Effect of fractionized exercise on nighttime central blood pressure, cognitive function, and cerebral tissue oxygenation under conditions of normal and long sleep duration

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ABSTRACT

Elevated blood pressure (BP), particularly central aortic BP, increases the risk for various chronic diseases. The aim of this study was to examine nighttime change in central BP following a day of fractionized exercise when sleep duration was controlled. Since central BP is closely linked to brain health, a secondary aim of this study was to examine relationships between the change in nighttime BP following exercise with indices of cognitive function. Eight healthy middle-aged adults (7 women, aged 46 $\pm$ 5y) completed three 10-minute bouts of moderate-intensity walking (60-75% age-predicted maximum heart rate) after one week of sleep consisting of normal and long sleep durations (8- and 11-hours time in bed) in a randomized, crossover fashion. Ambulatory BP and cognitive function (Switching, Manikin, Color/Word Stroop) were recorded before and in the morning following the exercise intervention. A 2-way repeated measures ANOVA was used to test for difference in time (before vs. after exercise) or sleep duration (normal vs. long sleep). There was no difference ($P > 0.05$) in nighttime peripheral or central BP following fractionized exercise irrespective of sleep duration. We observed a main effect for time for cognitive function such that reaction time, throughput, and correct responses improved for all cognitive tests following fractionized exercise ($P < 0.05$). The change in nighttime pulse pressure amplification (brachial – central pulse pressure) following exercise was correlated with faster reaction time ($r = -0.64$, $P < 0.01$) and higher throughput ($r = 0.71$, $P < 0.01$) for the Manikin cognitive test when data from both sleep durations were combined. In summary, our results suggest that fractionized exercise does not significantly change nighttime central BP in healthy middle-aged adults, but it does improve cognitive performance with evidence that

interindividual changes in nighttime pulse pressure amplication following exercise is associated with improved cognitive performance.

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CHAPTER I

INTRODUCTION

High blood pressure (BP) is one of the major risk factors for chronic disease risk and mortality (Wu, Hu, Chou, Huang, Chou, & Li, 2015). Hypertension is commonly referred to as the silent killer because there are often little to no symptoms before adverse effects develop. Blood pressure values change throughout the day, especially in pre-hypertensive and hypertensive individuals (Morris et al., 2013; Takenaka et al., 2010). Among the diurnal changes in BP, is a decrease at night when a person sleeps, commonly referred to as dipping (Musameh et al., 2017). Dipping refers to the nocturnal decrease in BP that is typically seen during regular sleep cycles (Bankir et al., 2008). Hypertensive individuals are often termed "non-dippers" due to an absent nocturnal drop in BP. Non-dippers and those who increase nighttime BP are at a greater risk of developing cardiovascular diseases (Bankir et al., 2008; de la Sierra et al., 2014).

While elevated peripheral BP (i.e., brachial artery) negatively impacts overall health and increases risk for chronic disease development, these negative connotations are further substantiated with elevated central aortic BP (Huang et al., 2011). Central aortic blood pressure refers to pressure at the proximal thoracic aorta. The aorta is a large elastic artery that supplies oxygen-rich blood to the entire body. It is at the proximal thoracic aorta that BP first appears in the arterial tree to drive blood flow through the system. The BP that develops at the central aorta is a complex phenomenon that depends on total peripheral resistance, the elastic tissue properties of the aorta, and left ventricular contractility (Westerhof, Lankhaar, & Westerhof, 2009). Elevated central BP results in the transmission of elevated BP to cerebral blood vessels, increasing vascular injury

potential (Grochowski, Litak, Kamieniak, & Maciejewski, 2018). For instance, there is a strong correlation between high central BP and brain atrophy (Hajar et al., 2010). Moreover, high central pulse pressure (PP; calculated as systolic minus diastolic pressure) has adverse effects on cerebral vascular function caused by elevated pulsatile load on cerebral endothelial cells leading to increased tension and cellular injury risk (Poggesi et al. 2016; van Sloten et al., 2015). These results indicate that high central BP or PP is damaging to a person's cerebrovascular health, with impaired cognitive function implications.

Interestingly, recent studies have described the change in central BP at night. A study by Argyris et al. (2018) demonstrated that middle-aged to older adults have a decrease in central systolic and diastolic BP overnight, though an increase in aortic PP. The drop in diastolic BP was greater than the central systolic drop, leading to increased central PP. An increase in central PP decreases PP-amplification as derived from the difference between peripheral PP and central PP (Phillips, Hedner, Berend, & Grunstein, 2005). The variance between the dipping pattern in peripheral BP and central BP at night may further explain the overnight decrease in PP-amplification when central PP increases or does not decrease as much as peripheral PP (Williams, Lacy, Baschiera, Brunel, & Dusing, 2013). These overnight changes in central PP and PP-amplification may be detrimental to cerebral health, thus requiring examination of preventive factors.

Factors that can alter overnight BP may serve as a strategy to reduce the risk of small vessel injury (i.e., cerebral vasculature) resulting from elevated nighttime central BP. An acute bout of moderate-to-vigorous aerobic exercise has been previously shown to reduce central PP in normotensive and hypertensive adults for a duration up to one

hour after exercise (Millen, Woodiwiss, & Norton, 2016; Sugawara, Komine, Miyazawa, Imai, & Ogoh, 2015; Compton, Figueroa, & Gonzales 2019); however, no studies have determined whether this lowering of central PP is also observed during sleep. Experimental studies have shown that moderate-to-vigorous intensity fractionized exercise effectively lowers ambulatory peripheral BP (Angadi et al., 2010; Bhammar, Angadi, & Gaesser, 2012). Fractionized exercise refers to shorter multiple bouts of aerobic exercise performed throughout the day rather than a single continuous bout of exercise. For example, a person could walk for 30-minutes and conclude exercise for the day or fractionize exercise and walk for 10-minutes in the morning, 10-minutes during the day, and 10-minutes in the evening to equal the same total of 30-minutes of exercise in a day. Fractionized exercise lowers ambulatory peripheral BP by inducing repeated periods of post-exercise hypotension (Angadi et al., 2010). Furthermore, fractionized exercise sustains a lowered peripheral systolic BP for up to 24-hours post-exercise (Miyashita, Burns, & Stensel, 2008). In a study comparing fractionized and continuous exercise on ambulatory peripheral BP in pre-hypertensive adults, nighttime and morning systolic BP were reduced only with fractionized exercise (Bhammar, Angadi, & Gaesser, 2012). Because of the benefit of lowering nighttime BP, fractionized exercise is the ideal choice to consider for altering central BP during sleep.

Purpose of the Study

The objective of this study was to determine the effect of fractionized exercise on overnight changes in central BP in middle-aged adults. Given that high central BP is linked to impaired cerebral vascular health, a secondary objective of this study was to

examine the association between changes in overnight central BP following fractionized exercise on cognitive function. Since sleep duration is linked to poor vascular-related outcomes (Sabanayagam & Shankar, 2019; Cappuccio et al., 2011), we deemed it important to control sleep duration when examining the effect of acute exercise on overnight BP. As such, these study objectives were carried out under two controlled sleep duration conditions.

Hypothesis

We hypothesized that fractionized exercise would decrease overnight central BP in middle-aged adults. Our secondary hypothesis was that the change in overnight central BP following fractionized exercise would correlate with improved cognitive function.

Delimitations

The following delimitations were associated with this study:

1. Only middle-aged adults were recruited for this study as we rationalized that they may be more susceptible to changes in their vascular system because they do not already present with gross vascular dysfunction as do older adults.
2. Due to the disruption of sleep that occurs when wearing an ambulatory BP device, we only measured overnight BP once for baseline, and once after the exercise protocol.
3. To focus our attention on an organ system sensitive to overnight BP, particularly central BP, we chose to investigate the impact of fractionized exercise on the cerebral vasculature rather than other organ systems.

4. In order to identify the capacity of fractionized exercise to lower overnight central BP, we chose to study the acute effect of fractionized exercise rather than the chronic effect.
5. To minimize the number of visits the participant had to attend for this study, we instructed participants to independently walk at a specific cadence at home rather than make multiple visits to the research laboratory.

Assumptions

The following assumptions were made regarding this study:

1. The participants reported honestly about their medical history, including prior sleep problems and taking sleep-inducing medication.
2. The participants accurately maintained their sleep diary throughout the study.
3. The participants followed the prescribed stepping cadence to the best of their ability to complete the fractionized exercise protocol.
4. The participants followed instructions to refrain from food and drink (besides water) for at least eight hours before vascular testing.
5. The participants did not change their lifestyle (diet or exercise patterns) throughout the study.

CHAPTER II

REVIEW OF LITERATURE

Introduction

Overnight BP is an important metric in terms of risk for disease as both the absolute level of nighttime BP and the 'dipping' pattern of BP during sleep can have interrelated and independent effects on vascular health. For instance, De la Sierra et al. (2014) found that individuals with the greatest risk factor for cardiovascular disease was in those who had both nocturnal hypertension and non-dipping BP patterns. The aim of this thesis project was to determine the effect of fractionized exercise on overnight changes in central PP since central BP is more reflective of the BP in vital organs like the brain. This review describes the current understanding of the overnight changes in peripheral and central BP, the relationship between overnight BP and vascular function, and the possible link between overnight BP changes to cognitive function. In addition, we identified studies that assessed the impact of fractionized exercise on BP.

Overnight Changes in Blood Pressure

BP is most commonly measured at the periphery in the brachial artery. In resting conditions, such as during sleep, peripheral BP decreases in response to reduced sympathetic activity at night. Several studies have characterized the drop in peripheral BP that occurs overnight. Bankir et al. (2008) observed overnight BP changes compared to daytime BP in 325 subjects without diagnosed cardiovascular medical conditions. The study participants were, on average, 46 years of age, with 55% of the participants being female. The authors found that the participants had a 10% drop in nighttime systolic BP,

with an 8% drop in nighttime PP than the values during the day. Furthermore, Williams, Lacy, Baschiera, Brunel, & Dusing (2013) reported changes in overnight peripheral systolic BP and PP. The study participants were diagnosed with either stage I or II hypertension and did not take hypertensive therapy medication or ceased to take medication for two weeks before BP measurements. Over 800 subjects, both male and female, with an average age of 53 years, underwent 24-hour ambulatory BP monitoring. The study results identified similar trends to overnight BP changes, with peripheral systolic BP dropping by 12 mm Hg from day-to-night and PP dropping by 5 mm Hg. As the literature shows, there is an expected day-to-night decrease in peripheral systolic BP and PP.

The overnight decrease in peripheral BP is evident, but it is even more critical to identify overnight changes in central BP and PP because of a potentially greater health risk (Argyris et al., 2018; de la Sierra et al., 2014). Phillips, Hedner, Berend, & Grunstein (2005) examined the effects of sleep on central systolic BP and PP in male patients with an average age of 44 years who were recommended for routine sleep studies. They measured BP in the evening before the subjects went to sleep and again in the morning within 15 minutes of the subjects waking up to capture overnight changes. Central systolic BP increased from 113 to 116 mm Hg from the evening to morning, and central PP slightly increased from 35 to 36 mm Hg. Jankowski et al. (2013) compared nighttime central BP in normotensive and hypertensive adults. Central systolic BP dropped by 9 mm Hg overnight in the normotensive subjects and by 10 mm Hg in hypertensives. Lastly, Argyris et al. (2018) examined 497 subjects with an average age of 54 years (56%

male, 80% hypertensive). These researchers showed central systolic BP decreased by 6 mm Hg during sleep and central PP increased by 7 mm Hg.

Interestingly, there is a difference in overnight BP changes between peripheral and central BP. Argyris et al. (2018) found a downward trend in central and peripheral overnight systolic and diastolic BP; however, there was less reduction in central systolic BP than peripheral systolic BP during sleep. This finding is consistent with Williams, Lacy, Baschiera, Brunel, & Dusing (2013) that found central systolic BP dipped by 6% overnight while peripheral systolic BP dipped by 8%. In addition, Jankowski et al. (2013) observed a 10 mm Hg drop in central systolic BP, but a 13 mm Hg drop in peripheral systolic BP from day-to-night in hypertensives, with similar trends in normotensives as well (9 vs. 10 mm Hg). Considering that systolic BP largely determines PP, these overnight changes in systolic BP would lead one to expect that overnight changes in PP would also differ between peripheral and central BP. Indeed, central PP is reported to increase overnight while peripheral PP is found to change little or increase less than central PP (Argyris et al., 2018; Williams, Lacy, Baschiera, Brunel, & Dusing 2013). This differing pattern in PP can be quantified by calculating the difference between peripheral and central PP (brachial – central PP), known as PP amplification. Previous studies have shown that PP amplification decreases overnight, consistent with the notion that central PP increases more than peripheral PP (Argyris et al. 2018; Phillips, Hedner, Berend, & Grunstein 2005).

Measuring BP during sleep is an important factor for identifying cardiovascular disease (Bankir et al., 2008; de la Sierra et al., 2014). A key identifier of hypertension during sleep is the presence of non-dipping BP patterns. Dipping refers to the decline in

BP during sleep, and normal dipping patterns are at least a 10% fall in peripheral and central systolic BP (Bankir et al., 2008; de la Sierra et al., 2014). When dipping is not present, there is likely a link to cardiovascular disease (de la Sierra, et al., 2014). There can be cases where central BP does not dip despite dipping patterns in peripheral BP. Phillips, Hedner, Berend, & Grunstein (2005) observed the dipping patterns between daytime and nighttime central and peripheral BP using pulse wave analysis. Their results identified a rise in central BP and PP, while peripheral BP did not significantly change. With these findings, they also saw a decrease in PP amplification. Factors that commonly exhibit a greater nighttime BP dipping are the female gender, hypertension, and decreased heart rate (Argyris et al., 2018; Avolio et al., 2009; Phillips, Hedner, Berend, & Grunstein, 2005). Another factor found to be important for overnight BP dipping is sympathetic activity. Sherwood, Steffen, Blumenthal, Kuhn, & Hinderliter, (2002) showed that non-dipping nighttime patterns in blood pressure could be attributed to less dipping patterns of epinephrine and norepinephrine during sleep compared to wake times. These hormones are considered to be released during the fight-or-flight response to stimulate HR and BP, but during sleep, they decline from their daytime levels (Dodt, Breckling, Derad, Fehm, & Born, 1997). Sherwood, Steffen, Blumenthal, Kuhn, & Hinderliter, (2002) reported that African Americans had less systolic BP dipping overnight (14 mm Hg drop) than Caucasians (18 mm Hg drop), which was accompanied by less overnight reductions in norepinephrine levels as compared to Caucasians (9 vs. 14 μg/mg). These results indicate that sympathetic nervous system activity during sleep may significantly impact overnight dipping in BP.

Blood Pressure Effect on Cognitive Function

It is evident that overnight BP is important in identifying risk factors for disease, and one of the most vital organs affected by BP is the brain. Several studies identify the prevalence of cerebrovascular disease with elevated BP. Cerebrovascular disease occurs when there is damage to the blood vessels that supply blood to the brain. These conditions can impair cognitive functioning and mobility, especially in older adults, due to the age-related increase in BP. Yano et al. (2015) studied the relationship between nocturnal BP dipping patterns in healthy young adults (n=224, 45% men, average age of 30 years) to the same adults' cognitive function 20 years later. They separated participants into groups based on nocturnal dipping patterns. The results showed that young adults with less peripheral BP dipping had reduced cognitive function in older age than adults with greater BP dipping. This study demonstrated that nighttime BP is an important determinant of cerebral health, especially over time. In addition, non-dipping patterns can also lead to brain atrophy. Hajjar et al. (2010) compared nighttime BP and brain volume in 80 male and female adults with an average age of 66 years with either a history of stroke or no history of stroke. Of the regions in the brain, the frontal and parietal lobes had the most significant decreases in volume when nocturnal systolic BP and PP were not dipping at night or decreased less than 10% of daytime BP. There was greater brain atrophy in stroke patients than non-stroke patients among non-dippers, and nighttime systolic BP explained more variance in brain atrophy than nighttime PP. The results indicate that non-dipping patterns in nighttime systolic BP is associated with brain atrophy and should be considered in terms of factors that can be detrimental to cerebral health.

Elevated BP also increases cognitive impairment risk (Guo et al., 2009; Hajar et al. 2010; Tadic, Cuspidi, & Hering, 2016). An increase in white matter lesions in the brain, often measured as white matter hyperintensities using MRI, causes cognitive and motor dysfunctions. Aging is associated with an increase in white matter hyperintensities (Zhuang, Chen, He, & Cai, 2018). A study conducted by Guo et al. (2009) showed a relationship between abnormal nighttime BP patterns and mild cognitive impairment. Subjects (N=144, average age of 68 years) were divided into groups based on nighttime BP dipping patterns. The BP change from day-to-night that identified each group were extreme dippers (-25%), normal dippers (-15%), non-dippers (-6%), and risers (+7%). The study results showed that normal dippers had the least cognitive impairment compared to the other three abnormal nocturnal BP patterns (extreme dippers, non-dippers, and risers). Moreover, 38 of the 144 participants were diagnosed with mild cognitive impairment, and the nighttime systolic BP drop was less (13 mm Hg) in these individuals than those with normal cognitive function (15 mm Hg).

Continuing the review on BP variation and cognitive decline, Conway et al. (2015) studied ambulatory BP and cognitive function in 319 adults (average age of 72 years, 66% female). Cognitive performance was measured using Montreal Cognitive Assessment, dividing subjects into impaired cognitive function (group I, score <26) or normal cognitive function (group II, score ≥ 26). In group I, systolic BP dropped by 13 mm Hg from day-to-night, while group II systolic BP dropped by 16 mm Hg. Thus, the impaired group showed less nighttime systolic BP dipping than the normal group. These results suggest that less overnight systolic BP dipping is related to impaired cognitive function. Another study by Li, Cui, Sun, Wang, & Lui (2017) examined 108 male and

female participants with cerebral small vessel disease (CSVD) divided into two groups based on cognitive impairment by the Montreal Cognitive Assessment. Thirty-nine participants were in the impaired group (average age of 66 years) and 69 participants were in the normal group (average age of 68 years). The impaired group showed a 5 mm Hg drop in nighttime PP as compared to an 8 mm Hg drop in the normal functioning group, indicating that patients with CSVD may have less overnight PP dipping. To understand the correlation even further, Paganini-Hill et al. (2019) assessed 121 subjects with an average age of 93 years considered to have normal cognitive function and 24 were classified as cognitively impaired through examination medical professionals. The normal subjects had a 6% nocturnal dip in systolic BP as compared to a 1% nocturnal dip in the impaired subjects. Within the impaired group, 50% of participants were non-dippers and 42% were reverse dippers meaning they had a rise in nighttime systolic BP. The participants in the impaired group were more likely to be non-dippers than those in the normal group. After reviewing the findings from these studies, it is evident that literature supports the link between overnight BP dipping patterns and cognitive function.

Blood Pressure Effects on Cerebral Vascular Health

Pulse pressure (PP) refers to the difference between systolic and diastolic BP and largely determines the pulsatility of blood flow in cerebral arteries. Large central arteries (e.g., aorta, common carotid artery) contain an abundance of elastin, which allows these vessels to stretch with elevated PP to dampen flow pulsatility to maintain a consistent blood flow through smaller downstream arteries. This mechanism is referred to as the Windkessel effect, and it is responsible for the maintenance of continuous flow in the

vascular system (Steppan, Barodka, Berkowitz, & Nyhan, 2011; Westerhof, Lankhaar, & Westerhof, 2009). The elasticity of large central arteries can be discussed in terms of compliance, which can be calculated by the change in volume per change in pressure. When large central arteries become stiff due to aging or vascular damage (Safar, Levy, & Struijker-Boudier 2003; Zieman, Melenovsky, & Kass, 2005), compliance decreases and results in elevated systolic BP (i.e., less dampening of pressure and flow occurs). Systolic hypertension, independent of diastolic hypertension, is the most common type of hypertension in middle-aged and older adults (Steppan, Barodka, Berkowitz, & Nyhan, 2011). When systolic BP increases and diastolic BP remains unchanged or decreases, there is a rise in PP. Therefore, elevated PP is a proxy for elevated central arterial stiffness (Safar, Levy, & Struijker-Boudier 2003). Health problems that can arise due to elevated PP are impairments to cerebral vascular functioning, which we will now discuss in more detail.

Injury to the cerebral vasculature can cause an array of issues. Cerebral small vessel disease (CSVD) refers to a variety of disorders in the small blood vessels of the brain. This condition can be due to cardiovascular diseases, such as hypertension or atherosclerosis. One of the issues of CSVD is oxidative stress, which is an imbalance of free radical and antioxidant production in favor of an increase in free radicals (Grochowski, Litak, Kamieniak, & Maciejewski, 2018; Uttara, Singh, Zamboni, & Mahajan, 2009). Animal research has shown that only one week of elevated PP in the brain of mice induces inflammation and increases free radicals (Poulet et al., 2006). When PP is abnormally elevated, there is decreased stretch within blood vessels promoting an environment at risk for injury to the endothelial cell layer, leading to an

inflammatory response accompanied by release of free radicals (Thorin-Trescases et al, 2018). One adverse effect of elevated free radical production is impaired endothelium-dependent vasorelaxation of arterial smooth muscle (Taniyama & Griendling, 2003). Free radicals can inactivate vasodilator substances produced by endothelial cells. For instance, endothelial nitric oxide can be converted to peroxynitrite when the free radical superoxide anion is present in abundance (Pacher, Beckman, & Liaudet, 2007). This results in a lower capacity of arteries to vasodilate in response to physiological stimuli. Another adverse effect is an impaired barrier to protect the brain from harmful substances that travel in the blood (Poulet et al., 2006). Garcia-Polite et al. (2017) examined the effects of pulsatile patterns in BP and flow on cerebral endothelium in mice. They found that high PP in the brain resulted in the breakdown of tight endothelial junctions, which hold the endothelial cells together and create the barrier between the blood and the brain. As a result, tissue inflammation and neurological impairment can occur as circulating substances enter brain tissue, disrupting homeostasis.

Damaged endothelial cells due to elevated BP may also impair cerebral blood flow, thus having implications for oxygen delivery to the brain leading to cognitive dysfunction. Alosco et al. (2014) examined the impact of peripheral hypertension on cerebral blood flow and cerebral cortex thickness. A total of 58 adults (average age of 66 years) were included in the study, with 23 of the subjects diagnosed with hypertension compared to the remaining 35 who did not have hypertension. Cerebral blood flow was lower in the hypertensive subjects, and total brain cortical thickness was also significantly lower in the hypertensive subjects than the normotensives (-0.04 mm). The implication of this study was that reduced blood flow to the brain might lead to ischemia-

related disease. Aging plays a role in these altered cerebral blood flow patterns, specifically playing a role in cerebral oxygenation changes (Hallacoglu et al., 2012), which could be explained through the age-related decline in cardiovascular health. Furthermore, lower oxygen levels in the brain can impact cognitive performance. Near-infrared spectroscopy (NIRS) measures oxygenated and deoxygenated hemoglobin and has been used to identify cerebral oxygen patterns in neurological diseases (Bonilauri et al., 2020). Niu et al. (2013) observed cerebral oxygenation patterns during working memory tasks in mild cognitively impaired participants (n=8, mean age 65 years) and healthy controls (n=16, mean age 63 years). They found a correlation between the number of correct answers on a Stroop test and oxygenated hemoglobin concentration in the frontal and temporal regions of the brain (mean $r = 6.71$, $p < 0.001$). Their results support the findings that alterations in oxygen patterns in the brain can lead to reductions in cognitive performance (Bonilauri et al., 2020).

Fractionized Exercise Lowers Blood Pressure

For years, research has shown that exercise improves BP (Goeder et al., 2019; Whelton et al., 2018; Shenouda et al., 2017). Fractionized exercise refers to shorter bouts of aerobic exercise performed throughout the day instead of one continuous bout performed at one time. In this review, we examined the effect of continuous and fractionized exercise on daytime and nighttime BP.

During exercise, systolic BP rises primarily due to elevated cardiac output to meet the oxygen demand of active skeletal muscle. Cardiac output increases due to elevations in heart rate and stroke volume, which is the amount of blood ejected per cardiac contraction into the systemic circulation from the left ventricle. Systemic vascular

resistance also alters BP during exercise. Vascular resistance decreases in the working muscle as local tissue factors induce smooth muscle dilation of arterioles to increase blood flow, while vascular resistance increases in inactive organs during higher intensity exercise to maintain mean arterial pressure. Understanding the factors that alter BP is important to further explain the changes between peripheral and central BP, specifically during exercise interventions.

Post-exercise hypotension refers to a decrease in resting BP following an acute bout of exercise. Post-exercise hypotension can occur minutes after the cessation of exercise and last for several hours. Baroreceptors are likely one of the physiological reasons behind a decrease in BP following exercise. At the end of an acute bout of aerobic exercise, BP is elevated, leading to increased baroreceptor activity at their aorta and carotid artery sites. Baroreceptors send afferent information to the brain (Chen & Bonham, 2010), causing the medulla oblongata to increase parasympathetic nerve impulses to the heart to lower heart rate (thus decreasing cardiac output) decrease sympathetic stimulation to the peripheral arteries causing dilation. In sum, these events lower mean BP after exercise, and this can be observed for several hours following exercise (Chen & Bonham, 2010). Combined with arterioles in skeletal muscle that remain dilated following exercise, the decrease in vascular resistance is thought to largely explain the sustained decrease in BP following exercise (Brito, Queiroz, & Forjaz, 2014).

Evidence exists that peripheral and central BP may differ following exercise. Sugawara et al. (2015) examined the influence of one bout of aerobic exercise on peripheral and central PP in 23 young men at an average age of 22 years. Central and peripheral PP decreased following exercise, but the researchers found that the decrease in

central PP following exercise was more significant than the reduction in peripheral PP. Another study by Goeder, Bohm, Oberhoffer, and Muller (2019) observed the post-exercise change in peripheral and central BP in 25 healthy men with an average age of 27 years. The subjects performed a maximum cardiopulmonary exercise test on a bicycle ergometer with 24-hour ambulatory BP monitoring following the exercise. The average drop in central systolic BP following the first hour of exercise was 6 mm Hg, while peripheral systolic BP was raised by an average of 2 mm Hg in the first hour following exercise. Central systolic BP slowly returned to baseline during the 12-hour daytime period following exercise, while peripheral systolic BP only tended to fall below baseline at 2-hours post-exercise and was elevated above baseline thereafter. During the night period, both central (average drop of 11 mm Hg over 9-hours) and peripheral (average drop of 9.9 mm Hg over 9-hours) systolic BP dropped below baseline. Lastly, Compton, Figueroa, and Gonzales (2019) also studied the effects of post-exercise hypotension in central BP following acute bouts of walking. They measured central systolic BP and PP in 16 adults (average age 22 years) who walked at a slow or fast pace (80 steps/min versus 125 steps/min). They found a decrease in central systolic BP (-2 mm Hg) and central PP (-3 mm Hg) after 60 minutes post-exercise. In summary, these studies suggest that an acute bout of exercise has the capacity to lower central BP following exercise.

Since exercise can result in lower BP for several hours following the activity, multiple bouts of exercise throughout the day may have a more significant effect on BP fluctuations than a single bout of continuous exercise. As little as 10-minutes of exercise can result in post-exercise hypotension (Angadi et al., 2010). Bhammer, Angadi, & Gaesser (2012) compared the effects of fractionized and continuous exercise on

ambulatory BP in 11 pre-hypertensive subjects (average age 28 years). Subjects were placed into three groups: three 10-minute sessions of aerobic exercise, one 30-minutes session of aerobic exercise, or a no exercise control group. Ambulatory 24-hour peripheral BP measurements were lower in both exercise groups compared to the control (averages were -3 mm Hg for fractionized group and -2 mm Hg for the continuous group). Daytime/evening BP (hours 1:00-11:00pm) were lower in both exercise groups than the control, but fractionized exercise lowered peripheral systolic BP more than the control in the nighttime hours (11:00pm-8:00am), while BP following continuous exercise was not different than control during the nighttime hours. There was also a significant decrease in morning (8:00am-12:00pm) systolic BP (-4 mm Hg) in the fractionized group compared to both the control and continuous group. Overall, this study showed that fractionized exercise reduces 24-hour ambulatory BP during all hours of the day and night, while the single 30-minute continuous bout of exercise only showed significant BP reductions during the daytime/evening hours.

Angadi et al. (2010) also compared the effect of fractionized exercise and continuous exercise on peripheral BP in normotensive people. In 29 adults (including 13 women, average age of 26 years), all subjects performed a day of fractionized exercise (three 10-minute bouts separated by 4-hours), a day of 30-minutes of continuous exercise performed in the morning (9:00am), and a control day. From 1:00-5:00pm and 5:00-9:00pm, peripheral systolic BP was lower in the fractionized group as compared to the continuous and control groups. These results also indicate a greater benefit of fractionized exercise compared to continuous exercise on ambulatory BP.

Evidence that intermittent bouts of exercise can benefit BP can also be observed from studies examining interval exercise. Miyashita, Burns, and Stensel (2008) compared the effects of short bouts of brisk walking to one continuous bout of brisk walking on resting BP. In 15 healthy men with an average age of 23 years, one group performed ten 3-minute bouts of brisk walking with 30-minute rest in-between. Another group performed one 30-minute bout of continuous brisk walking final group served as the no exercise control. Peripheral BP was measured before exercise, immediately when exercise ended, 5-minutes after walking, 15-minutes after walking, and the following day for resting conditions. In the intermittent group, peripheral systolic BP was significantly higher immediately after exercise, but lower as compared to the continuous exercise and control groups after 15-minutes if recovery from exercise. Both exercise groups had significantly lower resting systolic BP than the control group the day following exercise (-8 mm Hg intermittent and –7 mm Hg continuous compared to control). This study supports the effect of intermittent exercise on reducing BP post-exercise.

An important factor to consider when using fractionized exercise to lower BP is when exercise is performed. Brito et al. (2018) examined the effect of exercise performed in the morning and evening on ambulatory BP in pre-hypertensive men. At an average age of 33 years, 13 men performed two morning (9:00am) and two evening (6:30pm) bouts of exercise in a randomized order with peripheral BP compared to a no-exercise control at the same time of day. Morning exercise did not affect peripheral systolic BP during the day, but nighttime exercise significantly lowered overnight BP (4 mm Hg lower at night compared to control). Park, Jastremski, and Wallace (2005) compared morning and evening exercise on ambulatory BP in 14 dipping and non-dipping

hypertensives. Among the subjects, 6 were women and the average age was 57 years. They found that non-dippers had a significantly greater drop in nighttime peripheral systolic BP than dippers after both morning and evening exercise, while daytime BP changed similarly between dippers and non-dippers. Overall, exercise reduced 24-hour systolic BP regardless of the time of day in both hypertensive groups, but non-dippers had improved nighttime systolic BP responses compared to dippers. Since fractionized exercise includes bouts of exercise performed in the morning, midday, and evening, the hypotensive response to fractionized exercise may lead to daytime and nighttime reductions in high BP. However, this postulation requires further investigation.

CHAPTER III

METHODS

Study Design

This study aimed to determine the effect of fractionized exercise on overnight central BP and determine possible relationships between overnight BP and changes in cognitive function following the exercise protocol. Each participant was asked to follow a specific schedule for time in bed (TIB) which was completed in a crossover design. Each week consisted of six consecutive nights of 8-hours or 11-hours TIB. The justification for this TIB protocol is based on a study in adolescents that finds 10-hours TIB results in an average sleep time over 8.5-hours (Campbell, Kraus, Burright, & Feinberg, 2016). Thus, we asked participants to spend up to 11-hours TIB to ensure long duration sleep (9+ hours of sleep). The order of prescribed TIB was assigned randomly using Excel's randomize function, with 4 participants completing the 8-hours TIB protocol first and the other 4 participants completing the 11-hours TIB protocol first. Participants were encouraged to keep their normal morning rise time but to alter their bedtime in order to achieve the prescribed TIB. Laboratory testing took place on days 6 and 7 (Figure 1) and consisted of cognitive function testing, cerebral oxygenation, and resting blood pressure. Following data collection on the morning of the sixth day, each participant was given an exercise prescription to perform three bouts of walking throughout the day. Ambulatory blood pressure was measured overnight between days 2-4 (pre-exercise) and on day 6 (post-exercise).

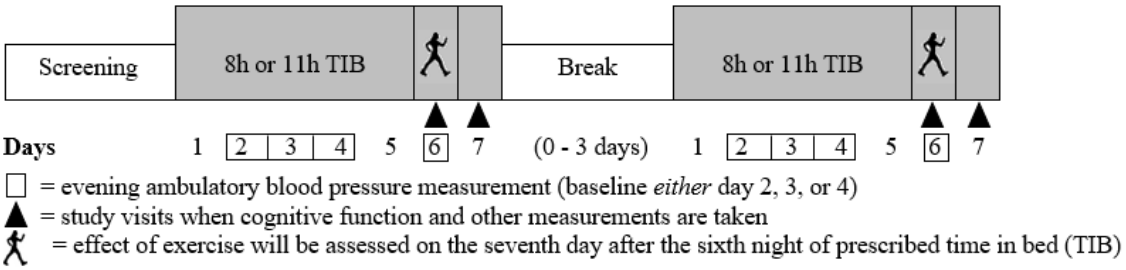

Figure 1. Experimental design.

Human Participants

Data for this study were collected from middle-aged adults (40-59 years). Middle-aged adults are an ideal population because this age-range becomes more sensitive to elevated nighttime central PP and resultant cerebrovascular dysfunction than older adults who experience elevated daytime central PP and systemic levels of oxidative stress with advancing age (Zieman, Melenovsky, & Kass, 2005). Based on information from a medical history questionnaire, participants in this study were not meeting daily physical activity guidelines (<150 minutes per week), reported no recent history of sleep problems, and did not take medication for sleep. All participants had a BMI <30 kg/m^2, fasting blood glucose <125 mg/dL, and resting seated BP less than 180/120 mm Hg (hypertensive crisis). Other exclusion criteria included smoking, vaping, and a history of stroke, diabetes, or cardiovascular disease.

Sample Size

To determine the necessary sample size for this study, we used data from a previous study by Bhammar, Angadi, & Gaesser (2012) that reported an average decrease of 4 mm Hg in peripheral SBP overnight following fractionized exercise in pre-hypertensive adults. Using a sample size calculation for paired t-test, a target power of

0.8, an alpha level of 0.05, and an estimated standard deviation of paired differences of 4 mm Hg, the estimated sample size was 10 participants. Another study by Angadi et al. (2010) in normotensive adults observed an average decrease in daytime peripheral systolic BP of 3 mm Hg following fractionized exercise. Using a sample size calculation for paired t-test, a target power of 0.8, an alpha level of 0.05, and an estimated standard deviation of paired differences of 3 mm Hg, the estimated sample size was 10 participants.

Twenty-one participants were screened for this study. One participant decided not to participate due to the altered sleep schedules involved in the study, three participants dropped out due to scheduling conflicts, one participant dropped out after feeling tired following the 8-hour TIB protocol, one participant dropped out due to discomfort associated with ambulatory BP measurements, four participants ended early due to non-compliance of following the TIB instructions, two participants stopped participation in the study due to the inability to sleep for more than 8.5 hours, and we were unable to use one participant's data due to identified non-compliance in wearing the sleep monitor. Consequently, data from 8 participants (seven women and one man) were used in the data analysis.

Experimental Procedures

Participants wore motion sensors throughout the study to monitor daily physical activity patterns and measure sleep. On testing visits, participants underwent the following set of procedures in this order. First, participants sat in a chair to establish resting levels of cerebral tissue oxygenation. Following this baseline measurement,

participants took a series of cognitive function tests on a computer with the cerebral tissue oxygenation measurement. After cognitive testing, participants rested in the supine position for laboratory measurement of peripheral and central BP. Testing visits were scheduled on two consecutive days, with the first visit serving as a pre-exercise assessment and the second visit serving as a post-exercise assessment.

Physical Activity Monitoring

Participants were asked to refrain from any activity outside of their normal daily routine to decrease the possibility of elevated physical activity influencing our study measurements. A triaxial accelerometer (GT9X, ActiGraph, Pensacola, FL, USA) was worn by our participants at their non-dominant wrist throughout the entire study to track physical activity levels. Accelerometers were initialized to collect data on all three axes at 30 Hz for daily activity and sleep monitoring. However, on day 6 that includes the three bouts of prescribed exercise, participants also wore a separate waist-worn accelerometer (GT3X+, ActiGraph) programmed to sample data at 30 Hz. The waist-worn accelerometer was used to measure stepping cadence during the three bouts of fractionized exercise.

Physical activity data were processed using ActiLife software (version 6.13.3). Data was reduced to 60-second epochs for analysis. First, data underwent wear-time validation using the Choi (2011) equation to ensure that wear periods less than 600 minutes (10-hours) were excluded from the analysis. The wrist-worn accelerometer was then analyzed for time spent in moderate-intensity and vigorous-intensity activity based on cut-off thresholds developed by Rhudy et al. (2019) that uses vector magnitude (combined all three axis data into one). The thresholds were 4836-8453 counts per minute

for moderate-intensity activity and >8453 counts per minute for vigorous-intensity activity. For the waist-worn accelerometer, the reduced 60-second epoch data was analyzed in Excel to identify the three 10-minute bouts of fractionized exercise based on increased stepping cadences (steps per minute) throughout the day. Once each bout was identified, we calculated the average cadence from all three bouts of brisk walking.

Sleep Monitoring

The same triaxial wrist-worn accelerometer (GT9X, ActiGraph) used to measure daily physical activity was also used to measure TIB and total sleep time using ActiLife software. Actigraphy has been shown to provide an accurate measurement of total sleep time compared to the gold-standard polysomnography method (Quante et al., 2018; Littner et al., 2003). We followed practice guidelines set by the American Academy of Sleep Medicine for using actigraphy to monitor sleep (Littner et al., 2003). Participants were asked to complete a sleep diary to help identify wake episodes, used in conjunction with the raw accelerometer data, to reduce actigraphy overestimation of sleep time. Participants were sent home with ActiLife's CentrePoint hub to remotely download their sleep data each morning. Participants were advised only to remove accelerometers for data downloads during bathing or swimming. The hub wirelessly transmitted the data collected by the accelerometer to the research laboratory, where we were able to check participant compliance with our TIB instructions every day of participation. The researchers provided daily feedback on whether the participants completed the 8-hour or 11-hour TIB protocol. Failure to comply with the protocol for more than two of the six days resulted in participants being dropped from the study.

The sleep data was reduced to 60-second epochs and processed using a combination of Cole-Kripke and Tudor-Locke algorithms in ActiLife's software (version 6.13.3). The Cole-Kripke algorithm determines which epochs are determined "sleep" versus "wake." The Tudor-Locke method is used to determine sleep periods by assessing bedtime as five consecutive minutes of sleep epochs and wake time as ten consecutive minutes of awake time at the end of a sleep period. To obtain the most accurate sleep analysis, these algorithms were paired with the participant's self-reported sleep diaries to identify the most accurate periods for TIB and sleep.

Ambulatory Blood Pressure

Ambulatory BP was measured using an Oscar2 device (SunTech Medical), which has been validated using the British Hypertension Society protocol (Goodwin, Bilous, Winship, Finn, & Jones, 2007). Following a typical brachial artery cuff measurement, this device re-inflates at the diastolic BP level to record pressure waveforms for an additional 10-seconds. The device then performs an automated pulse wave analysis and estimates central BP using a general transfer function (SphygmoCor technology, Atcor Medical). Participants wore the monitor once during days 2 through 4 (pre-exercise) and again on day 6 or the night after fractionized exercise (post-exercise). Participants were asked to wear the monitor approximately one hour before they planned to sleep to obtain at least one measurement while they were awake. The device was programmed to take measurements once every 30-minutes until 10pm than every 45-minutes after 10pm throughout the night. Participants were asked to turn off the device upon rising from bed in the morning.

Cognitive Function Testing

Cognitive function was assessed using a laboratory computer with specialized software, Automated Neuropsychological Assessment Metrics (ANAM, Vista LifeSciences). The ANAM software provides objective measures of cognitive performance through a variety of test batteries designed to measure variables such as reaction time, attention, and motor skill. Participants performed the baseline test during the first visit for familiarization. On all remaining visits, participants performed the same tests for pre- and post-exercise assessments. The test battery we used for our measurements was the Clinical Toolkit. This battery included 5 tests: Standard Continuous Performance Task (measuring sustained attention), Manikin (right/left orientation), Pursuit Circle Tracking (motor coordination), Switching (cognitive flexibility), and Stroop (response inhibition). Of the tests, Manikin, Switching, and Stroop were chosen for analysis. These three tests elicited greater cognitive output measures than the sustained attention and motor coordination tasks following the familiarization visit. Furthermore, these tests reflect similar measurements from previous research (Li, Cui, Sun, Wang, & Lui, 2017; Yano, et al., 2015; Niu, et al., 2013), thus we felt they were the ideal choice for data analysis following our protocol.

To minimize variability in the results from a potential learning effect, we analyzed the data as a change in score from the familiarization exam (pre- or post-exercise minus – baseline). The performance reports include the mean reaction time (RT) for correct responses measured in milliseconds (ms), the percent correct (%corr; number of correct divided by the total number of responses), and throughput (number of correct responses per minute of available response time).

Cerebral Oxygenation

To measure the effect of fractionized exercise on cerebral vascular function, near-infrared spectroscopy (NIRS; PortaLite, Artinis Medical Systems, Netherlands) was used to measure the change in oxygen saturation in the prefrontal cortex of the brain during cognitive function testing. The NIRS device was placed on the left side of the forehead, two centimeters from the midline above the eyebrow. The device was held in place with a headband and covered with a small black cloth to minimize light interference and movement artifacts. Oxygenated (O_2Hb) and deoxygenated (HHb) hemoglobin were measured using NIRS at a rate of 25 Hz when participants sat in a chair at rest prior to cognitive function testing and throughout the cognitive tests. The NIRS system calculates tissue saturation index (TSI; TSI = (O_2Hb/tHb) x 100), an index of tissue oxygenation.

Fractionized exercise

Participants were asked to walk at a set stepping cadence determined during the pre-exercise visit (i.e., visit 2) to induce a heart rate considered moderate-intensity, defined in this study as 60-75% of age-predicted maximal heart rate. Once we determined the stepping cadence they needed to walk to achieve the desired intensity, the participants were expected to replicate the cadence on their own to complete the fractionized exercise protocol. To assist participants with walking at a set cadence, they were given a metronome that sounded beeps that participants could match with each step. Upon leaving the laboratory on day 6, participants were instructed to walk at their specific cadence for three 10-minutes bouts with the aim of completing one bout before noon, at midday, and evening.

Statistical Analysis

Statistical analysis was performed using SigmaPlot version 13.0 (Systat Software, San Jose, California). All data were considered normally distributed based on the Shapiro-Wilk equation for normality, except for Switching TP, Stroop Task 3, and peripheral PP, which were log-transformed prior to analysis. A paired t-test was used to compare sleep duration and stepping cadence between the two TIB protocols. Two-way repeated-measures analyses of variance (ANOVA) with factors of time (pre- vs. post-exercise) and sleep duration (8-hours vs. 11-hours TIB) were used to assess change in central BP, cognitive function, and tissue oxygenation. A Tukey post-hoc test was used when main effects were identified. The relationship between central BP and cognitive function was assessed using Pearson correlation coefficients. Statistical significance was considered at $p < 0.05$.

CHAPTER IV

RESULTS

Participants

Table 1 identifies participant characteristics measured at the first study visit. All participants included in the analysis successfully completed both TIB protocols for the study (n = 8). Sleep duration was significantly different between the 8- and 11-hour TIB protocols (429 ± 21 min. vs. 549 ± 16 min., $P < 0.0001$). One participant did not perform the cognitive assessment with the NIRS device; therefore, data recorded for cerebral oxygenation included seven participants.

Table 1. Participant characteristics.

Age (years)	46 + 5
Gender (females)	7; 88%
Height (cm)	167.0 + 7.9
Weight (kg)	69.1 + 11.5
BMI (kg/m^2)	24.9 + 4.1
Waist Circumference (cm)	85.4 + 8.6
Seated Systolic BP (mm Hg)	114 + 10
Seated Diastolic BP (mm Hg)	75 + 9
Fasting Blood Glucose (mg/dL)	100 + 11

Values are expressed as mean ± standard deviation (SD). BMI, body mass index; BP, blood pressure.

Physical Activity

Fractionized exercise produced similar average stepping cadence between the two TIB protocols (8h: 123 ± 13 steps per minute vs. 11h: 123 ± 15 steps per minute, $P = 0.93$). Baseline physical activity (PA) values were recorded as the average of the first five days of the 6-days of assessment. Baseline PA was compared to PA measured on day #6, the day of fractionized exercise (**Figure 1**). A main effect for time (pre- vs. post-exercise) was found for vigorous PA (35.52 vs. 53.81 minutes, $P < 0.001$) such that time

spent in vigorous activity was higher on the day of fractionized exercise as compared to baseline PA. No other differences were found for moderate PA or total moderate-vigorous PA (**Table 2**).

Table 2. Time (minutes per day) spent in moderate and vigorous daily physical activity.

	8hr		11hr		2-way ANOVA P-values		
	Pre	Post	Pre	Post	Inter	Sleep	Time
Mod	145 + 44	146 ± 60	138 ± 53	125 ± 47	0.56	0.27	0.54
Vig	38 ± 28	57 ± 40	32 ± 17	50 ± 33	0.81	0.53	<0.01
MVPA	183 ± 66	204 ± 86	171 ± 53	176 ± 74	0.85	0.51	0.83

Values are expressed as mean ± SD. Pre-values are expressed as the average of days #1 through #5 of activity monitoring. Inter, Interaction; Mod, moderate; Vig, vigorous; MVPA, total moderate-vigorous physical activity.

Overnight Blood Pressure

Dipping pattern was calculated as the lowest drop of average hourly mean BP during sleep (hours 1-3, hours 4-6, or hours >6) from wake BP. On average, subjects were considered to have normal nighttime dipping patterns for peripheral and central systolic BP (>10%, **Table 3**). Central PP dipped during sleep, but there was no significant difference between sleep or exercise conditions (**Figure 2**). More importantly, there was no significant main effect for time (pre- vs. post-exercise) for the average overnight peripheral or central BP (**Table 3**).

Table 3. Mean wake and sleep blood pressure (mm Hg).

	8hr		11hr		2-way ANOVA P-values		
	Pre	Post	Pre	Post	Inter	Sleep	Time
WpSBP	122 ± 12	117 ± 12	119 ± 8	118 ± 6	0.59	0.74	0.53
SpSBP	100 ± 9	103 ± 13	102 ± 8	100 ± 7	0.20	0.62	0.84
WcSBP	115 ± 12	109 ± 10	111 ± 7	111 ± 7	0.43	0.69	0.39
ScSBP	94 ± 7	97 ± 12	96 ± 7	94 ± 6	0.26	0.65	0.84
WpPP	50 ± 13	49 ± 8	48 ± 6	48 ± 5	0.98	0.78	0.87
SpPP	44 ± 7	45 ± 7	45 ± 5	42 ± 4	0.09	0.47	0.53
WcPP	42 ± 12	39 ± 5	40 ± 5	39 ± 6	0.91	0.77	0.60
ScPP	37 ± 5	38 ± 5	38 ± 4	36 ± 3	0.13	0.40	0.44
WPP-amp	8 ± 2	8 ± 2	8 ± 1	9 ± 2	0.40	0.32	0.42
SPP-amp	7 ± 2	7 ± 2	7 ± 2	7 ± 1	0.23	0.80	0.88
% Dip (pSBP)	21 ± 6	16 ± 7	17 ± 7	19 ± 4	0.22	0.63	0.60
% Dip (cSBP)	22 ± 5	16 ± 7	17 ± 7	19 ± 4	0.11	0.15	0.49

Values are means ± SD. Inter, Interaction; W, wake; S, sleep; pSBP, peripheral systolic BP; cSBP, central systolic BP; pPP, peripheral PP; cPP, central PP; PP-amp, PP-amplification.

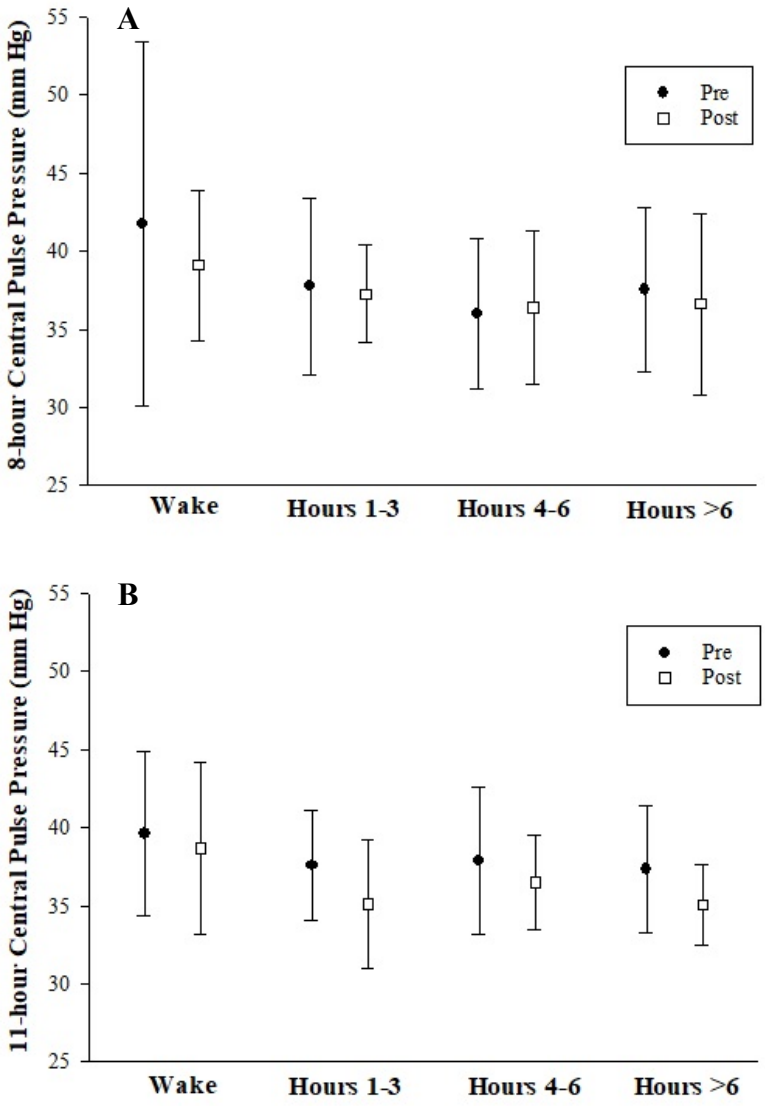

Figure 2. Central pulse pressure variability during sleep. (A) 8-hour TIB central PP. (B) 11-hour TIB central PP.

Cognitive Function

Cognitive test scores are shown as a change from the initial baseline visit to reduce the impact of the learning effect in our analysis. A main effect for time (pre- vs. post-exercise) was found for cognitive function (**Table 4**) such that all cognitive test scores improved following fractionized exercise except for Stroop Task 3 (P = 0.08). Mean response time significantly improved following exercise for Manikin (-517.63 vs. -

698.63ms, P = 0.03) and Switching (-447.88 vs. -536.25ms, P = 0.02). In addition, throughput values significantly increased following exercise for Manikin (13.88 vs. 19.38, P < 0.01) and Switching (0.68 vs. 0.85, P = 0.02). Data recorded for the Stroop tests were recorded as the number of correct answers in the allotted time. The average number of correct answers for Stroop Task 1 (3.01 vs. 7.94, P < 0.01) and Stroop Task 2 (-0.813 vs. 3.00, P < 0.001) significantly increased following fractionized exercise, while Stroop Task 3 only tended to increase (7.31 vs. 10.00, P = 0.08).

Table 4. Cognitive function test scores following exercise in 8hr vs 11hr sleep durations.

	8hr		11hr		2-way ANOVA P-values		
	Pre	Post	Pre	Post	Inter	Sleep	Time
Manikin RT	-560 ± 445	-799 ± 508	-475 ± 383	-597 ± 473	0.11	0.27	0.03
Manikin TP	14.9 ± 6	21.8 ± 6.7	12.9 ± 6.8	17 ± 9.9	0.34	0.30	0.01
Switching RT	-514 ± 414	-561 ± 371	-381 ± 533	-511 ± 521	0.09	0.35	0.03
Switching TP	5.4 ± 6.5	8.6 ± 2.5	4.8 ± 5.3	7.4 ± 5.4	0.10	0.10	0.03
Stroop Task 1 # Correct	3.3 ± 6.7	7.9 ± 3.6	2.8 ± 7.9	8 ± 7.3	0.76	0.94	0.01
Stroop Task 2 # Correct	0.5 ± 8	3 ± 6.1	-2.1 ± 3.9	3 ± 5.6	0.19	0.45	>0.01
Stroop Task 3 # Correct	8 ± 4.6	11.8 ± 3.8	6.6 ± 6.8	8.3 ± 8.5	0.81	0.37	0.08
Stroop Interscore	7.3 ± 4.7	8.9 ± 2.5	6.6 ± 5.3	5.4 ± 7.5	0.30	0.08	0.83

Values are means ± SD; n = 8 for all data. Inter, Interaction; RT, reaction time (ms); TP, throughput.

Table 5 shows the effect of fractionized exercise on tissue saturation index (TSI) measured in the brain during cognitive function testing. A main effect for sleep duration was that cerebral TSI values were significantly higher during the 11-hour TIB protocol than the 8-hour protocol for all reported cognitive tests ($P < 0.05$). Additionally, a main effect for time (pre- vs.post-exercise) was found for the Color/Word Stroop test such that fractionized exercise improved TSI values for all three Stroop tasks (Task 1: 0.93 vs. 1.34%, $P = 0.04$; Task 2: 0.84 vs. 1.25%, $P < 0.01$; Task 3: 0.89 vs. 1.25%, $P = 0.05$).

Table 5. Cerebral tissue saturation index (%) measured during cognitive function testing.

	8hr		11hr		2-way ANOVA P-values		
	Pre	Post	Pre	Post	Inter	Sleep	Time
Manikin	0.50 ± 0.73	0.84 ± 0.85	1.61 ± 0.79	1.26 ± 0.97	0.25	<0.01	0.96
Switching	0.57 ± 0.74	1.14 ± 1.18	1.52 ± 0.79	1.40 ± 0.97	0.31	<0.01	0.10
Stroop Task 1	0.44 ± 0.62	1.16 ± 1.19	1.42 ± 0.90	1.53 ± 1.08	0.23	<0.01	0.04
Stroop Task 2	0.29 ± 0.73	1.02 ± 0.93	1.39 ± 0.69	1.47 ± 0.93	0.16	<0.01	0.01
Stroop Task 3	0.34 ± 0.47	1.00 ± 0.94	1.44 ± 0.64	1.50 ± 0.77	0.19	<0.01	0.05

Values are means ± SD; n = 7 for all data. Values are expressed as the percent (%) change from baseline. Inter, Interaction.

Association between Overnight BP and Cognitive Measures

Relationships between the change in nighttime central BP following exercise and cognitive function was minimal and presented in **Table 6**. There was a positive correlation observed between increased nighttime PP-amplification and increased Manikin TP following exercise ($r = 0.718$, $P = 0.002$; **Figure 3A**) Additionally, there was

a negative correlation between the change in nighttime PP-amplification and the change in Manikin RT such that faster RT was observed in individuals with greater increases in nighttime PP-amplification ($r = -0.644$, $P < 0.01$; **Figure 3B**). There was also a positive correlation between the change in overnight central systolic BP (cSBP) and change in Manikin TSI values ($r = 0.541$, $P = 0.04$).

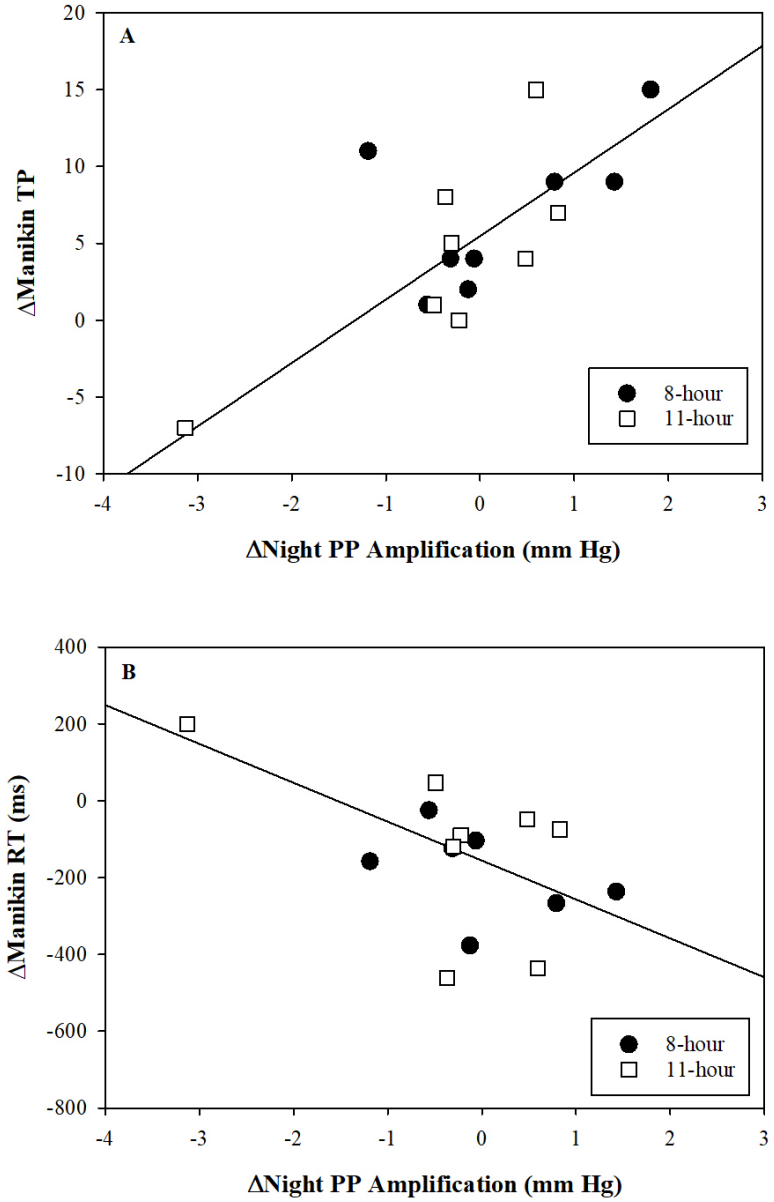

Figure 3. Relationship between change in nighttime pulse pressure (PP) amplification following fractionized exercise and Manikin (A) throughput (TP; $r = 0.718$, $P = 0.002$) and (B) reaction time (RT; $r = -0.644$, $P < 0.001$). Δ represents change (post – pre) following fractionized exercise.

Table 6. Pearson product correlation coefficients for overnight BP and cognitive measures.

	ΔcSBP	ΔcPP	ΔPPAmp
ΔManikin TSI	0.54*	0.46	-0.20
ΔSwitching TSI	0.27	0.36	-0.21
ΔStroop 1 TSI	0.22	0.29	-0.14
ΔStroop 2 TSI	0.44	0.42	-0.24
ΔStroop 3 TSI	0.37	0.45	-0.08
ΔManikin RT	0.03	-0.09	-0.64*
ΔManikin TP	-0.14	0.08	0.72*
ΔSwitching RT	-0.07	0.00	-0.17
ΔSwitching TP	-0.01	-0.38	-0.13
ΔStroop Task 1 # Correct	-0.10	-0.24	-0.34
ΔStroop Task 2 # Correct	-0.18	-0.15	-0.25
ΔStroop Task 3 # Correct	0.03	0.26	0.11
ΔStroop Interscore	0.05	0.29	0.20

Correlation coefficients. *P < 0.05. TSI, tissue saturation index; RT, reaction time (ms); TP, throughput.

CHAPTER V

DISCUSSION AND CONCLUSION

The primary aim of this study was to determine the effect of fractionized exercise on nighttime central BP. As little as 10-minutes of physical activity has been found to produce post-exercise hypotensive effects on peripheral BP (Angadi et al., 2010; Monahan 2007), and evidence exist that fractionized exercise can lower BP more than a single continuous bout of physical activity. We hypothesized that fractionized exercise would lower nighttime central PP due to the intermittent stimulus to lower BP throughout the day. Since lower BP has been correlated with improved brain health, a secondary hypothesis is that exercise-induced central BP changes would improve cognitive function. We did not observe fractionized exercise to lower nighttime central BP, but we did find cognitive function improved following exercise. Cerebral oxygenation patterns were also improved following fractionized exercise, but only for the Color/Word Stroop test.

Nighttime BP is an important determinant of cardiovascular disease risk, with greater indications from central BP. Elevated central systolic BP and PP results from arterial stiffness and/or endothelial cell dysfunction. Elevated central PP increases pulsatile stress on the aortic wall, leading to vascular damage and decreased elasticity (Mitchell 2014). Central pressures have more implications for health than peripheral values due to the close proximity to target organs supplied by the aorta. When a person sleeps, BP is typically lower than wake-time values due to decreased sympathetic activation. A normal BP dipping pattern is considered >10% drop in systolic BP. As such, we observed a normal nighttime decrease in central systolic BP in the present study,

but we observed only a marginal decrease in central PP. Our findings are similar to those by Serinel et al. (2019), who observed no nighttime central PP changes compared to daytime values. However, their findings observed middle-aged adults (n = 31, 45 $\pm$ 10 years) with obstructive sleep apnoea. Conversely, other studies observing the nighttime dipping patterns in hypertensives reported increases in central PP than daytime values (Argyris et al., 2018; Phillips, Hedner, Berend, & Grunstein, 2005). This is in opposition to the findings by Jankowski et al. (2013), who observed a decrease in nighttime central PP in both normotensive and hypertensive subjects. However, the observed studies were consistent in reporting that the nighttime fall in central pressures was not as great as the fall in peripheral pressures (Serinel et al., 2019; Argyris et al., 2018; Williams, Lacy, Baschiera, Brunel, & Dusing 2013; Jankowski et al., 2013; Phillips, Hedner, Berend, & Grunstein, 2005).

We found no change in central systolic BP or PP following fractionized exercise in either sleep condition. This contrasts with previous research that has observed a decrease in nighttime peripheral BP following fractionized exercise. Bhammer, Angadi, & Gaesser (2012) investigated the effects of fractionized exercise on peripheral pressure indices. Similar to our protocol, they had participants perform three bouts of 10-minutes of walking at 75-79%. Participants performed all three bouts of activity with the researchers on a treadmill at specific times of day (between 9:15-9:45 a.m., 1:15-1:45 p.m., and 5:15-5:45 p.m.). In our protocol, subjects completed the three walking bouts in the afternoon (beginning after 12:00 p.m.) based on their own schedules independently at home, and exercised as late as 7:00 p.m. Bhammer, Angadi, & Gaessar (2012) reported decreases in ambulatory peripheral systolic BP following their exercise protocol. One

reason for our varying results could be that they observed the affects of activity in pre-hypertensive adults while our adults were normotensive. Another possible explanation for conflicting results could be exercise performance and intensities. Our participants were not directly monitored, as subjects were sent home with a metronome set at the determined cadence. Furthermore, intensity was determined beforehand in the lab and was slightly lower than their study (60-75% HRmax vs. 75-79% HRmax). Another study by Park, Jastremski, and Wallace (2005) also observed the post-exercise hypotensive effects following morning and evening aerobic exercise in dipping and non-dipping hypertensives. Participants performed 30 minutes of walking on a treadmill at 70% HRmax between 6:00 – 8:00 a.m. and 5:00 – 7:00 p.m. Nighttime peripheral systolic BP dropped more in non-dippers than dippers after exercise at both times of day, with similar drops between groups for daytime pressures. According to their results, time of day did not impact nighttime peripheral BP parameters, but dipping patterns did. This could explain our findings since our participants were all considered normal dippers, as Park et al. (2005) reported BP decreased more in non-dippers compared to dippers.

Studies have shown that an acute bout of exercise can improve cognitive performance the next day after activity (Chang, Labban, Gapin, & Etnier 2012). Cross-sectional studies find elevated cognitive performance and cerebral oxygenation levels during various Stroop tasks in physically active adults compared to their sedentary peers (Goenarjo et al. 2020). Stroop tasks involve executive function requiring participants to incorporate inhibition responses and switching between multiple tasks. The Stroop task employed in the present study was a traditional Color/Word test to test inhibition. The Switching task measured the level of cognitive flexibility, or ability to switch between

various commands, of each subject while the Manikin task tested left and right orientation. Fractionized exercise was found to increase performance during the Color/Word Stroop tasks accompanied by elevated cerebral oxygenation in the present study (main effects for time). This is consistent with Chang et al. (2019) that observed improved response times during the Color/Word Stroop test in middle-aged adults (n = 40, 58 $\pm$ 5 years) following 20-minutes of moderate-intensity aerobic activity along with other studies that find acute bouts of aerobic exercise to improve cognitive performance (Mandolesi et al. 2018; Chang, Labban, Gapin, & Etnier 2012). Our study extends the conversation to indicate that fractionized exercise can also be considered as a modality of exercise to improve cognitive function in middle-aged adults.

We hypothesized that the change in nighttime central BP following fractionized exercise would correlate with cognitive performance. Our study did not show significant changes in nighttime central BP following fractionized exercise. However, our results did show correlations between overnight PP-amplification and cognitive performance during the Manikin test such that participants with faster reaction time and improved throughput scores were those that had experienced increased nighttime PP-amplification following exercise. An increase in PP-amplification means that central PP is either decreasing more than peripheral PP or there is a greater increase in peripheral PP than the change in central PP. Higher PP-amplification indicates greater dampening of PP in the elastic central arteries and is associated with a lower risk of vascular injury (Avolio et al., 2009). Thus, our study shows that participants with greater nighttime decreases in peripheral PP compared to central PP, leading to higher PP-amplification, improved more during cognitive testing compared to participants who had no change or decreases in PP-

amplification. Our results align with a cross-sectional study by Suleman et al. (2017) that reported significant associations (P=0.03) between lower PP-amplification and poor cognitive performance. Longitudinal work also finds central PP to associate with cognitive decline after 6 years in elderly participants (n=1223, 61 $\pm$ 9 years), alluding to the dangers of central PP on brain health (Tsao et al., 2016). The Manikin test assesses left and right orientation, a function within regions of the parietal lobe of the brain (Hjelmervik et al. 2015). This area of the brain is also responsible for spatial cognition, memory retrieval, and attention. A study by Xia et al. (2015) found that participants with type 2 diabetes mellitus, a cardiovascular disease risk factor, had decreased cerebral blood flow in the inferior parietal lobe and reported cognitive deficits such as visuospatial and executive function decline related to the reduced cerebral blood flow ($r = -0.351$, $P = 0.039$). The frontal and parietal lobes are susceptible to atrophy in the presence of BP abnormalities (Hajjar et al., 2010), and the parietal lobe is one of the most vulnerable regions of the brain to develop white matter hyperintensities, associated with cardiovascular disease and hypertension (Zhuang, Chen, He, & Cai, 2018). This indicates that BP improvements would improve cerebral vascular function in this area of the brain, supporting our finding in the correlation between the Manikin test and improved PP-amplification.

To our knowledge, this is the first study to observe the effects of long sleep duration on cerebral oxygenation and cognitive function. Most studies to date compare cerebral oxygenation with sleep focus on sleep apnea, making the present findings on sleep duration unique. Among the findings available, it has been reported that short sleep duration has negative effects on cerebral oxygenation. For example, Kato et al. (2017)

found that peak cerebral oxygenated hemoglobin measured with NIRS was lower in older adults (n = 73, 70.1 ± 3.9 years) who slept <7 hours a night compared to those who slept ≥7 hours. In our study, cerebral tissue oxygenation improved following the long duration (549 ± 16 min, 9.15 hrs) compared to the normal sleep duration (429 ± 21 min, 7.15 hrs) sleep time. This finding contradicted our expected results since previous literature has reported a correlation between longer periods of sleep with cardiovascular disease and mortality (Cappuccio et al., 2011). However, we are reporting improved cerebral oxygenation patterns with longer sleep duration than shorter sleep times (our control condition of 8h TIB), thus implying that improvements in cerebral oxygenation patterns are related to the length of sleep. So, while long sleep duration has been reported to associate with a higher risk for cardiovascular disease (Sabanayagam & Shankar, 2019; Cappuccio et al., 2011), is the link between long sleep duration and disease truly related to sleep time or some other underlying dysfunction that causes people to sleep longer durations? Further research should make direct comparisons in physiological function between habitually long sleepers and normal sleepers that sleep long durations to understand the negative bodily effects of long-duration sleep fully.

Limitations

There are several limitations present in this study. First, the study had a small sample size. We were strict with the TIB protocol that necessitates a flexibile schedule for sleep and wake times, so compliance with our instructions was challenging for several people. Second, we recorded physical activity using ActiGraph's wrist-worn accelerometer. Although a recent study has provided thresholds to estimate moderate-to-

vigorous physical activity from wrist-worn accelerometers (Rhudy et al. 2019), a more accurate assessment would have been using the more established technique of wearing a waist-worn accelerometer. Third, we recruited participants considered to have normal resting BP. As discussed earlier, improvements in nighttime BP following fractionized exercise has been reported previously for adults with elevated resting BP (Bhammer, Angadi, & Gaesser 2012). Moreover, our participants were all considered normal dippers at baseline, thus the likelihood of a further BP reduction after fractionized exercise may have been limited. Lastly, cognitive performance did improve after exercise, but this finding could be explained by the learning or practice effect. We tried to diminish the practice effect by i) using software that altered the order of stimuli within each test after each study visit, ii) randomizing the order of sleep duration protocols, and iii) analyzing performance scores as a change relative to the initial familiarization visit. Despite our efforts, we cannot fully discount the possibility that some of the observed improvement in cognitive performance was due to the practice effect.

Conclusion

Fractionized exercise was ineffective at changing nighttime central BP in healthy normotensive middle-aged adults. However, novel findings were observed in this study including improved cognitive function following fractionized exercise and higher cerebral tissue oxygenation following one week of long duration sleep. The change in nighttime PP-amplification following fractionized exercise was correlated with improved cognitive performance during a Manikin test of left and right orientation. We also did not observe health decrements following one week of long duration sleep in BP, cognitive

function, or tissue oxygenation. Rather, we observed improved tissue saturation during cognitive testing following long sleep duration. There is a need for more studies to observe the influence of long sleep duration on cardiovascular and cerebral health since the present findings do not support the claim that long sleep duration leads to vascular dysfunction. Furthermore, this study only included one day of exercise intervention, providing a need for future observations on chronic exercise adaptations altering central BP and cognitive performance.

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