oral SDMT displayed strong positive correlations ($r = 0.78$ to 0.82) with the written SDMT in healthy adults. The oral SDMT was proven to be reliable over multiple test-retest intervals over a 48-week period, had a test-retest reliability coefficient of 0.76 in healthy adults and had an excellent test-retest reliability coefficient of 0.89 in a group of stroke patients [81–83]. Therefore, the oral version is a reliable way to measure IPS.

It has been stated that the SDMT was the best test to predict cognitive impairment in a sample of MS patients. 75.4% of the patients were correctly classified [84]. SDMT is significantly associated with age, gender, cultural background, and level of education [85], therefore, these variables need to be taken into consideration when analyzing SDMT scores. SDMT has been used to screen for and diagnose cognitive impairment in MS patients. Even a small change in SDMT score by 3-4 points is clinically meaningful [67]. Another advantage of the SDMT is that it only takes about 5 minutes to complete the testing.

2.13.2 Stroop Test

The Stroop test is a neuropsychological test originally developed in 1935 by John Ridley Stroop to measure attention and response inhibition [86]. It can measure how well an individual is able to inhibit a dominant response and respond to an unusual one [87]. It has been regarded as a gold standard test to measure attention and is able to measure selective attention independently from processing speed [88,89]. The Stroop test requires the completion of three subtests which are each 45 seconds in duration. Each test is a sheet of paper containing 100 words of colours (i.e. blue, red, purple, brown, green). The participant is instructed to say out loud as many words as possible in the time given. The first subtest is referred to as the Word Stroop test (W). In this version the words of colours are written in black ink. The second subtest is referred to as the Colour Stroop test (C) and consists of words of colours written in the same colour of ink as the word. The participant must say out loud the colour of the ink. The third subtest is referred to as the Colour-Word Stroop test (CW). In this version the word of the colour and the colour of the ink that the word is printed in do not correspond. For example, the word may say blue but be printed in red ink. In this task the participant must say the colour of the ink and inhibit themselves from saying the word. The correct number of responses and the number of errors for each subtest are recorded. The W test and the C test are completed to obtain a baseline for comparison with the CW test.

The most important information that can be obtained from the Stroop test is Golden's interference (Ig) score. The interference score represents the amount of delay the participant has in naming the colour of the ink since they must inhibit themselves from saying the word. The interference score can be calculated using the score achieved in the CW trial subtract a predicted colour-word (Pcw) score. The CW score represents the amount of time it takes for an individual to identify the colour of the ink plus the amount of time it takes to suppress the reading the word. A predicted colour-word score is calculated based on how many correct answers were scored in the C trail and the W trial. This gives an estimate of how well the participant should score on the CW version. The lower the interference score, the worse the attention. The following equations are required to calculate the Ig score: $Pcw = \frac{(W x\ C)}{(W+C)}$ $Ig = CW - Pcw$

2.14 Conclusion

Current literature investigating NOH patients, cerebral hemodynamics, and cognitive functioning is limited, therefore future research related to this topic is necessary. When studying NOH patients, it is crucial to understand the physiology of the condition so that caution is taken when the patient is in the upright position. It is important to measure HR, BP, CBFv, and rSO_2 in NOH patients since these measures can fluctuate with positional changes. As well, if testing cognitive function in the supine and upright positions it is imperative to select tests that are short in duration so they can be completed in the upright position.

2.15 References

1. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013. doi:10.1016/j.cger.2013.07.002

2. Salthouse T. Selective review of cognitive aging. *J Int Neuropsychol Soc*. 2010. doi: 10.1017/S1355617710000706

3. Torrens-Burton A, Basoudan N, Bayer AJ, Tales A. Perception and Reality of Cognitive Function: Information Processing Speed, Perceived Memory Function, and Perceived Task Difficulty in Older Adults. *J Alzheimer's Dis*. 2017. doi:10.3233/JAD-170599

4. Eckert MA. Slowing down: Age-related neurobiological predictors of processing speed. *Front Neurosci*. 2011. doi:10.3389/fnins.2011.00025

5. Udow SJ, Robertson AD, Macintosh BJ, et al. "Under pressure": Is there a link between orthostatic hypotension and cognitive impairment in α-synucleinopathies? *J Neurol Neurosurg Psychiatry*. 2016. doi:10.1136/jnnp-2016-314123

6. Zhao Q, Zhou B, Ding D, et al. Cognitive decline in patients with Alzheimer's disease and its related factors in a memory clinic setting, Shanghai, China. *PLoS One*. 2014. doi:10.1371/journal.pone.0095755

7. Bocti C, Pépin F, Tétreault M, et al. Orthostatic hypotension associated with executive dysfunction in mild cognitive impairment. *J Neurol Sci*. 2017. doi:10.1016/j.jns.2017.09.028

8. Suzuki K, Asahina M, Suzuki A, Hattori T. Cerebral Oxygenation Monitoring for Detecting Critical Cerebral Hypoperfusion in Patients with Multiple System Atrophy during the Head-up Tilt Test. *Intern Med*. 2008. doi:10.2169/internalmedicine.47.1094

9. Novak P. Cerebral Blood Flow, Heart Rate, and Blood Pressure Patterns during the Tilt Test in Common Orthostatic Syndromes. *Neurosci J*. 2016. doi:10.1155/2016/6127340

10. Huang KL, Lin KJ, Ho MY, Chang YJ, Chang CH, Wey SP, Hsieh CJ, Yen TC, Hsiao IT LT. Amyloid deposition after cerebral hypoperfusion: Evidenced on [18F]AV-45 positron emission tomography. *J Neurol Sci*. 2012. doi:http://dx.doi.org/10.1016/j.jns.2012.04.014

11. Shields RW. Functional Anatomy of the Autonomic Nervous System. *J Clin Neurophysiol*. 1993. doi:10.1097/00004691-199301000-00002

12. Hall WD. *An Overview of the Autonomic Nervous System*.; 1990.

13. Robertson DW, Biaggioni I, Burnstock G, Low P, Paton JFR. *Primer on the Autonomic Nervous System*.; 2012. doi:10.1016/C2010-0-65186-8

14. Giuliano RJ, Karns CM, Bell TA, et al. Parasympathetic and sympathetic activity are associated with individual differences in neural indices of selective attention in adults. *Psychophysiology*. 2018. doi:10.1111/psyp.13079

15. Alderman BL, Olson RL. The relation of aerobic fitness to cognitive control and heart rate variability: A neurovisceral integration study. *Biol Psychol*. 2014. doi:10.1016/j.biopsycho.2014.02.007

16. Mathias CJ. Autonomic diseases: clinical features and laboratory evaluation. *J Neurol Neurosurg Psychiatry*. 2003. doi:10.1136/jnnp.74.suppl_3.iii31

17. Palma JA, Kaufmann H. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension. *Mov Disord Clin Pract*. 2017. doi:10.1002/mdc3.12478

18. Canadian Guidelines on Parkinson's Disease Executive Summary. *Can J Neurol Sci*. 2012. doi:10.1017/S0317167100015158

19. Norcliffe-Kaufmann L, Kaufmann H, Palma JA, et al. Orthostatic heart rate changes in patients with autonomic failure caused by neurodegenerative synucleinopathies. *Ann Neurol*. 2018. doi:10.1002/ana.25170

20. Low PA, Singer W. Update on Management of Neurogenic Orthostatic Hypotension. *Lancet Neurol*. 2008. doi:10.1016/S1474-4422(08)70088-7

21. Low PA. Neurogenic orthostatic hypotension: pathophysiology and diagnosis. *Am J Manag Care*. 2015.

22. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res*. 2011. doi:10.1007/s10286-011-0119-5

23. Freeman R. Neurogenic orthostatic hypotension Feb 08. *N Engl J Med*. 2008.

24. Gupta D, Nair MD. Neurogenic orthostatic hypotension: Chasing "the fall." *Postgrad Med J*. 2008. doi:10.1136/pgmj.2007.062075

25. Rascol O, Perez-Lloret S, Damier P, et al. Falls in ambulatory non-demented patients with Parkinson's disease. *J Neural Transm*. 2015. doi:10.1007/s00702-015-1396-2

26. Low PA, Opfer-Gehrking TL. The autonomic laboratory. *Am J Electroneurodiagnostic Technol*. 1999.

27. Karemaker JM. An introduction into autonomic nervous function. *Physiol Meas*. 2017. doi:10.1088/1361-6579/aa6782

28. Berger MJ, Kimpinski K. A practical guide to the treatment of neurogenic orthostatic hypotension. *Can J Neurol Sci*. 2014. doi:10.1017/S0317167100016528

29. Kaufmann H, Palma JA. Neurogenic orthostatic hypotension: the very basics. *Clin Auton Res*. 2017;27(S1):39-43. doi:10.1007/s10286-017-0437-3

30. Grolimund P, Seiler RW. Age dependence of the flow velocity in the basal cerebral arteries-A transcranial Doppler ultrasound study. *Ultrasound Med Biol*. 1988. doi:10.1016/0301-5629(88)90139-1

31. Peters R. Ageing and the brain. *Postgr Med J*. 2006;82(964):84-88. doi:10.1002/path.2089

32. Asahina M, Sato J, Tachibana M, Hattori T. Cerebral blood flow and oxygenation during head-up tilt in patients with multiple system atrophy and healthy control subjects. *Park Relat Disord*. 2006. doi:10.1016/j.parkreldis.2006.05.002

33. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989. doi:10.1161/01.STR.20.1.45

34. Duschek S, Schandry R. Cognitive performance and cerebral blood flow in essential hypotension. *Psychophysiology*. 2004. doi:10.1111/j.1469-8986.2004.00249.x

35. Novak V, Novak P, Spies JM, Low PA. Autoregulation of Cerebral Blood Flow in Orthostatic Hypotension. *Stroke*. 1998. doi:10.1161/01.STR.29.1.104

36. Purkayastha S, Sorond F. Transcranial doppler ultrasound: Technique and application. *Semin Neurol*. 2012. doi:10.1055/s-0032-1331812

37. Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial Doppler Ultrasound: A Review of the Physical Principles and Major Applications in Critical Care. *Int J Vasc Med*. 2013. doi:10.1155/2013/629378

38. Sonkaya AR. The use of functional near infrared spectroscopy technique in neurology. *NeuroQuantology*. 2018;16(7):87-93. doi:10.14704/nq.2018.16.7.1688

39. Marin T, Moore J. Understanding near-infrared spectroscopy. *Adv Neonatal Care*. 2011. doi:10.1097/ANC.0b013e3182337ebb

40. Liu T, Pelowski M, Pang C, Zhou Y, Cai J. Near-infrared spectroscopy as a tool for driving research. *Ergonomics*. 2016. doi:10.1080/00140139.2015.1076057

41. Marshall RS. Effects of altered cerebral hemodynamics on cognitive function. *J Alzheimers Dis*. 2012. doi:10.3233/JAD-2012-120949

42. Feeney J, O'Leary N, Kenny RA. Impaired orthostatic blood pressure recovery and cognitive performance at two-year follow up in older adults: The Irish Longitudinal Study on Ageing. *Clin Auton Res*. 2016. doi:10.1007/s10286-016-0340-3

43. Harms MPM, Colier WNJM, Wieling W, Lenders JWM, Secher NH, Van Lieshout JJ. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke*. 2000. doi:10.1161/01.STR.31.7.1608

44. Hunt K, Tachtsidis I, Bleasdale-Barr K, Elwell C, Mathias C, Smith M. Changes in cerebral oxygenation and haemodynamics during postural blood pressure changes in patients with autonomic failure. *Physiol Meas*. 2006. doi:10.1088/0967-3334/27/9/002

45. Tachtsidis I, Elwell CE, Leung TS, et al. Rate of change in cerebral oxygenation and blood pressure in response to passive changes in posture: A comparison between pure autonomic failure patients and controls. In: *Advances in Experimental Medicine and Biology*. ; 2005. doi:10.1007/0-387-26206-7_26

46. Passant U, Warkentin S, Minthon L, Fäldt R, Edvinsson L. Cortical blood flow during head-up postural change in subjects with orthostatic hypotension. *Clin Auton Res*. 1993. doi:10.1007/BF01827332

47. Mol A, Woltering JHH, Colier WNJM, Maier AB, Meskers CGM, van Wezel RJA. Sensitivity and reliability of cerebral oxygenation responses to postural changes measured with near-infrared spectroscopy. *Eur J Appl Physiol*. 2019. doi:10.1007/s00421-019-04101-0

48. Espay AJ, LeWitt PA, Hauser RA, Merola A, Masellis M, Lang AE. Neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease and related synucleinopathies: prioritisation of treatment targets. *Lancet Neurol*. 2016. doi:10.1016/S1474-4422(16)30079-5

49. Sambati L, Calandra-Buonaura G, Poda R, Guaraldi P, Cortelli P. Orthostatic hypotension and cognitive impairment: A dangerous association? *Neurol Sci*. 2014. doi:10.1007/s10072-014-1686-8

50. Mehrabian S, Duron E, Labouree F, et al. Relationship between orthostatic hypotension and cognitive impairment in the elderly. *J Neurol Sci*. 2010. doi:10.1016/j.jns.2010.08.056

51. Persson J, Nyberg L, Lind J, et al. Structure-function correlates of cognitive decline in aging. *Cereb Cortex*. 2006. doi:10.1093/cercor/bhj036

52. Morrison JH, Baxter MG. The ageing cortical synapse: Hallmarks and implications for cognitive decline. *Nat Rev Neurosci*. 2012. doi:10.1038/nrn3200

53. Trollor JN, Valenzuela MJ. Brain ageing in the new millennium. *Aust N Z J Psychiatry*. 2001. doi:10.1046/j.1440-1614.2001.00969.x

54. Erraji-Benchekroun L, Underwood MD, Arango V, et al. Molecular aging in human prefrontal cortex is selective and continuous throughout adult life. *Biol Psychiatry*. 2005. doi:10.1016/j.biopsych.2004.10.034

55. Salat DH, Buckner RL, Snyder AZ, et al. Thinning of the cerebral cortex in aging. *Cereb Cortex*. 2004. doi:10.1093/cercor/bhh032

56. Papp K V, Kaplan RF, Springate B, et al. Processing speed in normal aging: effects of white matter hyperintensities and hippocampal volume loss. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2014. doi:10.1080/13825585.2013.795513

57. Peters A, Sethares C, Luebke JI. Synapses are lost during aging in the primate prefrontal cortex. *Neuroscience*. 2008. doi:10.1016/j.neuroscience.2007.07.014

58. Moriguchi Y, Hiraki K. Prefrontal cortex and executive function in young children: a review of NIRS studies. *Front Hum Neurosci*. 2013. doi:10.3389/fnhum.2013.00867

59. Miller EK, Cohen JD. An Integrative Theory of Prefrontal Cortex Function. *Annu Rev Neurosci*. 2001. doi:10.1146/annurev.neuro.24.1.167

60. Braskie MN, Thompson PM. Understanding cognitive deficits in alzheimer's disease based on neuroimaging findings. *Trends Cogn Sci*. 2013. doi:10.1016/j.tics.2013.08.007

61. Su CY, Wuang YP, Lin YH, Su JH. The role of processing speed in post-stroke cognitive dysfunction. *Arch Clin Neuropsychol*. 2015. doi:10.1093/arclin/acu057

62. Willmott C, Ponsford J, Hocking C, Schönberger M. Factors Contributing to Attentional Impairments After Traumatic Brain Injury. *Neuropsychology*. 2009. doi:10.1037/a0015058

63. McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG. Mild Traumatic Brain Injury (mTBI) and chronic cognitive impairment: A scoping review. *PLoS One*. 2017. doi:10.1371/journal.pone.0174847

64. Haworth J, Phillips M, Newson M, Rogers PJ, Torrens-Burton A, Tales A. Measuring Information Processing Speed in Mild Cognitive Impairment: Clinical Versus Research Dichotomy. *J Alzheimer's Dis*. 2016. doi:10.3233/JAD-150791

65. Kail R, Salthouse TA. Processing speed as a mental capacity. *Acta Psychol (Amst)*. 1994. doi:10.1016/0001-6918(94)90003-5

66. Van Schependom J, D'Hooghe MB, Cleynhens K, et al. Reduced information processing speed as primum movens for cognitive decline in MS. *Mult Scler J*. 2015. doi:10.1177/1352458514537012

67. Benedict RHB, Morrow S, Rodgers J, et al. Characterizing cognitive function during relapse in multiple sclerosis. *Mult Scler J*. 2014. doi:10.1177/1352458514533229

68. Morrow SA, Jurgensen S, Forrestal F, Munchauer FE, Benedict RHB. Effects of acute relapses on neuropsychological status in multiple sclerosis patients. *J Neurol*. 2011. doi:10.1007/s00415-011-5975-3

69. Frewen J, Finucane C, Savva GM, Boyle G, Kenny RA. Orthostatic hypotension is associated with lower cognitive performance in adults aged 50 plus with supine hypertension. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2014. doi:10.1093/gerona/glt171

70. Schondorf R, Benoit J, Stein R. Cerebral autoregulation in orthostatic intolerance. *Ann N Y Acad Sci*. 2001.

71. Low PA, Opfer-Gehrking TL, McPhee BR, et al. Prospective Evaluation of Clinical Characteristics of Orthostatic Hypotension. *Mayo Clin Proc*. 1995. doi:10.4065/70.7.617

72. Heims HC, Critchley HD, Martin NH, Jäger HR, Mathias CJ, Cipolotti L. Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res*. 2006. doi:10.1007/s10286-006-0318-7

73. Frewen J, Savva GM, Boyle G, Finucane C, Kenny RA. Cognitive performance in orthostatic hypotension: Findings from a nationally representative sample. *J Am Geriatr Soc*. 2014. doi:10.1111/jgs.12592

74. Huang H, Zheng T, Liu F, Wu Z, Liang H, Wang S. Orthostatic hypotension predicts cognitive impairment in the elderly: Findings from a cohort study. *Front Neurol*. 2017. doi:10.3389/fneur.2017.00121

75. Torres R V., Elias MF, Crichton GE, Dore GA, Davey A. Systolic orthostatic hypotension is related to lowered cognitive function: Findings from the Maine-Syracuse Longitudinal Study. *J Clin Hypertens*. 2017. doi:10.1111/jch.13095

76. Guaraldi. P, Poda R, Calandra-Buonaura G, et al. *Executive Functions Worsen during Orthostatic Challenge in Patients with Neurogenic Orthostatic Hypotension (P03.035)*.; 2013.

77. Guaraldi P, Poda R, Calandra-Buonaura G, et al. Cognitive function in peripheral autonomic disorders. *PLoS One*. 2014. doi:10.1371/journal.pone.0085020

78. Poda R, Guaraldi P, Solieri L, et al. Standing worsens cognitive functions in patients with neurogenic orthostatic hypotension. *Neurol Sci*. 2012. doi:10.1007/s10072-011-0746-6

79. Smith A. Symbol Digit Modalities Test: Manual. *West Psychol Sci Los Angeles West Psychol Serv*. 1982.

80. Parmenter BA, Weinstock-Guttman B, Garg N, Munschauer F, Benedict RHB. Screening for cognitive impairment in multiple sclerosis using the Symbol Digit Modalities Test. *Mult Scler*. 2007. doi:10.1177/1352458506070750

81. Morrow SA, O'Connor PW, Polman CH, et al. Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Mult Scler*. 2010. doi:10.1177/1352458510378021

82. Benedict RHB, Duquin JA, Jurgensen S, et al. Repeated assessment of neuropsychological deficits in multiple sclerosis using the symbol digit modalities test and the MS neuropsychological screening questionnaire. *Mult Scler*. 2008. doi:10.1177/1352458508090923

83. Koh CL, Lu WS, Chen HC, Hsueh IP, Hsieh JJ, Hsieh CL. TestRetest reliability and practice

effect of the oral-format symbol digit modalities test in patients with stroke. *Arch Clin Neuropsychol*. 2011. doi:10.1093/arclin/acr029

84. Deloire MSA, Bonnet MC, Salort E, et al. How to detect cognitive dysfunction at early stages of multiple sclerosis? *Mult Scler*. 2006. doi:10.1191/1352458506ms1289oa

85. Kiely KM, Butterworth P, Watson N, Wooden M. The symbol digit modalities test: Normative data from a large nationally representative sample of Australians. *Arch Clin Neuropsychol*. 2014. doi:10.1093/arclin/acu055

86. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935. doi:10.1037/h0054651

87. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary, 2nd Ed.*; 1998.

88. MacLeod CM. Half a century of reseach on the stroop effect: An integrative review. *Psychol Bull*. 1991. doi:10.1037/0033-2909.109.2.163

89. Morrow SA. Normative data for the stroop color word test for a North American population. *Can J Neurol Sci*. 2013. doi:10.1017/S0317167100015997

Chapter 3

3 Neurogenic orthostatic hypotension impairs information processing speed and attention [1]

3.1 Introduction

Neurogenic orthostatic hypotension (NOH) is a condition characterized by a reduction in systolic blood pressure (SBP) ≥ 20mmHg or diastolic blood pressure (DBP) ≥ 10mmHg within three minutes of upright posture [1]. A sudden drop in BP can trigger symptoms such as lightheadedness, dizziness, weakness and fatigue soon after standing up. These symptoms make simple daily activities more challenging and increase the likelihood of falls [2].

NOH commonly occurs in the elderly population [3]. This population is also at an increased risk for cognitive decline; therefore, it is important to investigate if there is a relationship between NOH and changes in cognitive function. Current literature focusing on NOH and cognitive function investigates processing speed, attention, and executive function in the seated position but fails to investigate cognition in the standing position [4]. However, standing may be the time at which impairment of cognitive function is the most severe due to associated hypotension. It is also the time that affected individuals are at greater risk for complications from NOH such as falls.

It is well-known that with aging there are changes in cognitive function. Many cognitive abilities decline with aging such as memory, spatial visualization, attention, information processing speed,

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and conceptual reasoning [5,6]. Attention is the ability to attend to specific stimuli while inhibiting attention to other stimuli, which is required for many everyday tasks [7]. When an individual is unable to focus on the relevant stimuli, interference from the irrelevant stimuli occurs. Interference is commonly measured using the Stroop Test, where greater interference indicates worse attention. The amount of interference from irrelevant information increases with aging [8], therefore older individuals have a more difficult time inhibiting an undesired response. Information processing speed (IPS) is the time between receiving a stimulus and responding to a stimulus [9]. A common neuropsychological test to measure IPS is the Symbol Digit Modalities Test (SDMT). IPS is linked to higher cognitive functions [10] and, therefore, a decline in processing speed can affect other cognitive domains. It has been stated that IPS is a predictor of the ability to perform simple daily activities [11] and an indicator of independence [12]. It was found that IPS was the first cognitive deficit to surface in individuals with multiple sclerosis [13]. Consequently, a deficit in IPS or attention may also arise early on in other neurological conditions, such as NOH.

The objective of the current study was to investigate the potential changes in IPS and attention in NOH patients in both the supine and head-up tilt (HUT) positions. In addition, the study's further objective was to describe the relationship between cognitive function and the potential change in SBP in NOH patients.

It was hypothesized that NOH patients would experience a decline in IPS and attention in the HUT position compared to the supine position due to the associated reduction in postural BP. Controls would have an increase in IPS and attention in the HUT position compared to the supine position since they experience a burst of sympathetic activity when they stand up. It was also hypothesized that a greater drop in SBP during HUT would correspond with a worsening in IPS and attention.

3.2 Methods

3.2.1 Participants

The current study enrolled 43 participants including 23 participants with a diagnosis of NOH and 20 healthy age-matched controls. The clinical diagnosis of NOH was provided by a neurologist after evaluating the autonomic reflex screen (ARS) and a medical history. The criteria for NOH was a drop in SBP ≥ 30 mmHg on HUT as it reduced the false positive rate from 5% to <1% when compared to the ≥ 20/10 mmHg SBP/DBP criteria [14]. The conditions associated with NOH included Parkinson's disease (n=12), multiple system atrophy (n=4), pure autonomic failure (n=1) and Lewy body dementia (n=1). Five participants had a diagnosis of idiopathic NOH.

Participants were excluded from the study if they had a medical history of coronary artery disease, nerve damage in the peripheral nervous system, failure of other organ systems or diseases that could affect autonomic function, visual problems, or the inability to remain in the upright position for the duration of testing. All testing took place in the autonomic lab located at the University Hospital in London, Ontario. All participants provided written informed consent before being enrolled in the study. Ethical approval was obtained from the Health Science Research Ethics Board at Western University.

3.2.2 Physiological Measures

Testing began with a standardized autonomic reflex screen (ARS). The ARS is comprised of four tests; 1. quantitative sudomotor axon reflex test (QSART) to assess the quality of the postganglionic sympathetic sudomotor axons, 2. deep breathing to assess cardiovagal function, 3. Valsalva maneuver which allows for the calculation of a Valsalva ratio to assess cardiovagal and adrenergic function and 4. HUT (table tilted to 70 degrees), which measures heart rate (HR) and BP responses to an orthostatic challenge to assess adrenergic function [15].

HR was measured using an electrocardiography device (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems, Inc., Branford, CT) connected to electrocardiography electrodes (Ambu® Blue Sensor SP, Glen Burnie, MD). A beat-to-beat BP monitor (BMEYE Nexfin device, Amsterdam, Netherlands) was secured on the middle finger. All recordings were made using WR TestWorks TM software (WR Medical Electronics Co., Stillwater, MN).

3.2.3 Cognitive Measures

Cognitive function was assessed with two paper based neuropsychological tests; the oral version of the Symbol Digit Modalities Test (SDMT) and the Stroop test. SDMT was used to assess IPS. SDMT provides a key at the top of the page that has numbers 1 to 9 and each number corresponds with a symbol. Underneath the key there are 8 rows of symbols and each row consists of 15 symbols. Each participant had 90 seconds to say aloud what number corresponds with each symbol. The correct number of responses and the number of errors were recorded.

The Stroop test was used to measure attention. It consists of three different versions; each version is a sheet of paper containing 100 words of colours (i.e. blue, red, purple, brown, green). Each participant had 45 seconds to say aloud as many words as possible. The first version consists of words of colours written in black ink. The second version consists of the words of the colours printed in the same ink colour as the word. For example, the word “blue” is printed in blue ink. In the third version, the word and the ink colour that the word is printed in do not correspond. For example, the word “blue” could be printed in red ink. The participant must say the colour of the ink and inhibit themselves from saying the word. The number of correct responses and the number of errors were recorded for each version. The correct number of responses in each version was used to calculate Golden’s interference score which represents attention [16]

Prior to cognitive testing 90 seconds in the supine position was recorded to measure baseline HR and SBP. The order of cognitive testing in the supine position was as follows; SDMT, Stroop 1,

SDMT, Stroop 2, SDMT, Stroop 3, SDMT. The bed was then tilted to an angle of 70 degrees (HUT) and 90 seconds of HR and SBP were recorded in this position before beginning the cognitive testing. The order of the cognitive testing in the HUT position was as follows; Stroop 1, Stroop 2, Stroop 3, SDMT. The bed was then tilted back to the supine position and the participant completed 5 minutes of recovery to allow HR and BP to return to resting values.

The Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) were used to screen for significant pre-existing cognitive impairment. Both questionnaires are scored out of 30 points and assess a variety of cognitive functions such as visuospatial, executive, memory, attention, language, orientation, and delayed recall. A normal score on MMSE is a score ≥ 24 and ≥ 26 on the MoCA. A score lower than these values indicates cognitive impairment.

3.2.4 Statistical Analysis

Independent t-tests were used to compare characteristics such as HR, BP, age, BMI, MMSE and MoCA scores between groups. A two-way mixed ANOVA was used to compared cognitive testing between NOH patients and controls in both the supine and HUT positions. A Bonferroni post hoc test was used to compare within group effects for both positions. Results are presented in mean ± SD. A minimum significance level of $p < 0.05$ was used. The statistical analysis was performed using SPSS statistics software, Version 25, Manufactured by International Business Management (IBM) Corporation.

3.3 Results

3.3.1 Participants

A total of 40 participants completed the study, 20 control subjects and 20 NOH patients. Three NOH patients were excluded because they were unable to remain in the upright position for the duration of testing, consequently they were unable to complete the cognitive testing. Controls and

NOH patients were matched based on age, BMI, and education level. The NOH group had fewer females and more males than the control group, but no significant differences were found based on gender. NOH patients had significantly lower MoCA and MMSE scores (Table 1).

3.3.2 Hemodynamic Measurements

Hemodynamic measures are presented in Table 2. Resting HR, resting SBP, and the change in HR were not statistically different between groups. NOH patients had significantly lower scores for heart rate variability during the deep breathing task and Valsalva ratio (VR) indicating cardiovagal impairment [17]. The change in SBP during HUT was significantly different between groups. The drop in SBP during HUT was significantly greater in the NOH patients (-64.11 ± 18.96) compared to the control group (-5.69 ± 7.65).

Table 1. Participant Characteristics

Characteristic	**Control (mean ± SD)**	**NOH (mean ± SD)**
Age (years)	64.50 ± 9.25	69.55 ± 7.43
Gender (F:M)	12:8	8:12
BMI (kg/m^2)	21.50 ± 2.51	22.02 ± 4.71
Education Level (>high school)	16	13
MMSE Score	29.80 ± 0.41	28.74 ± 1.37 *
MoCA Score	28.60 ± 1.54	26.53 ± 2.37 *

BMI: body mass index, MMSE: Mini Mental State Examination, MoCA: Montreal Cognitive Assessment. * Represents significant difference of $p < 0.01$

Table 2. Physiological Characteristics

Characteristic	Control (mean ± SD)	NOH (mean ± SD)
Resting HR (bpm)	69.49 ± 11.91	74.28 ± 12.85
Change in HR during HUT (bpm)	15.04 ± 6.27	12.12 ± 8.60
Resting SBP (mmHg)	128.12 ± 18.75	139.50 ± 23.72
Change in SBP during HUT (mmHg)	-5.69 ± 7.65	-64.11 ± 18.96 **
Heart Rate Variability (bpm)	14.47 ± 6.96	4.48 ± 2.67 **
Valsalva Ratio	1.74 ± 0.33	1.29 ± 0.18 **

HR: heart rate, SBP: systolic blood pressure, HUT: head-up tilt, bpm: beats per minute, mmHg: millimeters of mercury, ** Represents significant difference of $p < 0.001$

3.3.3 Symbol Digit Modalities Test Scores

Mean SDMT scores in the supine and HUT positions are displayed in Figure 6. IPS was significantly slower in NOH patients in both the supine ($p < 0.001$) and HUT ($p < 0.001$) positions compared to controls. Controls had significantly faster IPS during HUT demonstrated by a mean SDMT score of 69.90 ± 12.02 compared to a supine score of 63.55 ± 9.96 ($p < 0.001$). Whereas, the NOH group had no statistical difference in IPS between the supine position 43.20 ± 15.26 and the HUT position 42.90 ± 14.33 ($p = 0.77$).

3.3.4 Stroop Test Scores

The mean interference scores calculated from the Stroop test are displayed in Figure 7. A more negative score represents worse attention, whereas a score closer to 0 represents better attention. Controls had significantly better attention during HUT (-8.68 ± 7.13) compared to the supine position (-14.01 ± 8.96; $p < 0.001$). In contrast, NOH patients had no statistical difference in attention between the supine and HUT positions ($p = 0.11$). During HUT, the mean interference score was significantly worse in NOH patients (-14.86 ± 8.96) compared to controls (-8.68 ± 7.13; $p = 0.029$).

3.3.5 Correlation between Blood Pressure & Cognitive Testing

Figure 8 shows no significant correlation between the change in SBP and SDMT score in NOH patients ($r = 0.284$; $p = 0.225$) or controls ($r = 0.293$; $p = 0.21$). Figure 9 shows no significant correlation between the change in SBP during HUT and interference score in NOH patients ($r = -0.147$; $p = 0.573$) or controls ($r = 0.078$; $p = 0.745$). NOH patients experienced a significant drop in SBP during HUT, but this drop did not relate to IPS or attention.

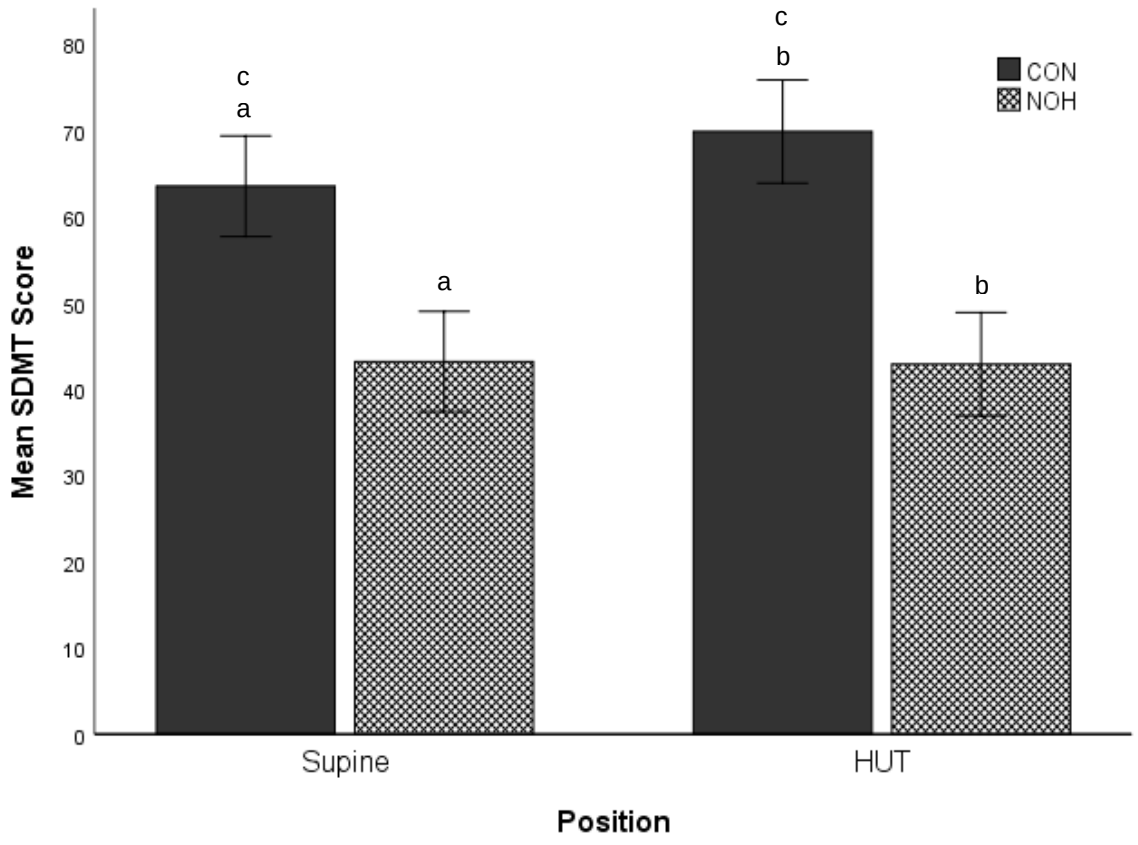

Figure 6. Mean SDMT Scores in the Supine and HUT Positions

Information processing speed (IPS) is represented by the mean SDMT score. NOH patients had significantly slower IPS than controls in the supine and HUT positions. Controls had significantly faster IPS in the HUT position compared to supine. NOH: neurogenic orthostatic hypotension, CON: control, HUT: head-up tilt, SDMT: symbol digit modalities test; a: $p < 0.001$, between CON and NOH in the supine position; b: $p < 0.001$, between CON and NOH in the HUT position; c: $p < 0.001$, between supine and HUT position in CON.

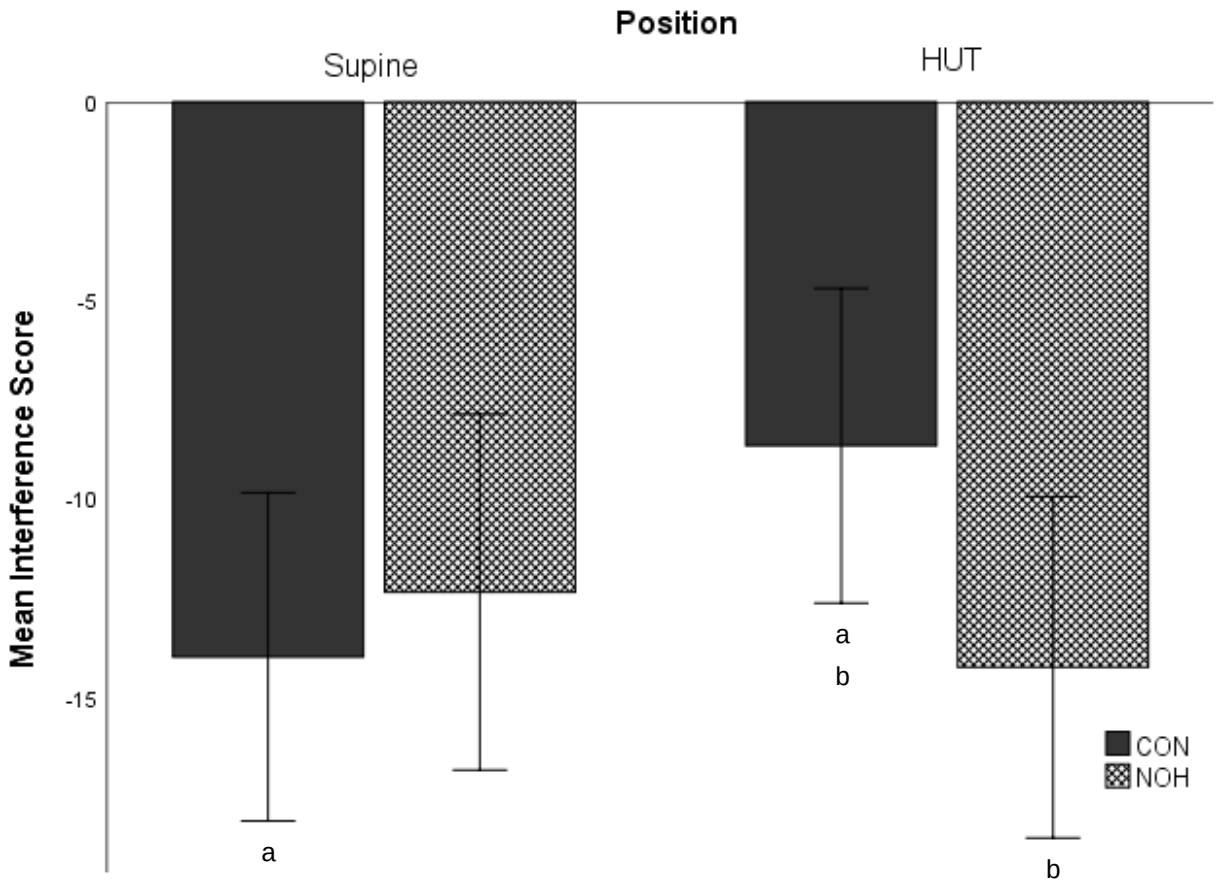

Figure 7. Stroop Test Scores in the Supine and HUT Positions

The Stroop test provides a mean interference score which represents attention. An interference score closer to 0 represents better attention whereas a more negative score represents worse attention. Controls had better attention in the HUT position compared to supine. NOH patients had significantly worse attention in the HUT position compared to controls. NOH: neurogenic orthostatic hypotension, CON: control, HUT: head-up tilt; a: $p < 0.001$, between supine and HUT positions in CON; b: $p = 0.029$, between CON and NOH in HUT position.

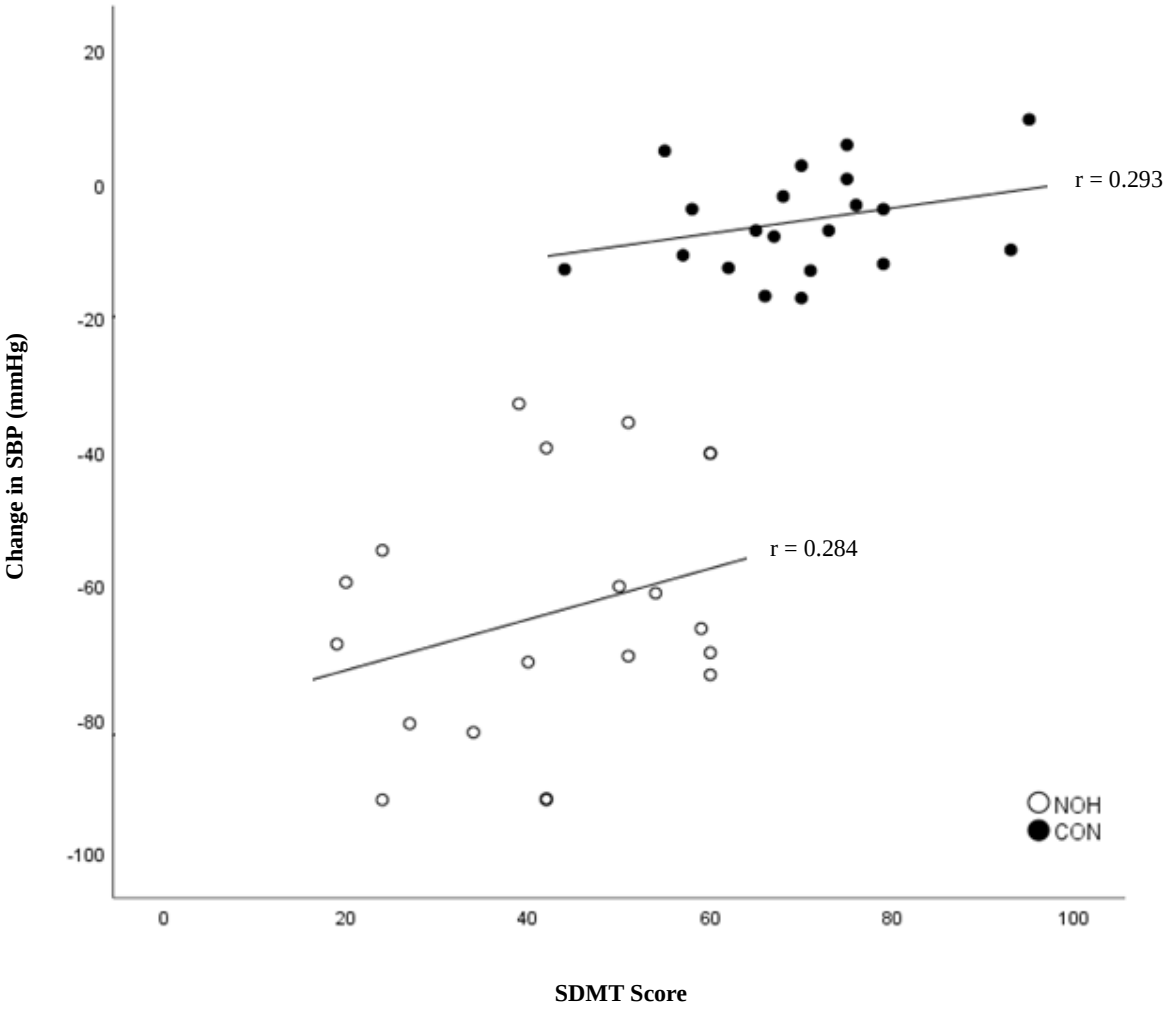

Figure 8. The Relationship Between SBP and SDMT Scores

There was no significant correlation between the change in SBP and SDMT score in NOH patients ($p = 0.225$) or controls ($p = 0.21$). NOH: neurogenic orthostatic hypotension, CON: control, HUT: head-up tilt, SDMT: symbol digit modalities test.

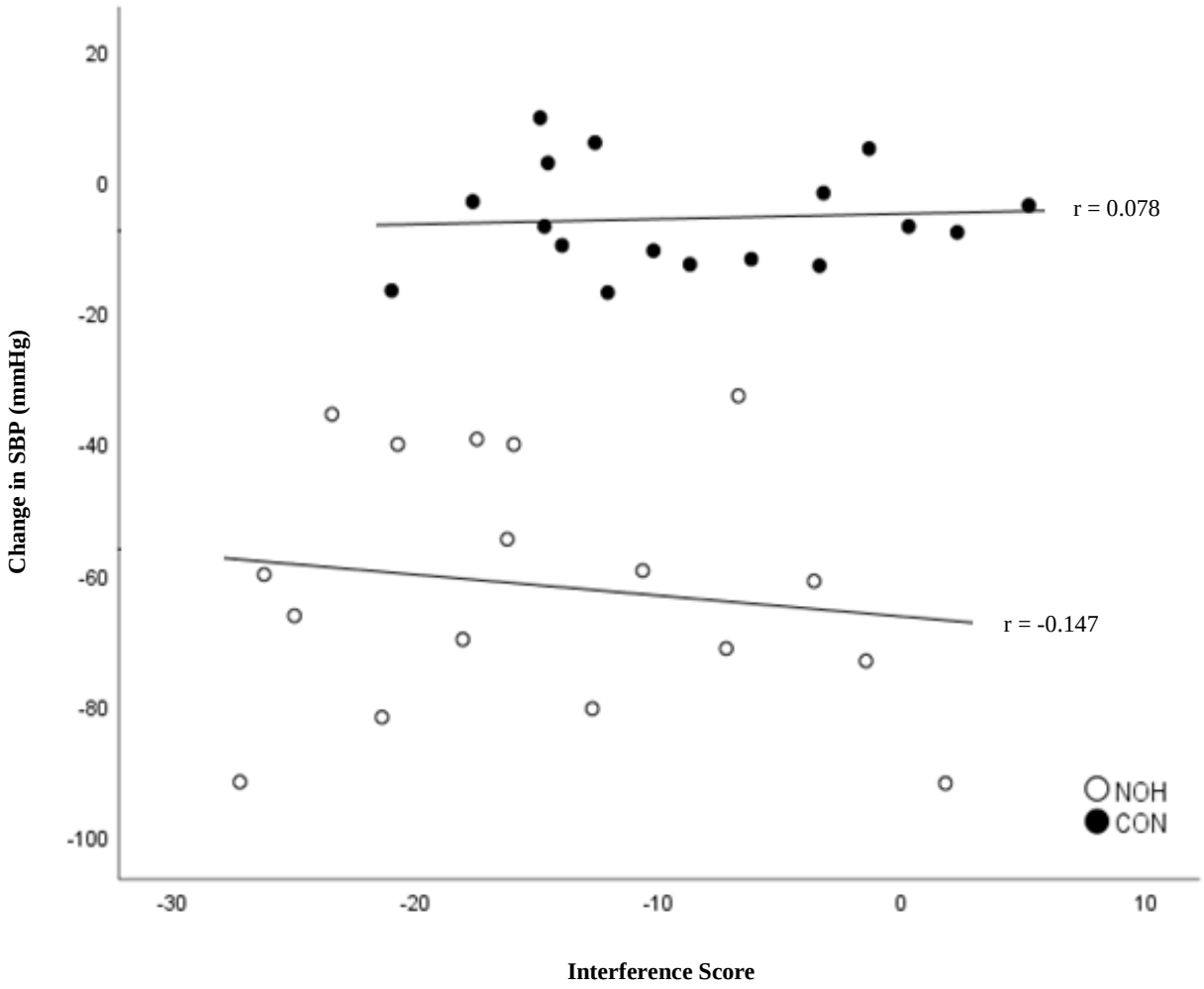

Figure 9. The Relationship Between SBP and Interference Scores

No significant correlation was found between the change in SBP and interference scores in NOH patients (p = 0.573) or controls (p = 0.745). NOH: neurogenic orthostatic hypotension, CON: control, HUT: head-up tilt.

3.3.6 MMSE and MoCA Scores

An additional analysis was completed excluding all participants with MMSE scores <24 and MoCA scores <26 to assess for the potential differences in underlying cognitive status between groups to influence the results related to IPS and attention. This resulted in the exclusion of 1 control subject and 5 NOH patients. Of note, the control subject had a MoCA score of 25 and an MMSE score of 29 and as such we did not feel elimination of this patient from the control group during the original analysis was warranted. When these 6 participants were excluded, NOH patients still had worse attention in the HUT position compared to controls, but this difference was no longer significant ($p = 0.066$). Therefore, when participants with pre-existing cognitive dysfunction were excluded only this one finding was altered.

3.4 Discussion

It is evident from the findings of the current study that NOH patients have undergone an alteration in cognitive function compared to healthy age-matched controls. NOH patients had significantly slower IPS than controls in both the supine and HUT positions. Controls had a significant increase in IPS and attention in the HUT position compared to supine, whereas NOH patients had no difference in IPS or attention with a change in position. NOH patients had significantly worse attention in the HUT position compared to controls. Overall, findings demonstrate that IPS and attention are impaired in NOH patients compared to controls.

It is important to note that NOH patients with slightly lower baseline cognitive functioning did not cause significant differences in SDMT or Stroop test scores compared to the NOH group as a whole. NOH patients with low MoCA scores (≤ 25) did not have significantly worse IPS or attention than NOH patients with high MoCA scores (≥ 28) in either the supine or HUT position. Therefore, it can be stated that NOH patients had significantly worse IPS and attention compared to controls and this finding was not only caused by NOH patients with low MoCA scores, but it was a result caused by the NOH group as a whole.

During HUT, NOH patients experienced a significant drop in SBP (-64.11 ± 18.96mmHg), demonstrating the severity of their condition. This extreme drop in SBP could be contributing to why they had worse cognitive function than controls. The current study found no significant correlation between the change in SBP during HUT and SDMT score or interference score in NOH patients or controls. Therefore, when changes in SBP occurred it did not relate to changes in IPS or attention. NOH patients experienced a significant decrease in SBP during HUT and had no significant change in IPS or attention compared to baseline. However, control subjects experienced very little change in SBP from the supine to HUT position but experienced a significant increase in IPS and attention during HUT. These results contradict other studies suggesting that cognitive function declines in patients with autonomic failure in the HUT position compared to supine [18–20]. Our findings are consistent with one study investigating patients with autonomic failure. Patients had a SBP drop of 61.4 mmHg during HUT and had no change in sustained attention from the supine to HUT position, whereas controls had better sustained attention in the HUT position compared to supine [21]. Consequently, the large drop in SBP experienced by NOH patients did not cause a worsening in IPS or attention, but it could be a factor as to why NOH patients did not experience an increase in IPS and attention during HUT like the controls.

Interestingly, NOH patients had significantly worse SDMT scores in the supine position compared to controls but experienced no drop in SBP in this position. This indicates that regardless of position NOH patients had slower IPS compared to controls. Prior research investigating cognitive function in individuals who experience a large drop in BP upon standing have found that these individuals also have alterations in many cognitive domains [4,22–27]. Heims et al. documented that out of 14 individuals with pure autonomic failure 43% showed cognitive impairment in speed, attention, and executive functioning when tested in the seated position [4]. A battery of neuropsychological tests was completed in the seated position in 961 community dwelling individuals. Participants with systolic orthostatic hypotension had worse global cognition, verbal memory, and scanning and tracking scores than individuals with a normal systolic BP change [22]. Orthostatic hypotension (OH) was associated with worse cognitive function [26], as well as poorer

global cognitive function and poorer memory, in women aged 65 and above [23]. Bocti et al. administered multiple neuropsychological tests to 2 groups of people; group 1, individuals with mild cognitive impairment (MCI) and OH and group 2, individuals with MCI without OH. Individuals with MCI and OH had a lower processing speed, visual working memory, and executive function compared to individuals without OH [24]. Together these studies demonstrate that repeated exposure to low BP may contribute to a decline in a variety of cognitive domains regardless of position. Our results strongly argue that IPS is among the earlier domains to be affected given that we controlled for significant other cognitive dysfunction by requiring normal values on standardized clinical tests of cognition (i.e. MMSE and MoCA).

Attention measured by Golden's interference score was significantly reduced in NOH patients compared to the controls in the HUT position. As well, NOH patients had no significant difference in attention from supine to HUT, but controls had a significant increase in attention from supine to HUT. It is important to note that although not significant ($p = 0.592$) NOH patients had slightly better attention in the supine position than controls. This was a surprising finding and may be a result of the way Golden's interference score is calculated since it takes into consideration a predicted colour-word score. Prior research has reported that using this interference score can be problematic in patient populations who have reduced IPS [28,29]. When IPS is impaired it can result in lower scores on the word trial and the colour trial of the Stroop test which results in a lower predicted colour-word score being calculated. A low predicted colour-word score is beneficial because it allows the participant to score low on the colour-word trial without worsening the interference score. In the current study, the raw score for the colour-word trial was lower in NOH patients in both the supine and HUT positions than the controls. Consequently, this demonstrates that NOH patients perform worse on the task although their interference is not significantly worse in the supine position.

Cerebral autoregulation maintains constant blood flow to the brain even when large fluctuations in systemic BP occur. It has been established that SBP can range from 80 to 160mmHg and cerebral blood flow will remain constant because of cerebral autoregulation. However, once mean BP drops

below 80mmHg this can cause a decrease in cerebral blood flow velocity [30]. This was demonstrated in multiple system atrophy where presyncopal patients had a decrease in SBP and a corresponding reduction in cerebral oxygenation during HUT [31]. Hunt et al. found a decrease in mean arterial pressure by 46.7 ± 26.5mmHg, which was associated with a reduction cerebral oxygenation by 8.6 ± 6.2% during HUT [32]. In the current study, 13 of the 20 NOH patients had a SBP of <80mmHg during HUT. These BP reductions are likely disrupting the normal regulation of cerebral blood flow in NOH patients. Consequently, monitoring cerebral hemodynamics in individuals with NOH could show an important link between BP and orthostatic symptoms. Future research investigating the changes in cerebral hemodynamics in NOH patients could reveal if these changes are a factor contributing to the impaired IPS and attention. Further work is continuing in our laboratory to address these issues.

A limitation of the current study was that all participants began cognitive testing in the supine position. Randomizing participants to start cognitive testing in either supine or HUT position may be beneficial. This would illustrate if cognitive test scores were affected by repeating the test in the HUT position after the supine position. The current study showed no change in cognitive test scores in NOH patients between the supine and HUT positions, demonstrating no learning effect associated with the tests. The current study did not randomize starting position because our experimental design followed the standardized HUT procedure [15]. An important limitation to note was that the NOH group had significantly lower MMSE and MoCA scores compared to controls, demonstrating a difference in baseline cognitive function. Reduced cognitive function in the patient group could be due to the underlying neurodegenerative disease since patients had conditions such as Parkinson's disease, multiple system atrophy, and Lewy body dementia. Therefore, future research should recruit a population with only PAF patients since this condition is not associated with cognitive changes. Another limitation was that the groups had a modest asymmetry of recruitment based on gender. However, statistical analysis did not reveal a significant effect of gender on our results.

3.5 Conclusion

The current study provides evidence that IPS is significantly reduced in individuals with NOH in both the supine and HUT positions compared to controls. Attention is also reduced in NOH patients compared to controls in the HUT position. These findings demonstrate that NOH patients have deficits in cognitive function compared to controls. NOH patients had no significant change in IPS or attention from the supine to HUT positions. Therefore, patients with NOH should be informed that they may have difficulty with how quickly they process information and that their attention may be reduced. They should be instructed to take caution when performing daily activities in the standing position to help reduce associated risks.

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3.6 References

1. Schatz IJ, Bannister R, Freeman RL, et al. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. In: *Clinical Autonomic Research*. ; 1996. doi:10.1007/BF02291236

2. François C, Biaggioni I, Shibao C, et al. Fall-related healthcare use and costs in neurogenic orthostatic hypotension with Parkinson's disease. *J Med Econ*. 2017. doi:10.1080/13696998.2017.1284668

3. Low PA. Neurogenic orthostatic hypotension: pathophysiology and diagnosis. *Am J Manag Care*. 2015.

4. Heims HC, Critchley HD, Martin NH, Jäger HR, Mathias CJ, Cipolotti L. Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res*. 2006. doi:10.1007/s10286-006-0318-7

5. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013. doi:10.1016/j.cger.2013.07.002

6. Salthouse T. Selective review of cognitive aging. *J Int Neuropsychol Soc*. 2010. doi:10.1017/S1355617710000706

7. Diamond A. 1 Executive functions. *Annu Rev Psychol*. 2013. doi:10.1146/annurev-psych-113011-143750

8. Comalli PE, Wapner S, Werner H. Interference effects of stroop color-word test in childhood, adulthood, and aging. *J Genet Psychol*. 1962. doi:10.1080/00221325.1962.10533572

9. Haworth J, Phillips M, Newson M, Rogers PJ, Torrens-Burton A, Tales A. Measuring Information Processing Speed in Mild Cognitive Impairment: Clinical Versus Research Dichotomy. *J Alzheimer's Dis*. 2016. doi:10.3233/JAD-150791

10. Kuznetsova KA, Maniega SM, Ritchie SJ, et al. Brain white matter structure and

information processing speed in healthy older age. *Brain Struct Funct*. 2016. doi:10.1007/s00429-015-1097-5

11. Torrens-Burton A, Basoudan N, Bayer AJ, Tales A. Perception and Reality of Cognitive Function: Information Processing Speed, Perceived Memory Function, and Perceived Task Difficulty in Older Adults. *J Alzheimer's Dis*. 2017. doi:10.3233/JAD-170599

12. Eckert MA. Slowing down: Age-related neurobiological predictors of processing speed. *Front Neurosci*. 2011. doi:10.3389/fnins.2011.00025

13. Van Schependom J, D'Hooghe MB, Cleynhens K, et al. Reduced information processing speed as primum movens for cognitive decline in MS. *Mult Scler J*. 2015. doi:10.1177/1352458514537012

14. Low PA, Singer W. Update on Management of Neurogenic Orthostatic Hypotension. *Lancet Neurol*. 2008. doi:10.1016/S1474-4422(08)70088-7

15. Low PA, Opfer-Gehrking TL. The autonomic laboratory. *Am J Electroneurodiagnostic Technol*. 1999.

16. Golden CJ. Stroop colour and word test. *Wood Dale, Stoelting Co*. 1978.

17. Baker J, Kimpinski K. An updated normative data set from the autonomic reflex screen representative of Southwestern Ontario. *Can J Physiol Pharmacol*. 2018. doi:10.1139/cjpp-2018-0611

18. Guaraldi. P, Poda R, Calandra-Buonaura G, et al. *Executive Functions Worsen during Orthostatic Challenge in Patients with Neurogenic Orthostatic Hypotension (P03.035)*.; 2013.

19. Poda R, Guaraldi P, Solieri L, et al. Standing worsens cognitive functions in patients with neurogenic orthostatic hypotension. *Neurol Sci*. 2012. doi:10.1007/s10072-011-0746-6

20. Guaraldi P, Poda R, Calandra-Buonaura G, et al. Cognitive function in peripheral autonomic disorders. *PLoS One*. 2014. doi:10.1371/journal.pone.0085020

21. Van Vliet P, Hilt AD, Thijs RD, Van Dijk JG. Effect of orthostatic hypotension on sustained attention in patients with autonomic failure. *J Neurol Neurosurg Psychiatry*. 2016. doi:10.1136/jnnp-2014-309824

22. Torres R V., Elias MF, Crichton GE, Dore GA, Davey A. Systolic orthostatic hypotension is related to lowered cognitive function: Findings from the Maine-Syracuse Longitudinal Study. *J Clin Hypertens*. 2017. doi:10.1111/jch.13095

23. Frewen J, Savva GM, Boyle G, Finucane C, Kenny RA. Cognitive performance in orthostatic hypotension: Findings from a nationally representative sample. *J Am Geriatr Soc*. 2014. doi:10.1111/jgs.12592

24. Bocti C, Pépin F, Tétreault M, et al. Orthostatic hypotension associated with executive dysfunction in mild cognitive impairment. *J Neurol Sci*. 2017. doi:10.1016/j.jns.2017.09.028

25. Matsubayashi K, Okumiya K, Wada T, et al. Postural dysregulation in systolic blood pressure is associated with worsened scoring on neurobehavioral function tests and leukoaraiosis in the older elderly living in a community. *Stroke*. 1997. doi:10.1161/01.STR.28.11.2169

26. Mehrabian S, Duron E, Labouree F, et al. Relationship between orthostatic hypotension and cognitive impairment in the elderly. *J Neurol Sci*. 2010. doi:10.1016/j.jns.2010.08.056

27. Allcock LM, Kenny RA, Mosimann UP, et al. Orthostatic hypotension in Parkinson's disease: Association with cognitive decline? *Int J Geriatr Psychiatry*. 2006. doi:10.1002/gps.1562

28. Denney DR, Lynch SG. The impact of multiple sclerosis on patients' performance on the Stroop Test: Processing speed versus interference. *J Int Neuropsychol Soc*. 2009. doi:10.1017/S1355617709090730

29. Sisco SM, Slonena E, Okun MS, Bowers D, Price CC. Parkinson's disease and the Stroop color word test: processing speed and interference algorithms. *Clin Neuropsychol*. 2016. doi:10.1080/13854046.2016.1188989

30. Novak V, Novak P, Spies JM, Low PA. Autoregulation of Cerebral Blood Flow in Orthostatic Hypotension. *Stroke*. 1998. doi:10.1161/01.STR.29.1.104

31. Suzuki K, Asahina M, Suzuki A, Hattori T. Cerebral Oxygenation Monitoring for Detecting Critical Cerebral Hypoperfusion in Patients with Multiple System Atrophy during the Head-up Tilt Test. *Intern Med*. 2008. doi:10.2169/internalmedicine.47.1094

32. Hunt K, Tachtsidis I, Bleasdale-Barr K, Elwell C, Mathias C, Smith M. Changes in cerebral oxygenation and haemodynamics during postural blood pressure changes in patients with autonomic failure. *Physiol Meas*. 2006. doi:10.1088/0967-3334/27/9/002

Chapter 4

4 The influence of cerebral hemodynamics on information processing speed and attention in patients with neurogenic orthostatic hypotension

4.1 Introduction

Cerebral blood flow requires a complex vascular system to transport oxygen and nutrients to the most important organ, the brain. Cerebral autoregulation is a mechanism used to ensure the brain receives adequate blood supply [1]. Findings have demonstrated that the autonomic nervous system (ANS) is involved in regulating cerebral autoregulation. Alterations to the ANS can cause a significant decrease in cerebral blood flow velocity (CBFv), systolic pressure, and pulse pressure [2]. Biochemical evidence has suggested that the sympathetic nervous system (SNS) affects CBFv [3]. Consequently, damage or modification of the ANS disrupts cerebral autoregulation.

Neurological conditions that involve ANS damage are often associated with cerebral hypoperfusion [4]. Neurogenic orthostatic hypotension (NOH) is a condition that results from autonomic failure and is associated with numerous neurological diseases including Parkinson's disease, Multiple system atrophy, and Lewy body dementia [5]. NOH presents with a severe drop in systolic blood pressure (SBP) ≥ 20mmHg or diastolic blood pressure (DBP) ≥ 10mmHg within three minutes of standing up or head-up tilt (HUT) [6]. Therefore, every time an individual with NOH stands up, they may feel lightheaded, dizzy, weak, and confused. Repeated exposure to orthostatic challenges with severely reduced BP can lead to cerebral hypoperfusion [7], which can provoke deficits in cognitive function.

Common techniques used to assess cerebral hemodynamics include transcranial doppler (TCD) which can measure cerebral blood flow velocity (CBFv) in the middle cerebral arteries and near infrared spectroscopy (NIRS) which measures regional cerebral oxygen saturation (rSO_2) in the frontal lobes. Measures of CBFv and rSO_2 display critical information about the immediate cerebral blood supply. Inadequate cerebral blood supply has been associated with damage to brain tissue and deficits in cognitive function. For example, insufficient CBFv can induce brain damage through ischemic injury [8]. Cerebral hypoperfusion can cause white matter lesions, which can lead to cognitive impairment due to disruptions in the neural networks [9]. It was found that decreased CBFv in individuals with white matter lesions was associated with greater subcortical brain atrophy [10].

Information processing speed (IPS) and attention are two important cognitive domains that are necessary to perform daily activities. IPS is a measure of time between receiving a stimulus and responding to that stimulus [11]. Attention is the ability to attend to a stimulus of interest without being distracted by surrounding stimuli [12]. Even in the early stages of neurological diseases such multiple sclerosis (MS), IPS is severely impaired [13–15]. Previous research found that individuals with NOH have decreased cognitive function, including reduced executive functions [16], immediate visual memory, and global cognitive functioning [17]. Patients with pure autonomic failure (PAF) presented with deficits of executive functioning, speed, and attention [18]. Individuals with Lewy body dementia and orthostatic hypotension had worse visuospatial and attentional dysfunction even after adjusting for cognitive impairment. These individuals also had reduced CBFv in the occipital and temporal lobes [19]. It is evident that neurological conditions associated with NOH have greater impairment of cognitive function. Additionally, there are a limited number of studies examining the role of CBFv, rSO_2, and BP in NOH patients. Further characterization of cerebral hemodynamics in these patient groups are likely to provide key insights into the reason why these individuals suffer from greater cognitive deficits. Consequently, further research is important to determine if the reduction in IPS and attention are affected by changes in cerebral hemodynamics.

The objectives of the current study were two-fold. The first objective was to determine the effects of postural blood pressure changes in NOH verses control subjects on cerebral hemodynamic parameters (i.e. CBFv and rSO_2). The second objective was to investigate cerebral hemodynamics during tests of IPS and attention.

It was hypothesized that NOH patients would experience a reduction in CBFv and rSO_2 in the HUT position compared to the supine position, whereas controls would experience no changes in CBFv and rSO_2 with the change in position.

4.2 Methods

4.2.1 Participants

Forty-three participants were enrolled in the study. Three NOH patients were excluded because they were unable to remain in the upright position for the duration of testing. Of the 40 participants, 20 had a diagnosis of NOH provided by a neurologist and 20 were healthy age-matched control subjects. To diagnose NOH the neurologist evaluated the results of an autonomic reflex screen, completed a neurological examination, and collected a medical history. A criterion of SBP $\geq$ 30mmHg was used to determine the diagnosis of NOH rather than the more liberal criteria (i.e. SBP $\geq$ 20mmHg or DBP $\geq$ 10mmHg). This was to reduce the false positive rate from 5% to 1 % [20]. Participants were excluded from the study if they were taking medication that could interfere with the regulation of BP or heart rate (HR), clinically significant coronary artery disease, presence of nerve damage in the peripheral nervous system, failure of other organ systems or diseases that can affect autonomic function, visual problems, the inability to remain in the upright position for the duration of testing. Testing was performed in the autonomic lab located at the University Hospital in London, Ontario. Written informed consent was provided before participants were enrolled in the study. The Health Science Research Ethics Board at Western University granted ethical approval for the current study.

4.2.2 Physiological Measures

A standardized autonomic reflex screen (ARS) was used to assess the integrity of the ANS [21]. The ARS evaluates the quality of the postganglionic sympathetic sudomotor axons using the quantitative sudomotor axon reflex test, cardiovagal function using a deep breathing test and the Valsalva maneuver, and adrenergic function using the Valsalva maneuver and head-up tilt (HUT).

During testing participants were connected to a HR monitor (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems, Inc., Branford, CT) attached using electrocardiography electrodes (Ambu® Blue Sensor SP, Glen Burnie, MD). Electrode placement was as follows; one just below the right clavicle, one just below the left clavicle, and one on the lower chest just above and left of the umbilicus. Participants were also connected to a beat-to-beat BP monitor (BMEYE Nexfin device, Amsterdam, Netherlands) fastened on the middle finger. TCD probes at 2MHz were positioned over the left and right middle cerebral arteries to continuously measure CBFv (Multigon 500M, DWL MultiDop-T, Neuroscan). The probes were fastened in place with an adjustable plastic headpiece. The strongest CBFv signal on either the left or right side was used for analysis. NIRS was used to measure rSO_2 in the left and right frontal lobes (NIRS ForeSight® cerebral oximeter, CASMED, Branford, CT). WR TestWorks TM software (WR Medical Electronics Co., Stillwater, MN) was used to record data.

4.2.3 Cognitive Measures

The Mini-Mental State Examination and the Montreal Cognitive Assessment were used to clinically screen participants to ensure they did not have any cognitive impairment. Two paper based neuropsychological tests were used to assess cognitive function; the oral version of the Symbol Digit Modalities Test (SDMT) to measure IPS and the Stroop test to measure attention. The SDMT is a sheet of paper with a key at the top of the page containing the numbers 1 to 9 and each number corresponds with a symbol below. Underneath the key there are 8 rows containing 15 symbols each. Participants were given 90 seconds to say out loud as quickly as possible the digit associated with each symbol [22]. The Stroop test consists of three subtests each containing 100 words of colours (purple, blue, red, green, and brown) and lasting 45 seconds in duration. The first

test is composed of words of colours written in black ink. The second test is composed of words of colours printed in the same colour ink as the word. In the third test the words of colours are printed in a colour of ink that does not correspond with the word. For example, the word blue could be printed in green ink. During this trial the participant must say the colour of the ink and inhibit themselves from saying the word. The number of correct responses and the number of errors were recorded for all tests.

Before cognitive testing commenced 90 seconds was recorded in the supine position to provide baseline resting values for HR, MAP, CBFv, and rSO_2. In the supine position cognitive testing was completed in the following order; SDMT, Stroop 1, SDMT, Stroop 2, SDMT, Stroop 3, SDMT. The bed was then tilted to the HUT position (70 degrees upright) and 90 seconds was recorded in this position before cognitive testing began. Cognitive testing in the HUT position was as follows; Stroop 1, Stroop 2, Stroop 3, SDMT. Total time in the upright position was about seven minutes. Upon completion of cognitive testing the bed was tilted back to the supine position and the participant was given five minutes of recovery.

4.2.4 Statistical Analysis

Characteristics such as age, BMI, HR and BP were compared between groups using independent-samples t-tests. Cognitive testing in the supine and HUT positions was compared using a two-way mixed ANOVA. CBFv, rSO_2, and MAP were measured during baseline, cognitive testing, and HUT and were analyzed using a two-way mixed ANOVA. These measures were also compared between NOH and controls using independent-samples t-tests. Repeated measures with a Bonferroni correction was used to compare each position to baseline. All data are expressed as mean ± SD. A significance level of $p < 0.05$ was used. SPSS statistics software, Version 25, Manufactured by International Business Management (IBM) Corporation was used for the statistical analysis.

4.3 Results

4.3.1 Participants

Various characteristics of NOH patients and controls are presented in Table 3. Participants with NOH had the following associated conditions; Parkinson's disease (n=11), multiple system atrophy (n=3) and early Lewy body dementia based on preganglionic dysfunction (n=1) and 5 participants had a diagnosis of idiopathic NOH. Controls and NOH patients were matched based on age, BMI, and education level. There were no significant differences found based on gender even though there was a slight difference in the female to male ratios. There was no significant difference in resting HR, resting BP, or the change in HR between groups. The change in SBP during HUT was significantly greater in NOH patients (64.11 ± 18.96) than controls (-5.69 ± 7.65).

Table 3. Participant Characteristics

Characteristic	Control (mean ± SD)	NOH (mean ± SD)	P-value
Age (years)	64.50 ± 9.25	69.55 ± 7.43	p = 0.065
Gender (F:M)	12:8	8:12	
Education Level (>high school)	16	13	
BMI (kg/m^2)	21.50 ± 2.51	22.02 ± 4.71	p = 0.67
Resting HR (bpm)	69.49 ± 11.91	74.28 ± 12.85	p = 0.228
ΔHR during HUT (bpm)	15.04 ± 6.27	12.12 ± 8.60	p = 0.227
Resting SBP (mmHg)	128.12 ± 18.75	139.50 ± 23.72	p = 0.101
ΔSBP during HUT (mmHg)	-5.69 ± 7.65	-64.11 ± 18.96 *	p < 0.001*

BMI: body mass index, bpm: beats per minute, HR: heart rate, HUT: head-up tilt, mmHg: millimeters of mercury, NOH: neurogenic orthostatic hypotension, SBP: systolic blood pressure.
* Represents significant difference of $p < 0.001$.

4.3.2 SDMT and Stroop Test Scores

NOH patients scored significantly worse on the SDMT in both the supine and HUT positions compared to the controls ($p < 0.001$), demonstrating significantly slower IPS. NOH patients had no significant difference in IPS from supine to HUT, whereas controls had a significant increase in IPS in the HUT position compared to supine. NOH patients also scored significantly worse on the Stroop test in the HUT position compared to controls, indicating worse attention. Controls had significantly better attention in the HUT position compared to the supine position, whereas the NOH patients had no significant difference (Table 4).

Table 4. Cognitive test scores in Supine and HUT Positions

Cognitive Test	Position	Control (mean ± SD)	NOH (mean ± SD)	P-value
SDMT	Supine	63.55 ± 9.96	43.20 ± 15.26	p < 0.001*
	HUT	69.90 ± 12.02	42.90 ± 14.33	p < 0.001*
Stroop Test	Supine	-14.01 ± 8.96	-12.38 ± 9.32	p = 0.592
	HUT	-8.68 ± 7.13	-14.86 ± 8.96	p = 0.029*

HUT: head-up tilt, NOH: neurogenic orthostatic hypotension, SDMT: symbol digit modalities test.

* Represents significant difference between groups

4.3.3 Cerebral Blood Flow Velocity

Baseline values for CBFv were not significantly different between groups. Controls had a resting CBFv of 50.78 ± 10.79cm/sec and NOH patients of 47.83 ± 10.77cm/sec. During the Stroop test (Figure 10) and the SDMT (Figure 11) in the supine position there was no significant change in CBFv from baseline in either group. NOH patients had a significant decrease in CBFv by -6.04cm/sec during HUT compared to baseline, whereas the control group had no significant change. During HUT, CBFv decreased significantly during the Stroop test by -6.24cm/sec and during the SDMT by -7.42cm/sec compared to baseline in NOH patients, whereas controls had no significant change in CBFv. CBFv was significantly different between NOH and controls during HUT, during Stroop testing in the supine and HUT positions and during the SDMT in the HUT position.

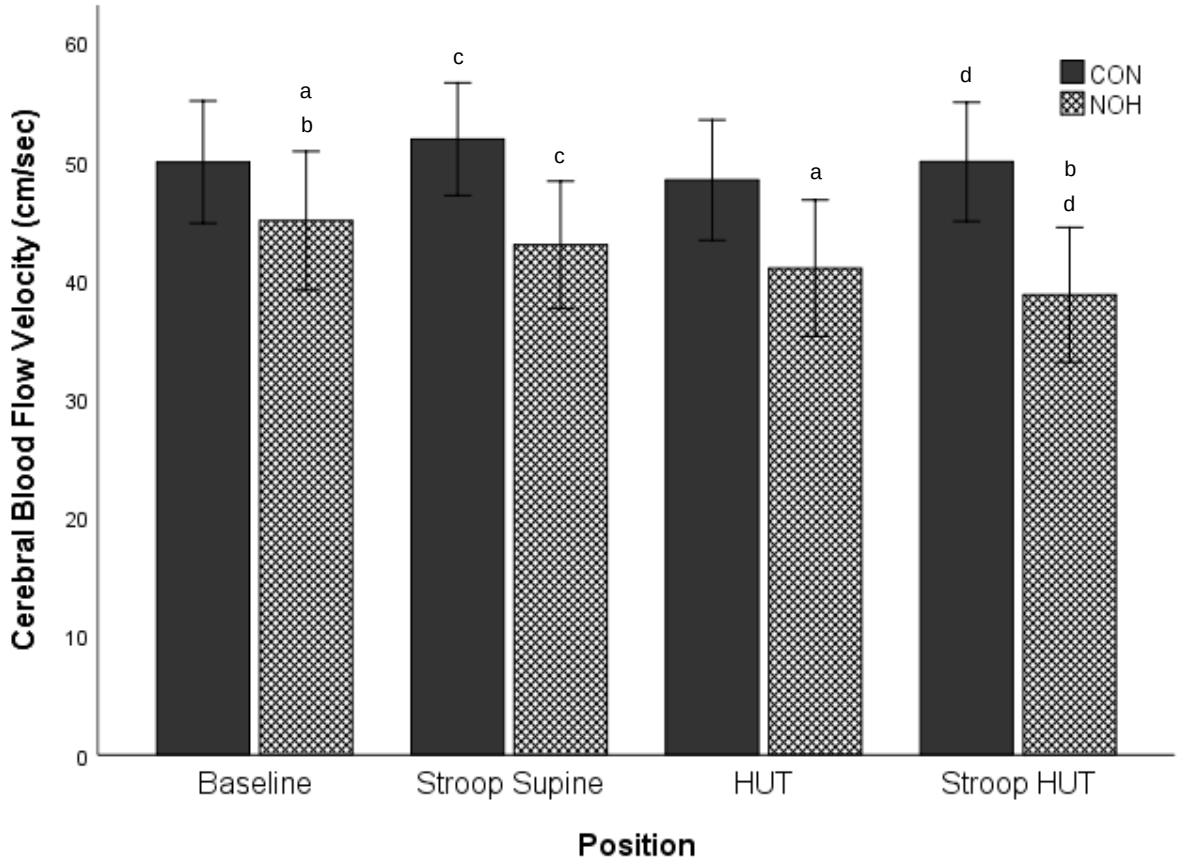

Figure 10. Cerebral Blood Flow Velocity during Baseline, Stroop Testing, and Head-up Tilt

There was a significant decrease in CBFv from baseline compared to HUT and from baseline compared to Stroop test in the HUT position in the NOH group. Controls had no significant changes in CBFv. There were differences in CBFv between groups during Stroop testing in the supine and HUT positions. CON: control, HUT: head-up tilt, NOH: neurogenic orthostatic hypotension. a: $p = 0.007$ between baseline and HUT; b: $p = 0.003$ between baseline and HUT Stroop test; c: $p = 0.017$ between NOH and CON during supine Stroop test; d: $p = 0.006$ between NOH and CON during HUT Stroop test.

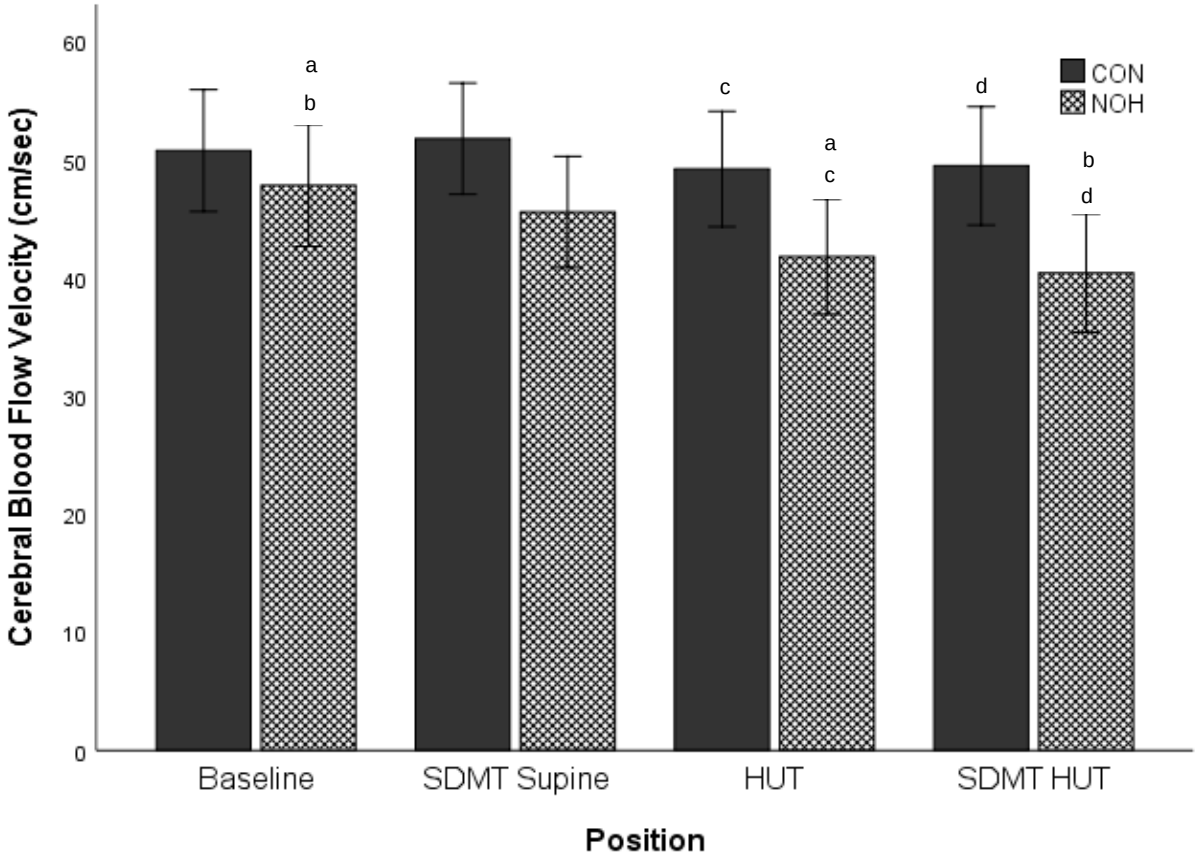

Figure 11. Cerebral Blood Flow Velocity during Baseline, SDMT Testing, and Head-up Tilt

There was a significant decrease in CBFv from baseline compared to HUT and from baseline compared to SDMT in the HUT position in the NOH group. Controls had no significant changes in CBFv. There were differences in CBFv between groups during HUT and HUT SDMT. CON: control, HUT: head-up tilt, NOH: neurogenic orthostatic hypotension, SDMT: symbol digit modalities test. a: $p = 0.003$ between baseline and HUT; b: $p = 0.002$ between baseline and HUT SDMT; c: $p = 0.036$ between NOH and CON during HUT; d: $p = 0.014$ between NOH and CON during HUT SDMT.

4.3.4 Regional Cerebral Oxygen Saturation

At baseline there was no significant difference in rSO_2 between groups. Baseline rSO_2 was 69.74 ± 3.55% for controls and 70.31 ± 4.58% for NOH patients. When cognitive testing commenced in the supine position rSO_2 increased significantly in both groups by 3.78% and 1.55% during the Stroop test (Figure 12) and 4.25% and 1.85% during SDMT (Figure 13) in control and NOH groups respectively. During HUT, rSO_2 decreased significantly from baseline by -1.85% in the NOH group and no significant change in the control group. During cognitive testing in the HUT position, NOH patients had a significant decrease in rSO_2 during the Stroop test by -5.87% and during the SDMT by -5.48% compared to baseline. The controls had no significant change in rSO_2 during cognitive testing in the HUT position compared to baseline. There were significant differences in rSO_2 between NOH and controls during the HUT Stroop test and HUT SDMT.

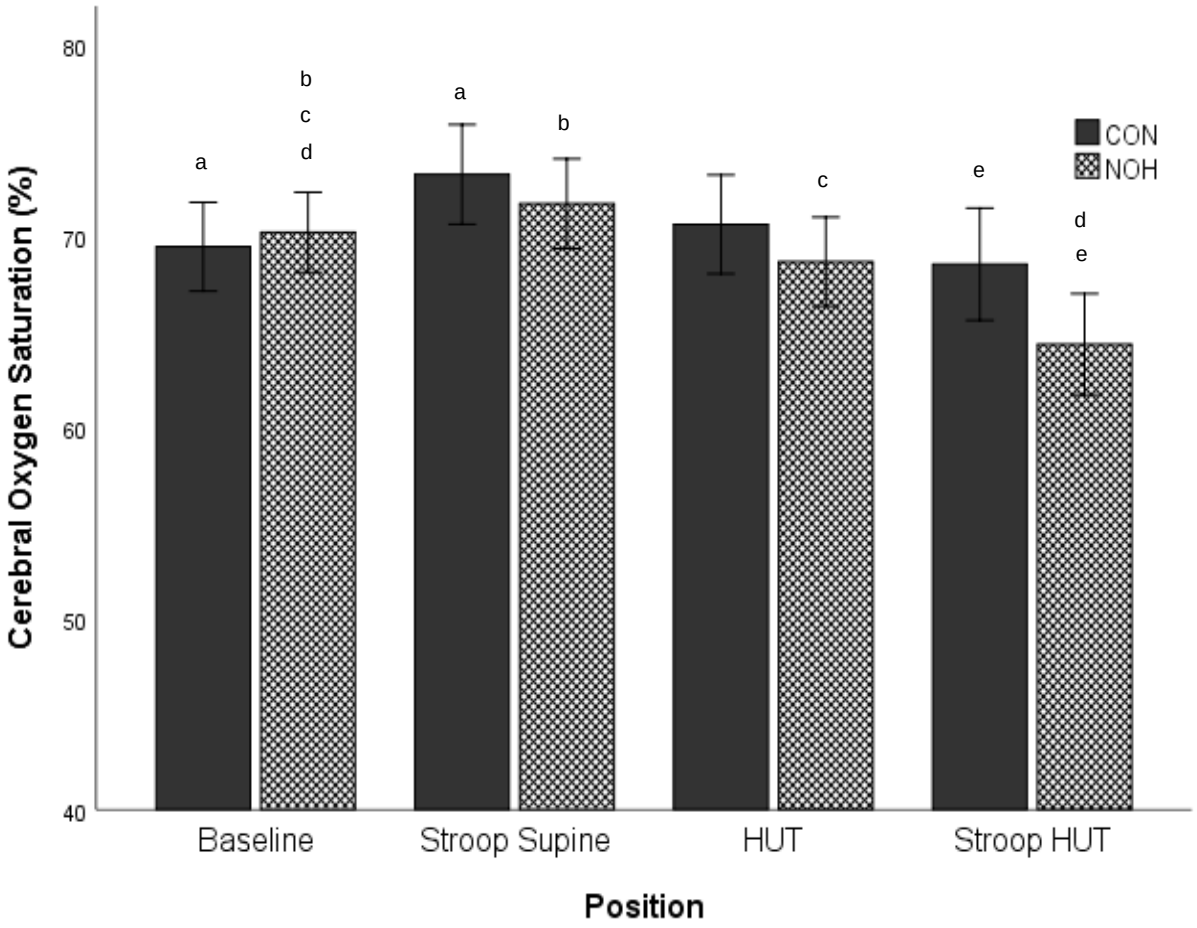

Figure 12. Cerebral Oxygen Saturation during Baseline, Stroop Testing, and Head-up Tilt

Controls and NOH had a significant increase in rSO_2 between baseline and Stroop testing in the supine position. NOH patients experienced a significant decrease in rSO_2 between baseline and HUT and between baseline and Stroop testing in the HUT position. There was a difference in rSO_2 between groups during HUT Stroop test. NOH: neurogenic orthostatic hypotension, CON: control, HUT: head-up tilt. a: $p = 0.00009$ between baseline and Stroop testing in the supine position; b: $p = 0.019$ between baseline and Stroop testing in the supine position; c: $p = 0.041$ between baseline and HUT positions; d: $p = 0.0001$ between baseline and Stroop testing in the HUT position; e: $p = 0.029$ between NOH and CON during the HUT Stroop test.

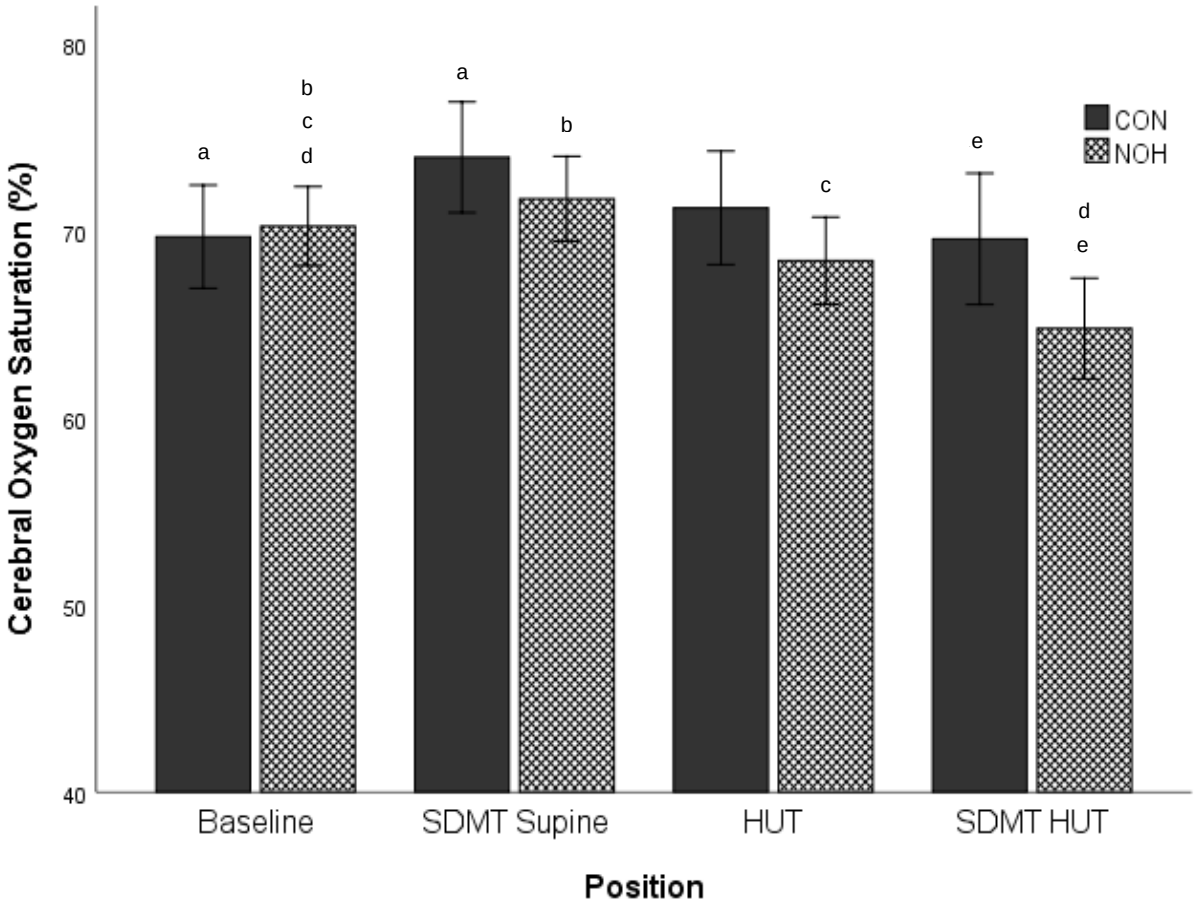

Figure 13. Cerebral Oxygen Saturation during Baseline, SDMT Testing, and Head-up Tilt

Controls and NOH had a significant increase in rSO_2 between baseline and SDMT testing in the supine position. NOH patients experienced a significant decrease in rSO_2 between baseline and HUT and between baseline and HUT SDMT. There was a difference in rSO_2 between groups during HUT SDMT. CON: control, HUT: head-up tilt, NOH: neurogenic orthostatic hypotension, SDMT: symbol digit modalities test. a: $p = 0.003$ between baseline and supine SDMT testing in CON; b: $p = 0.043$ between baseline and supine SDMT testing in NOH; c: $p = 0.025$ between baseline and HUT in NOH; d: $p = 0.004$ between baseline and HUT SDMT testing in NOH; e: $p = 0.013$ between NOH and CON during the HUT SDMT.

4.3.5 Mean Arterial Pressure

Mean arterial pressure (MAP) at baseline was not significantly different between groups. Resting MAP for controls was 94.02 ± 15.01mmHg and 92.87 ± 19.66mmHg for NOH patients. There was no significant change in MAP during cognitive testing in the supine position compared to baseline in either group. During HUT there was a significant decrease in MAP from baseline in the NOH group, MAP dropped by -24.62mmHg, whereas there was no significant change in controls. MAP remained significantly reduced from baseline during the Stroop test in the HUT position (Figure 14) and the SDMT in the HUT position (Figure 15), MAP decreased by -19.25mmHg and -24.02mmHg, respectively. There was no significant change in MAP in the control group during cognitive testing in the HUT position. MAP was significantly different between groups during HUT and during HUT Stroop and HUT SDMT.

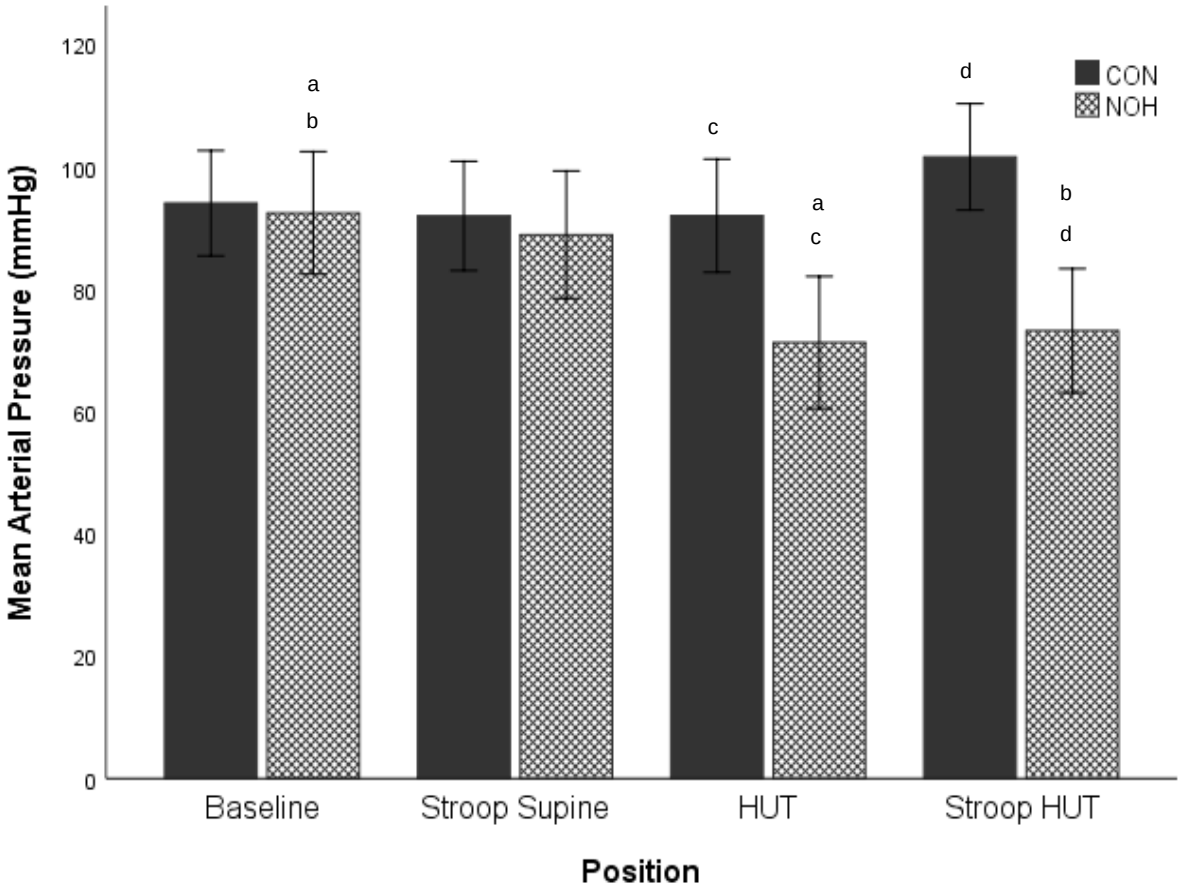

Figure 14. Mean Arterial Pressure during Baseline, Stroop Testing and Head-up Tilt

NOH patients experienced a significant decrease in MAP between baseline and HUT and between baseline and HUT Stroop testing. Controls had no significant changes in MAP. There were differences in MAP between groups during HUT and HUT Stroop test. CON: control, HUT: head-up tilt, NOH: neurogenic orthostatic hypotension. a: $p = 0.004$ between baseline and HUT; b: $p = 0.035$ between baseline and HUT Stroop testing; c: $p = 0.006$ between NOH and CON during HUT; d: $p = 0.0002$ between NOH and CON during the HUT Stroop test.

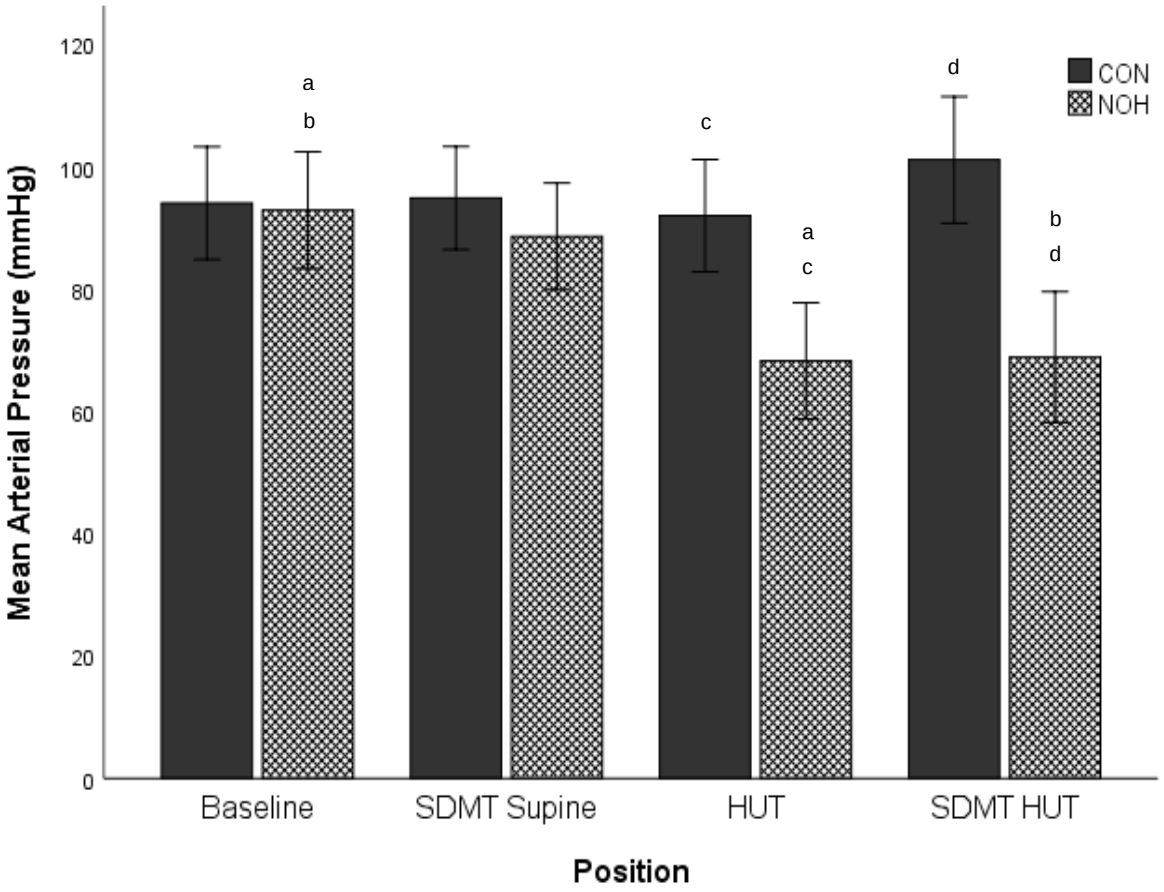

Figure 15. Mean Arterial Pressure during Baseline, SDMT Testing and Head-up Tilt

NOH patients experienced a significant decrease in MAP between baseline and HUT and between baseline and HUT SDMT testing. Controls had no significant changes in MAP. There were differences in MAP between groups during HUT and HUT SDMT. CON: control, HUT: head-up tilt, NOH: neurogenic orthostatic hypotension, SDMT: symbol digit modalities test. a: $p = 0.0004$ between baseline and HUT; b: $p = 0.01$ between baseline and HUT SDMT testing; c: $p = 0.001$ between NOH and CON during HUT; d: $p = 0.0001$ between NOH and CON during HUT SDMT.

4.4 Discussion

Findings demonstrated that NOH patients had significantly impaired CBFv, rSO_2, and MAP during HUT. NOH patients had a significant decrease in these three measurements during HUT compared to baseline, whereas controls had no significant difference. Baseline values for mean CBFv, rSO_2, and MAP were not significantly different between groups. This revealed that the two groups had similar resting hemodynamic values. These measures differed significantly between groups during the orthostatic challenge and during cognitive testing. Previous research analyzing changes in CBFv, rSO_2, and MAP presented similar findings [23–27]. A five minute orthostatic challenge produced a larger decrease in MAP and rSO_2 in patients with sympathetic failure than controls [25]. A study assessed changes in cerebral hemodynamics during HUT in 18 patients with autonomic failure and 10 controls. Results showed that 10 minutes of HUT caused a greater reduction in MAP (-46.7 ± 26.5mmHg) and cerebral oxygenation (-8.6 ± 6.2%) in patients than controls [28]. It was found that 13 individuals with orthostatic hypotension had decreased MAP (-19.1 ± 11.6mmHg) and cerebral oxygenation (-5.4 ± 4.2%) during HUT [23]. During HUT, individuals with multiple system atrophy who experienced presyncopal symptoms had a significant decline in SBP and a corresponding reduction in rSO_2 [26]. Therefore, it has been established that individuals who experience a significant drop in BP upon standing likely have profound changes in cerebral hemodynamics.

An interesting finding was that rSO_2 increased significantly from baseline in both the NOH patients and controls when cognitive testing commenced in the supine position. This increase in rSO_2 with no positional change reveals that cognitive testing likely triggered the rise in rSO_2. Attention and IPS was required to complete the cognitive tasks, consequently the region of the brain responsible for these cognitive functions had an increased metabolic demand. Evidence has supported the finding that cognitive testing causes an increase in rSO_2. It has been stated that increased in rSO_2 demonstrates increased neural activity, which is necessary during cognitive testing. A group of highly fit women had better cognitive performance than a group of low fit women likely due to the fact that the highly fit women also experienced a greater increase in rSO_2 [29]. In the current study, NOH patients had lower rSO_2 during cognitive testing and had worse cognitive test scores than controls. Consequently, reduced rSO_2 could be contributing to impaired cognitive function.

A study assessing patients undergoing chronic hemodialysis demonstrated that rSO_2 was significantly lower in cognitively impaired patients compared to cognitively normal patients (48 ± 9 vs. 57 ± 10%, p = 0.01) [30]. It is apparent that reduced rSO_2 is related to changes in cognitive function.

The second objective of the study was to assess cerebral hemodynamics and investigate if it changes during cognitive testing in the supine and HUT positions. The current study provides insight that NOH patients had an alteration in cerebral hemodynamics which can help provide a reason as to why these individuals also have decreased IPS and attention compared to controls. NOH patients had a significant decrease in CBFv and rSO_2 compared to baseline during cognitive testing in the HUT position suggesting that during this time oxygen availability was insufficient to meet the metabolic demands of the cognitive processes [31]. Compared to controls, NOH patients had significantly reduced CBFv and rSO_2 during cognitive testing in the HUT position and reduced CBFv during the Stroop test in the supine position. Cerebral hypoperfusion occurs in the upright position in NOH patients and is likely playing a role in why they have impaired cognitive functioning. Surprisingly, NOH patients had no significant difference in IPS or attention when they changed position from supine to HUT but compared to controls had significantly worse IPS and attention. Therefore, NOH patients had impaired IPS and attention regardless of their position. These findings are in line with a study that assessed 10 patients with symptomatic NOH and 10 healthy controls. They found that NOH patients had no significant difference in sustained attention from the supine to HUT position but the controls did have a significantly better attention in HUT position [32]. It is important to note that controls had an increase in CBFv and a significant increase in rSO_2 during cognitive testing in the supine position compared to baseline values. As well, controls also had an increase in CBFv during cognitive testing in the HUT position compared to HUT values. These findings indicate that cerebral hemodynamic values may increase during cognitive tasks since they trigger an increase in cognitive activation.

In the current study, controls had a significant increase in attention and IPS in the HUT position compared to supine. The activity of standing results in an increase in sympathetic activation which

may contribute to a brief improvement in cognitive function. When cognitive tasks are performed they elicit greater sympathetic nervous system activation [33]. It has been stated that greater sympathetic activity is associated with improved attention processing and greater parasympathetic activity is an indicator of increased selective attention [34]. Given that NOH patients have no improvement or possibly worse cognitive function in the standing position reveals that the ANS damage in this group of individuals that results in impaired sympathetic activation could result in this cognitive dysfunction. This provides evidence that deficits in cognitive function experience by NOH patients are partly due to direct ANS damage

Our study proposes that NOH patients have impaired cognitive function independent of position. NOH patients experience repeated exposure to cerebral hypoperfusion. This could be related to why they have a persistent deficit in cognitive functioning. When SBP drops below 80mmHg, cerebral autoregulation may not be able to function properly resulting in decreased cerebral blood flow. Individuals with neutrally mediated syncope are close to losing consciousness when SBP drops to 60mmHg, at this time they also experience a large reduction in mean CBFv to 30cm/s [35]. It has been stated that cerebral hypoperfusion has negative consequences on brain structures [8,9]. Therefore, daily exposure to reduced CBFv, rSO_2, and MAP elicited by an orthostatic challenge could damage the integrity of neural connections involved in cognitive processes. For example, cerebral white matter damage has been strongly associated with decreased executive functions and IPS [36]. Alterations in BP and cerebral hemodynamics are likely a contributing factor to the decline in cognitive function.

The current study consisted of a diverse patient population, but as a group these patients had a homogeneous drop in BP as a result of autonomic function. Patients had a diagnosis of NOH but had different associated conditions, such as Parkinson's disease, multiple system atrophy, and Lewy body dementia. Future studies could repeat this protocol with a specific group of patients, for example Parkinson's disease patients with NOH. This could provide evidence if the changes in cerebral hemodynamics and cognitive function are related to NOH or the associated condition. Another limitation of the study was that some participants only had unilateral TCD recordings if a

signal could not be obtained bilaterally. Bilateral recordings are important since CBFv responses during cognitive tasks strongly differ between hemispheres [37,38]. Fortunately, most of the participants in the current study had bilateral recording but not all, consequently we measured the strongest recording obtained. Therefore, future studies should attempt to attain bilateral TCD recordings on all participants when assessing cognitive function.

4.5 Conclusion

The current study has provided evidence that NOH patients experience decreased CBFv and rSO_2 during an orthostatic challenge which could be a contributing factor to impaired IPS and attention. NOH patients experienced reduced IPS and attention in both the supine and HUT positions compared to controls and have no significant difference in these cognitive processes with a change in position. Therefore, this decline in cognitive function in NOH patients is likely in part a result of daily exposure to hypoperfusion and damage of the ANS.

4.6 References

1. Lagi A, Bacalli S, Cencetti S, Paggetti C, Colzi L. Cerebral autoregulation in orthostatic hypotension. A transcranial Doppler study. *Stroke*. 1994. doi:10.1161/01.STR.25.9.1771

2. Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, Levine BD. Autonomic neural control of dynamic cerebral autoregulation in humans. *Circulation*. 2002. doi:10.1161/01.CIR.0000031798.07790.FE

3. Mitchell DA, Lambert G, Secher NH, Raven PB, van Lieshout J, Esler MD. Jugular venous overflow of noradrenaline from the brain: A neurochemical indicator of cerebrovascular sympathetic nerve activity in humans. *J Physiol*. 2009. doi:10.1113/jphysiol.2008.167999

4. Espay AJ, LeWitt PA, Hauser RA, Merola A, Masellis M, Lang AE. Neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease and related synucleinopathies: prioritisation of treatment targets. *Lancet Neurol*. 2016. doi:10.1016/S1474-4422(16)30079-5

5. Baker J, Kimpinski K. Management of Supine Hypertension Complicating Neurogenic Orthostatic Hypotension. *CNS Drugs*. 2017. doi:10.1007/s40263-017-0453-9

6. Schatz IJ, Bannister R, Freeman RL, et al. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. In: *Clinical Autonomic Research*. 1996. doi:10.1007/BF02291236

7. Fukuoka S, Hayashida K, Nishiooeda Y, et al. Cerebral hypoperfusion in orthostatic hypotension with globally denervated myocardium. *J Nucl Med*. 1996.

8. Fantini S, Sassaroli A, Tgavalekos KT, Kornbluth J. Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics*. 2016. doi:10.1117/1.NPh.3.3.031411

9. Marshall RS. Effects of altered cerebral hemodynamics on cognitive function. *J Alzheimers Dis*. 2012. doi:10.3233/JAD-2012-120949

10. Appelman AP, van der Graaf Y, Vincken KL, et al. Total cerebral blood flow, white matter lesions and brain atrophy: the SMART-MR study. *J Cereb Blood Flow Metab*. 2008. doi:10.1038/sj.jcbfm.9600563

11. Haworth J, Phillips M, Newson M, Rogers PJ, Torrens-Burton A, Tales A. Measuring Information Processing Speed in Mild Cognitive Impairment: Clinical Versus Research Dichotomy. *J Alzheimer's Dis*. 2016. doi:10.3233/JAD-150791

12. Diamond A. 1 Executive functions. *Annu Rev Psychol*. 2013. doi:10.1146/annurev-psych-113011-143750

13. Bobholz JA, Rao SM. Cognitive dysfunction in multiple sclerosis: A review of recent developments. *Curr Opin Neurol*. 2003. doi:10.1097/00019052-200306000-00006

14. Van Schependom J, D'Hooghe MB, Cleynhens K, et al. Reduced information processing speed as primum movens for cognitive decline in MS. *Mult Scler J*. 2015. doi:10.1177/1352458514537012

15. Chiaravalloti ND, Deluca J. Cognitive impairment in multiple sclerosis - neurologie. *Lancet Neurol*. 2008;7(12):1139-1151. doi:S1474-4422(08)70259-X

16. Guaraldi P, Poda R, Calandra-Buonaura G, et al. Cognitive function in peripheral autonomic disorders. *PLoS One*. 2014. doi:10.1371/journal.pone.0085020

17. Poda R, Guaraldi P, Solieri L, et al. Standing worsens cognitive functions in patients with neurogenic orthostatic hypotension. *Neurol Sci*. 2012. doi:10.1007/s10072-011-0746-6

18. Heims HC, Critchley HD, Martin NH, Jäger HR, Mathias CJ, Cipolotti L. Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res*. 2006. doi:10.1007/s10286-006-0318-7

19. Robertson AD, Messner MA, Shirzadi Z, et al. Orthostatic hypotension, cerebral hypoperfusion, and visuospatial deficits in Lewy body disorders. *Park Relat Disord*. 2016. doi:10.1016/j.parkreldis.2015.11.019

20. Low PA, Singer W. Management of neurogenic orthostatic hypotension: An update. *Lancet Neurol*. 2008. doi:10.1016/S1474-4422(08)70088-7

21. Low PA, Opfer-Gehrking TL. The autonomic laboratory. *Am J Electroneurodiagnostic Technol*. 1999.

22. Smith A. Symbol Digit Modalities Test: Manual. *West Psychol Sci Los Angeles West Psychol Serv*. 1982.

23. Bachus E, Holm H, Hamrefors V, et al. Monitoring of cerebral oximetry during head-up tilt test in adults with history of syncope and orthostatic intolerance. *EP Eur*. 2017. doi:10.1093/europace/eux298

24. Bondar RL, Dunphy PT, Moradshahi P, et al. Cerebrovascular and cardiovascular responses to graded tilt in patients with autonomic failure. *Stroke*. 1997. doi:10.1161/01.STR.28.9.1677

25. Harms MPM, Colier WNJM, Wieling W, Lenders JWM, Secher NH, Van Lieshout JJ. Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure. *Stroke*. 2000. doi:10.1161/01.STR.31.7.1608

26. Suzuki K, Asahina M, Suzuki A, Hattori T. Cerebral Oxygenation Monitoring for Detecting Critical Cerebral Hypoperfusion in Patients with Multiple System Atrophy during the Head-up Tilt Test. *Intern Med*. 2008. doi:10.2169/internalmedicine.47.1094

27. Lucas SJE, Tzeng YC, Galvin SD, Thomas KN, Ogoh S, Ainslie PN. Influence of changes in blood pressure on cerebral perfusion and oxygenation. *Hypertension*. 2010. doi:10.1161/HYPERTENSIONAHA.109.146290

28. Hunt K, Tachtsidis I, Bleasdale-Barr K, Elwell C, Mathias C, Smith M. Changes in cerebral oxygenation and haemodynamics during postural blood pressure changes in patients with autonomic failure. *Physiol Meas*. 2006. doi:10.1088/0967-3334/27/9/002

29. Albinet CT, Mandrick K, Bernard PL, Perrey S, Blain H. Improved cerebral oxygenation response and executive performance as a function of cardiorespiratory fitness in older women: A fNIRS study. *Front Aging Neurosci*. 2014. doi:10.3389/fnagi.2014.00272

30. Kovarova L, Valerianova A, Kmentova T, Lachmanova J, Hladinova Z, Malik J. Low Cerebral Oxygenation Is Associated with Cognitive Impairment in Chronic Hemodialysis Patients. *Nephron*. 2018. doi:10.1159/000487092

31. Ando S, Kokubu M, Yamada Y, Kimura M. Does cerebral oxygenation affect cognitive function during exercise? *Eur J Appl Physiol*. 2011. doi:10.1007/s00421-011-1827-1

32. Van Vliet P, Hilt AD, Thijs RD, Van Dijk JG. Effect of orthostatic hypotension on sustained attention in patients with autonomic failure. *J Neurol Neurosurg Psychiatry*. 2016. doi:10.1136/jnnp-2014-309824

33. Berntson GG, Cacioppo JT, Fieldstone A. Illusions, arithmetic, and the bidirectional modulation of vagal control of the heart. *Biol Psychol*. 1996. doi:10.1016/S0301-0511(96)05197-6

34. Giuliano RJ, Karns CM, Bell TA, et al. Parasympathetic and sympathetic activity are associated with individual differences in neural indices of selective attention in adults. *Psychophysiology*. 2018. doi:10.1111/psyp.13079

35. Novak P. Cerebral Blood Flow, Heart Rate, and Blood Pressure Patterns during the Tilt Test in Common Orthostatic Syndromes. *Neurosci J*. 2016. doi:10.1155/2016/6127340

36. Jacobs HIL, Leritz EC, Williams VJ, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: The impact of vascular health. *Hum Brain Mapp*. 2013. doi:10.1002/hbm.21412

37. Vingerhoets G, Stroobant N. Lateralization of cerebral blood flow velocity changes during cognitive tasks: A simultaneous bilateral transcranial Doppler study. *Stroke*. 1999. doi:10.1161/01.STR.30.10.2152

38. Boban M, Črnac P, Junaković A, Garami Z, Malojčić B. Blood flow velocity changes in anterior cerebral arteries during cognitive tasks performance. *Brain Cogn*. 2014. doi:10.1016/j.bandc.2013.10.006

Chapter 5

5 General Discussion

This thesis aimed to determine if there was a relationship between NOH patients, cerebral hemodynamics, IPS and attention. Analysis of the data revealed that NOH patients had significant differences in cerebral hemodynamics and cognitive functioning compared to healthy controls. The findings of the current thesis support some and reject some of the hypotheses made.

5.1 Supported and Rejected Hypotheses

The first hypothesis that NOH patients would experience a decline in IPS and attention in the HUT position due to the associated reduction in postural BP compared to the supine position was rejected. Even though during HUT NOH patients had a large drop in SBP they experienced no significant difference in IPS or attention between the supine and HUT positions. The hypothesis that control subjects would have increased IPS and attention in the HUT position compared to the supine position was accepted. It was found that controls had significantly faster IPS and better attention in the HUT position compared to supine. This could be due to the fact that they experience a burst of sympathetic activity when they stand up, which could increase cognitive function. NOH patients have ANS damage therefore they lack the burst of sympathetic activity when they stand up and consequently do not experience an increase in IPS and attention. Overall, NOH patients had worse IPS in the supine and HUT positions compared to controls. As well, NOH patients had worse attention in the HUT position compared to controls.

The second hypothesis predicted that the magnitude of the postural SBP drop would correspond with a worsening in IPS and attention. This hypothesis was rejected since no correlation was found between the postural SBP drop and IPS or attention in either NOH patients or controls. Therefore, the drop in SBP was not related to worse performance on the cognitive tasks.

The third hypothesis that NOH patients would experience a reduction in CBFv and rSO_2 in the HUT position compared to the supine position was accepted. NOH patients experienced a significant reduction in both CBFv and rSO_2 during the HUT position, therefore these measures were also reduced during cognitive testing in the HUT position. As well, the hypothesis that controls would experience no change in CBFv and rSO_2 from the supine to HUT position was also accepted. This finding indicates that controls have adequate cerebral blood supply during cognitive testing in the HUT position.

It is likely that the fourth hypothesis was accepted. It was predicted that reduced measures of CBFv and rSO_2 could be related to a decline in IPS and attention. Evidence to support this hypothesis is that NOH patients have significantly reduced IPS and attention compared to controls and they also experience reductions in cerebral blood supply when they are in the upright position. It is believed that repeated exposure to reduced CBFv and rSO_2 could lead to a decline in cognitive functioning.

The most important finding was that overall NOH patients had reduced IPS compared to controls regardless of their position. Therefore, IPS is permanently reduced in NOH patients compared to controls. Reduced IPS and attention could be related to the fact that NOH patients experience repeated episodes of cerebral hypoperfusion every time they perform an activity in the upright position. Consequently, exposure to cerebral hypoperfusion could be negatively affecting cognitive function.

5.2 Strengths and Limitations

There were several strengths with regards to the current study. This study investigated a clinical population that is rarely studied and provided information about their cognitive function and cerebral hemodynamics. The current study assessed cognitive function in both the supine and HUT positions. It was beneficial to measure cognition in these two positions since NOH patients experience positional BP changes. There is limited literature about cerebral hemodynamics in

NOH patients, therefore this study introduced information about these measurements during cognitive testing and during changes in position. Another strength of the current study was that a group of healthy age-matched control subjects was included to provide baseline cognitive function and cerebral hemodynamics, which was then compared to the NOH patients.

Despite the strengths highlighted there were a few limitations of the current study. Randomizing participants to start cognitive testing in either the supine or the HUT position would have been beneficial. This would prove if cognitive test scores were affected by repeating the test in the HUT position after the supine position. The current study showed no change in cognitive test scores in NOH patients between the supine and HUT positions, demonstrating no learning effect associated with the tests. The study had a modest asymmetry in the male to female ratios in both the NOH and control groups. However, statistical analysis did not reveal a significant effect of gender on the results. The study consisted of a diverse patient population, but as a group these patients had a homogeneous drop in BP as a result of autonomic function. Patients had a diagnosis of NOH but had different associated conditions, such as PD, MSA, and LBD. Future studies should repeat this protocol with a specific group of patients, for example PD patients with NOH. This would provide evidence if the changes in cerebral hemodynamics and cognitive function are related to NOH or the associated condition.

5.3 Future Directions

Future research should aim to investigate if repeated exposure to cerebral hypoperfusion in NOH patients is related to changes in brain structure and function. This could provide evidence as to why NOH patients have permanently reduced IPS and attention compared to controls. Future research should also investigate other cognitive domains to determine if NOH patients have impairments in functions other than IPS and attention.

5.4 Conclusion

This is the first study to investigate the relationship between NOH patients, cerebral hemodynamics and cognitive function in both the supine and HUT positions. Findings revealed that NOH patients had a significant decrease in CBFv and rSO_2 during HUT compared to supine, as well NOH patients experienced reduced IPS and attention compared to control subjects.

Appendices

Appendix A. Copyright for Elsevier

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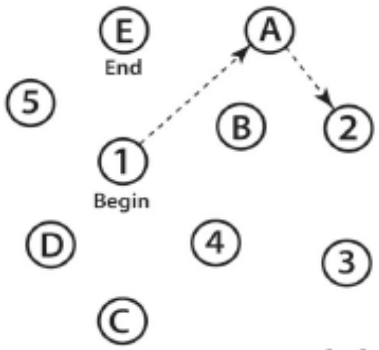
Appendix B. Montreal Cognitive Assessment

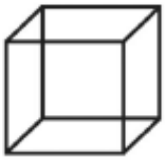
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

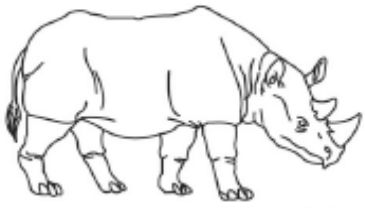
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

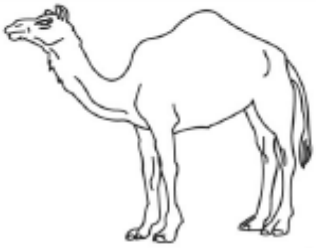
__/5

NAMING

[ ]



[ ]



[ ]

__/3

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
__/2

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

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

DELAYED RECALL

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

__/5

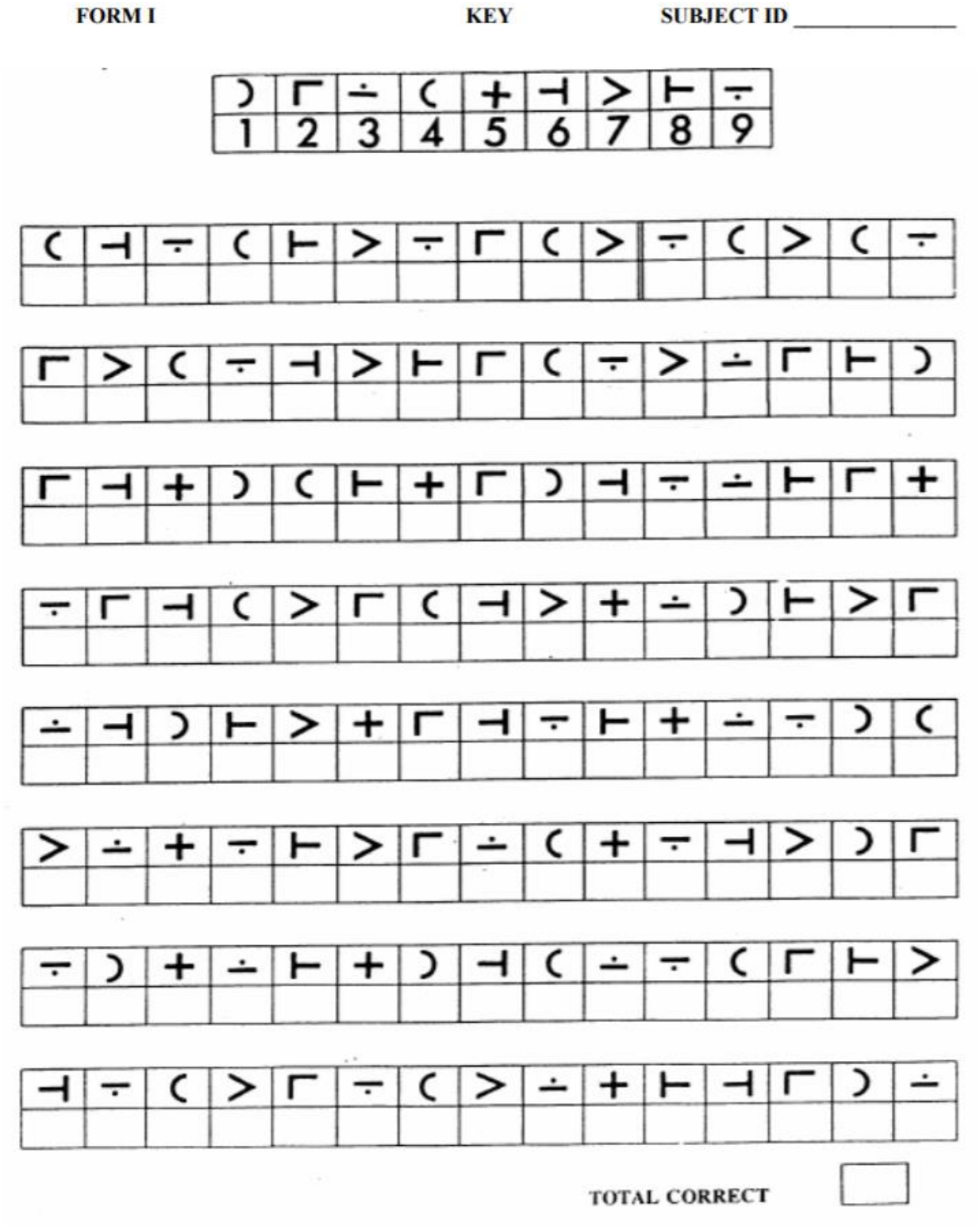
ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix C. Symbol Digit Modalities Test



Appendix D. Stroop Colour-Word Test

green	purple	blue	brown	brown	green	green	purple	red	green
purple	red	brown	brown	red	blue	blue	blue	purple	red
brown	blue	red	purple	purple	brown	green	blue	red	green
blue	green	brown	red	green	purple	red	blue	purple	brown
brown	green	brown	brown	red	purple	brown	purple	purple	green
blue	blue	blue	blue	green	green	red	purple	red	red
brown	blue	red	purple	red	purple	red	red	purple	blue
brown	purple	green	green	blue	blue	green	brown	brown	green
purple	purple	red	green	purple	red	green	blue	blue	purple
blue	brown	brown	red	brown	brown	green	blue	red	green

Appendix E. Research Ethics Approval Notice

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Full Board Initial Approval Notice

Principal Investigator: Dr. Kurt Kimpinski
Department & Institution: Schulich School of Medicine and Dentistry,London Health Sciences Centre

Review Type: Full Board
HSREB File Number: 107108
Study Title: Impact of autonomic dysfunction on cognition in individuals with neurological diseases with autonomic impairment and healthy control as a comparison

HSREB Initial Approval Date: October 21, 2015
HSREB Expiry Date: October 20, 2016

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Instruments	Autonomic Symptom Profile questionnaire	2015/08/20
Instruments	Symbol-Digit Modalities Test.	2015/08/20
Data Collection Form/Case Report Form		2015/10/08
Letter of Information & Consent	Control Group	2015/10/08
Letter of Information & Consent	Patient Group	2015/10/08
Recruitment Items	Poster-Received Oct 8, 2015	
Western University Protocol	Received Oct 9, 2015	

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

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