THE EFFECTS OF AEROBIC EXERCISE TIMING ON SLEEP ARCHITECTURE

A Thesis
by
KIMBERLY ROSE FAIRBROTHER

Submitted to the Graduate School
Appalachian State University
in partial fulfillment of the requirements for the degree of
MASTER OF SCIENCE

May 2011
Department of Health, Leisure, and Exercise Science

THE EFFECTS OF AEROBIC EXERCISE TIMING ON SLEEP ARCHITECTURE

A Thesis
by
KIMBERLY ROSE FAIRBROTHER
May 2011

APPROVED BY:

_____
Scott R. Collier
Chairperson, Thesis Committee

_____
N. Travis Triplett
Member, Thesis Committee

_____
David M. Morris
Member, Thesis Committee

_____
Paul L. Gaskill
Chairperson, Department of Health, Leisure, and Exercise Science

_____
Edelma D. Huntley
Dean, Research and Graduate Studies

FOREWORD

The research detailed in this thesis will be submitted to the journal *Sleep*, a peer-reviewed scientific and medical journal of the Associated Professional Sleep Societies, LLC. The thesis has been prepared according to the guidelines of the journal.

TABLE OF CONTENTS

ABSTRACT

THE EFFECTS OF AEROBIC EXERCISE TIMING ON SLEEP ARCHITECTURE

Kimberly Rose Fairbrother, B.S., West Virginia University

M.S., Appalachian State University

Chairperson: Scott R. Collier

Objectives: It is well known that the quality of sleep has direct effects on the manifestations of disease. Further, exercise has been shown to enhance the quality of sleep, yet little is known regarding how exercise effects sleep stages. Our laboratory has shown that the timing of exercise is important for cardiovascular benefits which may be derived from the improved quality of sleep. Therefore, the purpose of this study was to investigate the effects of aerobic exercise timing on sleep architecture. **Methods:** Thirteen subjects, 4 male and 7 female, (mean age 40 ± 3 years) with no self-reported sleep disorders and not on any medications participated in this study. Visit one consisted of informed consent and a graded exercise test to exhaustion peak oxygen consumption (VO_{2peak}) and equipment familiarization. During visits 2-4 subjects reported for 3 pre-determined exercise times at 7am, 1pm, and 7pm in a random counterbalanced order to perform a 30 minute treadmill protocol at 65% of their predetermined VO_{2peak}. A Zeo™ ambulatory sleep electroencephalogram (EEG) monitoring headband was worn during sleep. This system transmitted brainwave data to a receiver which was analyzed for sleep stage time and quality of sleep. **Results:** Aerobic exercise at 7am invoked significantly greater time spent in light and deep sleep (85% and 75% greater time in minutes, respectively, $p < 0.05$) and the greatest

frequency of sleep cycles (12% greater cycles, $p< 0.05$) compared to exercise in the afternoon or evening. However, exercise at 7pm showed less time in Rapid Eye Movement (REM) sleep compared to 7am and 1pm exercise times (40% less time in minutes REM, $p<0.05$). **Conclusion:** These data show that engaging in aerobic exercise during the early morning hours may be the most beneficial epoch of time for greater quality of sleep.

ACKNOWLEDGEMENTS

This thesis was completed through the support of an Office of Student Research Grant, a Graduate Student Association Senate Research Grant, and the Zeo™ Sleep Research Grant.

I would like to first and foremost thank my mentor and friend, Dr. Scott Collier. You always believed in me as a student, researcher, and person. You taught me how to be a great scientist and gave me confidence in myself to succeed in life.

Thank you to my thesis committee, Dr. David Morris and Dr. Travis Triplett, for your guidance, support, and friendship. The time you took to help me improve myself as a scientist and writer are greatly appreciated.

I would like to thank the graduate students in the Vascular Biology and Autonomic Studies lab, especially Ben Cartner and Chelsea Curry. This project would not have been possible without your hard work and dedication. Thank you to Tyler Kirby for your understanding and support, and for helping me to better understand and appreciate research. Also, thank you to Jared Skinner and Tracie Haines for keeping my spirits up when things were tough.

Lastly, I would like to thank my family, Mom, Dad, Jay, and Brent, for your unconditional love. You all have seen me grow from the little girl flipping around the house to the woman I am today and have supported and encouraged me every step of the way.

Introduction

It has been well observed that poor sleep quality is detrimental to one's mood, physical and mental performance, health, and overall quality of life.[1, 2] Throughout the night, most individuals follow a predictable, cyclic, sleep stage pattern of Non Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep. The stages of sleep have previously been reviewed by Kubitz et al.,[3] and are classified as follows. Stage 1 sleep is classified as the beginning phase between awakeness and the early onset of light sleep where electroencephalogram (EEG) activity is at a low voltage with mixed frequencies. Stage 2 is when the individual becomes disengaged from the environment, body temperature begins to drop, but minute ventilation and heart rate stay the same. In addition, EEG activity is very similar to that at stage 1. Stages 3 and 4 are the deepest stages of sleep where blood pressure (BP) significantly drops, tissue growth and repair occurs, blood supply to muscles increase, and hormone secretion is at its highest. Stage 3 is characterized by high amounts of high amplitude and slow wave activity, while stage 4 is characterized by even larger amounts of high amplitude and slow wave activity on an EEG. Following stage 4 is the REM stage where the eyes are constantly darting back and forth while the brain remains active. During this period, a relatively low voltage is seen with mixed frequency EEG. According to the National Sleep Foundation (NSF), good sleep quality is considered when one can experience all of the sleep stages necessary to reap the restorative and energizing benefits of sleep.[4] Previous studies have suggested that increased amount of time in deep sleep;[1, 5] decreased sleep onset latency;[1, 6] decreased time spent in light sleep;[1] and a decreased number of awakenings after the onset of sleep,[1] independent of total sleep time, all correlate to a better subjective sleep quality.

Poor sleep quality, specifically less that 6-7 quality hours per night, correlates to clinical manifestations such as hypertension,[7-11] stroke,[12] obesity,[11, 13]other cardiovascular consequences,[11] and ultimately an increased risk of mortality.[12] Hypertension is a significant modifiable risk factor for stroke, coronary artery disease, end-stage renal disease, and congestive heart failure;[14-16] and detection and control of high BP is crucial to the prevention of these outcomes.[14] The risk of cardiovascular disease increases as BP rises above 115/75 mmHg, and this risk doubles with each 20/10 mmHg increase.[17] A large cohort study done by Gangwish et al.[8] reported that short sleep duration is likely to have direct effects on the risk for the incidence of hypertension independent of its influence on body weight. In comparison, Javaheri et al., [9] compared sleep efficiency to sleep duration and the prevalence of hypertension. After an adjustment for sex and obesity, poor sleep efficiency was associated with average increases in systolic BP of 4 mmHg.[9] Short sleep duration was also associated with a 2.5- fold increase in odds for developing prehypertension (systolic BP (SBP) 120-139 and diastolic BP (DBP) 80-89 mmHg[18]), but short sleep duration was most directly related to poor sleep quality. Therefore, poor sleep quality may be more directly related to hypertension than short sleep duration.

Youngstedt and Kline [19] stated that daytime exercise is a leading factor associated with the best quality night-time sleep. Moreover, the National Sleep Foundation recommends exercise as a non-pharmacological intervention of improving sleep quality. The definition of exercise during the daytime hours is any fatiguing activity that in turn results in a greater metabolic requirement for compensatory night-time sleep.[20] Sleep researchers have predicted that duration and quality of sleep are higher in physically fit individuals, especially on nights following exercise perturbations. [3] Additionally, Brand et al.,[6] found that

adolescent athletes reported better sleep patterns as well as psychological functioning when compared to sedentary controls. Through a meta-analysis review by Kubitz et al.,[3] it was reported that exercise increased the total sleep time; times in stages 3 and 4, and decreased sleep onset latency. Previous studies have documented that aerobic exercise, specifically, is associated with the decreases in light stages of sleep as well as the increases in the deeper most restorative stages of sleep.[19, 21, 22]

Aerobic exercise is currently recommended as a modality for decreasing cardiovascular risk by decreasing resting BP. An acute, moderate intensity aerobic exercise bout elicits a post-exercise hypotension effect which resets the baroreflex to lower operating pressures.[23-25] These lower BPs are observed for up to 24-hours in hypertensive individuals.[26] No previous literature has used objective measures with a comparison of various exercise times to look at possible differences in overall sleep quality. Aerobic exercise contributes to numerous health benefits including improved sleep quality, but there is limited data examining exercise timing and how this may augment its effects on sleep stages. There may be important timing considerations due to the physiological responses elicited by a bout of aerobic exercise. Therefore, the purpose of our investigation was to examine how aerobic exercise timing affects the quality of sleep. We hypothesized that exercise at 7pm would elicit more favorable changes in sleep architecture than exercise at 7am or 1pm in accordance with the post exercise hypotension response.

Methods

Subjects

Thirteen prehypertensive men and women (SBP range of 120-139, DBP 80-89 mmHG) between the ages of 30 and 60 years old were recruited from the local community.

No subjects had a self-reported sleep disorder, and all were non-smokers and were not on any medications, including aspirin therapy or sleep aids as identified in health and activity history questionnaires. Investigators reviewed the screening questionnaire to ensure subjects met the required guidelines of the study. The investigation was approved by the Institutional Review Board of Appalachian State University (Appendix A).

Experimental Design

Subjects reported to the laboratory on four separate occasions. On the first visit, each subject completed a written informed consent as well as a physical activity/health history questionnaire (ACSM; Appendix B). Age, height, weight, and blood pressure were all recorded, followed by an assessment of peak aerobic capacity. Each subject performed a graded treadmill exercise test to volitional exhaustion while expired air was collected and analyzed to determine peak oxygen uptake (VO_{2peak}). Additionally, subjects were familiarized with all of the data collection equipment utilized within the study.

During visits two, three, and four, participants completed the randomized aerobic exercise protocol at either 7 AM (7A), 1 PM (1P), or 7 PM (7P). An average washout period of 72 hours was allotted between subsequent exercise sessions which all took place during a weekday (Monday, Thursday, Monday). Subjects were asked to refrain from alcohol and caffeine 12 hours prior to each exercise session and for the 24-hours following data collection. Following each exercise session, participants wore an ambulatory blood pressure device (SunTech Medical Oscar 2, Morrisville, NC) for the next 24 hour period as well as an ambulatory sleep monitoring system (Zeo^{TM}, Newton, MA) on the nights following exercise. Subjects were instructed to maintain the same time to bed and time to wake following each exercise bout in order to control for total sleep time.

Maximal aerobic capacity

VO_{2peak} was assessed using a customized treadmill protocol (Modified Armstrong protocol). Intensity started at 2.5 miles per hour (mph) and increased by 1 mph every two minutes until a comfortable pace was established at which point the test began. If additional intensity was required, the grade of the treadmill was increased (2.5%) at two-minute intervals until volitional fatigue was reached. Heart rate was recorded once per minute during the protocol, and a minimum of four minutes into recovery, using a Polar Heart Rate Monitor (Polar Electro Inc., Woodbury, NY). Ratings of perceived exertion (RPE) were also assessed within the last 15 seconds of each stage. Expired gases were analyzed using a True One metabolic system (Parvo Medics, Sandy, UT). Exercise capacity was assessed by exercise time and total workload expressed in metabolic equivalent of task (METS). Maximal effort was considered reached when the subjects met the three following criteria: no change in heart rate with a change in workload, a final RPE of 10 or maximal exertion, and a respiratory exchange ratio (RER) > 1.14. A 12-lead electrocardiogram (EKG) was used to monitor the test for men and women greater than 45 and 50 years of age, respectively.

Exercise protocol

Values attained from the preliminary exercise testing session were used to design the aerobic exercise prescription. All individuals performed a 30 minute, aerobic exercise bout on a motorized treadmill at an intensity corresponding to 65% of their heart rate (HR) matching at their VO_{2peak}. HR was monitored throughout every 30 minute session using a Polar Heart Rate Monitor to ensure subjects remained at 65% of their corresponding VO_{2peak}.

Ambulatory blood pressure measurement (ABPM)

Upon completion of each exercise session, subjects were outfitted with a SunTech Medical Oscar2 ambulatory blood pressure device. The device was programmed to take oscillatory blood pressure measurements every 20 minutes throughout the 24-hour post-exercise time and every 40 minutes during sleep. Data was stored within the device until it was later uploaded onto the laboratory computer.

Ambulatory sleep stage measurement

On nights following the completed exercise sessions, subjects wore a Zeo™ ambulatory sleep monitoring headband. The system consists of a soft headband (metallic fibers woven into the material) and a bedside display. The two-piece system utilizes dry sensor EEG technology to transmit brainwave data wirelessly to the bedside display where it was stored for later analysis. The Zeo™ system has been validated against an in-laboratory polysomnography and shown to be an accurate and easy way to measure sleep stages.[27]

Treatment of the data

A 1 x 3 univariate repeated measures analysis of variance was employed to determine the differences between exercise time and each outcome variable. If a significant interaction was detected, then a Bonferroni post-hoc correction was applied to determine the level of pairwise comparison. Data were analyzed by SPSS version 15 (SPSS, Chicago, IL). All data are shown as mean ± standard error (SEM).

Results

Subject characteristics are shown in Table 1. The subjects were classified as prehypertensive (BP > 120/80 mmHg) and overweight (BMI > 25). Each subject performed each time-of-day exercise bout. Aerobic exercise timing has distinct effects on several

components of sleep quality. In the nights following each exercise bout, there was no significant difference in total sleep time. This allowed for the comparison of absolute differences in the various components of sleep architecture amongst the separate exercise timing bouts.

Sleep variables

Time spent in deep sleep was significantly altered by the time of exercise (p=0.008; Figure 1). More time was spent in deep sleep at the 7A (63.385 minutes ± 6.133) time point than at 1P (43.000 minutes ± 3.193; p=0.008). Time spent in REM sleep was also significantly altered by the time of exercise (p=0.038; Figure 1). The bout of exercise at 7A presented significantly less time spent in REM sleep (98.231 minutes ± 12.945) than at 1P (117.462 minutes ± 12.468; p=0.050). Exercise timing had no significant effects on time spent in light sleep, although it followed a comparable trend (Table 2).

Exercise timing significantly altered sleep onset latency (p =.001), with 7A resulting in decreased latency (11.250 minutes ± 2.471), than either 1P (32.833 minutes ± 4.024; p=0.001) or 7P (21.333 minutes ± 3.003; p=0.001; Figure 2). Partaking in the 7P exercise bout also elicited less time to sleep onset than exercising at 1P (p =0.002). Awakenings after the onset of sleep were significantly changed with exercise timing (p= 0.018; Figure 3). With the 7A exercise there were a decreased number of awakenings (3.462 ± 0.637) when compared to 1P (5.923 ± 0.625; p=0.021) and 7P (5.308 ± 0.444; p=0.016). Time spent in wake after sleep onset was not significantly different between exercise time points (Table 2).

Discussion

The present study investigated the effects of aerobic exercise timing on the quality of sleep via the comparison of time spent in deep, light, and REM sleep, as well as sleep onset

latency, and the number of awakenings. Contrary to our hypothesis, the main finding was that a bout of moderate intensity aerobic exercise at 7A improved overall sleep quality more so than exercise at 1P or 7P. Exercise completed at the 7A time point elicited more time spent in deep sleep, less time spent in REM sleep, shorter sleep onset latency, and decreased number of awakenings following the onset of sleep. Our findings coincide with a review conducted by Kubitz et al.,[3] that presented the effects of acute and chronic exercise on sleep. They reported increases in deep sleep, and decreases in sleep onset latency, REM sleep, and wake time following acute and chronic exercise which correlate to an improved subjective sleep quality. Our study was novel in the aspect of comparing exercise timing to these effects.

The deep stages of NREM sleep, represent cortical recovery from wakefulness,[28] heightened neurophysiological restoration,[29] and increased physiological recuperation in muscle and tissue.[3] Since prior amount of awake time is directly related to the amount of deep sleep, controlling for this in the current investigation allows for the delineation of the effect of the exercise bout on subsequent deep sleep. Sleep is a period of reduced metabolic requirements essential to energy conservation and tissue restoration. In support of energy conservation during sleep, findings have suggested that deep sleep will increase as a result of increased daytime energy expenditure where exercise is the sole stimulus to deplete energy stores.[30] Likewise, we see a decrease in deep sleep during periods of restricted energy intake and weight loss.[31] It is commonly found that exercise increases levels of deep sleep, [3, 30] but there are variances among the type of exercise performed. Aerobically trained athletes have higher amounts of deep sleep when compared to anaerobic athletes.[32] Also, previous literature that shows an increase in deep sleep after exercise only show this after moderate

bouts of aerobic exercise and not with resistance exercise.[30, 32, 33] It was recently shown that 30 minutes of high-intensity aerobic exercise 3-4 hours prior to bed time elicited increased deep sleep in children compared to a baseline night of no exercise,[21] and vigorous late-night exercise just 2 hours prior to the onset of sleep was shown to increase deep sleep and light sleep as well.[34] Previous literature has focused on a single time of day for exercise and found that after both moderate and high-intensity exercise there were resultant increases in deep sleep.[20, 30] Our results are consistent with similar studies, but analysis of exercise timing revealed that deep sleep was significantly higher following the 7A exercise bout when compared to the 1P and the 7P times. Several physiological factors may have contributed to this finding; however, the limited evidence regarding the biological factors that control deep sleep only allow for the discussion of the possible underlying mechanisms to remain purely speculative.

A significant reduction in REM sleep is generally seen following exercise conditions,[20, 30] and this reduction is greater with longer exercise bouts.[20] The implications of decreased REM sleep in regards to sleep quality remains unclear. The timing of deep sleep is coupled to sleep onset, but the timing of REM sleep is potentially governed by the circadian system.[20, 35]Therefore, exercise may alter and delay the circadian rhythm phases seen in humans.[20] Alternatively, there may be a compensatory mechanism for the increases in NREM sleep seen in response to exercise. Our results showed a larger decrease in REM sleep at 7A than at 1P or 7P, which coincides with the increased deep sleep and light sleep that was seen.

Sleep onset latency (SOL) drastically shortened at the 7A time point, but was also significantly decreased at 7P when compared with 1P. Previous studies have reported

inconsistent findings on SOL, but mostly when exercise was during the late-evening hours. Youngstedt et al.,[20] reported an increase in SOL if exercise was performed within 4 hours of bed time, but several other studies have shown a decrease in SOL when exercise was performed within this time period at various intensities.[21, 34] A high-intensity cycling bout performed for 30 min within the 2 hours prior to sleep time showed a shortened SOL,[34] concurring with the results found with high-intensity exercise in children.[21] To our knowledge, no other studies have compared SOL between several different exercise time points within the day. Previous literature on SOL tends to focus on high-intensity exercise in the hours just prior to bed time. Our results show that aerobic exercise in the morning hours improves SOL more so than evening exercise.

Mechanisms regarding the beneficial effects of exercise on sleep are speculative, but have been correlated to energy conservation, tissue restitution, and temperature downregulation.[21, 30, 34] Temperature downregulation from the anterior hypothalamus in response to exercise-induced body heating has been the most accepted hypothesis,[34, 36] but lacks support in the literature. Therefore, hormonal influences may be responsible for improved sleep quality at 7A and 7P when compared to 1P. Dietary changes, energy expenditure, and specific hormonal factors such as insulin and cortisol expression alter the release of leptin. Schmid et al.[37] reported an increase in deep sleep with a concomitant increase in leptin levels, suggesting a possible relationship between leptin and sleep quality. As previously stated, deep sleep correlates to energy intake and energy expenditure, both of which are known to be regulated by circulating levels of leptin. Single bouts of acute exercise have differing effects on leptin concentrations. When trained rowers were put through 30 minutes of a maximal rowing, exercise leptin levels significantly declined immediately. [38]

Additionally, after trained males underwent a running protocol for 60 minutes at 70% of their $VO_{2\ peak}$, leptin concentrations were decreased at both 24-hours and 48-hours post exercise.[39] None of the aforementioned studies reported leptin concentrations throughout the entire day and night following exercise or when compared to a non-exercise day. The secretion of leptin follows a pulsatile fashion, with its highest levels in the evening and early morning hours.[40,41] Therefore, the timing of exercise may alter the pulsatile secretion of leptin and should be further researched in respects to sleep architecture.

Conclusions and implications

The present study indicates that partaking in a moderate bout of aerobic exercise in the early morning (7A) changes several aspects of sleep architecture and results in an improvement in overall sleep architecture. As one approaches middle age, research consequently finds decreases in the deep stages of sleep with concomitant increases in the lighter stages and a longer period of sleep onset.[42-44] To date, there are no well accepted nonpharmacological or pharmacological interventions to increase the amount of deep sleep.[45] Thus, utilizing aerobic exercise may be a non-pharmacological way to attenuate these alterations and improve sleep quality as one ages. The present investigation depicts that the timing of exercise is an important aspect to maximize these effects. It seems that the effect of exercise on the various components of sleep architecture is a complicated phenomenon involving several physiological aspects. Future research should focus on the mechanisms involved. In conclusion, aerobic exercise in the early morning (at 7A) may be the most beneficial time of day for better sleep quality.

References

1. Akerstedt T, Hume K, Minors D, Waterhouse J. Good sleep--its timing and physiological sleep characteristics. J Sleep Res 1997;6:221-9.

2. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med 2007;3:519-28.

3. Kubitz KA, Landers DM, Petruzzello SJ, Han M. The effects of acute and chronic exercise on sleep. A meta-analytic review. Sports Med 1996;21:277-91.

4. National Sleep Foundation Let Sleep Work for You. How Sleep Works 2011 [cited 2011 February 20].

5. Kryger MH, Steljes D, Pouliot Z, Neufeld H, Odynski T. Subjective versus objective evaluation of hypnotic efficacy: experience with zolpidem. Sleep 1991;14:399-407.

6. Brand S, Gerber M, Beck J, Hatzinger M, Puhse U, Holsboer-Trachsler E. High exercise levels are related to favorable sleep patterns and psychological functioning in adolescents: a comparison of athletes and controls. J Adolesc Health 2010;46:133-41.

7. Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Predictors of all-cause mortality in clinical ambulatory monitoring: unique aspects of blood pressure during sleep. Hypertension 2007;49:1235-41.

8. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension 2006;47:833-9.

9. Javaheri S, Storfer-Isser A, Rosen CL, Redline S. Sleep quality and elevated blood pressure in adolescents. Circulation 2008;118:1034-40.

10. Loredo JS, Nelesen R, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in normal adults. Sleep 2004;27:1097-103.

11. Buxton OM, Marcelli E. Short and long sleep are positively associated with obesity, diabetes, hypertension, and cardiovascular disease among adults in the United States. Soc Sci Med;71:1027-36.

12. Kronholm E, Laatikainen T, Peltonen M, Sippola R, Partonen T. Self-reported sleep duration, all-cause mortality, cardiovascular mortality and morbidity in Finland. Sleep Med.

13. Van Cauter E, Knutson KL. Sleep and the epidemic of obesity in children and adults. Eur J Endocrinol 2008;159 Suppl 1:S59-66.

14. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension 2007;49:69-75.

15. Park S, Jastremski CA, Wallace JP. Time of day for exercise on blood pressure reduction in dipping and nondipping hypertension. J Hum Hypertens 2005;19:597-605.

16. Cutler JA, Sorlie PD, Wolz M, Thom T, Fields LE, Roccella EJ. Trends in hypertension prevalence, awareness, treatment, and control rates in United States adults between 1988-1994 and 1999-2004. Hypertension 2008;52:818-27.

17. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 2004;36:533-53.

18. Franklin PJ, Green DJ, Cable NT. The influence of thermoregulatory mechanisms on post-exercise hypotension in humans. J Physiol 1993;470:231-41.

19. Youngstedt SD, Kline CE. Epidemiology of exercise and sleep. In: Sleep & Biological Rhythms: Wiley-Blackwell, 2006:215-21.

20. Youngstedt SD, O'Connor PJ, Dishman RK. The effects of acute exercise on sleep: a quantitative synthesis. Sleep 1997;20:203-14.

21. Dworak M, Wiater A, Alfer D, Stephan E, Hollmann W, Struder HK. Increased slow wave sleep and reduced stage 2 sleep in children depending on exercise intensity. Sleep Med 2008;9:266-72.

22. Reid KJ, Baron KG, Lu B, Naylor E, Wolfe L, Zee PC. Aerobic exercise improves self-reported sleep and quality of life in older adults with insomnia. Sleep Medicine 2010;9:934-40.

23. MacDonald JR, MacDougall JD, Hogben CD. The effects of exercise duration on post-exercise hypotension. J Hum Hypertens 2000;14:125-9.

24. Rueckert PA, Slane PR, Lillis DL, Hanson P. Hemodynamic patterns and duration of post-dynamic exercise hypotension in hypertensive humans. Med Sci Sports Exerc 1996;28:24-32.

25. Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension 1993;22:653-64.

26. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc 2004;36:533-53.

27. Shambroom JR, Johnstone J, Fabregas SE. Evaluation of portable monitor for sleep staging. Sleep (Rochester) 2009;32:(Suppl.): A386. Abstract 1182.

28. Walsh JK, Snyder E, Hall J, et al. Slow wave sleep enhancement with gaboxadol reduces daytime sleepiness during sleep restriction. Sleep 2008;31:659-72.

29. Benington JH, Heller HC. Restoration of brain energy metabolism as the function of sleep. Prog Neurobiol 1995;45:347-60.

30. Driver HS, Taylor SR. Exercise and sleep. Sleep Med Rev 2000;4:387-402.

31. Karklin A, Driver HS, Buffenstein R. Restricted energy intake affects nocturnal body temperature and sleep patterns. Am J Clin Nutr 1994;59:346-9.

32. Trinder J, Paxton SJ, Montgomery I, Fraser G. Endurance as opposed to power training: their effect on sleep. Psychophysiology 1985;22:668-73.

33. Faria AP, Cavagnolli DA, Rossi MV, et al. Effects of resistance exercise on the sleep patterns of sedentary individuals. Sleep Science 2009;2:141-6.

34. Myllymaki T, Kyrolainen H, Savolainen K, et al. Effects of vigorous late-night exercise on sleep quality and cardiac autonomic activity. J Sleep Res 2011;20:146-53.

35. Lavie P. Ultrashort sleep-wake cycle: timing of REM sleep. Evidence for sleep-dependent and sleep-independent components of the REM cycle. Sleep 1987;10:62-8.

36. McGinty D, Szymusiak R. Keeping cool: a hypothesis about the mechanisms and functions of slow-wave sleep. Trends Neurosci 1990;13:480-7.

37. Schmid DA, Wichniak A, Uhr M, et al. Changes of sleep architecture, spectral composition of sleep EEG, the nocturnal secretion of cortisol, ACTH, GH, prolactin, melatonin, ghrelin, and leptin, and the DEX-CRH test in depressed patients during treatment with mirtazapine. Neuropsychopharmacology 2006;31:832-44.

38. Jurimae J, Jurimae T. Leptin responses to short term exercise in college level male rowers. Br J Sports Med 2005;39:6-9.

39. Olive JL, Miller GD. Differential effects of maximal- and moderate-intensity runs on plasma leptin in healthy trained subjects. Nutrition 2001;17:365-9.

40. Brennan AM, Mantzoros CS. Drug Insight: the role of leptin in human physiology and pathophysiology--emerging clinical applications. Nat Clin Pract Endocrinol Metab 2006;2:318-27.

41. Dardeno TA, Chou SH, Moon HS, Chamberland JP, Fiorenza CG, Mantzoros CS. Leptin in human physiology and therapeutics. Front. Neuroendocrinol 2010;31:377-93.

42. Carrier J, Land S, Buysse DJ, Kupfer DJ, Monk TH. The effects of age and gender on sleep EEG power spectral density in the middle years of life (ages 20-60 years old). Psychophysiology 2001;38:232-42.

43. Faubel R, Lopez-Garcia E, Guallar-Castillon P, et al. Sleep duration and health-related quality of life among older adults: a population-based cohort in Spain. Sleep 2009;32:1059-68.

44. Hirshkowitz M, Moore CA, Hamilton CR, Rando KC, Karacan I. Polysomnography of adults and elderly: sleep architecture, respiration, and leg movement. J Clin Neurophysiol 1992;9:56-62.

45. King AC, Pruitt LA, Woo S, et al. Effects of moderate-intensity exercise on polysomnographic and subjective sleep quality in older adults with mild to moderate sleep complaints. J Gerontol A Biol Sci Med Sci 2008;63(9):997-1004.

Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	VO_2 (mL/kg/min)	BP (mmHg)
40 ± 3	173 ± 2.2	75 ±3.2	25 ± 2.5	40 ± 3.3	133/80 ± 3.14

Table 1: Subject Descriptive Characteristics. (Mean ± SEM)

	7A	1P	7P	*p*-value
Light Sleep (min)	260.385±17.522	274.769±13.484	266.615±11.725	0.67
Wake Time (min)	16.385±5.334	28.385±6.925	20.538±4.483	0.29

Table 2. Light Sleep and Wake Time compared to time-of-day exercise. *P*-value represents the result of the repeated measures ANOVA. (Mean ± SEM)

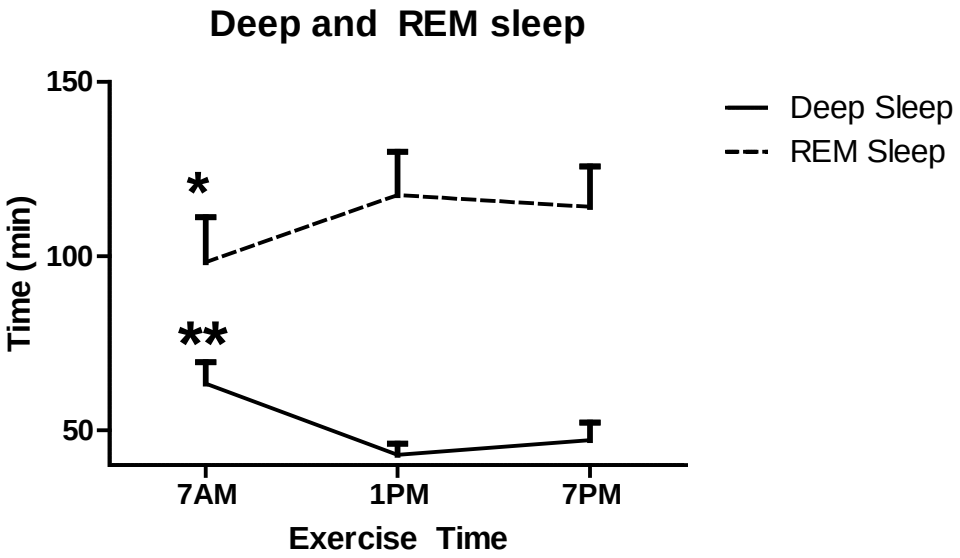

Figure 1. Time spent in Deep and REM Sleep compared to each time-of-day exercise bout. * denotes 7AM significantly different from 1PM ($p<0.05$). ** denotes 7AM significantly different from 1PM ($p<0.01$). (Mean ± SEM)

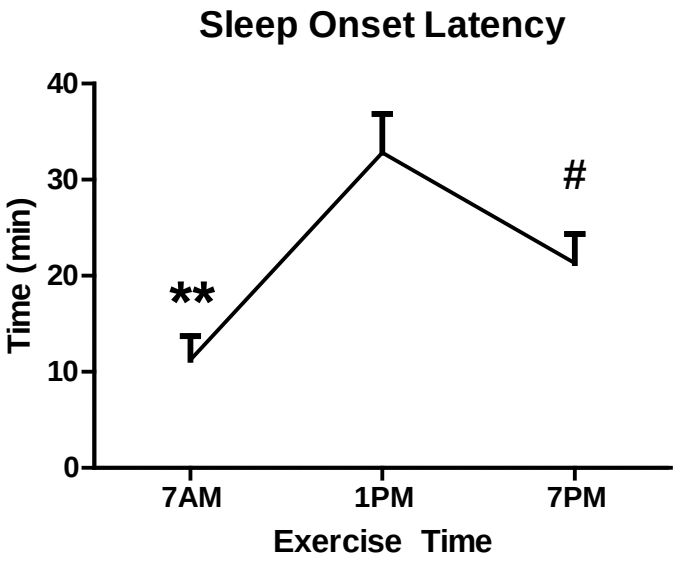

Figure 2. Time of Sleep Onset Latency compared to each time-of-day exercise bout. ** denotes 7AM significantly different from both 1PM and 7PM (p<0.01). # denotes 7PM significantly different from 1PM (p<0.01). (Mean ± SEM)

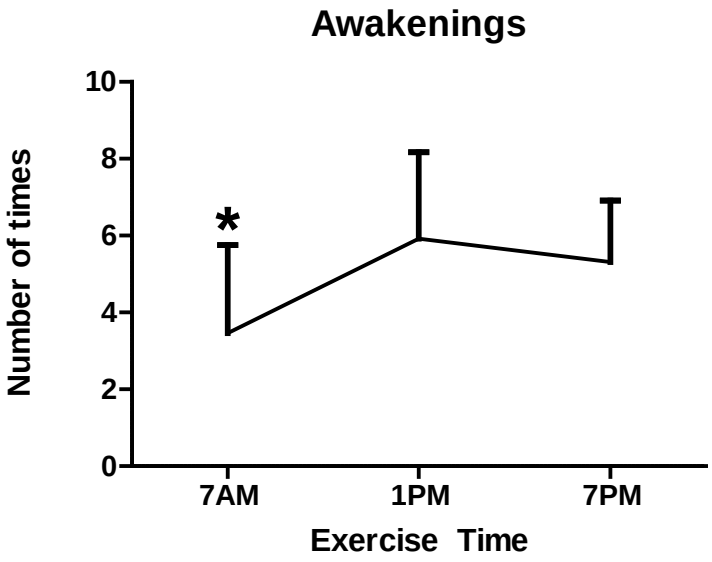

Figure 3. Number of awakenings after the onset of sleep. * denotes 7AM significantly different from 1PM ($p<0.05$). (Mean ± SEM)

APPENDIX A

APPALACHIAN STATE UNIVERSITY

Official Use Only _____-____

REQUEST FOR REVIEW OF HUMAN PARTICIPANTS RESEARCH

Please complete and send the form electronically to irb@appstate.edu. The first page with signatures must be submitted to IRB, Research & Graduate Studies, John E. Thomas Building.

1. Date: 1 / 27 / 10

2. Project Title: The effects of exercise timing on sleep hemodynamics and behavior.

3. Principal Investigator(s): Dr. Scott Collier, Dr. David Dickinson

4. Phone: x7145 (Collier) Email: colliersr@appstate.edu

5. Academic Department/Unit: HLES (Collier) Economics (Dickinson)

6. ASU Status: Faculty/Staff___X___ Graduate Student ____ Undergraduate Student_____ Other

7. If student, name of faculty mentor: _____

8. Faculty mentor's e-mail address: _____

Phone: _____

9. This is: Honors or Master's Thesis _____ Capstone or Project of Learning _____ Dissertation _

Faculty Research _____ Other _____

10. Project Support: __X_____ Non-Sponsored

_____ Sponsored: Sponsor_____ Proposal # _____

Pending __ Funded _____

11. Plan to publish or present off-campus: Yes __X___ No_____

12. Projected data collection dates: 2 /25 /10 to 10 /15 / 2010_____

13. Does this research involve any out-of-country travel? Yes _____ No____X_____

Proposals cannot be considered until the researchers have completed the online CITI Training (http://www.citiprogram.org/default.asp?language=english) required for human subject research.

I have read Appalachian State University's Policy and Procedures on Human Subjects Research and agree to abide them. I also agree to report any significant and relevant changes in procedures and instruments as they relate to participants to the Chairperson of the Institutional Review Board.

_____	_2/05/2010 _	_____	_____
PI	Date	Co-investigator	Date
_____	_____	_____	_____
PI	Date	Co-investigator	Date

CHECKLIST FOR RESEARCH INVOLVING HUMAN PARTICIPANTS

1. Purpose of proposed research:

Blood pressure (**BP**) and the incidence of hypertension increases with age. Hypertension is the most prevalent cardiovascular disease that afflicts the elderly population and hypertension-associated cardiovascular disease is the leading cause of morbidity and mortality in the Western world. It is well established that nocturnal dipping of blood pressure is a healthy adjustment and helps reset the bodies sensitivity to their blood pressure range. Clinically, if an individual with resistant hypertension does not realize a dip in blood pressure at night, they show an exponential increase in mortality and morbidity and a decrease in life expectancy.

Currently, our lab has shown a post-exercise hypotensive (PEH) response, or the decrease in blood pressure following a bout of exercise. This PEH is an important physiological event as it helps reset the baroreflex to lower operating pressures, lending clinical benefit to a population with elevated blood pressure. While a moderate-intensity aerobic exercise bout leads to PEH, the magnitude and length of PEH is not well established.

Therefore, the purpose of this study is to investigate the time course and magnitude of PEH on the nocturnal blood pressure response in unmedicated pre-hypertensive men and women. A secondary objective of this study will be to evaluate post-exercise behavioral (i.e., decision-making) effects by administering a set of decision experiments to subjects at baseline, end-of-study, and following one bout of exercise.

2. Briefly describe your subject population. Will any individuals be excluded solely on the basis of gender, race, color, or any other demographic characteristic? If so, please explain.

Our subject population will consist of 30-60 yr. old prehypertensive (systolic blood pressure range of 120-139, diastolic 80-89 mmHg) males and females, with no self-reported sleep disorders. All subjects will be non- medicated, including aspirin therapy. No subjects will be discriminated based on any demographic characteristic.

3. Give a brief description of your research procedures as they relate to the use of human participants. This description should include, at least, the following:

Procedures:

- Name and description of data gathering instrument (attach copy, if applicable)
- How will the data be collected? (e.g., audio, video, written records)

- Sample size
- How long will the procedures take?
- What, if any, relationship exists between the researcher(s) and the participants?
- What, if any, relationship exists between the researcher(s) and the agencies (e.g., schools, hospitals, homes)?
- Attach statement of approval from any agencies (e.g., schools, hospitals, homes) that will be involved with recruitment of participants or data collection.

Individuals from the Appalachian State University greater community will be recruited for this study. This population will not have more than one risk factor identified by the ACSM guidelines and using the attached form "Screening Questionnaire", therefore this is a relatively safe population to undertake 3 moderate intensity exercise bouts. The Investigators will review the screening questionnaire and medical health questionnaire to identify and exclude participants with more than 1 risk factor (Screening Questionnaire, See attached .pdf). Risk factors include: men aged 45 years or older, women aged 55 years or older,Essential Hypertension, Diabetes, hypercholesterolemia, coronary artery disease, history of myocardial infarction or stroke or a present cigarette smoker.

All individuals will be provided with a supervised moderate intensity (walking or jogging on a motorized treadmill at 65% of their HR matching 65% of their VO_{2peak}) aerobic exercise bout that will be performed at the Vascular Biology and Autonomic Studies (VBAS) Laboratory located within the Institute for Health and Human Services. If an individual has an inappropriate blood pressure response as outlined by the American College of Sports Medicine Guidelines, we will discontinue them from the study and have them report to their physician immediately. To avoid diurnal variation, all measurements will be repeated at the same time of day in the postprandial state (> 3 hours) and in the same order as the pre-measurements. Subjects will be instructed to refrain from alcohol and caffeinated product consumption for 12 hours prior to testing.

Justification of Sample Size and Treatment of the Data

A power calculation was conducted to estimate the minimum sample size necessary to provide adequate statistical power to detect possible statistically significant differences between groups as well as training effects and training by group interactions. This study was powered by 2 dependent variables, (a. pulse wave velocity, b. PEH BP response). Based on existing data from our laboratory (Collier et al. *In Press*, JSCR 2010), the estimated sample size of 32 subjects gives us an effect size of 0.82 and 0.84, respectively, with an alpha set at 0.05. Statistical power calculations were performed using SamplePower 2.0 (SPSS, Inc., Chicago, IL) For blood flow data, area under the curve above baseline values will be calculated using GraphPad Prism 3.02 (San Diego, CA) and the trapezoidal rule on the basis of actual datum points above baseline flow. Further statistical calculations will be performed with SPSS v17 (SPSS, Inc., Chicago, IL). A 1 x 3 ANOVA with repeated measures [exercise by time (morning, noon and night)] will be employed on all dependent variables. If a significant interaction is detected, an appropriate post hoc test will be conducted to determine where the significant change in the dependent variable occurred.

Equipment to be used

All subjects will perform all 3 exercise bouts following our baseline assessment.

On visit 1, Subjects will provide written consent, complete a physical activity/health questionnaire (ACSM approved), and height and weight will be recorded. Body composition will be assessed using the Tanita scale (bioelectrical impedence, BIA) system. Subjects will then be given a randomized exercise time for their first through third exercise visits. A graded exercise test to volitional exhaustion with metabolic measurements will be completed after a body composition analysis is finished. For objective verification of sleep and sleep-staging, subjects will also wear a wrist-based actigraphy and ambulatory sleep stage monitor during each evening of the study.

Visit 1

Body Composition Testing. We will use a bio-electrical impedence scale by Tanita to determine body composition. Body weight will be measured to the nearest 0.01 kg using a calibrated laboratory electronic scale. The subject will stand on the scale for approximately one minute at which time the computer will calculate reactance and resistance which gives the researcher an estimate of body composition.

Maximal Exercise Testing. Aerobic capacity will be assessed using a customized treadmill protocol. Briefly, intensity will start at 2.5 mph for two minutes and increase by 1 mph every two minutes until a comfortable pace is established. If additional intensity is required, the grade of the treadmill will be increased (% 2.5) at two-minute intervals until volitional fatigue is reached. Heart rate will be recorded once per minute during the protocol, and a minimum of four minutes into recovery, using a Polar Heart Rate Monitor (Polar Electro Inc., Woodbury, NY). Expired gases will be analyzed using a MedGraphics Ultima breath-by-breath metabolic system. Exercise capacity will be assessed by exercise time and total workload expressed in MET. A 12-lead EKG will be used to monitor the test for men and women greater than 45 and 50 years of age, respectively.

Ambulatory Blood Pressure Measurement (ABPM).

Upon completion of each exercise session, the subject will be outfitted with a SunTech Medical Oscar2 ambulatory blood pressure device. This device will take oscillatory blood pressure measurements every 20 minutes throughout the 24-hour post-exercise time and every 40 minutes during sleep. The data will be stored in the device for later uploading to the VBAS computer.

Wrist worn actigraphy and ambulatory sleep staging (head-band based dry EEG device)

Though overlap exists in the measurements provided by these two devices, the ambulatory sleep-stage monitor is newer technology still at the validation stage, which is why subjects will also generate a basic sleep scoring variable with well-validated actigraphy technology

Actigraphy: The actigraphy used (Actiwatch 64®, Minimitter (now Phillips Respironics)) is an accelerometer with sensitivity of .05 g-force, worn on the non-dominant wrist to measure its activity as a proxy for gross motor activity. At user-selected sampling epoch length of 30-seconds, the device can record over 3 weeks of data. The device has battery life of 6 months and is also water-proof to 1-meter depth for 30 minutes, and so it can be worn 24-hours a day in most cases. For our study, subjects will only wear at night during attempted sleep episodes. The actigraphy data will be scored using the manufacturer's software, which scores each 30-second epoch as either sleep or wake. Thus, we generate an objective measure of total sleep time based on a validated algorithm [Oakley, 1997 "Validation with polysomnography of the Sleep-watch sleep/wake scoring algorithm used by the Actiwatch activity monitoring system." Technical Report to Mini Mitter, Co., Inc.].

Ambulatory sleep stage measurement: During attempted sleep episodes, subjects will also wear the Zeo™ ambulatory sleep monitoring headband. The two-piece Zeo™ system includes a soft headband (metallic fibers woven into the material) and bedside display. The system utilizes dry sensor EEG technology to transmit brainwave data wirelessly to the bedside display that doubles as a clock-radio. Though still in validation stage, the device has promise of generating data on distinct sleep phases (e.g,., slow wave, REM, light sleep) that the actigraphy is incapable of generatin. An initial validation study for the Zeo™ system is: Shambroom JR, Johnstone J, Fabregas SE. Evaluation of a portable monitor for staging sleep. *Sleep*. 2009;32 (Suppl.):A386. Abstract 1182.

Each subject will be instructed on the use of the ambulatory blood pressure device and sent home with a pre-programmed device. Each subject will return the device the following day and given further study instructions at that time.

The **second, third and fourth visit** will consist of the following resting measurements;

Sphygmacor Cardiovascular Management System

Arterial Pulse Wave Velocity and Aortic Blood Pressure Waveforms (PWV, ABPW respectively). All measurements will be conducted in accordance with guidelines set forth by the Clinical Application of Arterial Stiffness, Task Force III. The applanation tonometer (Sphygmacor, Sydney, Australia) will be used to derive the ascending aortic blood pressure waveform and a range of central arterial indices. The Sphygmacor is used with a tonometer over a radial artery calibrated with a standard cuff blood pressure measurement. Also we will use the PWV (measure of arterial distensibility)

module of the Sphygmacor to obtain indexes of arterial stiffness. The Sphygmacor system is used to obtain the pulse wave between: (1) left common carotid artery and the left femoral artery, and (2) between the left femoral and the ipsilateral dorsalis pedis pulse (3) between the left common carotid artery and the left radial artery. Distance from the carotid sampling site to the mid point of the manubrium sterni, manubrium sternum to femoral artery, and femoral artery to dorsalis pedis will be measured between these points as straight lines with a tape measure. The distance from the carotid artery to the manubrium sterni will then be subtracted from the manubrium to femoral artery distance PWV will be determined from the foot-to-foot flow wave velocity. The foot of the pressure wave will be identified visually as the point of systolic upstroke. The time delay between a minimum of 15 simultaneously recorded flow waves will be averaged. PWV will then be calculated from the distances between measurement points and the measured time delay (Dt) between proximal and distal foot waveforms as follows: PWV = D / Dt (m/s); where D is distance in meters and Dt is the time interval in seconds. Values attained from carotid to femoral artery will be taken as an index of central compliance while values attained from the carotid and radial artery along with the measurement from the femoral to dorsalis pedis will be taken as an index of peripheral compliance. All data will be stored and analyzed off-line after completion of testing.

Finometer Beat to Beat Blood Pressure Machine

Blood Pressure Variability (BPV). Beat-to-beat blood pressures will be measured using finger plethysmography (FMS, Amsterdam). Blood pressure peaks will be detected via an established spectral peak detection algorithm. The sequence of the systolic peaks will then be interpolated to provide a continuous data stream, and the resulting systolic peak data detrended using a robust locally weighted regression procedure. The resulting data are split in sections, and each section is tapered using a split cosine window. Finally, Fast Fourier transform algorithms will be used to convert the data into frequency spectra and smoothed across blocks of frequencies to produce a spectrum. The power of the systolic peaks is calculated by measuring the area under the peak of the power spectra. Power spectra within the 0.04 – 0.15 Hz range are defined as low-frequency components and are considered to be representative of sympathetic vasomotor modulation.

Finometer Beat to Beat Blood Pressure Machine

Baroreflex Sensitivity (BRS). Spontaneous BRS will be derived via the sequence method. With the subjects in a supine position, R-R intervals will be recorded for 10-minutes as described above. Beat-to-beat blood pressure will be ascertained via the Finometer (FMS, the Netherlands). The spontaneous baroreflex response will be determined from the Beat-to-beat changes in the R-R interval and systolic blood pressure (SBP) by a modification of the technique of Bertinieri, et al. Any episodes of

three or more consecutive heartbeats in which R-R interval and the corresponding (SBP) change in the same direction (either up or down) will be recorded. The slope of the regression line for each episode will be calculated and the mean slope taken as an index of BRS. If the observed correlation coefficient is not statistically significant, results are discarded. In our lab, values <0.8 are not accepted.

Hokanson Strain Gauge Technology

Forearm and calf blood flow. Forearm blood flow (FBF) and calf blood flow (CBF) will be measured using mercury-filled strain-gauge plethysmography (EC-6, D.E. Hokanson, WA), as previously described. Briefly, a cuff will be placed around the upper left arm and thigh, a strain gauge around the widest part of the forearm and calf, and an additional cuff around the wrist and ankle to occlude hand and foot circulation, respectively, the wrist and ankle cuffs will be inflated and held at 50 mmHg above SBP for one minute. Arm and thigh cuffs will be inflated to 50mmHg for 7 seconds, followed by 8 seconds deflation, during a 15-second cycle, as previously described. The plethysmographic signal will be captured by a digital recorder for later analysis (BioPac Systems, CA). An average of six cycles will be used for analysis of FBF and CBF and will be expressed as milliter per minute per 100 ml of calf/forearm tissue.

Bio Pac systems

Heart Rate Variability (HRV) with head-up tilt. A modified CM5 ECG lead will be used to collect continuous R-R intervals (resolution of 1 ms) “on-line” in real time, and will stored on the computer (BioPac Systems, CA) for later analysis by Heart Signal software (Oulu, Finland). During all HRV data collection, paced breathing (12 breaths/minute) will be employed. The subject will be allowed to rest supine for 10 minutes and then will be tilted to 80 degrees for 10 minutes followed by a return to supine for 10 minutes of recovery data. The R-R intervals will be visually inspected and then filtered by the HRV software to eliminate undesirable noise or premature beats. The filtering and analysis of the R-R intervals will be conducted according to procedures described by Huikuri et al. Any R-R interval that deviates more than 30% from the previous interval will be considered premature. Following filtering, only those recordings in which less than 2% of beats are filtered will be included in HRV analysis. In the time domain, the standard deviation of all R-R intervals (SDNN), and the square root of the mean squared differences of successive R-R intervals, (RMSSD) will be determined at rest and after exercise. In addition, the percentage of R-R intervals that deviate more than 50 ms from the previous R-R interval (Dev>50) will be calculated. Power spectrum densities of HRV will be calculated for high-frequency (HF, 0.15-0.40 Hz) and low-frequency (LF, 0.04-0.15 Hz) components and the LF/HF ratio during rest and after exercise. An autoregressive model will be used to determine LF and HF power as previously described by Tulppo et al. The power spectral densities are calculated in both absolute and normalized (nu) units (normalize to total spectral power). All data

acquisitions and post-acquisition analyses will be carried out in accordance with the standards put forth by the Task Force on heart rate variability interpretation.

Hokanson Strain Gauge Technology

Vasodilatory Capacity of the Forearm. Vasodilatory capacity will be assessed in the forearm using reactive hyperemia (RH), as previously described. A blood pressure cuff placed around the upper left arm will be inflated to pressure 100 mmHg above SBP, occluding arterial inflow for 5-minutes. One minute prior to release of the cuff, a wrist cuff will be inflated to 50 mmHg above SBP. After rapid release of the arm cuff, FBF will be measured for 3-minutes, as described above. The plethysmographic signal will be captured by a digital recorder for later analysis (BioPac Systems, CA).

Cardiac Output (CO) and Total Peripheral Resistance (TPR). Co and TPR will be derived from beat-to-beat arterial waveforms, using Modelflow, as previously described. This method has been shown valid and reliable under resting conditions.

Approximately 3 days will elapse between subject visits to ensure all physiological adaptations have returned to baseline (Monday and Thursday will be assessment days).

BEHAVIORAL EXPERIMENT ADMINISTRATION

Full instructions for the behavioral experiments are included as an attachment. The set of experiment tasks will include 3 distinct individual decision tasks, to be administered to subjects at baseline, following their midday exercise episode, and on the final day of the study (return to baseline). The tasks involve a "lottery choice task", a "Bayes rule task" and a "Delayed reward" task. Real monetary incentives are at stake on each administration (i.e., each day) of the set of tasks. The Bayes and lottery choice tasks will be administered on a laptop computer (as these tasks are already programmed and being utilized as part of an existing IRB approved study), and the Time delay tasks will be administered paper and pencil. The short descriptions of each are:

Bayes Rule task (BR instructions)

This task examines how individuals make decisions based on prior information and new information about an event's likelihood. The decision to be made by the subject is whether an observed series of "draws" from an unknown box came from the Box on the Left or the Box on the Right. Both the prior odds as well as the sample variation vary across trials, such that the decisions range from relatively easy to difficult. One trial will be randomly selected from all trials, and subjects will be compensated $10 in the event that their choice was correct for that trial (otherwise, payoff is zero for this task).

Lottery Choice task (LC instructions)

In this task, subjects indicate their preferences of one gamble (or "risky event") over another. Each trail contains a relatively safer gamble and a relatively riskier gamble, thought the expected payoff

of each gamble is the same. One block of treatments includes only gambles of monetary gains, while the other includes only gambles over monetary losses. A randomly selected trial will be made from each block (gains and losses), and for the randomly selected trial, the gamble that was chosen as preferred by the subject will be played out for their actual monetary payoff. Thus, the subject's monetary payoff for this task will include a gain as well as a loss. The loss amount will be subtracted from the subject's overall decision task earnings in the event the loss outweighs the gain for this task.

Time delay task (TD instructions)

This task will ask subjects to indicate preference over receiving different amounts of money sooner rather than a larger amount of money later. The amounts of money, percent difference in monetary amounts, and time delay variables will differ across trials. One trial will be chosen at random, and the subject will receive his/her choice for that trial. Notice, this trial has a payoff to the subject that may take place the day of the experiment, or possibly 2 or 4 weeks into the future. The instructions make this clear to the subject, and payoffs for this task will be in the form of a check mailed to the subject on the specified day.

4. Is deception involved? YES _____ NO __X___

If yes, please describe.

5. Does the data to be collected relate to any illegal activities (e.g. drug use, abuse, assault)?

YES_____ NO_X____

If yes, please explain.

6. The benefits of this activity to the participants must outweigh the potential risks. To this end, please:

a. Describe the benefits to the individual participants and to society.

Knowledge of exactly how blood pressure responds to exercise throughout the day will allow us to efficiently train at the optimal time of day in order to achieve the nocturnal blood pressure changes throughout sleep. Achievement of dipping blood pressure status reduces the instance for cardiac events and may provide knowledge that could provide a longer lifespan. Further, it is possible that resting blood pressure may decrease in response to the exercise bout.

For each individual subject, each subject will gain knowledge about their present fitness level, their sleep architecture, and each will receive a personalized exercise prescription. Also, each subject will be compensated when they finish the behavior analyses questionnaires (with average compensation including a fixed $35 payment and a variable pay component that depends on decisions made in the experiment). We anticipate setting variable pay incentives so that total monetary compensation of subjects in the study will be $60-$99 (with $35 guaranteed). The fixed

payment will not be paid until the end of the study, but subjects will receive the remaining decision experiment compensation as it is earned and determined by the subject's decisions.

b. Describe the potential risks to any individual participating in this project. Please explain any possible risks of psychological, legal, physical, or social harm. What provisions have been made to insure that appropriate facilities and professional attention necessary for the health and safety of the participants are available and will be utilized?

Exercise Testing: The risks associated with exercise testing include increased blood pressure and possible heart arrhythmias (abnormal heart beats). There is a very small risk of heart attack during exercise testing/training. To minimize this risk we have the subjects complete a medical history questionnaire showing a history for these individuals. Further, all maximal exercise testing will be supervised by a trained clinical exercise physiologist. Although the electrocardiogram (ECG) poses minimal risk, occasionally a person allergic to the adhesive electrodes may develop a local irritation. Lastly, individuals may experience localized fatigue or muscle soreness especially after their initial workout sessions, however this soreness will dissipate within 24-48 hours post exercise. Rest breaks will be incorporated into the training to help minimize possible muscle soreness associated with exercise training.

Body Composition Testing: There are no known risks associated with this measure. It is essentially the same as stepping on a bathroom scale at home.

Reactive Hyperemia: No substantial risks are associated with reactive hyperemia. Subjects may feel some discomfort in their arm during the occlusion portion of the test. The sensation is similar to the "pins and needles" individuals feel if their arm "falls asleep." This feeling will immediately disappear once the occluding pressure cuff is released and blood flow returns to normal. This is a common technique employed to determine vascular function, and 5 minutes of occlusion is the minimum amount of time needed to yield accurate measures. No tissue damage is associated with this method.

Pulse wave velocity: There are no known risks associated with the Doppler ultrasounds used in this technique. A small Doppler sensor will be placed on the surface of the skin against the carotid artery, radial artery, femoral artery and the dorsalis pedis (ankle). The signal probe uses ultrasound to measure the direction and speed of blood blow through an artery. No physical disomfort should be experienced during this assessment. Patient privacy will be upheld with great care during the assessment of the femoral artery, as this is located near the pubic area.

Electrocardiography (ECG): There are no known risks associated with standard ECG. Trained technicians will perform all ECG preparation and measurements. Again, care will be taken to uphold patient privacy during preparation and assessments, as the chest area will need to be somewhat exposed for electrode placement.

Blood Pressure Assessment: There are no known risks associated with finger plethysmography or ABPM. A small cuff is placed around the idex finger or the biceps and it is inflated similar to an arm blood pressure cuff. Subjects may feel slight discomfort in their finger with this cuff but this will disappear almost immediately when the cuff is released. A trained technician will demonstrate and fit the cuff for each subject.

Ambulatory Sleep Monitoring: Minor risk of discomfort is possible wearing the actigraphy of soft-fabric Zeo™ headband. Because the back side of the actigraphy is metal and because metallic fibers are used in the Zeo™ headband to transmit brainwave data, there is risk of skin rash or reaction in individuals who may be allergic to metals. Subjects will be informed to remove either device in such a case and contact one of the investigators.

7. Please describe how participants will be informed of their rights and how informed consent will be obtained and documented. Attach a copy of the consent form and any materials used in the recruitment of participants.

Participant will be informed of their rights by written (informed consent) and verbal explanation. All questions regarding the issue of participant rights will be addressed before obtaining informed consent. Any questions that arise after consenting to the study will be addressed before continuation of the procedures.

8. The confidentiality of all participants must be maintained. To this end, please respond to the following.

Like any study, participation will involve some loss of privacy, but the information collected from each subject will be handled as confidentially as possible. The individuals file and hardcopy data will be locked in a file cabinet within a locked office in a secure building and each data file will be encoded without the individuals name to associate it.

b. How will confidentiality of data be maintained?

Also, the data will be coded and entered into a computer spreadsheet and all individual identifiers will be removed.

c. Describe the process of final disposition of the data. How long will the data be stored and how will they be destroyed?

Data will remain secured in a locked office, and/or on investigators' harddrives. As noted above, individual identifiers will be destroyed from the secondary data set once the data has been properly organized into its final spreadsheet form. This guarantees that subjects will never be identified in any dissemination of the data (e.g., presentations, papers, etc.).

d. How are participants protected from the future harmful use of the data collected in this protocol?

All data will be used only for the purpose of this study and no data will be shared with anyone outside the immediate study team. Further, all study data on computer files will be decoded so there will be no identifying features left on the spreadsheets.

*The study team consists of:

PI's - Scott R. Collier, PhD, David Dickinson, PhD.

Research Assistants:

Ben Cartner, B.S.

Kimberly Fairbrother, B.S.

Jeff Soukupt, PhD

Cate Trate, MD

Carol Cooke, MS

All of the study team will have their CITI training completed prior to the start of this study

APPENDIX B

Appalachian State University

Informed Consent for Participants in

Research Projects Involving Human Subjects

Title of Study: *The Effect of Aerobic Exercise on Behavior and Nocturnal Blood Pressure Response in Pre-Hypertensive Individuals*

Background/Purpose:

You are being asked to participate in a research study because you are a healthy male or female between 30 and 60 years of age, with no diabetes, kidney or heart problems, no history of stroke, and on no medications and have been diagnosed with untreated pre-stage 1 essential hypertension (high normal blood pressure). Dr.'s David Dickinson and Scott Collier (Departments of Economics and Health, Leisure and Exercise Science at Appalachian State University) are conducting this study.

Blood pressure (**BP**) and the incidence of hypertension increases with age. Hypertension is the most prevalent cardiovascular disease that afflicts the elderly population and hypertension-associated cardiovascular disease is the leading cause of morbidity and mortality in the Western world. It is well established that nocturnal dipping of blood pressure is a healthy adjustment and helps reset the body's sensitivity to their blood pressure range. Clinically, if an individual with resistant hypertension does not realize a dip in blood pressure at night, they show an exponential increase in mortality and morbidity and a decrease in life expectancy.

We will study the effects of aerobic exercise performed at preset times during the morning, noon and evening, to determine which time is best suited for exercise based on your night-time blood pressure response.

The purpose of this study is to examine the potential changes on nocturnal blood pressure in men and women following aerobic exercise training during a specific time of day. In addition we are interested in examining how aerobic exercise affects your body's ability to change blood pressure, heart rate and blood vessel size. A final objective of this study is to evaluate whether decision making is effected following a bout of moderate aerobic exercise.

If you have a known cardiovascular heart disease, such as congenital heart disease, hypertrophic cardiomyopathy, complex supraventricular or ventricular dysrhythmias at rest or dysrhythmias that worsen with exercise, this study may not be appropriate for you. The remainder of this form will explain the study in greater detail. If you have any questions, please ask the study personnel that gave you this form.

Study Procedures:

If you choose to participate, you will be asked:

1. To report to the Institute for Health and Human Services (IHHS) at Appalachian State University (Room 068C, University Hall Rd) on 4 separate occasions for 1 to 1.5 hours per visit for exercise measures.
2. To wear a small, mobile, blood pressure monitor that will record your blood pressure at 20 minute intervals for the 24-hour period following your scheduled aerobic exercise.

3. To wear both a wrist-based actigraphy (like wearing a wrist watch) on your non-dominant wrist and a soft headband during your attempted nightly sleep episode the evening following your scheduled aerobic exercise.

At visit 1 (Initial visit)

The morning of your initial visit, you will report to the IHHS, Rm 71, on University Hall Rd.

During this visit, you will be familiarized with the study instruments and procedures in the Research Laboratory. You will also be randomized into the group that will determine what time of day you will begin the training regimen. You will exercise during the morning time (7-8am), noon time (12-1pm), or evening (6-7pm). Your exercise times will be randomized during the first visit and we will give you a schedule for all your appearances at the laboratory. You will be asked to answer a medical and exercise history questionnaire. You will be administered a set of decision experiments, and then we will measure your height, weight, baseline blood pressure and evaluate your cardio-respiratory fitness as described below.

Graded exercise test: You will be evaluated for cardio-respiratory fitness using the graded exercise test on a treadmill. In this test, you will start walking on a treadmill at about 2.5 miles per hour and every 2 minutes the speed or grade will be increased slightly until you get tired. This test is designed to make you tired in about 10 to 12 minutes. You will be wearing a facemask (so that we can collect and analyze your expired air) and a heart rate monitor to measure your heart rate. This test will determine your maximum oxygen consumption (VO2) which is your ability to take oxygen out of the air, to the working muscles. This will help us determine the correct starting point for your aerobic exercise prescription.

Visits 2-4

At these visits you will be asked to undergo a similar exercise test for 30 minutes at 65% of your peak VO2 established during the initial visit. The aerobic exercise will consist of walking and jogging on the treadmill. Qualified clinical staff will be present at all exercise performances. On your randomly chosen noon time exercise day (could be day 2, 3, or 4), you will be administered the set of decision experiments immediately following your bout of exercise.

Risks:

The risks and discomforts involved with participating in this study are:

Exercise testing: The risks associated with exercise testing include increased blood pressure and possible heart arrhythmias (abnormal heart beats). There is a very small risk of a heart attack during the exercise testing and training. To minimize this risk, we will have you answer questions regarding your medical history and family history to screen for any significant heart disease that might exist without any symptoms.

Individuals may experience localized fatigue during the exercise testing/ training, and possibly some muscle soreness after the exercise testing/training. This should subside within 24-48 hours after testing. Soreness is rare in normal, healthy individuals. Rest breaks will be incorporated into the training to help minimize possible soreness associated with exercise training. We will also try to minimize this risk by taking you through a series of light stretches after testing is completed.

Another possible risk may be abnormal changes in your heart rate and blood pressure. We will attempt to minimize this risk by carefully monitoring your heart rate and blood pressure responses during aerobic

training. Any male greater than 45 years of age and any female greater than 50 years of age will have their heart rate and EKG monitored.

Blood pressure assessment: There may be slight discomfort due to pressure felt in the upper arm that the cuff is placed on. However, this slight pressure is only felt for about one minute while the measurement is being taken.

Ambulatory sleep monitoring: There may be minor risk of discomfort from wearing the wrist-device and/or soft headband during your attempted nightly sleep. Both devices contain metal, and so there is a minor risk of allergic reaction if your skin reacts to metals.

Answering Questionnaires should not pose any risk to you.

Decision Experiments: There may be minor risk of dissatisfaction with your monetary payoffs from these decision tasks, though average compensation is set to be satisfactory for most participants.

The investigators involved in this project have extensive experience in exercise testing, which should minimize the above risks.

Benefits:

You will benefit from having a personal fitness assessment. You will receive information about your current aerobic or muscular fitness level. Additionally, you will receive information on how well your heart and blood vessels respond to exercise training during specific times during the day. Finally, you will receive information on your sleep during the nights you wore the ambulatory sleep devices (information on both total sleep time as well as stages of deep, light, and REM sleep).

Monetary Compensation:

In addition to the health related information you will be provided (described above), you will be compensated a guaranteed $35 for participation in this study (i.e., all 4 days of the study), payable on the last day of the study. You will also earn a variable amount of money (over and above your $35 minimum) as a result of your actual decisions in the decision experiments. Because this component of your monetary compensation for this study depends on the decisions you make in the decision tasks, we cannot tell you in advance how much this will be. However, we will say that a variable compensation opportunity is available on each of the experiment days where decision tasks are administered. The level of the variable compensation will be set so that average variable compensation will be approximately $55 per subject. Thus, TOTAL monetary compensation from this study will average about $90 per subject. This means that some subjects will earn more than $90 monetary compensation, some will earn less than $90 monetary compensation, but no one will receive less than $35 monetary compensation.

You will need to provide your address and your Banner ID or your social security number for compensation.

The information learned may also help others in the future.

Voluntary Participation:

Your participation in this study is entirely voluntary and you may refuse to participate or discontinue participation at any time without penalty or loss of benefits to which you would normally be entitled. Your

decision about whether or not to participate in the study will not affect your relationship with Appalachian State University.

Alternatives:

You are free to choose not to participate in this study.

Costs/Payments:

In addition to the health related information you will be provided (described above), you will be compensated a guaranteed $35 for participation in this study. You will also earn a variable amount of money (over and above your $35 minimum) as a result of your actual decisions in the decision experiments.

Questions:

If you have any questions about the research, or in the event of a research-related injury, please contact Dr. Scott Collier at (828) 262-7145 or Dr. David Dickinson at (828) 262.7652. If you have any questions about your rights as a research subject, please contact Dr. Tim Ludwig at the Appalachian State University Institutional Review Board Office at (828) 262-2692.

In Case Of Injury:

In the event of illness or physical injury resulting from taking part in this research study, medical treatment will be provided at Watauga Medical Hospital. You will be responsible for any costs not paid by your insurance company. No other compensation is offered by Appalachian State University. We have no plans to give you money if you are injured. You have not waived any of your legal rights by signing this form.

Confidentiality of Records and Authorization to Use/Share Protected Health Information for Research:

If you agree to participate in this research, identifiable health information about you will be used and shared with others involved in this research. For you to be in this research we need your permission to collect and share this information. Federal law protects your right to privacy concerning this information.

When you sign this consent form at the end, it means that you have read this section and authorize the use and/or sharing of your protected health information as explained below.

Individually identifiable health information under the federal privacy law is considered to be any information from your medical record, or obtained from this study, that can be associated with you, and relates to your past, present, or future physical or mental health or condition. This is referred to as protected health information.

Your protected health information will be kept confidential. Your identity will not be revealed in any publication or presentation of the results of this research.

Why is it necessary to use/share your protected health information with others?

The main reason to use and share your health information is to conduct the research as described in this consent form. Your information may also be shared with people and organizations that make sure the research is being done correctly, and to report unexpected or bad side effects you may have.

In addition, we may be required by law to release protected health information about you; for example, if a judge requires such release in a lawsuit, or if you tell us of your intent to harm yourself or others.

What protected health information about you will be used or shared with others as part of this research?

We may use and share the results of tests, questionnaires, and interviews. We may also use and share information from your medical and research records. We will only collect information that is needed for the research.

Who will be authorized to use and/or share your protected health information?

The researchers will use your protected health information for this research study. In addition, the Appalachian State Institutional Review Board (IRB) committee responsible for protecting the rights of research subjects who supervise the way the research is done may have access to your protected health information.

The researchers and their staff will determine if your protected health information will be used or shared with others outside of Appalachian State University for purposes directly related to the conduct of the research.

With whom would the protected health information be shared?

Your protected health information may be shared with:

- Federal agencies that supervise the way the research is conducted, such as the Department of Health and Human Services' Office for Human Research Protections, or other governmental offices as required by law.
- If so desired, you can request your information be shared with your primary care physician

All reasonable efforts will be used to protect the confidentiality of your protected health information. However, not all individuals or groups have to comply with the Federal privacy law. Therefore, once you're protected health information is disclosed (leaves Appalachian State University); the Federal privacy law may not protect it.

For how long will your protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be used and analyzed for many years and it is not possible to determine when this will be complete.

Can you withdraw your authorization to collect/use/share your protected health information?

You always have the right to withdraw your permission (revoke authorization) for us to use and share your health information, by putting your request in writing to the investigator in charge of the study. This means that no further private health information will be collected.

Even after you withdraw your permission, Appalachian State University may continue to use and share information needed for the integrity of the study; for example, information about an unexpected or bad side effect you experienced related to the study.

Can you have access to your health information?

At the end of the study, you have the right to see and copy health information about you in accordance with the Appalachian State University policies; however, your access may be limited while the study is in progress.

Consent To Participate In Research & Authorization To Use And Share Personal Health Information:

I have read and understand the Informed Consent and conditions of this project. I have had all my questions answered. I hereby acknowledge the above and give my voluntary consent:

_____Date_____

Subject signature

_____ Date _____

Witness (Optional except for certain classes of subjects)

Should I have any questions about this research or its conduct, I may contact:

David Dickinson at 828.262.7652 or email him at dickinsondl@appstate.edu

Investigators Telephone/e-mail

Scott Collier at 828.262.7145 or email him at colliersr@appstate.edu

Investigators Telephone/e-mail

Tim Ludwig, PhD 828-262-2692 irb@appstate.edu

Administrator, IRB Telephone e-mail

Graduate Studies and Research

Appalachian State University

Boone, NC 26608

PRE-EXERCISE MEDICAL HISTORY FORM

All information given is confidential. It will enable us to better understand you and your health and fitness habits.

Name. _____Date: _____

Birthdate: _____ Age: _____

Height: _____ Weight: _____

Address: _____

_____

Phone Numbers: Home: _____Other: _____

Health History Questionnaire

	Yes	No
Do you ever get chest pains while at rest and /or during exertion?	____	____
If yes, has a physician diagnosed these pains?	____	____
Have you ever had a heart attack?	____	____
If yes, was your heart attack within the last year?	____	____
Do you have high blood pressure (i.e., a reading of more than 150 / 100)?	____	____
If yes, is your high blood pressure currently		
Have you ever been diagnosed with high cholesterol?	____	____
Do you lose your balance because of dizziness or do you ever lose	____	____

consciousness?

Are you currently being treated for any heart or circulatory condition, such as vascular disease, stroke, angina, hypertension, congestive heart failure, poor circulation, valvular heart disease, blood clots, or pulmonary disease? ____ ____

Have you ever been diagnosed with a spinal problem or do you experience frequent low back pain? ____ ____

Has your physician ever specifically told you not to do "heavy" or "hard" exercise? ____ ____

Do you know of <u>any other reason</u> why you should not do physical activity? ____ ____

Medical History

Do you have or have you ever had: (check if yes)

____ heart murmur
____ extra/skipped heart beats
____ chest pain or pressure
____ high blood pressure
____ heart attack
____ stroke
____ leg cramps
____ varicose veins
____ dizziness/fainting
____ back pain
____ shortness of breath
____ injuries to back, knees, ankles

_____ arthritis
_____ asthma
_____ bronchitis
_____ cancer
_____ diabetes
_____ emphysema
_____ epilepsy
_____ pneumonia
_____ rheumatic fever
_____ scarlet fever
_____ surgery
_____ joint pain

Explanations/Commments/Descriptions:_____
_____

Other diseases/injuries/medical problems that we should be aware of:

_____

_____

Medicines/Drugs you are now taking (please list dosages):_____

_____

Family History

Please indicate the <u>number</u> of blood relative (mother, father, grandparents, siblings who have or have had the following:

Heart attack or stroke before age 50	_____
Heart attack or stroke after age 50	_____
Congenital heart disease	_____
Heart operations	_____
High blood pressure	_____
Diabetes	_____
Substantially overweight	_____
High cholesterol levels	_____

Remarks:

_____

_____

Present Symptoms Review

Do you ever experience any of the following during exercise?

_____ Chest pain

_____ Shortness of breath

_____ Heart palpitations

_____ Cough on exertion

Health Inventory

Smoking Habits

Do you smoke cigarettes at present? Yes _____ No _____

If yes, how many per day? <1/2 pack _____ 1/2 to 1 pack _____

1 - 2 packs _____ >2 packs _____

Did you smoke cigarettes in the past and quit permanently? Yes _____ No _____

How may years has it been since you quit? _____

How many packs per day were you smoking before you quit? _____

How many years did you smoke before you quit? _____

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

_____ _____

Participant's Name Today's Date

_____

Participants Signature

Biographical Information

Kimberly Rose Fairbrother was born to Robert and Kathleen Fairbrother on June 6, 1987 in Vestal, New York. It was there that she attended Vestal Senior High School where she graduated in 2005 with an Advanced Regents Degree. She was a member of the National Honor Society, the varsity swimming and diving team, and a competitive gymnast with Southern Tier Gymnastics Academy. She then went on to West Virginia University where she majored in Exercise Physiology. After graduation in 2009, she continued on with her education at Appalachian State University. During her time there, she received five grants and researched in the Vascular Biology and Autonomic Studies laboratory. In May 2011, Kimberly graduated with a Master of Science.