The Effects of Obstructive Sleep Apnea Syndrome on Cardiovascular Function with Exercise Testing in Young Adult Males

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(ABSTRACT)

Obstructive sleep apnea syndrome (OSAS) is a serious disorder that affects an estimated 24% of middle-age males, and 9% of middle-aged females. In addition, a large portion of individuals with OSAS go undiagnosed. OSAS is associated with several adverse health problems, including the metabolic syndrome. Therefore, there is a clear need to identify new methods for assessing OSAS risk. The exercise test has been used effectively as a diagnostic and prognostic tool for those at high risk for cardiovascular disease and hypertension. Research into the cardiopulmonary responses to exercise testing in young adult men with OSAS has not been examined. **Objectives:** The objectives of this study were to: 1) evaluate whether OSAS is characterized by exaggerated ventilatory responses to ramp exercise testing, with a secondary aim to evaluate if variations in serum leptin concentration might exert a regulatory in ventilatory responses during exercise; 2) To evaluate whether autonomic control of the cardiovascular response during exercise is distorted by OSAS in young overweight men, as manifested by a blunting of heart rate and exaggeration of blood pressure responses.; 3) To explore whether various simple clinical measures and response patterns from graded exercise testing might serve to discriminate between young men with and without OSAS. **Methods:** For objectives one and two, 14 obese men with OSAS [age = 22.4 ± 2.8; body mass index (BMI) = 32.0 ± 3.7; apnea-hypopnea index (AHI) = 22.7 ± 18.5], 16 obese men without OSAS (age = 21.4 ± 2.6; BMI = 31.4 ± 3.7), and 14 normal weight subjects (objective 2) (age = 21.4 ± 2.1; BMI = 22.0 ± 1.3) were recruited. For objective three, 91 men (age = 21.6 ± 2.8; AHI range = 0.6 – 60.5; BMI range = 19.0 – 43.9) were recruited. Subjects completed a ramp cycle ergometer exercise test, and a fasting blood sample was obtained to measure plasma leptin and blood lipid levels. Repeated measures ANOVA and stepwise linear regression was used to examine objectives 1 and 2. For objective 3, stepwise linear regression and receiver operator curve (ROC) analysis was utilized. **Results:** Ventilation (V_E), the ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2) were greater in the OSAS subjects vs. the overweight subjects without OSAS ($P = 0.05$, $P < 0.05$ and $P < 0.005$, respectively) at all exercise intensities. Heart rate (HR) recovery was attenuated in the overweight OSAS subjects compared to the No-OSAS and Control groups throughout 5 minutes of active recovery ($P = 0.009$). Oxygen uptake, HR, and blood pressure did not differ throughout exercise. Leptin was not associated with ventilatory responses at any exercise intensity. Linear regression analysis revealed hip-to-height ratio (HHR), hip circumference (HC), triglyceride levels, and recovery systolic blood pressure ratio (SBPR) at 2 and 4 minutes were independent predictors of AHI (model fit: $R^2 = 0.68$, $p < 0.0001$). ROC analysis determined that

percent body fat, HHR, and recovery HR at 2 minutes and 4 minutes were the best single predictors of OSAS risk (AUC = 0.77 for each measure, p = 0.003). **Conclusions:** Unique ventilatory and hemodynamic characteristics to maximal exercise testing are exhibited in young men with OSAS. These characteristics may be related to alterations in the sympathetic nervous system and chemoreceptor activation, and may be early clinical signs in the progression of OSAS. These exercise characteristics, along with anthropometric and body composition measures may provide useful information in identifying young men at risk for OSAS.

DEDICATION

To Dani:

Thank you for your love and support. Your encouragement has gotten me through this project. I love you very much.

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I would not have achieved what I have in my academic and professional development without the support and encouragement of many people. My parents, Dean and Beth Hargens, have always supported me, and made me believe that I can do anything that I set my mind to. Their love and support over the years has been a blessing.

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CHAPTER 1

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is the most prevalent form of sleep disordered breathing (SDB), and is a disorder which adversely affects the health and quality of life of those afflicted. Numerous questions remain to be answered about OSAS, including its association to several adverse health problems, the underlying mechanisms responsible, and the unique physiological characteristics that may result. One particular area of interest, and the focus of this research, is the physiological responses to exercise in OSAS. To date, limited published literature exists examining how individuals with OSAS respond to acute bouts of exercise, as well as the effect of longer term exercise training. This chapter will briefly discuss the pathophysiology of OSAS, how it is diagnosed, the increasing prevalence of OSAS, followed by the specific aims of this research. The chapter continues with a review of what is currently known about OSAS and exercise and areas in which research is lacking. The chapter concludes with a brief description of preliminary work done in our research laboratory, as well as the research design and methods for the current research investigation.

OSAS represents a significant public health problem which impacts the use of healthcare resources. It has been estimated that in the 10 years prior to diagnosis, OSAS patients utilize double the healthcare resources to that of non-OSAS sufferers ($3,972 per OSAS patient vs. $1,969 for non-OSAS).[1] Previous research has reported associations between OSAS and stroke,[2-4] congestive heart failure,[5-9] insulin resistance and glucose intolerance,[10, 11] cardiac arrhythmias,[12-15] and hypertension (HTN).[16, 17] Recent data suggests that OSAS may also increase the risk for fatal and non-fatal cardiovascular (CV)

events,[7, 18] although no longitudinal, randomized, interventional studies have been conducted to conclusively demonstrate independent causation.[19]

The most compelling evidence linking OSAS and increased CV risk appears to be through the role OSAS plays in the pathogenesis of HTN. The Sleep Heart Health Study[17] and the Wisconsin Sleep Cohort Study,[16] two large-scale community-based studies offer compelling evidence that OSAS independently increases risk for HTN in a dose-response manner. Peppard et al.[16] report that after a four-year follow-up, individuals with mild OSAS had double the risk for HTN, while those with moderate OSAS had a three-fold higher risk. Goodfriend et al.[20] estimates that 50% of those with HTN also have concurrent OSAS.

OSAS is characterized by repetitive partial and/or total collapse of the upper airway, resulting in a partial (hypopnea) or total (apnea) cessation of airflow during sleep. With this disruption in the normal airflow pattern, decreases in arterial oxygen saturation (hypoxia) occur, with subsequent repeated arousals to re-establish breathing. What results is a poor quality of sleep and excessive daytime sleepiness (EDS), a cardinal symptom identified in OSAS patients. Several other signs and symptoms indicate a high risk for the presence of OSAS as well, including habitual snoring, witnessed nocturnal breathing pauses, gasping or choking. Cognitive functioning complaints such as memory problems, irritability, personality changes, school and/or work performance deficits, lack of concentration, and also are associated with OSAS. Visual and psychomotor performance deficits have also been noted in OSAS patients.[21-23]

Risk Factors for OSAS

The typical OSAS patient presents as an overweight or obese middle-aged male, who is frequently sleepy and a habitual snorer.[22] Obesity and OSAS are frequent co-morbid conditions, with a recent longitudinal analysis suggesting that a 10% increase in weight results in a 6-fold increase in the risk for development of OSAS after four years.[24] Furthermore, Newman et al.[25] demonstrated that OSAS severity increased with weight gain and decreased with weight loss. Large neck circumference (males > 43 cm; females >40 cm), suggesting greater adiposity and pressure over the airway also places an individual at risk for OSAS.[22] Recent evidence further suggests that distribution of body fat, specifically visceral adiposity, is a more important predictor of OSAS risk than general obesity.[26-28] Vgontzas et al.[26] reports a significant association between OSAS severity and visceral adiposity ($r=0.70$; $P<0.01$), but not with subcutaneous adiposity. Anatomical abnormalities, such as maxillary and mandibular retrognathia, also increase the risk for the development of OSAS, and often are present in those without the typical risk profile.

Family history of OSAS may also significantly increases the risk for OSAS, by as much as two to fourfold.[23, 29, 30] This may be due to genetic factors such as craniofacial structure and body fat distribution,[29] or may reflect risk factors related to shared familial lifestyle.[22] Smoking appears to affect OSAS, but data are scarce. Wetter et al.[31] report that current cigarette smokers had a significantly greater risk for moderate to severe SDB (odds ratio 4.44), independent of confounders. Former smokers' risk was no greater than non-smokers.[31]

Diagnosis of OSAS

A diagnosis of OSAS is established via nighttime polysomnography (PSG), which consists of multiple, simultaneous measurements of physiological parameters related to sleep and wakefulness during an overnight stay in the sleep clinic under the direction of a licensed sleep physician. The PSG findings from these physiological measures include the presence of significant apneas or hypopneas, often accompanied by oxygen desaturation.[23] Apneas or hypopneas lasting >10 seconds are clinically significant. Some have been seen to last >1 minute. A hypopnea is defined as a decrease of 30-50% in airflow in the presence of respiratory effort.[23] OSAS is quantified primarily through the Apnea-Hyponea Index (AHI), which is the average number of apneas and hypopneas per hour of sleep. An AHI of 5 – 15 events/hour signifies mild OSAS, 15 – 30 denotes moderate OSAS, and > 30 is severe OSAS. Less comprehensive, at-home versions of PSG have been developed, some showing good agreement to regular PSG,[32] but they have not yet been recommended for clinical use.

Prevalence of OSAS

Results from a large epidemiological study report that OSAS occurs in 2-4% of middle-aged adults,[23, 33] with estimates as high as 24% in males, and 9% in females.[33] Another estimate, based on several large prevalence studies utilizing similar methods, suggests that 20% of white adults with an average BMI of 25-28 kg/m^2 have mild OSAS and 7% have moderate OSAS.[34] Under-diagnosis, however, occurs in a large number of cases.[23, 35] Young et al.[36] estimates that 93% of females, and 82% of males with moderate to severe OSAS have not been diagnosed clinically. The reason that females are often more overlooked in OSAS diagnosis is not entirely clear. Many women with

OSAS do not fit the typical risk factor profile,[23] and frequently underreport significant clinical signs such as snoring, gasping, and partner-observed apnea.[23, 37]

Data on the prevalence of OSAS in adolescents and younger adults is scarce. No definitive population-based study has evaluated the prevalence of OSAS in younger individuals. Data suggests prevalence rates similar to adults at 1 – 3%.[38] A few studies have reported snoring rates in adolescents that range between 5 – 29%,[39, 40] with rates increasing in those with higher BMI, anatomical problems such as adenoid/tonsillar enlargement, and elevated hemoglobin levels which is suggestive of nocturnal hypoxemia.[40] Given the increasing prevalence of overweight and obese adolescents and young adults, and the frequent co-morbidity with OSAS, the prevalence of OSAS in this age group is likely on the rise, however definitive data remains lacking.

Summary

OSAS is a serious disorder that affects greater than 20% of middle-aged males, with even greater numbers that go undiagnosed. Data on the prevalence of OSAS in younger individuals is scarce; however, current trends in obesity and the increased risk for OSAS associated with obesity suggests a significant portion of younger individuals may suffer from OSAS without their knowledge. Thus, there is a clear need for early identification and intervention for the large proportion of young who may have latent OSAS, especially among the rapidly growing numbers of individuals who are overweight, pre-hypertensive, and at risk for cardiovascular and metabolic diseases by mid-life. The exercise test is widely used for diagnostic and prognostic purposes, and is effective in identifying unique physiological responses to exercise that demonstrate at-risk individuals. Unfortunately, literature examining the exercise response in OSAS is

scarce, particularly in the younger population. By examining and identifying potential differences in the response to exercise in the OSAS individual, an increased identification of those at risk for OSAS may result.

SPECIFIC AIMS

Specific Aim 1: 1) To evaluate whether OSAS is characterized by exaggerated ventilatory responses to graded exercise testing in young men with and without OSAS, to examine the independent effect of OSAS; 2) To evaluate if variations in its serum leptin concentration might exert a regulatory role during exercise. Ventilatory measures, including minute ventilation (V_E), oxygen uptake (VO_2), ventilatory equivalent for carbon dioxide (V_E/VCO_2), V_E/VCO_2 slope, and respiratory exchange ratio (RER) were measured during ramp exercise testing in young overweight adult men with untreated OSAS and without OSAS. Plasma leptin levels were measured during fasting conditions to assess the role that leptin plays in ventilatory regulation.

Specific Aim 2: To evaluate whether autonomic control of the cardiovascular response during exercise is distorted by OSAS in young overweight men, as manifested by a blunting of heart rate and exaggeration of blood pressure responses. Hemodynamic measures, including heart rate (HR), blood pressure (BP) and its determinants were measured during ramp exercise testing via cycle ergometry and immediately post-exercise in young overweight adult men with untreated OSAS and without OSAS.

Specific Aim 3: **To examine how various simple clinical measures and response patterns from graded exercise testing might serve to increase discrimination between young men with and without OSAS.** Anthropometric measures, including

height, weight, BMI, and circumference measurements were obtained. Body composition variables including body fat mass, percent body fat, central abdominal fat, and lean body mass were measured. Hemodynamic measures including HR and BP were measured at rest, during ramp exercise testing, and immediate post-exercise. Stepwise multiple regression analysis and receiver operator curve (ROC) analysis was employed to predict AHI using multiple independent variables.

BACKGROUND AND SIGNIFICANCE

Several potential mechanisms linking OSAS and HTN have been hypothesized (Table 1), many of which may also contribute to obesity-induced HTN, making it difficult to determine the independent contribution of OSAS.[34, 41, 42] Studies have suggested that several of these mechanisms contribute an effect above obesity alone in the presence of OSAS.[42] One key mediator appears to be heightened sympathetic nervous system activation. Several of the proposed mechanisms may contribute directly to sympathetic activation. Grassi et al.[43] in 2005 demonstrated a significantly heightened resting muscle sympathetic nerve activation (MSNA) in obese subjects with OSAS (73.1 ± 2.5 bursts/100 heart beats) compared to BMI, gender, age, and blood pressure matched, non-OSAS controls (59.3 ± 2.0 bursts/100 heart beats). They further report that in lean individuals with OSAS, MSNA was similar to the non-OSAS obese subjects, suggesting that the sympathetic activation seen with obesity is independent of OSAS and that OSAS stimulates sympathetic activation independent of body weight, but additive to the overweight state.[43] They confirm previous studies showing higher sympathetic activation in OSAS subjects.[44, 45]

Table 1. Potential Mechanisms Linking Obstructive Sleep Apnea Syndrome and Hypertension

Insulin Resistance
Oxidative Stress
Systemic Inflammation
Endothelial Dysfunction
Renin-Angiotensin-Aldosterone System Activation
Hyperleptinemia / Leptin Resistance
Baroreflex Dysfunction
Chemoreflex Activation
Sympathetic Activation

Chemoreflexes

Chemoreflexes exert powerful control over ventilation and cardiovascular functions in response to hypoxia and hypercapnia. Narkiewicz et al.[46] noted a tonic activation of excitatory chemoreflex afferents, and that chemoreflex deactivation by hyperoxia resulted in a decrease in MSNA and BP in OSAS subjects. In another study, Narkiewicz et al.[47] noted that the peripheral chemoreflex response to hypoxia is potentiated in OSAS. Exposed to acute bouts of hypoxic breathing, the OSAS subjects demonstrated a significantly greater ventilatory response than that of control subjects without OSAS.[47] The central chemoreflex response to hypercapnia however, was not altered suggesting hypoxia to be the predominant influence on the chemoreflex-mediated contribution to sympathetic nervous activity in OSAS.

Exercise and Chemoreflexes

Exercise is another condition in which chemosensitivity augmentation occurs, even in healthy individuals.[48] Research into the responses to exercise in OSAS patients is limited. Reduced exercise capacity has been reported in OSAS subjects in some studies,[49, 50] while another shows similar exercise capacity to control subjects.[51]

Measures of chemosensitivity with exercise also showed equivocal results, which may be due to the influence of confounding variables such as gender, differences in aerobic capacity,[49] or a high percentage of smokers in the study groups.[51] Studies by Arzt et al.[52] and Meguro et al.[53] examining individuals with congestive heart failure and (CHF) central sleep apnea (CSA) showed a heightened ventilatory response to exercise suggesting a heightened chemosensitivity. CHF patients have previously shown to have a hypersensitivity to carbon dioxide (CO_2), and these two studies demonstrate a greater ventilatory response, above that previously seen in CHF alone. They also report significant correlations between CSA severity and the V_E/VCO_2 slope, a ventilatory marker of chemosensitivity and a predictor of poor prognosis with CHF.[52, 53]

Leptin and Ventilation

Hyperleptinemia is another of the proposed mechanisms linking OSAS to HTN, due to its direct stimulatory effect on sympathetic activation.[42] Recent evidence suggests that OSAS patients demonstrate resistance to the body weight regulation function that leptin also possesses.[54] OSAS patients are predisposed to excessive weight gain, despite significantly higher leptin levels.[54] There is growing evidence that leptin also exerts control over respiration, particularly the response to CO_2.[55] Wolk et al.[55] report that in CHF patients, leptin is an independent predictor of the V_E/VCO_2 slope in graded exercise testing. No literature exists examining the relationship between leptin and ventilation in OSAS subjects.

Hemodynamic Responses to Exercise and Recovery

The limited research available on the exercise responses of OSAS subjects indicates that there may be alterations in metabolic responses[56] or reduced functional

capacity.[49, 50] No study has examined the hemodynamic responses to exercise in OSAS while controlling for confounding factors, nor has any study examined the exercise responses in younger individuals. It has been well established that alterations in HR and BP responses to both exercise and immediately post-exercise have been shown to be significant predictors of future CV and HTN risk,[57-63] however these studies have not examined the effect that OSAS may have in those responses. Given the predisposition for HTN as a result of OSAS, the hemodynamic responses to exercise in the OSAS population needs examined.

PRELIMINARY STUDIES

Previous research conducted by our research group has demonstrated that OSAS subjects may exhibit altered circulatory and metabolic responses to exercise testing. Hargens et al.,[64, 65] in two separate linear regression analyses on middle-aged OSAS patients, reported that anthropometric measurements (BMI, waist:hip ratio, body weight, neck circumference) and exercise test responses (peak SBP, HR recovery at 4 minutes) were contributors in models that predicted AHI. Kaleth et al.[66, 67] showed that in middle-aged normotensive OSAS patients, HR response to graded exercise was blunted, and that peak systolic and diastolic BP were higher than control subjects. They also reported that BP remained higher in the OSAS subjects for the first 3 minutes of recovery.[66, 67]

Preliminary data from the current research project involving younger adult males with OSAS further shows potential alterations in exercise testing responses. One interesting finding in this preliminary analysis is the potential effect of age in exercise responses. Mabry et al.[68] reports that at the ventilatory threshold, HR was 13% higher in the OSAS subjects vs. age and BMI-matched control subjects, opposite to what Kaleth et

al.[66, 67] reported in middle-aged individuals. Hargens et al.[69] reported that in young adults with OSAS, the ventilatory equivalent for CO_2 (V_E/VCO_2) was significantly greater when considered across all workloads, particularly at submaximal exercise levels, suggesting that chemosensitivity may be altered in OSAS. These two studies were conducted with small numbers of subjects and confirmation is needed with larger samples that afford adequate statistical power.

RESEARCH DESIGN AND METHODS

The protocol was designed to establish two groups of overweight subjects (BMI > 25 kg/m^2), and one group of normal weight subjects recruited from the campus of Virginia Tech, as well as the surrounding communities. Groups consisted of college-aged males only (18-26 yr) who did not participate in regular physical activity ($\geq$ 30 minutes/day, $\geq$ 3 days/week) for the previous 6 months. Additional exclusion criteria were: no acute respiratory infections during the previous 6 weeks; no diagnosed or medically-treated cardiovascular, pulmonary (including asthma) or metabolic disorders; not receiving any vasoactive medications; and no musculoskeletal conditions that would preclude maximal aerobic exercise testing. Upon qualification, all subjects completed written informed consent, followed by a health history questionnaire, Epworth Sleepiness Scale (ESS) to assess EDS, and the Veteran's Specific Activity Questionnaire (VSAQ) to estimate functional capacity. If no additional exclusion criteria were identified, subjects proceeded to Stage 1 testing. Stage 1 testing consisted of: overnight unattended home sleep evaluation with the Embletta device. Individual instruction and demonstration was provided to subjects, as needed, for the Embletta procedure. Embletta recordings were downloaded to computer immediately after the overnight tests, scored by our sleep

technician, and interpreted by a sleep physician. Embletta scores from the data were scaled continuously, using approximation of the Apnea-Hypopnea Index (AHI); for most analyses, scores were transposed into coarse AHI categories so subject data can be grouped by response classes for analyses, i.e. No-OSA (AHI<5); positive OSA (AHI>5). Goal for recruitment was to achieve 20 subjects for each subject group. In Stage 2 testing, subjects completed the following tests: (a) anthropometric measurements, resting HR and BP measurements, followed by maximal ramping exercise test on an electronic cycle ergometer, with measurements for HR and BP in exercise and recovery and gas exchange for determination of ventilatory and functional capacity measures (VO_2, VCO_2, V_E, V_E/VCO_2, RER) (b) blood samples for fasting leptin; samples prepared/stored at -80°C for later batch analyses. Plasma leptin determined via radioimunnoassy (RIA) (Linco Research, Inc., St. Charles, Missouri) (c) Dual energy X-ray absorptiometry (DEXA) for central abdominal fat.

Statistical Analysis

ANOVA was utilized to analyze exercise ventilatory and hemodynamic responses for main effect of group and for differences at each exercise level, as well as exercise recovery responses. Recovery BP responses were converted to ratios (i.e., BP at 1 minute recovery / BP at peak) while HR differences between peak HR and recovery were calucated (i.e., HR at peak – HR at 1 minute recovery). Biochemical markers were analyzed for group differences utilizing ANOVA, and correlated to markers of OSA severity. Multiple linear regression and receiver operator curve (ROC) analysis was used to predict AHI score from multiple independent variables including anthropometric and

body composition measures, and exercise test responses, including post-exercise recovery responses.

PROTECTION OF HUMAN SUBJECTS

All study materials (i.e., informed consent forms, questionnaires, study protocols) have been submitted to the Virginia Tech Institutional Review Board for Human Subjects (IRB # 04-370), and was approved by full IRB review on August 9, 2004, with 12 month renewal approved August 9, 2005.

INCLUSION OF WOMEN AND MINORITIES

OSAS is a disorder that affects all racial groups. Primary recruitment for study subjects took place on the Virginia Tech campus, where student population consists of 71.5% caucasian, 6.3% asian, 4.8% african-american, 2.2% hispanic, and 15.2% other. We anticipated that subjects recruited would include a representative example of all groups. Females were excluded from the current study due to possible confounding affects of menstrual cycle and oral contraception use on several biochemical markers. As a result the current study included only males.

Table 2. Targeted/Planned Enrollment

Study Title: The Effects of Obstructive Sleep Apnea Syndrome on Cardiovascular Function with Exercise Testing in Young Adult Males: Utility in Improving Disease Recognition?

Total Planned Enrollment: 60

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	2	2
Not Hispanic or Latino	0	58	58
Ethnic Category: Total of All Subjects *	0	60	60
Racial Categories			
Asian	0	4	4
Black or African American	0	3	3
White	0	43	43
Other	0	10	10
Racial Categories: Total of All Subjects *	0	60	60

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

ASSUMPTIONS

1. Subjects accurately reported current and previous physical activity (previous 6 months).
2. Subjects complied with all pre-test instructions, i.e. graded exercise test (GXT), fasting blood sample, DXA.
3. Subjects exhibited a maximal effort with GXT.
4. The bicycle ergometer was accurately calibrated to proper workloads for each GXT.
5. Sensormedics Vmax229® metabolic cart was accurately calibrated, and accurately measured all cardiopulmonary exercise variables.

DELIMITATIONS

1. Subjects were volunteers recruited from the Virginia Tech campus and surrounding communities.
2. No medication use of any kind.
3. No previous history of cardiovascular, pulmonary or metabolic, or endocrine disease.
4. No orthopedic or musculoskeletal disorders that precluded participation in a maximal exercise effort.
5. No recent history of moderately vigorous physical activity $\geq$ 3 days/wk, $\geq$ 30 min/session, over the last 6 months.

LIMITATIONS

1. Overnight polysomnography was not performed on the subjects. Unattended, home polysomnography utilizing the Embletta PDS unit was utilized, which has shown good validity with PSG performed in a sleep clinic [32].
2. Plasma levels of the soluble leptin receptor (sOB-R) were not measured. The sOB-R may be a significant factor determining free leptin in circulation, and may alter the actions of leptin, though further clarification is warranted on this role.
3. Direct measurement of sympathetic nervous system activity, either through MSNA or plasma catecholamine measurements was not done.

ABBREVIATIONS OF TERMS

AHI	Apnea-hypopnea index (events ● $hour^{-1}$)
ANOVA	Analysis of variance
BMI	Body mass index (kg/m^2)
BP	Blood pressure (mmHg)
CHF	Congestive heart failure
CO_2	Carbon dioxide
CSA	Central sleep apnea
CV	Cardiovascular
DEXA	Dual x-ray absorptiometry
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
ESS	Epworth sleepiness scale
HR	Heart rate (beats ● min^{-1})
HTN	Hypertension
MSNA	Muscle sympathetic nerve activation
OSAS	Obstructive sleep apnea syndrome
PSG	Polysomnography
RER	Respiratory exchange ratio (VCO_2 / VO_2)
RIA	Radioimmunoassay
ROC	Receiver operator curve
SDB	Sleep disordered breathing
sOB-R	Soluble leptin receptor
V_E	Minute Ventilation (L ● min^{-1})
V_E / VO_2	Ventilatory equivalent for oxygen
V_E / VCO_2	Ventilatory equivalent for carbon dioxide
VO_2	Oxygen consumption (L ● min^{-1})

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CHAPTER 2

Altered Ventilatory Responses to Exercise Testing in Overweight, Young Men with Untreated Obstructive Sleep Apnea Syndrome

Abstract

Obstructive sleep apnea syndrome (OSAS) is disorder characterized by repetitive obstructions of the upper airway. Individuals with OSAS experience intermittent hypoxia, hypercapnia, and arousals during sleep, resulting in increased sympathetic drive which continues during waking hours. Chemoreflex activation, arising from the resultant oscillatory disturbances in blood gases that can occur during apneas and hypopneas, exerts powerful control over ventilation which may elicit marked increases in sympathetic vasoconstrictor activity, contributing to increased long-term risks for hypertension (HTN) and cardiovascular (CV) disease. Leptin, an adipocyte-derived protein, may also regulate ventilation in response to disturbances in blood gasses. To evaluate whether OSAS is characterized by exaggerated ventilatory responses to exercise testing in young men, and whether leptin is associated with any regulatory role in those responses, we studied 14 overweight men with mild-moderate OSAS and 16 overweight men without OSAS who performed maximal ramping cycle ergometer exercise tests. Oxygen consumption (VO_2), ventilation, (V_E), ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2), and V_E/VCO_2 slope were measured. Circulating plasma leptin was measured via radioimmunoassay from a fasting sample. The VO_2 response to exercise did not differ between groups. The V_E, V_E/VCO_2, and V_E/VO_2 were higher ($P = 0.045$, 0.001, and $P < 0.02$, respectively) in the OSAS group across all workloads, in comparison to the No-OSAS group. V_E/VCO_2 slope, assessed

over the range of workloads, did not reach significance (P = 0.06). Leptin was not associated with ventilatory responses at any intensity. Thus, young, overweight men with mild-moderate OSAS do exhibit unique ventilatory responses to exercise when compared to overweight counterparts without OSAS. This may reflect alterations in chemoreflex sensitivity, which may contribute to increased sympathetic drive and HTN risk in OSAS. This response pattern, as assessed through standard exercise testing, may have utility in triaging young overweight men to diagnostic testing for OSAS.

Keywords: Obstructive sleep apnea syndrome, Chemoreflexes, Sympathetic nervous system, V_E/VCO_2 slope, Exercise testing, Leptin

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a sleep disorder characterized by repetitive partial and/or complete collapse of the upper airway, despite continued respiratory effort, resulting in bouts of oxyhemoglobin desaturation, sympathetic activation to re-establish breathing, and fragmented sleep. Excessive daytime sleepiness is a cardinal symptom of OSAS, and places an individual with OSAS at significantly increased risk for motor vehicle accidents (15, 21). Prevalence of OSAS in the middle-aged adult population is approximately 2 – 4% (71). One estimate suggests that mild OSAS is present in 1 in 5 adults with a body mass index (BMI) of 25 – 28 kg/m^2, with moderate-to-severe OSAS present in 1 in 15 (8). Frequently, OSAS goes unrecognized in routine medical evaluation. It is estimated that in the United States, 75 – 80% of OSA cases that would benefit from treatment, go undiagnosed (29, 70).

Several adverse health conditions and components of the metabolic syndrome have been associated with OSAS, thought to be attributable to obesity, a frequent co-morbid condition in OSAS patients. It is estimated that 60 – 90% of OSAS patients are obese (61). Several recent studies have suggested, however, that OSAS may be associated with insulin resistance and glucose intolerance (23, 54, 55), dyslipidemia (24), congestive heart failure (CHF) (4, 25, 28, 35, 57, 58), stroke (6, 39, 68), and hypertension (HTN) (45, 51) independent of obesity. In addition, it has been recently reported that OSAS may also independently increase the risk for cardiovascular morbidity and mortality (36, 57).

The strongest relationship appears to be that between OSAS and the occurrence of HTN. The Wisconsin Sleep Cohort Study (51) demonstrated an independent, dose-

response relationship between the severity of OSAS and the occurrence of HTN. After four-year follow-up, individuals with mild OSAS had double the risk for developing HTN, while in those with moderate OSAS, the risk was three-fold (51).

The mechanisms linking OSAS to HTN are unclear, but several proposed mechanisms suggest a complex interaction of several factors. Heightened sympathetic nervous system activation has been demonstrated in OSAS, which persists during waking hours (9, 18, 60). Grassi et al. demonstrated that sympathetic activity in obese OSAS subjects is greater than what is seen in obese subjects alone, and is also heightened in lean OSAS subjects, suggesting that OSAS has a sympatho-stimulating effect that is independent of body weight (18). Treatment of OSAS with nasal continuous positive airway pressure (nCPAP) has been shown to decrease sympathetic activity in the OSAS patients (18, 41).

Chemoreflexes exert powerful control over ventilation and contribute directly to sympathetic activation in response to hypoxia and hypercapnia (30), which may contribute to the heightened sympathetic activation and increased risk for HTN in OSAS. Tonic activation of the chemoreflexes, and a significantly greater ventilatory response to acute hypoxic breathing has been documented in OSAS patients at rest (42, 43) above that which has been previously noted in obesity alone (40). Exercise is another instance when chemoreflex sensitivity augments (66), and recent studies examining individuals with central sleep apnea (CSA) and CHF demonstrated an exaggerated ventilatory response to exercise in CSA subjects, suggesting an enhanced chemosensitivity above that which is normally seen in CHF (5, 37). Significant correlations between AHI and V_E/VCO_2 slope, a marker of chemosensitivity and predictor of poor prognosis with CHF,

were also reported (5, 37). Research into the exercise response of OSAS subjects has resulted in equivocal results. Decreased functional capacity in OSA subjects has been reported by some investigators (33, 65), while others report similar functional capacity to controls (1, 26, 48). These investigations were all conducted on middle-aged adults with moderate-to-severe untreated OSA.

Leptin is an adipocyte-produced protein that regulates body weight by reducing appetite and food intake (19). In obese individuals, leptin levels are markedly increased, suggesting a resistance to the weight regulating effects (10). In OSAS subjects, higher leptin levels above that seen in obesity alone and independent of body weight, have been reported (24, 52). Animal models have reported significantly higher sympathetic activation with leptin infusion (20), suggesting that increased leptin production may contribute to the increased sympathetic activation in OSAS, as well as the increased risk for the development of HTN (52).

In addition to the appetite control and sympathetic activation functions of leptin, animal models have also suggested that leptin may also posses an important regulatory function with ventilation, particularly in response to CO_2 (47, 62, 63). In humans, a significant correlation between leptin and the V_E/VCO_2 slope was reported in CHF patients, another condition in which chemoreflex sensitivity is exaggerated (67). This correlation was independent of age, gender, or body mass indices. The greatest V_E/VCO_2 slope was seen in those with the highest tertile of leptin levels (67).

To date, no published studies have examined the ventilatory response to graded exercise testing in young men with undiagnosed OSAS. Therefore, it is the purpose of this study to evaluate whether OSAS is characterized by exaggerated ventilatory

responses to graded exercise testing in young men. A secondary purpose was to explore the relationship of leptin to such ventilatory responses, to evaluate if variations in its serum concentration might exert a regulatory role during exercise.

METHODS

Subjects: Sedentary overweight males with untreated OSAS (n = 14), and control subjects matched for age, BMI, and central adiposity, but without OSAS (n = 16) were recruited from the local university community through campus notices as well as newspaper advertisements. Subjects were between 18 and 27 years of age and were classified as overweight according to body mass index criteria (2). All subjects underwent pre-screening which included an initial qualification questionnaire to identify any potential exclusion criteria, as well as a detailed health history questionnaire. All subjects were non-smokers, who were free from acute respiratory infection during the previous six weeks, including tonsillitis and adenoiditis. Subjects were free from significant cardiovascular, pulmonary, metabolic, or musculoskeletal disorders that would preclude maximal aerobic exercise testing. Subjects were not taking any prescribed vasoactive medications, hypnotics, sedatives, analgesics, psychotropics, steroids, or sympathomimetics. Individuals who had participated in regular physical activity (> 3 days/week, > 30 minutes/day) for the previous six months were considered sedentary and excluded (50). All methods and procedures, approved by the Institutional Review Board of Virginia Polytechnic Institute and State University (Virginia Tech), Blacksburg, VA, were explained to the subjects, who then read and gave written informed consent.

Home sleep evaluation: Subjects underwent an unattended home sleep evaluation to screen for the presence of OSAS, utilizing the Embletta portable device (Embla, Broomfield, CO), which has previously been validated vs. nighttime polysomnography (PSG), the gold-standard method for OSAS diagnosis (14). Embletta data was interpreted by a sleep technician and transposed into an AHI, with the results verified by the physician investigator who is a sleep specialist. Subjects were then classified into either the OSAS group (OSAS) (AHI > 5 events/hour), or the no-OSAS group (No-OSAS) (AHI < 5 events/hour).

Leptin measurement: Venous blood samples were drawn at rest, in the fasting state, and were obtained in the supine position. Samples were stored at -80°C for later batch analyses. Plasma leptin was determined by radioimmunoassay (Linco Research, Inc., St. Charles, Missouri) (intra- and inter-assay variability 3.4% to 8.3% and 3.0% to 6.2%, respectively).

Body composition measurement: Subjects completed total body dual-energy x-ray absorptiometry (DXA) scans (QDR4500A, Hologic Inc., Bedford, MA) to measure fat-free soft tissue mass (FFM), fat mass (FM) and body fat percentage. Central abdominal fat was measured from total body DXA scans by examining the region of interest defined by the top edge of the second to bottom edge of the fourth lumbar vertebra (27). All DXA measures were conducted and analyzed by one investigator. Weekly scans of an external soft tissue bar (Hologic Inc., Bedford, MA) were completed to ensure quality control for soft tissue mass measurements. Test-retest reliability data for this DXA have been reported elsewhere (38, 44).

Ramping exercise testing: Subjects completed a maximal cycle ergometer exercise test in the Laboratory for Health and Exercise Science on the campus of Virginia Tech. Anthropometric measures of height, weight, neck circumference (NC), waist circumference (WC), and hip circumference (HC) were measured prior to the exercise test. Resting heart rate (HR) and blood pressure (BP) were obtained in the seated position, after minimum of 5 minutes of rest. An electronically braked cycle ergometer (SensorMedics®, Yorba Linda, CA) was utilized for each exercise test. A one minute warm up period at a workload of 25 watts was followed by a ramping protocol that increased by 5 watts every 20 seconds to volitional fatigue. Exercise tests were supervised by American College of Sports Medicine (ACSM) certified Exercise Specialists, and conducted by trained personnel. Test termination criteria was in accordance with standards set by the ACSM (2) and the American Heart Association (AHA) (17). Subjects were monitored from a continuous electrocardiographic (ECG) monitoring device (Schiller AT-10^{TM}, Schiller AG, Baar, Switzerland) to assess HR and rhythm, and recorded each minute. Blood pressure measurements via auscultation were obtained every 2-min during exercise. During the 5 min post-exercise recovery period, BP was measured every 15-seconds. Borg Scale ratings of perceived exertion (RPE) (6 – 20) were obtained every minute during exercise. Respiratory gas exchange measurements were obtained during the exercise test using a computer controlled, breath-by-breath system (SensorMedics Vmax 229®, Yorba Linda, CA.). Values were calculated to 10 second averages. Measurements included oxygen consumption (VO_2), minute ventilation (V_E), carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and Peak VO_2 (VO_{2pk}). The two highest 10 sec VO_2 values achieved during the

last minute of exercise were averaged to obtain the VO_{2pk} value. The V_E/VO_2 and V_E/VCO_2 were calculated throughout submaximal exercise and at peak. The V_E/VCO_2 slope was calculated as previously described (3).

Statistical analysis: All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL). Independent *t*-tests were used to evaluate differences in baseline descriptive characteristics between groups. Effects of group, exercise intensity (Watts), and interactions on ventilatory measures were evaluated using 2-way repeated measures ANOVA. In order to assess the independent relationship between leptin and ventilation during exercise, multiple stepwise regression was utilized with VO_{2peak}, V_{Epeak}, V_E/VCO_{2peak}, and V_E/VCO_2 slope used as dependent variables. Independent variables included age, BMI, body fat, central abdominal fat, waist circumference, neck circumference, and leptin. Pearson *r* correlations were calculated to explore potential relationships between select ventilatory measures, leptin and AHI. A value of $P \leq 0.05$ was considered significant.

RESULTS

Subject Characteristics: Demographic and descriptive characteristics for the study participants are presented in Table 1. No differences were noted between groups for age, BMI, NC, WC, percent body fat, central abdominal fat, and leptin. AHI was positively correlated with hip circumference ($r = 0.44$, $P < 0.02$) and central abdominal fat ($r = 0.42$, $P < 0.03$).

Exercise Test Measures: The VO_2 responses between groups did not differ at any submaximal exercise intensity or at maximum effort ($P = 0.66$). Neither did peak work rate (Watts) achieved differ between groups ($P = 0.30$). As shown in Figure 1, V_E,

V_E/VCO_2, and V_E/VO_2 responses were higher in the OSAS group at all workloads (P = 0.045, P = 0.001 and P < 0.02, respectively). No difference in the RER between groups was noted at any submaximal workload or at peak. Peak exercise responses for both groups are summarized in Table 2. Maximal test endpoints were achieved in both groups (Peak RER > 1.1; Peak RPE > 16).

V_E/VCO_2 Slope: The V_E/VCO_2 slope was positively correlated with AHI (r = 0.56, P = 0.02) and there was a trend toward a higher response for this measure in the OSAS group (27.4 ± 0.8; 25.6 ± 0.5 for OSAS vs. No-OSAS, respectively; P = 0.06) (Table 2).

Leptin: Plasma leptin did not differ between the OSAS and No-OSAS groups (Table 1). In univariate analyses, leptin was related to VO_{2peak} (r = -0.56, P < 0.001), but not to V_{Epeak}, V_E/VCO_{2peak}, or V_E/VCO_2 slope. Plasma leptin concentration was also positively associated with BMI (r = 0.50, P = 0.005), waist circumference (r = 0.53, P = 0.003) percent body fat (r = 0.86, P < 0.001), and central fat (r = 0.67, P < 0.001). In multivariate stepwise regression analyses, no independent variable, including leptin, were significant predictors of the respiratory metabolic measures.

DISCUSSION

This study represents the first attempt to evaluate ventilatory responses to exercise in young, overweight men with untreated OSAS. The major finding is that OSAS, and not obesity, results in unique ventilatory responses to graded exercise testing in young men, reflected by significantly greater V_E, V_E/VCO_2, and V_E/VO_2 measures across all submaximal exercise intensities and peak exercise (Figure 1). In subjects matched for age, BMI, VO_2, and central abdominal fat, those with OSAS demonstrated an exaggerated ventilatory response relative to carbon dioxide output and oxygen

consumption. Results from this study demonstrate potential utility of ventilatory responses from exercise testing in OSAS risk assessment and improving patient selection for diagnostic PSG testing.

Limited research is available on the cardiopulmonary responses to exercise testing in OSAS, particularly in younger adults who have not yet been diagnosed. From the published studies, equivocal findings have been proffered relative to the issue of whether functional capacity is impaired by presence of OSAS. Investigations by Vanuxem et al. (65) and Lin et al. (33), conducted on middle-aged to older adults, reported significantly decreased peak VO_2 and V_E values in overweight patients with OSAS compared to age and BMI matched control subjects without OSAS. Lin et al. (33), in their study, also evaluated peak V_E/VO_2 and V_E/VCO_2 responses in their OSAS patients. In contrast to the current study, they reported no difference between the OSAS and control group for either of these measures (33).

Several other investigations reported no differences in peak VO_2 responses for middle-aged patients with moderate to severe OSAS vs. age- and BMI-matched controls (1, 26, 48). Kaleth et al. (26) recently reported absence of differences in peak V_E responses middle-aged OSAS patients and controls of the same age and BMI. Previous published studies examining exercise responses in OSAS subjects have been conducted on middle-aged adults. Results from the current study agree with those of Ozturk (48), Alonso-Fernandez (1), and Kaleth (26), and extend those findings to a younger OSAS population, that likely is in the earlier stages of OSAS progression.

The possible mechanisms underlying the unique ventilatory responses may be multifaceted. The repetitive nocturnal bouts of hypoxia and hypercapnia operant in

OSAS have been implicated to induce alterations in the central and peripheral chemoreceptors (12). Narkiewicz and colleagues (42) demonstrated a tonic activation of the chemoreceptors in OSAS patients, through evidence of deactivation of the chemoreflexes when affected patients breathed hyperoxic air at rest. When OSAS patients breathed a hyperoxic mixture, muscle sympathetic nerve activation (MSNA) and mean arterial pressure (MAP) decreased significantly ($P = 0.008$ and 0.02, respectively) (42). Narkiewicz et al. (43) further demonstrated exaggerated chemoreflex sensitivity in OSAS patients by activating the peripheral chemoreceptors through breathing a hypoxic mixture. The MSNA, MAP, and HR were all significantly greater in the OSAS group vs. non-OSAS controls ($P = 0.04$, 0.001, and 0.03, respectively) (43). In addition, they demonstrated an increased V_E with hypoxic breathing in the OSAS subjects ($P = 0.02$) (43). However, when they activated the central chemoreceptors through hypercapnic breathing, no differences were noted between the OSAS group and the controls, suggesting the peripheral chemoreceptors be the predominant influence on chemoreflex sensitivity. Central chemoreceptors, in response to increases in CO_2, contribute significantly to increases in ventilation (64). This response, however, occurs slower than that mediated by peripheral chemoreceptors, during the steady-state, following several minutes of exposure to elevated CO_2. During ramping exercise testing, however, when intensity, CO_2 concentration, and pH are changing dynamically, the peripheral chemoreceptors are able to respond rapidly to those changes, and thus are the primary initiators of the ventilatory response (64). Results of the current study agree with, and extend those of Narkiewicz et al. (43) which suggest that OSAS may increase sensitivity to CO_2 in the peripheral chemoreceptors, possibly in response to the repetitive bouts of

hypoxia and hypercapnia experienced throughout the night, resulting in an exaggerated ventilation relative to CO_2 during exercise.

Another potential mechanism has been suggested by several recent investigations that have reported alterations in the skeletal muscle function and fiber type histology, as a result of OSAS (7, 56, 65). Data from these studies indicated that OSAS patients have a reduced peak blood lactate response during maximal exercise, as well as a diminished rate of blood lactate clearance. Taken together, these findings suggest a defect in muscle oxidative metabolism in OSAS subjects (7, 65). Sauleda et al. (56) reported structural differences in the type II muscle fibers in OSAS subjects compared to controls. While we did not measure lactate or catecholamine levels in the current study, we observed no differences in the VO_2 or RER responses in the two study groups at intensities representing low fractions of the aerobic power. At these low work rates, despite a protocol of incremental ramp loading, muscle aerobic metabolism should predominate. Thus, absence of differences in VO_2 or RER in our groups at these low levels suggests oxygen cost at the same power output, as well as a similar metabolic fuel mix. Taken together, it is unlikely that possible OSAS-related differences in muscle oxidative metabolism would be a likely explanation for exaggerated ventilatory responses observed in these young men with OSAS.

One important finding in the current study is that OSAS and not obesity, is associated with an exaggerated exercise ventilatory response. Obesity is another condition that results in increased chemoreflex sensitivity (40) and reduced efficiency of breathing relative to VO_2 (V_E/VO_2) (32, 49). In the current study, both overweight groups were matched for age, BMI, percent body fat, and central abdominal fat,

indicating that the increased V_E/VCO_2 and V_E/VO_2 observed with exercise in the OSAS group was independent of obesity. This finding is in contrast to that reported by Lin et al. (33),which report no difference between the OSAS and control group in either peak V_E/VO_2 or V_E/VCO_2.

Exaggerated V_E/VCO_2 slope has previously been found to be a potent predictor of poor prognosis in patients with CHF (31, 53), a condition frequently seen in OSAS as well as central sleep apnea syndrome (CSAS), and a marker of chemoreflex sensitivity. Artz and colleagues (5) found in middle-age individuals with CHF and CSAS, the V_E/VCO_2 slope, with exercise, was significantly greater than those without CSAS (29.7 ± 0.9 vs. 24.9 ± 0.6; $P < 0.001$). They also report a significant correlation between the V_E/VCO_2 slope and AHI ($r = 0.613$; $P < 0.001$) (5). More recently, Meguro et al. (37) reported a significantly greater V_E/VCO_2 slope in middle-aged CHF patients with CSAS compared to CHF subjects without CSAS ($P < 0.01$). In their analysis, V_E/VCO_2 slope and AHI were moderately associated($r = 0.44$), but this finding was not statistically significant ($P = 0.07$). The symptoms of CSAS and OSAS are similar, despite different causes. To our knowledge, no studies have examined the response with exercise in OSAS subjects. Results from the current study indicate that this measure of chemoreflex sensitivity may be altered in young men with OSAS. The mean difference in V_E/VCO_2 slope values between groups did not reach significance, but there was a trend similar to that reported previously (5). We report a correlation between the V_E/VCO_2 slope and AHI similar to that of Artz et al. ($r = 0.56$ vs. 0.61) (5). Further examination of this relationship with OSAS is required.

The relation of circulating leptin to the ventilatory responses in graded exercise in young men with OSAS appears to be minimal. Previous animal models have demonstrated that leptin mediates a significant ventilatory increase, acting through the central respiratory controls centers (46, 62), and leptin infusion may reverse obesity related hypoventilation at rest (46). While leptin did positively correlate with VO_{2peak}, results from the current study showed no difference in circulating leptin between the OSAS and No-OSAS groups and no independent relationship with any ventilatory measure, despite an exaggerated V_E, V_E/VCO_2 and V_E/VO_2 response in the OSAS group.

The findings of the present study agree with those of Considine et al. (11) who report a similar correlation between leptin and percent body fat ($r = 0.85$, $P < 0.001$). We extend those findings to central abdominal fat ($r = 0.79$, $P < 0.001$), a component of the metabolic syndrome. In contrast, results from the present study differ from studies that report significantly greater leptin levels in OSAS, above that of obesity alone (24, 52). Ip and colleagues (24) report that, in middle-aged subjects, circulating leptin levels were significantly greater in OSAS (9.18 ± 4.24 ng/mL) compared to BMI matched controls (6.54 ± 3.81 ng/mL). Phillips et al. (52) report similar findings, but slightly higher measured leptin values in both middle-aged groups (13.7 ± 1.3 and 9.2 ± 1.2 ng/mL for OSAS and controls, respectively). Findings from the current study on younger men may reflect an age difference of OSAS on leptin levels, and this issue requires further studies.

One potential limitation is that nighttime PSG testing was not utilized for OSAS diagnosis in the current study. Nighttime PSG is the standard and accepted tool for OSAS diagnosis. The Embletta has been validated relative to PSG results, but is dependent upon the subject's ability to properly setup the device independently. Subjects

were provided verbal and visual instruction by study personnel, written instructions for device setup, and contact information for study personnel in case further instruction was needed over the phone.

Another potential limitation of the study is that we did not measure plasma levels of the soluble leptin receptor (sOB-R), as previously suggested by Wolk et al. (67). Leptin not only circulates in its free form, but also bound to the sOB-R (16, 34), which may affect the availability of free leptin. The sOB-R may be a significant factor determining free leptin in circulation, and thus may alter the actions of leptin (22, 69, 72). Free leptin has previously been reported to more accurately reflect body fat mass (13, 59). Further clarification is warranted on the role of the sOB-R and the regulatory role of leptin and ventilation.

In conclusion, the results of the current study indicate that exercise testing results in unique ventilatory responses in young, overweight men with untreated OSAS. These responses are suggestive of alterations in chemoreflex sensitivity and breathing efficiency in these individuals, beyond that seen with obesity alone. In addition, circulating free leptin does not appear to have an impact on ventilatory regulation in these young men with OSAS. These findings also suggest the potential for clinical exercise testing in improving risk stratification and clinical decision making leading to patient selection for OSAS diagnostic testing with polysomnography.

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Table 1. Subject Characteristics

	OSAS (n = 14)	No-OSAS (n = 16)
Age (yr)	22.4 (2.8)	21.4 (2.6)
AHI (events/hr)	22.7 (18.5)	2.5 (1.3)*
Height (cm)	171.6 (18.6)	178.2 (6.1)
Weight (kg)	99.6 (13.4)	99.4 (12.4)
BMI (kg/m^2)	32.0 (3.7)	31.4 (3.7)
NC (cm)	40.8 (2.1)	40.6 (2.6)
WC (cm)	100.5 (8.1)	95.4 (9.7)
% body fat	28.5 (4.7)	25.9 (4.5)
Central abdominal fat (kg)	8.7 (2.4)	7.0 (1.9)
Leptin (ng/mL)	10.9 (4.3)	9.4 (4.9)

Values are means with SD in parentheses.
AHI = Apnea/Hypopnea Index; BMI = Body Mass Index; NC = Neck Circumference; WC = Waist circumference
* Significant difference (P < 0.0001)

A

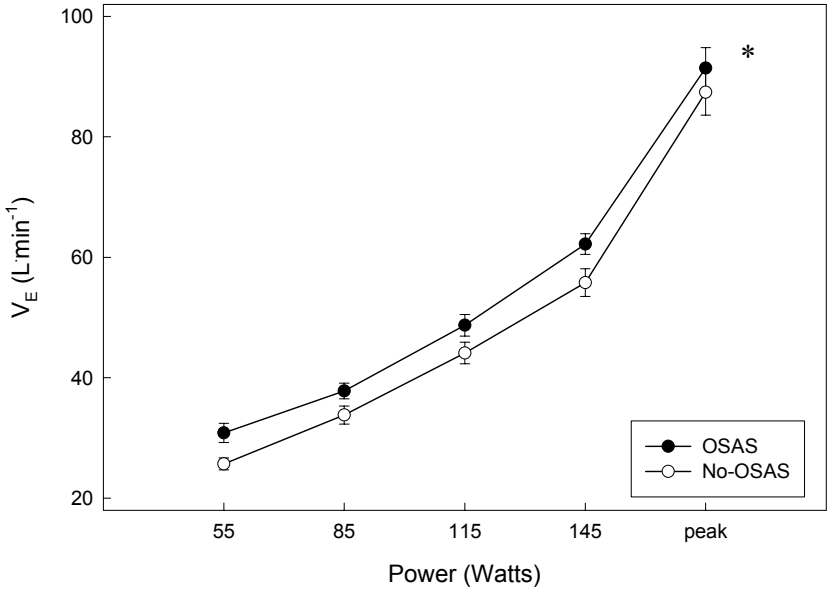
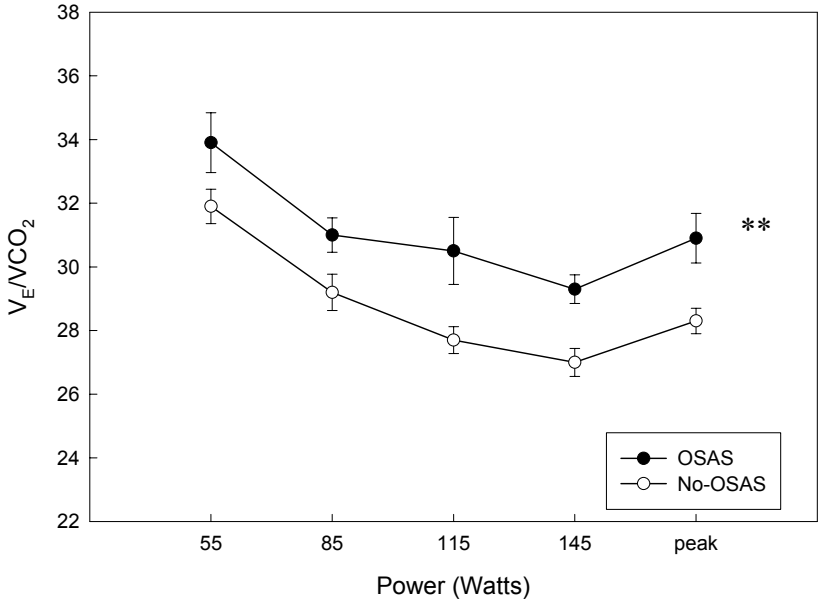


Figure 1. Submaximal and maximal ventilatory responses during cycle ergometer exercise in young, sedentary men: A) VE was greater across all workloads in the OSAS vs. No-OSAS group (*P = 0.045)

B



C

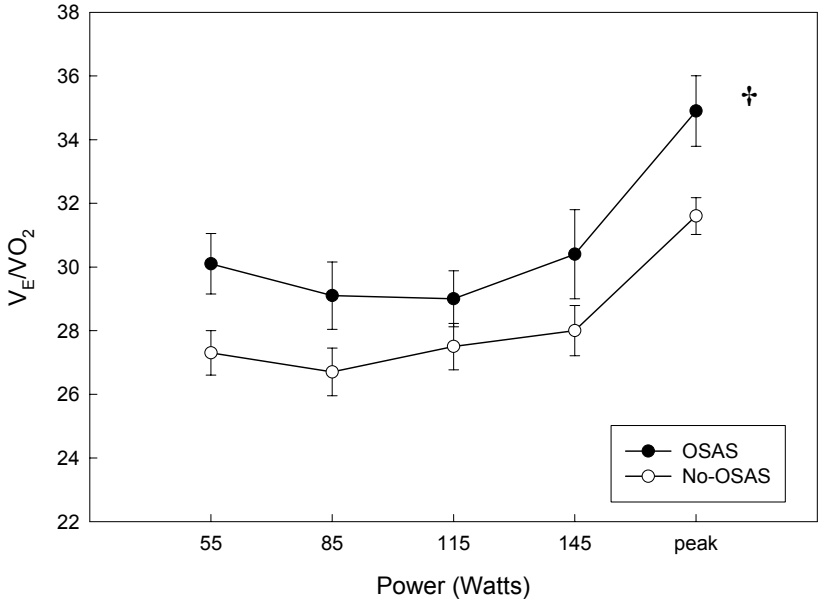


Figure 1. Submaximal and maximal ventilatory responses during cycle ergometer exercise in young, sedentary men: B) V_E/VCO_2 was greater across all workloads in the OSAS vs. No-OSAS group (**P = 0.001).

Table 2. Cardiopulmonary and Perceptual Responses to Exercise

	OSAS	No-OSAS
VO_2 peak ($mL \cdot kg^{-1} \cdot min^{-1}$)	27.1 (4.5)	28.0 (5.8)
RER peak	1.14 (0.06)	1.13 (0.04)
RPE peak	17.5 (1.6)	17.4 (1.3)
V_E/VCO_2 slope	27.4 (3.0)	25.6 (1.8)

Values are means with SD in parentheses.
RER = Respiratory Exchange Ratio; RPE = Rating of Perceived Exertion

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CHAPTER 3

Attenuated Heart Rate Recovery Following Exercise Testing in Overweight, Young Men with Untreated Obstructive Sleep Apnea Syndrome

Abstract

Study Objective: To evaluate whether cardiovascular responses to maximal exercise testing and recovery are altered with obstructive sleep apnea syndrome (OSAS) in overweight, young adult men.

Design: Three sedentary subject groups were recruited: Overweight with OSAS (OSAS), overweight without OSAS (No-OSAS), and normal weight without OSA (Control). Presence of OSAS was screened via portable diagnostic device. Body composition was measured with dual x-ray absorptiometry (DXA). Subjects performed maximal ramping exercise testing on a cycle ergometer with 5 minutes of active recovery. Exercise measurements included heart rate (HR), blood pressure (BP), respiratory exchange ratio, and oxygen consumption (VO_2). Recovery HR data was converted to a HR difference (HR_{diff}) calculation ($HR_{peak} - HR_{1\text{-minute recovery}}$), and BP was converted to a recovery ratio for each minute.

Setting: The study was carried out on the campus of Virginia Tech, Department of Human Nutrition, Foods, and Exercise, Blacksburg, Virginia.

Participants: 14 OSAS, 16 No-OSAS, and 14 Control volunteers.

Intervention: N/A

Measurements and Results: In OSAS subjects, HR recovery was significantly attenuated compared to the No-OSAS and Control groups throughout recovery (P =

0.009). No differences were noted in the HR or BP response to exercise in any group. The VO_2, adjusted for lean body mass, did not differ between groups.

Conclusions: We found that OSAS elicits alterations in the cardiovascular response to exercise, reflected by an attenuated HR recovery. This may indicate an imbalance in the autonomic regulation of HR. Exercise tests may provide utility in risk stratification for those at risk for OSAS.

INTRODUCTION

Obstructive sleep apnea syndrome affects approximately 2 – 4% of middle-aged adults,[1] with estimates reaching 20% and 7% for mild and moderate-to-severe OSAS, respectively in overweight individuals with a body mass index (BMI) of 25 – 28 kg/m^2.[2] Furthermore, it is estimated that 93% of females, and 82% of males with moderate to severe OSAS, those that would most benefit from treatment, remain undiagnosed clinically.[3] This disorder represents a significant public health concern, as OSAS markedly increases the risk for motor vehicle accidents through daytime sleepiness [4, 5], as well as increasing the risk for several adverse health conditions including stroke,[6-8] insulin resistance and glucose intolerance,[9, 10] congestive heart failure,[11-16] cardiac arrhythmias,[17-20] and hypertension (HTN).[21-23] In addition, OSAS appears to result in an increased risk for the development of cardiovascular disease (CVD),[12, 24] although no longitudinal, randomized, interventional studies have been conducted to conclusively demonstrate independent causation.[25]

The underlying mechanisms linking OSAS to HTN and CVD remain unclear. At night, repeated apneas and hypopneas result in decreased arterial oxygen saturation and carbon dioxide retention which cause sympathetic nervous system activation and stressful arousals to re-establish breathing. In OSAS patients, exaggerated sympathetic nervous system activation which persists during waking has been demonstrated,[26-28] which can lead to surges in heart rate (HR) and blood pressure (BP). In response to short-term increases in HR and BP, normal baroreceptor activation results in a net decrease in central nervous system outflow which decreases HR and BP. With OSAS patients, an alteration in the baroreflex activation appears to occur. Over time, depressed baroreflex

sensitivity in OSAS patients has been demonstrated,[29-31] suggesting an impairment of cardiovascular autonomic function, which may result in increased risk for HTN and CVD.

Graded exercise testing (GXT) has long been used as an effective tool for the identification of those at high risk for CVD.[32] Furthermore, alterations in the HR and BP response to exercise and immediately post-exercise have shown prognostic value, and may reflect impairment in autonomic regulation. Exaggerated BP response during exercise is predictive for the development of future HTN.[33-37] Following exercise, attenuated BP [38-41] and HR [42, 43] recovery have both shown to predict future CVD and mortality. Given the predisposition for HTN as a result of OSA, the hemodynamic responses to exercise in the OSAS individual may provide useful information to further risk stratify those in need of further diagnostic testing. Research into the exercise response of OSAS subjects has resulted in equivocal results. Decreased functional capacity in OSAS subjects has been reported by some investigators [44, 45] while others report similar functional capacity to controls.[46, 47] One recent investigation found a significantly altered HR and BP response to exercise in OSAS subjects vs. non-OSAS control subjects.[48]

In addition to the exercise response, Kaleth et al.[48] were the first to examine the post-exercise recovery period in OSAS subjects, reporting a significantly delayed systolic blood pressure (SBP) recovery response compared to non-OSAS controls.[48] These investigations were all conducted on middle-aged adults with moderate-to-severe untreated OSAS. To date, no published literature has examined the cardiovascular responses associated with graded exercise testing in young, overweight men with

untreated OSAS. In recent years, heart rate and blood pressure have been identified as important surrogates of autonomic dysfunction in graded exercise testing and appear to have promise in forecasting future cardiac risk. Whether these changes occur early in the development and progression of the disorder has not been examined. Thus, the purpose of this study was to evaluate whether autonomic control of the cardiovascular response during exercise is distorted by OSAS in young overweight men, as manifested by a blunting of heart rate and exaggeration of blood pressure responses.

METHODS

Subjects

Sedentary overweight males with untreated OSAS (n = 14), and control subjects matched for age, BMI, and central adiposity, but without OSAS (n = 16) were recruited from the local university community through campus notices as well as newspaper advertisements. Subjects were between 18 and 27 years of age and were classified as overweight according to body mass index criteria. [32, 49] Sedentary, normal weight control subjects without OSAS (n = 14) were also recruited. All subjects underwent a pre-screening which included an initial qualification questionnaire to identify any potential exclusion criteria, as well as a detailed health history questionnaire. All subjects were non-smokers, who were free from acute respiratory infection during the previous six weeks, including tonsillitis and adenoiditis. Subjects were free from significant cardiovascular, pulmonary, metabolic, or musculoskeletal disorders that would preclude maximal aerobic exercise testing. Subjects were not taking any prescribed vasoactive medications, hypnotics, sedatives, analgesics, psychotropics, steroids, or sympathomimetics. Individuals who had participated in regular physical activity (> 3

days/week, > 30 minutes/day) for the previous six months were considered sedentary[50] and excluded. All methods and procedures, approved by the Institutional Review Board of Virginia Polytechnic Institute and State University, Blacksburg, were explained to the subjects, who then read and signed a written informed consent form.

Home Sleep Evaluation

Subjects underwent an unattended home sleep evaluation to screen for OSAS, utilizing a previously validated device vs. nighttime polysomnography.[51] Sleep data was interpreted by a sleep technician and transposed into an AHI score, with results verified by the physician investigator who is a sleep specialist. Normal weight subjects (BMI < 25 kg/m^2) with an AHI $\geq$ 5 events/hour were excluded. The OSAS group included those overweight subjects with an AHI > 5 events/hour, and the no-OSA group included those overweight subjects with an AHI < 5 events/hour.

Body Composition Measurement

Total body dual-energy x-ray absorptiometry (DXA) (QDR4500A, Hologic Inc., Bedford, MA) was utilized to measure percent body fat, fat-free soft tissue mass (FFM), fat mass (FM). Central abdominal fat was measured from total body DXA scans as previously described.[52] One investigator conducted and analyzed DXA measures for all study subjects. Quality control for soft tissue mass measurements was completed with weekly scans of an external soft tissue bar (Hologic Inc., Bedford, MA). Test-retest reliability for the DXA unit has been previously reported.[53, 54]

Ramp exercise testing

Subjects completed a maximal cycle ergometer exercise test on the campus of Virginia Polytechnic Institute and State University. Prior to the test height, weight, neck,

waist, and hip circumferences, HR and BP in a sitting posture was measured. The exercise tests were performed on an electronically braked cycle ergometer (SensorMedics®, Yorba Linda, CA) utilizing a standardized protocol previously described.[48] Respiratory gas exchange measurements including oxygen consumption (VO_2), minute ventilation (V_E), and respiratory exchange ratio (RER) were obtained during the exercise test using a computer controlled, breath-by-breath system (SensorMedics Vmax 229®, Yorba Linda, CA.) and values were calculated to 10 second averages. Peak VO_2 (VO_{2pk}) was defined as the highest VO_2 achieved during the last minute of exercise. To summarize results across study groups that included subjects with different VO_{2pk}, HR and VO_2 values were input into spreadsheet software (Microsoft Excel, Microsoft Corp, Bellevue, WA) as time-down columns from the start of exercise to peak. HR and VO_2 were designated the y- and x-axis, respectively. Polynomial regression was employed with the line of best fit option of the spreadsheet software to establish response values that corresponded to 20%, 40%, 60%, and 80% of VO_{2pk}. A mean $R^2 > 0.80$ was achieved by assessing the lowest order polynomial regression that produced the highest R^2 for each subject. For exercise recovery, BP data was converted to a recovery BP ratio (BPR) (i.e., systolic blood pressure at 1-minute recovery / systolic blood pressure at peak) for the 5 minute recovery period. Recovery HR data was converted to a HR difference (HR_{diff}) calculation. The difference between HR peak (HR_{pk}) and HR at each post-exercise minute (i.e., HR_{pk} – HR at 1-minute post-exercise) was calculated for the 5 minute recovery period.

Statistical Analysis

All statistical analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, IL). Comparisons of the effect of group over exercise intensity for the cardiovascular measures were made with repeated measures ANOVA, with exercise intensity as the within-subject factor, and group as the between-subject factor. Comparisons for the effect of group over time for the post-exercise cardiovascular measures were also made with repeated measures ANOVA with time as the within-subject factor, and group as the between-subject factor. When ANOVA results showed significant differences between groups, post hoc multiple comparisons were made with the Bonferroni test when measures satisfied equal variance analysis, and with the Tamhane test when measures did not satisfy the equal variance test. Pearson *r* correlations were calculated to explore potential relationships between select cardiovascular measures and AHI. Cardiovascular measures included: HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), post-exercise systolic blood pressure ratio (SBPR), post-exercise diastolic blood pressure ratio (DBPR), heart rate recovery (HRR) measurements. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Subject Characteristics

Baseline subject characteristics for each group are presented in Table 1. No significant differences were noted between the three groups with respect to age, height, HR_{rest}, or SBP_{rest}. DBP_{rest} in the No-OSA group was significantly higher than the normal weight control group ($P = 0.03$), and MAP_{rest} tended higher in the No-OSAS group vs.

the normal weight controls, but did not reach significance (P = 0.069). The OSAS and No-OSAS groups did not differ from each other in weight, BMI, neck circumference, waist circumference, and central abdominal fat. AHI was positively correlated with BMI (r = 0.45, P = 0.002), neck circumference (r = 0.31, p = 0.05), fat mass (r = 0.43, P = 0.004) and central abdominal fat (r = 0.51, P < 0.0001). However, when adjusted for body weight, only BMI (r = 0.34, P = 0.03) and central abdominal fat (r = 0.42, P = 0.006) remained significant.

Exercise Test Responses

The VO_2 response did not differ between the OSAS and No-OSAS groups across all exercise intensities, including peak. Normal weight control subjects had a higher VO_2 response vs. both overweight groups (P < 0.02 and < 0.05 vs. OSAS and No-OSAS, respectively). When VO_2 was adjusted for lean body mass, however, no significant differences were noted between the OSAS, No-OSAS, or control groups at any submaximal intensity or at peak exercise (P = 0.25). In addition, HR, SBP, DBP, and MAP did not differ between subject groups at any submaximal workload or at peak exercise. Both groups achieved maximal exercise test endpoints, confirmed by Borg Scale (6-20) ratings of perceived exertion (RPE) at peak > 16 and peak respiratory exchange ratio (RER) > 1.11 (OSAS = 1.14 ± 0.02 vs. No-OSAS = 1.13 ± 0.01) Peak exercise responses are presented in Table 2.

Exercise Recovery Responses

One normal weight control subject experienced post-exercise hypotension with symptoms during the exercise recovery period, and did not complete five minutes of active recovery, and was excluded from the analysis. The HR recovery was significantly

attenuated in the OSAS group throughout the recovery period when compared to the No-OSAS ($P < 0.03$) and normal weight controls ($P < 0.03$) respectively (Figure 1). No significant group differences were noted in SBPR or DBPR during the recovery exercise period. AHI was positively correlated with SBPR at 4 minutes ($r = 0.36$, $P = 0.02$) and 5 minutes ($r = 0.42$, $P = 0.005$) post-exercise, DBPR at 5 minutes post-exercise ($r = 0.33$, $P = 0.03$), and negatively correlated with HR_{diff} for minutes 1 – 4 of the recovery period ($r = -0.34$, $P = 0.023$; $r = -0.48$, $P = 0.001$; $r = -0.33$, $P = 0.033$; $r = -0.39$, $P = 0.011$ for minutes 1 – 4, respectively). There was a trend for a negative correlation between AHI and HR_{diff} at 5 minutes post-exercise, but did not reach significance ($r = -0.29$, $P = 0.057$). When corrected for body weight, these relationships remained significant with the exception of HR_{diff} at 3 minutes ($P = 0.069$).

DISCUSSION

To our knowledge, this study represents the first evaluation of cardiovascular responses to exercise in young, overweight men with untreated OSAS. The major finding of the current study was the attenuated HR recovery with OSAS following maximal exercise (Figure 1). When compared to subjects with similar body mass and adiposity but without OSAS, young, overweight men with OSAS showed a blunted heart rate recovery response (Avg. $\downarrow HR_{diff} = 8.4$ bt·min^{-1} for the post-exercise period). Results suggest that graded exercise testing may be a useful tool in identifying significant clinical signs in the early stages of OSAS progression, which may aid clinicians in improving risk stratification and patient selection for overnight polysomnography.

Research data on the cardiovascular responses to exercise testing in OSAS patients is limited. Available literature reporting on the OSAS effect on functional

capacity has shown conflicting results. Decreased VO_{2pk} in overweight, moderate to severe OSAS patients, compared to age and BMI matched control subjects was reported by Vanuxem et al. [45] Similar findings were reported in a more recent investigation by Lin et al. [44] who also reported a lower VO_{2pk} in 20 overweight OSAS patients (21.6 ± 3.3 $ml \cdot kg^{-1} \cdot min^{-1}$) compared to 20 matched controls (30.1 ± 3.4 $ml \cdot kg^{-1} \cdot min^{-1}$) ($P < 0.05$). These previous investigations were conducted on middle-aged to older individuals, who likely have been afflicted with significant OSAS longer than the young subjects in the current study. In contrast to Lin [44] and Vanuxem, [45] Ozturk et al. [47] reported no significant differences in VO_{2pk} in middle aged patients with moderate to severe OSAS (19.8 ± 3.1 $ml \cdot kg^{-1} \cdot min^{-1}$) compared to age and BMI matched controls (21.8 ± 5.9 $ml \cdot kg \cdot min^{-1}$) ($P < 0.05$). Measured VO_{2pk} in the OSAS patients was, however, significantly lower than predicted VO_{2pk} ($P < 0.001$). Alonso-Fernandez et al.,[46] also demonstrated no significant differences in VO_{2pk} in similar subjects to Ozturk.[47] Findings from the current study agree with the findings from Ozturk et al. [47] and Alonso-Fernandez et al. [46] and extend those findings to a younger patient population, who likely are not as far along in their disease progression. Utilizing the same prediction formula as Ozturk[47, 55] in the current study, measured VO_{2pk} (27.1 ± 1.2 $ml \cdot kg^{-1} \cdot min^{-1}$) was significantly lower than predicted (42.4 ± 0.28 $ml \cdot kg^{-1} \cdot min^{-1}$) in the OSAS group. The overweight No-OSAS group and the normal weight control group also showed a significantly lower measured VO_{2pk} ($ml \cdot kg^{-1} \cdot min^{-1}$) than predicted (28.0 ± 1.5 vs. 43.8 ± 0.24 $ml \cdot kg^{-1} \cdot min^{-1}$ and 33.2 ± 6.2 vs. 42.8 ± 0.97 $ml \cdot kg^{-1} \cdot min^{-1}$ for No-OSAS and control, respectively). All three subject groups in the current study were previously sedentary for greater than 6 months (regular exercise < days/week; 30 minutes/day). The differences

seen in measured and predicted VO_{2pk} likely reflect deconditioning. Several of the other studies that examine functional capacity in OSAS also report sedentary subject groups,[45-47] but do not specify criteria for qualification as a sedentary individual.

Only two previous studies have reported the HR and BP responses at rest, submaximal exercise intensities, and at peak exercise.[45, 48] Kaleth et al.[48] report a significantly lower HR at all submaximal workloads and at peak exercise despite no differences in VO_2. They suggest the impaired chronotropic response to exercise may be a due to downregulation of beta-adrenergic receptors in response to exaggerated sympathetic activation. In addition, a significantly greater DBP in the OSAS group vs. control group at rest, across all submaximal intensities, and a peak was observed.[48] In contrast, Vanuxem et al. [45] report no significant differences in the HR response with exercise in OSAS subjects vs. controls at any submaximal exercise level or at peak. They also a significantly greater SBP at rest in OSAS vs. controls ($P < 0.05$), and a significantly greater SBP and DBP at peak exercise ($P < 0.05$).[45] Results from the current study agree with those of Vanuxem in that no differences were observed in the HR response to exercise. We show that DBP is greater in both overweight subject groups at rest (OSAS and No-OSAS) vs. controls (Table 1), but did not differ from each other, indicating this increase may be a result of obesity and not OSAS. At peak exercise, those differences disappeared (Table 2). Other studies report resting and/or peak HR and BP values only,[44, 46] and show no significant differences in HR or BP at rest, or at peak exercise.

The study by Kaleth and colleagues is the only other study that reports recovery HR and BP data.[48] In contrast to the current study, they show no difference in the HR

recovery response between the OSAS group and control group (when differences in peak HR response were taken into account), but report SBP recovery was significantly attenuated with OSAS. A delayed recovery response in the SBP may indicate an autonomic imbalance, in response to chronic sympathetic activation with OSA, which slows the normal rapid response in cardiac output and peripheral vascular function to cessation of exercise.[48] The different recovery cardiovascular responses seen in the current study vs. that of Kaleth and colleagues may indicate an age effect. Kaleth et al. utilized middle-aged individuals as study subjects, who presumably have been exposed to the detrimental affects of OSAS for a longer duration, compared to the younger age group studied in the current examination.

Attenuated HR recovery has been identified as an independent predictor of cardiovascular and all-cause mortality in individuals undergoing diagnostic symptom-limited exercise testing[42, 43] as well as in a generally healthy adult cohort.[56] This is thought attributable to a reduction in parasympathetic activity, which predominates during the recovery phase of exercise.[42, 57, 58] These studies utilized relatively short recovery periods of 1 – 2 minutes. More recently, however, Cheng and colleagues [59] demonstrate that a decreased HR recovery, measured for as long as 5 minutes, was also independently predictive of cardiovascular and all-cause mortality in men with diabetes mellitus. Results of the current study are similar to Cheng et al. [59] in that a significantly blunted HR recovery was seen in the OSAS group through 5 minutes of recovery.

The mechanism for the attenuated HR recovery in OSA is unclear. During exercise, HR is under the control of both the sympathetic and parasympathetic branches of the autonomic nervous system.[60] During the initial phases of exercise, HR increase is

mediated primarily by withdrawal of parasympathetic activity. After a HR of approximately 100 beats·min^{-1}, the HR increase is due primarily to increased sympathetic activity, which acts much slower on HR than the parasympathetic system.[60] Following exercise, the decrease in HR is due to sympathetic withdrawal and parasympathetic activation.[57, 58, 61] Belozeroff et al.,[62] utilizing a model-based approach, concluded that OSAS results in abnormal sympathetic and parasympathetic control of HR. Their model was able to control for the fluctuations in HR due to respiration, known as the respiratory sinus arrhythmia.[62] Exaggerated sympathetic activation has previously been reported in OSAS patients,[26-28] which persists throughout normal waking hours. Attenuation of the HR recovery response in OSAS may reflect predominance and/or slower withdrawal of sympathetic influence; how this pattern may be affected by parasympathetic reactivation that normally slows HR in early post-exercise recovery is uncertain.

Obesity is itself an independent risk factor for the development of HTN,[63, 64] and is associated with elevated sympathetic nervous system activation.[65-68] Distinguishing between the independent effect of OSAS on sympathetic activity vs. that previously noted in obesity presents a challenge in OSAS research. In the current study, both overweight subject groups were matched in all body composition variables, including central abdominal fat, which may be a significant link between obesity and exaggerated sympathetic activation.[65] We have shown that in age, body size, and body adiposity matched subjects, those with OSAS have a significant attenuation of their recovery HR response, suggestive of autonomic imbalance. In addition, those in the No-OSAS group did not differ from the normal weight control group in recovery HR response, suggesting a limited effect of obesity on autonomic control of HR during recovery.

One limitation of the study is no direct evidence of sympathetic nervous system activity, either through MSNA or plasma catecholamine measurements. Future studies need to examine these direct measures of sympathetic activation in younger OSAS patients to determine if exaggerated sympathetic activity is an early sign in the development and progression of OSAS. In addition, cycle ergometry was utilized as the exercise mode rather than treadmill walking. Cycle ergometry can result in lower VO_{2pk} values compared to treadmill walking. However, in the current study, peak RER values for each subject group were above maximal exercise criteria (> 1.10) (RER = 1.14 ± 0.02, 1.13 ± 0.04, 1.17 ± 0.02 for the OSAS, No-OSAS, and control groups, respectively), suggesting that maximal or near maximal efforts were achieved in all subjects.

In conclusion, this is the first study to examine the cardiovascular responses to ramp exercise testing and post-exercise recovery in young, overweight men with untreated OSAS. Results indicate that OSAS elicits unique cardiovascular responses during recovery from maximal exercise. These results suggest an imbalance in the autonomic control of HR during recovery, and may be an early clinical sign in the progression of OSAS. These findings also suggest the potential for graded exercise testing in improving risk stratification and clinical decision making leading to patient selection for diagnostic testing with polysomnography. Further clinical studies, across a wider variety of age groups, are needed to examine whether there is an age-related influence in the exercise and post-exercise responses in obstructive sleep apnea syndrome.

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Table 1. Baseline Subject Characteristics

	OSAS (n = 14)	No-OSAS (n = 16)	Control (n = 14)
Age (yr)	22.4 (2.8)	21.4 (2.6)	21.4 (2.1)
AHI (events/hr)	22.7 (18.5)	2.5 (1.3)†	2.0 (1.1)†
Height (cm)	171.6 (18.6)	178.2 (6.1)	177.1 (6.7)
Weight (kg)	99.6 (13.4)	99.4 (12.4)	69.1 (6.6)*
BMI (kg/m^2)	32.0 (3.7)	31.4 (3.7)	22.0 (1.3)*
CAF (kg)	8.7 (2.4)	7.0 (1.9)	3.4 (0.98)*
HR ($bts \cdot min^{-1}$)	92.4 (14.2)	86.0 (14.0)	85.9 (11.6)
SBP (mmHg)	125.9 (9.9)	124.9 (10.9)	121.4 (9.1)
DBP (mmHg)	85.7 (5.4)	87.6 (8.1)	80.9 (6.2)**
MAP (mmHg)	99.1 (5.5)	100.0 (8.2)	94.4 (5.3)

Values are means with SD in parentheses. Values are taken at rest.
AHI = Apnea/Hypopnea Index; BMI = Body Mass Index; CAF = Central Abdominal Fat; HR = Heart Rate; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; MAP = Mean Arterial Pressure
* Significantly different from OSAS, No-OSAS ($P < 0.05$)
** Significantly different from No-OSAS ($P < 0.03$)
† Significantly different from OSAS ($P < 0.005$)

Table 2. Peak Exercise Data

	OSAS (n = 14)	No-OSAS (n = 16)	Control (n = 14)
HR ($bt \cdot min^{-1}$)	179.9 (3.7)	180.4 (3.4)	181.3 (3.7)
SBP (mmHg)	196.9 (7.0)	202.6 (6.5)	193.4 (7.2)
DBP (mmHg)	90.7 (3.1)	91.4 (2.9)	89.5 (3.2)
MAP (mmHg)	126.1 (14.9)	128.4 (14.5)	124.5 (9.8)
VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	27.1 (4.5)	28.0 (5.8)	33.2 (6.2)*

Values are means with SD in parentheses.
* Significantly different from OSAS, No-OSAS ($P < 0.05$)

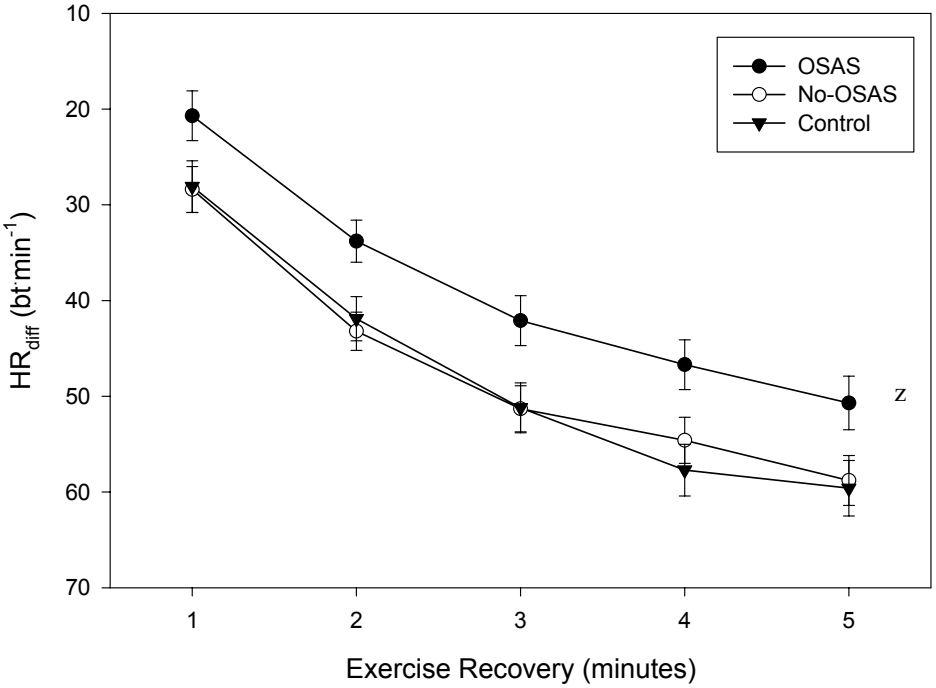

Figure 1. HR responses during exercise recovery following cycle ergometer exercise in young, sedentary men. HR_{diff} was significantly decreased in the OSAS group across all workloads vs. No-OSAS and normal weight control groups respectively, suggesting impairment of autonomic function in OSAS subjects early in their disease progression (^{z} P = 0.009).

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CHAPTER 4

Anthropometric and exercise markers of risk for obstructive sleep apnea syndrome in young men

Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is a disorder that contributes to the development of hypertension and for motor vehicle accidents. It often goes unrecognized in routine clinical evaluation. Exercise testing has been a useful tool for identifying those at risk for hypertension (HTN) and coronary artery disease (CAD), but its utility in identifying OSAS risk has been given limited attention. The purpose of this study was to explore how various simple measures and results from exercise testing might serve to increase discrimination between young men with and without OSAS.

Patients and Methods: Ninety-one young men (age = 21.6 ± 0.30 yr) underwent evaluation at home using a simplified polysomnographic screening device for assessing OSAS, with data transposed into an Apnea-Hypopnea Index (AHI). All subjects donated fasting blood samples for lipid analysis and were evaluated for neck and trunk girths, body composition via dual-energy x-ray absorptiometry (DXA), and cardiorespiratory responses during and after maximal ramping exercise tests on an electronically braked cycle ergometer. Exercise measures included oxygen consumption (VO_2), ventilation, (V_E), heart rate (HR), and blood pressure (BP). HR data and BP indices were also calculated to express rates of change in early post-exercise recovery, i.e. HR difference (HR_{diff}) calculation ($HR_{peak} - HR_{1\text{-minute recovery}}$), and BP was converted to a recovery ratio (systolic $BP_{1\text{-minute recovery}}$ / systolic BP_{peak}) for each minute.

Results: Hip-to-height ratio (HHR) Hip circumference (HC), triglyceride levels, and recovery systolic blood pressure ratio (SBPR) at 2 and 4 minutes were independent predictors of AHI (model fit: $R^2 = 0.68$, $p < 0.0001$). Percent body fat, HHR, and HR_{diff} at 2 minutes and 4 minutes were the best single predictors of OSAS risk (AUC = 0.77 for each measure, $p = 0.003$). The Epworth Sleepiness Scale was not a significant predictor of OSAS risk (AUC = 0.39, $p = 0.23$).

Conclusion: For young adult men, simple anthropometric measures and routine clinical exercise testing may serve to improve discrimination of individuals at increased risk for OSAS. In contrast to studies done on older adults, these measures may be better predictors of OSAS risk than more conventional risk variables established for older individuals.

Keywords: Obstructive sleep apnea syndrome, exercise testing, heart rate, blood pressure, exercise recovery, area under the curve, receiver operator characteristic curve analysis

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) affects 1 – 4% of the overall population [1, 2], with estimates as high as 20% for presence of some degree of OSAS in overweight individuals with a body mass index (BMI) of 25 – 28 kg/m^2 [3]. Frequently OSAS goes undiagnosed in routine clinical examination [4]. It has been estimated that 93% of females and 82% of males with moderate to severe OSAS, i.e. those that would most benefit from treatment, are undiagnosed [5]. This disorder is associated with an elevated risk for several adverse health problems including insulin resistance and glucose intolerance [6, 7], stroke [8-10], cardiac arrhythmias [11-14], dyslipidemia [15], and congestive heart failure [16-21]. In addition, OSAS has shown a strong, independent, dose-response relationship with hypertension (HTN) [22-24], and may, partly through this link with HTN, increase the risk for the development of cardiovascular disease (CVD) [19, 25].

While often going unrecognized, OSAS constitutes a significant public health problem, both financially and from a public safety standpoint. In the 10 years prior to diagnosis, OSAS patients have been reported to utilize double the healthcare resources compared to similar patients without OSAS [26]. In addition, OSAS markedly increases the risk for motor vehicle accidents by way of excessive daytime sleepiness (EDS), a cardinal symptom of OSAS [27, 28]. Commercial truckers represent a driver subset with an increased prevalence of OSAS [29, 30]. One study of commercial truck drivers demonstrated the presence of sleep disordered breathing (AHI > 5 events/hour), and the presence of OSAS (AHI > 5 with EDS assessed by Epworth Sleepiness Scale) in 35% and 16%, respectively, in those screened with polysomnography [30]. Those drivers

reporting the greatest EDS had a significantly greater risk for a motor vehicle accident (odds ratio [OR] 1.91), as well as multiple accidents (OR 2.67) [30].

The typical OSAS patient presents clinically as middle-aged or older, is overweight-to-obese, with a thick neck and large waist circumference, habitually snores, and exhibits EDS [31]. The prevalence of OSAS in older individuals ($\geq$ 65 years old) is 2-3 fold higher than those aged 30-64 years [31]. Men are at greater risk for OSAS, with prevalence rates for middle-aged men estimated at 24%, compared to 9% in middle-aged, premenopausal women [2]. In addition, there is a graded increase in OSAS prevalence among adults with increasing BMI [31, 32]. Other evidence supports that decreases in body weight may decrease severity of OSAS [33]. No definitive prevalence studies have been conducted on younger individuals. One estimate of risk for young adults suggests similar prevalence rates to adults (1 – 3%) [34]. As obesity rates in younger individuals continue to rise or exceed rates among older individuals, overall prevalence of OSAS among adults may be expected to increase even further.

The typical risk profile for OSAS, however, does not encompass all of those at risk. Craniofacial or upper airway structure abnormalities such as mandibular or maxillary retrognathia, enlarged tonsils or adenoids, can all place an individual at increased risk for airway closure [31, 35, 36]. These factors are frequently seen in individuals who do not fit into the typical profile, and may contribute a portion of the OSAS seen in younger individuals. One sleep clinic reports that only 50% of those diagnosed with OSAS in their clinic are obese and fit the typical OSAS risk profile [37].

Graded exercise testing (GXT) has long been used as an effective tool for the identification of those at high risk for CVD [38], and has been effective in the prediction

of future HTN [39-41] and CVD [42-45]. Given the predisposition for HTN as a result of OSA, the hemodynamic responses to exercise may provide useful information to cost-effectively risk stratify those at increased risk of OSAS who need further diagnostic testing. One recent study suggests that older overweight patients with diagnosed OSAS show a unique physiological response profile to ramp exercise testing [46]. However, exercise response in young, overweight adults in whom the signs and symptoms of OSAS may be even less definitive, have not been studied. Thus, the purpose of our investigation was to examine how various simple clinical measures and response patterns from graded exercise testing might serve to increase discrimination between young men with and without OSAS.

METHODS

Subjects were recruited from the local community, with a high percentage being university students. All subjects underwent a pre-screening which included an initial qualification questionnaire to identify any potential exclusion criteria, a detailed health history questionnaire, and the Epworth Sleepiness Scale (ESS), a validated questionnaire that quantifies levels of daytime sleepiness [47]. The ESS is scored in a range from 0 to 24. A subject with an ESS score ≥ 11 is considered to have excessive daytime sleepiness [47]. All subjects were non-smokers, who were free from acute respiratory infection during the previous six weeks, including tonsillitis and adenoiditis. Subjects were free from significant cardiovascular, pulmonary, metabolic, or musculoskeletal disorders that would preclude maximal aerobic exercise testing. Subjects were not taking any prescribed vasoactive medications, hypnotics, sedatives, analgesics, psychotropics, steroids, or sympathomimetics.

Home Sleep Evaluation

Subjects underwent a home sleep evaluation to screen for the presence of OSAS, utilizing the Embletta portable device (Embla, Broomfield, CO), which has previously been validated vs. nighttime polysomnography (PSG) [48]. Embletta data was interpreted by a sleep technician, verified by the physician investigator who is a sleep specialist, and transposed into an AHI score. An AHI > 5 events/hour was defined as positive for OSAS.

Subject Classification

Subjects were assigned to study groups for comparison on the based on their status for the following measures: (1) recent history of physical activity; (2) BMI; and (3) Embletta score for OSAS (See group definitions below). The sedentary criterion (Se) applied to those who reported that, in the previous 6 months, they routinely engaged in moderate/vigorous activity less than 30 minutes/day for less than 3 days/week [49]. In contrast, the active criterion (A) applied only to those who reported exercising vigorously more than 60 minutes/day for at least 4 days/week. The criterion for assigning subjects to the normal weight (NW) groups was a BMI of less than 25 kg/m^2, whereas the overweight (OW) criterion was a BMI equal to or greater than 25 kg/m^2. Finally, on Embletta testing, those with physician-interpreted AHI scores positive for OSAS were classified as Obstructive Sleep Apnea Syndrome (OSAS), whereas those with AHI scores less than 5 were classified as No-OSAS (NoOSAS). Combining these criteria, five study groups were defined: (1) Normal weight, sedentary, without OSAS (NWSe-NoOSAS); (2) Overweight sedentary, without OSAS (OWSe-NoOSAS); (3) Overweight, sedentary,

with OSAS (OWSe-OSAS); (4) Normal weight, mixed physical activity history, with OSAS (NWM-OSAS); (5) Normal weight, physically active, without OSAS (NWA-NoOSAS). The NWM-OSAS group constituted all those who were anticipated to qualify for sedentary or active groups, but then unexpectedly had AHI scores of >5 on Embletta testing.

Blood Lipid Analysis

Venous blood samples were drawn at rest, in the fasting state, and in the supine position. Blood samples of approximately 50 mL were collected from each subject. Measures of total cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, and blood glucose (BG) were obtained with the Cholestech LDX® system using a 35 μL sample of whole blood (inter- and intra-assay variability range of 1.6 – 8.0% and 2.2 – 6.3%, respectively for lipid variables) [50]. The remaining portion of the 50 mL blood sample was separated into aliquots of approximately 1.2 mL samples of serum and plasma, separated from whole blood via centrifugation and stored at -80°C for later batch analysis of biomarkers not associated with the current study.

Body Composition Measurement

Body composition measurements were made via total body dual-energy x-ray absorptiometry (DXA) scans (QDR4500A, Hologic Inc., Bedford, MA) to measure percent body fat, fat-free soft tissue mass (FFM), fat mass (FM), and central abdominal fat. Central abdominal fat was measured as previously described [51]. All DXA measures were conducted and analyzed by one investigator. Scans of an external soft tissue bar (Hologic Inc., Bedford, MA) were completed weekly to ensure quality control

for soft tissue measurements. Test-retest reliability for soft tissue composition for this DXA unit has produced coefficients of variation of 1.07%, 1.75%, and 1.79% for FFM, FM, and percent body fat [52, 53].

Exercise Test Procedures

Maximal cycle ergometer exercise tests were completed by each subject on the campus of Virginia Polytechnic Institute and State University. Prior to the exercise test, height, weight, neck, hip, and waist circumferences were measured on each subject. Neck and hip circumferences were measured at the widest portion of the neck and buttocks, respectively. Waist circumference was measured at the narrowest portion above the umbilicus and below the xyphoid process. Resting heart rate and blood pressure was measured in a sitting posture. The exercise tests were conducted on an electronically braked cycle ergometer (SensorMedics®, Yorba Linda, CA) as previously described [46]. Blood pressure measurements via auscultation were obtained at 2-min intervals during exercise, and at 1-min intervals for 5 min post-exercise. Ratings of perceived exertion (RPE) (Borg 6 – 20) were obtained every minute during exercise. Respiratory gas exchange measurements including oxygen consumption (VO_2), minute ventilation (V_E), and respiratory exchange ratio (RER) were obtained during the exercise test using a computer controlled, breath-by-breath system (SensorMedics Vmax 229®, Yorba Linda, CA.) and values were calculated to 10 second averages. Peak VO_2 (VO_{2pk}) was defined as the highest VO_2 achieved during the last minute of exercise. For exercise recovery, BP data was converted to a recovery BP ratio (BPR) (i.e., systolic blood pressure at 1-minute recovery / systolic blood pressure at peak), similar to methods used previously by other investigators [43, 45] for the 5 minute recovery period. Recovery HR

data was converted to a HR difference (HRdiff) calculation, also used previously by other investigators [42, 44]. The difference between HR peak (HR_{pk}) and HR at each post-exercise minute (i.e., HR_{pk} – HR at 1-minute post-exercise) was calculated for the 5 minute recovery period.

Data Analysis

Data analyses were performed using the Statistical Package for the Social Sciences, version 14.0 (SPSS Statistical Software, Chicago, IL). To asses the degree of correlation of various potential variables in relation to AHI, Pearson's correlation coefficient (r) was used. To assess the independent relationship between the conventional clinical risk markers of OSAS, as well as for the exercise test measures, stepwise linear regression was utilized with AHI as the dependent variable. Independent variables included conventional risk variables of BMI, neck and waist circumference, Epworth Sleepiness Scale (ESS), baseline demographic and body composition variables, as well as variables obtained during exercise testing and a period of unloaded pedaling in the early minutes of post-exercise recovery. To further evaluate the predictive accuracy of these clinical and exercise variables, Receiver Operating Characteristic (ROC) Curve analysis was performed, to assess sensitivity and specificity through area-under-the-curve (AUC) analysis [54, 55]. An AHI cutoff of ≥ 10 event/hour was utilized in ROC analyses, similar to previous investigations [56-59]. A p value < 0.05 was used throughout to determine statistical significance.

RESULTS

Subject Characteristics at Baseline

Table 1 presents baseline characteristics for the five study groups. Eleven subjects in the OWSe-OSAS group were classified with mild (AHI = 5 – 14), 5 with moderate (AHI = 15-29), and 4 with severe (AHI ≥ 30) OSAS. In the NWM-OSAS group, all subjects were classified with mild OSAS. All five groups were similar in age. Waist-to-hip ratio (WHR) and systolic blood pressure did not differ between groups. In addition, despite two of the five subject groups possessing positive home sleep evaluations for OSAS, ESS scores did not differ between groups. Body weight, BMI, percent body fat, neck, and waist circumferences were all greater in the overweight groups compared to the normal weight groups ($p<0.001$), but did not differ from each other. Central abdominal fat was greater in the overweight groups vs. the normal weight groups ($p<0.001$), and was greater in the NWSe-NoOSAS vs. the NWA-NoOSAS group ($p<0.02$). Hip circumference (HC) was greater in the OWSe-OSAS group compared to the OWSe-NoOSAS group ($p<0.001$), and greater in the OWSe-NoOSAS group vs. the three normal weight groups ($p<0.001$). Resting HR was greater in the OWS-OSAS group compared to the NWA-NoOSAS group ($p<0.001$), and diastolic blood pressure was greater in the OWSe-OSAS group vs. the three normal weight groups ($p<0.05$).

Exercise Test Measures

Peak exercise results for the ramping exercise tests are presented in Table 2. One test was stopped before the subject indicated maximal effort, due to an exaggerated BP response. Two subjects experienced symptomatic post-exercise hypotension early in recovery and so did not complete five minutes of active recovery. Maximal exercise

criteria was confirmed in all subjects, verified by peak RER > 1.1 and peak RPE values > 16 (Table 2). Peak HR and systolic BP did not differ between groups. Peak diastolic BP and V_E were greater in the OWSe-OSAS, OWSe-NoOSAS, and NWSe-NoOSAS groups compared to the NWA-NoOSAS group ($p<0.03$ and $p<0.03$, respectively), but not differ from each other. Peak VO_2 was greater in the NWA-NoOSAS group compared to all other groups ($p<0.003$), and greater in the NWM-OSAS and NWSe-NoOSAS groups compared to the two overweight groups ($p<0.05$).

Linear Regression Analysis

Presented in Table 3 are associations between AHI and the independent variables, as derived from univariate and multivariate stepwise linear regression analyses. As expected, AHI positively correlated with BMI, NC, WC, percent body fat, and central abdominal fat (Table 3). In addition, AHI was also correlated to blood lipid variables of total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides, as well as to exercise and post-exercise recovery variables obtained from the ramp exercise test including peak VO_2, recovery systolic blood pressure ratio (SBPR) at minutes 3 – 5 of recovery, and HRdiff throughout the 5 minute recovery period (Table 3). The strongest correlations to AHI were HC (r = 0.52) and height (r = -0.49), but were not significantly correlated to each other (r = 0.07, $p=0.54$). To further explore the relationship of HC and height to OSAS severity, the hip-to-height ratio (HHR) was calculated for each subject. The HHR was significantly correlated to AHI (r = 0.68, $p<0.001$). In contrast, ESS did not correlate significantly with AHI (r = 0.01, $p = 0.34$) (Table 3).

In multivariate analysis, HHR, HC, SBPR at minutes 2 and 4 of recovery, and triglycerides were independent predictors of AHI (model fit: $R^2 = 0.69$, $p < 0.0001$) (Table 3). Conventional clinical OSAS risk variables such as weight, BMI, % body fat, and WC were no longer associated with AHI, and no significant relationship between AHI and ESS was found in this younger study cohort.

ROC Curve Analysis

The ROC results for the individual variables, consisting of conventional clinical OSAS risk variables, anthropometric, and exercise variables are presented in Table 4. As with linear regression analysis, ESS score continued to be a poor predictor of OSAS in this younger study cohort (Figure 1). The HHR performed better (AUC = 0.77, $p = 0.003$) as a predictor of OSAS in these subjects than the more conventional body composition variables frequently associated with increased OSAS risk (BMI, NC, and WC), and similarly to percent body fat. If HHR measured is greater than 0.62, then OSAS could be predicted with 82% specificity and 75% sensitivity. With percent body fat, measured by DXA, OSAS could be predicted with 73% specificity and 83% sensitivity when percent body fat is greater than 25.5%. In addition to the anthropometric and body composition variables, measures obtained during the ramp exercise tests, particularly during the recovery phase following maximal exercise, were significant predictors of OSAS risk. Attenuated heart rate and systolic blood pressure recovery, reflected in the HRdiff and SBPR variables (Table 4), appear to be predictive of OSAS. The HRdiff at minutes 2 – 5 of recovery all were significant predictors of OSAS, with minutes two and four performing slightly better. The HRdiff at 1 minute was not significant. Only the SBPR at 4 minutes of recovery was a significant predictor of

OSAS. If HRdiff at 2 minutes of recovery is measured at 41 beats per minute or less, OSAS can be predicted with 62% specificity and 83% sensitivity. The combination of HHR and percent body fat, as well as HHR and HRdiff at 2 minutes of recovery, provide good balance of sensitivity and specificity. A younger man with an HHR greater than 0.62, and a percent body fat greater than 25.5% or a HRdiff at 2 minutes of recovery of 41 beats per minute or less could be predicted to have OSAS with 82% specificity and 83% sensitivity.

DISCUSSION

The results from this study suggest that in this sample of young men, anthropometric measures, as well as those obtained from exercise tests, may be equal to, or more effective that conventional OSAS risk variables in identifying those at increased risk for OSAS. These findings suggest the potential for exercise testing in improving risk stratification and clinical decision making leading to patient selection for diagnostic testing with polysomnography, which may decrease the number of individuals in need of OSAS treatment that remain undiagnosed. Compared to conventional variables used to identify OSAS risk, i.e., BMI, NC, and WC, alternative anthropometric measures (HHR) and exercise test measures, particularly those during the post-exercise recovery period (HRdiff, SBPR), performed better in predicting OSAS risk. Only percent body fat performed as well in predicting OSAS risk (Table 4). In addition, the ESS, a well established and validated questionnaire for assessing daytime sleepiness [47, 60, 61], and cardinal sign of OSAS, performed poorly in predicting OSAS risk in this younger study sample.

To our knowledge, the current study represents the first attempt to assess the utility of exercise test variables for identifying individuals at increased risk for OSAS. Our focus on young men was to evaluate whether males, for whom prevalence rates for OSAS are significantly greater than females, express unique physiological characteristics at a younger age resulting from OSAS, and whether these characteristics could facilitate earlier recognition of OSAS. If more individuals are able to receive treatment for OSAS at an earlier age, those individuals will benefit, not only from decreased daytime sleepiness and other primary effects of OSAS, but also will reduce their future risk for several comorbidities, which may share etiologic pathways with OSAS, e.g. HTN, insulin resistance, and congestive heart failure.

Several studies have attempted to predict the presence of OSAS using conventional OSAS risk variables such as age, BMI, NC, snoring, or witnessed apneas [56-58, 62-64]. These studies have generally been restricted to older rather than young adults. Crocker et al. [62], reported a sensitivity of 92% and a specificity of 51% in a prediction model that included age, BMI, witnessed apneas, and presence of HTN. They defined OSAS as AHI $\geq$ 15. Studies by Viner et al. [58] and Maislin et al. [56] reported similar AUC results for their prediction models (0.77 and 0.79, respectively), with both studies utilizing similar prediction variables of age, gender, BMI, and snoring. Sensitivities and specificities for the prediction models by Viner [58] and Maislin [56] were 94 and 88%, and 28 and 55%, respectively. Both investigations defined OSAS as AHI $\geq$ 10. Similarly, our study also defined OSAS as AHI $\geq$ 10, which is greater than the standard clinical definition of mild OSA (AHI $\geq$ 5), yet below the threshold where nCPAP treatment is initiated (AHI $\geq$ 15).

More recently, Sharma and colleagues attempted to predict the occurrence of OSAS in middle-aged and obese individuals without overt signs of OSAS [63, 64]. In these two studies, and AHI cutoff $\geq$ 15 was used to signify presence of OSAS. They developed two prediction models that included gender, waist/hip ratio, and NC [64], as well as gender, BMI, and indexes for both snoring and choking [63]. Area under the curve results for both models were 0.874 [64] and 0.869 [63], respectively. Sensitivities for the prediction models ranged from 90.4% - 91.3%, while specificities ranged from 68.5% - 69.8% [63, 64].

These previous studies all utilized multiple logistic regression to predict presence of OSAS, with ROC curve analysis to assess the sensitivity and specificity of the derived prediction models. In contrast, the current study used multiple linear regression to examine the independent predictive accuracy of variables as they relate to the severity of OSAS, reflected in a predicted AHI score. Our study utilized ROC curve analysis to examine the predictive ability of individual measures vs. prediction models on presence of OSAS. Subjects in the current study were also significantly younger, and included normal weight subjects as well as overweight and obese subjects. We were able to demonstrate that in younger men, alternative single anthropometric and exercise variables could be effective in predicting OSAS. With the difference in OSAS predictors found in the current study, this may suggest possible age-related changes in risk markers for OSAS, and thus require different approaches in clinical risk stratification for OSAS.

Other recent investigations have included body composition variables to attempt to predict OSAS [59, 65-67]. Shinohara et al. [67], using multiple linear regression on obese, middle-aged adults, reported that intra-abdominal or visceral fat, at the level of the

umbilicus, was a significant predictor of AHI. They further report that visceral fat was greater in the OSAS group, and that total fat amounts were not different between OSAS and controls. Similarly, Schafer et al. [59] found a significant relationship between AHI and intra-abdominal fat in their sample of middle-aged, and obese adults. In contrast to Shinohara, they report that percent body fat, the sum of skinfolds, body weight, and BMI to be independent predictors of AHI by linear regression [59], and not intra-abdominal fat. Dixon et al. [66] found NC to be the best single predictor of AHI through linear regression, but study subjects were all significantly obese (BMI > 40). Results from the current study also show a significant correlation between AHI and central abdominal fat, similarly to Shinohara [67]and Schafer [59], as well as with percent body fat as with Schafer. We demonstrate through the ROC curve analysis that percent body fat may be as effective, or more effective than central abdominal fat, while being easier to measure, in assessing OSAS risk. We extend the findings of Schafer et al. [59] to a younger study sample.

In a recent investigation, Ogretmenoglu et al. [65], using Pearson correlation and ROC curve analysis in a similar fashion to the current study, also found body composition to significantly predict the presence of OSAS. Using an AHI cutoff of ≥ 5, they report highly significant AUC values for percent body fat (0.93, $p< 0.001$), body fat mass (0.95, $p< 0.001$), visceral abdominal fat (1.00, $p< 0.001$), and BMI (0.89, $p< 0.001$) [65]. They report that through a combination of body fat mass and percent body fat, they were able to obtain 100% specificity and 95% sensitivity [65], and for those with a cross sectional area of visceral abdominal fat larger than 106.2 cm^2, sensitivity and specificity for OSAS diagnosis was 100%, albeit with in a highly selective subject cohort. Subjects

in their investigation ranged in age from 26 – 60, and were all overweight. We were able to show high levels of specificity and sensitivity with the HHR and percent body fat. While central abdominal fat was also a significant predictor of OSAS in our younger subject group, it did not perform as well as the other investigations.

Visceral or central abdominal fat is a key component of the metabolic syndrome. Several factors contribute to the development of central abdominal fat, a major contributor being sympathetic hyperactivity [68]. Lipolysis of central abdominal fat is mediated through catecholamine action on beta-3 adrenoreceports in the central abdominal fat [68]. As previously demonstrated, OSAS patients exhibit exaggerated sympathetic activation during waking hours [69-71], which may result in down-regulation of the beta-3 adrenoreceptors, and a decrease in the lipolytic response in OSAS patients. The down-regulation of beta-3 adrenoreceptors may be more advanced in older OSAS subjects, resulting in the greater predictive accuracy seen with central abdominal fat in the previous investigations [65, 67], compared to the younger subjects in the current study.

An attenuated HR and SBP recovery immediately post exercise appears to provide potential insight into OSAS risk in a younger population. The mechanism for this attenuated response is unclear. During exercise, HR is under the control of the sympathetic and parasympathetic branches of the autonomic nervous system [72]. At low exercise intensities, HR increases are due to parasympathetic withdrawal and are followed by increased sympathetic activation above 100 beats·min^{-1} [72]. During recovery, decreases in HR are due to sympathetic withdrawal and parasympathetic activation [73-75]. The exaggerated sympathetic activation that OSAS patients exhibit

[69-71], is likely is a significant contributor to the development of HTN [76]. In addition, a recent report suggests that OSAS results in abnormal control of HR which is mediated through both the sympathetic and parasympathetic pathways [77]. As a result, attenuation of the post-exercise HR and BP in untreated OSAS more likely reflects a sympathetic predominance, rather than reduced parasympathetic tone, and thus HR and BP appear to provide easily assessed and definitive markers of this autonomic imbalance in OSAS.

Only one previous study has reported on post-exercise HR and BP responses in OSAS patients [46]. That study [46] utilized middle-aged subjects, and the investigators reported no differences in the post-exercise HR response between OSAS and controls. However, SBP recovery was delayed in the OSAS subjects [46]. Presumably, the middle-aged OSAS patients in the previous study [46] have been exposed to the deleterious effects of augmented sympathetic activity of OSAS for a greater period of time compared to the younger subjects of the current study. This may contribute to a decrease in endothelial function, manifesting in impaired vasodilation or increased vasoconstriction of the vasculature, which has been reported in OSAS patients, independent to the affects of obesity [78-80]. Results from the current study, which show SBPR4 to be an independent predictor of AHI in young men, may indicate an early sign in the development of endothelial dysfunction, in response to augmented sympathetic activity. This may further suggest an age effect in the progression of physiological risk markers in OSAS.

Another important finding of the current study is poor predictive performance of the ESS in assessing OSAS risk in this younger subject group. Excessive daytime

sleepiness is a cardinal risk factor for OSAS, and the ESS is a well-validated, and frequently used tool to assess sleepiness [47, 60, 61, 81]. The ESS has previously been shown to significantly correlate to AHI [47, 61], but were based on results from middle-aged to older adults. Results from the current study show that ESS scores did not differ between any subject group, suggesting that among younger, college-aged men, the ESS cannot distinguish between clinically relevant daytime sleepiness, and that typified by a lifestyle of frequent sleep restriction.

One limitation of the current study is that only males were utilized as subjects, eliminating the ability to examine a gender effect. OSAS is more prevalent in premenopausal men than in women. It was determined that an insufficient number of females would be recruited who fit the inclusion criteria, and were not taking oral contraceptives. As a result, males were exclusively recruited for this current study. Another potential limitation was the unattended at-home PSG was utilized to quantify AHI, rather than nighttime PSG, the current gold standard for OSAS diagnosis. The Embletta device has been validated relative to PSG results [48], but is dependent upon the subject's ability to properly setup the device independently. Subjects were provided verbal and visual instruction by study personnel, written instructions for device setup, and contact information for study personnel in case further verbal instruction was needed over the phone, in an effort to minimize setup errors. In addition, subjects recruited for the current study were highly selected, in that, subjects who did not meet the inclusion criteria, were excluded. This could impact the specificity and sensitivity of the prediction variables reported in this investigation. The inclusion and exclusion criteria for this study

were set to control for confounding factors, to better examine the independent physiological affects of OSAS in isolation.

Conclusions

We conclude that in younger men, measures obtained from routine anthropometric and exercise testing may be useful in OSAS risk stratification, and may be better predictors of OSAS risk than more conventional risk variables established for older adults. This may suggest and age effect in the salient physiological risk markers for OSAS. These findings suggest the potential for exercise testing in improving risk stratification and clinical decision making leading to a greater number of individuals diagnosed and treated for OSAS, and decreasing the deleterious effects of this disorder. Further clinical studies with larger sample sizes, utilizing cross-validation, across a wide variety of ages health histories are needed to further examine the utility of these tests in determining OSAS risk.

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Table 1. Baseline subject characteristics and home sleep evaluation results

	OWSe-OSAS (n = 20)	OWSe-NoOSAS (n = 22)	NWM-OSAS (n = 10)	NWSe-NoOSAS (n = 17)	NWA-NoOSAS (n = 22)
Age (years)	22.6 (2.7)	22.2 (3.5)	21.4 (3.0)	21.1 (2.1)	20.7 (2.4)
AHI (events·hr^{-1})	17.6 (17.3)[g]	2.6 (1.4)	7.8 (2.6)[g]	1.9 (1.1)	1.6 (1.2)
ESS	9.1 (4.7)	8.2 (3.4)	6.3 (2.9)	6.3 (2.3)	7.0 (3.6)
Height (cm)	173.8 (16.0)	177.6 (5.4)	174.5 (7.0)	176.7 (6.1)	177.4 (6.7)
Weight (kg)	96.9 (13.6)[b]	98.8 (15.8)[b]	66.4 (8.4)	70.4 (7.4)	71.1 (8.1)
BMI (kg/m^2)	30.8 (3.9)[b]	31.3 (4.8)[b]	21.7 (1.5)	22.4 (1.6)	22.5 (1.8)
Neck circumference (cm)	40.4 (2.4)[b]	40.6 (3.2)[b]	36.2 (1.4)	36.3 (1.5)	36.1 (1.6)
Waist circumference (cm)	97.5 (9.2)[b]	96.2 (12.3)[b]	75.3 (5.2)	78.4 (6.5)	76.6 (4.7)
Hip circumference (cm)	123.1 (34.9)[a]	110.5 (9.5)[c]	94.6 (5.0)	96.5 (4.7)	95.8 (6.2)
Body fat (%)	27.4 (4.6)[b]	26.4 (5.2)[b]	16.8 (4.3)	18.9 (4.9)	14.0 (3.1)[f]
Central abdominal fat (kg)	7.9 (2.5)[b]	7.1 (2.4)[b]	3.2 (1.6)	3.6 (1.4)	2.6 (0.87)
Heart rate (bt·min^{-1})	91.5 (14.9)[d]	87.2 (14.0)	80.9 (15.3)	85.2 (11.4)	74.3 (13.1)
Blood pressure (mmHg)					
Systolic	124.6 (9.7)	123.0 (11.6)	115.8 (8.8)	121.8 (9.5)	119.3 (9.0)
Diastolic	91.6 (22.5)[e]	85.1 (8.8)	77.4 (6.3)	81.5 (6.8)	80.7 (7.3)

Data reported are mean values (SD)
Abbreviations: AHI = Apnea/Hypopnea Index; ESS = Epworth Sleepiness Scale; BMI = Body Mass Index
[a] Statistically significant difference (p <0.04) between OWSe-OSAS and all other subject groups
[b] Statistically significant difference (p <0.001) between overweight and normal weight subject groups
[c] Statistically significant difference (p <0.001) between OWSe-NoOSAS and normal weight subject groups
[d] Statistically significant difference (p <0.001) between OWSe-OSAS and NWA-NoOSAS groups
[e] Statistically significant difference (p <0.05) between OWSe-OSAS and NWM-OSAS groups
[f] Statistically significant difference (p <0.05) between NWA-NoOSAS and NWSe-NOSAS groups
[g] Statistically significant difference (p <0.002) from normal weight, sedentary subject groups

Table 2. Cardiopulmonary and Perceptual Results at Peak Exercise

	OWSe-OSAS	OWSe-NoOSAS	NWM-OSAS	NWSe-NoOSAS	NWA-NoOSAS
Heart rate (bt·min^{-1})	179.4 (13.4)	179.3 (11.1)	182.6 (11.3)	181.3 (12.6)	177.7 (12.5)
Blood pressure (mmHg)					
Systolic	195.1 (23.1)	199.0 (25.4)	175.8 (10.8)	195.5 (23.0)	196.3 (16.6)
Diastolic	91.2 (10.9)[a]	91.2 (12.1)[a]	80.6 (13.5)	89.0 (8.6)[a]	77.1 (9.4)
VO_2 (ml·kg^{-1}·min^{-1})	27.9 (4.5)	27.9 (5.4)	35.6 (6.5)[b]	34.7 (7.1)[b]	45.7 (9.4)[c]
V_E (L·min^{-1})	89.4 (13.2)[a]	92.7 (20.9)[a]	95.4 (21.8)	86.4 (21.7)[a]	119.9 (38.3)
RER	1.13 (0.06)	1.13 (0.05)	1.16 (0.07)	1.17 (0.07)	1.14 (0.07)
RPE	17.7 (1.4)	17.5 (1.4)	18.3 (1.3)	17.5 (1.3)	18.1 (1.4)

Data reported are mean values (SD)
Abbreviations: HR = heart rate; BP = blood pressure; VO_2 = oxygen consumption; V_E = minute ventilation; RER = respiratory exchange ratio; RPE = ratings of perceived exertion
[a] Statistically significant difference (p <0.03) from NWA-NoOSAS group
[b] Statistically significant difference (p <0.05) from overweight subject groups
[c] Statistically significant difference (p <0.003) from all other subject groups

Table 3. Associations between AHI and independent variables in univariate and multivariate analysis

	Univariate		Multivariate (Stepwise Linear Regression)		
	r	*p*	β	t-statistic	*p*
ESS	0.01	NS			
Weight	0.32	0.001			
Height	-0.49	<0.001			
BMI	0.39	<0.001			
Neck circumference	0.29	0.003			
Waist circumference	0.38	<0.0001			
Hip circumference	0.52	<0.0001	-0.86	-4.44	<0.001
TC (mg/dL)	0.33	<0.0001			
HHR	0.68	<0.0001	1.44	7.21	<0.001
HDL (mg/dL)	-0.25	0.01			
LDL (mg/dL)	0.30	0.004			
Triglycerides (md/dL)	0.33	0.001	0.22	2.92	0.005
Body fat (%)	0.37	<0.0001			
Central abdominal fat (kg)	0.43	<0.0001			
VO_{2pk}	-0.29	0.003			
$SBPR_{1min}$	0.09	NS			
$SBPR_{2min}$	0.12	NS	-0.25	-2.38	0.02
$SBPR_{3min}$	0.18	0.046			
$SBPR_{4min}$	0.28	0.004	0.41	3.90	<0.001
$SBPR_{5min}$	0.34	0.001			
$HRdiff_1$	-0.26	0.006			
$HRdiff_2$	-0.38	<0.0001			
$HRdiff_3$	-0.31	0.002			
$HRdiff_4$	-0.34	0.001			
$HRdiff_5$	-0.29	0.003			

Blank spaces indicate the variables removed during the stepwise regression process.
β: standardized regression coefficient.
Abbreviations: ESS = Epworth sleepiness scale; BMI = Body mass index; TC = Total cholesterol; HHR = hip-to-height ratio; SBPR = Recovery systolic blood pressure ratio; HRdiff = Recovery heart rate difference

Table 4. Receiver operator curve analysis results for predicting OSAS risk with an AHI cutoff of ≥ 10.

				95% CI	
	AUC	SEE	*p*	Lower	Upper
Conventional OSA Risk Markers					
ESS	0.39	0.09	0.23	0.22	0.56
BMI	0.71	0.09	0.02	0.54	0.88
Neck circumference	0.69	0.07	0.03	0.55	0.83
Waist circumference	0.71	0.09	0.02	0.54	0.89
Anthropometric Measures					
HHR	0.77	0.09	0.003	0.60	0.94
Hip circumference	0.71	0.08	0.02	0.55	0.88
% Body fat	0.77	0.07	0.003	0.63	0.91
Body fat mass	0.73	0.07	0.011	0.58	0.88
Central abdominal fat	0.75	0.08	0.006	0.59	0.90
Exercise Test Measures					
VO_{2pk}	0.68	0.07	0.04	0.55	0.82
HRdiff2	0.77	0.08	0.003	0.62	0.92
HRdiff4	0.77	0.07	0.003	0.63	0.91
SBPR4	0.71	0.09	0.02	0.54	0.89

Abbreviations: AUC = Area under the curve; SEE = Standard error of the estimate; ESS = Epworth sleepiness scale; BMI = Body mass index; HHR = Hip-to-height ratio; VO_{2pk} = peak oxygen consumption ($ml \cdot kg^{-1} \cdot min^{-1}$); HRdiff = Recovery heart rate difference; SBPR = Recovery systolic blood pressure ratio

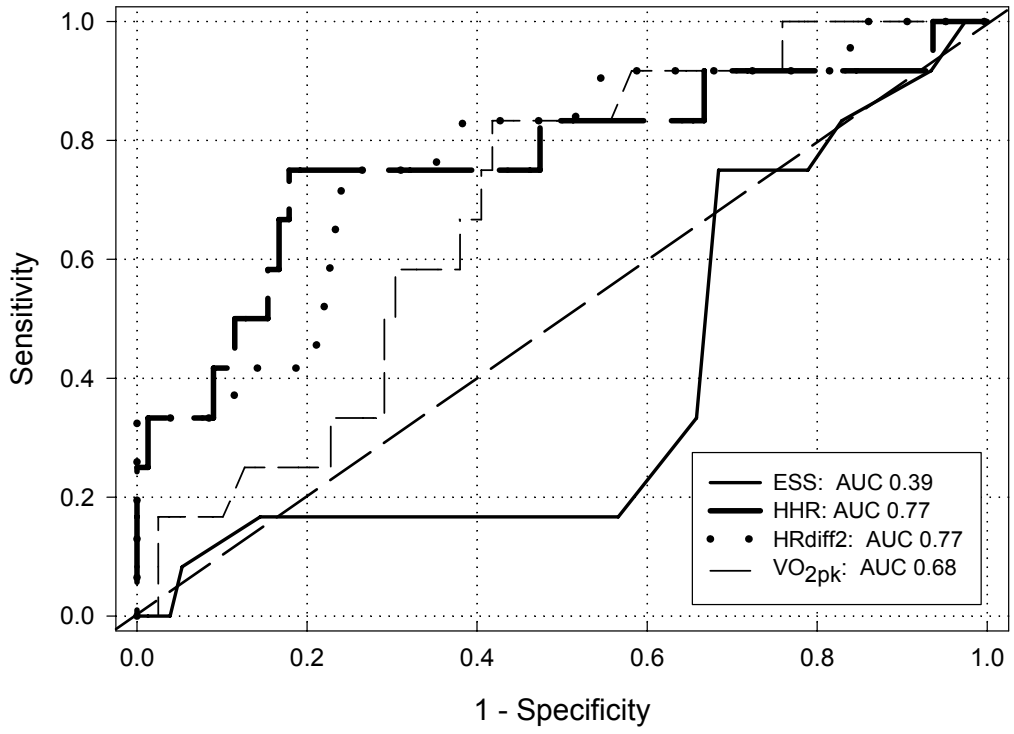

Figure 1. Receiver operator curve characteristics for variables obtained in young adult men, with respect to sensitivity and specificity for presence of OSAS (AHI cutoff ≥ 10).
Abbreviations: AUC = Area under the curve; ESS = Epworth sleepiness scale; HHR = Hip-to-height ratio; HRdiff2 = Recovery heart rate difference at 2 minutes; VO_{2pk} = peak oxygen consumption ($ml \cdot kg^{-1} \cdot min^{-1}$)

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CHAPTER 5

SUMMARY AND RECOMMENDATIONS

Obstructive sleep apnea syndrome is a serious condition that dramatically impacts the health and quality of life of those afflicted, and has been identified as a significant contributor to several adverse health conditions. While prevalence rates vary, epidemiological studies have estimated that as high as 24% of men and 9% of women have some form of OSAS.[1] While OSAS has gained in attention recently, under diagnosis remains a significant problem. It has been estimated that 82% of men and 93% of women with moderate to severe OSAS remain undiagnosed clinically.[2] Another concern is the lack of prevalence data on younger individuals. Given that OSAS and obesity are frequent comorbid conditions, and that obesity significantly increases the risk for developing OSAS[3] along with the increasing rates of overweight and obese individuals in all age groups, it is strongly suggestive of a significant portion of younger individuals who may be suffering from OSAS and are going undiagnosed. If these younger individuals could be diagnosed and treated earlier, many of the debilitating effects of OSAS could be delayed or prevented, increasing the quality of life of those individuals, while decreasing the financial impact of OSAS on the healthcare system.[4]

Individuals with OSAS experience frequent and intermittent bouts of hypoxia, hypercapnia, and stressful arousals during sleep. Chemoreflex activation, in response to changes in blood gases resulting from apneas and hypopneas, exerts powerful control over ventilation. Previously, OSAS patients have been shown to exhibit a heightened activation of the chemoreflexes.[5, 6] In addition, leptin, an adipocyte-produced protein previously been shown to be greater in obese OSAS patients than in obese individuals

alone, [7, 8] may also possess an important regulatory function with ventilation, particularly in response to CO_2.[9-11] Young, overweight male OSAS subjects in the current study demonstrated an exaggerated ventilatory response in relation to their CO_2 output (V_E/VCO_2) and their oxygen consumption (V_E/VO_2) compared to matched control subjects without OSAS across all exercise intensities, including peak exercise. Leptin levels had no relationship to the ventilatory response to exercise at any intensity. Leptin levels, however, were higher in all overweight subjects (with or without OSAS) compared to normal weight control subjects. We concluded that these unique ventilatory responses in overweight OSAS subjects may reflect alterations in chemoreflex sensitivity, particularly in the peripheral chemoreceptors, which respond more quickly than those centrally located.[12]

In addition to the unique ventilatory characteristics exhibited by the young, overweight male OSAS subjects in this study, we reported that the heart rate recovery, following maximal exercise, was altered with OSAS. The heart rate response to exercise is controlled by the interaction of the sympathetic and parasympathetic nervous systems. At higher exercise intensities, the heart rate response is primarily due to sympathetic activation.[13] Following exercise, the heart rate decrease is due to sympathetic withdrawal and parasympathetic activation.[13] Individuals with OSAS have previously been shown to express exaggerated sympathetic activation, which persists during waking hours.[14-16] When we examined the heart rate and blood pressure response during and after exercise, we found no difference in those responses at any exercise intensity between overweight OSAS subjects, overweight subjects without OSAS, or in normal weight controls. During recovery, however, the heart rate recovery response was attenuated in the

overweight OSAS subjects throughout a five minute, active recovery period of unloaded cycling, expressed as a difference between the peak heart rate and the heart rate at each minute of recovery. We found no difference in the recovery blood pressure response between our subject groups. We concluded that this attenuated heart rate recovery response, may be a early manifestation of exaggerated sympathetic activation found in OSAS, resulting in a sympathetic predominance during the recovery phase of exercise. The may be an early sign in the physiological adaptations to OSAS.

This study also reported the potential utility of simple anthropometric and exercise measures in predicting OSAS risk in younger individuals. There is a significant portion of individuals with OSAS, who would benefit from treatment, who remain undiagnosed. Overnight polysomnography (PSG) is the gold-standard for the diagnosis of OSAS. The substantial cost and inconvenience of PSG testing often make timely diagnosis and treatment of OSAS difficult. Our results identified several anthropometric and body composition variables (hip-to-height ratio, percent body fat, central abdominal fat), as well as those obtained from routine exercise testing (recovery heart rate and systolic blood pressure response) that significantly predicted the presence of OSAS (defined at AHI $\geq$ 10 in this investigation). With a combination hip-to-height ratio and percent body fat, or hip-to-height ratio and the difference between peak heart rate and heart rate at two minutes of recovery, 82% specificity and 83% sensitivity was achieved in identifying OSAS in a subject group consisting of 91 young men, ranging from normal weight to obese. Conventional OSAS risk markers, established previously in older individuals, such as the Epworth Sleepiness Scale (ESS), body mass index (BMI), neck circumference (NC), and waist circumference (WC) performed less effectively (BMI,

NC, and WC), or not at all (ESS) in predicting OSAS in our young male subjects. We concluded that these alternative anthropometric, body composition, and exercise measures may be more useful in identifying OSAS risk in young individuals, and may suggest an age-effect in the salient risk markers of OSAS.

Research related to the exercise responses of individuals with OSAS is limited.[17-21] These studies all utilized middle-aged to older adults, with only one previous study examining exercise recovery measures as well.[18] These studies also report conflicting results with respect to the observed functional capacity of the OSAS subjects. In the current study, measured VO_{2pk} was not significantly different between the overweight subjects with OSAS and those without OSAS who were of similar age and BMI. This study increases the research available on the functional capacity of OSAS patients, and extends the available information to younger OSAS patients. Furthermore, the previous data available on the cardiopulmonary responses to exercise testing in OSAS patients is conflicting. Kaleth et al.[18] report an attenuated HR response and a greater DBP response throughout all exercise intensities, including peak exercise in the OSAS patients, suggesting a downregulation of beta-adrenergic receptors in response to exaggerated sympathetic activation. They also report no significant differences in peak V_E, whereas Vanuxem et al.[21] report no differences in the HR response to exercise at any intensity in the OSAS patients, or any difference in the peak V_E. Results from the current study agree with those reported by Vanuxem et al.[21], and extend those findings to the younger OSAS patient. Lin et al.[17] report that, despite a significantly lower VO_{2pk} and peak V_E, no differences were noted in the peak V_E/VO_2 or V_E/VCO_2 between the OSAS patients

and control subjects. This may reflect an exaggerated response in these measures at similar VO_2 values, similar to results reported in the current study.

Kaleth et al.[18] is the only other study to examine post-exercise recovery measures. In contrast to the current study, they found no differences in the HR response post-exercise, but an attenuated SBP response. In our study, the HR recovery response was attenuated compared to controls. Both responses could reflect an imbalance in autonomic control following maximal exercise, possibly due to chronic activation of the sympathetic nervous system in response to OSAS. The difference in responses could reflect an age effect in the physiological adaptations to OSAS, given the young age of subjects in the current study, and the middle-aged to older individuals in the study by Kaleth et al.[18]

Practical and Clinical Applications

Findings from this study suggest that there may be future value in including anthropometric, body composition, and exercise testing as part of a routine clinical evaluation. We demonstrated that measures obtained from these tests, not typically associated with OSAS evaluation, may significantly improve the identification of those at increased risk for OSAS. Primary care physicians could implement simple anthropometric and body composition tests, along with an exercise test, to get a more complete risk profile of a patient they deem at risk for OSAS. Results from these simple tests may aid in discriminating those who need further diagnostic PSG testing. This study, however, highlights the potential allowances that may need made for age in determining the best screening techniques. The Epworth Sleepiness Scale has been shown to be a useful tool in identifying OSAS risk in older adults. We reported that the

Epworth Sleepiness Scale did not provide a useful marker of OSAS risk in young men. It appears that, among college men, the Epworth Sleepiness Scale cannot distinguish between clinically relevant daytime sleepiness and that typified by their lifestyle of frequent sleep restriction. By identifying those at greatest need for further diagnostic PSG testing, a greater number of will potentially be diagnosed with OSAS and treated earlier. This could have a wide reaching impact on the healthcare system, by reducing OSAS related costs, reducing the risks for the development of, and costs related to, comorbid conditions, for which OSAS contributes.

Recommendations for Future Research

Based on the findings of the current study and the available research pertaining to the cardiopulmonary responses to exercise and recovery and the unique physiological characteristics which may improve risk stratification in patients with obstructive sleep apnea syndrome, the following recommendations are made:

1. Exercise testing in OSAS patients may provide useful information for diagnosis and treatment of OSAS. The results from this study, along with previously published research, suggest that age may be a factor in the unique physiological responses to exercise in OSAS patients. Further studies on the exercise testing responses of OSAS patients, across a wide range of age, may help identify a cascade of physiological adaptations to OSAS, leading to different criteria for OSAS risk based on age. In addition, these unique responses may be related to OSAS severity as well as age. Exercise testing among patients with a broad range

of disease severity will help elucidate the effects of age and disease severity on exercise responses.

2. Results from this study suggest that anthropometric, body composition, and exercise testing variables may have utility in identifying OSAS risk. This study, however, was a study done on a highly selective section of the population: young men. Future studies examining these variables in association with OSAS risk should be expanded to a large scale study, including a wide sample of the overall population. From this type of study, the development of a multivariate OSAS risk score could be explored, with the ability to cross-validate the results on an independent subject sample.
3. Daytime sleepiness is a cardinal symptom of OSAS in older adults, and one that results in an increased risk for motor vehicle accidents, as well as decreased productivity in those who suffer from OSAS. It may also lead to a decrease in the amount of daily physical activity by OSAS patients, leading to an increase in sedentary behavior and the development of other adverse health problems. To date, no published research has examined the physical activity habits of OSAS patients, and whether excessive daytime sleepiness significantly impacts their physical activity. The gold standard treatment for OSAS, nCPAP, has been shown to decrease daytime sleepiness with treatment. Future studies are needed to examine how OSAS, nCPAP treatment, exercise training, and a combination of nCPAP and exercise impact the physical activity habits of OSAS patients.
4. To date, no definitive, well-controlled study has examined the effect of exercise training, coupled with nCPAP treatment (and nCPAP compliance) in OSAS

patients. The available literature has suggested that small improvements in body composition may improve OSAS severity. Exercise training is a well established method for improving body composition, as well as an effective method for improving other cardiovascular disease risk factors that are frequent comorbidities with OSAS, such as hypertension and impaired fasting glucose. Future studies that carefully control for confounding variables, a frequent problem with studies on OSAS patients, are needed to establish the independent effect of exercise training in OSAS.

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APPENDIX A

DETAILED METHODOLOGY

SUBJECT RECRUITMENT

Primary recruitment for eligible subjects took place on the Virginia Tech campus, with additional recruitment efforts targeting the surrounding communities. To better facilitate recruitment and initial screening of potential subjects, the study group developed and launched a secure, internet website (www.sleep.hnfe.vt.edu) that contained a description of the study design and all subject tests. In addition, initial screening questionnaires (informed consent, health history, ESS and VSAQ) were embedded into the website. Potential subjects were instructed to complete the questionnaires on the website, which were sent electronically to a secure email address (sleep@vt.edu), where study personnel could identify those potential subjects eligible for study inclusion. Information submitted for individuals determined not to be eligible for inclusion were deleted electronically, with any paper information destroyed. Information submitted for individuals determined to be eligible for inclusion was printed and compiled in a paper file, secured in a locked file cabinet.

Several recruitment methods were employed to identify potential study subjects. Campus-wide and targeted email listservs were utilized to disseminate information about the research study to large numbers of individuals within the age limits. Recruitment flyers were utilized campus-wide, as well ad throughout the surrounding communities. In addition, community advertisements were placed in local newspapers and on local public transportation.

EXPERIMENTAL DESIGN

Participants completed a health history questionnaire, as part of the initial screening questionnaires included on the study website, to exclude those with a history of cardiovascular, pulmonary, or metabolic disorders. Additional exclusion criteria included:

- Acute respiratory infections during previous 6 weeks, including tonsillitis and adenoiditis.
- Receiving any prescribed vasoactive medications, hypnotics, sedatives, analgesics, psychotropic, steroids, and sympathomimetics.
- Musculoskeletal conditions that would preclude maximal aerobic exercise testing.
- Habitual use of tobacco products within the past year.

Those who qualified were then scheduled for their initial visit to the Laboratory for Health and Exercise Sciences, which consisted of setup of the unattended, at-home sleep evaluation with the Embletta device (Embla, Broomfield, CO). Patients were provided with verbal instruction by study staff on proper setup and activation of the Embletta, and were given written instructions to take with them. Phone numbers of study staff were also provided if the subject required further instruction at home. Detailed instructions for the Embletta device are presented in Appendix B. Anthropometric data was also collected, i.e. height, weight, and neck, waist, and hip circumference from each subject. Subjects returned the Embletta device to the Laboratory for Health and Exercise Sciences following the night of testing Subjects returned the device following the night of testing and the data were downloaded and evaluated using proprietary software (Somnologica, Version 3.1.2, Embla, Broomfield, CO) for the Embletta®. These records were

interpreted by a trained sleep technologist and scores were confirmed and/or adjusted by the sleep physician investigator.

After completing the at-home sleep evaluation, subjects were scheduled for a second visit to the Laboratory for Health and Exercise Sciences where they completed the ramp cycle exercise test (detailed description presented below), followed by a third visit during the morning hours to obtain a fasting blood sample following a 8 – 12 hour fast (detailed description presented below). Subjects completed one final visit to the BONE Metabolism, Osteoporosis and Nutritional Evaluation Laboratory on the campus of Virginia Polytechnic Institute and State University for the composition measurements. Measurements were obtained via dual x-ray absorptiometry (DEXA) device (detailed description presented below). The Institutional Review Board of Virginia Polytechnic Institute and State University approved the study and all subjects gave their informed consent to participate.

MEASUREMENTS

Anthropometric Data

Anthropometric measures included height (centimeters), weight (kilograms), neck circumference (centimeters), waist circumference (centimeters), and hip circumference (centimeters). Body Mass Index (BMI) was calculated (kg/m^2) from measures of height and weight. A flexible tape measure was used to obtain neck, waist, and hip circumference measurements. Neck circumference was defined as the widest portion around the neck. Waist circumference was defined as the narrowest portion

around the waist between the xyphoid process and the umbilicus. Hip circumference was defined as the widest portion around the hips.

Resting Measures

Prior to the ramp cycle exercise test, resting hemodynamic measures were obtained while subjects were seated for a minimum of 5 minutes. Resting blood pressure was measured via manual auscultation with a standard sphygmomanometer and stethoscope. The appropriate cuff was used (bladder within the cuff should encircle at least two-thirds of the upper arm) to ensure accurate measurement. Resting heart rate and electrocardiogram was obtained with the Schiller AT-10® ECG system, as well as during the ramp cycle exercise test. Resting and exercise expired gas data was collected and analyzed by the SensoMedics Vmax 229® metabolic system (Yorba Linda, CA).

Ramp Cycle Exercise Test

All subjects completed a maximal exercise test on a SensorMedics® electronically braked cycle ergometer (Yorba Linda, CA) using a standardized ramping protocol. Participants were free to choose any pedal cadence above 50 revolutions per minute and resistance was adjusted internally by the ergometer to produce a constant load of 25 watts for a one minute warm-up period. Work load was automatically ramped 15 watts/min to volitional fatigue. Trained technicians closely monitored the exercise and recorded perceived exertion scores (Borg 6-20) each minute. Blood pressure measurements were taken at 2-min intervals during exercise and at 15 second intervals in the post-exercise period, via auscultation. Subjects performed an active recovery with no resistance on the ergometer for 5 minutes and observed by study personnel until all responses returned to resting levels. All tests will be conducted and supervised by staff

certified by the American College of Sports Medicine (ACSM) as Exercise Specialists. According to the ACSM's Guidelines for Exercise Testing and Prescription, 7th edition, given the young age of the study subjects, physician supervision is not required for maximal exercise testing [1]. Test termination criteria, according to the American College of Sports Medicine, were used for all tests [1]. Measurements of interest included oxygen consumption (VO_2), minute ventilation (V_E), ventilatory equivalents for oxygen (V_E/VO_2) and carbon dioxide (V_E/VCO_2), V_E/VCO_2 slope, respiratory exchange ratio (RER), as well as heart rate, blood pressure during exercise recovery.

Fasting Blood Sample

Subjects were instructed to refrain from eating 8 hours prior to the blood draw, and this was confirmed immediately before the collection. Blood pressure was recorded before and after the blood draw. Blood samples of ~50mL were collected from each subject. Afterwards, participants were given a light snack and observed for any negative reaction to the process before leaving. All blood samples were processed by the senior lab technician and graduate students, which included a complete lipid profile to analyze levels of the following:

- Total cholesterol
- Triglycerides
- High-density lipoprotein
- Low-density lipoprotein
- Glucose

The Cholestech LDX® device (Cholestech, Hayword, CA) was utilized for all lipid profile analyses. Aliquots of 1.2mL each, plasma and serum samples, were separated

from whole blood via centrifugation and frozen at -80°C for later batch analysis of leptin levels. A detailed description of leptin radioimmunoassay presented in Appendix C.

DEXA Body Composition Analysis

Subjects completed total body (TB, version 8.26a:3*) DEXA scans (QDR4500A, Hologic Inc., Bedford, MA, USA) to measure fat-free soft tissue mass (FFM, kg), fat mass (FM, kg), and body fat percentage (BF%). Central abdominal fat was measured from TB DEXA scans by examining the region of interest defined by the top edge of the second to bottom edge of the fourth lumbar vertebra [2]. All DEXA measures were conducted and analyzed by one investigator. Weekly scans of an external soft tissue bar (Hologic, Inc., Bedford, MA) were completed to ensure quality control for soft tissue mass measurements. Test-retest reliability data for this DXA have been reported elsewhere [3, 4].

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APPENDIX B

INSTITUTIONAL REVIEW BOARD
PROTECTION OF HUMAN SUBJECTS APPROVAL

Virginia Tech
VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

Institutional Review Board

Dr. David M. Moore
IRB (Human Subjects)Chair
Assistant Vice President for Research Compliance
CVM Phase II- Duckpond Dr., Blacksburg, VA 24061-0442
Office: 540/231-4991; FAX: 540/231-6033
email: moored@vt.edu

DATE: December 22, 2004

MEMORANDUM

TO: William G. Herbert Human Nutrition, Foods, & Exercise 0351

FROM: David Moore

SUBJECT: **IRB Amendment Approval**: "Risk Factors for cardiovascular and metabolic dysfunction in overweight adolescents vs. young adults at risk for sleep apnea syndrome(SAS)" IRB # 04-370 FR

This memo is regarding the above referenced protocol which was previously granted approval by the IRB on August 9, 2004. You subsequently requested permission to amend your approved protocol to include the addition of the listed changes. Since the requested amendment is nonsubstantive in nature, I, as Chair of the Virginia Tech Institutional Review Board, have granted approval for requested protocol amendment, effective as of December 22, 2004. The anniversary date will remain the same as the original approval date.

Virginia Tech has an approved Federal Wide Assurance (FWA00000572, exp. 7/20/07) on file with OHRP, and its IRB Registration Number is IRB00000667.

cc: File

Virginia Tech
VIRGINIA POLYTECHNIC INSTITUTE
AND STATE UNIVERSITY

Institutional Review Board

Dr. David M. Moore
IRB (Human Subjects) Chair
Assistant Vice President for Research Compliance
1880 Pratt Drive, Suite 2006, Blacksburg, VA 24061-0442
Office: 540/231-4991; FAX: 540/231-6033
email: moored@vt.edu

DATE: August 23, 2005

MEMORANDUM

TO: William G. Herbert Human Nutrition, Foods, & Exercise 0351

FROM: David Moore

SUBJECT: **IRB Full Review Continuation**: "Risk Factors for cardiovascular and metabolic dysfunction in overweight adolescents vs. young adults at risk for sleep apnea syndrome(SAS)" IRB # 05-424 FR ref 04-370 FR

This memo is regarding the above referenced protocol which was previously granted expedited approval by the IRB on August 9, 2004. The proposed research, having been previously approved at a convened IRB meeting, required full IRB review prior to granting an extension of approval, according to the specifications authorized by 45 CFR 46.110 and 21 CFR 56.110. The above referenced protocol was submitted for full review continuation and approval by the IRB at the August 8, 2005 meeting. Pursuant to your request, I, as Chair of the Virginia Tech Institutional Review Board, have, at the direction of the IRB, granted approval for this study for a period of 12 months, effective August 9, 2005.

Approval of your research by the IRB provides the appropriate review as required by federal and state laws regarding human subject research. It is your responsibility to report to the IRB any adverse reactions that can be attributed to this study.

To continue the project past the 12 month approval period, a continuing review application must be submitted (30) days prior to the anniversary of the original approval date and a summary of the project to date must be provided. Our office will send you a reminder of this (60) days prior to the anniversary date.

Virginia Tech has an approved Federal Wide Assurance (FWA00000572, exp. 7/20/07) on file with OHRP, and its IRB Registration Number is IRB00000667.

cc: File

APPENDIX C

LEPTIN RADIOIMMUNOASSAY METHODOLOGY

The Human Leptin RIA kit (Linco Research Inc., St. Charles, Missouri) was used to assess serum leptin levels through competitive binding between ^{125}I-Human leptin tracer and unknown samples. ^{125}I-Human leptin tracer and leptin antibody were added to study subject samples (100 µl each) and incubated at 4°C overnight. On day two, cold (4°C) precipitating reagent (1.0 mL) was added to all study samples and control samples, and incubated for 20 minutes at 4°C. All samples were centrifuged for 20 minutes at 2,500 rpm and 4°C, with the supernatant immediately decanted by one-time inversion. All samples were then counted in a gamma counter for one minute. A standard curve was generated based on 100 µl samples of standard leptin concentrations. The intra-assay variability for this kit ranges from 3.4 – 8.3%. the inter-assay variability ranges from 3.0 – 6.2%.

APPENDIX D

INFORMED CONSENT FORM

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Informed Consent for Participants in Investigative Project
(For 18-26 year old subjects)

Title of Study: Risk factors for cardiovascular and metabolic dysfunction in adolescents vs. young adults at risk for sleep apnea syndrome (SAS)

Location of Study: 231 War Memorial Hall and 225 Wallace Hall, Virginia Polytechnic Institute and State University, Blacksburg, Virginia

Investigators: William Herbert, Ph.D., Don Zedalis, MD, John Gregg, DDS, Ph.D., Sharon Nickols-Richardson, RD, Ph.D., Stephen Guill, MS, Trent Hargens, MS.

I. Purpose of This Research

The purpose of you being in this study is to provide information on how young adults develop sleep apnea syndrome. Sleep apnea is a sleeping disorder that occurs when you stop breathing multiple times over the course of the night. The results of this study may help researchers identify risk factors for sleep apnea that can be identified and treated at a younger age. Before you begin the study, you will be asked some questions about your health history, complete forms on your quality of life and sleep habits, and have your weight and resting blood pressure measured in order to see if you meet the levels to be in this study. If you qualify, you will be asked to take an in-home, overnight sleep test to determine if, and to what extent, you may be affected by sleep apnea. Upon completing this test, you will then be asked to perform several exercise, blood vessel, body fat, and blood tests. All of these tests will take place on the Virginia Tech campus and will take a total of about 3 hours over the course of 3 days. If you decide to be in this study, your results may help researchers better understand how sleep apnea develops in your age group.

The scientific purposes for this study are: 1) to see how sleep apnea affects the heart and circulation, physical fitness, and risk factors for heart and metabolic disease; and 2) to identify risk factors for developing sleep apnea that may be present, yet unknown, in young adults.

To be in this study, you will be asked to make sure that you do not currently have, or have a history of, any of the following:

- Heart problems, including heart attack, chest pain that may be related to heart problems (this is called angina pectoris), surgery for your heart or its blood vessels, or heart failure;
- Chronic lung diseases (including asthma);
- Diabetes mellitus;
- Use of blood pressure medications or antihistamines (cold or allergy medicine);
- Bone or joint problems, muscular or bone conditions, or other conditions that would prevent you from doing vigorous exercise;

- Use of tobacco products use (only non-smokers can participate);
- Any problem affecting your breathing (cold, sinus infection, etc.) during the previous 6 weeks;
- Current pregnancy;
- Use of birth control pills;

If researchers are concerned by any part of your health history, we will ask you to contact your personal physician with a copy of this form in addition to the health history form. Your physician should review these and fax our office with his/her permission or refusal for you to participate in this study.

II. Procedures

You will be asked to complete the following procedures for this study:

Introduction, Informed Consent, and Advanced Screening (up to 3 meetings)

This session will last about 80 minutes. Before session 1, you will be provided a copy, either through mail, email, or access to the study website, of this informed consent form as well as a simple health history form. Please read these carefully and write down any questions you may have for the research team before you report to our lab for the first meeting.

You will then report to the Laboratory for Health and Exercise Science in 231 War Memorial Hall on the Virginia Tech campus. Once there, a researcher will read through this form with you and will answer any questions or concerns that you may have. The researcher will also go over a more detailed health history form with you and may ask you more questions about your health. This allows researchers to identify if any past or current health problems will place you in or keep you from being in this study. After these forms are completed and signed, you will be asked to sit quietly for 10 minutes and have your resting blood pressure taken. After this, a researcher will take your height, weight, neck, and waist measurements. If any of these numbers do not meet the study minimum, you will not be able to continue in this study. You will also complete more interviews and forms on your quality of life and sleep patterns.

Session 1 – Setup for At-Home Sleep Test

This session will last about 30 minutes and you will report to 231 War Memorial Hall on the Virginia Tech campus. You will have another blood pressure measurement taken. One of the researchers will then inform and instruct you about setting up and using a small pocket-sized recorder, the Embletta (At-Home sleep device, see attached picture). It is equipped with straps, wires, and small sensors. You will be asked to wear the Embletta for one entire night at home while you sleep. It measures your breathing activity, pulse, and blood oxygen levels. The Embletta is a harmless non-invasive monitor sometimes used by sleep doctors to screen people who may need more medical tests for possible nighttime breathing disorders. The researcher will make plans for you to take the Embletta home, assist you by phone if needed to properly set it up for one night, and make plans for you to return it the next day.

Session 2 – Blood Sample and Body Fat and Bone Health Tests

This session will last about 60 minutes. Within one or two weeks of your Embletta test, you will be asked to report to the 299 Wallace Hall on the Virginia Tech campus for more testing. On the first day, you will be asked to give a small amount of blood (~75ml, about 4 tablespoons), which will be taken from a blood vessel in your arm.

After having your blood drawn, you will undergo a dual energy x-ray absorptiometry (DXA) scan to measure the mineral content and density of your bones as well as body fat. This involves lying quietly for about 10 minutes on an exam table while the DXA scan slowly passes over your whole body. After this test, the researcher will set up a meeting date and time for the final day of testing.

Session 3 – Blood Vessel Health and Bicycle Exercise Tests

This session will last about 90 minutes. On this day, you will report to the Laboratory for Health and Exercise Science in 231 War Memorial Hall on the Virginia Tech campus. Once there, you will lie quietly for 10 minutes on a padded table and you will be given a simple, external measurement of blood vessel health. This involves having inflatable cuffs placed around your upper arm and wrist, in addition to an elastic band placed around your forearm.

Finally, you will perform an exercise test on a stationary bike. As you pedal longer on the bike, it will become harder to pedal. It is your goal to pedal as long as you can. Researchers will encourage and cheer you to do your best. After this test, you will rest quietly in the lab for 15 minutes to recover from the test and a researcher will provide you with several results from your tests. Both the blood vessel health and bicycle exercise tests are explained more in the next section.

More details about the **specific tests** are shown below:

a) Forms

In all, you will be asked to fill out several forms asking your opinion on several things. These include a detailed health history, a couple of forms about the quality of your sleep and daytime sleepiness, a form about your current quality of life, and forms about your daily physical activities. If any of these forms suggest a sleep problem other than sleep apnea, you will not be allowed to be in this study and we will suggest that you see a sleep physician for further testing and treatment.

b) Blood Pressure

You will have several blood pressures taken during this study. This involves you sitting quietly for 10 minutes. A cuff will be placed around your upper arm, between your shoulder and your elbow. The cuff will be pumped up to stop blood flow to your arm for a few seconds. The cuff pressure is slowly released and a researcher will read your blood pressure and remove the cuff from your arm. The cuff will get tight on your arm, but it only lasts a few seconds.

c) Other Physical Tests

Your height and weight will also be measured on a balance beam physician scale. A researcher will also use a tape measure to measure the size of your waist, neck, and hips.

d) At-Home Sleep Test

For this test, you will be given a recorder with straps, wires, and small sensors to take home. First, you will attach a flexible strap to your abdomen and chest to measure how they expand and contract when you sleep. You will also wear a nasal cannula, a device that attaches to your nostrils and measures if you are breathing. Finally, you will attach a small sensor to your finger that measures the amount of oxygen in your blood. You will wear this entire device for one whole night of your usual sleep.

e) Blood Sample

You will have blood samples drawn in order to look at blood glucose, lipids (fats), and several markers of blood vessel function. The total amount of blood that you will give will be small, i.e. less than 75 ml (about 5 tablespoons). A qualified technician will draw the blood samples, and accepted medical procedures will be followed. A laboratory specialist will examine, process, and store your blood to be analyzed at the end of the study.

If a technician or other person who handles your blood sample is accidentally exposed to your blood, you will be required to have your blood tested for HIV/AIDS. This testing will be confidential and will be done at the Montgomery County Health Department. This test will cost $50 and funds provided by the research sponsor will cover this cost. It is required that you provide the Montgomery County Health Department with your social security number and your name; if you have a positive test for HIV/AIDS, and only then, this result must be reported to the State Health Department (this is a legal requirement). The names of persons with HIV/AIDS positive tests that are reported to the state remain confidential; however, this information will be placed in your permanent medical records. The test facility requires pre-test and post-test counseling. They will contact you within 2 weeks to notify you that you must return there to receive your test results. No results will be given by phone.

f) Body Fat and Bone Health Test

Dual energy x-ray absorptiometry (DXA) will be used to measure your body fat. This test also tells us the mineral content and density of the bones in your arm and leg. Bone mineral content and density provides information on general bone health. The DXA is much like an X-ray machine. The dose of radiation that you will receive with this test is very small and no greater than you normally receive each day from your surroundings over the course of a year. The DXA will scan your entire body very slowly; so, you will need to lie on a table without moving for almost 10 minutes, while the DXA is passed over your entire body. You will feel no discomfort associated with this test.

Exposure to radiation will occur during DXA scans for measurement of your bone mineral density. Radiation exposure will occur from the DXA scans because the DXA machine uses x-ray technology. Radiation exposure is measured in millirads (or mR). The total amount of exposure is 40 mR (whole body = 1 mR, lumbar spine = 7 mR, hip = 7 mR, forearm = 5 mR) or 20 mR at two testing times. This represents 4% of the estimated exposure to increase cancer risk in only 0.03% of the population. This dose is very small and poses minimal risk.

NIH-OPRR Radiation Limits for an Adult Research Participant per Year	**Exposure During Participation in this Research Study**
Whole body (single dose) = 3,000 mR	Whole body (single dose) = 1 mR
Lumbar spine (single dose) = 5,000 mR	Lumbar spine (single dose) = 7 mR
Hip (single dose) = 5,000 mR	Hip (single dose) = 7 mR
Forearm (single dose) = 5,000 mR	Forearm (single dose) = 5 mR
CUMULATIVE EXPOSURE = 18,000 mR	**CUMULATIVE EXPOSURE = 20 mR**

Any individual may choose to not complete any one, combination, or all of these DXA scans. If in the event that any scan is unreadable or unusable, a replacement scan will not be conducted to avoid further exposure. I**f you are pregnant or think that you may be pregnant, you should not undergo DXA scans because radiation exposure from DXA scans may cause harm to your unborn fetus.** It is unknown how much or how little damage may occur to an unborn fetus during DXA scans. The risk of harm to an unborn fetus is unknown but is possible. It is best to not have DXA scans done if you think that you are or if you know that you are pregnant. In fact, before DXA scans are done, a pregnancy test kit will be completed for each adolescent or young woman who is post-menarcheal (have started menstrual cycles) or pre-menopausal (have not yet stopped having menstrual cycles) with a sample of her urine. If this pregnancy test is negative (or shows "not pregnant"), participation in the study may continue. If this pregnancy test is positive (or shows "pregnant"), participation in the study will not be allowed and you will be instructed to seek care from your Primary Care Physician or Obstetrician/Gynecologist. If the pregnancy test is positive, any and all costs related to this pregnancy will be borne by the individual and not by Virginia Tech. **If you are under the age of 18 and your pregnancy test is positive, your parent or guardian will be informed of this positive test result.** So that there is an equal opportunity to be in this study, any woman who is not pregnant and meets other study criteria will be given the chance to participate in this study if desired. DXA scans will be conducted in the BONE Laboratory, Room 299 Wallace Hall, on the Virginia Tech campus by an investigator who is a Licensed Radiologic Technologist – Limited in the Commonwealth of Virginia.

g) Blood Vessel Health Test

Plethysmography (PTG) is a simple test of the ability of your blood vessels to expand and contract. For this test, you will be asked to lie supine on a padded table for 10 minutes. Your forearm will be measured and a flexible band will be placed across the largest part of your forearm. A blood pressure cuff will be placed around

your wrist and your upper arm. As the cuffs are pumped up, the flexible band placed around your forearm sends blood vessel measurements to the computer to which it is connected. These cuffs may be pumped up for up to 10 minutes and you may feel some slight discomfort and numbness in your fingers, which will go away quickly after the cuffs are removed.

h) Bicycle Exercise Test

Your exercise test will be on a stationary bike. We will measure the electrical output of your heart by placing 10 electrodes directly on your skin across your chest and stomach. A female researcher will be available to place and remove electrodes for female subjects. During the test, researchers will measure your heart's electrical activity, heart rate, blood pressure, effort, and how much oxygen your body is using. To see how much oxygen you use, we will ask you to breathe into a rubber mouthpiece. During the bicycle test, you will breathe only through the mouthpiece and may experience some dryness in your mouth. The intensity of the cycling exercise will increase as you pedal, over about 14 minutes. At first it will be very easy and then become harder; during the last few minutes, the work will become very intense and should be a best effort on your part. It may be as hard as any exercise that you remember doing. The exercise test will last about 10 minutes.

The total time involved to complete all of the above procedures over the 3 or 4 days you are in the study is about 4 hours. If we find unusual results from any of these tests, we will suggest you see your personal doctor. We will provide you with specific information about these tests to give to him/her.

III. Risks

a) Blood Sample

During the blood draws, you may have pain and/or bruising at the place on your arm where the blood is taken. In about 1 in 10 or 10% of the cases, a small amount of bleeding under the skin will cause bruises. The risk of a blood clot forming in the vein is about 1 in 200 (0.005%), while the risk of infection or significant blood loss is 1 in 1000 (0.001%). To reduce these discomforts, a trained phlebotomist (person skilled in collecting blood by needle) will draw your blood from a vein in your arm. The amount of blood taken is less than NIH guidelines for single blood draws.

b) Bicycle Exercise Test

There is a very small chance of abnormal changes during the bicycle exercise test. These changes may include abnormal blood pressure, fainting, heart rhythm disorders, stroke, heart attack, and death. The chances of serious heart problems during maximal exercise among adults who seem to be healthy is very small, e.g. risk of cardiac death is less than 1 per 10,000 in maximal treadmill exercise tests. The researcher present during your exercise test will have current certification from the American Heart Association in Basic Cardiopulmonary Life Support (BCLS) or the equivalent. A phone will be available to contact the local Emergency Medical System (EMS). The

response time for our EMS, the Virginia Tech Rescue Squad, to reach the strength testing/training facility averages less than 5 minutes.

Every effort will be made to minimize abnormal responses to the exercise test by a review of your health history in addition to close supervision of your response to the exercise test. If the health history form shows conditions that may make you more likely to have exercise-related complications, you cannot be in the study.

c) Body Fat and Bone Health Test

The amount of radiation that you will receive in the DEXA exam is less than the amount permitted by the Food and Drug Administration (FDA) per year. The amount you will receive is equal to 1/20 of a chest x-ray. The more radiation you receive over the course of your lifetime, the more likely your risk increases in developing cancer. The radiation in this study is not expected to greatly increase these risks, however the exact increase in such risk is not known. You should not be pregnant for this study because of risks from the DEXA scan radiation to the embryo or fetus.

All other tests in this study have very little risks. We believe the overall risks of you being in this study are small. It is not possible to identify all possible risks in a study, however the study staff will take all possible steps to lessen any risks to your well-being.

IV. Benefits of Your Participation in This Project

- You will be provided with the results from your exercise test, which can be used for evaluating the condition of your heart and lungs. The researchers suggest that you take a copy of the test to your personal physician to be placed in your permanent medical records.
- A physician will act as a research coordinator and stay in contact with you to monitor and manage your progress throughout the study.
- A trained nutritionist or dietitian will evaluate and make general recommendations to you about the type and amount of foods that you are eating. This information may be beneficial for your health and controlling risk factors for chronic diseases, such as coronary heart disease. Were you not in the study, this type of analysis normally costs $50 per evaluation.
- You will be provided with the results of your blood test, including blood glucose, total cholesterol, HDL (good) cholesterol, LDL (bad) cholesterol, and triglycerides.
- You will also be provided with the results of your DXA scan, including bone density measurements and body composition. These analyses normally cost $500.
- You will be given the results of your at home sleep test.

We suggest that you take a copy of the home sleep report, the exercise test report, and the blood test report to your doctor. Should you have abnormally high scores on the at home sleep test, we will notify you and strongly encourage you and to see a sleep specialist. This is particularly important if you drive or operate heavy equipment, as excessive daytime sleepiness is associated with these higher scores. If your doctor notes a concern

after reviewing any of these tests, you and your doctor may decide that you should consult with a healthcare specialist. However, any and all costs related to such a referral and medical care will by paid by you and not by Virginia Tech, nor any of its agents, including the researchers.

V. Extent of Anonymity and Confidentiality

The results of this study will be kept strictly confidential. At no time will the researchers release your individual results to anyone other than the researchers working on the project without your written consent. The information that you provide will have your name removed and only a subject number (excluding social security numbers) will identify you during analyses and written reports of this research. Your file will be kept in a locked file cabinet and your data will also be kept in a password secured electronic database in 213 War Memorial Hall.

VI. Compensation

You will receive the following for being in this study:

- For session 1 of this study (blood pressures, weight, interviews, forms, and the At-Home Sleep test), you will be paid $15.
- For session 2 of this study, you will be paid $15.
- For session 3 of this study, you will be paid $15.

VII. Freedom to Withdraw

Your participation in this study is completely voluntary. Your refusal to participate in this study will, in no way, affect your standing at Virginia Tech (if you are enrolled as a student). Once you agree to be in the study, you are free to stop at any time without penalty. To withdraw, please contact one of the listed investigators.

VIII. Injury during Participation in This Study

Neither the researchers nor the university have money set aside to pay for medical treatment that would be necessary if injured as a result of you being in this study. Any expenses that you have including emergencies and long-term expenses would be your own responsibility.

IX. Approval of Research

This research project has been approved, as required, by the Institutional Review Board for projects involving human subjects at Virginia Polytechnic and State University and the Department of Human Nutrition, Foods, and Exercise. IRB approval of this project is in effect from August 15, 2004-August 15, 2005.

X. Subject's Responsibilities

By being in this study, you accept that it is your responsibility to:

- Accurately and completely report your medical history;
- Refrain from participation in vigorous physical activity for the 24 hours prior to any measurement for this study;
- Consume no food, caffeine, or nicotine products during the 12-hour period before arriving at the testing lab;
- Remain in the testing and/or exercise area 15 minutes after each of the exercise testing periods;

Report any physical or medical problems that might occur outside the lab during the period of testing, even if you feel it is not related to the testing to: Carol Haskell (951-8814), Stephen Guill (231-6374/951-5665), Trent Hargens (231-6374/818-5884) or Dr. William Herbert (231-6565/951-0974).

XI. Subject's Permission

You have read and understand the informed consent and conditions of this research study. You agree to undergo all screening procedures described above prior to acceptance into this study. It is your right to withdraw from the study at anytime without penalty and that you can be dropped from the study by the investigators without your consent. You also understand the risks of your participation and the nature of any potential benefits. Any questions that you have asked have been answered to your complete satisfaction. If you have questions that arise at a later time, please contact one of the listed investigators. You hereby acknowledge the above and give your voluntary consent for participation in this study.

Questions/Response: _____

_____

_____

_____

_____

_____

_____ _____

Signature Date

_____ _____

Witness (Research Coordinator) Date

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

Carol Haskell, MD 951-8814
Research Coordinator

William G. Herbert, Ph.D. 231-6565
Principal Investigator
Human Nutrition, Foods, & Exercise

Stephen Guill, M.S. 231-6374
Investigator

David M. Moore, Ph.D. 231-4991
Chair, IRB, Research Division

Trent Hargens, M.S. 231-6374
Investigator

Kevin Davy, Ph.D. 231-3487
Departmental Reviewer

Nadine Guignel, B.S. 231-6375
Investigator

APPENDIX E

GRADED EXERCISE TEST DATA COLLECTION SHEET

OBSTRUCTIVE SLEEP APNEA: RESMED 3
GRADED EXERCISE TEST DATA SHEET

Name_____ Age_____ Wt_____lb/kg Ht_____ in/cm Date_____

Subject #_____ BMI_____

Neck Circ:_____ Waist Circ:_____ Hip Circ:_____

MEDICATIONS:

Name	Dose	Time last taken	Name	Dose	Time last taken

Rest HR_____/_____ **Rest BP_____/_____**
standing/ sitting standing/ sitting

Protocol: 15 W/min Ramp (25 W warm-up for 1-min)

Time	Watts	HR	BP	RPE	ECG /Symptoms/Comments
0-1	40		/		
1-2	55		/		
2-3	70		/		
3-4	85		/		
4-5	100		/		
5-6	115		/		
6-7	130		/		
7-8	145		/		
8-9	160		/		
9-10	175		/		
10-11	190		/		
11-12	205		/		
12-13	220		/		
13-14	235		/		
14-15	250		/		
15-16	265		/		

Immediate Post-Test Symptoms: Chest Discomfort Shortness of Breath Lightheadedness Other:

RECOVERY IPE	HR	BP	ECG /Sympytoms/Comments
0:15		/	
0:30		/	
0:45		/	
1:00		/	
1:15		/	
1:30		/	
1:45		/	
2:00		/	
2:15		/	
2:30		/	
2:45		/	
3:00		/	
3:15		/	
3:30		/	
3:45		/	
4:00		/	
4:15		/	
4:30		/	
4:45		/	
5:00		/	

REASON FOR STOPPING TEST: _____

Comments: _____
_____
_____

APPENDIX F

SCREENING QUESTIONNAIRES

EPWORTH SLEEPINESS SCALE
MEDICAL HISTORY QUESTIONNAIRE

ResMed3 Clinical Trial

Epworth Sleepiness Scale

Subject ID_____ Name_____ Date Completed ____/____/____

This questionnaire asks you to indicate the chances of you becoming drowsy during hours of the day that you are not in bed sleeping. "How likely are you to doze off or fall asleep in the following situations?"

Use the following scale and indicate the most appropriate number for each situation.

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

	Situation	**Chance of Dozing**
1.	Sitting and reading	_____
2.	Watching T.V.	_____
3.	Sitting, inactive in a public place (ex. Theatre or meeting)	_____
4.	As a passenger in a car for an hour without a break	_____
5.	Lying down to rest in the afternoon when circumstances permit	_____
6.	Sitting and talking with someone	_____
7.	Sitting quietly after a lunch without alcohol	_____
8.	In a car, while stopped for a few minutes in the traffic	_____

Sum of Scores, items 1-8 (staff use only) **_____/24**

VIRGINIA TECH
LABORATORY FOR HEALTH AND EXERCISE SCIENCE
Medical and Health History Form for Adult Candidates
Sleep Apnea Syndrome Study

Name: _____ Age: _____ yr Date of Birth: _____

Ethnicity: _____

Height: _____ ft Weight: _____ pounds

Gender: Female_____ Male_____

Campus Address: _____

Campus Telephone Number: _____ Campus Email Address: _____

Address for Permanent Residence: _____

Person to contact in case of emergency: _____

Relationship: _____ Daytime Telephone: _____ Home Telephone: _____

Primary Care Physician: _____ Telephone: _____

Medical History
Please indicate any current or previous conditions or problems you have experienced or have been told by a physician you have had:

	Yes	**No**
Heart disease or any heart problems:	_____	_____
Rheumatic fever:	_____	_____
Respiratory disease or breathing problems:	_____	_____
Circulation problems:	_____	_____
Kidney disease or problems:	_____	_____
Urinary problems:	_____	_____
Reproductive problems:	_____	_____
Musculoskeletal problems:	_____	_____
Fainting or dizziness, especially with exertion:	_____	_____
Neurological problems/disorders:	_____	_____
High blood pressure:	_____	_____
Low blood pressure:	_____	_____
High blood cholesterol:	_____	_____
Diabetes:	_____	_____
Thyroid problems:	_____	_____
Eating disorders (bulimia, anorexia):	_____	_____
Allergies:	_____	_____

If "yes" to any of the above please indicate the date, explain, and describe:

_____

_____

_____

Please list any hospitalizations/operations/recent illnesses (Type/Date):_____

_____

_____

Family Health History

Has anyone in your family (blood relatives only) been diagnosed or treated for any of the following?

	Yes	**No**	**Relationship**	**Age**
Heart attack	_____	_____	_____	_____
Heart disease	_____	_____	_____	_____
High blood pressure	_____	_____	_____	_____
Stroke	_____	_____	_____	_____
Kidney disease	_____	_____	_____	_____
Diabetes	_____	_____	_____	_____

Health Habits

Do you add salt to your food? Yes ___ No ___ Are you on any special type of diet? Yes ___ No ___

If "yes" please describe _____

_____

Do you drink caffeinated beverages? Yes _____ No _____ How many cups per day? _____

Do you drink alcoholic beverages? Yes _____ No _____ How many drinks per week? _____

What is the average number of drinks that you consume on the weekend? _____

Did you use tobacco products in the past (more than 12 months ago)? Yes _____ No _____

Sleep Habits Evaluation

Do you have episodes of parasomnias (disorders such as sleep walking, sleep talking, night terrors, body rocking, bedwetting that will cause partial or full awakening?) Yes_____ No_____

Do you show signs of sleep disturbances (such as insomnia, daytime sleepiness) when you are anxious, stressed? Yes_____ No_____

Do you have difficulties to fall asleep if a certain object or a certain situation is absent such as listening to the radio, watching the television, having a teddy bear …?) Yes_____ No_____

Do you have difficulties to fall asleep earlier or later of your usual bedtime? Yes_____ No_____

Do you wake up at night to get a little snack? Yes_____ No_____

If "yes", do you think that the snack is helping you to go back to sleep? Yes____ No_____

Do you ever feel very tired, sleepy at school? Yes_____ No_____

Do you have hallucinations (vivid images that look like dreams occurring when you sleep) or find yourself physically weak or paralyzed for a few seconds? Yes_____ No_____

Tonsils and Adenoids evaluation questionnaire

Do you have a history of recurrent tonsillitis which is an inflammation of the tonsils (clusters of tissue that lie in bands on both sides of the back of the throat) caused by an infection? In tonsillitis, the tonsils are enlarged, red, and often coated either partly or entirely? Yes_____ No_____

Did you ever have inflammation of the adenoids (single clump of tissue in the back of the nose) causing a blockage of the back of the nose, chronic and recurrent fluid or infections of your ears, or chronic or recurrent sinus infections? Yes_____ No_____

Did you have tonsillectomy (tonsils removed) or adenoidectomy (adenoids removed)? Yes_____ No____

Exercise Habits

Do you engage in regular exercise? Yes _____ No _____

If "yes" please list:

Activity	**Frequency (times per week)**	**Duration (minutes)**
_____	_____	_____
_____	_____	_____

Do you ever feel faint, short of breath, or chest discomfort with exertion? Yes: _____ No: _____

If "yes", please explain : _____

_____

Are there any orthopedic limitations you have that may restrict your ability to perform hard running exercise or intense strength-type exercises? (back, hips, knees, ankles) Yes _____ No _____

If "yes" please explain: _____

_____

Questions Related to Reproductive Function (skip to the next part if you are a male)

Do you use birth control? Yes _____ No _____

Date of last menses: _____

Have you had any abnormal menses or absence of menses in the last 12 months? Yes _____ No _____

If "yes", describe this menstrual problem: _____

_____

Medications

Please list all medications (prescription and over-the-counter) you are currently taking or have taken in the past week: _____

_____

_____

Please sign to indicate the above information is correct:

_____ _____

Print Name Signature Date

Follow Up Review and Interview by: _____

Signature of Project Staff Member Date

Results of Screening - Routine Findings: Make certain that all questions on this form are properly completed. Query candidate, immediately after they complete this questionnaire, about any items left blank or for which clear answers are not provided. If no unusual problems are disclosed that may affect the candidate's safety or eligibility for the study, note this finding below and submit file materials to the Research Coordinator.
THIS CANDIDATE QUALIFIES FOR PARTICIPATION IN THE STUDY, SUBJECT TO VERIFICATION BY THE RESEARCH COORDINATOR. Yes: ___ No: ___.
If No, complete next section, below.

Results of Screening - Uncertain Findings: Note and discuss ANY potential health problem listed on this Health History form. Next, contact the candidate for clarification and report outcome to the Research Coordinator, Carol Haskell, M.D. Follow-up to appropriate health care professionals will be recommended, if deemed necessary, based on published guidelines (e.g., fasting blood glucose >109 mg/dL, fasting total cholesterol >200 mg/dL). Any and all costs related to such referral will be borne by the subject and not by Virginia Tech. **CANDIDATE HAS THE FOLLOWING UNDEFINED/UNCLARIFIED HEALTH PROBLEM(S) THAT WARRANT FURTHER REVIEW AND POSSIBLE EXCLUSION FROM THIS STUDY:**

_____

_____

_____

_____

APPENDIX G

RAW DATA

Chapter 2 and 3 Raw Data

Table 1. OSAS Subject Characteristics

OSAS	AGE (yrs)	AHI (events/hr)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	CENTRAL AB. FAT (g)	LEPTIN (ng/mL)
1	19	8.5	183	96.2	28.8	41.6	114.5	8177.2	11.5
2	19	8.2	174	96.6	31.6	39.5	102.0	9110.3	13.3
3	18	6.3	185.5	90.0	26.0	39.5	88.3	4694.6	3.2
4	25	21.5	182	103.6	31.3	43.0	104.5	9146.6	6.1
5	22	37.8	162	85.9	32.7	37.7	94.0	6481.8	13.5
6	23	13.3	172	84.1	28.4	39.7	96.3	6203.0	12.0
7	25	44.1	174	115.5	38.0	44.0	116.0	11918.0	16.2
8	21	7.3	178	102.7	32.7	43.0	96.0	7100.7	6.0
9	20	54.0	178	121.8	38.4	41.5	100.0	9813.3	11.3
10	26	11.5	168	80.9	28.7	37.0	90.0	6379.7	9.5
11	23	19.9	172.5	106.4	35.6	42.0	105.0	11511.7	17.8
12	27	60.5	115.5	98.9	31.6	41.5	105.0	10332.0	9.6
13	24	16.9	175	89.1	29.1	39.0	96.0	7549.7	6.8
14	21	8.5	187	122.7	35.1	42.0	100.0	13014.1	15.7

Table 2. OSAS Subject Resting and Exercise Measures of Cardiovascular Function

OSAS	REST HR	REST SBP	REST DBP	REST MAP	HR at 20% peak	HR at 40% peak	HR at 60% peak	HR at 80% peak	PEAK HR	PEAK SBP	PEAK DBP	PEAK MAP
1	88	122	88	99.3	113	128	145	166	190	196	70	112.0
2	124	116	88	97.3	110	136	159	179	198	184	86	118.7
3	95	128	92	104.0	102	123	144	166	180	200	94	129.3
4	105	132	78	96.0	87	125	157	181	196	164	70	101.3
5	79	120	80	93.3	105	125	145	166	186	170	82	111.3
6	88	112	82	92.0	82	100	118	137	159	170	88	115.3
7	92	126	90	102.0	100	109	122	140	161	186	98	127.3
8	96	144	92	109.3	95	116	138	159	177	246	94	144.7
9	76	122	86	98.0	77	104	130	157	183	220	112	148.0
10	65	110	86	94.0	78	98	118	138	158	162	92	115.3
11	99	124	74	90.7	94	119	144	169	190	228	110	149.3
12	93	140	86	104.0	101	127	152	178	195	198	86	123.3
13	105	134	88	103.3	101	124	148	172	193	208	90	129.3
14	88	132	90	104.0	82	99	117	134	152	224	98	140.0

Table 3. OSAS Subject Exercise Measures of Ventilatory Function

OSAS	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 55 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 85 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 115 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 145 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 20% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 40% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 60% peak
1	12.1	14.9	17.9	32.2	5.9	11.8	17.8
2	9.5	13.0	19.7	31.3	4.7	9.4	14.1
3	10.9	13.9	23.2	30.4	7.1	14.1	21.2
4	12.1	14.3	20.6	39.8	5.4	10.7	16.1
5	10.1	14.8	24.8	21.6	6.3	12.5	18.8
6	14.0	17.4	33.0	25.7	7.1	14.1	21.2
7	10.7	13.6	19.1	44.7	4.2	8.5	12.7
8	9.6	12.3	18.3	25.2	4.7	9.4	14.2
9	10.3	12.1	17.7	32.7	5.2	10.4	15.7
10	10.1	14.4	23.5	26.9	5.4	10.8	16.2
11	9.2	11.3	17.2	29.7	4.4	8.8	13.3
12	9.2	12.4	19.1	27.2	4.9	9.8	14.7
13	11.7	15.6	23.0	31.2	5.9	11.7	17.6
14	9.9	11.0	16.1	33.5	4.8	9.6	14.4

Table 3 Continued

OSAS	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 80% peak	VO_{2pk} ($ml \cdot kg^{-1} \cdot min^{-1}$)	V_E ($L \cdot min^{-1}$) at 55 Watts	V_E ($L \cdot min^{-1}$) at 85 Watts	V_E ($L \cdot min^{-1}$) at 115 Watts	V_E ($L \cdot min^{-1}$) at 145 Watts	V_E ($L \cdot min^{-1}$) at 20% peak
1	23.7	29.6	32.2	41.7	48.9	59.6	22.0
2	18.8	23.5	31.3	37.2	42.7	54.9	22.2
3	28.2	35.3	30.4	36.8	48.7	61.9	24.9
4	21.4	26.8	39.8	36.0	52.1	65.2	32.1
5	25.0	31.3	21.6	34.2	43.3	64.0	19.9
6	28.2	35.3	25.7	31.1	36.9	52.7	18.3
7	16.9	21.2	44.7	51.6	67.2	80.0	33.1
8	18.9	23.6	25.2	37.0	42.7	56.3	14.8
9	20.9	26.1	32.7	36.9	48.9	59.9	22.2
10	21.6	27.0	26.9	38.8	49.7	66.1	15.8
11	17.7	22.1	29.7	35.8	47.1	62.3	19.2
12	19.6	24.5	27.2	39.7	51.1	63.5	18.5
13	23.4	29.3	31.2	37.8	52.0	63.5	19.5
14	19.2	24.0	33.5	35.1	51.4	61.2	17.6

Table 3 Continued

OSAS	V_E ($L \cdot min^{-1}$) at 40% peak	V_E ($L \cdot min^{-1}$) at 60% peak	V_E ($L \cdot min^{-1}$) at 80% peak	Peak V_E ($L \cdot min^{-1}$)	V_E/VCO_2 at 55 Watts	V_E/VCO_2 at 85 Watts	V_E/VCO_2 at 115 Watts
1	31.9	46.2	65.1	98.9	31.0	30.8	29.0
2	29.4	40.4	55.1	78.2	35.8	31.5	31.1
3	37.8	54.5	75.0	100.0	35.8	32.3	28.1
4	35.6	46.5	64.7	79.7	35.2	31.3	30.7
5	27.4	44.3	70.8	111.6	30.1	28.8	28.2
6	25.8	35.1	46.2	66.3	34.6	32.1	28.4
7	36.6	49.1	70.6	100.8	39.6	33.2	31.5
8	26.3	40.9	58.8	86.1	29.9	30.1	43.5
9	33.0	49.6	71.9	101.5	31.2	29.0	28.9
10	28.6	43.6	60.9	82.8	37.5	33.2	31.1
11	28.9	42.6	60.2	80.3	40.2	34.7	30.2
12	29.2	45.6	67.7	100.1	31.9	30.5	29.8
13	31.0	45.9	64.1	88.6	31.1	28.3	28.1
14	32.1	50.1	71.7	104.6	30.9	28.1	28.8

Table 3 Continued

OSAS	V_E/VCO_2 at 145 Watts	V_E/VCO_2 At 20% peak	V_E/VCO_2 At 40% peak	V_E/VCO_2 At 60% peak	V_E/VCO_2 At 80% peak	PeakV_E/VCO_2	V_E/VCO_2 Slope
1	28.8	36.88	31.4	29.2	26.7	28.4	24.2
2	28.4	45.27	36.3	30.9	29.0	31.4	25.7
3	28.2	39.49	32.3	28.3	27.4	28.8	25.5
4	30.1	44.14	36.3	31.3	29.2	27.6	25.9
5	28.3	33.13	29.8	27.9	29.1	35.2	32.7
6	26.4	43.10	34.6	29.0	26.5	28.3	22.6
7	32.6	58.91	43.3	34.6	32.6	36.7	30.5
8	29.5	39.21	32.1	29.3	29.1	30.8	28.8
9	28.6	35.77	30.9	28.2	27.6	28.8	26.8
10	31.5	44.07	36.6	32.4	31.4	33.1	29.6
11	31.3	43.26	38.8	30.9	30.5	31.3	26.5
12	29.8	39.91	31.6	29.7	29.8	34.0	31.7
13	27.4	35.26	31.3	28.5	27.0	27.5	24.7
14	29.7	33.15	30.0	28.6	28.6	31.1	28.9

Table 4. No-OSAS Subject Characteristics

No-OSAS	AGE (yrs)	AHI (events/hr)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	CENTRAL AB. FAT (g)	LEPTIN (ng/mL)
1	22	2.9	183.0	88.1	26.6	38.5	92.8	7122.7	12.7
2	23	3.7	166.4	73.5	27.0	37.0	82.0	4033.2	2.5
3	21	1.1	177.8	112.0	35.5	42.0	98.5	8157.8	14.8
4	18	2.3	184.0	108.9	32.2	41.0	98.5	8017.1	20.3
5	18	3.7	178.0	112.0	35.5	41.0	115.0	11099.2	16.3
6	23	3.4	185.4	108.2	31.6	38.5	92.8	5548.7	5.37
7	21	1.8	172.3	120.0	40.1	47.5	115.0	10627.1	11.8
8	23	3.4	184.0	105.9	31.3	N/A	N/A	7680.4	8.30
9	26	1.2	184.0	100.5	30.1	41.0	95.5	8214.3	6.50
10	21	3.4	187.5	98.4	28.1	38.5	87.5	6221.7	12.4
11	23	1.1	173.0	102.7	34.3	41.5	91.0	6357.5	6.5
12	18	4.7	170.0	86.0	29.7	40.0	92.0	5242.6	7.9
13	26	2.9	178.0	98.6	30.9	42.0	96.0	7360.9	9.0
14	21	2.7	177.0	102.3	32.7	42.0	103.0	6119.0	5.0
15	20	0.6	177.0	85.0	27.1	37.0	86.0	5092.1	3.7
16	18	0.3	174.0	88.0	29.1	41.0	86.0	5615.7	7.1

Table 5. No-OSAS Subject Resting and Exercise Measures of Cardiovascular Function

No-OSAS	REST HR	REST SBP	REST DBP	REST MAP	HR at 20% peak	HR at 40% peak	HR at 60% peak	HR at 80% peak	PEAK HR	PEAK SBP	PEAK DBP	PEAK MAP
1	120	122	98	106.0	122	136	152	169	190	216	108	144.0
2	83	124	82	96.0	101	104	115	135	164	214	108	143.3
3	83	120	88	98.7	98	121	143	166	186	206	88	127.3
4	65	122	84	96.7	91	120	145	167	163	174	84	114.0
5	95	124	82	96.0	84	109	135	160	187	212	90	130.7
6	87	132	100	110.7	97	117	137	157	177	194	102	132.7
7	69	118	88	98.0	76	99	123	147	173	142	92	108.7
8	75	132	82	98.7	84	102	120	138	160	240	88	138.7
9	89	110	78	88.7	121	137	154	170	184	176	84	114.7
10	72	122	90	100.7	79	106	132	159	182	206	100	135.3
11	74	158	102	120.7	82	106	130	153	184	214	104	140.7
12	95	112	78	89.3	109	137	166	195	208	180	64	102.7
13	79	128	100	109.3	83	109	134	159	183	228	80	129.3
14	95	124	86	98.7	115	136	156	176	193	240	108	152.0
15	95	118	82	94.0	101	117	133	149	167	168	80	109.3
16	100	132	82	98.7	128	144	160	176	186	230	82	131.3

Table 6. No-OSAS Subject Exercise Measures of Ventilatory Function

No-OSAS	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 55 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 85 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 115 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 145 Watts	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 20% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 40% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 60% peak
1	9.4	13.1	16.9	21.3	4.9	9.8	14.7
2	10.8	15.7	20.1	25.2	5.8	11.6	17.3
3	8.4	12.6	14.0	18.3	5.2	10.4	15.5
4	9.7	13.8	17.2	19.9	5.2	10.3	15.5
5	9.0	11.4	14.8	17.8	4.5	9.1	13.6
6	10.7	13.2	14.6	20.6	5.3	10.5	15.8
7	7.7	9.6	12.8	15.5	3.9	7.8	11.8
8	8.0	11.1	14.6	19.1	5.0	10.0	14.9
9	7.5	11.0	12.8	16.4	5.2	10.4	15.6
10	7.4	10.2	14.5	17.1	5.0	10.0	15.1
11	9.1	11.9	15.8	20.7	5.3	10.6	15.9
12	8.9	12.0	16.3	20.5	6.9	13.7	20.6
13	9.2	12.0	15.2	19.6	6.3	12.5	18.8
14	10.6	12.9	17.0	21.8	7.0	14.0	21.1
15	11.2	15.5	21.6	26.7	5.3	10.7	16.0
16	13.4	20.9	25.3	27.5	8.8	17.7	26.5

Table 6 Continued

No-OSAS	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 80% peak	VO_{2pk} ($ml \cdot kg^{-1} \cdot min^{-1}$)	V_E ($L \cdot min^{-1}$) at 55 Watts	V_E ($L \cdot min^{-1}$) at 85 Watts	V_E ($L \cdot min^{-1}$) at 115 Watts	V_E ($L \cdot min^{-1}$) at 145 Watts	V_E ($L \cdot min^{-1}$) at 20% peak
1	19.6	24.5	25.2	34.9	42.5	55.0	14.9
2	23.1	28.9	18.9	27.1	34.4	48.4	11.4
3	20.7	25.9	28.3	40.5	47.4	65.6	15.7
4	20.6	25.8	25.6	36.5	48.0	59.3	19.5
5	18.1	22.7	27.2	31.9	47.4	58.4	20.0
6	21.0	26.3	24.8	32.2	42.9	53.8	13.8
7	15.7	19.6	24.8	29.3	38.6	50.1	18.6
8	19.9	24.9	22.3	28.5	41.5	54.7	13.8
9	20.8	26.0	23.5	30.1	36.3	45.3	19.6
10	20.1	25.2	24.6	33.7	44.8	51.5	20.3
11	21.2	26.5	26.7	33.0	44.3	52.7	22.1
12	27.4	34.3	20.7	26.9	37.9	50.9	18.5
13	25.1	31.4	23.5	30.7	34.9	41.5	22.2
14	28.1	35.1	30.6	35.6	47.0	59.8	21.9
15	21.4	26.7	28.1	41.0	55.6	80.0	18.7
16	35.3	44.2	36.0	49.2	62.1	66.4	28.3

Table 6 Continued

No-OSAS	V_E ($L \cdot min^{-1}$) at 40% peak	V_E ($L \cdot min^{-1}$) at 60% peak	V_E ($L \cdot min^{-1}$) at 80% peak	Peak V_E ($L \cdot min^{-1}$)	V_E/VCO_2 at 55 Watts	V_E/VCO_2 at 85 Watts	V_E/VCO_2 at 115 Watts	V_E/VCO_2 at 145 Watts
1	24.7	35.7	48.0	67.7	31.5	30.5	27.9	27.3
2	17.9	28.4	42.9	65.9	31.8	27.7	25.5	26.2
3	33.7	52.7	72.4	101.3	32.5	29.7	28.9	29.0
4	28.5	42.4	61.4	86.8	30.0	27.9	26.7	27.4
5	26.2	39.6	60.4	82.9	30.6	28.0	28.1	27.3
6	26.5	41.1	57.6	82.9	28.2	26.3	28.6	25.0
7	24.5	35.4	51.2	70.9	28.2	28.6	26.6	26.4
8	27.7	43.2	60.3	80.9	31.6	26.5	26.2	26.4
9	29.2	42.1	58.2	82.2	33.8	28.9	28.6	26.5
10	30.5	44.8	63.2	84.2	35.9	34.4	29.0	28.5
11	28.8	40.2	56.3	83.4	34.8	32.4	29.9	28.2
12	30.5	48.7	73.3	108.6	31.2	28.0	26.3	26.0
13	29.0	43.7	66.4	103.8	31.8	28.7	24.5	23.4
14	37.0	54.5	74.4	97.7	32.5	30.8	29.8	28.1
15	27.4	40.0	56.5	80.0	33.7	31.7	29.8	31.0
16	43.1	63.5	89.4	119.9	33.2	26.4	26.5	26.1

Table 6 Continued

No-OSAS	V_E/VCO_2 At 20% peak	V_E/VCO_2 At 40% peak	V_E/VCO_2 At 60% peak	V_E/VCO_2 At 80% peak	PeakV_E/VCO_2	V_E/VCO_2 Slope
1	31.7	30.5	28.2	26.2	27.0	N/A
2	34.8	30.5	27.0	25.7	28.4	25.4
3	34.6	30.8	28.7	28.3	30.2	27.7
4	37.0	29.7	27.1	27.1	27.9	26.0
5	39.4	30.2	27.3	28.2	29.4	28.5
6	30.6	29.0	26.6	25.0	26.6	23.4
7	37.3	30.9	27.1	25.9	26.9	23.9
8	35.5	29.3	26.9	26.7	27.5	25.3
9	33.7	29.7	27.0	25.8	26.8	23.8
10	41.4	31.5	28.3	28.8	30.2	26.5
11	39.2	33.0	29.5	28.1	29.0	25.6
12	33.3	27.2	25.6	26.9	30.9	27.5
13	35.6	27.5	24.0	24.0	27.9	23.2
14	33.5	30.4	27.8	26.1	26.3	23.5
15	31.7	33.2	31.3	29.3	31.0	28.4
16	34.9	29.1	26.0	25.9	27.5	25.6

Table 7. Control Subject Characteristics

Control	AGE (yrs)	AHI (events/hr)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	CENTRAL AB. FAT (g)	LEPTIN (ng/mL)
1	21	2.6	172.7	68.0	22.8	35.5	80.0	3576.0	3.47
2	24	1.4	189.0	76.4	21.4	37.0	75.0	3627.2	4.80
3	20	2.0	173.0	64.0	21.4	36.2	71.0	2401.9	N/A
4	24	3.9	182.2	68.0	22.5	36.5	90.0	3710.9	N/A
5	21	2.3	167.6	66.7	23.7	35.0	77.5	3164.1	4.80
6	24	1.0	182.0	81.6	24.6	38.0	86.0	6029.7	6.83
7	19	0.7	181.1	67.7	20.2	35.5	75.5	2766.3	4.14
8	23	3.0	179.0	66.0	20.6	35.0	76.0	3625.1	5.90
9	19	1.0	179.0	74.0	23.1	38.0	77.0	2595.1	2.40
10	21	2.8	184.0	77.0	22.7	37.5	78.0	2665.2	4.00
11	23	0.9	166.0	57.3	20.8	33.0	68.0	3175.7	3.20
12	19	2.3	174.0	72.0	22.5	N/A	85.0	4546.9	7.80
13	23	3.7	170.0	60.0	20.8	35.0	69.0	2271.3	1.80
14	18	0.4	180.0	68.5	21.2	38.0	76.5	3212.5	3.10

Table 8. Control Subject Resting and Exercise Measures of Cardiovascular Function

Control	REST HR	REST SBP	REST DBP	REST MAP	HR at 20% peak	HR at 40% peak	HR at 60% peak	HR at 80% peak	PEAK HR	PEAK SBP	PEAK DBP	PEAK MAP
1	77	130	90	103.3	111	139	163	181	195	200	100	133.3
2	95	118	86	96.7	92	111	129	148	164	168	84	112.0
3	71	122	84	96.7	89	113	138	165	186	188	100	129.3
4	80	112	80	90.7	103	126	149	173	188	192	98	129.3
5	85	124	78	93.3	98	117	139	162	193	222	86	131.3
6	82	122	86	98.0	88	107	126	145	166	202	96	131.3
7	91	132	84	100.0	96	113	129	145	164	192	92	125.3
8	100	116	84	94.7	94	118	142	167	190	194	98	130.0
9	71	128	82	97.3	99	118	137	156	179	202	82	122.0
10	83	124	82	96.0	92	113	134	155	176	218	100	139.3
11	94	108	70	82.7	83	106	130	154	180	138	86	103.3
12	89	106	84	91.3	94	114	133	152	171	168	88	114.7
13	74	120	70	86.7	98	119	141	162	181	206	72	11637
14	111	138	72	94.0	143	160	176	1925	205	216	80	125.3

Table 9. Control Subject Exercise Measures of Ventilatory Function

Control	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 20% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 40% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 60% peak	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) at 80% peak	VO_{2pk} ($ml \cdot kg^{-1} \cdot min^{-1}$)	V_E ($L \cdot min^{-1}$) at 20% peak	V_E ($L \cdot min^{-1}$) at 40% peak
1	7.7	15.4	23.1	30.8	38.5	18.2	29.1
2	5.5	10.9	16.4	21.8	27.3	14.9	23.8
3	7.9	15.8	23.7	31.6	39.5	13.4	22.3
4	6.5	13.0	19.5	26.0	32.5	15.0	28.5
5	6.3	12.7	19.0	25.3	31.7	17.1	25.8
6	5.1	10.2	15.2	20.3	25.4	20.9	27.7
7	5.9	11.8	17.7	23.6	29.5	17.6	27.0
8	5.5	11.0	16.5	22.0	27.5	13.2	21.9
9	7.7	15.3	23.0	30.6	38.3	24.5	36.7
10	7.6	15.2	22.8	30.4	38.1	24.3	33.8
11	5.3	10.6	16.0	21.3	26.6	12.1	17.7
12	5.3	10.6	15.8	21.1	26.4	12.5	23.0
13	8.5	16.9	25.4	33.8	42.3	20.1	34.3
14	8.3	16.6	24.9	33.2	41.5	27.8	35.7

Table 9 Continued

Control	V_E ($L \cdot min^{-1}$) at 60% peak	V_E ($L \cdot min^{-1}$) at 80% peak	Peak V_E ($L \cdot min^{-1}$)	V_E/VO_2 At 20% peak	V_E/VO_2 At 40% peak	V_E/VO_2 At 60% peak	V_E/VO_2 At 80% peak	PeakV_E/VO_2
1	41.8	58.2	80.4	34.6	27.7	26.5	27.7	30.6
2	34.6	47.0	61.6	35.7	28.7	27.7	28.2	29.1
3	35.9	54.3	79.6	26.4	22.0	23.7	26.8	31.5
4	46.5	68.9	103.3	30.5	29.1	31.6	35.1	42.2
5	38.1	54.0	79.5	40.6	30.6	30.1	32.0	37.7
6	36.7	47.9	63.7	50.5	33.5	29.6	28.9	30.8
7	38.2	51.0	73.0	44.1	33.8	31.8	31.9	36.5
8	33.0	46.3	66.0	37.7	31.3	31.4	33.1	37.7
9	51.7	69.5	86.5	43.3	32.4	30.4	30.7	30.6
10	47.2	64.5	86.7	41.5	28.9	26.9	27.5	29.6
11	27.6	41.5	57.8	40.1	29.4	30.4	34.4	38.3
12	35.9	51.1	69.8	32.9	30.3	31.5	33.6	36.7
13	51.9	72.9	100.8	39.7	33.8	34.2	36.0	39.8
14	54.5	84.1	134.4	48.7	31.3	31.9	36.9	47.2

Table 9 Continued

Control	V_E/VCO_2 At 20% peak	V_E/VCO_2 At 40% peak	V_E/VCO_2 At 60% peak	V_E/VCO_2 At 80% peak	PeakV_E/VCO_2	V_E/VCO_2 Slope
1	34.4	30.6	28.2	27.2	27.4	26.0
2	38.8	31.4	28.5	27.4	25.8	23.7
3	33.2	25.2	23.5	24.7	26.5	24.1
4	38.4	31.1	28.5	29.7	35.1	31.4
5	44.8	32.8	28.5	28.6	31.3	28.1
6	48.3	40.0	34.2	30.8	31.7	24.1
7	44.9	37.9	33.1	30.4	31.3	26.2
8	44.3	37.3	32.6	30.5	30.7	27.5
9	56.5	36.4	30.3	30.5	29.0	24.9
10	39.4	30.8	26.2	24.6	25.9	21.5
11	44.9	34.0	30.3	29.2	39.8	28.5
12	38.8	31.5	29.1	29.1	29.8	27.6
13	45.9	36.5	32.3	32.0	34.1	30.4
14	32.0	31.7	30.8	31.2	37.8	35.5

Table 10. OSAS Subject Exercise Recovery Measures

OSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	33	49	58	61	64	0.82	0.78	0.79
2	17	40	45	54	56	0.85	0.73	0.60
3	27	42	49	58	61	0.75	0.69	0.68
4	9	23	30	35	42	0.88	0.78	0.77
5	17	36	47	55	60	0.79	0.65	0.67
6	30	37	39	49	45	0.79	0.73	0.79
7	17	23	30	32	34	0.88	0.85	0.78
8	20	35	46	50	53	0.75	0.67	0.63
9	23	33	53	49	63	0.85	0.84	0.81
10	33	43	49	54	57	0.91	0.85	0.75
11	25	40	44	45	48	0.79	0.69	0.64
12	12	25	37	41	45	0.88	0.86	0.86
13	5	18	28	36	40	0.91	0.88	0.88
14	22	29	34	35	42	0.82	0.80	0.70

Table 10 Continued

OSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.73	0.68	0.86	0.91	0.83	0.83	0.91
2	0.62	0.61	0.86	0.79	0.74	0.77	0.81
3	0.64	0.59	0.77	0.79	0.83	0.83	0.81
4	0.77	0.73	0.91	0.86	0.86	0.86	0.80
5	0.71	0.65	0.95	0.76	0.73	0.80	0.73
6	0.78	0.74	0.91	0.93	1.0	1.0	0.98
7	0.82	0.83	0.96	0.96	0.92	0.94	0.94
8	0.59	0.55	0.77	0.72	0.68	0.66	0.66
9	0.80	0.77	0.91	0.89	0.98	1.02	0.96
10	0.74	0.68	0.67	0.65	0.63	0.67	0.67
11	0.58	0.61	0.87	0.80	0.82	0.84	0.82
12	0.82	0.87	0.86	1.02	1.05	1.09	1.05
13	0.84	0.86	0.98	0.96	0.96	0.93	0.93
14	0.64	0.70	0.88	0.84	0.80	0.82	0.98

Table 11. No-OSAS Subject Exercise Recovery Measures

No-OSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	61	48	35	42	41	0.75	0.71	0.76
2	25	39	46	51	50	0.81	0.76	0.76
3	26	48	55	60	63	0.71	0.69	0.70
4	34	43	49	52	61	0.90	0.91	0.83
5	31	46	59	60	67	0.87	0.76	0.73
6	26	42	52	59	62	0.91	0.89	0.79
7	25	39	47	50	54	0.99	0.92	0.87
8	31	45	52	51	57	0.93	0.79	0.73
9	15	34	47	45	57	0.89	0.86	0.81
10	31	51	61	66	68	0.81	0.73	0.75
11	34	56	71	71	84	0.86	0.82	0.79
12	30	54	67	68	71	0.72	0.62	0.60
13	26	42	56	61	69	0.79	0.75	0.64
14	10	29	40	44	46	0.73	0.71	0.65
15	30	42	40	50	44	0.77	0.77	0.70
16	19	33	43	43	46	0.94	0.81	0.74

Table 11 Continued

No-OSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.69	0.67	0.72	0.74	0.78	0.78	0.74
2	0.70	0.68	0.74	0.76	0.81	0.74	0.74
3	0.70	0.67	0.93	0.80	0.84	0.80	0.80
4	0.77	0.70	0.98	0.74	0.76	0.71	0.74
5	0.68	0.69	0.89	0.80	0.82	0.87	0.96
6	0.79	0.67	0.90	0.88	0.90	0.90	0.88
7	0.83	0.85	0.87	0.87	0.83	0.91	0.87
8	0.65	0.66	0.95	0.80	0.77	0.82	0.84
9	0.85	0.83	0.83	0.86	0.90	0.88	1.00
10	0.70	0.65	0.82	0.86	0.80	0.80	0.80
11	0.75	0.72	0.96	0.94	0.90	0.88	0.85
12	0.57	0.56	0.94	0.91	0.94	1.09	0.94
13	0.58	0.52	0.95	0.88	0.80	0.80	0.88
14	0.63	0.59	0.85	0.76	0.74	0.74	0.74
15	0.70	0.71	0.85	0.88	0.88	0.98	0.98
16	0.70	0.69	1.00	1.02	1.00	1.02	1.02

Table 12. Control Subject Exercise Recovery Measures

Control	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	32	48	59	74	75	0.87	0.76	0.75
2	13	29	33	44	46	0.82	0.82	0.74
3	26	51	60	70	71	0.84	0.79	0.72
4	19	42	N/A	N/A	N/A	0.65	0.60	N/A
5	48	58	72	72	73	0.67	0.65	0.67
6	19	33	49	64	69	0.87	0.74	0.72
7	27	39	47	46	58	0.85	0.81	0.74
8	42	50	50	65	54	0.88	0.71	0.71
9	25	37	47	50	52	0.80	0.74	0.70
10	26	40	48	54	56	0.84	0.81	0.77
11	30	35	47	46	52	0.78	0.78	0.74
12	30	42	47	48	53	0.77	0.65	0.62
13	28	45	56	59	58	0.77	0.68	0.68
14	19	38	50	58	58	0.90	0.84	0.79

Table 12 Continued

Control	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.71	0.68	0.90	0.84	0.84	0.90	0.90
2	0.73	0.65	0.98	0.95	0.95	0.95	0.98
3	0.69	0.68	0.90	0.80	0.84	0.80	0.80
4	N/A	N/A	0.76	0.73	N/A	N/A	N/A
5	0.60	0.59	0.84	0.79	0.67	0.70	0.70
6	0.69	0.64	0.92	0.90	0.90	0.90	0.88
7	0.72	0.69	1.00	0.93	0.91	0.89	0.93
8	0.71	0.41	0.90	0.82	0.88	0.82	N/A
9	0.65	0.60	0.83	0.85	0.80	0.73	0.80
10	0.74	0.74	0.80	0.78	0.72	0.68	0.78
11	0.71	0.72	0.86	0.86	0.91	0.88	0.86
12	0.62	0.61	0.89	0.86	0.89	0.93	0.93
13	0.62	0.60	0.94	0.94	0.94	0.94	0.92
14	0.72	0.68	1.05	1.03	0.90	0.98	1.03

Chapter 4 Raw Data

Table 1. Baseline Overweight, Sedentary, OSAS Subject Characteristics

OWS-OSAS	AGE (yrs)	AHI (events/hr)	EPWORTH (x/24)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	HIP (cm)
1	19	8.5	8	182.9	96.2	28.8	41.6	114.5	119.0
2	19	8.2	12	174.0	96.6	31.6	39.5	102.0	110.0
3	18	6.3	17	185.5	90.0	26.0	39.5	88.3	105.0
4	22	5.0	2	173.0	77.3	25.8	38.1	86.4	98.0
5	25	21.5	6	182.0	103.6	31.3	43.0	104.5	115.0
6	26	5.7	12	175.0	84.1	27.5	38.0	89.5	104.5
7	20	6.8	10	176.0	79.5	25.7	36.5	85.0	103.5
8	22	37.8	6	162.0	85.9	32.7	37.7	94.0	107.0
9	25	5.5	19	182.4	101.6	30.3	42.0	92.0	114.5
10	25	5.0	12	182.0	109.1	32.9	44.0	105.5	117.0
11	23	13.3	12	172.0	84.1	28.4	39.7	96.3	112.0
12	25	44.1	2	174.0	115.5	38.0	44.0	116.0	129.0
13	21	7.3	11	178.0	102.7	32.7	43.0	96.0	116.5
14	20	54.0	6	178.0	121.8	38.4	41.5	100.0	221.0
15	26	11.5	4	168.0	80.9	28.7	37.0	90.0	107.0
16	21	6.0	5	185.0	91.4	26.7	38.0	84.0	109.0
17	23	19.9	6	172.5	106.4	35.6	42.0	105.0	224.5
18	27	60.5	14	111.5	98.9	31.6	41.5	105.0	111.5
19	24	16.9	6	175.0	89.1	29.1	39.0	96.0	109.0
20	21	8.5	11	187	122.7	35.1	42.0	100.0	129.0

Table 1 Continued

OWS-OSAS	REST HR (bpm)	REST SBP (mmHg)	REST DBP (mmHg)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TRIG (mg/dL)	% Body Fat
1	88	122	88	185	111	48	133	26.7
2	124	116	88	187	113	30	222	33.7
3	95	128	92	187	111	65	57	17.6
4	81	122	84	194	114	45	176	21.7
5	105	132	78	249	194	29	128	26.6
6	69	124	86	169	111	46	60	26.3
7	97	126	100	163	98	45	105	26.7
8	79	120	80	195	96	41	290	27.2
9	89	104	88	165	106	28	150	21.8
10	80	122	92	187	126	39	108	29.6
11	88	112	82	152	111	34	45	27.2
12	92	126	90	225	150	33	213	34.2
13	96	144	81	134	75	35	124	23.6
14	76	122	86	172	115	28	144	29.2
15	65	110	86	127	84	31	66	27.1
16	120	132	82	139	N/A	29	45	21.9
17	99	124	74	178	129	37	61	35.9
18	93	140	86	233	188	19	131	29.5
19	105	134	88	164	97	54	73	28.4
20	88	132	90	163	111	25	134	32.2

Table 2. Overweight, Sedentary, OSAS Subject Peak Exercise Measures

OWS-OSAS	HR (bpm)	SBP (mmHg)	DBP(mmHg)	RPE	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	VE ($L \cdot min^{-1}$)	RER
1	190	196	70	N/A	29.6	96.8	1.21
2	198	184	86	17	23.5	77.8	1.10
3	180	200	94	15	35.3	98.3	1.09
4	173	172	78	19	35.3	76.6	1.03
5	196	164	70	18	26.8	77.6	1.04
6	181	198	92	17	34.8	99.8	1.11
7	173	174	96	18	29.1	70.2	1.15
8	186	170	82	18	31.3	110.3	1.18
9	183	188	90	18	27.5	98.9	1.17
10	176	208	100	18	24.5	79.1	1.05
11	159	170	88	17	35.3	62.8	1.12
12	161	186	98	18	21.2	99.8	1.13
13	177	246	94	17	23.6	83.6	1.14
14	183	220	112	16	26.1	104.2	1.11
15	158	162	92	20	27.0	80.2	1.14
16	184	206	98	19	27.3	64.6	1.08
17	190	228	110	19	22.1	77.0	1.09
18	195	198	86	17	24.5	98.5	1.22
19	193	208	90	20	29.3	87.5	1.24
20	152	224	98	15	24.0	101.1	1.15

Table 3. Overweight, Sedentary, OSAS Subject Exercise Recovery Measures

OWS-OSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	33	49	58	61	64	0.82	0.78	0.79
2	17	40	45	54	56	0.85	0.73	0.60
3	27	42	49	58	61	0.75	0.69	0.68
4	24	42	63	75	77	0.84	0.88	0.85
5	9	23	30	35	42	0.88	0.78	0.77
6	29	45	52	64	70	0.89	0.83	0.80
7	13	31	39	44	44	0.84	0.82	0.72
8	17	36	47	55	60	0.79	0.65	0.67
9	11	27	37	43	49	0.78	0.72	0.70
10	33	45	55	56	65	0.79	0.79	0.67
11	30	37	39	49	45	0.79	0.73	0.79
12	17	23	30	32	34	0.88	0.85	0.78
13	20	35	46	50	53	0.75	0.67	0.63
14	23	33	53	49	63	0.85	0.84	0.81
15	33	43	49	54	57	0.91	0.85	0.75
16	48	63	68	73	73	0.87	0.80	0.75
17	25	40	44	45	48	0.79	0.69	0.64
18	12	25	37	41	45	0.88	0.86	0.86
19	5	18	28	36	40	0.91	0.88	0.88
20	22	29	34	35	42	0.82	0.80	0.70

Table 3 Continued

OWS-OSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.73	0.68	0.86	0.91	0.83	0.83	0.91
2	0.62	0.61	0.86	0.79	0.74	0.77	0.81
3	0.64	0.59	0.77	0.79	0.83	0.83	0.81
4	0.78	0.79	0.82	0.92	1.03	1.05	1.05
5	0.77	0.73	0.91	0.86	0.86	0.86	0.80
6	0.76	0.71	0.89	0.91	0.93	0.87	0.78
7	0.69	0.69	0.83	0.85	0.83	0.83	0.83
8	0.71	0.65	0.95	0.76	0.80	0.80	0.73
9	0.66	0.70	0.93	0.96	0.91	0.91	0.84
10	0.63	0.63	0.82	0.84	0.90	0.90	0.98
11	0.78	0.74	0.91	0.93	1.00	1.00	0.98
12	0.82	0.83	0.96	0.96	0.94	0.94	0.94
13	0.59	0.55	0.77	0.72	0.66	0.66	0.66
14	0.80	0.77	0.91	0.89	1.02	1.02	0.96
15	0.74	0.68	0.67	0.65	0.67	0.67	0.67
16	0.72	0.69	0.92	0.90	0.84	0.84	0.82
17	0.58	0.61	0.87	0.80	0.84	0.84	0.82
18	0.82	0.87	0.86	1.02	1.09	1.09	1.05
19	0.84	0.86	0.98	0.96	0.93	0.93	0.93
20	0.64	0.70	0.88	0.84	0.82	0.82	0.98

Table 4. Baseline Overweight, Sedentary, No-OSAS Subject Characteristics

OWS-NoOSAS	AGE (yrs)	AHI (events/hr)	EPWORTH (x/24)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	HIP (cm)
1	22	2.9	5	183.0	88.1	26.6	38.5	92.8	108.0
2	28	3.2	7	175.3	78.9	25.8	39.0	85.5	102.0
3	23	3.7	12	166.4	73.5	27.0	37.0	82.0	95.0
4	27	0.9	7	175.0	134.4	43.9	48.8	123.3	130.0
5	21	1.1	15	177.8	112.0	35.5	42.0	98.5	109.5
6	18	2.3	1	184.0	108.9	32.2	41.0	98.5	123.0
7	18	3.7	8	178.0	112.0	35.5	41.0	115.0	118.0
8	23	3.4	9	185.4	108.2	31.6	38.5	92.8	102.0
9	24	4.5	11	171.5	76.2	25.5	37.0	77.0	99.0
10	21	1.8	8	172.3	120.0	40.1	47.5	115.0	120.0
11	26	4.6	7	179.1	90.0	27.8	39.0	92.5	109.0
12	23	3.4	9	184.0	105.9	31.3	N/A	N/A	N/A
13	26	1.2	12	184.0	100.5	30.1	41.0	95.5	100.0
14	21	3.4	6	187.5	98.4	28.1	38.5	87.5	115.0
15	15	4.2	1	179.0	121.0	36.1	43.0	118.0	124.0
16	23	1.1	8	173.0	102.7	34.3	41.5	91.0	119.0
17	18	4.7	11	170.0	86.0	29.7	40.0	92.0	103.0
18	26	2.9	8	178.0	98.6	30.9	42.0	96.0	117.0
19	21	2.7	8	177.0	102.3	32.7	42.0	103.0	113.0
20	20	0.6	10	177.0	85.0	27.1	37.0	86.0	105.5
21	18	0.3	12	174.0	88.0	29.1	41.0	86.0	104.0
22	26	1.0	5	175.0	84.0	27.4	37.0	93.0	104.0

Table 4 Continued

OWS-NoOSAS	REST HR (bpm)	REST SBP (mmHg)	REST DBP (mmHg)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TRIG (mg/dL)	% Body Fat
1	120	122	98	173	128	26	92	27.0
2	68	110	74	N/A	N/A	N/A	N/A	17.8
3	83	124	82	152	107	34	56	18.7
4	98	102	72	173	118	25	154	35.2
5	83	120	88	178	119	32	134	29.1
6	65	122	84	169	117	33	95	31.2
7	95	124	82	238	198	27	66	35.3
8	87	132	100	188	109	49	150	24.7
9	84	118	74	152	N/A	50	45	20.0
10	69	118	88	176	127	38	60	31.8
11	100	118	88	222	141	22	295	31.1
12	75	132	82	180	N/A	56	N/A	26.3
13	89	110	78	137	95	29	69	24.3
14	72	122	90	122	N/A	48	N/A	25.7
15	105	136	78	158	104	24	147	34.2
16	74	158	102	119	N/A	70	45	25.3
17	95	112	78	137	84	37	79	24.6
18	79	128	100	229	164	43	114	27.0
19	95	124	86	235	182	33	100	22.2
20	95	118	82	149	97	40	63	19.8
21	100	132	82	174	117	35	109	22.3
22	121	108	78	231	162	52	85	28.1

Table 5. Overweight, Sedentary, No-OSAS Subject Peak Exercise Measures

OWS-NoOSAS	HR (bpm)	SBP (mmHg)	DBP(mmHg)	RPE	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	VE ($L \cdot min^{-1}$)	RER
1	190	216	108	16	25.4	64.7	1.15
2	176	196	98	16	21.9	97.0	1.19
3	164	214	108	17	28.7	65.1	1.09
4	176	186	84	15	23.3	115.1	1.15
5	186	206	88	18	25.5	99.7	1.16
6	163	174	84	18	25.7	85.1	1.10
7	187	212	90	17	22.1	80.0	1.10
8	177	194	102	18	25.6	78.6	1.08
9	177	172	96	19	27.1	58.0	1.17
10	173	142	92	17	19.2	69.6	1.11
11	175	192	102	18	24.5	75.3	1.15
12	160	240	88	15	24.2	76.0	1.09
13	184	176	84	17	26.1	82.0	1.15
14	182	206	100	20	24.7	81.9	1.13
15	175	192	74	19	23.6	85.2	1.10
16	184	214	104	19	26.3	82.6	1.05
17	208	180	64	18	33.5	102.2	1.19
18	183	228	80	16	30.8	99.3	1.20
19	193	240	108	16	36.1	106.4	1.03
20	167	168	80	19	27.4	83.7	1.14
21	186	230	82	18	43.3	116.7	1.12
22	198	184	80	19	33.5	142.1	1.28

Table 6. Overweight, Sedentary, No-OSAS Subject Exercise Recovery Measures

OWS-NoOSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	61	38	35	42	41	0.75	0.71	0.76
2	47	56	69	76	78	0.83	0.73	0.68
3	25	39	46	51	50	0.81	0.76	0.76
4	13	27	34	40	45	0.87	0.75	0.69
5	26	48	55	60	63	0.71	0.69	0.70
6	34	43	49	52	61	0.90	0.91	0.83
7	31	46	59	60	67	0.87	0.76	0.73
8	26	42	52	59	62	0.91	0.89	0.79
9	11	28	35	43	47	0.91	0.84	0.83
10	25	39	47	50	54	0.99	0.92	0.87
11	17	35	43	49	49	0.85	0.81	0.78
12	31	45	52	51	57	0.93	0.79	0.73
13	15	34	47	45	57	0.89	0.86	0.81
14	31	51	61	66	68	0.81	0.73	0.75
15	33	43	50	52	57	0.71	0.74	0.73
16	34	56	71	71	84	0.86	0.82	0.79
17	30	54	68	68	71	0.72	0.62	0.60
18	26	42	56	61	69	0.79	0.75	0.64
19	10	29	40	44	46	0.73	0.71	0.65
20	30	42	40	50	44	0.77	0.77	0.70
21	19	33	43	43	46	0.94	0.81	0.74
22	11	23	32	32	41	0.92	0.82	0.80

Table 6 Continued

OWS-NoOSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.69	0.67	0.72	0.74	0.78	0.78	0.74
2	0.57	0.59	0.92	0.88	0.82	0.73	0.76
3	0.7	0.68	0.74	0.76	0.81	0.74	0.74
4	0.67	0.67	0.98	0.79	0.76	0.76	0.81
5	0.70	0.67	0.93	0.80	0.84	0.80	0.80
6	0.77	0.70	0.98	0.74	0.76	0.71	0.74
7	0.68	0.69	0.89	0.80	0.82	0.87	0.96
8	0.79	0.67	0.90	0.88	0.90	0.90	0.88
9	0.79	0.79	0.83	0.75	0.75	0.75	0.77
10	0.83	0.85	0.87	0.87	0.83	0.91	0.87
11	077	0.79	0.88	0.80	0.78	0.82	0.82
12	0.65	0.66	0.95	0.80	0.77	0.82	0.84
13	0.85	0.83	0.83	0.86	0.90	0.88	1.00
14	0.70	0.65	0.82	0.86	0.80	0.80	0.80
15	0.69	0.61	0.95	0.92	0.86	0.81	0.78
16	0.75	0.72	0.96	0.94	0.90	0.88	0.85
17	0.57	0.56	0.94	0.91	0.94	1.09	0.94
18	0.58	0.52	0.95	0.88	0.80	0.80	0.88
19	0.63	0.59	0.85	0.76	0.74	0.74	0.74
20	0.70	0.71	0.85	0.88	0.88	0.98	0.98
21	0.70	0.69	1.00	1.02	1.00	1.02	1.02
22	0.73	0.65	1.00	0.98	0.95	0.95	0.95

Table 7. Baseline Normal Weight, Sedentary, No-OSAS Subject Characteristics

NWS-NoOSAS	AGE (yrs)	AHI (events/hr)	EPWORTH (x/24)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	HIP (cm)
1	21	2.6	7	172.7	68.0	22.8	35.5	80.0	95.0
2	19	1.8	9	174.0	67.2	22.0	35.5	75.0	90.0
3	24	1.4	2	189.0	76.4	21.4	37.0	75.0	99.5
4	20	2.0	8	173.0	64.0	21.4	36.2	71.0	92.0
5	24	3.9	N/A	182.2	68.0	22.5	36.5	90.0	92.0
6	21	2.3	5	167.6	66.7	23.7	35.0	77.5	93.0
7	24	1.0	7	182.0	81.6	24.6	38.0	86.0	104.0
8	19	0.7	5	181.1	67.7	20.2	35.5	75.5	97.0
9	23	3.0	5	179.0	66.0	20.6	35.0	76.0	94.0
10	19	1.0	7	179.0	74.0	23.1	38.0	77.0	101.0
11	21	2.8	6	184.0	77.0	22.7	37.5	78.0	101.0
12	23	0.9	8	166.0	57.3	20.8	33.0	68.0	92.0
13	19	2.3	9	174.0	72.0	22.5	37.0	85.0	103.0
14	23	3.7	4	170.0	60.0	20.8	35.0	69.0	91.0
15	21	0.5	5	173.0	77.3	25.8	37.0	88.0	98.0
16	19	1.6	11	177.0	85.3	24.1	38.5	85.5	103.0
17	18	0.4	3	180.0	68.5	21.2	38.0	76.5	95.5

Table 7 Continued

NWS-NoOSAS	REST HR (bpm)	REST SBP (mmHg)	REST DBP (mmHg)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TRIG (mg/dL)	% Body Fat
1	77	130	90	193	122	36	175	17.7
2	68	108	78	120	79	31	50	10.9
3	95	118	86	197	156	34	44	21.2
4	71	122	84	N/A	N/A	N/A	N/A	15.4
5	80	112	80	132	88	26	93	18.8
6	85	124	78	170	102	33	172	18.7
7	82	122	86	142	91	38	65	27.2
8	91	132	84	165	136	22	45	16.6
9	100	116	84	207	146	38	120	18.5
10	71	128	82	142	80	40	106	14.5
11	83	124	82	149	73	60	79	14.3
12	94	108	70	147	N/A	66	45	24.2
13	89	106	84	100	N/A	25	52	25.8
14	74	120	70	183	111	63	45	13.7
15	85	134	96	186	100	32	269	27.8
16	92	128	80	112	63	42	45	18.3
17	111	138	72	148	83	54	54	16.9

Table 8. Normal Weight, Sedentary, No-OSAS Subject Peak Exercise Measures

NWS-NoOSAS	HR (bpm)	SBP (mmHg)	DBP(mmHg)	RPE	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	VE ($L \cdot min^{-1}$)	RER
1	195	200	100	17	39.6	82.4	1.12
2	164	180	82	17	45.6	98.9	1.14
3	164	168	84	18	26.8	60.6	1.14
4	186	188	100	18	38.6	74.9	1.16
5	188	192	98	16	31.9	91.2	1.17
6	193	222	86	19	33.2	85.2	1.21
7	166	202	96	18	25.2	62.3	1.01
8	164	192	92	20	29.2	67.8	1.13
9	190	194	98	17	26.9	64.4	1.18
10	179	202	82	19	38.1	87.0	1.06
11	176	218	100	15	36.6	82.8	1.14
12	180	138	86	17	26.0	60.2	1.30
13	171	168	88	17	26.3	67.8	1.22
14	181	206	72	18	41.1	97.2	1.16
15	196	232	90	19	31.9	104.9	1.28
16	184	206	80	17	46.1	122.2	1.17
17	205	216	80	16	41.1	135.5	1.25

Table 9. Normal Weight, Sedentary, No-OSAS Subject Exercise Recovery Measures

OWS-NoOSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	32	48	59	74	75	0.87	0.76	0.75
2	15	36	43	47	54	0.82	0.82	0.78
3	13	29	33	44	46	0.82	0.82	0.74
4	26	51	60	70	71	0.84	0.79	0.72
5	19	42	N/A	N/A	N/A	0.65	0.60	N/A
6	48	58	72	72	73	0.67	0.65	0.67
7	19	33	49	64	69	0.87	0.74	0.72
8	27	39	47	46	58	0.85	0.81	0.74
9	42	50	50	65	54	0.88	0.71	0.71
10	25	37	47	50	52	0.80	0.74	0.70
11	26	40	48	54	56	0.84	0.81	0.77
12	30	35	47	46	52	0.78	0.78	0.74
13	30	42	47	48	53	0.77	0.65	0.62
14	28	45	56	59	58	0.77	0.68	0.68
15	43	54	81	95	N/A	0.69	0.66	0.57
16	28	44	55	59	60	0.87	0.76	0.73
17	19	38	50	58	58	0.90	0.84	0.79

Table 9 Continued

OWS-NoOSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.71	0.68	0.90	0.84	0.84	0.90	0.90
2	0.79	0.77	0.90	0.85	0.73	0.73	0.90
3	0.73	0.65	0.98	0.95	0.95	0.95	0.98
4	0.69	0.68	0.90	0.80	0.84	0.80	0.80
5	N/A	N/A	0.76	0.73	N/A	N/A	N/A
6	0.60	0.59	0.84	0.79	0.67	0.70	0.70
7	0.69	0.64	0.92	0.90	0.90	0.90	0.88
8	0.72	0.69	1.00	0.93	0.91	0.89	0.93
9	0.71	0.41	0.90	0.82	0.88	0.82	0.82
10	0.65	0.60	0.83	0.85	0.80	0.73	0.80
11	0.74	0.74	0.80	0.78	0.72	0.68	0.78
12	0.71	0.72	0.86	0.86	0.91	0.88	0.86
13	0.62	0.61	0.89	0.86	0.89	0.93	0.93
14	0.62	0.60	0.94	0.94	0.94	0.94	0.92
15	0.48	N/A	0.80	0.78	0.78	0.67	N/A
16	0.72	0.67	1.00	0.98	0.98	1.00	1.00
17	0.72	0.68	1.08	1.03	0.90	0.98	1.03

Table 10. Baseline Normal Weight, Active, No-OSAS Subject Characteristics

NWA-NoOSAS	AGE (yrs)	AHI (events/hr)	EPWORTH (x/24)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	HIP (cm)
1	24	0.7	3	191.0	81.0	22.2	38.0	81.0	102.0
2	20	3.1	N/A	175.0	74.0	24.2	38.0	81.0	98.0
3	24	2.0	11	172.0	66.8	22.8	37.0	74.0	89.0
4	19	0.3	9	173.0	65.0	21.7	35.0	75.0	87.0
5	18	0.2	3	177.0	62.7	20.0	34.5	67.0	92.0
6	23	0.9	3	183.0	77.5	22.9	35.0	83.0	97.0
7	18	0.2	11	171.0	62.7	21.4	35.0	71.5	89.5
8	22	2.7	11	174.0	69.0	22.8	36.0	72.0	95.0
9	19	3.2	8	188.0	77.0	21.8	37.0	77.0	103.0
10	19	3.8	10	183.0	80.5	24.0	37.5	81.5	104.0
11	25	0.2	3	177.0	68.0	21.7	34.0	77.0	98.0
12	23	1.5	8	179.0	79.0	24.7	39.0	83.0	100.0
13	19	2.9	8	186.0	78.0	22.6	37.0	78.0	98.0
14	22	2.2	4	179.0	61.0	19.0	36.0	72.0	88.0
15	25	2.6	4	177.5	71.4	22.5	34.5	74.5	96.0
16	19	1.6	8	176.0	65.8	21.3	35.5	76.0	97.0
17	22	0.2	14	172.0	82.0	27.7	37.0	83.0	98.0
18	20	1.6	2	179.0	73.0	22.8	36.0	78.0	92.0
19	18	1.0	3	187.5	84.5	23.9	38.0	82.0	112.0
20	21	2.6	9	170.0	68.6	23.7	37.0	76.0	92.0
21	18	0.5	5	166.0	55.0	20.0	34.0	70.0	88.0
22	18	0.4	10	168.0	61.7	21.9	33.0	72.0	91.0

Table 10 Continued

NWA-NoOSAS	REST HR (bpm)	REST SBP (mmHg)	REST DBP (mmHg)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TRIG (mg/dL)	% Body Fat
1	92	142	94	153	82	45	124	12.2
2	72	108	74	138	93	38	45	12.1
3	45	118	82	153	104	36	64	9.3
4	78	122	88	165	93	51	107	15.1
5	81	126	80	129	N/A	49	45	15.6
6	69	118	78	132	87	31	68	18.1
7	82	114	82	153	100	41	62	11.0
8	85	114	86	150	88	53	47	12.3
9	88	140	90	151	104	39	45	12.3
10	57	118	80	132	72	47	66	20.2
11	83	124	70	158	90	60	45	16.4
12	66	120	82	152	95	49	45	13.2
13	72	122	84	123	62	52	45	13.8
14	82	118	92	163	97	46	96	11.7
15	53	112	70	115	66	44	45	9.8
16	83	118	80	140	81	52	45	17.6
17	71	114	72	191	125	48	93	19.0
18	55	118	76	147	74	61	56	8.9
19	90	122	84	159	88	51	97	14.9
20	85	124	84	123	N/A	44	45	13.5
21	82	102	66	169	111	38	104	12.7
22	63	110	82	138	82	43	61	12.8

Table 11. Normal Weight, Active, No-OSAS Subject Peak Exercise Measures

NWA-NoOSAS	HR (bpm)	SBP (mmHg)	DBP(mmHg)	RPE	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	VE ($L \cdot min^{-1}$)	RER
1	176	200	78	20	39.3	79.6	1.04
2	195	172	60	20	51.2	163.2	1.18
3	160	176	74	17	54.0	183.5	1.21
4	183	184	84	20	48.7	81.5	1.08
5	187	182	86	17	40.4	83.5	1.12
6	156	184	74	19	45.3	129.4	1.18
7	192	186	84	16	50.6	93.5	1.14
8	175	186	80	17	40.4	80.2	1.08
9	192	190	82	18	46.1	110.5	1.16
10	152	230	92	20	30.3	66.6	1.03
11	171	178	70	17	47.3	89.0	1.22
12	171	218	80	20	35.8	85.0	1.07
13	177	210	78	16	42.7	97.7	1.09
14	183	208	78	18	21.0	52.6	1.18
15	163	170	70	18	45.6	87.0	1.15
16	183	204	86	18	49.7	108.1	1.20
17	182	208	60	20	30.4	61.0	1.03
18	173	216	80	16	64.0	130.3	1.12
19	173	216	60	17	35.3	80.4	1.06
20	200	206	92	18	50.2	89.3	1.08
21	179	200	68	18	46.0	69.0	1.07
22	186	194	80	17	55.0	129.6	1.12

Table 12. Normal Weight, Active, No-OSAS Subject Exercise Recovery Measures

NWA-NoOSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	21	38	51	55	61	0.75	0.70	0.69
2	18	42	53	55	57	0.81	0.79	0.73
3	24	42	60	63	75	0.73	0.67	0.73
4	33	52	63	65	71	0.90	0.87	0.85
5	34	54	61	67	71	0.90	0.77	0.80
6	20	40	53	56	62	0.74	0.71	0.70
7	39	58	74	78	80	0.78	0.76	0.70
8	34	43	50	52	53	0.76	0.65	0.62
9	19	44	50	68	58	0.79	0.68	0.69
10	25	32	42	41	47	0.76	0.72	0.70
11	19	37	49	56	56	0.98	0.94	0.89
12	29	48	61	68	65	0.79	0.74	0.72
13	35	61	65	71	73	0.80	0.79	0.71
14	27	52	62	65	70	0.63	0.62	0.62
15	27	52	73	76	78	0.93	0.87	0.87
16	17	35	47	55	68	0.83	0.85	0.69
17	32	56	56	62	61	0.87	0.82	0.72
18	40	65	79	78	83	0.88	0.73	0.65
19	23	38	54	52	65	0.84	0.74	0.76
20	34	51	67	71	77	0.84	0.79	0.73
21	28	48	58	59	65	0.80	0.75	0.70
22	36	74	86	79	95	0.89	0.78	0.72

Table 12 Continued

NWA-NoOSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.62	0.64	1.00	0.97	0.92	0.95	0.95
2	0.71	0.64	0.83	0.70	0.60	0.63	0.70
3	0.68	0.63	0.81	0.76	0.78	0.86	0.81
4	0.73	0.67	0.98	0.95	0.95	0.95	0.95
5	0.78	0.75	0.81	0.84	0.77	0.74	0.77
6	0.68	0.62	0.65	0.78	0.76	0.78	0.78
7	0.70	0.66	0.81	0.95	0.98	1.00	0.98
8	0.54	0.54	0.80	0.75	0.75	0.68	0.73
9	0.68	0.69	0.83	0.71	0.78	0.78	0.76
10	0.67	0.66	0.76	0.87	0.85	0.85	0.87
11	0.78	0.72	0.97	1.00	1.03	0.94	1.00
12	0.71	0.68	0.88	0.85	0.88	0.83	0.90
13	0.66	0.60	0.79	0.87	0.82	0.87	1.03
14	0.58	0.55	0.51	0.87	0.87	0.95	0.95
15	0.85	0.80	0.91	0.94	1.00	1.00	1.09
16	0.71	0.70	0.93	0.98	1.00	0.95	0.93
17	0.63	0.59	1.03	1.17	1.13	1.13	1.30
18	0.63	0.56	0.95	1.00	0.95	0.90	0.95
19	0.66	0.64	1.07	1.03	1.17	1.30	1.33
20	0.73	0.71	0.78	0.91	1.02	1.00	1.00
21	0.69	0.65	0.85	0.94	0.88	1.29	1.18
22	0.67	0.65	1.00	1.00	1.00	1.03	1.00

Table 13. Baseline Normal Weight, Mixed Activity, OSAS Subject Characteristics

NWM-OSAS	AGE (yrs)	AHI (events/hr)	EPWORTH (x/24)	HEIGHT (cm)	WEIGHT (kg)	BMI (kg/m^2)	NECK (cm)	WAIST (cm)	HIP (cm)
1	25	5.5	3	173.0	61.8	20.7	35.5	79.5	96.5
2	19	6.8	3	172.0	58.0	19.6	34.0	70.0	89.0
3	25	10.4	3	170.0	64.1	22.2	37.0	74.0	96.0
4	20	10.7	7	179.0	74.0	23.1	36.0	78.0	98.0
5	22	12.4	7	175.0	63.0	20.6	38.0	72.0	90.0
6	21	7.2	7	190.5	82.5	22.7	36.5	83.5	103.0
7	26	5.0	12	165.1	59.1	21.7	36.0	74.5	92.5
8	19	6.2	5	178.5	76.0	23.9	38.0	81.5	99.0
9	18	9.0	8	171.0	58.0	19.9	34.0	67.0	87.0
10	19	5.1	8	171.0	67.0	22.9	37.0	73.0	95.0

Table 13 Continued

NWM-OSAS	REST HR (bpm)	REST SBP (mmHg)	REST DBP (mmHg)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TRIG (mg/dL)	% Body Fat
1	72	104	76	129	N/A	50	N/A	16.2
2	99	110	82	136	65	62	46	12.9
3	95	110	80	180	124	47	48	25.7
4	86	120	80	135	82	36	84	17.9
5	54	118	80	162	115	37	48	13.3
6	82	134	84	N/A	N/A	N/A	N/A	20.2
7	100	124	78	247	183	54	52	17.1
8	68	108	72	150	77	58	74	18.3
9	67	116	80	150	N/A	64	45	10.6
10	86	114	62	N/A	N/A	N/A	N/A	15.3

Table 14. Normal Weight, Mixed Activity, OSAS Subject Peak Exercise Measures

NWM-OSAS	HR (bpm)	SBP (mmHg)	DBP(mmHg)	RPE	VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$)	VE ($L \cdot min^{-1}$)	RER
1	175	186	94	19	34.3	73.3	1.13
2	195	184	90	19	45.3	87.2	1.12
3	187	172	78	19	29.4	82.8	1.11
4	163	170	58	19	26.5	68.3	1.10
5	190	180	100	16	41.9	97.7	1.21
6	176	176	86	17	25.7	67.0	1.08
7	198	178	78	19	38.9	76.3	1.18
8	184	152	78	20	36.8	123.4	1.22
9	170	190	84	17	36.9	72.1	1.08
10	188	170	60	18	35.7	80.9	1.17

Table 15. Normal Weight, Mixed Activity, OSAS Subject Exercise Recovery Measures

NWM-OSAS	HR Diff at 1 min	HR Diff at 2 min	HR Diff at 3 min	HR Diff at 4 min	HR Diff at 5 min	SBP ratio at 1 min	SBP ratio at 2 min	SBP ratio at 3 min
1	31	49	52	56	71	0.72	0.67	0.67
2	18	38	55	61	63	0.74	0.70	0.73
3	21	37	53	55	55	0.71	0.77	0.64
4	29	37	45	49	47	0.76	0.74	0.64
5	35	53	64	69	74	0.89	0.83	0.78
6	23	42	47	52	57	0.88	0.82	0.80
7	23	34	52	58	67	0.72	0.72	0.67
8	34	47	62	65	70	0.82	0.82	0.76
9	34	52	61	68	65	0.78	0.67	0.62
10	35	53	63	63	63	0.78	0.71	0.72

Table 15 Continued

NWM-OSAS	SBP ratio at 4 min	SBP ratio at 5 min	DBP ratio at 1 min	DBP ratio at 2 min	DBP ratio at 3 min	DBP ratio at 4 min	DBP ratio at 5 min
1	0.67	0.66	0.77	0.81	0.68	0.74	0.74
2	0.70	0.74	0.69	0.71	0.76	0.78	0.78
3	0.69	0.57	0.90	0.90	0.77	0.77	0.77
4	0.65	0.62	1.07	1.00	1.03	1.00	1.07
5	0.72	0.73	0.78	0.72	0.68	0.66	0.64
6	0.75	0.76	0.98	0.98	0.98	1.00	0.98
7	0.69	0.64	0.79	0.82	0.77	0.90	0.85
8	0.72	0.71	0.90	0.87	0.90	0.92	0.95
9	0.61	0.57	0.76	0.83	0.81	0.83	0.83
10	0.66	0.66	0.83	0.70	0.80	0.80	0.87

VITA

Trent Alan Hargens was born in January of 1974, and raised by his parents, Dean and Beth in Solon, Iowa. After graduating from high school in 1992, he attended Iowa State University for one year, before transferring to the University of Iowa. He received a Bachelor of Science degree in Health Promotion, with a Health Fitness Specialty in 1996. During his time at the University of Iowa, Trent was an active volunteer and employee of the Iowa CHAMPS Cardiac Rehabilitation Department, with the University of Iowa Hospitals and Clinics. It was there that he developed an interest in the field of Exercise Science, and decided to pursue a graduate degree in that field. After graduation, Trent attended Ball State University, where he studied under Drs. Leonard Kaminsky and Mitchell Whaley in the Adult Fitness/Cardiac Rehabilitation program in the Human Performance Laboratory. After graduating with his Master of Science in Exercise Science in 1999, Trent moved south to North Carolina, where he took a an Exercise Physiologist position within the Cardiopulmonary Rehabilitation Department at Cape Fear Valley Medical Center in Fayetteville, NC. He remained there for two years, before moving to Greenville, North Carolina, with the HealthSteps Cardiopulmonary Rehabilitation Program. It was there in Greenville that two major things happened in Trent's life. First, he met the woman who would later become his wife, Dani. Second, he decided that he was ready for a new challenge in life. He enjoyed his work in the clinical exercise setting, but was ready to return to school to pursue his Ph.D. By the time that Trent enrolled at Virginia Tech in 2003, to work under Dr. William Herbert, Dani was well into her graduate program in Physical Therapy at East Carolina University in Greenville. It was after only a few months in different locations that Trent decided to

propose. Trent and Dani were married in January 2005. While at Virginia Tech, Trent served as the Clinical Coordinator of the Therapeutic Exercise and Community Health Program for three years. In August 2006, Trent returned to his old stomping grounds of Ball State University to take a position as Associate Coordinator of the Clinical Exercise Physiology Program in the Human Performance Laboratory, the same program he was a student in several years earlier. He signed a one-year teaching contract at Ball State while he completed his dissertation work. In May 2007, Trent will graduate from Virginia Tech with a Ph.D. in Clinical Exercise Physiology. He has currently applied for several Assistant Professor positions in Exercise Science.