Aerobic Exercise Training and Nasal CPAP Therapy: Adaptations in Cardiovascular Function in Patients with Obstructive Sleep Apnea

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(ABSTRACT)

Obstructive sleep apnea (OSA) is a serious disorder that affects up to 24% of middle-aged males. The substantial cost and inconvenience associated with polysomnography limits the number of people who seek treatment. Therefore, information concerning exercise tolerance and hemodynamic function in obstructive sleep apnea (OSA) patients may add new and clinically meaningful information to the process of grading disease severity and/or assessing treatment outcomes. **Objectives:** The primary objective of this study was to explore relationships between polysomnography (PSG) markers of sleep function and resting and exercise measures of hemodynamic function in patients diagnosed with mild-to-severe OSA. A family of clinical markers including heart rate (HR), blood pressure (BP), cardiac index (CI), stroke volume index (SVI), total peripheral resistance (TPR), and oxygen uptake (VO_2) were assessed in this study. A second objective was to explore differences in hemodynamic function at rest and during graded exercise in OSA patients versus control subjects matched for age and body mass index (BMI). A final objective was to evaluate the extent that treatment with nCPAP alone, or combined with a moderate aerobic exercise training program impacted markers of hemodynamic function *(results not reported here)*. **Methods:** Eleven newly diagnosed OSA patients [5 male, 6 female; age: 46.5 $\pm$ 12.0 yrs; respiratory disturbance index (RDI) = 30.2 $\pm$ 15.0] and 10 apparently healthy control subjects (4 male, 6 female; age: 39.8 $\pm$ 6.9 yrs) completed daytime resting measurements of heart rate variability (HRV) and blood pressure (BP); and underwent a maximal cycle ergometer exercise test at baseline and 6 wk post-treatment initiation. Pearson product moment correlations were calculated between PSG markers of sleep function and: **(1)** daytime measures of HRV; **(2)** BP; and **(3)** submaximal and peak exercise measures of hemodynamic function. Independent *t* tests were used to explore differences between OSA patients and controls. **Results:** Stage 1 sleep duration was significantly related to daytime SBP ($r = 0.69$; $P < 0.05$) and MAP ($r = 0.72$; $P < 0.05$). Daytime MAP ($P = 0.01$) and DBP ($P = 0.02$) were significantly different between groups. Exercise testing yielded the following results: RDI was significantly related to HR at 60 watts ($r = -0.70$; $P = 0.02$) and 100 watts ($r = -0.69$; $P = 02$); stage 2 sleep duration was inversely related to CI at 60 ($r = -0.76$; $P = 0.03$) and 100 watts. In addition, stage 1 sleep duration was significantly correlated with TPR at 60 watts ($r = 0.70$; $P = 0.06$) and 100 watts ($r = 0.71$; $P = 0.05$). At peak exercise, a significant relationship was noted between peak HR and stage 2 sleep duration ($r = -0.73$; $P = 0.02$); and RDI ($r = -0.66$; $P = 0.03$). Furthermore, relative VO_{2pk} was positively correlated to REM sleep duration ($r = 0.62$; $P = 0.04$). **Conclusions:** Distinct patterns exist in measures of daytime HRV and BP may provide physicians unique and clinically useful information. In addition, peak exercise capacity is reduced in the OSA patient and may be related to a blunted HR response to graded exercise.

DEDICATION

To Jennifer:

Thank you for the love, support, and encouragement you have shown me during this project. I love you dearly!

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Many people have put their time and effort into my academic and professional development. My parents, Dan and Yvonne Kaleth, helped me to realize my full potential and always encouraged me to pursue my dreams. I can always rely on them for their love and support.

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CHAPTER I

INTRODUCTION

Clinical research has shown correlations between OSA and systemic and pulmonary hypertension [1-3], myocardial infarction [4], dysrhythmias [5, 6], and cerebrovascular accidents [5]. Research also has shown sleep apnea to be common in patients with heart failure [7-9], in that more than half such patients suffer sleep-related breathing disorders [7, 8]. Furthermore, OSA predisposes individuals to increased mortality and this increased risk is exacerbated by factors of age, body mass index (BMI), hypertension (HTN), and a high apnea-hypopnea index (AHI) [10, 11].

One important clinical consequence for those suffering from excessive daytime sleepiness caused by OSA is a dramatic increase in the risk for automobile accidents [12]. In recent clinical trials, George et al. [13, 14] reported lower simulated driving scores in OSA patients. Of these subjects, approximately 25% reported falling asleep at least once a week while driving. In 1987, George found 90% of sleep apnea patients have been involved in at least one automobile accident [15]. Other research has reported that OSA patients are seven times as likely to be involved in a car accident as subjects without the sleep disorder [15]. Falling asleep behind the wheel is the number one cause of lethal automobile accidents in Germany and the estimated yearly cost of this type of mishap in the United States has been reported to exceed $40 million [16]. Much of this could be avoided through the proper diagnosis and treatment for those suffering from sleep-related illness such as OSA. A recent report in the New England Journal of Medicine showed that proper medical intervention for OSA patients reduced the risk of automobile accidents for those individuals [17]. Although there appears to be an increased risk of

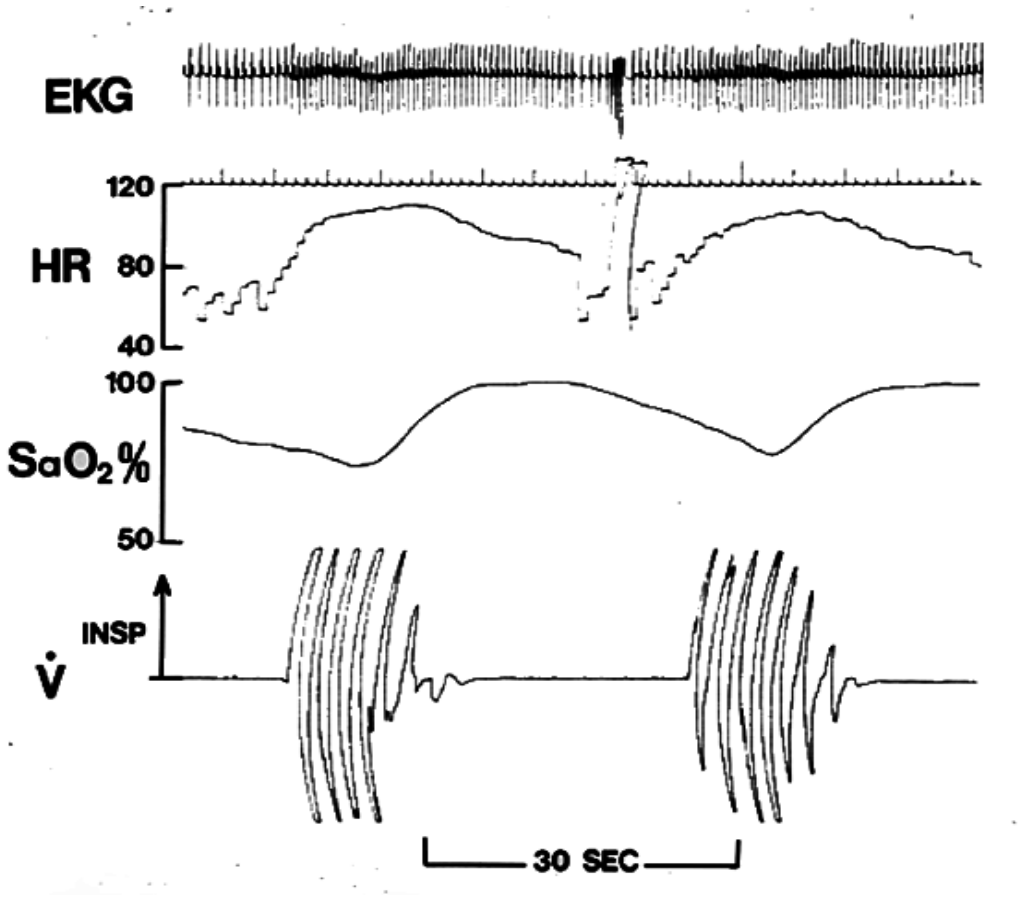
motor vehicle accidents in this population, presently there are no assessment measures to accurately predict driving performance in OSA patients.

Obstructive sleep apnea (OSA) is a serious disorder caused by repetitive obstructions in the upper airway during sleep. This disturbance in airway patency constitutes the primary pathophysiological event in OSA. Although this common condition is still under-recognized by many health care professionals, epidemiological studies have identified this syndrome in 2% to 4% of middle-aged adults with prevalence rates reported as high as 9% for women and 24% for men when OSA was defined as an apnea-hypopnea score of 5 or higher [18]. A substantial number of individuals go undiagnosed, which suggests an even higher prevalence, particularly given the trend toward rising obesity, a common co-morbidity of OSA. Although most medically diagnosed OSA patients are obese male snorers between 30 to 60 years of age, a growing number of non-obese women are now being identified with this condition [19]. The underestimated prevalence of OSA in women, however, remains unclear. [19] Studies have shown that women tend to under-report typical conditional symptoms such as snoring, gasping, and apnea. Some clinicians suggest that women have a reduced ability to generate oronasal tissue vibrations due to smaller anatomical structure. In turn, their snoring or apneic episodes go unnoticed by bed partners. Furthermore, the majority of women afflicted with sleep-disordered breathing are non-obese and do not fit the typical patient profile. These circumstances make recognition difficult and many women are often undiagnosed [19].

A clinical diagnosis of OSA is confirmed by overnight polysomnography (PSG) in a sleep laboratory. During the observation period, the patient's sleep stages are

monitored by the electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). The monitoring period also includes the evaluation of respiratory effort, airflow, oxygen saturation, and body position and movements [20-23]. The polysomnographic findings indicative of OSA include the appearance of five or more apneas or hypopneas per hour of sleep. Apnea is defined as the cessation of airflow for at least 10 seconds, whereas obstructive hypopnea is defined as a decrease of 30% to 50% in airflow for 10 seconds despite continued respiratory efforts [20]. These events are frequently accompanied by arterial oxygen desaturation (SaO2 levels < 90%). The severity of OSA is categorized by the apnea-hypopnea index (AHI), also known as the respiratory disturbance index (RDI). The RDI is determined by combining the number of apneas and hypopneas and dividing by the total time of sleep in hours [20].

Figure 1 – An example of the effects of an apneic event on various cardiovascular and neurological measures, as indicated by a simplified polysomnographic record. EKG = electrocardiograph, HR = heart rate, SaO_2% = percentage oxygen saturation of the blood, V_{INSP} = inspiratory airflow. Illustration provided by ResMed Inc., San Diego, CA.



Several assessment tools are also available to the primary care physician to aid in the diagnosis of sleep-related disorders. The Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness questionnaire are two such tools. These inventories attempt to assess a person's sleep quality and sleep quantity. Patients who present with an Epworth Sleepiness score > 12 and/or a Pittsburgh Sleep Quality Index global score > 5, along with a body mass index > 28 kg/m^2 should be further considered for possible OSA [24]. By combining the Epworth sleepiness score and/or the Pittsburgh Sleep Quality Index score

with a careful history evaluation, the primary care physician has fairly robust criteria to identify the patient at increased risk for OSA.

The typical OSA patient may present with several anatomical abnormalities that may predispose to the development of OSA (Table 1). Therefore, each patient should have a complete physical examination as this may influence the treatment choice and possibly identify other comorbidities. One of the strongest and most commonly studied risk factors for OSA is obesity. Among patients with OSA, research suggests the distribution of excess fat with an associated anatomical obstruction may compromise upper airway function by altering pharyngeal size or shape [25]. Furthermore, Kushida et al., [26] found that a neck circumference of > 40 cm had a sensitivity of ~ 60% and a specificity of ~ 90% for the development of OSA and is more closely related to the severity of sleep apnea than is BMI.

Besides the typical physical and physiological manifestations of OSA, recent studies suggest that family history is an established risk factor that increases the likelihood of OSA two to fourfold [19, 20, 27, 28]. Moreover, certain types of endocrinologic conditions such as hypothyroidism, acromegaly and various genetic disorders including Marfan's syndrome have also been implicated as predisposing factors in OSA.

Table 1. Clinical Features Associated With Obstructive Sleep Apnea

Obesity (BMI > 28 kg/m^2)
Neck Circumference > 40 cm
Enlarged nasal turbinates
Deviated nasal septum
Narrow mandible
Narrow maxilla
Dental overbite and retrognathia
Elongated uvula
Enlarged tonsils and adenoids
Macroglossia

BMI: Body Mass Index

Excessive daytime sleepiness (EDS) is the most commonly reported symptom in OSA patients (Table 2). Behavioral manifestations of EDS include impairments in concentration, memory, and cognitive function. This can result in irritability, poor school or work performance, and mood disorders. Sufferers often change lifestyle patterns by napping, ingesting large amounts of caffeine, and sleeping in on the weekends. Excessive fatigue along with the cognitive and affective limitations of excessive daytime sleepiness are often what prompt many patients to seek medical attention [29]. While presentation of OSA in the obese, male snorer with excessive daytime sleepiness is commonly seen, other less specific signs and symptoms may be consistent with this diagnosis such as mild fatigue, decreased energy, difficulty concentrating, and inadequacies in emotional or social interaction [20]. Patients with these less specific symptoms are often misdiagnosed and treated for the wrong condition when OSA is not considered.

Table 2. Symptoms of Obstructive Sleep Apnea

Nocturnal	Daytime
Snoring	Sleepiness (EDS)
Witnessed apnea	Fatigue
Choking	Morning headaches
Dyspnea	Poor concentration
Restlessness	Decreased attention
Nocturia	Depression
Diaphoresis	Decreased dexterity
Drooling	Personality changes
Reflux	Decreased libido

EDS: Excessive Daytime Sleepiness

Adequate intervention has been shown to improve daytime alertness and perceived quality of life, daytime hypertension and neuropsychiatric performance, and to reduce nocturnal oxyhemoglobin desaturation and respiratory arousals [20]. Long term nasal continuous positive airway pressure (nCPAP) therapy is effective in reversing OSA-related daytime hypertension and excessive daytime sleepiness [30, 31], however, compliance is problematic, with 2% to 36% of patients refusing try nCPAP at home and 6% to 35% discontinuing treatment after a period of home use [32]. Discomfort experienced during exhalation while on nCPAP, negatively affects compliance rates. Therefore, autotitrating nCPAP devices have been developed that simultaneously detect and administer the appropriate pressure, only when required, to maintain upper airway patency and prevent obstruction.

Exercise may be a viable means to increase daily energy expenditure as well as reducing secondary risk factors in the OSA patient. To date, only a few clinically based studies have been conducted in patients evaluating the effects of physical activity on the symptoms and severity of OSA [33-35]. Netzer et al. [33] noted a significant decrease in the RDI after six months of exercise training even though a reduction in body weight did not

occur. Giebelhaus et al. [35] reported similar results, noting a 28% decrease in the respiratory disturbance index after 6 months of combined aerobic and resistance training. Norman et al. [34] investigated the effects of a 6-month aerobic conditioning program on measures of aerobic capacity, daytime sleepiness, quality of life, and number of apneic episodes in 9 obese adult OSA patients. The patients reported enhanced feelings of energy and physical vigor, lessened self-reports of daytime fatigue, decreased weight, and even showed improved sleep function when evaluated by nighttime polysomnography. However, many confounding variables, including the simultaneous use of nCPAP by half of the subjects, make data interpretation difficult. Clearly, more investigation is needed with regards to such behavioral interventions.

Significance of the Study

OSA is a serious disorder that affects up to 24% of middle-aged males. Excessive daytime sleepiness is the most commonly reported symptom among OSA patients and has been implicated as the cause of a growing number of transportation and industrial accidents resulting in numerous fatalities and injuries every year. The substantial cost and inconvenience associated with polysomnography may deter patients from routine evaluation. Therefore, information concerning exercise tolerance and hemodynamic function in OSA patients may add new and clinically meaningful information to the process of grading disease severity and/or assessing outcomes following treatment with nCPAP or surgery. In addition, a physically active lifestyle that includes daily aerobic activities may have long-term potential to forestall or even reverse signs and symptoms associated with OSA. Regular endurance exercise is thought capable of modifying autonomic balance [47, 48] and has been suggested to be associated with increased heart rate

variability [49-51]. Therefore, effective nCPAP treatment coupled with exercise and weight loss, thus may better control manifestations of OSA that interfere with daily function and reduce the primary risk factors, i.e. hypertension and obesity, that otherwise would accelerate development of ischemic heart disease.

Purpose of Research

The purpose of this study was to explore relationships between polysomnography (PSG) markers of sleep function and resting and exercise measures of hemodynamic function in patients diagnosed with mild-to-severe OSA. A family of clinical markers including heart rate (HR), blood pressure (BP), cardiac index (CI), stroke volume index (SVI), total peripheral resistance (TPR), and oxygen uptake (VO_2) were assessed in this study. A second objective was to explore differences in hemodynamic function at rest and during graded exercise in OSA patients versus control subjects matched for age and body mass index (BMI). A final objective was to evaluate that the extent that treatment with nCPAP alone, or combined with a moderate aerobic exercise training program impacted markers of hemodynamic function.

Specific Aims

Specific Aim 1: **To evaluate the relationships between PSG markers of sleep function and disease severity and clinical measures of daytime cardiovascular autonomic function (heart rate variability, HRV) and resting blood pressure (Chapter IIIa)**. Heart rate variability (HRV) was determined from precise heart rate records of 8-hour waking periods using a small battery powered single-lead ECG recorder. An automated digital blood pressure device was used to obtain multiple measurements of daytime blood pressure and determine mean arterial pressure (MAP).

To evaluate circadian rhythm patterns for HRV and daytime blood pressure, measurement periods were defined as follows: morning (AM); noon (N); afternoon (AN); and evening (PM).

Specific Aim 2 (Chapter IIIb): To evaluate the relationships between PSG markers of sleep function and disease severity and exercise response characteristics during graded exercise. Hemodynamic measures, including blood pressure (BP) and its determinants, cardiac output (Qc) and total peripheral resistance (TPR), were measured during graded exercise in patients with OSA and related to polysomnographic markers of sleep function and disease severity.

Specific Aim 3: To evaluate the effects of treatments (nasal CPAP and exercise) on objective measures of exercise performance (Chapter IIIc). Exercise performance, evaluated through ramping exercise tests, was measured primarily from submaximal cardiorespiratory and hemodynamic measures including peak oxygen consumption. Other primary indicators were derived from changes in heart rate, blood pressure, cardiac output, and total peripheral resistance at a fixed percentage of aerobic capacity in the cycle ergometer test.

Assumptions

1. Subjects accurately completed and reported all medical and health history questionnaires, i.e. health history questionnaire, Epworth Sleepiness Scale, Medical Outcomes Survey Short Form 36 (MOS SF-36), Veteran's Specific Activity Questionnaire.

2. Subjects accurately reported recent (previous 6 months) and current physical activity habits.
3. Subjects complied with all pre-testing instructions.
4. Subjects accurately followed instructions regarding use of the Polar R-R Recorder™ (HRV) and the Omron® HEM 705CP automated digital blood pressure device.
5. Subjects randomized to the nCPAP plus exercise group complied with all exercise instructions, i.e. frequency, duration, and intensity of exercise; and accurately recorded physical activity for each day.
6. Subjects did not alter their diet throughout the study.
7. For each exercise test (2), subjects exhibited a maximal effort.
8. The testing bicycle ergometer was accurately calibrated and maintained throughout the study.
9. The SensorMedics Vmax229® metabolic cart accurately measured all cardiopulmonary exercise variables.

Delimitations

1. Subjects were volunteers referred to the Allergy and Sleep Disorders Center in Christiansburg, VA for evaluation of a suspected sleeping disorder;
2. Subjects diagnosed with mild-severe OSA (RDI scores: 5-60);
3. No current use of anti-hypertensive medication or severe hypertension;
4. No current use of sedatives and/or muscle relaxers;

5. No history of cardiovascular or pulmonary disease; or metabolic or endocrine disorders;
6. No orthopedic, musculoskeletal, or neuromuscular disabilities that would preclude moderate physical activity;
7. 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 tests were not performed on control subjects.
2. Due to difficulties in accommodating both patient and sleep staff schedules, exercise tests were not all scheduled within the same time period.
3. Due to technical difficulties in obtaining cardiac output measurements during the exercise test, baseline measurements were not obtained from 3 OSA patients. For similar reasons, 6-week cardiac output measurements were not obtained from 1 OSA subject.
4. Due to difficulties in performing the cardiac output breathing maneuver, measurements were not obtained at peak exercise.
5. Two OSA subjects exhibited an abnormal blood pressure and heart rate response in the post-exercise period, secondary to a low blood glucose level, after failing to eat prior to the exercise test. These subjects were excluded from certain analyses, i.e. recovery heart rate and blood pressure responses/patterns as these values represented abnormal physiologic responses.

6. For three subjects (1 OSA; 2 control), the Polar RR Recorder did not record data or the leads were not connected properly. Therefore, these subjects were excluded from analyses measuring aspects of heart rate variability.
7. For 1 OSA subject, the automated digital blood pressure device could not detect a blood pressure. Therefore, blood pressure was manually taken and recorded using the same criteria.
8. Three subjects (all control subjects) failed to complete all materials, i.e. questionnaires, Polar monitor, blood pressure, at each period. One subject was out of town and 2 voluntarily dropped out of the study. These subjects were excluded from these analyses.

Definitions of Terms

1. **Apnea** – the cessation of airflow at the nostrils and mouth for at least 10 seconds.
2. **Apnea/Hypopnea index (AHI)** – the number of apneas and hypopneas per hour.
3. **Arousal** - abrupt change from sleep to wakefulness, or from a "deeper" stage of non-REM sleep to a "lighter" stage.
4. **Cardiac Index** – An index relating cardiac output to body size derived by dividing the cardiac output by the body surface area in square meters; expressed as $L \bullet min^{-1} \bullet m^2$; normal values at rest: 2.6 - 4.2 $L/min/m^2$.
5. **Cardiac Output –** the volume of blood (liters) pumped out by the heart per minute; normal values at rest: 4 - 6 L/min.

6. **CPAP – Continuous Positive Airway Pressure** - the device used to treat sleep apnea by sending positive airway pressure at a constant, continuous pressure to help keep an open airway, allowing the patient to breathe normally through his/her nose and airway.
7. **Electroencephalogram (EEG)** – recording through the scalp of electrical potentials from the brain and the changes in these potentials. The EEG is one of the three basic variables (along with the EOG & EMG) used to score sleep stages and waking. Surface electrodes are used to record sleep in humans, recording potential differences between brain regions and a neutral reference point, or between brain regions.
8. **Electromyogram (EMG)** – recording of electrical activity from the muscular system. The chin EMG, along with EEG and EOG, is one of the three basic variables used to score sleep stages and waking.
9. **Electrooculogram (EOG)** – recording of voltage changes resulting from shifts in position of the eyeball-possible because each globe is a positive (anterior) and negative (posterior) dipole; along with the EEG and the EMG, one of the three basic variables used to score sleep stages and waking. Human sleep recordings utilize surface electrodes placed near the eyes to record the movement of the eyeballs.
10. **Epworth Sleepiness Scale** – index of sleep propensity during the day as perceived by patients, and derived from the answers to 8 questions.

11. **Excessive daytime sleepiness (EDS)** – subjective report of difficulty in staying awake, accompanied by a ready entrance into sleep when the individual is sedentary.
12. **Frequency Domain –** pertains to heart rate variability; estimates are made through Fast Fourier Transformation over time.
13. **Heart Rate Variability (HRV)** – refers to the beat-to-beat alterations in heart rate. Under resting conditions, the ECG of healthy individuals exhibits periodic variation in R-R intervals.
14. **High-Frequency Component –** pertains to frequency domain measures of heart rate variability; associated with parasympathetic nervous system.
15. **Hypertension** – High blood pressure; usually considered high if greater than 140/90 mmHg.
16. **Hypopnea** – shallow breathing in which the air flow in and out of the airway is less than half of normal; usually associated with oxygen desaturation.
17. **Hypoxemia** – abnormal lack of oxygen in the blood in the arteries specific criterion).
18. **Low-Frequency Component –** pertains to frequency domain measures of heart rate variability; associated with sympathetic nervous system.
19. **Metabolic Equivalent (MET)** – a unit used to estimate the metabolic cost of activity. One MET is equal to the approximate resting metabolic rate of 3.5 ml $O_2 \bullet kg^{-1} min^{-1}$.
20. **Minute Ventilation** – the volume of air exhaled from the lungs in one minute.

21. **NN50** – pertains to time domain measures of heart rate variability; expressed as the percentage of beat-to-beat variation greater than 50 milliseconds; equal to the NN50 count divided by the total number of all NN intervals.
22. **NREM or non-REM sleep** – characterized by slower and larger brain waves and little or no dream behavior; quiet sleep, slow-wave sleep; approximately 80% of sleep.
23. **Obesity-Hypoventilation Syndrome** – term applied to obese individuals, with the problem of hypoventilating during wakefulness.
24. **Obstructive apnea** – cessation of airflow (at least 10 seconds) in the presence of continued inspiratory effort.
25. **Oxygen Desaturation** – less than normal amount of oxygen carried by hemoglobin in the blood; values below 90% are considered abnormal.
26. **Peak Oxygen Uptake (VO_{2pk})** – the highest oxygen uptake obtained during the ramp exercise test.
27. **Pharynx** – area posterior to the nares and the oral cavity; passageway for air from the nasal cavity and/or the mouth to the lungs via the larynx and the trachea, for food and liquids from the mouth to the esophagus.
28. **Polysomnogram (PSG)** – continuous and simultaneous recording of physiological variables during sleep, i.e., EEG, EOG, EMG (the three basic stage scoring parameters), EKG, respiratory air flow, respiratory excursion, lower limb movement, and other electrophysiological variables.

29. **Ratings of Perceived Exertion (RPE)** – A person's subjective assessment of how hared he or she is working; Borg Scale (6-20 or 0-10) commonly used to tool to assess RPE.
30. **Respiratory Disturbance Index** – includes all respiratory events (apneas and hypopneas) per hour.
31. **REM sleep** (rapid eye movement sleep) – sleep characterized by the active brain waves, flitting motions of the eyes, and weakness of the muscles; accounts for about 20% of sleep in adults.
32. **SDNN** – standard deviation of all normal-to-normal intervals, i.e. all intervals between adjacent QRS complexes resulting from sinus node depolarizations.
33. **Sleep Apnea** – cessation of breathing for 10 or more seconds during sleep.
34. **Sleep Disorders** – broad range of illnesses arising from many causes, including, dysfunctional sleep mechanisms, abnormalities in physiological functions during sleep, abnormalities of the biological clock, and sleep disturbances that are induced by factors extrinsic to the sleep process.
35. **Sleep stage 1** – a stage of NREM sleep occurring after wake. Its criteria consist of a low-voltage EEG with slowing to theta frequencies, alpha activity less than 50%, EEG vertex spikes, and slow rolling eye movements; no sleep spindles, K-complexes, or REMS. Stage 1 normally assumes 4-5% of total sleep.
36. **Sleep stage 2** – a stage of NREM sleep characterized by sleep spindles and K complexes against a relatively low-voltage, mixed-frequency EEG background; high-voltage delta waves may comprise up to 20% of stage 2 epochs; usually accounts for 45-55% of total sleep time.

37. **Sleep stage 3** – a stage of NREM sleep defined by at least 20 and not more than 50% of the period (30 second epoch) consisting of EEG waves less than 2 Hz and more than 75 uV (high -amplitude delta waves); a "delta" sleep stage; with stage 4, it constitutes "deep "NREM sleep; appears usually only in the first third of the sleep period; usually comprises 4-6% of total sleep time.
38. **Sleep stage 4** – all statements concerning NREM stage 3 apply to stage 4 except that high-voltage, slow EEG waves, cover 50% or more of the record; NREM stage 4 usually takes up 12-15% of total sleep time. Somnambulism, sleep terror, and sleep-related enuresis episodes generally start in stage 4 or during arousals from this stage.
39. **Snoring** – noise produced primarily with inspiratory respiration during sleep owing to vibration of the soft palate and the pillars of the oropharyngeal inlet. Many snorers have incomplete obstruction of the upper airway, and may develop obstructive sleep apnea.
40. **Stroke Volume** – the volume of blood ejected from the heart per beat, expressed in $ml \bullet beat^{-1}$.
41. **Time Domain** – pertains to heart rate variability; simple statistical measures used to determine heart rate at any point in time or the intervals between successive normal complexes.
42. **Total Peripheral Resistance** – the resistance of the entire systemic circulation.
43. **Total sleep time (TST)** – amount of actual sleep time in a sleep period; equal to total sleep period less movement and awake time. Total sleep time is the total of all REMS and NREMS in a sleep period.

Abbreviations of Terms

CPAP	Continuous Positive Airway Pressure
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
ECG	Electrocardiogram
EMG	Electromyogram
EOG	Electrooculogram
ESS	Epworth Sleepiness Scale
GXT	Graded Exercise Test
HF	High Frequency (heart rate variability)
HRV	Heart Rate Variability
LF	Low Frequency (heart rate variability)
LF/HF	Low Frequency: High Frequency Ratio
NREM	Non-Rapid Eye Movement
O_2	Oxygen
OSA	Obstructive Sleep Apnea
pNN50	NN50 count divided by the total number of all NN intervals
PSG	Polysomnogram
PSQI	Pittsburgh Sleep Quality Index
Qc	Cardiac Output ($L \bullet min^{-1}$)
RDI	Respiratory Disturbance Index
REM	Rapid Eye Movement (sleep)
RPE	Ratings of Perceived Exertion
RPP	Rate Pressure Product
SAS	Sleep Apnea Syndrome
SDNN	Standard deviation of all NN intervals
SV	Stroke Volume ($mL \bullet min^{-1}$)
SWS	Slow Wave Sleep
TIB	Time in Bed
TPR	Total Peripheral Resistance ($mmHg \bullet L^{-1} \bullet min^{-1}$)
TST	Total Sleep Time
V_E	Minute Ventilation ($L \bullet min^{-1}$)
VO_2	Oxygen Consumption ($L \bullet min^{-1}$)
VO_{2pk}	Peak Oxygen Consumption ($L \bullet min^{-1}$)

Chapter II

REVIEW OF LITERATURE

The following chapter provides background information on research related to obstructive sleep apnea (OSA). This chapter focuses first on estimates of morbidity and mortality, in particular, hypertension and cardiovascular disease. Next, is a review of the pathophysiology and treatment options for obstructive sleep apnea. Third, this chapter focuses on the impact of OSA on the autonomic nervous system. Particular attention is given to heart rate variability, a method increasingly being used to quantitate and differentiate autonomic nervous system activity. Finally, this chapter will review the available literature pertaining to exercise as a potential therapeutic tool in the treatment of obstructive sleep apnea.

MORBIDITY AND MORTALITY

It now is clear that OSA patients are at an elevated risk of developing hypertension (HTN) [52-57], type 2 diabetes [58-61], and coronary artery disease (CAD) [3, 62-64]. Research also has shown sleep apnea to be common in patients with heart failure [7-9], in that more than half such patients suffer sleep-related breathing disorders [7, 8]. Furthermore, OSA predisposes individuals to increased mortality and this increased risk is exacerbated by factors of age, body mass index (BMI), hypertension (HTN), and a high apnea-hypopnea index (AHI) [10, 11].

Hypertension

According to the American Heart Association, hypertension remains a major modifiable risk factor for cardiovascular disease (CVD). Thus, daytime systemic hypertension is the cardiovascular outcome variable most often studied when attempting to establish a link between obstructive sleep apnea and CVD [65]. Systemic hypertension is frequently associated with OSA and can be directly attributed to the repeated and partial apneic events that disrupt autonomic cardiovascular reflexes during sleep [66-69]. Hypertension affects more than 50 million Americans and is present in 50% of patients diagnosed with OSA [70]. A few studies have shown that the prevalence of hypertension is higher in persons with OSA than those without [53, 71]. However, interpretation of these studies has proven problematic since confounding variables, particularly obesity, predispose an individual to both OSA and hypertension. While it is not currently known whether OSA contributes to the development of hypertension in humans, many researchers believe the relationship between the respiratory disturbance index (RDI) and blood pressure is well established, even when the effects of obesity, age, and gender were accounted for [53, 57, 71, 72].

Although the direct etiologic association between OSA and hypertension in humans has not been established definitively, several factors that characterize OSA may contribute to this relationship, including repetitive episodes of hypoxia, hypercapnia, and arousals resulting in increased sympathetic nervous system activity [65]. Apneic events during sleep result in decreased blood oxygen levels and increased carbon dioxide retention, both of which cause increased sympathetic nerve activity resulting in elevations in blood pressure [73]. Studies have also shown that patients with OSA exhibit increased

sympathetic activity during the day [74, 75]. These fluctuations in sympathetic nervous system activity may be involved in the pathogenesis of hypertension. Studies supporting this link between OSA and hypertension have shown a decrease in resting sympathetic nervous system activity [76] and blood pressure [77, 78] following nasal continuous positive airway pressure (nCPAP) treatment.

Sleep-disordered breathing (SDB) has been hypothesized to have a close relationship with hypertension, but previous studies have produced mixed results. Garcia-Rio et al. [79] assessed the relationship between hypertension and three forms of SDB (chronic snoring, breathing pauses and OSA using representative samples of the non-institutionalized population of the UK, Germany and Italy inhabitants. OSA was found in 1.9% of the UK sample, 1.8 % of the German sample and 1.1% of the Italian sample. OSA was found to be an independent risk factor for hypertension after controlling for possible confounding effects of age, gender, obesity, smoking, alcohol consumption, life stress, and, heart and renal disease. Others have found similar results. Grote et al. [80] reported that SDB was independently associated with hypertension when potential confounders such as age, body mass index, sex, menopause, use of hormone replacement therapy, race, alcohol use, and smoking were controlled for in the logistic regression analysis. The strength of the association decreased with age and was proportional to the severity of SDB. These findings appear to support the findings of Lavie et al [81]. These researchers investigated the mortality rates of 1,442 male OSA patients from 1976 to 1988. The subjects' age at time of diagnosis ranged from 21 to 79 years. Observed/expected mortality rates were calculated by comparing the expected death rates derived from Israeli national mortality data to actual subject death rates in each decade of

life. This study revealed significant excess mortality in the forth and fifth decades and that myocardial infarction was the major cause of death. Surprisingly, this mortality ratio decreased from 1.34 in the sixth decade to 0.34 in the seventh decade. While Lavie et al. provided no definitive explanation for their findings, this age-related phenomenon may be associated with enhanced endothelial function and a subsequent decrease in peripheral resistance in response to chronic disease-induced hypoxia.

In one of the largest studies to date, Peppard et al. [82] found a dose-response relationship in 709 participants of the Wisconsin Sleep Cohort Study between sleep-disordered breathing at baseline and the presence of hypertension four years that was independent of known confounding factors. Patients with a baseline RDI of 0.1 to 4.9 events per hour had 42% greater odds of having hypertension at follow-up than did patients with no episodes. Persons with mild sleep-disordered breathing (RDI = 5.0-14.9 events/hr) and those with more severe disease (RDI $\geq$ 15 events/hr) had approximately two and three times, respectively, the odds of having hypertension at follow-up compared to those with no episodes of apnea or hypopnea. They concluded that sleep-disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population.

It is has been postulated that intermittent nocturnal decreases in arterial oxygen saturation may cause hypertension and endothelial dysfunction in OSA patients. To this end, Bixler et al. [83] evaluated the central inspiratory drive response to hypoxia in patients with OSA and in healthy control subjects. They also examined the relationships among sleep architecture, hypoxic sensitivity, urinary catecholamine excretion, and BP. OSA patients were categorized as being normotensive (type 1), having BP elevation only

during sleep (type 2), and as being hypertensive with elevated BP at all times (type 3). They found a significant difference in the response to hypoxia among control subjects and type 1, type 2, and type 3 OSA patients. In the OSA patients, chemosensitivity was related to the apnea-hypopnea index and to the nocturnal excretion of epinephrine. Significant relationships between the nocturnal excretion of epinephrine and BP were also noted. On multiple linear regression analysis, the response to hypoxia was the only variable significantly related to diurnal and nocturnal mean BP. Their findings suggest a possible mediating role of peripheral chemosensitivity in the association between sleep apnea and hypertension. Furthermore, Kraiczi et al. [84] studied vasoconstrictor sensitivity and cholinergic responsiveness of the forearm vasculature in 10 male patients with OSA and 10 healthy controls. With the use of three dosage steps each, angiotensin II and acetylcholine were infused into the brachial artery. During infusion of angiotensin II, mean conductance was 39.6% lower in the OSA patients compared with that in the control subjects. Vascular responsiveness to increasing dosages of acetylcholine was not significantly altered in the OSA group. Their results suggest enhanced vasoconstrictor sensitivity in the forearm vasculature in OSA.

In hypertensive OSA that is associated with a damaged endothelium, vasoconstrictor influences predominate. Phillips et al. [85] evaluated 22 patients with severe OSA and associated hypertension before and after nCPAP therapy. They concluded that sleep apnea elicits increases in both blood pressure and endothelin-1 (ET-1); a potent vasoconstrictive and mitogenic peptide produced by endothelial cells and degraded predominantly in pulmonary vasculature, and a reduction in plasma renin activity. Although nCPAP treatment had no effect on renin activity, it did decrease mean

arterial pressure and plasma endothelin-1 levels. Their study design did not include the evaluation of nitric oxide (NO) and inducible NO synthase (iNOS) expression, thus a definitive conclusion as to the suppression of the renin-angiotensin-aldosterone system after CPAP therapy could not be drawn. Regulation of the renin-angiotensin-aldosterone system is extremely sensitive to NO levels and dependent upon the target tissue. He et al. [86] reported that under conditions of low afferent arteriolar shear stress and low NaCl concentration, NO produced in the macula densa by NOS-1 stimulated renin secretion. On the other hand, in the presence of increased vascular shear stress and elevated NaCl, endothelial cells of the afferent arteriole produced NO that inhibited renin secretion. These findings support recent evidence that this mechanism plays a role in increasing blood pressure during exercise. Although exercise is associated with increased blood flow and shear stress to the endothelium of active tissue, blood flow to the spleen and kidneys drops from approximately 2.8 liters/minute at rest to approximately 500mL/minute during maximal effort. This reduction in blood flow effectively lowers arterial wall stress in the afferent arteriole, thus reducing the release of NO and allowing for the increased secretion of renin normally seen with exercise. However, aberrations in this control mechanism may be related to the development of some types of hypertension [87].

Although the causes of primary hypertension are presently unknown, secondary hypertension, as commonly seen in OSA patients with vascular dysfunction, may be endocrine and/or structurally related. Chronic hypertension abnormally affects vessel wall thickness, lumen diameter, and endothelium function, all of which can increase peripheral resistance. A healthy endothelium is essential for the formation of NO. Nitric

oxide stimulates vasodilation in response to both vagal stimulation and exercise stress. At night, mean arterial pressure (MAP) decreases and increased vagal activity releases acetylcholine. This promotes the formation of NO and inhibits the release of norepinephrine. Acutely during exercise, blood flow increases to both skeletal muscle and the myocardium. The widely accepted explanation for this phenomenon is that the increased mechanical stress associated with larger blood volume causes shear forces to act upon the endothelium to release NO. Furthermore, this increased wall stress activates nitric oxide synthase, the enzyme associated with NO production in the endothelium. This NO response to exercise plays a crucial role in normal blood pressure regulation[5].

Although a scarcity of research exists in the area of exercise and sleep disordered breathing, there is ample data to support the efficacy of aerobic exercise for the treatment of hypertension. Proposed mechanisms of exercise induced blood pressure normalization include, the diminution of cardiac output and peripheral resistance both at rest and during submaximal exercise, reductions in serum catecholamines and plasma renin activity, a decrease in the ratio of visceral adipose to subcutaneous fat deposits, and enhanced carbohydrate metabolism [88, 89]. Research has shown that aerobic exercise training elicits an average reduction of 10 mm Hg for both systolic and diastolic blood pressures in individuals with stage 1 or stage 2 essential hypertension (systolic/diastolic blood pressure in the range of 140-179/90-109 mm Hg) [90, 91]. Moreover, low-moderate intensity exercise (e.g. 40 to 70% VO_{2pk}) appears to lower blood pressure, as much, if not more than, exercise at higher intensities [91], which may be especially important to consider in the counseling of hypertensive OSA patients who also frequently suffer from obesity. It may be postulated that the additive effects of aerobic exercise, which include increased

parasympathetic tone, enhanced vascular function, and decreased serum catecholamine levels may serve to help reduce the catacholaminergic spillover associated with daytime systemic hypertension in OSA patients. Over time, this type of exercise in conjunction with nCPAP therapy, might improve overall autonomic balance thus reducing disease severity.

Cardiovascular Disease. Also associated with OSA is the possibility for myocardial infarction and stroke. The prevalence of OSA in patients with coronary artery disease (CAD) is estimated to be 20-35% [92]. However, the available evidence suggesting a link between OSA and myocardial infarction is equivocal [93]. Many studies on this question have failed to control for confounding variables, therefore making the available evidence somewhat tenuous. Obesity is a risk factor for the development of both coronary artery disease and OSA and without controlling for this factor; it is difficult to conclude a causal relationship. It has also been suggested that myocardial infarction may increase the risk for the development of OSA [93]. Therefore, a link establishing OSA and coronary artery disease needs to be further evaluated before more definitive conclusions can be drawn.

Studies showing a link between OSA and stroke have come under similar scrutiny. As with myocardial infarction, it has been argued that stroke may contribute to the development of sleep apnea [93]. Palomake et al. [94] studied 167 men with stroke and found that 35.5% experienced their strokes during sleep. Furthermore, they reported that the odds ratio of snoring as a risk factor for stoke was strongly increased if snoring was accompanied by excessive daytime sleepiness and obesity [94]. Dyken et al. [95] extended these findings noting that OSA was found in 10 of 13 stroke patients and in only 3 of 13 patients without stroke. However, while some studies have shown a diminished cerebral

artery flow at the termination of an apneic event [96, 97], no definitive evidence exists establishing a link between OSA and cerebrovascular events.

Diabetes. There is increasing evidence to suggest that OSA might be a contributing factor to the development of diabetes. Some studies suggest that insulin resistance and abnormal glucose metabolism may be independently associated with OSA [59, 60] and that repetitive hypoxemia experienced in many of these patients during sleep may lead to alterations in insulin, insulin-like growth factors, and growth hormone [98, 99]. While there is disagreement about the incidence of sleep apnea in patients with diabetes, Sakakibara et al. [60] found that in patients with moderate-to-severe sleep apnea (RDI $\geq$ 20), OSA was a contributing factor to the development of type 2 diabetes, abnormal glucose metabolism, and hyperinsulinemia independent of age, family history of diabetes, and obesity. Brooks et al. [58] found that in 31 patients with type 2 diabetes, 22 (70%) had moderate or severe OSA. Furthermore, after treatment with nCPAP for 4 months, improvements in insulin responsiveness were seen in those with a higher BMI (>40 $kg \bullet m^{-2}$) [58].

In the OSA patient, the appearance of glucose intolerance or insulin resistance in the presence of sleep apnea could be attributed to other comorbid conditions, e.g. obesity. However, it has been suggested that the apneic events in OSA induce different and perhaps distinct alterations in metabolic processes involving insulin action and glucose regulation [99]. Further research is needed to isolate the effects of OSA before it may be determined if it is an important etiologic factor in development of type 2 diabetes. Meanwhile, since many OSA patients present with characteristics similar to those with type 2 diabetes, i.e. obesity, hypertension, and sedentary lifestyle, it is important for both

clinicians and health-fitness professionals to emphasize the value of exercise in helping to normalize blood glucose and lipid levels, lower blood pressure, reduce and/or maintain weight, and ultimately help patients with OSA and diabetes achieve a more active and healthy lifestyle.

OSA PATHOGENESIS

OSA is associated with loss of upper-airway (UA) patency during sleep. This narrowing or closure of the upper-airway that generally occurs during rapid-eye-movement (REM) sleep is caused by the interaction of multiple anatomic and physiological abnormalities. In addition, genetic and environmental influences may also play a role in the determination of airway size. The increased occurrence of OSA in some families cannot be fully explained by obesity alone. Although the proposed inherited association is still not fully understood, genetically determined craniofacial abnormalities and/or ventilatory control dysfunction may account for this pattern of familial apnea [28, 100].

Anatomically, upper-airway size is determined by soft-tissue involvement, adipose tissue deposition, and craniofacial factors such as maxillomandibular positioning [4]. Repeated exposure of the soft palate to vibratory trauma such as snoring and collapsing transmural pressure during inspiration can cause lengthening of this tissue, due to stretching and thickening caused by edema [101]. In obese patients, increased adipose tissue deposition in the neck is related to stenosis of the upper-airway. However, the development of OSA in non-obese individuals may arise from tonsillar hypertrophy

and/or craniofacial abnormalities that predispose the upper-airway to narrowing or closure during sleep [102].

Physiological factors related to upper-airway patency during sleep include: upper-airway dilating muscle activity; reduced transmural pressure during inspiration; changes in caudal traction; vasomotor tone; and mucosal adhesive forces [103]. Research has shown that physiological dysfunction generally occurs during rapid-eye-movement (REM) sleep. This stage of sleep is associated with hypotonia of the upper-airway muscles [4]. However, the majority of data on sleep-disordered breathing has been derived from studies that involve non-rapid-eye-movement (NREM) sleep, due to the difficulty of achieving REM during invasive procedures in a laboratory setting [103].

The absence of upper-airway narrowing in the OSA patient during wakefulness points to the obligatory removal of the wakeful stimulus during sleep as the key factor underlying sleep-disordered breathing. REM sleep causes hypotonia of the musculature in the upper-airway [4]. This phenomenon is linked to reduced upper-airway caliber and increased pharyngeal wall compliance in snorers that is manifested by decreased airflow during inspiration. This corollary of increased resistance and inspiratory airflow limitation causes increased respiratory work, hypoventilation, and sleep arousals that lead to excessive daytime sleepiness [103, 104].

The capacity of the ventilatory control system to compensate for the increased workload in the OSA patient is lessened during NREM sleep. Thus, this pathophysiological state is associated with decreased tidal volume and minute ventilation. These events eventually lead to alveolar hypoventilation and an increase in arterial P_aCO_2. NREM sleep also eradicates the ability of upper-airway muscles to respond to

increased negative transmural pressure during inspiration. During wakefulness, this negative inspiratory pressure gradient evokes activation of the genioglossus or the tensor palatinii muscle. This wakeful reflex response dilates the upper-airway, whereas during NREM sleep this activation mechanism is not present, suggesting sleep abolishes a protective mechanism that maintains upper-airway patency during deformation [103, 105]. The failure of the ventilatory control system to adequately compensate for the relative increase in workload results in hypoventilation and increased respiratory effort. This may explain why OSA patients have abnormal nocturnal CO_2 retention in the presence of increased respiratory muscle activity [103, 106].

Although the exact mechanisms of upper-airway obstruction during sleep are still not fully understood, Badr et al. [103, 106] believe that the underlying defect in the development of OSA is a small pharynx vulnerable to collapse. Their research has also led them to believe that reduced ventilatory drive and decreased neural output to the upper-airway dilating musculature sets off a chain of events that eventually leads to sleep related pharyngeal obstruction. This narrowing of the pharyngeal airway that is caused in part by a collapsing transmural pressure leads to increased velocity of airflow. The consequent diminution in intramural pressure promotes increased pharyngeal narrowing that ultimately advances to total upper-airway obstruction. After complete obstruction transpires, the combination of gravity and mucosal adhesion promotes continuance of the apneic event. In most instances, arousal from sleep is needed to achieve pharyngeal opening. This event leads to hyperpnea, hypocapnia, and as restoration of sleep occurs, a decrease in ventilatory drive [103, 106].

MEDICAL & SURGICAL MANAGEMENT OF OSA

The importance of early detection and treatment of OSA cannot be overstated. Adequate intervention has been shown to improve daytime alertness and perceived quality of life, daytime hypertension and neuropsychiatric performance, and to reduce nocturnal oxyhemoglobin desaturation and respiratory arousals [20]. Treatment options for sleep apnea depend on the severity of the disorder, magnitude of clinical complications, and the predominant type of apnea (central, obstructive, or mixed). Therapy for OSA has many options, including behavioral, medical, and surgical strategies, and is often not limited to only one form of treatment. However, in all cases, the primary aim of treatment is to prevent the posterior movement of the tongue as well as the narrowing of the airway that accompanies a large tongue or soft palate. Behavioral techniques that may effectively reduce snoring and mild OSA include restricting the use of alcohol and sedatives, which further relax the upper airway and contribute to obstruction [4]. Positional sleep training is useful for those patients who primarily experience upper airway obstruction when sleeping in the supine position. However, this technique may not be tolerated for the long term in treatment of OSA.

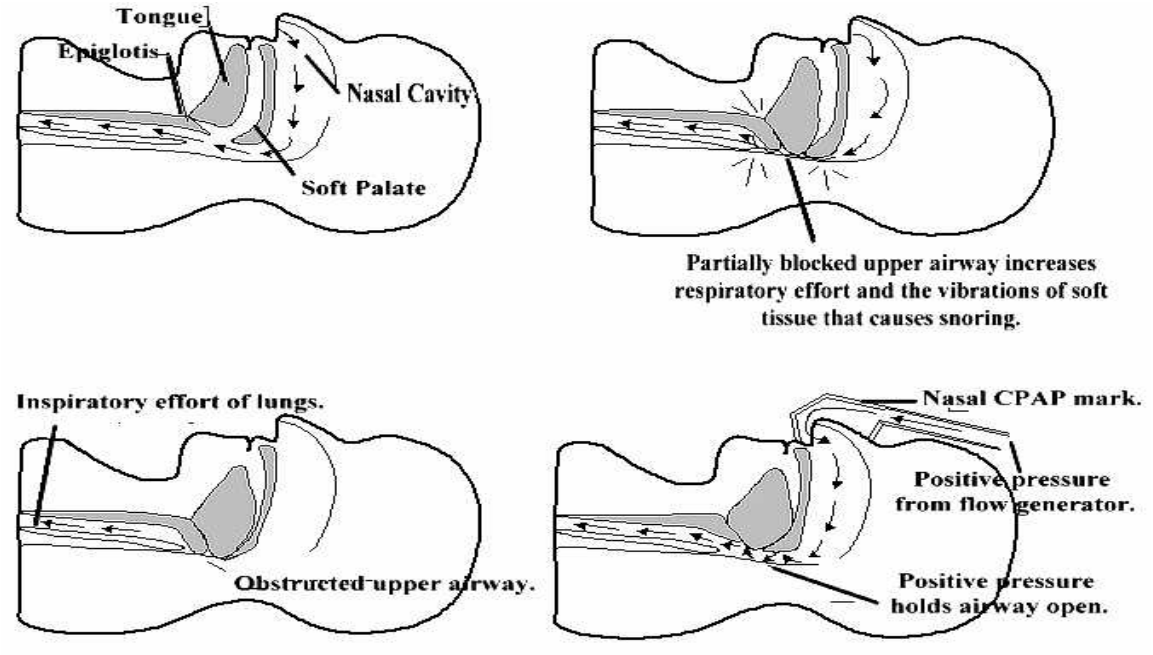
Oral appliances are also used to treat snoring, apnea, or both. Various manufacturers produce these devices, which can be grouped into those that position the tongue forward and support the soft palate to suppress its movement, or reposition the mandible to optimize the opening behind the tongue [107]. The effectiveness of oral appliances has been variable in the past, but newer, more comfortable devices, will likely improve the success of this mode of therapy. At this time, though, oral appliances are indicated for patients with mild to moderate OSA severity who do not tolerate nasal

continuous positive airway pressure or who fail behavioral management including positional therapy and weight loss [108].

In all patients with moderate to severe OSA and in most with mild OSA, the usual initial treatment prescribed is nasal continuous positive airway pressure (nCPAP). Nasal CPAP reduces the negative pressure generated in the throat during inspiration and acts as a "pneumatic splint" pushing the soft palate and tongue forward and away from the posterior oropharyngeal wall (Figure 2). In addition to the treatment of nocturnal apneic and hypopnic events, long term nCPAP use has been shown to be effective in reversing OSA related daytime hypertension, excessive daytime sleepiness, and in weight loss [30, 31]. The high levels of sympathetic nervous activity that occur in OSA during sleep and wakefulness [73, 109] are ameliorated by nCPAP therapy [67, 73, 110]. Unfortunately, compliance is problematic, with 2% to 36% of patients refusing try nCPAP at home and 6% to 35% discontinuing treatment after a period of home use [32]. Discomfort experienced during exhalation while on nCPAP, negatively affects compliance rates. Bilevel positive airway pressure, which provides a lower exhalation pressure, may be indicated in those patients who do not tolerate standard nCPAP. Autotitrating nCPAP devices have recently been developed that simultaneously detect and administer the appropriate pressure, only when required, to maintain upper airway patency and prevent obstruction. Humidification devices may reduce irritation of the airway and improve compliance with nasal continuous positive airway pressure. Adherence to nCPAP therapy is well known to be problematic for selected patients and poor adherence has been documented to preclude physiological benefits that otherwise are associated with this treatment, such as reduction in blood pressure [109]. For patients who are able to

comply with nCPAP therapy, very favorable short-term improvements have been noted in self-reports of sleep quality, overall health, and physical vigor, even for treatment periods as brief as 4 weeks [77, 111].

Figure 2. Depicts nasal continuous positive airway pressure restoration of airflow during a typical apneic or hypopnic event. Illustration provided by ResMed Inc., San Diego, CA.



Surgical treatment of OSA is reserved for those who do not tolerate nCPAP. Tracheostomy remains the most effective surgical intervention, but should be reserved for patients who have failed other forms of medical and surgical management [112]. Other types of surgical intervention that have a potential to improve quality of life should be considered before tracheostomy. Uvulopalatopharyngoplasty (UPPP), for example, enlarges the posterior oropharynx by removing much of the soft tissue in that area. However, this procedure provides only a 50% cure rate and has poor efficacy for patients

with severe OSA [113]. Laser assisted uvulopalatopharyngoplasty (LAUP) is an effective surgery for snoring, but should not be used as the only means to treat OSA. Maxillofacial surgery, especially maxillomandibular osteotomy (MMO), has emerged over the past several years as a viable surgical treatment. In this skeletal reconstructive procedure, both the maxilla and mandible are moved anteriorly and the hyoid bone is suspended anteriorly [114]. This procedure has generally been reserved for those with severe OSA in the past, and those with severe mandibular deficiency. Success rates for maxillomandibular osteotomy have been shown to be greater than 90 percent. For example, in a recent outcome based investigation, at five months post surgery, mean blood pressure and body mass index were significantly lowered in those undergoing the maxillomandibular osteotomy procedure [115]. Surgery may be a potential means of therapy for many OSA patients, but the pros and cons for each type of procedure should be evaluated.

Obese patients should be encouraged to lose weight since obesity is associated with an increase in soft tissue in the lateral pharyngeal area [3, 116]. Although there is a population of nonobese OSA patients who do not obtain benefit from weight reduction, obese patients should always be encouraged to lose weight. The long-term benefits of weight loss may include a reduction in the severity of OSA symptoms and possibly the prevention of other obesity-related disorders, i.e. CAD and type 2 diabetes. Research has shown a consistent pattern of improvements in RDI and OSA symptoms with weight loss [117-119]. Unfortunately, despite initial weight loss success reported for both surgical and dietary intervention approaches, long-term management and maintenance of weight loss is generally poor [119]. Furthermore, there are relatively few studies that have reported

long-term follow-up results in OSA patients. Although weight reduction may have a beneficial impact on upper airway function during sleep, it is likely that the degree of improvement is not linearly related to the amount of weight that is lost. The magnitude of this weight reduction probably varies across patients and even a relatively modest weight loss may provide a significant benefit for some patients. Furthermore, while weight reduction may not eliminate the need for further therapy, i.e. nCPAP, it may minimize the required degree of aggressiveness in treatment.

OSA AND CARDIOVASCULAR AUTONOMIC FUNCTION

The cyclical changes in heart rate and systemic blood pressure that accompany apneic events are predominantly mediated by fluctuations in the activity of the autonomic nervous system. Increased vagal efferent parasympathetic activity is responsible for the cyclical reductions in heart rate during apnea. In contrast, the cyclical elevations in systemic blood pressure are believed to result from recurrent peripheral vasoconstriction mediated by repetitive activation of the sympathetic nervous system [120]. Maximal sympathetic activation resulting in elevated arterial pressures coincides with apnea termination and brief arousal from sleep. These cyclical elevations in systemic pressure during sleep increase ventricular workload and, thereby, may contribute to the development of ventricular hypertrophy. In the OSA patient with congestive heart failure, these effects would seem to exacerbate ventricular dysfunction and partly account for their very poor prognosis.

These cyclic elevations in blood pressure reach peak frequencies between 6 AM and noon, generally within several hours of awakening. Although sleep is associated with

decreased frequencies of these adverse cardiovascular events in the general population, there is some published evidence linking REM sleep to an increased risk of myocardial infarction. This increased sympathetic activity in OSA patients during sleep has been proposed to spillover into daytime hours as manifested by an increase in plasma norepinephrine as well as decreased sensitivity of the baroreceptors to changes in arterial blood pressure [70, 79, 121-125]. Myocardial ischemia, infarction, sudden death, and stroke also follow similar circadian variations in time of onset, with peak frequencies occurring between 6 AM and noon and could be partially dependent on this catecholaminergic spillover [124]. In fact, the risk for cardiac events was more positively correlated with the severity of RDI than with the clinical diagnosis of OSA, lending support to the hypothesis that these nocturnal breathing fluctuations are intimately involved in both cardiovascular mortality and hypertension [126].

As a result of increased sympathetic activity secondary to apneic episodes, oscillations in both heart rate and blood pressure occur with some investigators noting an increase in the frequency of atrial and ventricular arrhythmias. In one large study of 400 patients, cardiac arrhythmias were noted in almost half the subjects [127]. The majority of these cardiac disturbances noted were bradyarrhythmias with 43 of the 400 patients experiencing sinus arrest of 2.5 to 13 seconds. In this study and in subsequent studies, ventricular arrhythmias were relatively uncommon [128]. Some investigators dispute the high prevalence of arrhythmias associated with OSA, claiming that the patients in the aforementioned studies had severe sleep apnea and were not representative of a greater spectrum of disease severity [93]. While the available literature is equivocal in establishing a causal relationship between sleep apnea and cardiovascular morbidity, it seems likely

that the hemodynamic changes associated with apneic events may contribute to acute and chronic cardiac disorders in certain individuals.

Heart Rate Variability: Methodology

Until recently, subtle beat-to-beat fluctuations in cardiovascular signals had received little attention, most probably due to a lack of high-resolution electrocardiographic (ECG) recordings and digital computers with adequate calculation capacity. Since the introduction of such computers, computation of heart rate variability (HRV) using various algorithms to assess the frequency and amplitude of heart rate oscillatory components has been possible [129]. Since beat-to-beat fluctuations in heart rate partly reflects the interplay between the sympathetic and parasympathetic nervous systems, measures of HRV, i.e. time and frequency domain measures, have provided prognostic information regarding the significance of these fluctuations and the subsequent response(s) of the cardiovascular regulatory systems.

Time Domain Analysis of Heart Rate Variability

Heart rate variability may be evaluated by a number of methods. The time domain methods are generally the simplest to perform. With these methods, measures of HRV are assessed by determining the heart rate at any point in time or by calculating the time (milliseconds) between successive normal RR intervals. The most widely used time domain index is the average heart rate. Time domain analyses can be performed on short electrocardiogram (ECG) segments, i.e. 5 minutes or on 24-hour ECG recordings. The value of the estimate depends on the recording length. Therefore, measures should be compared within segments of similar length. Other commonly used time domain indices based on interval differences are: the standard deviation of all normal-to-normal RR

intervals (SDNN); pNN50, which is a measure (percentage) of the instantaneous difference over 50 ms between two consecutive normal-to-normal RR intervals [130], and RMSSD, which is the square root of the mean squared differences of successive RR intervals. Since artifact and outliers could affect the time domain measures, these measures require a systematic means which non-physiologic data and extrasystoles can be eliminated.

Frequency Domain Analysis of Heart Rate Variability

Another commonly used method in the analysis of heart rate variability is spectral analysis. Various spectral methods for the analysis of HRV have been applied since the late 1960's [131]. The main advantage of spectral analysis of signals is the possibility to study their frequency-specific oscillations. Spectral analysis involves the breakdown of a series of sequential RR intervals into different amplitudes and frequencies. The magnitude of variability can then be displayed as a function of frequency, i.e. power spectrum. Methods based on Fast Fourier Transformation and autoregressive analysis are most commonly used to transform signals into the frequency domain. Investigators typically divide the power spectrum into different spectral bands and calculate the powers within these bands. The spectrum is usually divided into three or four different bands, depending on the major frequency bands. The boundaries of the most commonly used frequency bands are as follows: ultra low frequency (ULF) < 0.0033 Hz; very low frequency (VLF) from 0.0033 − 0.04 Hz; low frequency (LF) from 0.04 − 0.15 Hz; and high frequency (HF) from 0.15 to 0.4 Hz. Standards that should be used in physiological studies have been recommended by European Society of Cardiology and the North American Society of Pacing and Electrophysiology [132]. While spectral analysis can be

used to analyze the sequence of NN intervals in both short- and long-term recordings, the results of long-term recordings are less well defined when mechanisms responsible for heart rate modulations, i.e. activity, outside stimuli, and respiration, are not stable [132].

Clinical Significance of Heart Rate Variability

Recent studies have shown that decreased variability of RR intervals might implicate an increased risk for arrhythmic events and an increased mortality rate in patients with a previous myocardial infarction [133, 134]. The mechanism by which HRV is reduced after myocardial infarction (MI) is not yet known, but is likely to involve abnormalities in the neural activity of cardiac origin [132]. Depressed HRV post-infarction may reflect a decrease in vagal activity directed to the heart, which results in a predominance of sympathetic nervous system activity. There is also evidence to suggest the reduction in HRV correlates with the angiographic severity of coronary artery disease [135], however, the effect of the severity is controversial. Myocardial ischemia has been suggested to destroy the cardiac receptors resulting in altered autonomic regulation [136], however, aging also affects autonomic activity [137].

Several reports have also shown a decrease in the spectral measures of heart rate variability after a myocardial infarction [138-140]. However this reduction in HRV post-infarction may be a transient feature. Evidence of a "recovery" in HRV post-MI has been observed, but is still depressed compared to healthy controls [140, 141].

Several investigators have reported an association between depressed HRV and post-MI mortality [142-144]. Rich et al. [143] showed that decreased HRV and low left ventricular ejection fraction were the best and independent predictors of mortality in patients with angina pectoris but without recent myocardial infarction. Furthermore,

impaired HRV was proposed to be a better predictor of cardiac death and arrhythmic events than left ventricular ejection fraction in patients with prior myocardial infarction [144, 145]. Cripps et al. [146] found that the relative risk of sudden death or ventricular tachycardia was seven times greater in post-infarction patients with low HRV compared to those with high HRV.

Heart rate variability has been observed to be an independent predictor of sudden death. Odemuyiwa et al. [147] and Hartikainen et al. [148] showed decreased heart rate variability to be related to both arrhythmic and non-arrhythmic death in post-infarction patients. Both case-control and epidemiological studies have suggested that low heart rate variability increases the risk of arrhythmic events and death. The recent data suggest that impaired HRV increases the risk of non-fatal cardiac events, i.e. myocardial infarction and unstable angina pectoris, suggesting that low HRV analyzed with conventional methods is strongly related to cardiovascular events and not specifically to arrhythmic events [149]. In addition to cardiovascular-related diseases, depressed HRV has been reported in various other disorders, including congestive heart failure [150, 151], diabetic neuropathy [152], neurological conditions [153, 154], and chronic renal failure [155].

Heart Rate Variability and Obstructive Sleep Apnea

Altered cardiovascular variability is a prognostic indicator for cardiovascular events. Several studies have shown that patients with sleep apnea have very high levels of sympathetic activity even during waking hours when breathing patterns are normal and no evidence of hypoxia or hypercapnia is apparent [73, 75, 109, 156]. Possible mechanisms underlying the derangement in neural control in sleep apnea include abnormalities in chemoreflex function [157-159] and increases in endothelin-1 release [85]. As a result, altered

cardiovascular variability may precede, and potentially predispose to, subsequent clinically significant cardiac and vascular dysfunction in OSA patients.

Narkiewicz, et al. [109] compared variability characteristics of simultaneous recordings of muscle sympathetic nerve activity (MSNA), RR interval, blood pressure, and respiration in 18 patients with mild OSA (age = 45 $\pm$ 10 yrs; BMI = 32 $\pm$ 5 kg/m^2), 15 patients with moderate-to-severe OSA (age = 40 $\pm$ 9 yrs; BMI = 36 $\pm$ 7 kg/m^2), and in 16 matched normal control subjects (age = 41 $\pm$ 9 yrs; BMI = 33 $\pm$ 7 kg/m^2). Patients with OSA were newly diagnosed, never treated for OSA, free of any other known diseases, and on no medications. Furthermore, because of the high prevalence of occult OSA in apparently normal, asymptomatic obese subjects, sleep disordered breathing was excluded in all control subjects by complete overnight polysomnographic studies. Patients with moderate-to-severe OSA had shorter RR intervals (793 $\pm$ 27 ms) and increased sympathetic burst frequency (49 $\pm$ 4 bursts/min) compared with control subjects (947 $\pm$ 42 ms; 24 $\pm$ 3 bursts/min; $P = 0.008$ and $P < 0.001$, respectively). In these patients, total variance of RR was reduced ($P = 0.01$) and spectral analysis of RR variability showed an increase in low frequency normalized units, a decrease in high frequency normalized units, and an increase in the ratio of low to high frequency (all $P < 0.05$). Even though blood pressure was similar to that of the control subjects, blood pressure variance in patients with moderate-to-severe OSA was more than double the variance in control subjects ($P = 0.01$). Patients with mild OSA also had a reduction in RR variance ($P = 0.02$) in the absence of any significant difference in absolute RR interval. For all patients with OSA, linear regression showed a positive correlation ($r = 0.40$; $P = 0.02$) between sleep apnea severity and blood pressure variance. The authors

concluded that cardiovascular variability is altered in OSA even in the absence of other disease states, and may be linked to the severity of OSA.

Wiklund, et al. [160] attempted to assess autonomic function using HRV in 51 patients with OSA and 66 non-OSA controls. Spectral analysis of HRV was analyzed after supine rest during controlled breathing and after tilting in each subject. Individuals with an apnea-hypopnea index (AHI) $\geq$ 20 were regarded as OSAS patients and those with AHI < 20 as snorers. During free and controlled breathing there was a significant decrease in indices reflecting vagal modulation, indicating parasympathetic dysfunction in OSAS patients compared with controls. However, no correlation was seen between vagal function and severity of OSA. The authors concluded that autonomic dysfunction does exist in patients with OSA, and may involve the parasympathetic nervous system. Furthermore, this dysfunction may be related to the increased cardiovascular mortality and malignant arrhythmia described in OSAS.

Exercise and Heart Rate Variability

Exercise training may decrease cardiovascular mortality and sudden cardiac death [161], however the relationship between physical fitness and heart rate variability is less clear. Regular endurance exercise training is thought capable of modifying autonomic balance [47, 48] and has been suggested to be associated with increased heart rate variability [49-51]. Stahle et al. [162] reported significant improvements in time domain measures of HRV ($p < 0.01$) compared to controls after 3 months of exercise training (3x per week; 50 minutes per session) in 65 patients recovering from an acute cardiac event, i.e. myocardial infarction; episode of unstable angina.

Migliaro et al. [163] explored the relationship between age, sedentary lifestyle, and HRV in 34 apparently healthy volunteers. Subjects were divided into two groups. Eighteen subjects (age range: 15 to 20 years; 9 sedentary, 9 active) were in the young group. The elderly sedentary group consisted of 16 sedentary subjects aged 39 to 82 years. HRV was assessed using a short-term, i.e. 5 minutes, procedure. Time domain analysis of consecutive R-R intervals was assessed by calculating the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD). Frequency-domain HRV was evaluated by power spectrum analysis considering high frequency and low frequency bands. All tests were performed 2 hours post-prandial, between 10am and 1pm. Each subject in the young group underwent a cycle ergometer test following HRV analysis to determine training rank. The exercise test began at 50 watts and increased 50 watts every 3 minutes until muscular fatigue or maximal heart rate was achieved. Subjects in the elderly sedentary group two did not perform the stress test. Within each group, HRV displayed a negative correlation with HR. Although the physically active young group had a higher functional capacity than the young sedentary group, results showed no significant differences in HRV between sedentary and non-sedentary subjects in the young group, however significant differences were seen in HRV between the elderly sedentary group and the young group. The authors concluded that age and HR are the most powerful determinants of HRV.

In another study, Levy et al. [164] examined whether exercise training would affect the reduced HRV experienced with aging. They compared 13 older apparently healthy male subjects (age 60 to 82 years) with 11 younger (age 24 to 32 years) male subjects. Before the study and after the 6-month training, subjects performed a cycle ergometer

protocol consisting of increases every 3 minutes. HRV was taken during the final 2 minutes of each stage. Each subject underwent a six-month supervised training program consisting of 45 minutes of aerobic exercise 4 to 5 times per week. The training began at 50 - 60% of heart rate reserve and increased to 80 - 85% of heart rate reserve by the fourth month. Before exercise training, the older subjects had a 47% lower HRV at rest compared with the young subjects (31 $\pm$ 5 ms vs. 58 $\pm$ 4 ms, p = 0.0002). During peak exercise, the older subjects had less parasympathetic withdrawal than the young subjects (-45% vs. -84%, p = 0.0001). Six months of intensive aerobic exercise training increased maximum oxygen consumption by 21% in the older group and 17% in the young group (analysis of variance: overall training effect, p = 0.0001; training effect in young versus old, p = NS). Training decreased the heart rate at rest in both the older (-9 beats/min) and the young groups (-5 beats/min, before vs. after, p = 0.0001). Exercise training increased HRV at rest (p = 0.009) by 68% in the older subjects (31 +/- 5 ms to 52 +/- 8 ms) and by 17% in the young subjects (58 $\pm$ 4 ms to 68 $\pm$ 6 ms). Levy et al. concluded that exercise training increases parasympathetic tone at rest in both the healthy older and young men, which may contribute to the reduction in mortality associated with regular exercise. Furthermore, the decrease in heart rate was due to an increase in parasympathetic tone, and that the increases in HRV were more prominent in older subjects.

Iellamo et al. [165] explored the potential benefits of exercise training (n=45, age = 59.4 $\pm$ 7.8 years) on baroreflex sensitivity compared to a non-training group (n=41, age = 58.5 $\pm$ 7.3 years), all with documented coronary artery disease (with or without a previous myocardial infarction). All subjects resided at a rehabilitation center for a period of 3 weeks and performed calisthenics and walking as part of their daily activities

(2 times/day). All patients underwent a symptom-limited cycle ergometer exercise test (20 watts/minute) with gas exchange. Heart rate variability (HRV) was measured via electrocardiography in a supine position for 10 to 15 minutes. The patients were studied in the morning $\geq$ 2 hours after breakfast. HRV was measured in the time domain using the standard deviation of the mean RR intervals (SDNN). The exercise program consisted of two daily sessions of calisthenics combined with 30 minutes of stationary cycling for 2 weeks (total of 24 sessions). Subjects in the training program exercised at 75% to 85% of their maximal heart rate. Subjects in the non-training group continued their daily regimen of walking and calisthenics. There were no significant differences in any variable between the training and non-training groups. After 2 weeks of exercise, the training group displayed a significant increase in HRV, measured as SDRR (18.7 $\pm$ 1.4 ms to 23.6 $\pm$ 1.6 ms; $P < 0.01$) compared to the non-training group. In addition, the mean RR interval, measured in milliseconds, was also significantly improved in the training group (792. 0 $\pm$ 15.5 to 851.3 $\pm$ 20.5 ms; $P < 0.001$). No significant changes occurred in non-training patients. The increase in RRSD was significant in patients either with or without a previous MI. The authors concluded that exercise training increases heart rate variability in patients with coronary artery disease. Furthermore, improved cardiac autonomic function might add to the other benefits of exercise training in secondary prevention of ischemic heart disease.

Pardo et al.[166] concluded that exercise conditioning improves HRV in cardiac patients, particularly in patients who achieve a threshold of > 1.5 training METS increase over a 12-week period. They prospectively studied 20 cardiac patients enrolled in a Phase 2 12-week cardiac rehabilitation program following a recent cardiac event. The

patients underwent 24-hr holter monitoring at program entry and 12 weeks later. HRV analysis was assessed for both time domain and spectral analysis. Overall, 15 of 20 patients demonstrated increased total and high-frequency power, and mean high-frequency power was significantly increased (P = 0.05). When stratified according to the magnitude of exercise conditioning, patients achieving an increase of > 1.5 training METS demonstrated significant increases in SDNN, SDANN index, SDNN index, pNN50, total power, and high-frequency power (all $p < 0.05$).

OBSTRUCTIVE SLEEP APNEA AND EXERCISE

There is a striking paucity of research data on exercise in the OSA patient. A search of the published literature yielded eight studies with high relevance to exercise issues in OSA patients. Most were from European journals and only the abstracts are available in English [38, 44, 167]. One of these studies employed exercise testing to differentiate the OSA patient from those with obesity-hypoventilation syndrome (OHS), demonstrating that only the OHS patients exhibited hypercapnia during exercise [43]. Fourteen patients (12 males, 2 females) with OHS (53.2 $\pm$ 9.5 years, BMI: 41.7 $\pm$ 9.6 kg/m2, PCO2: 50.7 $\pm$ 4.5 mmHg) and 28 patients (27 males, 1 female) with severe OSA (54.5 $\pm$ 8.3 years, BMI: 35.7 $\pm$ 4.9 kg/m2, PCO2: 37.3 $\pm$ 3.3 mmHg) completed a 4 minute cycle ergometer exercise test at baseline and after 3 months of positive pressure ventilation (PPV). Compared to the OSA group the load tolerance of the OHS group was lower (112 $\pm$ 20 watts versus 81 $\pm$ 26 watts, $P < 0.0001$). Furthermore, the OHS group demonstrated an exercise induced increase in $PaCO_2$ from minute 1 to minute 4 both

before (50.7 to 56.6 mmHg) and after PPV treatment (39.1 to 45.6 mmHg), while the OSA group did not show display did not.

Schafer et al. [41] studied blood gas and exercise test responses in 13 patients (9 male, 4 female; age = 57 years; BMI = 44.4; RDI = 44.4) who failed to respond to nCPAP in a 15-month period. These patients were compared to an age- and RDI-matched control group successfully treated by CPAP. Despite similar RDI scores, there were significant differences in BMI (44.2 $\pm$ 7.7 vs. 31.2 $\pm$ kg/m^2); nocturnal SaO_2 ($P < 0.0001$); and time spent below 90% oxygen saturation level ($P < 0.0001$). At baseline, the failure group was hypercapnic and hypoxemic compared to controls at rest and after 4 minutes of steady state exercise at 50 watts (Resting: failure group PaO_2 = 58.5 mmHg, $PaCO_2$ = 44.7 mmHg; control group PaO_2 = 71.3 mmHg, $PaCO_2$ = 38.3 mmHg, Exercise: failure group PaO_2 = 68.7 mmHg, $PaCO_2$ = 47.3 mmHg; control group PaO_2 = 86.4 mmHg, $PaCO_2$ = 36.9 mmHg) ($P < 0.05$). After 3 months of treatment with BIPAP, the patients blood gas values while awake improved significantly ($P < 0.05$). The authors concluded that BIPAP is adequate for nocturnal ventilation, and improves awake blood gas values.

Another study by Levy et al. [39] measured ejection fraction and myocardial perfusion in a small group of OSA and chronic obstructive pulmonary disease (COPD) patients, comparing their responses during sleep, daytime wakeful resting conditions, and maximal exercise. In that study, both OSA and chronic obstructive pulmonary disease patients exhibited similar cardiac functional changes during REM sleep and maximal exercise that might increase risk of cardiac mortality in these two diagnoses [39].

Aguillard et al. [168] utilized exercise testing as an objective measure of fatigue and related the results to subjective measures of fatigue (Fatigue Severity Scale, FSS) and objective measures of sleepiness (multiple sleep latency test, MSLT) in 32 OSA patients (27 males, 5 females; age = 47.1; BMI = 35.2 $\pm$ 7.2; RDI = 53.1 $\pm$ 34.2). Maximal oxygen uptake (VO_{2max}) during the cycle ergometer test was used as the criterion measure of fatigue. Patients achieved 91% of age-predicted VO_{2max}. While no significant relationship appeared to exist between VO_{2max} and RDI, FSS, or MSLT score, patients who spent a greater percentage of total sleep time (TST) in rapid eye movement (REM) sleep, tended to have higher functional capacities (R^2 = 0.19; $P < 0.05$). However, neither VO_{2max} nor maximal heart rate (HR_{max}) were related to objective measures of fatigue, i.e. RDI or MSLT scores.

Vanuxem et al. [46] reported that OSA patients (n = 11) do have lower maximal oxygen uptakes (26.4 $\pm$ 1.2 $ml \bullet kg^{-1} \bullet min^{-1}$ vs. 33.2 $\pm$ 1.4 $ml \bullet kg^{-1} \bullet min^{-1}$; $P < 0.05$) as assessed by cycle ergometry compared to nine apparently healthy controls matched for age and BMI. Resting systolic blood pressure (SBP: 143 $\pm$ 4/ mmHg vs. 132 $\pm$ 3 mmHg; $P < 0.05$) and diastolic blood pressure (DBP: 99 $\pm$ 4 mmHg vs. 83 $\pm$ 3 mmHg; $P < 0.05$) were significantly higher in the OSA group compared to controls. While peak SBP was similar for both groups, the OSA patients reached a significantly higher peak DBP (104 $\pm$ 5 mmHg vs. 92 $\pm$ 4 mmHg; $P < 0.05$). These investigators also found the OSA patients to have low peak blood lactate levels and delayed lactate elimination post-exercise, suggesting impaired glycolytic and oxidative muscle metabolism that may be implicitly related to this disorder. These studies on the acute effects of exercise in OSA patients help characterize the nature of cardiovascular stress attendant to the disorder. These

studies also lend support to the notion that OSA is associated with a lower than normal functional capacity and metabolic responses that may partly explain self-reports of patients that sustained exercise is unusually fatiguing.

In general, the published research indicates that nCPAP treatment is associated with improved exercise capacity [37, 38, 44]. Taguci et al. [44] showed that OSA patients (n = 6; 44.7 $\pm$ 13.7 yrs; BMI = 29.9 $\pm$ 2.3 kg/m^2; RDI = 62.5 $\pm$ 8.6) improved their maximal oxygen uptakes by 15.4% after only 7 days of nCPAP therapy, but no improvement in heart rates during submaximal exercise. The researchers speculated that the improvements in VO_{2max} might be attributed to an improved ventilatory response to exercise-induced increase in circulating carbon dioxide, secondary to nCPAP treatment. However, the most plausible explanation might be increased motivation.

In another study, Konnermann et al. [38], using cycle ergometry, evaluated the effectiveness of a 6-month trial of nCPAP therapy in a group of 30 OSA patients. They interpreted their findings by calculating a "cardiovascular efficiency" index for exercise, i.e. by calculating ratios of heart rate or blood pressures at the 100-Watt workload divided by the corresponding value for these measures, taken the resting state before exercise. After 6 months of nCPAP therapy, the patients' exercise heart rate and systolic blood pressure ratios indicated 15-20% greater efficiency. The improvements in exercise efficiency reported by the Konnermann et al. [38] coincided with a 44.5% improvement in self-reports of "well-being". They showed that heart rates in steady-state exercise were reduced in OSA patients as early as 2 weeks after starting nCPAP treatment. Their patient's work rate at maximal effort also improved by 27.5% after the nCPAP treatment period.

Shifflett et al. [169] documented an improvement in the cardiovascular response to moderately vigorous aerobic exercise after 4 wk of nCPAP treatment. These findings were consistent with those of the Konnerman group[26] in Europe, which showed that heart rates in steady-state exercise were reduced in OSA patients as early as 2 wk after starting PAP treatment. The evidence from these few studies on selected OSA patients undergoing successful nCPAP treatment shows a consistent pattern of reduced cardiovascular and perceptual demand of submaximal aerobic exercise and increases in maximal exercise tolerance.

In one of the few studies that evaluated the effects of exercise on OSA symptoms and disease severity, Netzer et al. [33], trained 11 patients 2 hr/session, 2 sessions/wk, for 6 months. They reported significant reductions in the respiratory distress index (RDI) by polysomnography after training, but did not find any improvements in polysomnography indicators of sleep efficiency and SaO_2. Unfortunately, the investigators did not report several key variables, i.e. training program regimen, changes in functional capacity, nCPAP compliance, nor did they speculate whether the improvements in RDI were attributed to nCPAP treatment, weight loss, or the exercise training program.

Norman et al. [34] investigated the effects of a 6-month aerobic conditioning program on measures of aerobic capacity, daytime sleepiness, quality of life, and number of apneic episodes. In this study of 9 obese adult OSA patients, patients reported enhanced feelings of energy and physical vigor, lessened self-reports of daytime fatigue, decreased weight, and even showed improved sleep function when evaluated by nighttime polysomnography. However, there were many confounding variables in this study that make data interpretation difficult, i.e. 4 of 9 subjects had mild-moderate

pulmonary disease. Furthermore, over half the subjects (5) were currently using nCPAP. Obviously, more investigation is needed with regards to exercise as a potential adjunctive therapeutic tool in the treatment of obstructive sleep apnea.

In another study, Giebelhaus et al. [35] determined that an exercise training regimen consisting of alternating aerobic exercise with resistance training is safe in the management of sleep apnea, despite an improvement in functional capacity. Eleven patients (age = 52.2 yrs; BMI = 27.5 kg/m^2, RDI = 32.8) were treated $\geq$ 3 months with nCPAP before beginning the exercise program. The authors believed this approach would isolate the exercise effect. Patients exercised 2 days/wk; the first day consisted of a 2-hour aerobic session, i.e. jogging, games, and gymnastics; the second day consisted of a 2-hour power exercise program, i.e. light weight lifting. Results showed no significant change in body weight (79.7 kg pre-training; 80.4 kg post-training), however there was a 28% decrease in RDI post-training (32.8 events/hr pre-training; 23.6 events/hr post-training; $P < 0.05$). This study demonstrates the potential effectiveness of low-moderate exercise as an adjunctive therapy in the treatment of obstructive sleep apnea.

SUMMARY

Obstructive sleep apnea is a serious disorder that has gained increasing amounts of attention over recent years. Limited public appreciation and acceptance of this disorder as a valid health concern reduces the number of individuals who seek medical evaluation. In the healthcare community, standards and criteria for diagnosis of OSA are still evolving and randomized trials are needed to clearly establish the long-term efficacy of alternative medical and surgical interventions. It is now known that OSA predisposes

individuals to increased cardiovascular morbidity and mortality and this increased risk is exacerbated by factors of age, body mass index (BMI), hypertension, and a respiratory disturbance index. Early detection and treatment are critical in slowing and possibly preventing the progression of this disorder and its related co-morbidities. While conventional treatments such as surgery and nasal continuous positive airway pressure are beneficial and can help lessen the severity of symptoms associated with OSA, they are expensive, not available to everyone and are sometimes not well tolerated. A physically active lifestyle, when used as an adjunct to surgery or nCPAP, can provide key health benefits for many of the comorbidities related to OSA and may help to lessen the severity of OSA-related symptoms. The available research suggests that nCPAP treatment alone may improve daytime cardiovascular hemodynamics and exercise tolerance. Unfortunately, information on exercise tolerance of OSA patients in notably limited in the published literature, as is the potential for physical activity in the long-term management of OSA. Exercise testing may add new and meaningful data in assessing OSA disease severity and treatment outcomes following intervention with nCPAP or surgery. Furthermore, exercise training may have the potential to prevent development of more severe OSA and slow the rate of development of other frequent co-morbid conditions. Further research is needed on the potential benefits of a physically active lifestyle in the treatment and potentially the prevention of obstructive sleep apnea.

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Daytime Cardiovascular Function in Obstructive Sleep Apnea Patients

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ABSTRACT

PURPOSE: The purpose of this study was to explore the relationships between polysomnography (PSG) markers of sleep function and OSA disease severity and resting daytime measures of cardiovascular function in patients diagnosed with obstructive sleep apnea (OSA). **METHODS**: Eleven newly diagnosed patients [5 male, 6 female; age = 46.5 $\pm$ 12.0 yrs; respiratory disturbance index (RDI) = 30.2 $\pm$ 15.0] and 10 apparently healthy control subjects (4 male, 6 female; age = 39.8 $\pm$ 6.9 yrs) completed daytime resting measurements of heart rate variability (HRV); blood pressure (BP); and non-invasive cardiac output (Qc). Stroke volume (SV) and total peripheral resistance (TPR) were estimated from Qc measurements. Pearson product moment correlations were calculated between PSG markers of sleep function [stage 1; stage 2; slow wave sleep (SWS); rapid eye movement (REM) sleep]; and OSA disease severity [RDI; percent time less than 90% arterial oxygen saturation; and lowest arterial oxygen saturation] and daytime HRV, BP, Qc, SV, and TPR. Independent *t* tests were used to analyze differences between OSA patients and controls. **RESULTS**: No significant results were noted between PSG markers of sleep function or disease severity and daytime measures of HRV, Qc, SV, and TPR. Correlation analysis revealed that stage 1 sleep was significantly related to daytime systolic blood pressure (SBP; $r = 0.69$; $P < 0.05$) and mean arterial pressure (MAP; $r = 0.72$; $P < 0.05$). A significant correlation also was found between stage 2 sleep and morning SBP ($r = 0.70$; $P < 0.05$). Furthermore, daytime DBP and MAP were significantly different between OSA patients and controls ($P = 0.02$ and 0.01, respectively). **CONCLUSIONS**: Several trends in daytime measures of HRV and BP were noted in this study. While not statistically significant, these measures, along with measures of central and peripheral cardiovascular function, i.e. cardiac output and total peripheral resistance, warrant further investigation.

Key Words: autonomic nervous system; sleep apnea; heart rate variability; blood pressure; sympathetic nervous system, cardiac output, total peripheral resistance

INTRODUCTION

Obstructive sleep apnea (OSA) predisposes individuals to increased cardiovascular morbidity and mortality and this increased risk is exacerbated by factors of age, body mass index (BMI), hypertension, and a high respiratory disturbance index (RDI) as determined through overnight polysomnography (PSG) [1, 2]. Moreover, data from the Wisconsin Sleep cohort study have shown a consistent relationship between even mild degrees of sleep-disordered breathing and hypertension [3, 4]. Unfortunately, the mechanisms underlying the association between OSA and cardiovascular disease are not known. Sympathetic nervous system activity is elevated in OSA patients [5, 6] which may suggest that altered cardiovascular autonomic regulation is implicated. This increased sympathetic activity in OSA patients during sleep has been proposed to spillover into daytime hours and remain elevated when breathing patterns are normal and no evidence of hypoxia or hypercapnia is evident [5-8]. Furthermore, previous research has shown that repetitive surges in blood pressure during sleep and increased sympathetic drive during wakefulness may decrease baroreflex sensitivity and/or alter the baroreflex set point to higher levels of pressure [9, 10].

For several years, heart rate variability (HRV) analysis has been utilized as a noninvasive technique for assessment of cardiovascular autonomic control [11, 12]. New evidence in the medical literature indicates that HRV is also altered in patients with sleep-disordered breathing. This alteration is evident even in the absence of hypertension, heart failure, or other disease states [7]. Previous research has shown distinctly abnormal patterns of variability during sleep in patients with OSA [13-15]. However, Roche et al. [16] concluded that differences between night and day values of selected time-domain HRV

measures are more powerful predictors than night values obtained separately. Nocturnal polysomnography (PSG) remains the gold standard for grading the severity of sleep-disordered breathing. However, information concerning daytime patterns only of HRV and blood pressure may provide unique information regarding sleep function and disease severity independent of measures obtained during a 24-hr period? To date, few studies have examined daytime measures of cardiovascular function in awake, otherwise healthy patients with OSA compared with matched control subjects [7]. Therefore, the objective of this study was to explore the relationships between PSG markers of sleep function and OSA disease severity and resting daytime measures of cardiovascular function including HRV and blood pressure (BP). Measures of cardiovascular function then were compared with those obtained in normal control subjects closely matched for age and body mass index (BMI).

METHODS

Subjects. Eleven subjects (5 male, 6 female) were recruited from a group of volunteers referred for overnight polysomnography (PSG) to the Sleep Disorders Network of Southwest Virginia, Christiansburg, VA, between August 2001 and May 2002. Two subjects were diagnosed with mild (RDI = 5-14); 4 with moderate (RDI = 15-29); and 5 with severe OSA (RDI $\geq$ 30). The Institutional Review Board of Virginia Polytechnic Institute and State University approved the study and each subject gave informed consent before participating. Medical records were reviewed to exclude candidates with the following physician-diagnosed conditions: history of cardiovascular or pulmonary disease; history of metabolic or endocrine disorders; current use of anti-hypertensive

medication or severe hypertension; current smoking or use of sedatives and/or muscle relaxants; orthopedic, musculoskeletal, or a recent history (< 6 months) of regular participation in moderately vigorous physical activity. At baseline, each OSA patient completed a health history questionnaire, standardized sleep questionnaire (Epworth Sleepiness Scale, ESS)[17] and overnight polysomnography study (PSG) from which a diagnosis of OSA was made. Conventional techniques were employed when performing the PSG studies and included, electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). The monitoring period also included the evaluation of respiratory effort, airflow, oxygen saturation, and body position and movements. Baseline characteristics and PSG data for all sleep apnea subjects are reported in Table 1.

In addition, 10 apparently healthy subjects (4 male, 6 female) matched for age and body mass index (BMI) were recruited to serve as controls. Suspicion for sleep-disordered breathing was diminished in control subjects via a health history questionnaire, standardized sleep questionnaire (ESS), sleep-related symptom review, and clearance to participate from their primary care physician. Subjects answered questions related to snoring and apnea history, witnessed snoring, sleep quality, and daytime sleepiness; none reporting a history of nocturnal gasping, apnea or witnessed apnea (by bedpartner). None of the control subjects report symptoms of excessive daytime sleepiness. Despite some of the subjects reporting infrequent snoring, all control subjects reported that their sleep was refreshing. Control subject characteristics are listed in Table 2. In an attempt to account for job-related physical and emotional stressors, all subjects were asked to subjectively rate their physical and emotional demands for the

measurement day (Table 3). In addition, the job-specific estimated metabolic cost was evaluated for both OSA subjects and controls [18].

Heart Rate Variability Analysis and Procedures. Heart rate variability was assessed from precise (+/- 1 ms) heart rate records of 8-hour waking periods using a small battery powered single-lead ECG recorder (Polar R-R Recorder™, Polar Electro, Kempele, Finland). Only time domain measures of HRV were analyzed for this study since standard spectral measures, i.e. low and high frequency power and the ratio of low frequency to high frequency power (LF: HF ratio), can be confounded by unstable breathing patterns [19]. All measures were calculated for the daytime period, i.e. 9:00 AM to 5:00 PM. Subjects were instructed to wear the device shortly after awakening in the morning and to wear it for a period of approximately 8 to 10 hours. In addition, subjects were asked to refrain from moderate-to-vigorous physical activity and avoid alcoholic and caffeinated beverages a minimum of 24-hr prior to data collection. A subset of the total number of cardiac cycles recorded (~ 36,000 beats) was used in the final analyses. To standardize which subset to evaluate, it was decided to analyze those cardiac cycles obtained 30 minutes after the device started recording. To evaluate circadian rhythm patterns for HRV, measurement periods were further defined as follows (~ 9,000 beats/period): morning; noon; afternoon; and evening. The following measures were calculated after manually filtering data for ECG artifact, non-physiologic readings and extrasystoles: mean R-R interval; standard deviation of all normal R-R intervals (SDNN); and the percentage of beat-to-beat variation greater than 50 milliseconds (pNN50).

Daytime Blood Pressure Measurement and Procedures. Recordings of daytime blood pressure were obtained using an automated digital blood pressure device (Omron HEM-

705CP). Following the manufacturer's instructions, multiple recordings were taken upon awakening in the morning; noon; afternoon; and evening. Subjects were instructed to obtain recordings in a seated position after a 5-min rest period and to abstain from caffeine and nicotine products and refrain from vigorous physical activity for a minimum of 12- and 24-hr, respectively prior to taking measurements. A minimum of 2 measurements were taken at each specified time until two systolic blood pressure measurements were recorded that were $\leq$ 6 mmHg apart. Systolic (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) were evaluated at each of the four time periods. In addition, an overall mean (SBP, DBP, MAP) was calculated for the entire day.

Data Analyses. Data were analyzed using SPSS statistical software (SPSS Inc., Version 10.0, Chicago, IL). Pearson *r* correlation coefficients were calculated to explore relationships between polysomnographic markers of sleep function including total sleep time (TST), Stage 1 and Stage 2 sleep, slow wave sleep (SWS), rapid eye movement (REM) sleep, respiratory disturbance index (RDI), lowest SaO_2 during sleep, percent of TST below 90% SaO_2 and HRV measures (mean RR interval, SDNN, and pNN50). Furthermore, correlations were calculated to examine relationships between PSG markers of sleep function and resting daytime measures of blood pressure (SBP, DBP, MAP). Independent samples *t* tests were used to explore differences between OSA patients and control subjects concerning daytime measures of HRV and blood pressure. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Subject characteristics. Descriptive and PSG characteristics for the 11 OSA patients (5 male, 6 female) who participated in the study are presented in Table 1. Mean descriptive characteristics for the 10 control subjects (4 males, 6 females) are presented in Table 2. Utilization of multiple exclusion criteria in this study limited the size of the sample that could be recruited. OSA patients exhibited significantly larger neck (P = 0.04) and waist (P = 0.02) circumferences compared to controls and scored higher on the Epworth Sleepiness Scale questionnaire (P = 0.002). No significant differences were noted for age or BMI between the two groups. However, OSA patients weighed significantly more than controls (P = 0.01). Furthermore, the OSA patients and controls reported similar physical (mean = 2.0 and 2.3, respectively) and emotional (mean = 2.0 for both groups) demands during the measurement period (Table 3). The job-specific estimated metabolic cost for OSA patients and controls were also similar (1.9 and 1.8 METS, respectively).

Heart Rate Variability. For one OSA patient, technical difficulties with the equipment resulted in a loss of data. Therefore, this subject was excluded from all HRV analyses (N = 10). No statistically significant relationships were found between time domain measures of HRV (mean RR interval, SDNN, pNN50) and PSG markers of sleep function or disease severity (Figures 1-3). Furthermore, no significant correlations were noted between PSG markers of sleep function and disease severity even after HRV measures were divided into daytime components (morning, noon, afternoon, and evening). Independent *t* tests revealed no significant differences in mean RR interval, SDNN, or pNN50 between OSA patients and controls when averaged over the entire day.

Daytime Blood Pressure. None of the subjects had a clinical diagnosis of hypertension, nor were any taking anti-hypertensive medications. For one OSA subject, evening BP, DBP, and MAP were not obtained. For evening blood pressure analyses, only 10 subjects were analyzed. Correlation analyses between PSG markers of sleep function and disease severity and daytime measures of blood pressure are presented in Table 4. No statistically significant relationships were found between average daytime SBP, DBP, or MAP and PSG markers of sleep function or disease severity ($P > 0.05$). When divided into daytime components, stage 1 sleep was significantly related to morning SBP and MAP; noon SBP and MAP; afternoon SBP and MAP; and evening SBP (Table 4). Furthermore, afternoon DBP was significantly related to RDI. Independent *t* tests revealed that average daytime SBP was higher in OSA patients compared to controls ($P = 0.06$). In addition, OSA patients exhibited significantly higher DBP ($P = 0.02$) and MAP ($P = 0.01$) compared to controls. Furthermore, after separating BP measures into daytime components, OSA patients displayed significantly higher SBP readings later in the later hours of the day (Figure 4). Figure 5 displays similar results for DBP in the morning, afternoon, and evening periods. Significant differences were also seen overall MAP in the afternoon and evening periods (Figure 6).

DISCUSSION

The goal of this ongoing clinical study was to recruit ~ 45 subjects with a diagnosis of OSA and match them to ~ 20 control subjects. However, the use of multiple exclusion criteria in this study, i.e. comorbidities, cardiovascular medications, and physical activity habits limited the size of the sample that could be recruited. In the time

under consideration here, these findings indicate significant relationships between measures of sleep function and daytime blood pressure in patients diagnosed with obstructive sleep apnea. In addition, significant differences were noted between OSA patients and controls for resting BP measured throughout the day. Further investigation is needed before definitive conclusions can be made regarding these relationships and others. However, trends noted in certain measures, i.e. HRV, make discussion of them here relevant and potentially useful for future research. Multiple tables and figures are used clarify these trends.

Relationships Between Sleep Function and Disease Severity and Daytime Measures of HRV and Blood Pressure. The normal healthy adult spends an average of 2-5% of total sleep time (TST) in stage 1 sleep; 45-55% in stage 2 sleep; 3-15% in SWS; and 20-25% in REM sleep. OSA patients in this study spent more time in stage 1 and 2 sleep and less time in REM sleep compared to normals (Table 1). Indirectly, this may indicate sleep fragmentation. Furthermore, our results suggest a direct association between stage 1 and stage 2 sleep duration and daytime blood pressure (Table 4). Previous research has shown that hypertension can be directly attributed to the repeated and partial apneic events that disrupt autonomic cardiovascular reflexes during sleep [21-24]. Several factors may contribute to this relationship, including repetitive episodes of hypoxia and arousals resulting in increased sympathetic nervous system activity [25]. With each disturbance in sleep during a given night, OSA patients regress to an earlier sleep stage or awaken completely. Therefore, they have a more difficult time reaching and maintaining deeper levels of sleep. While a direct causal link between OSA and hypertension has not been established, a relationship between the number of arousals and blood pressure is well

documented [26-29]. Although BP was significantly different between patients and controls, the OSA patients were not hypertensive. Further investigation is needed in this area, including the collection of more data sets.

Heart Rate Variability. Heart rate variability was analyzed between OSA patients and controls to evaluate variations in autonomic activity during the daytime period. Time domain measures of HRV, including mean RR interval, SDNN, and pNN50, were not significantly related to PSG markers of sleep function or disease severity. Furthermore, HRV was not significantly different between OSA patients and controls. However, several unique circadian patterns were noted between OSA patients and controls when HRV measures were separated into daytime periods (Figures 1 and 2). Surprisingly, OSA patients had *lower* resting HR's throughout the day (except for PM) and displayed greater variability as determined by the mean SDNN scores (Figures 1 and 2, respectively). These results contrast data reported by Narkiewicz et al. [7] and may be attributed to several differences including HRV analysis technique, sample size, OSA disease severity, occupation, and physical fitness. Furthermore, distinct patterns of HRV measures exist during the day and may be independent of measures obtained during a 24-hr recording period. While it is generally considered inappropriate to compare time domain measures of HRV obtained from recordings of different durations [19], comparisons made here are fitting to potentially help explain differences in HRV patterns when measurements are obtained during different times of day as well as for different durations. The most notable difference between this study and that of the Narkiewicz group [7] was the measurement duration. Previous research has shown that repetitive apneas during sleep result in distinct alterations in both blood pressure and heart rate [13-15]

and ultimately affect measurements of blood pressure and heart rate variability [6]. Narkiewicz et al. [7] analyzed short-term time domain measures of HRV in the morning *or* early afternoon. Data was collected during 10 minutes of awake, undisturbed supine rest in patients with mild OSA (age = 45 $\pm$ 10 yrs; BMI = 32.0 $\pm$ 5 kg/m^2; RDI < 20), moderate-severe OSA (age = 40 $\pm$ 9 yrs; BMI = 36.0 $\pm$ 7 kg/m^2; RDI > 20) and controls (age = 41 $\pm$ 9 yrs; BMI = 33.0 $\pm$ 7 kg/m^2). Narkiewicz et al. [7] reported that patients with moderate-to-severe OSA had shorter RR intervals (793 $\pm$ 27 ms; average HR =76 bt/min) compared with control subjects (947 $\pm$ 42 ms; average HR = 63 bt/min; P = 0.008). In our study, controls exhibited higher resting heart rates compared to OSA patients (Figure 1). However, the average heart rates for each daytime period in the OSA patients (range = 87 bt/min to 90 bt/min) were higher than those reported by Narkiewicz et al [7]. Our findings suggest that time domain HRV measures may be dependent on duration of the collection period and time of day. These results further demonstrate that durations of recordings used to determine time domain values of HRV should be standardized.

Daytime Blood Pressure. In this sample of 11 OSA patients and 10 controls, significant differences were noted between groups regarding several daytime measures of systolic, diastolic and mean arterial blood pressure (Figures 3-5). These differences were most notable in the afternoon and evening hours, which might suggest augmented sympathetic activity that persists later into the day. Over time, this enhanced sympathetic activity, secondary to repeated BP surges, might result in impaired baroreceptor sensitivity [6]. Studies have shown that OSA patients exhibit increased sympathetic activity during the day [5, 30]. Furthermore, these fluctuations in sympathetic nervous system activity may be involved in the pathogenesis of hypertension. Apneic events during sleep result in

decreased blood oxygen levels and increased carbon dioxide retention, both of which cause increased sympathetic nerve activity resulting in elevations in blood pressure. The few published studies on 24-hr BP profiles in patients with OSA report elevated BP during wakefulness and sleep [27] and disturbances of the circadian BP rhythm, primarily through an absence or a reduced drop in nocturnal BP [31-33]. Pankow et al. [34] utilized 24-hr BP recording made at 15-min intervals in 93 patients (87 male, 6 female) suspected of sleep apnea. The evaluation of sleep-disordered breathing was made with a portable monitoring device that provided an oxygen desaturation index (ODI) score. ODI score (mean = 26 $\pm$ 21 events/hr; range 0 to 71 events/hr), when used as a marker of disease severity, was significantly related to systolic BP (r = 0.42; P < 0.001) and diastolic BP (r = 0.40; P < 0.001). Furthermore, Lavie et al. [32] found that 24-hr measures of SBP, DBP, and MAP in sleep apnea patients were significantly related to disease severity in 38 male OSA patients (age = 45 $\pm$ 7.8 yrs; BMI = 29.6 $\pm$ 4.4 kg/m^2). In this study, only afternoon DBP was significantly related to RDI (Table 3). Our study is unique in that we isolated measurements to distinct time periods during the waking hours, instead of averaging the entire recording duration. Therefore, variability characteristics are not confounded by fluctuations in heart and blood pressure, secondary to apneic events or arousal. Furthermore, HRV is not influenced by circadian changes. In addition, we avoided the so-called "white coat effect" by having patients obtain the measurements themselves. The late afternoon/evening trends noted in this study might be an indication of enhanced sympathetic activation and future hypertension. However, despite significant differences noted between OSA patients and controls, mean systolic and diastolic blood pressures

were not clinically elevated to warrant a diagnosis of hypertension or alter the course of treatment beyond nasal CPAP.

CONCLUSIONS

The strengths of this study include the following: (1) OSA patients were newly diagnosed and untreated; (2) control subjects and OSA patients were matched for age and BMI, thus ruling out any potential confounding influences of these variables; (3) all participants were normotensive and on no medications; (4) HRV and blood pressure measurements obtained during the day in the absence of apnea and hypoxia. Potential limitations include the absence of PSG data for control subjects to definitively rule out any type of sleep-related breathing disorder. However, several steps were taken to reduce this likelihood including physician referral, standardized questionnaires, and a sleep-related symptom review. In addition, we were unable to make comparisons between OSA patients and controls concerning select indicators of sleep function. The study's sample size was small relative to the number of variables measured. However, subject recruitment is ongoing. Meals and daytime activities were not controlled for while HRV measurements and blood pressure recordings were obtained. However, each participant was instructed to abstain from alcoholic and caffeinated beverages 24 hours prior to the data collection period and to rate their perceived physical and emotional demand for that day.

In conclusion, distinct daytime patterns in HRV and blood pressure may exist, independent of measures obtained over 24 hours. The results of this study should be interpreted cautiously. Although several significant relationships were noted between

stage 1 and stage 2 sleep duration and measures of daytime blood pressure, we cannot definitively conclude that prolonged early stage sleep duration is associated with increases in blood pressure. First, stage 1 and stage 2 sleep duration are known to increase with age and might be related to disease severity. Second, patients who spend more time in early sleep would therefore spend less time in later sleep stages, i.e. SWS and REM sleep. In this study, no significant correlations were noted between any cardiovascular measure and REM sleep. Finally, none of the subjects in our study were hypertensive; therefore it would be impractical to assume a causal relationship between sleep stage duration and the development of hypertension. Further investigation is needed before determining the clinical significance of these results.

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Table 1. OSA Patient Characteristics and Polysomnographic Test Results (N = 11)

Variable	Mean	SD	Range
Physical Measures			
Age (years)	46.5	12.0	25 - 62
Weight (kg)	98.4	15.9	75.6 - 133.2
Waist Girth (cm)	107.1	9.5	93.2 – 121.9
BMI (kg/m^2)	32.5	6.2	25.3 – 43.5
Neck Circumference (cm)	39.1	2.1	36.5 – 44.0
Epworth (x/24)	12.6	4.0	7 – 17
PSG Measures			
RDI	30.2	15.0	10.5 – 55.1
Time in bed (min)	366.8	6.9	359.5 – 385.0
Total sleep time (min)	292.8	36.8	246.5 – 347.0
Stage 1(%)	6.7	4.2	0.5 – 16.9
Stage 2 (%)	54.2	7.9	41.2 – 69.6
Slow wave sleep (%)	18.9	9.9	1.7 – 31.6
REM (%)	13.0	6.9	0.4 – 25.7
Baseline SaO_2 (%)	96.2	1.1	94.0 – 98.0
Time $SaO_2 < 90\%$ (%)	4.4	4.4	0.0 – 10.0
Lowest SaO_2 (%)	85.0	5.9	74.0 – 92.0

Table 2. Control Subject Characteristics (N = 10)

Variable	Mean	SD	Range
Physical Measures			
Age (years)	39.8	6.9	28 - 51
Weight (kg)	80.9	12.5	58.1 – 100.0
Waist Girth (cm)	90.9	11.4	71.2 – 111.0
BMI (kg/m^2)	28.8	4.9	20.3 – 34.6
Neck Circumference (cm)	36.5	3.0	32.4 – 42.8
Epworth (x/24)	6.6	3.9	2 - 14

Table 3. Subjective Rating of Physical and Emotional Demands

Physical Demands
(Circle appropriate response)

1 – Sitting most of day and very little walking or other activity for rest of day.
2 – Sitting 2/3 of the day, with walking or other light activity 1/3 of the day.
3 – Sitting 1/3 of the day, with walking or other light physical activity 2/3 of the day.
4 – Little or no sitting during the day, with walking or other physical activities most of the day.

Emotional Demands

1 – Less stress than normal
2 – Normal amount of stress
3 – A little more than normal amount of stress
4 – Much more than normal amount of stress

Table 4. Pearson Correlation Coefficients Between Selected PSG Measures of Sleep Function and Measures of Daytime Blood Pressure

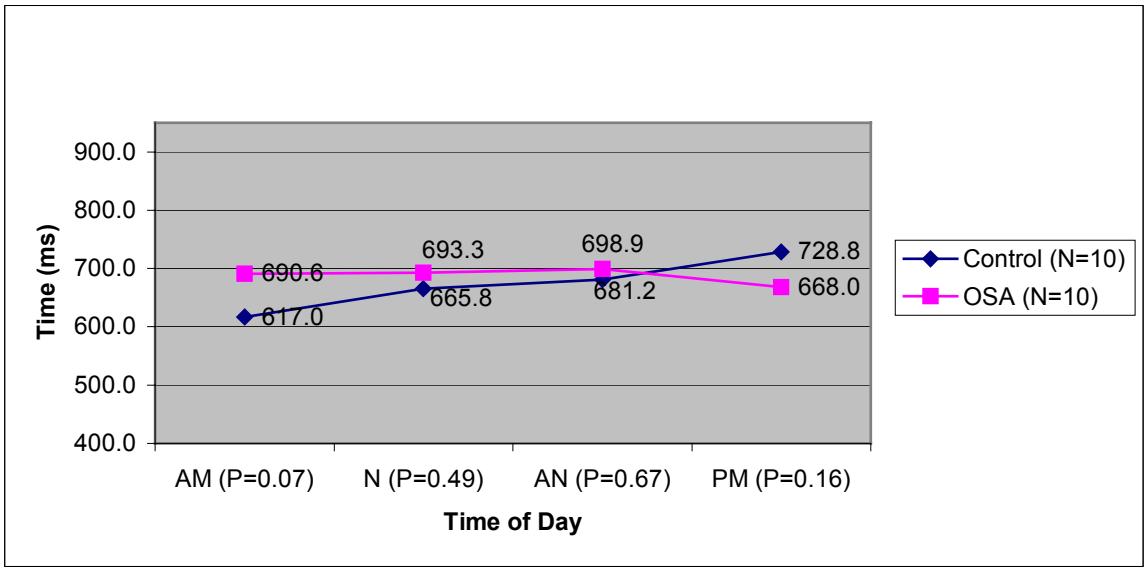
Variable	St 1	St 2	SWS	REM	RDI
Morning (AM)					
SBP	0.63*	0.46	-0.47	-0.15	-0.18
DBP	0.40	0.60	-0.22	-0.01	0.50
MAP	0.78*	0.70*	-0.45	-0.17	0.03
Noon (N)					
SBP	0.78**	0.46	-0.30	-0.32	0.08
DBP	0.39	0.49	-0.62	-0.12	0.54
MAP	0.71*	0.42	-0.17	-0.35	0.07
Afternoon (AN)					
SBP	0.64*	0.44	-0.79	-0.18	0.07
DBP	0.30	0.41	-0.13	0.08	0.65*
MAP	0.64*	0.45	-0.02	-0.10	0.29
Evening (PM)					
SBP	0.65*	0.37	-0.35	-0.16	0.13
DBP	0.18	0.29	-0.05	0.05	0.58
MAP	0.47	0.17	-0.22	0.01	0.02
Average Daytime					
SBP	0.69*	0.42	-0.30	-0.16	0.01
DBP	0.33	0.51	-0.06	-0.01	0.58
MAP	0.72*	0.52	-0.21	-0.19	0.13

Abbreviations: stage 1 sleep (St 1); stage 2 sleep (St 2); slow wave sleep (SWS); rapid eye movement sleep (REM); respiratory disturbance index (RDI); systolic blood pressure (SBP); diastolic blood pressure (DBP); mean arterial pressure (MAP)
* $P \leq 0.05$; ** $P \leq 0.01$

Table 5. Resting Cardiovascular and Hemodynamic Measures

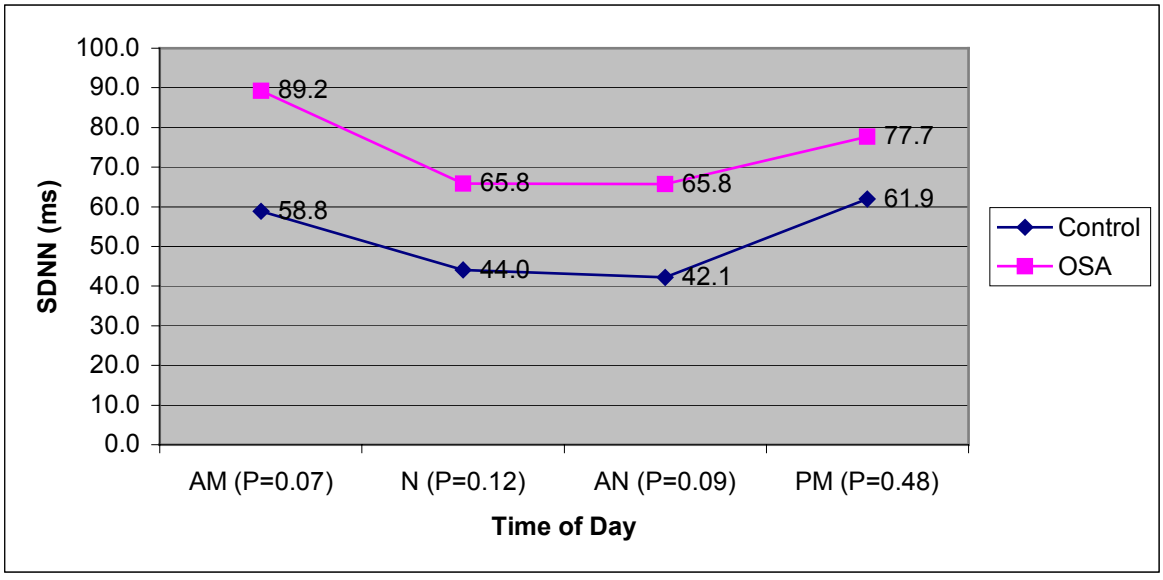
Resting Measures	Mean	SD	Range
OSA Patients (N = 8)			
Heart Rate (bt/min)	82.4	10.0	68.0 – 98.9
Blood Pressure (mmHg)			
Systolic	139.0*	12.0	118.0 – 158.0
Diastolic	91.5	8.7	78.0 – 106.0
Cardiac Index (L/min/m^2)	2.6	0.5	1.7 – 3.3
SV Index (ml/bt/m^2)	33.5	6.8	20.2 – 40.7
TPR (mmHg/L/min)	19.8	6.3	12.6 – 32.3
Control Patients (N = 10)			
Heart Rate (bt/min)	81.1	4.3	62.0 – 101.0
Blood Pressure (mmHg)			
Systolic	124.6	3.7	98.0 – 142.0
Diastolic	83.8	2.4	68.0 – 92.0
Cardiac Index (L/min/m^2)	2.6	0.1	2.1 – 3.2
SV Index (ml/bt/m^2)	32.5	2.1	22.5 – 45.0
TPR (mmHg/L/min)	19.8	0.8	16.1 – 23.1

* $P < 0.05$



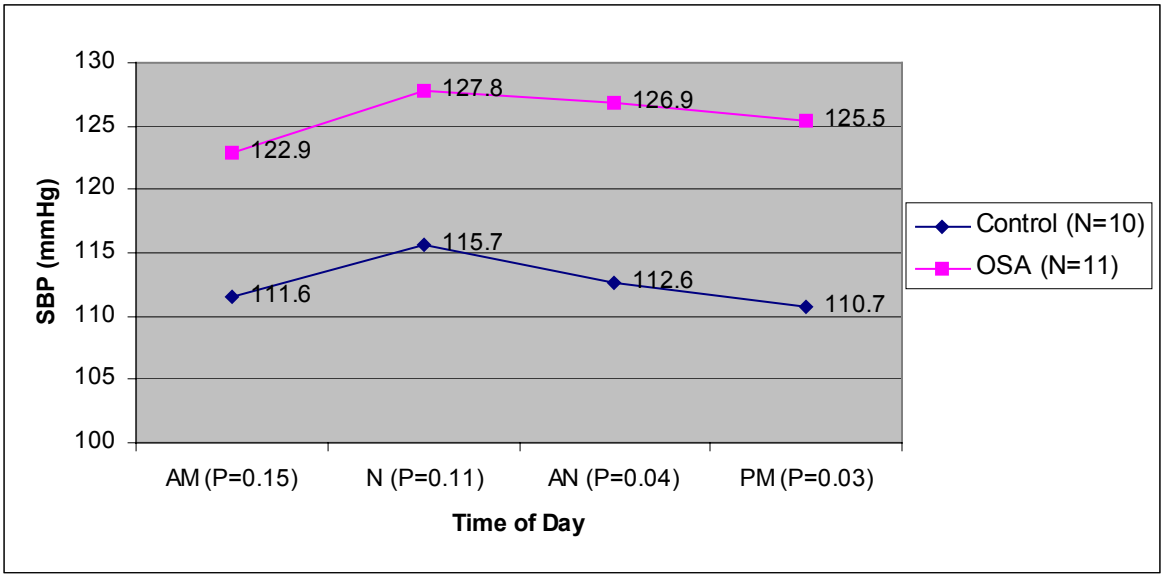
Abbreviations: AM (morning); N (noon); AN (afternoon); PM (evening).

Figure 1. OSA vs. Control: Mean RR Interval (OSA: n=10; Control: n=10)



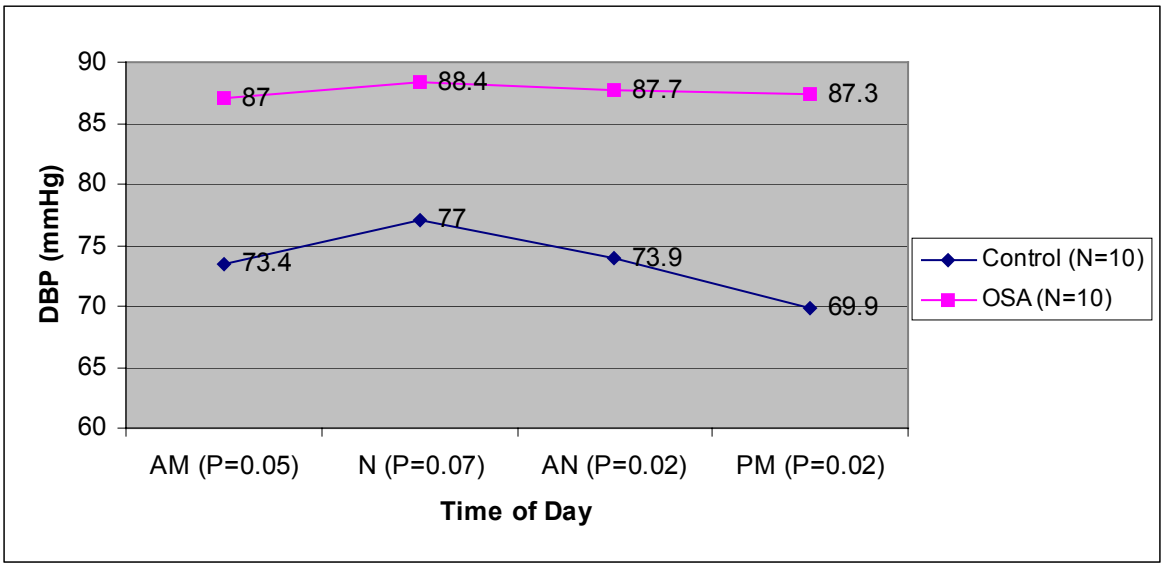
Abbreviations: AM (morning); N (noon); AN (afternoon); PM (evening).

Figure 2. OSA vs. Control: Standard Deviation of RR Intervals (SDNN)



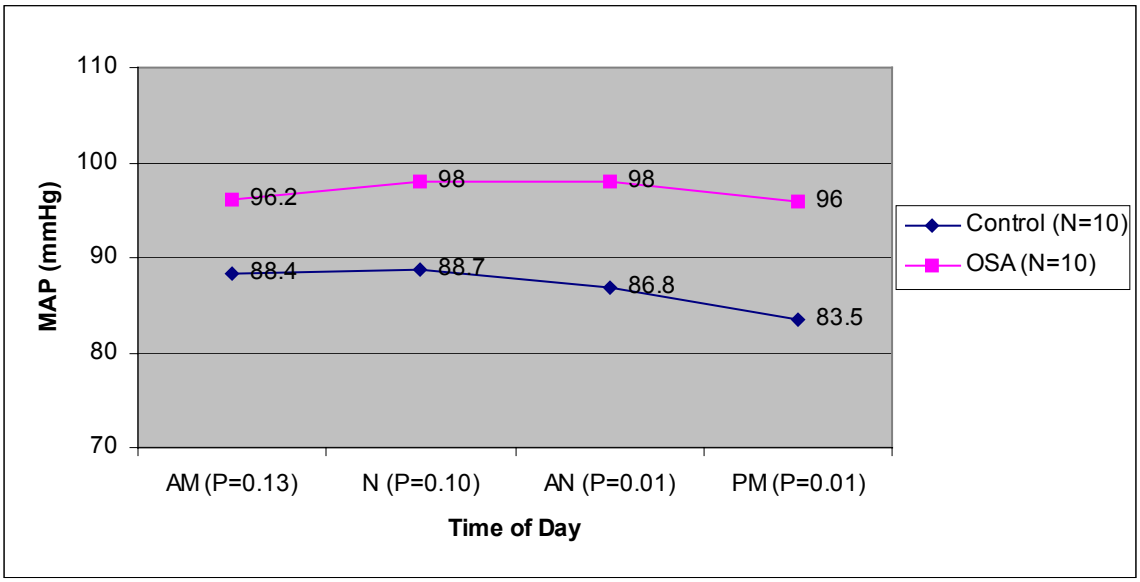
Abbreviations: SBP (systolic blood pressure); AM (morning); N (noon); AN (afternoon); PM (evening).

Figure 3. OSA vs. Control: Systolic Blood Pressure



Abbreviations: DBP (diastolic blood pressure); AM (morning); N (noon); AN (afternoon); PM (evening).

Figure 4. OSA vs. Control: Diastolic Blood Pressure



Abbreviations: MAP (mean arterial pressure); AM (morning); N (noon); AN (afternoon); PM (evening).

Figure 5. OSA vs. Control: Mean Arterial Pressure

Journal Manuscript II

The Utility of Cardiopulmonary Exercise Testing Among Patients Referred for Overnight Polysomnography

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ABSTRACT

PURPOSE: The purpose of this study was to explore relationships between these exercise response characteristics during graded exercise and polysomnography (PSG) markers of sleep function. A second objective was to address the question of whether differences exist between obstructive sleep apnea (OSA) patients and matched controls regarding these measures of cardiopulmonary function. **METHODS**: Eleven newly diagnosed patients [5 male, 6 female; age = 46.5 $\pm$ 12.0 yrs; respiratory disturbance index (RDI) = 30.2 $\pm$ 15.0] and 10 apparently healthy control subjects (4 male, 6 female; age = 39.8 $\pm$ 6.9 yrs) completed a maximal exercise test on a cycle ergometer. Measures of interest included heart rate (HR), blood pressure (BP), cardiac output (Qc), and oxygen uptake (VO_2). Stroke volume (SV) and total peripheral resistance (TPR) were estimated from Qc measurements. Pearson product moment correlations were calculated between PSG markers of sleep function [stage 1; stage 2; slow wave sleep (SWS); rapid eye movement (REM) sleep]; and OSA disease severity [RDI; percent time less than 90% arterial oxygen saturation; and lowest arterial oxygen saturation] and submaximal and peak exercise hemodynamic measures. **RESULTS**: Respiratory disturbance index (RDI) was significantly related to heart rate at 60 watts (r = -0.70; P = 0.02) and 100 watts (r = -0.69; P = 02); stage 2 sleep duration was inversely related to cardiac index at 60 (r = -0.76; P = 0.03) and 100 watts. Stage 1 sleep duration was significantly correlated with TPR at 60 watts (r = 0.70; P = 0.06) and 100 watts (r = 0.71; P = 0.05). A significant relationship was noted in the OSA group between peak HR and stage 2 sleep duration (r = -0.73; P = 0.02); and RDI (r = -0.66; P = 0.03). Relative VO_{2pk} was significantly correlated with REM sleep duration (r = 0.62; P = 0.04). **CONCLUSIONS**: Abnormalities in exercise response characteristics may exist in patients with OSA. Exercise testing may help reveal abnormalities in hemodynamic function that are not seen in a resting state.

INTRODUCTION

Obstructive sleep apnea (OSA) increasingly is being recognized as a major health concern [1]. Epidemiological studies have identified this syndrome in 2% to 4% of middle-aged adults with prevalence rates reported as high as 9% for women and 24% for men [2]. Moreover, OSA predisposes individuals to increased cardiovascular morbidity and mortality [3, 4]. The mechanisms underlying the association between OSA and cardiovascular disease are not known. Sympathetic nervous system activity is elevated in OSA patients [5, 6] which may suggest that altered cardiovascular autonomic regulation is implicated. Furthermore, previous research has shown that repetitive surges in blood pressure during sleep and increased sympathetic drive during wakefulness may impair baroreflex sensitivity [7, 8]. Overnight polysomnography (PSG) remains the gold standard in the diagnosis of sleep-disordered breathing. However, new techniques for the evaluation of OSA are rapidly developing. Despite the many advances in technology, the exercise test remains one of the most widely used diagnostic and prognostic clinical tools. It's numerous applications, widespread availability, and high yield of clinically useful information continue to make it an important gatekeeper for more expensive and invasive diagnostic procedures [9]. However, what evidence do we have about the exercise response characteristics and functional capacities of OSA patients? Unfortunately, we know very little as data related to exercise in OSA patients is sparse. A search of the published literature yielded only nine studies with relevance to physiologic aspects of exercise in the OSA patient [10-18]. Previous research has shown that OSA is associated with a reduced functional capacity and impaired metabolic responses [14], which may partly explain self-reports that sustained physical activity is unusually fatiguing.

However, no studies have evaluated hemodynamic measures of blood pressure (BP) and its determinants, cardiac output (Qc) and total peripheral resistance (TPR), during graded exercise in patients with OSA. In the present study, we assessed resting and exercise measures of heart rate (HR), BP, Qc, TPR, and oxygen uptake (VO_2). The primary objective was to explore relationships between exercise response characteristics during graded exercise and polysomnography (PSG) markers of sleep function. A second objective was to address the question of whether differences exist between OSA patients and matched controls regarding these measures of cardiopulmonary function.

METHODS

Subjects. Eleven subjects (5 male, 6 female) were recruited from a group of volunteers referred for overnight polysomnography (PSG) to the Sleep Disorders Network of Southwest Virginia, Christiansburg, VA, between August 2001 and May 2002. Two subjects were diagnosed with mild (RDI = 5-14); 4 with moderate (RDI = 15-29); and 5 with severe (RDI $\geq$ 30) OSA. The Institutional Review Board of Virginia Polytechnic Institute and State University approved the study and each subject gave informed consent before participating. Medical records were reviewed to exclude candidates with the following physician-diagnosed conditions: history of cardiovascular or pulmonary disease; history of metabolic or endocrine disorders; current use of anti-hypertensive medication or severe hypertension; current smoking or use of sedatives and/or muscle relaxers; orthopedic, musculoskeletal, or a recent history (< 6 months) of regular participation in moderately vigorous physical activity. At baseline, each OSA patient completed a health history questionnaire, standardized sleep questionnaire (Epworth

Sleepiness Scale, ESS)[19] and overnight polysomnography study (PSG) from which a diagnosis of OSA was made. Conventional techniques were employed when performing the PSG studies and included, electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). The monitoring period also included the evaluation of respiratory effort, airflow, oxygen saturation, and body position and movements. PSG measures of interest included: total sleep time (TST), stage 1 and stage 2 sleep, slow wave sleep (SWS), rapid eye movement (REM) sleep, respiratory disturbance index (RDI); lowest arterial oxygen concentration (SaO_2) during sleep; and percent of TST below 90% SaO_2. Polysomnography data and baseline characteristics for all sleep apnea subjects are reported in Tables 1 and 2, respectively.

In addition, 10 apparently healthy subjects (4 male, 6 female) matched for age and body mass index (BMI) were recruited to serve as controls. Sleep studies were not performed in control subjects. However, suspicion for sleep-disordered breathing was diminished in control subjects via a health history questionnaire, standardized sleep questionnaire (ESS), sleep-related symptom review, and clearance to participate from their primary care physician. Subjects answered questions related to snoring and apnea history, witnessed snoring, sleep quality, and daytime sleepiness. None of the subjects reported a history of nocturnal gasping, apnea or witnessed apnea (by bedpartner) nor did any of the subjects report symptoms of excessive daytime sleepiness. Despite some of the subjects reporting infrequent snoring, all control subjects reported that their sleep was refreshing. Control subject characteristics are listed in Table 2.

Cycle Ergometry Test Procedures. Each subject completed a maximal cycle ergometer test at the Sleep Center. The following measures were obtained: height; weight; neck,

and waist circumferences; HR and BP at rest in a sitting posture; and body mass index (BMI). The exercise test was performed on a MedGraphics® electronically braked cycle ergometer ($CardioO_2$, St. Paul, MN). Subjects began pedaling at an initial work rate of 25 watts and then ramped 5 watts every 20 seconds. Exercise was monitored by trained technicians and supervised by a licensed physician. Test termination criteria were in accordance with standards set by the American College of Sports Medicine (ACSM) [20]. Heart rate and rhythm were assessed and recorded each minute from continuous electrocardiographic (ECG) monitoring throughout exercise. Ratings of perceived exertion were also recorded each minute while blood pressure measurements via auscultation were taken at 2-min intervals. Respiratory gas exchange measurements including oxygen consumption (VO_2) were obtained during the exercise test using a computer controlled breath-by-breath gas exchange system (SensorMedics Vmax 229®, Yorba Linda, CA). Methodology used for the Qc procedure is described by Zenger et al. [21] and was performed in accordance with the manufacturer's protocol for the device using proprietary computer software (SensorMedics®, Yorba Linda, CA). From Qc measurements, resting and submaximal exercise measures of cardiac index (CI), TPR, stoke volume (SV), and stroke volume index (SVI) were calculated. Cardiac output, TPR, and SV were not measured at peak exercise due to difficulties in performing the breathing maneuver.

Data Analysis. Data were analyzed using SPSS statistical software (SPSS Inc., Version 10.0, Chicago, IL). Pearson *r* correlation coefficients were calculated to explore potential relationships between select cardiopulmonary measures and PSG markers of sleep function. Cardiopulmonary measures included: HR, SBP, DBP, MAP, CI, SVI, TPR, and

VO_2. PSG markers of sleep function included: TST, stage 1 and stage 2 sleep, slow wave sleep (SWS), rapid eye movement (REM) sleep, respiratory disturbance index (RDI); lowest SaO_2 during sleep, and percent of TST below 90% SaO_2. Independent *t* tests were used to explore differences between OSA patients and control subjects concerning exercise test responses. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Subject characteristics. Descriptive and PSG characteristics for the 11 OSA patients (5 male, 6 female) who participated in the study are presented in Table 1. Mean descriptive characteristics for the 10 control subjects (4 males, 6 females) are presented in Table 2. The inclusion of multiple exclusion criteria in this study limited the size of the sample that could be recruited. OSA patients exhibited significantly larger neck ($P = 0.04$) and waist ($P = 0.02$) circumferences compared to controls and scored higher on the Epworth Sleepiness Scale questionnaire ($P = 0.002$). No significant differences were noted for age or BMI between the two groups. One exercise test had to be stopped due to an exaggerated blood pressure response. All other tests were stopped owing to general fatigue. Symptoms occurring during the exercise test included muscular fatigue and dry mouth. Two patients experienced an abnormal blood pressure response and dizziness in the post-exercise recovery period, which was attributed to a low blood glucose level.

Resting Measures. Resting hemodynamic variables OSA patients ($N = 11$) and controls ($N = 10$), including HR, SBP, DBP, MAP, Qc, SV, and TPR, are presented in Table 3. To standardize indices of Qc and SV for body size, cardiac index (CI) and stroke volume index (SVI) were used in the analyses. Resting SBP ($P = 0.03$) and MAP ($P = 0.04$) were significantly different between OSA patients and controls (Table 3). However, no

significant differences were noted in resting measures of HR, DBP, CI, SVI, or TPR. In the OSA patients, no significant relationships were found between resting HR, SBP, DBP, MAP, CI, SVI, or TPR and PSG markers of sleep function or disease severity ($P > 0.05$).

Submaximal Exercise. Eight OSA patients and 10 control subjects completed Qc measurements during the exercise test. Results of ramp exercise test measures taken at power outputs of 60 watts and 100 watts are presented in Tables 4 and 5, respectively. No significant differences were noted between groups regarding measures of VO_2, SBP, DBP, CI, or SVI at 60 watts or 100 watts ($P > 0.05$). However, several significant relationships were noted in OSA patients regarding PSG markers of sleep function and disease severity and submaximal exercise test measures. RDI was significantly related to HR at 60 watts (r = -0.70; P = 0.02) and 100 watts (r = -0.69; P = 02); stage 2 sleep duration was inversely related to CI at 60 (r = -0.76; P = 0.03) and 100 watts (Figure 1). In addition, stage 1 sleep duration was significantly correlated with TPR at 60 watts (r = 0.70; P = 0.06) and 100 watts (r = 0.71; P = 0.05). Although not significant, TPR also was moderately correlated with stage 2 sleep duration (Figure 2).

Peak Exercise. Peak measures of Qc and estimates of SV and TPR were not obtained due to the difficulty in performing the breathing maneuver at higher exercise intensities**.** OSA patients achieved 87 % of age-predicted maximal HR (HR_{max}) compared to 90 % for control subjects. No significant differences were noted at peak exercise between groups concerning HR, BP, or VO_{2pk} ($P > 0.05$). A significant relationship was noted in the OSA group between peak HR and stage 2 sleep duration (r = -0.73; P = 0.02); and RDI (Figure 3). Furthermore, relative VO_{2pk} appeared to increase linearly with increases

in REM sleep duration (Figure 4). Results of selected ramp exercise test measures taken at peak exercise for OSA patients and controls are presented in Table 4.

DISCUSSION

The strengths of this study include the following: (1) OSA patients were newly diagnosed and untreated; (2) control subjects and OSA patients were matched for age and body mass index, thus ruling out any potential confounding influences of these variables; and (3) all participants were normotensive and on no medications. Potential limitations include the absence of PSG data for control subjects to definitively rule out any type of sleep-related breathing disorder. However, several steps were taken to reduce this likelihood including physician referral, standardized questionnaires, and a sleep-related symptom review. In addition, we were unable to make comparisons between OSA patients and controls concerning select indicators of sleep function. The study's sample size was small relative to the number of variables measured. However, subject recruitment is ongoing.

The question of whether exercise testing might help to reveal abnormalities in hemodynamic function in OSA patients has not been answered. The primary objective of this study was to explore relationships between exercise response characteristics during graded exercise and polysomnography (PSG) markers of sleep function in patients newly diagnosed with OSA. A second objective was to examine differences in these exercise responses with those of matched control subjects.

All OSA patients and control subjects in this study were normotensive. Furthermore, exercise measures of HR, Qc, BP, and TPR were not significantly different

between OSA patients and controls. Nonetheless, several trends were noted between PSG markers of sleep function and submaximal and maximal exercise measures of cardiopulmonary function in the patient group: (1) stage 1 sleep was negatively correlated with Qc during submaximal exercise (Figure 1); (2) stage 2 sleep duration was positively correlated with TPR during submaximal exercise (Figure 2); (3) OSA disease severity (RDI) was negatively correlated with submaximal and peak exercise HR, which may suggest that HR response to exercise is blunted in patients with OSA disease severity (Figure 3); and (4) REM sleep duration was significantly correlated with peak exercise capacity (Figure 4).

Several reasons may explain these findings including OSA disease severity and altered baroreflex function. Patients in this study spent a greater percentage of time in stage 1 and stage 2 sleep; and less time in REM sleep (13.0 $\pm$ 6.9 % of TST) compared to normals (20% to 25% of TST). This may be considered an indirect indicator of sleep fragmentation. In addition, excess circulating catecholamines secondary to chronic intermittent hypoxia may play an important role in blood pressure regulation. Previous research has shown that repeated and partial apneic events during sleep result in sleep fragmentation and hypoxia, both of which cause increased sympathetic nerve activity resulting in elevations in blood pressure [5, 6]. Furthermore, repetitive surges of blood pressure during sleep and increased sympathetic activity during wakefulness may result in structural downregulation of cardiac beta-adrenergic receptors [7, 8, 22] which might serve as a protective mechanism from the adverse effects of increased catecholamine levels. However, previous studies of baroreflex gain in OSA patients are inconsistent, reporting either depressed baroreflex gain [23, 24] or no difference in baroreflex function in OSA

patients [25]. Moreover, baroreflex gain is influenced significantly by obesity [26] and the presence of hypertension [27]. Excess catecholamine stimulation, such as that found in sleep apnea patients [28], might be implicated in this process. One potential consequence of downregulation may be an inability to elevate HR sufficient enough to meet the physiological demands imposed by graded exercise. Furthermore, this may impact oxygen transport capabilities and the ability to perform sustained physical activity.

Since oxygen consumption is determined by the rate at which O_2 is transported and the amount of O_2 extracted from the blood (VO_2 = HR x SV x a-vDO_2), a decrease in one variable, i.e. HR, will result in a lower VO_2 without a concomitant increase in SV or increased peripheral extraction of O_2. Previous research has shown that peak exercise capacity is reduced in OSA patients [14, 15, 29]. Vanuxem et al. [14] reported lower maximal oxygen uptakes in OSA patients (26.4 $\pm$ 1.2 ml·kg·min^{-1}) compared to a group of healthy controls (33.2 $\pm$ 1.4 ml·kg·min^{-1}, $P < 0.005$). These investigators also found the OSA patients to have low peak blood lactate levels and delayed lactate elimination post-exercise, suggesting impaired glycolytic and oxidative muscle metabolism that may be implicitly related to this disorder. In addition, VO_{2pk} was significantly related to disease severity, i.e. RDI ($P = -0.69$; $P < 0.005$). This is consistent with findings reported by Tremel et al. [29]. They evaluated 34 patients with heart failure (age = 62 $\pm$ 9.0 yrs; BMI = 27.0 $\pm$ 5 kg/m^2) for the prevalence of sleep-disordered breathing 1 month after recovering from acute pulmonary edema. Twenty-eight of the 34 patients had sleep apnea. Furthermore, significant correlations were found between RDI and VO_{2pk} ($r = -0.73$; $P < 0.01$). We did not find a relationship between RDI and $VO2_{pk}$. Furthermore, measured VO_{2pk} was not significantly differently from the control group (20.3 $\pm$ 3.6 ml·kg·min^{-1}

and 23.6 $\pm$ 5.2 ml·kg·min^{-1}, respectively). However, measured VO_{2pk} in the OSA group was significantly lower than the predicted VO_{2pk} for this same group (30.3 ml·kg·min^{-1}; $P < 0.001$) [30].

Few studies have reported on the HR response to graded exercise in patients with OSA. Vanuxem et al. [14] reported that OSA patients and controls each achieved 93% of age-predicted HR_{max} as measured during cycle ergometry. However, Aguillard et al. [31] reported that 50% of OSA patients performing maximal cycle ergometry (N = 37; age = 47.1 yrs; BMI = 35.2 $\pm$ 7.2 kg/m^2; RDI = 53.1 $\pm$ 34.2) achieved a HR_{max} that was at least 2 standard deviations below their predicted HR_{max}. Furthermore, patients who spent a greater percentage of TST in REM sleep, tended to have higher functional capacities (r = 0.44; $P < 0.05$). Our study extends these findings. Patients in our study achieved 87.0 % of age-predicted HR_{max} compared to 90.0 % for controls. However, it is debatable if achieving 87% of age-predicted peak HR represents a clinically significant deficit. Furthermore, we noted a significant relationship between REM sleep duration and VO_{2pk}. Previous studies comparing physically fit and unfit subjects have found significant differences between groups on SWS, but not REM sleep [32, 33]. It may be that REM sleep positively impacts exercise capacity, or greater levels of physical fitness produce a greater percentage of REM sleep.

CONCLUSIONS

This study noted several significant relationships between select exercise response characteristics in OSA patients and PSG markers of sleep function and disease severity. Exercise testing may help reveal abnormalities in hemodynamic function that are not

manifested in a resting physiological state. In this study, PSG markers of sleep function were associated with submaximal measures of heart rate, cardiac output, and total peripheral resistance. Furthermore, significant relationships were noted between markers of sleep function and peak measures of heart rate and oxygen uptake. In conclusion, exercise testing may provide unique and clinically relevant information in the diagnosis of OSA disease severity. However, further investigation is needed before definitive conclusions can be made regarding these relationships and others.

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Table 1. OSA Patients - Polysomnographic Test Results (N = 11)

Variable	Mean	SD	Range
PSG Measures			
RDI	30.2	15.0	10.5 – 55.1
Time in bed (min)	366.8	6.9	359.5 – 385.0
Total sleep time (min)	292.8	36.8	246.5 – 347.0
Stage 1(%)	6.7	4.2	0.5 – 16.9
Stage 2 (%)	54.2	7.9	41.2 – 69.6
Slow wave sleep (%)	18.9	9.9	1.7 – 31.6
REM (%)	13.0	6.9	0.4 – 25.7
Baseline SaO_2 (%)	96.2	1.1	94.0 – 98.0
Time $SaO_2 < 90\%$ (%)	4.4	4.4	0.0 – 10.0
Lowest SaO_2 (%)	85.0	5.9	74.0 – 92.0

Table 2. OSA Patient and Control Subject Characteristics

Variable	Mean	SD	Range
OSA Patients (N = 11)			
Physical Measures			
Age (years)	46.5	12.0	25 - 62
Weight (kg)	98.4	15.9	75.6 - 133.2
Waist Girth (cm)	107.1	9.5	93.2 – 121.9
BMI (kg/m^2)	32.5	6.2	25.3 – 43.5
Neck Circumference (cm)	39.1	2.1	36.5 – 44.0
Epworth (x/24)	12.6	4.0	7 – 17
Control Subjects (N = 10)			
Physical Measures			
Age (years)	39.8	6.9	28 - 51
Weight (kg)	80.9	12.5	58.1 – 100.0
Waist Girth (cm)	90.9	11.4	71.2 – 111.0
BMI (kg/m^2)	28.8	4.9	20.3 – 34.6
Neck Circumference (cm)	36.5	3.0	32.4 – 42.8
Epworth (x/24)	6.6	3.9	2 - 14

Table 3. Resting Cardiovascular and Hemodynamic Measures

Resting Measures	**OSA (N = 8)**	**Control (N = 10)**
Heart Rate (bt/min)	82.4 ± 10.0	81.1 ± 4.3
Blood Pressure (mmHg)		
Systolic	139.0 ± 12.0	124.6 ± 3.7
Diastolic	91.5 ± 8.7	83.8 ± 2.4
Cardiac Index (L/min/m^2)	2.6 ± 0.5	2.6 ± 0.1
SV Index (ml/bt/m^2)	33.5 ± 6.8	32.5 ± 2.1
TPR (mmHg/L/min)	19.8 ± 6.3	19.8 ± 0.8

Values are means and standard deviations.

Table 4. Submaximal and Peak Exercise Hemodynamic and Cardiorespiratory Responses in OSA Patients and Controls During a Cycle Ergometer Graded Exercise Test

Measure	**OSA (N = 8)**	**Control (N = 10)**
Submaximal Exercise – 60 Watts		
Heart Rate (bt/min)	105.0 ± 15.9	115.1 ± 15.2
Blood Pressure (mmHg)		
Systolic	153.3 ± 24.1	144.4 ± 13.9
Diastolic	89.3 ± 7.9	83.0 ± 6.1
Cardiac Index (L/min/m^2)	4.7 ± 0.9	4.4 ± 0.9
Stroke Volume Index (ml/bt/m^2)	45.4 ± 8.6	38.7 ± 7.0
TPR (mmHg/L/min)	11.1 ± 2.4	12.5 ± 2.4
Oxygen Uptake (ml/kg/min)	10.3 ± 2.0	10.7 ± 1.7
Percent of VO_{2pk}	50.7 ± 7.8	46.3 ± 7.9
Submaximal Exercise – 100 Watts		
Heart Rate (bt/min)	123.3 ± 4.6	131.7 ± 17.9
Blood Pressure (mmHg)		
Systolic	174.0 ± 8.2	160.8 ± 16.3
Diastolic	88.0 ± 2.4	84.0 ± 6.2
Cardiac Index (L/min/m^2)	4.9 ± 0.3	5.7 ± 0.8
Stroke Volume Index (ml/bt/m^2)	39.6 ± 2.4	44.3 ± 7.9
TPR (mmHg/L/min)	11.3 ± 0.9	10.1 ± 1.4
Oxygen Uptake (ml/kg/min)	15.0 ± 2.1	16.3 ± 3.1
Percent of VO_{2pk}	73.4 ± 9.0	70.3 ± 13.3
Peak Exercise		
Heart Rate (bt/min)	150.4 ± 13.7	162.0 ± 18.6
Blood Pressure (mmHg)		
Systolic	203.3 ± 23.7	182.6 ± 18.2
Diastolic	88.3 ± 9.3	85.2 ± 9.0
Oxygen Uptake (ml·kg·min^{-1})	20.3 ± 3.6	23.6 ± 5.2

Values are means and standard deviations.

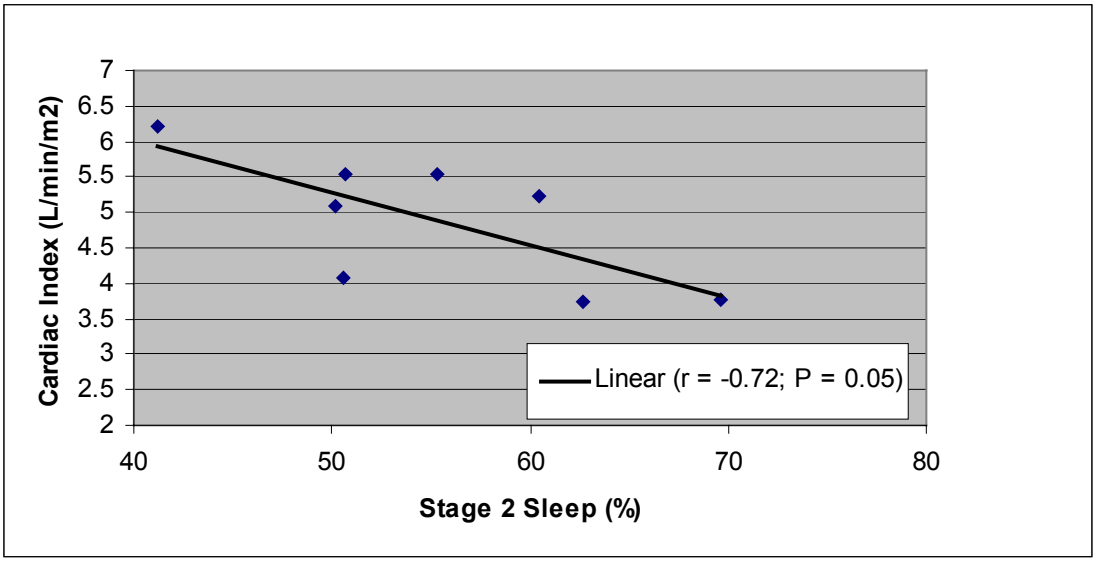

Figure 1. Stage 2 Sleep and Cardiac Index at 100 Watts (N=8)

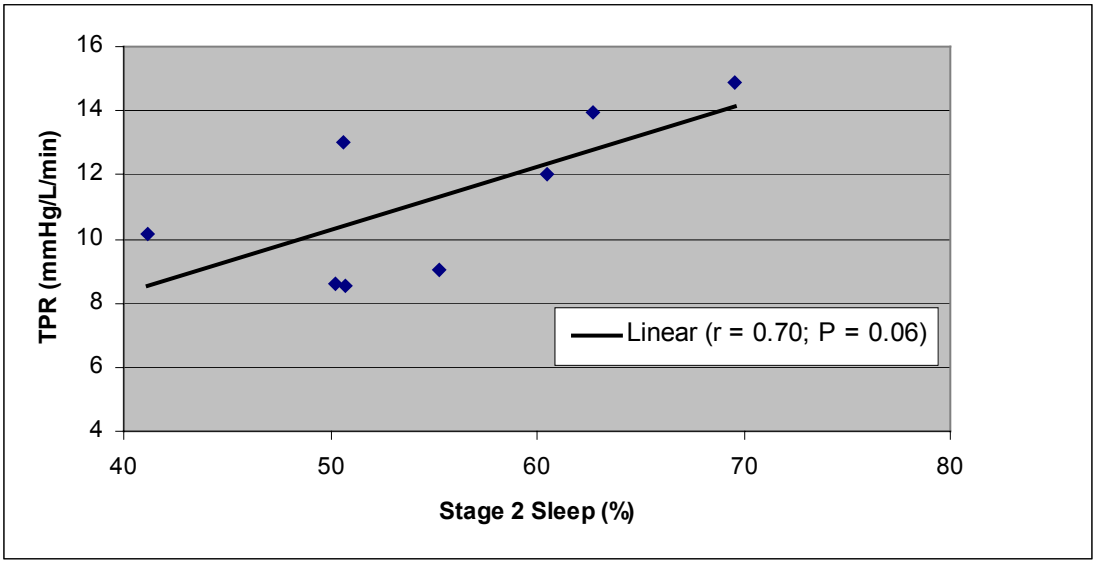

Figure 2. Stage 2 Sleep and TPR at 100 Watts (N = 8)

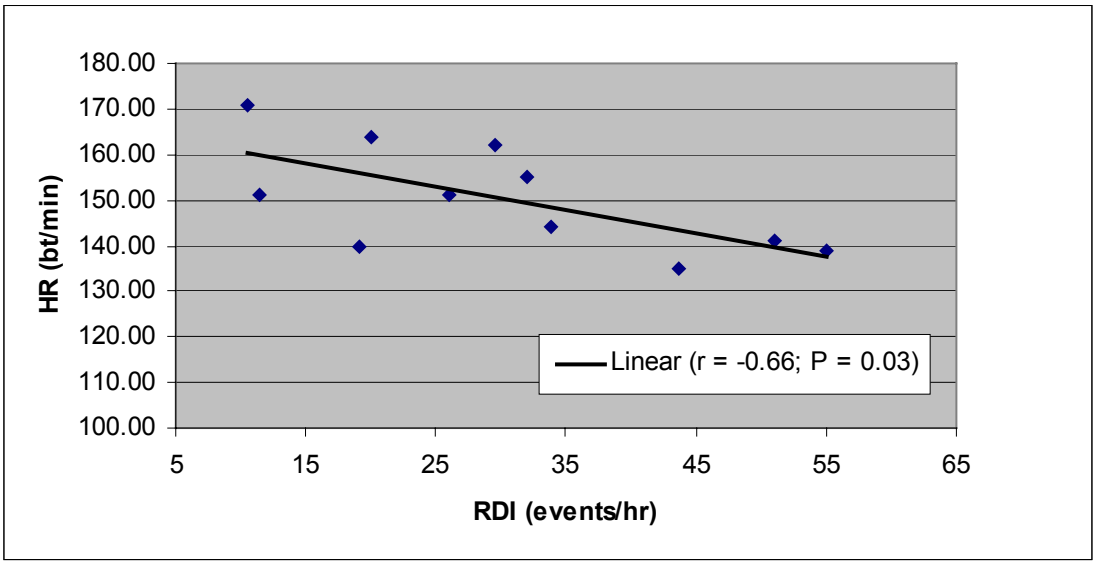

Figure 3. Respiratory Disturbance Index and Peak HR (N = 11)

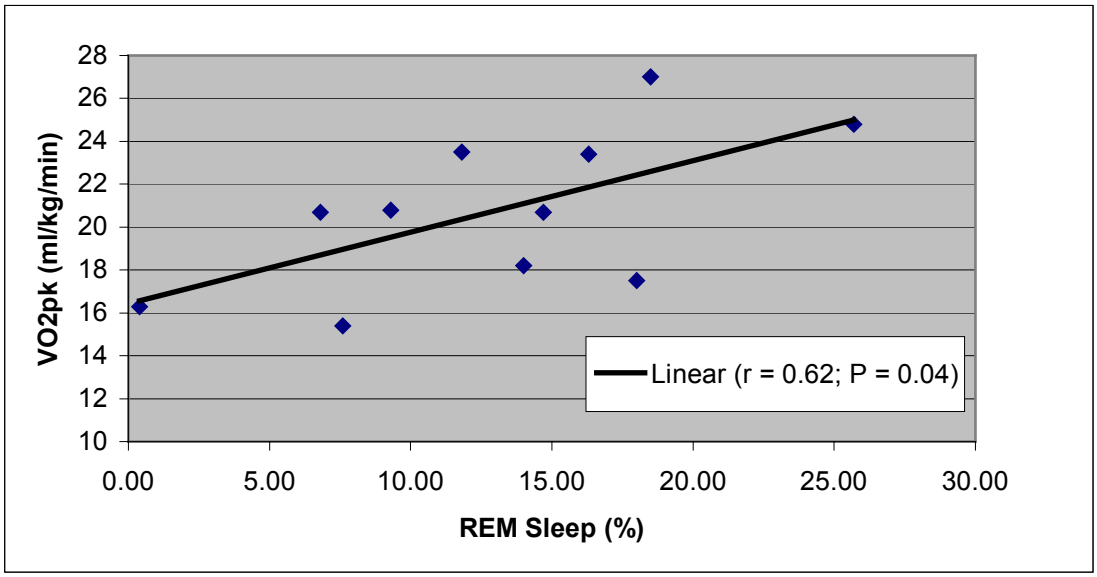

Figure 4. REM Sleep and Peak VO_2 (ml/kg/min) (N = 11)

Journal Manuscript III

Aerobic Exercise Training and nCPAP Therapy: Adaptations in Cardiovascular Function in Patients with Obstructive Sleep Apnea

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Abstract

PURPOSE: The purpose of this study was to examine the effects of nCPAP, with or without a 6-wk moderate-intensity aerobic exercise program, on resting measures of cardiovascular autonomic function, daytime blood pressure (BP) and submaximal and peak exercise measures of cardiopulmonary function in patients with obstructive sleep apnea (OSA). **METHODS:** Eight OSA subjects (4 male, 4 female; age = 43.5 $\pm$ 12.6 yr) were stratified by age and OSA disease severity and randomized to treatment with nasal continuous airway pressure (nCPAP) only (CPO) or nCPAP plus a moderate intensity aerobic exercise training program (CPE). In addition, 4 apparently healthy subjects (2 male, 2 female; age = 40.0 $\pm$ 10.1 yr) were recruited to serve as controls. Each participant completed daytime resting measurements of heart rate variability (HRV); BP; and non-invasive cardiac output (Qc). Stroke volume (SV) and total peripheral resistance (TPR) were estimated from Qc measurements. In addition, each subject completed a maximal exercise test on a cycle ergometer. Measures of interest included heart rate (HR), BP, Qc, and oxygen uptake (VO_2). **RESULTS:** Post-treatment resting HR decreased 7.4 % and 5.5 % for the CPO and CPE groups, respectively, compared to the slight increase in resting HR noted in controls. Only minor differences were noted in measures of systolic and diastolic BP between groups before and after treatment(s). Pre- and post-treatment measures of submaximal and peak exercise cardiopulmonary function were similar between groups. **CONCLUSIONS:** A small sample size has limited the ability to draw definitive conclusions in this study. Further investigation is needed after patient enrollment concludes and all participants have completed the 12-wk protocol.

Introduction

Obstructive sleep apnea (OSA) is a serious disorder that affects up to 24% of middle-aged males [1]. Some of the recently published literature strongly suggests that OSA may have a powerful and independent influence on cardiovascular morbidity and mortality in middle-aged and older adults [2, 3]. Unfortunately, the mechanisms underlying the association between OSA and cardiovascular disease are not known. Sympathetic nervous system activity is elevated in OSA patients [4, 5] which may suggest that altered cardiovascular autonomic regulation is implicated. Furthermore, this increased sympathetic activity during sleep has been proposed to spillover into daytime hours and remain elevated when breathing patterns are normal and no evidence of hypoxia or hypercapnia is evident [4-7]. Thus, hypertension (HTN) associated with repetitive nocturnal apneas/hypopneas may be an important contributing mechanism to a cardiovascular pathophysiology in OSA that advances over time in susceptible individuals [8, 9]. The numerous health and fitness benefits of a physically active lifestyle are well-documented [10]. Of special relevance to OSA patients, it is particularly promising that regular aerobic physical activity is associated with a lower incidence of hypertension (HTN), obesity, and type 2 diabetes [11]. Thus, regular moderate-intensity exercise may be an especially effective intervention for reducing coronary risk factors in OSA patients. When used in conjunction with other front-line therapeutic measures, e.g. surgery and/or nasal continuous positive airway pressure (nCPAP), exercise may counter tendencies toward HTN by promoting autonomic balance, thereby improving cardiovascular regulation. To date, little attention has been given to physical activity as an adjunct to surgery or nCPAP in the treatment of OSA [12-14]. Therefore, the purpose of this study was to examine the

effects of nCPAP, with or without a 6-wk moderate-intensity aerobic exercise program, on resting measures of cardiovascular autonomic function, daytime blood pressure (BP), and submaximal and peak exercise measures of cardiopulmonary function in a group of OSA patients and matched control subjects. A family of clinical markers including heart rate variability (HRV), BP, cardiac output (Qc), total peripheral resistance (TPR), and oxygen uptake (VO_2) were assessed in this study.

METHODS

Subjects. Eight patients (4 male, 4 female) were recruited from a group of volunteers referred for overnight polysomnography (PSG) to the Sleep Disorders Network of Southwest Virginia, Christiansburg, VA, between August 2001 and May 2002. The Institutional Review Board of Virginia Polytechnic Institute and State University approved the study and each subject gave informed consent before participating. Medical records were reviewed to exclude candidates with the following physician-diagnosed conditions: history of cardiovascular or pulmonary disease; history of metabolic or endocrine disorders; current use of anti-hypertensive medication or severe hypertension; current smoking or use of sedatives and/or muscle relaxers; orthopedic, musculoskeletal, or neuromuscular disabilities that would preclude moderate physical activity; and a recent history (< 6 months) of regular participation in moderately vigorous physical activity. At baseline, each OSA patient completed an overnight polysomnography study (PSG) from which a diagnosis of OSA was made. Baseline characteristics of all sleep apnea subjects recruited are reported in Table 1. In addition, 4 apparently healthy subjects (2 male, 2 female) matched for age and body mass index (BMI) were recruited to serve as controls.

Suspicion for sleep-disordered breathing was reduced in control subjects via a thorough health history questionnaire, standardized sleep questionnaire (Epworth Sleepiness Scale, ESS) [15], sleep-related symptom review, and clearance to participate from their primary care physician. Control subject characteristics are listed in Table 2.

Polysomnography and Administration of Nasal CPAP Treatment. A full overnight PSG study was performed with each patient by trained technicians at the Sleep Center. Conventional techniques were employed when performing the PSG studies and included, electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). The monitoring period also included the evaluation of respiratory effort, airflow, oxygen saturation, and body position and movements. Eligible patients with resulting respiratory disturbance index (RDI) scores > 5 and less than 60 and identified as candidates for nCPAP therapy were asked to return on a second night to undergo a repeat PSG for the purpose of nCPAP titration. Each patient was provided an auto-titrating positive airway pressure device (AutoSet Therapeutic®, ResMed, Poway, CA). Each device was equipped with a memory chip and utilizing proprietary software (AutoScan®, ResMed), data such as mask leakage, dates and hours used, and the RDI was transmitted directly from the device to a computer.

Treatment Randomization. Research suggests that OSA predisposes individuals to increased mortality and this increased risk is exacerbated by factors of age and a high RDI as determined through a polysomnography study [16, 17]. To reduce the potential effect of these confounding variables, eligible subjects were first stratified according to age (25 to 44 yrs; and 45 to 60 yrs) and disease severity (RDI = 5 to 14; and 15 to 60) and then randomized to either nasal CPAP only (CPO) or nasal CPAP + exercise (CPE) such

that, upon completion of the trial, the groups were balanced (Figure 1). Treatment group characteristics are listed in Table 2.

Cycle Ergometry Test Procedures. Each subject completed two maximal cycle ergometer tests at the Sleep Center. The following measures were obtained: height; weight; neck, and waist circumferences; HR and BP at rest in a sitting posture; and body mass index (BMI). The exercise test was performed on a MedGraphics® electronically braked cycle ergometer (CardioO_2, St. Paul, MN). Subjects began pedaling at an initial work rate of 25 watts and then ramped 5 watts every 20 seconds. Exercise was monitored by trained technicians and supervised by a licensed physician. Test termination criteria were in accordance with standards set by the American College of Sports Medicine (ACSM) [11]. Heart rate and rhythm were assessed and recorded each minute from continuous electrocardiographic (ECG) monitoring throughout exercise. Perceived exertion scores were also recorded each minute while blood pressure measurements via auscultation were taken at 2-min intervals. Respiratory gas exchange measurements including oxygen consumption (VO_2) were obtained during the exercise test using a computer controlled breath-by-breath gas exchange system (SensorMedics Vmax 229®, Yorba Linda, CA.). Methodology used for the Qc procedure is described by Zenger et al. [18] and was performed in accordance with the manufacturer's protocol for the device using proprietary computer software (SensorMedics®, Yorba Linda, CA). From Qc measurements, resting and submaximal exercise measures of cardiac index (CI), TPR, stoke volume (SV), and stroke volume index (SVI) were calculated. Cardiac output, TPR, and SV were not measured at peak exercise due to difficulties in performing the

breathing maneuver. The results from the RXT were used to design an individualized aerobic exercise program for subjects randomized to the CPE group.

Aerobic Exercise Training Program. Patients randomized to the CPE group exercised 3 to 4 times per week for 30 to 40 minutes per session for 6 weeks. For the first two weeks, patients performed supervised exercise training sessions on a cycle ergometer or treadmill. During this time, patients were familiarized with their individualized exercise prescription, i.e. exercise modes, frequency and duration of exercise, target heart rate (50-60% of VO_{2pk}) and ratings of perceived exertion. Two weeks after the start of the supervised exercise training program, patients were requested to transition systematically into a pattern of exercising outside of the supervised sessions on days when they are not scheduled for supervised exercise, and given the option to exercise unsupervised on one of their scheduled 3 days/wk. Exercise logs were distributed to document the additional quantity of exercise over this period and weekly contact was made to answer questions and obtain feedback on current training program and physical activity status. By the end of the first 4 weeks, patients were fully transitioned to a schedule of exercising 2 to 3 days/wk unsupervised and 1-day/wk supervised.

Heart Rate Variability Analysis and Procedures. Heart rate variability was assessed from precise (+/- 1 ms) heart rate records of 8-hour waking periods using a small battery powered single-lead ECG recorder (Polar R-R Recorder™, Polar Electro, Kempele, Finland). Only time domain measures of HRV were analyzed for this study since standard spectral measures, i.e. low and high frequency power and the ratio of low frequency to high frequency power (LF: HF ratio), can be confounded by unstable breathing patterns [19]. All measures were calculated for the daytime period, i.e. 9:00am to

5:00pm. Subjects were instructed to wear the device shortly after awakening in the morning and to wear it for a period of approximately 8 to 10 hours. In addition, subjects were to refrain from moderate-to-vigorous physical activity and avoid alcoholic and caffeinated beverages a minimum of 24-hr prior to data collection. A subset of the total number of cardiac cycles recorded (~ 36,000 beats) was used in the final analyses. To standardize which subset to evaluate, it was decided to analyze those cardiac cycles obtained 30 minutes after the device started recording. The following measures were calculated after manually filtering data for ECG artifact, non-physiologic readings and extrasystoles: mean R-R interval (average heart rate); and standard deviation of all normal R-R intervals (SDNN).

Daytime Blood Pressure Measurement and Procedures. Recordings of daytime blood pressure were obtained using an automated digital blood pressure device (Omron HEM-705CP). Following the manufacturer's instructions, multiple recordings were taken upon awakening in the morning (AM); mid-day (N); afternoon (AN); and evening (PM). Subjects were instructed to obtain recordings in a seated position after a 5-min rest period and to abstain from caffeine and nicotine products and refrain from vigorous physical activity for a minimum of 12- and 24-hr, respectively prior to taking measurements. A minimum of 2 measurements were taken at each specified time until 2 systolic blood pressure measurements were recorded that were $\leq$ 5 mmHg apart. Systolic (SBP) and diastolic blood pressure (DBP) and mean arterial pressure (MAP) were evaluated at each of the 4 time periods. In addition, an overall mean (SBP, DBP, MAP) was calculated for the entire day.

Statistical Analyses. Due to the relatively small sample size associated with each group thus far, statistical analyses were not performed. Instead, multiple tables and figures are utilized to display specific trends. Upon enrollment completion, 2-way repeated measures ANOVA will be used to analyze differences over time and between groups. Post-hoc tests will be used to delineate any significant differences among the treatment groups.

RESULTS

Patient Demographics. Descriptive and PSG data for the OSA patients who participated in this study are presented in Table 1. The inclusion of multiple exclusion criteria in this study limited the size of the sample that could be recruited. To date, only 4 controls and 8 OSA (4 nCPAP only; 4 nCPAP + exercise) patients have completed measurements through week 6 (Table 2). Therefore, results are reported only for these individuals. This OSA group had moderate-severe OSA, as suggested by a mean RDI of 31.4 (range = 11.4 – 55.1). After 6 wks, body weight remained relatively unchanged among the three treatment groups (control ↑ 2 %; CPO and CPE ↑ < 1 %). However, scores on the Epworth decreased 33.8 % and 35.2 %, respectively for CPO and CPE groups compared to controls (↓ 3.1 %).

Utilization data from the auto-titrating nasal CPAP devices suggested that adherence was not uniform among the patients in either the CPO or CPE groups. Patients in the CPO group averaged 34.0 days with a range of 22-51, while average time of use/day was 5.1 h/day of recorded use with a range of 3.2-7.1. Patients in the CPE group averaged 37.3 days with a range of 18-49, while average time of use/day was 5.9 h/day of

recorded use with a range of 5.1-7.3. Patients in the CPE group averaged 18.8 days with a range of 14-24 days of aerobic exercise training. This is out of a maximum of 24 days as defined in the experimental design. The average exercise session lasted 34.9 minutes with a range of 27.5-51.3 min/session.

Cardiovascular Autonomic Function. Pre- and post-treatment measures of cardiovascular autonomic function, including average HR and HRV (SDNN) are presented in Figures 2 and 3, respectively. Post-treatment resting HR averaged over an 8-hr period decreased 7.4% and 5.5% for the CPO and CPE groups, respectively, compared to the slight increase in resting HR noted in controls. Cardiovascular variability (SDNN) in control subjects increased 32.6% after 6 wks. The CPO group exhibited a 13.5% decrease in daytime HRV, while patients in the CPE group displayed a 34.5% increase in HRV.

Daytime Blood Pressure. Pre- and post-treatment measures of daytime systolic blood pressure (SBP) and diastolic blood pressure (DBP) are presented in Figures 4 and 5, respectively. Relatively minor changes were noted between groups before and after treatment(s).

Resting and Exercise Measures of Cardiopulmonary Function. Pre- and post-treatment measures of resting cardiovascular function are presented in Table 3. After 6 wks, mean resting HR in the control subjects increased 22.2% while SBP decreased 9.8%. Mean resting HR and SBP remained relatively unchanged in the CPO and CPE groups. No change in mean CI was observed post-treatment in the control group. However, CI decreased 20.0% and 10.7%, respectively in the CPO and CPE groups.

Select cardiopulmonary and perceptual response measures to cycle ergometry during submaximal exercise are presented in Figures 6-8. After 6 wks, HR at 55 watts was increased 7.1% in controls; 6.7% in the CPO group; and relatively no change in the CPE group. Ventilation increased 16.4% in controls; and decreased 11.9% and 9.3% in the CPO and CPE groups, respectively (Figure 6). Cardiac index and TPR remain relatively unchanged 6 wks post-treatment(s) (Figure 7). At a relative percentage of VO_{2pk} (50%), HR was slightly elevated in all groups post-treatment. Submaximal ventilation was increased 17.1% in controls; decreased 13.6% in the CPO group; and relatively unchanged in the CPE group (Figure 8).

Cardiopulmonary and perceptual responses to cycle ergometry at peak exercise are presented in Table 4. Peak power output increased 8.5% in the CPE group compared to the CPO (↑ 1.4%) and control groups (↓ 0.8%). After 6 wks, peak exercise VO_2 and ventilatory threshold remained relatively unchanged among the 3 treatment groups.

DISCUSSION

The purpose of this study was to examine the effects of nCPAP, with or without a 6-wk moderate-intensity aerobic exercise program, on resting measures of cardiovascular autonomic function, daytime BP, and submaximal and peak exercise measures of cardiopulmonary function. The use of multiple exclusion criteria in this study, i.e. comorbidities, cardiovascular medications, and physical activity habits, has limited the size of the sample that could be recruited. To date, only 8 OSA patients and 4 control subjects have completed all measures through the 6 wk period. Therefore, this

preliminary paper tried to delineate any potential trends noted in the current study. Statistical analyses were not performed due to the small sample size in each group (n=4).

Pre- and post-treatment resting HR measured over an 8-hr period was higher in controls compared to either OSA treatment group. This contrasts previous data reported by Narkiewicz et al. [6]. However, OSA patients in the current study exhibited higher resting HR's (CPE: 87.3 bt/min; CPO: 87.5 bt/min) compared to OSA patients (75.7 bt/min) in the Narkiewicz study. Furthermore, in the current study, one control subject had a resting HR of 90 bt/min at baseline and 112 bt/min post-treatment, despite a 5-min rest period. Post-treatment resting HR was improved in both OSA groups compared to controls. These improvements may be attributed to the elimination of nocturnal BP surges and increased sympathetic activity with nCPAP, thus reducing daytime catecholamine spillover. Moreover, the addition of aerobic exercise training may have the added effect of improving vagal tone.

Pre- and post-treatment measures of HRV are difficult to interpret in this study. Relatively minor differences in SDNN were noted between the control and CPO groups at baseline. However, SDNN was lower in the CPE group compared to controls and the CPO group (19.3% and 18.3%, respectively). Several explanations may account for these differences. Narkiewicz et al. [6] previously reported that altered cardiovascular variability in OSA patients might be linked to the severity of OSA. Furthermore, although resting HR does not change significantly with advancing age, there is a decline in HRV, which has been attributed to a decrease in efferent vagal tone and reduced beta-adrenergic responsiveness. Thus far, our results don't support these conclusions. Patients in CPO group were older and diagnosed with more severe disease (age = 50.0 yrs; RDI = 31.8)

than patients in the CPE group (age = 36.8 yrs; RDI = 28.0). Other potential reasons for these differences include the number of subjects/group and the large variability noted in each group; and/or the reliability of the testing instrument. Day-to-day variation in physical and emotional demands also may impact daytime sympathetic activity as well as nCPAP compliance during the immediate time prior to data collection.

Previous research has concluded that exercise training improves measures of HRV in patients with coronary artery disease [20, 21]. Iellamo et al. [22] reported that aerobic exercise training 2 session/day, 6 days/wk increased measures of HRV in CAD patients post-bypass surgery. To date, no studies have evaluated the influence of exercise training in OSA patients. In this study, post-treatment measures revealed an increase in SDNN scores for both the control group (32.6 % ↑) and the CPE group (34.5 % ↑) while patients in the CPO group demonstrated a 13.5 % decrease. The reason for the increase in HRV in the control group is not known. However, the improvement noted in the CPE group might be attributed to an improvement in vagal tone secondary to aerobic exercise training.

Resting daytime SBP and DBP were slightly higher in the CPO and CPE groups compared to controls (Figures 4 and 5, respectively). Systemic hypertension is frequently associated with OSA and can be directly attributed to the repeated and partial apneic events that disrupt autonomic cardiovascular reflexes during sleep [23-26]. However, treatment with nCPAP with or without exercise training did not result in any significant decreases in resting SBP or DBP. This is not surprising since all OSA patients enrolled in this study were normotensive.

Previous research has shown that sympathetic activity is increased in OSA patients [4-6]. As previously noted, resting HR was higher in control subjects compared to either OSA group. This most likely is attributed to the tachycardia noted in one control subject post-treatment. Furthermore, the results in this study indicate that cardiac index relative to body size decreased in the CPO (20.0%) and CPE groups (10.7%). The reason for this in not known. However, since resting Qc generally is not affected by exercise training, the most plausible reason might be reliability associated with the Qc measurement technique and/or patient technique during the breathing maneuver.

Pre- and post-treatment submaximal and peak exercise cardiopulmonary responses did not change dramatically in any group. In the current study, neither the CPO nor CPE groups demonstrated an increase in VO_{2pk}. Previous research has shown that nCPAP treatment is associated with improved exercise capacity [27-30]. Taguci et al. [28] speculated that the improvements in VO_{2pk} might be attributed to an improved ventilatory response to exercise-induced increase in circulating carbon dioxide, secondary to nCPAP treatment. However, increased motivation might have been the most plausible explanation. Konnermann et al. [27] noted a 27.5 % increase in work rate at maximal effort after a 6-month trial of nCPAP therapy in a group of 30 OSA patients. The results of this study extend the findings of the Konnerman group [27]. An 8.5 % increase in peak work rate post-treatment was demonstrated in patients in the CPE group, despite no increase in functional capacity. It may be that these patients did not provide a maximal effort during the exercise test. Patients in the CPE group perceived the work rate at peak exercise to be "hard" (Pre-treatment RPE = 14.8 $\pm$ 2.5; post-treatment RPE = 15.3 $\pm$ 2.1).

Therefore, the increase in work rate most likely is attributed to increased motivation and/or habituation with the exercise test.

CONCLUSIONS

This study is hampered by a low patient enrollment. The small sample size and wide variability noted within each group make interpretation of the available data difficult. In addition, 6 weeks of light-moderate exercise training, i.e. 50% to 60% of VO_{2pk}, may not be sufficient time for changes in cardiovascular function and physical fitness to be observed. Data in this study will be re-evaluated after the patient enrollment concludes and all participants have completed the 12-wk protocol. We believe that a physically active lifestyle, in addition to effective primary treatment with surgery or nCPAP, may help attenuate tendencies toward the development of HTN and guard against further accumulation of excess body fat that may place these patients at increased long-term risk for exacerbation of their OSA.

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Table 1. OSA Individual Patient Characteristics

Subject No.	Age (yrs)	Gender	Ht (m)	Wt (kg)	BMI (kg/m^2)	Neck Cir (cm)	ESS (x/24)	RDI	Time SaO_2 < 90% (%)	Lowest SaO_2 (%)
1	50	Male	1.80	90.0	27.8	38.1	15	33.8	8.2	74.0
2	58	Female	1.65	102.5	37.7	38.0	19	11.4	8.3	80.0
3	25	Female	1.75	133.2	43.5	40.6	9	26.0	0.0	92.0
4	37	Female	1.75	114.5	37.4	39.4	14	29.6	0.0	92.0
5	33	Male	1.81	90.6	27.7	40.3	10	32.0	7.8	82.0
6	44	Male	1.80	87.6	27.0	39.4	16	55.1	3.0	90.0
7	62	Male	1.83	99.5	29.7	44.0	10	43.6	10.0	84.0
8	39	Female	1.61	106.0	40.9	36.6	8	20.0	10.0	79.0
Mean ± SD	**43.5 ± 12.6**	**4 Male 4 Female**	**1.75 ± 0.08**	**103.0 ± 15.2**	**34.0 ± 6.6**	**39.6 ± 2.2**	**12.6 ± 3.9**	**31.4 ± 13.5**	**4.7 ± 4.3**	**84.1 ± 6.6**

Values are means ± standard deviation. Abbreviations: Ht: height (meters); Wt: weight (kilograms); BMI: Body Mass Index (kg/m^2); Neck Cir: Neck Circumference (centimeters); ESS: Epworth Sleepiness Scale (score/24); RDI: Respiratory Disturbance Index (events per hour); SaO_2 (percent time oxygen saturation levels < 90%).

Table 2. Treatment Group Characteristics

Subject	Total (N)	Age (yrs)	Gender	Ht (m)	Wt (kg)	BMI (kg/m^2)	Neck Cir (cm)	ESS (x/24)	RDI	Time SaO_2 < 90% (%)
Control	4	40.0 ± 10.1	2 Male 2 Female	1.69 ± 0.07	91.6 ± 6.2	32.3 ± 1.8	38.5 ± 3.2	6.5 ± 5.2	N/A	N/A
Nasal CPAP Only	4	50 ± 10.2	2 Male 2 Female	1.77 ± 0.08	100.6 ± 9.6	32.3 ± 4.9	39.7 ± 2.5	15.2 ± 3.4	31.8 ± 17.8	2.3 ± 3.6
Nasal CPAP + Exercise	4	36.8 ± 10.5	2 Male 2 Female	1.74 ± 0.09	104.0 ± 20.2	35.0 ± 8.4	38.9 ± 1.9	10.5 ± 3.1	28.0 ± 6.3	6.5 ± 4.4

Values are means ± standard deviation. Abbreviations: N: sample size; Ht: height (meters); Wt: weight (kilograms); BMI: Body Mass Index (kg/m^2); Neck Cir: Neck Circumference (centimeters); ESS: Epworth Sleepiness Scale (score/24); RDI: Respiratory Disturbance Index (events per hour); SaO_2 (percent time oxygen saturation levels < 90%).

Table 3. Cardiopulmonary Measures Obtained Prior to GXT (Baseline and Week 6)

Resting Measures	Pre-Tx	Post-Tx
Control Subjects (N = 4)		
Heart Rate (bt/min)	71.8 ± 13.2	87.8 ± 18.2
Systolic BP (mmHg)	128.0 ± 4.3	115.5 ± 8.7
Diastolic BP (mmHg)	87.5 ± 2.5	83.5 ± 3.4
Cardiac Index (L/min/m^2)	2.4 ± 0.3	2.4 ± 0.3
TPR (mmHg/L/min)	20.3 ± 2.8	18.9 ± 1.7
Nasal CPAP plus exercise (N = 4)		
Heart Rate (bt/min)	84.5 ± 4.8	87.8 ± 18.2
Systolic BP (mmHg)	136.5 ± 20.5	139.0 ± 20.7
Diastolic BP (mmHg)	91.0 ± 13.9	92.5 ± 5.3
Cardiac Index (L/min/m^2)	3.0 ± 0.3	2.4 ± 0.3
TPR (mmHg/L/min)	15.0 ± 2.9	19.3 ± 3.0
Nasal CPAP Only (N = 4)		
Heart Rate (bt/min)	76.3 ± 7.5	77.3 ± 7.1
Systolic BP (mmHg)	137.0 ± 16.5	135.0 ± 24.8
Diastolic BP (mmHg)	89.5 ± 7.7	90.5 ± 11.9
Cardiac Index (L/min/m^2)	2.8 ± 0.4	2.5 ± 0.5
TPR (mmHg/L/min)	16.9 ± 3.6	19.8 ± 6.1

Values are means ± standard deviations.
Abbreviations: BP (blood pressure); TPR (total peripheral resistance)

Table 4. Cardiopulmonary and Perceptual Responses to Cycle Ergometry at Peak Exercise.

Measures	Pre-Tx	Post-Tx
Control Subjects (N = 4)		
Power (watts)	153.8 ± 12.5	152.5 ± 8.7
Heart Rate (bt/min)	153.3 ± 27.4	156.0 ± 26.3
Systolic BP (mmHg)	191.5 ± 11.6	197.5 ± 14.2
Diastolic BP (mmHg)	91.0 ± 7.4	92.5 ± 6.6
RPE (Borg 6-20)	15.3 ± 1.7	17.0 ± 1.6
VO_2 (L/min)	1.9 ± 0.3	2.1 ± 0.04
VT (L/min)	1.3 ± 0.2	1.4 ± 0.2
Nasal CPAP plus exercise (N = 4)		
Power (watts)	162.5 ± 29.6	176.3 ± 22.1
Heart Rate (bt/min)	153.5 ± 8.3	160.5 ± 8.5
Systolic BP (mmHg)	199.0 ± 35.3	205.5 ± 36.8
Diastolic BP (mmHg)	89.0 ± 21.1	94.5 ± 17.1
RPE (Borg (6-20)	14.8 ± 2.5	15.3 ± 2.1
VO_2 (L/min)	2.2 ± 0.5	2.3 ± 0.2
VT (L/min)	1.6 ± 0.4	1.7 ± 0.3
Nasal CPAP Only (N = 4)		
Power (watts)	173.8 ± 38.2	176.3 ± 22.1
Heart Rate (bt/min)	146.8 ± 12.2	143.0 ± 8.5
Systolic BP (mmHg)	216.5 ± 23.7	218.0 ± 15.6
Diastolic BP (mmHg)	96.0 ± 7.8	89.5 ± 7.7
RPE (Borg 6-20)	17.0 ± 3.2	17.8 ± 1.5
VO_2 (L/min)	2.3 ± 0.4	2.1 ± 0.3
VT (L/min)	1.7 ± 0.4	1.6 ± 0.4

Values are means ± standard deviations.
Abbreviations: BP (blood pressure); TPR (total peripheral resistance)

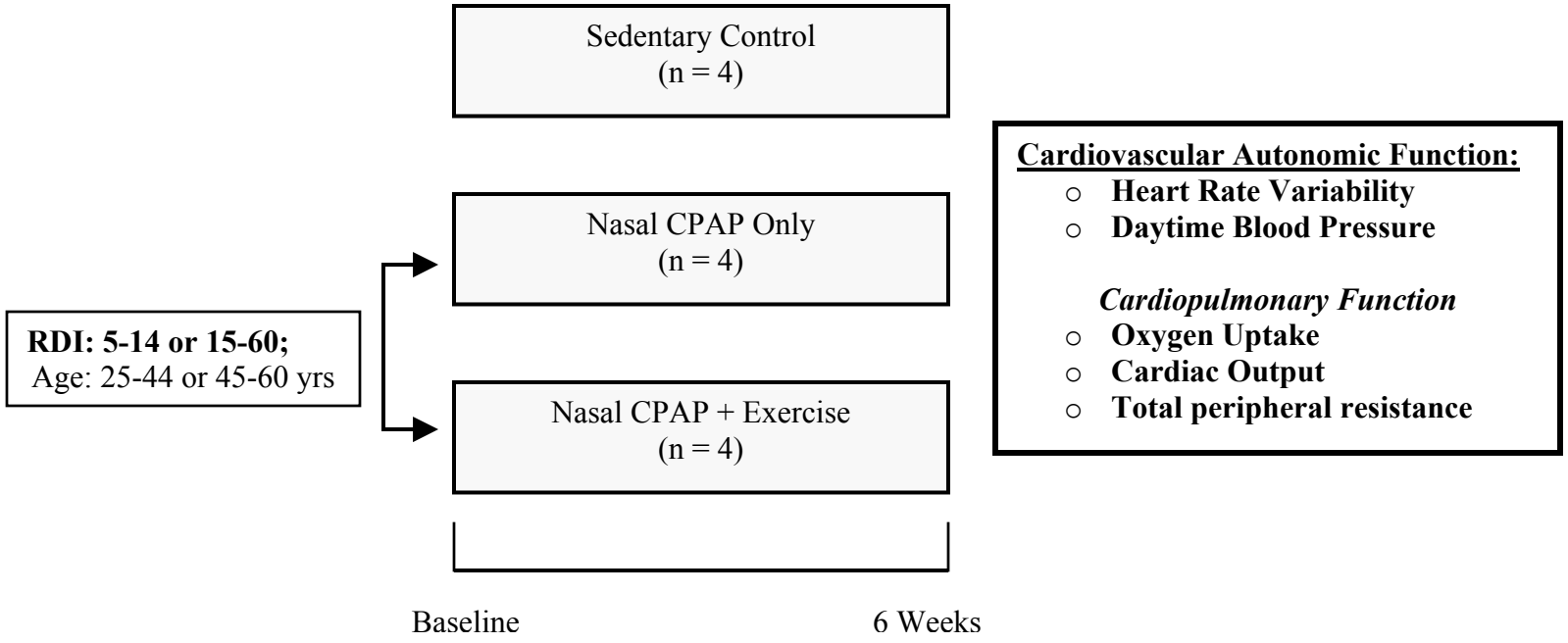

Figure 1. OSA Treatment Group Randomization

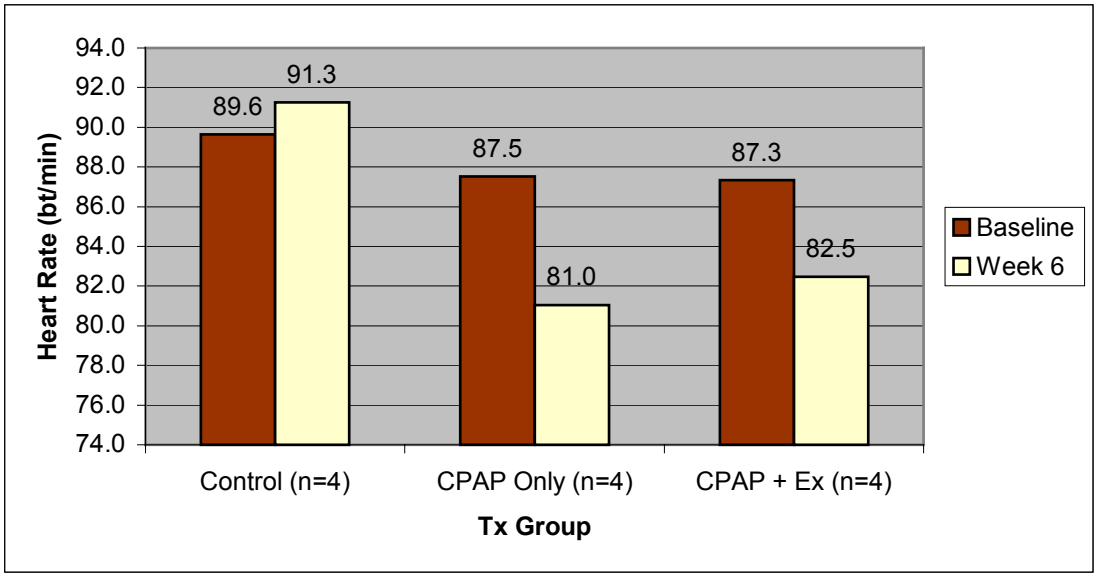

Figure 2. Effects of Treatments on Average Daytime Heart Rate

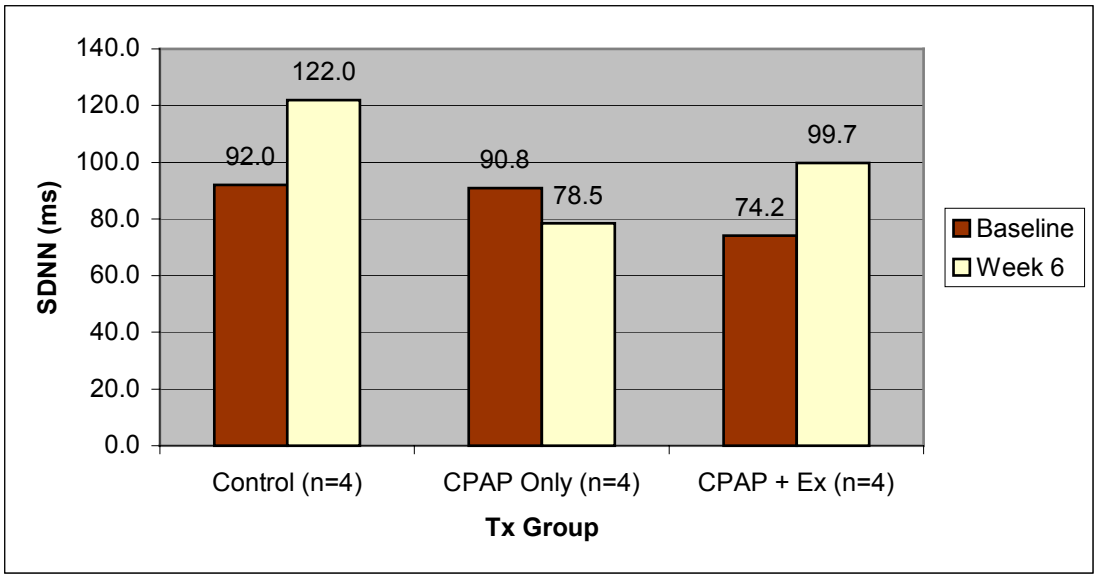

Figure 3. Effects of Treatments on Daytime Heart Rate Variability (SDNN)

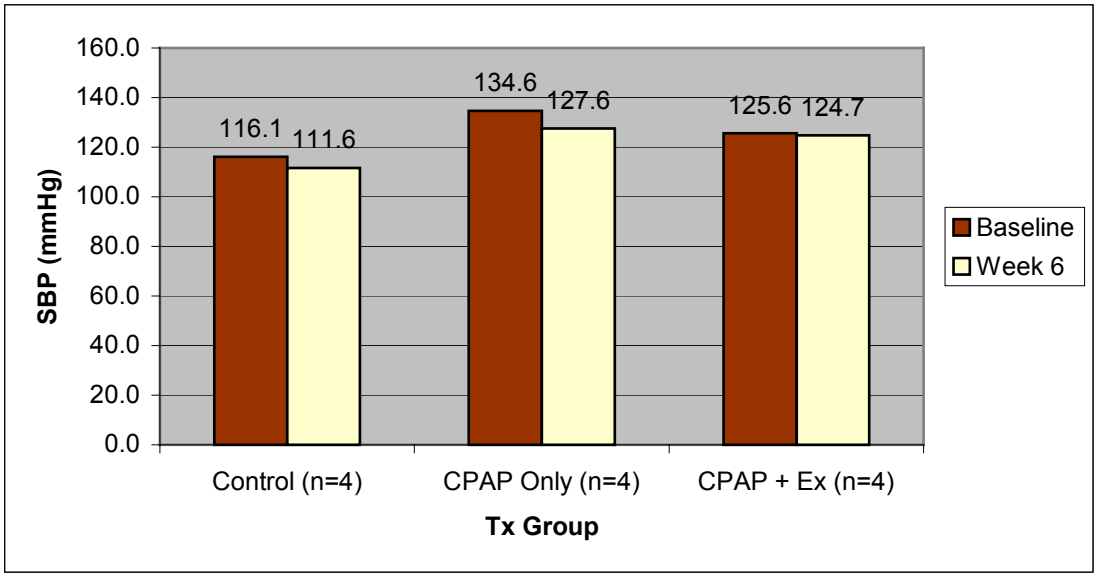

Figure 4. Effects of Treatments on Daytime Systolic Blood Pressure

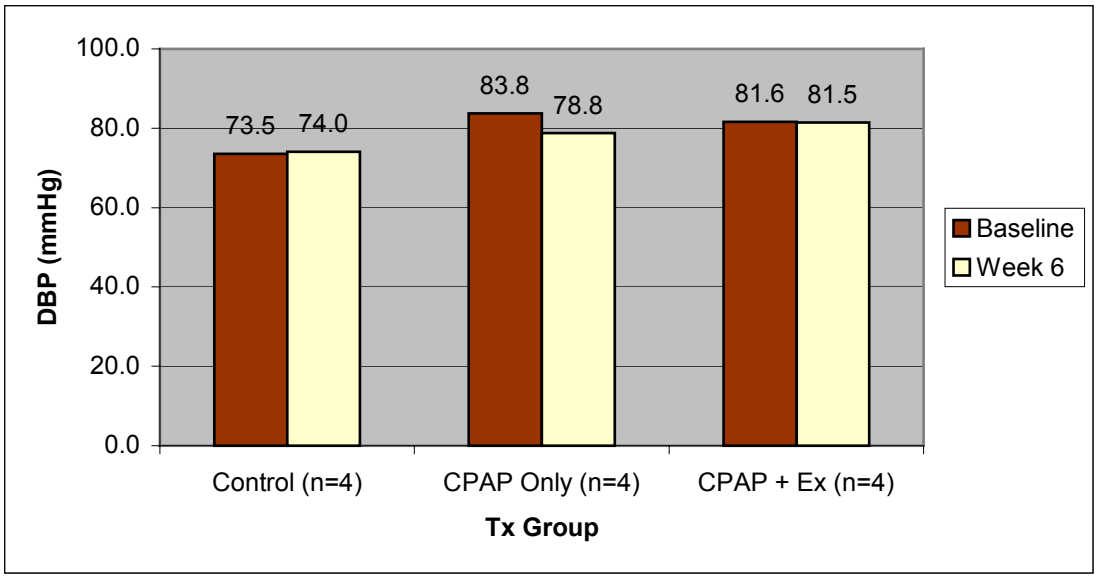

Figure 5. Effects of Treatments on Daytime Diastolic Blood Pressure

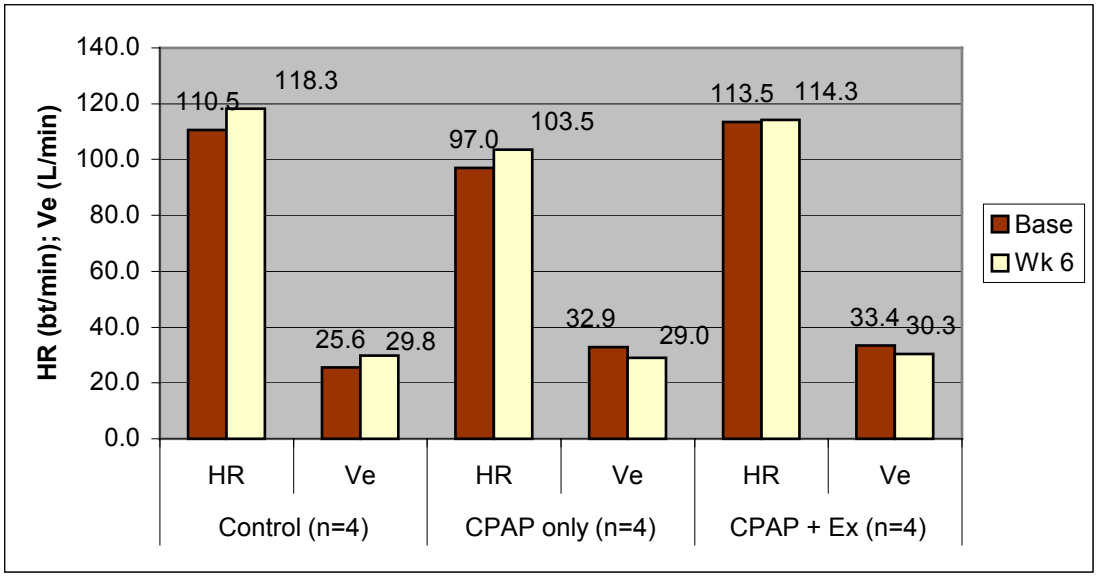

Figure 6. Cardiopulmonary Responses to Cycle Ergometry at Fixed Work Rate (55 Watts) before and after 6-week treatment(s).

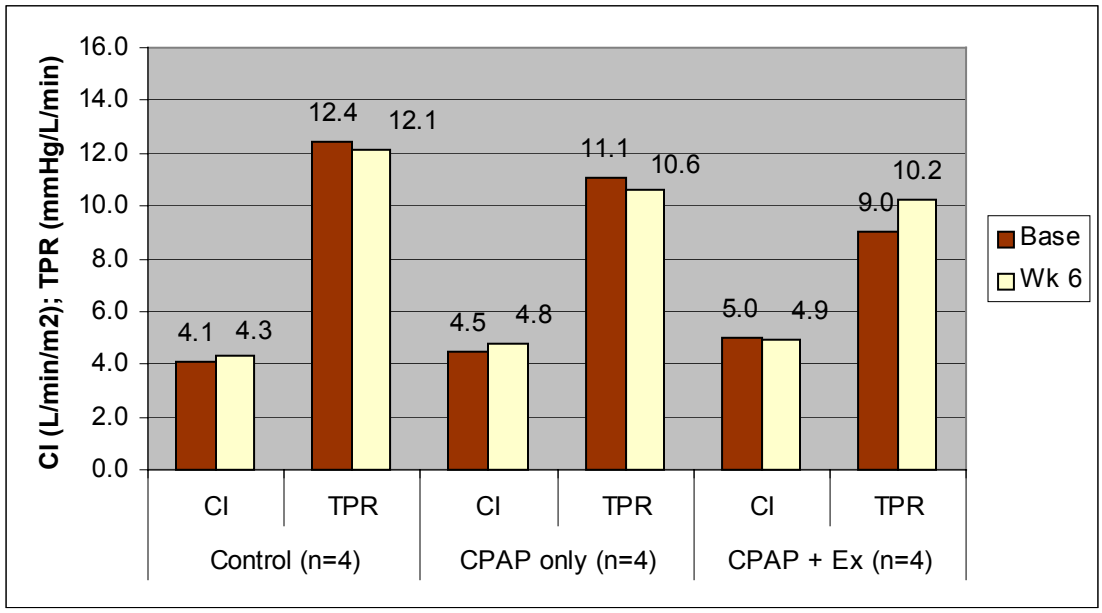

Figure 7. Hemodynamic Responses to Cycle Ergometry at Fixed Work Rate (55 watts) before and after 6-week treatment(s).

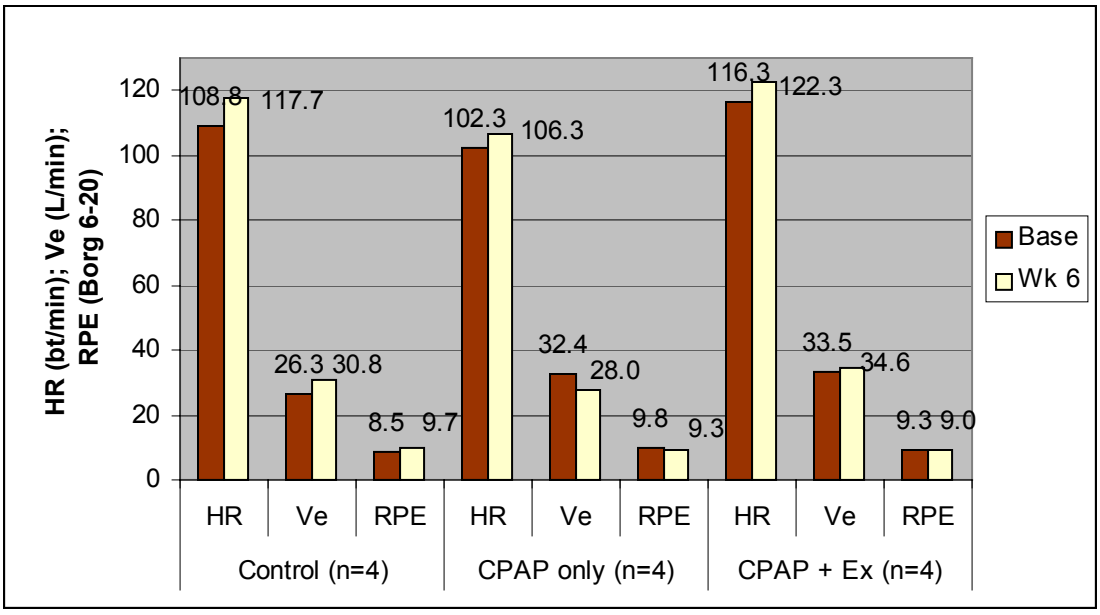

Figure 8. Cardiopulmonary Responses to Cycle Ergometry at 50% of Peak Oxygen Uptake before and after 6-week treatment(s).

CHAPTER IV

SUMMARY AND CONCLUSIONS

Obstructive sleep apnea is a serious disorder that has gained increasing amounts of attention over recent years. Epidemiological studies have identified this syndrome in 2% to 4% of middle-aged adults with prevalence rates reported as high as 9% for women and 24% for men [18]. In the healthcare community, standards and criteria for diagnosis of OSA are still evolving and randomized trials are needed to clearly establish the long-term efficacy of alternative medical and surgical interventions. Overnight polysomnography (PSG) remains the gold standard in the diagnosis of sleep-disordered breathing. However, despite the high cardiovascular morbidity and mortality associated with OSA, the substantial inconvenience and cost of overnight PSG may delay and/or prevent routine evaluation. Therefore, might the introduction of simpler, less expensive screening tools further help recognize patients with high probabilities of OSA and thus help physicians focus on candidates likely to be afflicted with this disorder? To date, only pulse oximetry [196] has shown results consistent with disease severity when compared to PSG. For several years, heart rate variability (HRV) analysis has been utilized as a noninvasive technique for assessment of cardiovascular autonomic control [129, 173]. Decreased HRV, indicating a decline in parasympathetic nerve activity, is an established indicator of risk for sudden cardiac death following myocardial infarction [132]. Furthermore, new evidence in the medical literature indicates that HRV is also altered in patients with sleep-disordered breathing, even in the absence of hypertension, heart failure, or other disease states [109]. In addition to HRV, what evidence do we have about the exercise response characteristics and functional capacities of OSA patients? Exercise

testing has a wide range of clinical applications and provides physicians with a high yield of clinically useful information. Unfortunately, we know very little about these clinical tools in patients with OSA. Therefore, we explored the relationships between PSG markers of sleep function OSA disease severity and cardiovascular function using HRV, blood pressure (BP), and exercise testing.

OSA patients in this study spent more time in non-rapid eye movement sleep (NREM) and less time in rapid eye movement (REM) sleep compared to normals, which may be an indirect indicator of sleep fragmentation. Previous research has shown that hypertension can be directly attributed to the repeated and partial apneic events that disrupt autonomic cardiovascular reflexes during sleep [66-69]. Our results identified several unique circadian patterns in daytime HRV between OSA patients and controls. Surprisingly, OSA patients had lower resting HR's throughout the day (except for PM) and displayed greater cardiovascular variability. These results contrast data reported by Narkiewicz et al. [109] and may be attributed to several differences including HRV analysis technique, sample size, OSA disease severity, occupation, and physical fitness. Furthermore, we noted distinct patterns of HRV during the day, which may be independent from measures obtained during a 24-hr recording period. We concluded that time domain HRV measures may be dependent on duration of the collection period and time of day. Furthermore, standardization of HRV techniques and time intervals is necessary to compare results with previous and future research.

This study also reported several significant differences in daytime measures of systolic and diastolic blood pressure. These differences were most notable in the afternoon and evening hours, which might suggest augmented sympathetic activity that

persists later into the day. The recurring surges of blood pressure during sleep and increased sympathetic activity during wakefulness may result in excess circulating catecholamine levels [191]. Over time, this may decrease baroreflex sensitivity and/or reset the baroreceptor function curve to higher levels of pressure, possibly leading to hypertension.

Research related to exercise tolerance of OSA patients is sparse. A search of the published literature yielded only nine studies with relevance to physiologic aspects of exercise in the OSA patient [33-35, 38, 39, 43, 44, 46, 167]. These studies have utilized exercise as a means to perturb physiological regulations to better understand functional abnormalities associated with OSA. In the current study, measured VO_{2pk} was not significantly different between OSA patients and control subjects. However, when compared to predicted VO_{2pk} values, measured values were significantly lower. Furthermore, REM sleep duration was positively related to peak functional capacity in the OSA group. Our study extends the research information available on exercise tolerance of OSA patients. Vanuxem et al. [46] reported lower maximal oxygen uptakes in OSA patients compared to a group of healthy controls. These investigators also found the OSA patients to have low peak blood lactate levels and delayed lactate elimination post-exercise, suggesting impaired glycolytic and oxidative muscle metabolism that may be implicitly related to this disorder. In addition, VO_{2pk} was significantly related to disease severity. This is consistent with findings reported by Tremel et al. [192]. They found a significant relationship between RDI and VO_{2pk} in 34 patients with heart failure. Inherently related to exercise capacity, we noted several inverse relationships between disease severity (RDI) and submaximal and peak heart rates. These finding extend the results of Aguillard

et al. [168]. They reported that 50% of OSA patients performing maximal cycle ergometry achieved a HR_{max} that was at least 2 standard deviations below their predicted HR_{max}. The reasons for these associations are unknown. However, it may be that the repetitive surges in blood pressure during sleep and augmented sympathetic activity during wakefulness may result in structural downregulation of cardiac beta-adrenergic receptors [171, 172, 186]. Receptor desensitization might serve as a protective mechanism from the adverse effects of increased catecholamine levels. As a result, HR response in OSA patients may be blunted, thus impacting oxygen transport capabilities and the ability to perform sustained physical activity.

Practical and Clinical Implications

OSA is a serious disorder that affects up to 24% of middle-aged males. Excessive daytime sleepiness is the most commonly reported symptom among OSA patients and has been implicated as the cause of a growing number of transportation and industrial accidents resulting in numerous fatalities and injuries every year. Unfortunately, a vast majority of people with OSA are simultaneously sleep deprived secondary to a demanding work schedule and various other lifestyle factors. This fact limits the number of people who seek treatment and hampers the ability of physicians to successfully recognize and diagnose sleep apnea. The substantial cost and inconvenience associated with polysomnography may also deter patients from routine evaluation. Therefore, information concerning exercise tolerance and hemodynamic function in OSA patients may add new and clinically meaningful information to the process of grading disease severity and/or assessing outcomes following treatment with nCPAP or surgery.

Recommendations for Future Research

Based on the findings of the current study and the available research pertaining to heart rate variability, exercise tolerance, and cardiovascular dysfunction in patients with obstructive sleep apnea, the following recommendations are made:

1. Sample size has been problematic in terms of describing physiological differences among patients with OSA and matched control subjects. Suspicion for sleep-disordered breathing was diminished in control subjects via thorough medical history including sleep-related questionnaires and symptom review. However, a lack of polysomnography measures in control subjects prohibited meaningful comparisons regarding relationships noted between markers of sleep function and measures of HRV, blood pressure, and exercise response characteristics. The findings in this study warrant further investigation. Therefore, upon completion of the current study and resultant publications, a grant proposal should be developed and submitted thus allowing for more advanced diagnostic testing, i.e. plethysmography and polysomnography studies for a larger sample of patients.
2. Exercise testing among OSA patients may provide new and clinically meaningful data in diagnosing the severity of OSA. The results of this study, although preliminary, may indicate that OSA patients exhibit a blunted heart rate response to graded exercise. Furthermore, this may be related to OSA disease severity. Exercise testing among consecutive patients with a broad range of documented OSA severity may help delineate this relationship.
3. Carefully controlled exercise training studies in OSA patients are needed. The available literature has the confounding problems of medications, weight loss, and

OSA-related comorbidities, i.e. cardiovascular disease, diabetes, and hypertension. Furthermore, age and range of OSA disease severity should be aptly defined prior to recruitment since both may affect certain response variables, i.e. blood pressure.

4. Previous research has demonstrated that exercise capacity is improved even after a short trial with nasal continuous positive airway pressure. However, studies investigating the changes in functional capacity following surgical intervention are non-existent. Studies should focus on the physical (exercise tolerance) and perceived (quality of life) improvements post-surgical intervention.

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APPENDIX A

DETAILED METHODOLOGY

Subject Recruitment

Despite a significant number of new patients (~20-25 per month) referred for overnight polysomnography, an inability to make a sufficient number of patient contacts was a limiting factor in previous research done at this facility. Many patients did not satisfy admission criteria for medical reasons or declined due to the fact they lived inconveniently far from the clinical and exercise training facilities. In addition, many patients did not follow-up with their scheduled appointments. Previous attempts to recruit subjects were less than optimal since personnel were only able to be present one half-day per week to meet patients. Since clinic staff was busy with routine patient care and related office management work, they were not able to do much but present informational flyers and refer names and telephone numbers of prospective volunteers to the study coordinator. When presented with information in this manner, a high percentage of patients simply commented that participation appeared to "involve too much time" and therefore, they would not be interested in speaking with the study coordinator. Therefore, the research team decided it would be beneficial to hire a Clinical Research Coordinator (CRC) that would be available in the clinic on every occasion when eligible patients were first identified to assess patient eligibility and interest; educate in a timely way about the study requirements and benefits; and to answer any questions related to the study protocol. The primary responsibilities for the CRC are presented in Table 1.

Table 1: Clinical Research Coordinator Responsibilities

- Assist research staff in identification, recruitment ($\geq$ 5/month), of medically eligible patients;
- Schedule initial and follow-up evaluation procedures;
- Promote adherence to medical treatments and study protocol via follow-up telephone calls, office visits, and home visits, i.e. case management;
- Assist research staff in subject exercise testing and evaluation procedures.
    - Assist research staff in measurement of autonomic nervous system responses, i.e. Schiller and Polar heart rate variability setup and measurement;
    - Collect pre-exercise test blood samples.
- Assist research staff in management and storage of data from medical records, questionnaires, and PSG.
    - Duties include review of polysomnography (PSG) and medical records for indications, contraindications, and special medical considerations that pertain to the study;
    - Administration, scoring, and storage of data in the computer database for questionnaires, PSG, and evaluation procedures.

EXPERIMENTAL DESIGN

A flow chart detailing patient progression through the study protocol is presented in Figure 1. After an initial medical evaluation at the Southwest Virginia Sleep Disorders Center (SVSDC) in Christiansburg, VA, the Clinical Research Coordinator (CRC) briefed each eligible patient who was referred for a full-overnight polysomnography (PSG) study about the purposes, requirements, and benefits of participation in the study. Only newly diagnosed patients with a respiratory disturbance index (RDI) between 5 to 60 events/hour were eligible to participate. In addition, each patient was screened by medical history to exclude those with a history of cardiovascular or pulmonary disease; or history of metabolic or endocrine disorders. Additional exclusion criteria included:

- Current use of anti-hypertensive medication or severe hypertension;
- Current smoking or use of sedatives and/or muscle relaxers;

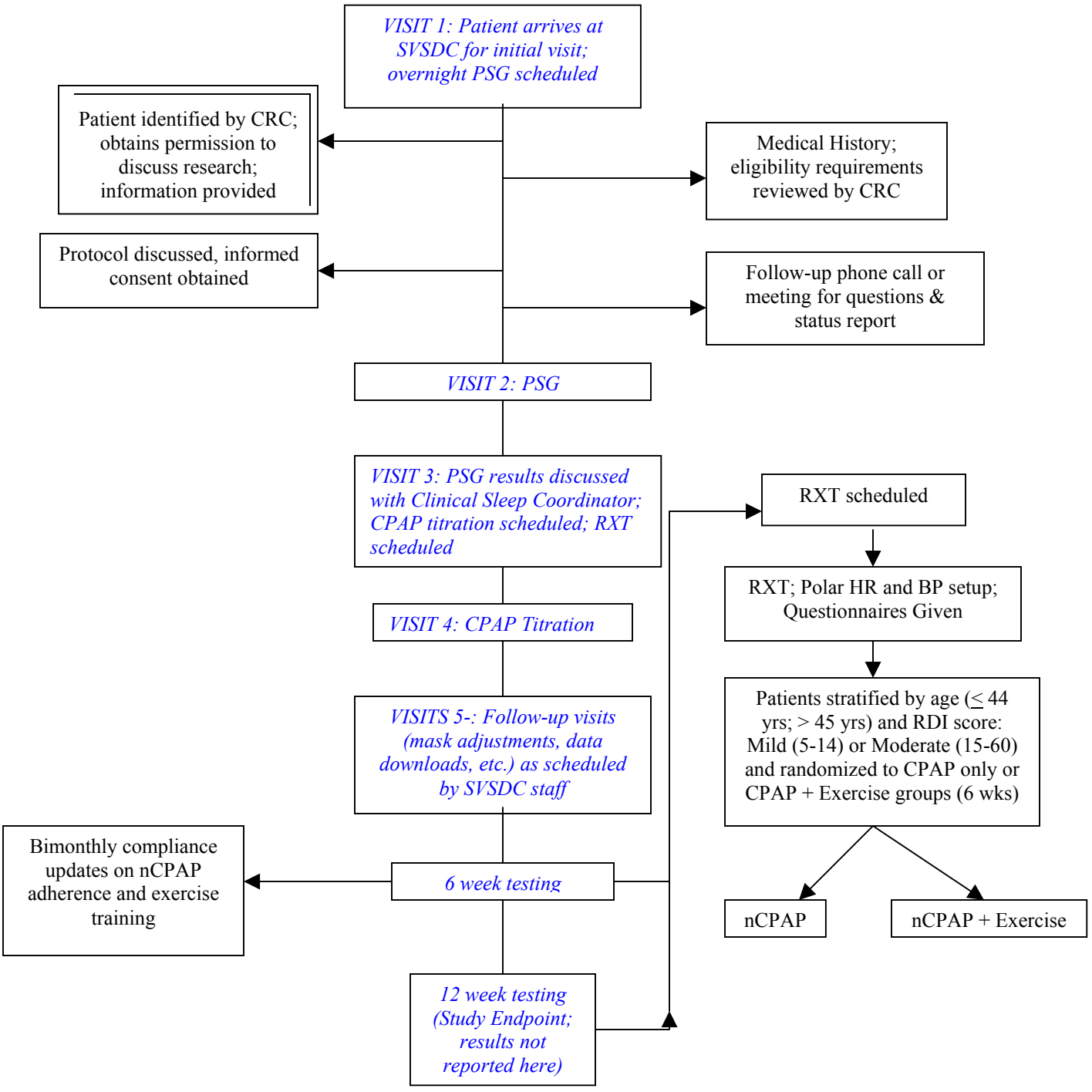
- Recent history (< 6 months) of moderately vigorous physical activity greater than 3 days per week (> 30 minutes per session); or
- Any orthopedic, musculoskeletal, or neuromuscular disabilities that would preclude moderate physical activity.

Those who qualified were then scheduled for their baseline exercise test. Prior to the exercise test, the CRC collected anthropometric data, i.e. height, weight, and neck, waist, and hip circumferences from each patient. Afterwards, each was provided with several subjective questionnaires used in this investigation. These included: Veterans Specific Activity Questionnaire (VSAQ) to subjectively predict functional capacity (METS); Epworth Sleepiness Scale (ESS) to subjectively assess daytime sleepiness; Medical Outcomes Study Short Form-36 (MOS SF-36), a multi-item scale that assesses various health concepts related to quality of life; and a 4-day dietary recall. Dietary intervention was not included in this investigation, however as a courtesy to those who volunteered, a dietary analysis and recommendations were made upon completion of the study. Each patient was also instructed on the use of the Polar RR Recorder™ to measure heart rate variability, and the Omron HEM-705CP, an automated digital blood pressure device used to measure daytime blood pressure. Detailed instructions for these devices are presented in Appendix B and C, respectively.

After completing the exercise test, each OSA patient was stratified by age and disease severity and then randomly assigned to a treatment of nasal CPAP only, or nasal CPAP plus moderate aerobic exercise. All subjects were subsequently followed for a period of 6 weeks before repeating all measures. The CRC and research staff attempted

to make regular contact, i.e. bimonthly, with each person regarding nCPAP and exercise compliance.

Figure 1. Flow Chart: Patient Progression Through Study Protocol



SUBJECTS

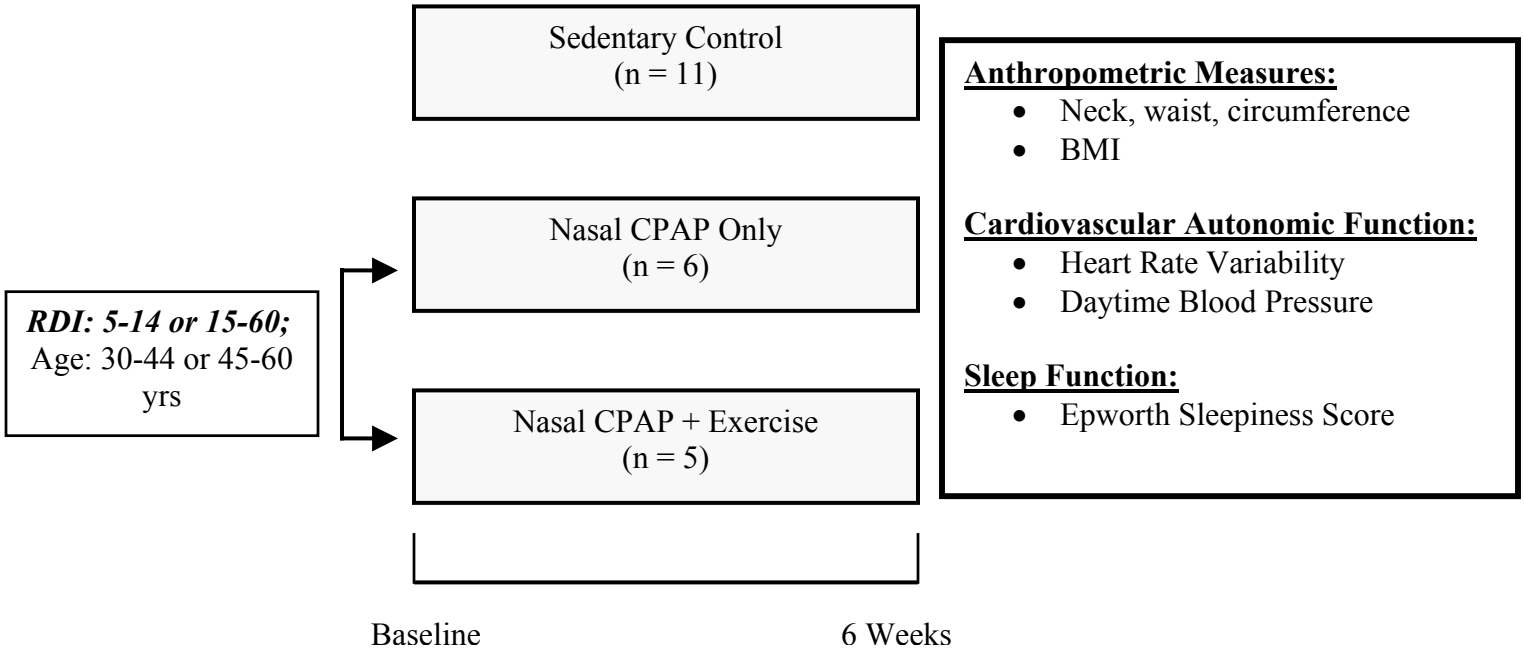
All patients in this study were referred to the Southwest Virginia Sleep Disorders Center (SVSDC) in Christiansburg, Virginia for suspicion of a sleep-related breathing disorder. Ten subjects (4 male, 6 female) with newly diagnosed OSA were recruited from a group of volunteers referred for overnight polysomnography (PSG). Each subject was screened by medical history to exclude those with a history of cardiovascular or pulmonary disease; or history of metabolic or endocrine disorders. Additional exclusion criteria included: current use of anti-hypertensive medication or severe hypertension; current smoking or use of sedatives and/or muscle relaxers; recent history (< 6 months) of moderately vigorous physical activity greater than 3 days per week (> 30 minutes per session); or any orthopedic, musculoskeletal, or neuromuscular disabilities that would preclude moderate physical activity. In addition, 10 apparently healthy (non-OSA) subjects (5 male, 6 female) matched for age and body mass index (BMI) were recruited to serve as controls. Suspicion of a sleep-related breathing disorder was reduced in control subjects via a thorough health history questionnaire, standardized sleep questionnaire (Epworth Sleepiness Scale, ESS)[178], sleep-related symptom review, and clearance to participate from their primary care physician.

The Institutional Review Board of Virginia Polytechnic Institute and State University approved the study and all subjects gave their informed consent to participate.

Treatment Randomization

After identification by the CRC, eligible subjects were stratified according to age and disease severity (Respiratory Disturbance Index, RDI) and then randomized to either **nasal CPAP only** (CPO) or **nasal CPAP + exercise** (CPE) such that, upon completion of the trial, the groups were balanced (Figure 2). Subjects were not informed of their assigned treatment until after completing the baseline exercise test.

Figure 2. OSA Patient Treatment Randomization



MEASUREMENTS

Polysomnography

Each OSA patient completed a health history questionnaire, standardized sleep questionnaire (Epworth Sleepiness Scale, ESS)[178] and overnight polysomnography study (PSG) from which a diagnosis of OSA was made. Conventional techniques were employed when performing the PSG studies and included, electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG). The monitoring period also included the evaluation of respiratory effort, airflow, oxygen saturation, and body position and movements.

Anthropometric Data

Anthropometric measures included height (meters), weight (kilograms), and neck 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 (cm). All measurements were taken at baseline and 6 weeks.

Resting Measures

Immediately prior to the exercise test, resting hemodynamic measures were taken while subjects were in a seated position for a minimum of 5 minutes. Blood pressure was assessed with a standard sphygmomanometer and stethoscope. Resting heart rate (HR) and 12 lead electrocardiogram (ECG) were assessed with the Schiller AT-10® ECG system. The Vmax 229® (SensorMedics, Yorba Linda, CA) metabolic system was used to collect and analyze expired respiratory gases at rest and during each exercise test. Each subject was fully informed of the testing procedures and measurements that would

be obtained during the test, i.e. blood pressure (BP), electrocardiogram (ECG), heart rate (HR), rating of perceived exertion (RPE, Borg 6-20), cardiac output (Qc), and oxygen uptake (VO_2).

Cardiac Output Measurement

Prior to fitting subjects with the breathing apparatus, i.e. mouthpiece, the procedure for the non-invasive determination of Qc was explained and demonstrated in detail. Subjects then practiced the technique several times until they felt comfortable with the procedure. For each Qc measurement, subjects were instructed to continue normal breathing. At each pre-determined measurement, i.e. rest, 2 minutes, and 5 minutes, subjects exhaled to near residual volume. A hand signal informed the technician that the subject could no longer exhale any additional volume. At this time, the Vmax 229® system switched to a test gas mixture containing 0.3% acetylene, 0.3% methane, 0.3% carbon monoxide, 21% oxygen, and the balance nitrogen. Subjects were then instructed to inhale to near maximal lung capacity and perform a breath hold of approximately 1 to 2 seconds after which they slowly exhaled for a period lasting 6 to 8 seconds [180]. Proprietary software (SensorMedics, Yorba Linda, CA) was used to determine Qc. From Qc measurements, resting and submaximal exercise measures of cardiac index (CI), total peripheral resistance (TPR), stoke volume (SV), and stroke volume index (SVI) were calculated.

Ramp Exercise Test

The ramp exercise test (RXT) was completed on an electronically braked cycle ergometer ($CardioO_2$, MedGraphics, St. Paul, MN). Subjects began pedaling at an initial work rate of 25 watts and then ramped 5 watts every 20 seconds. The test was planned

for a total duration of 8-12 minutes. Cardiopulmonary measurements were obtained throughout the RXT with the SensorMedics Vmax 229® (SensorMedics, Yorba Linda, Ca.) metabolic cart. Subjects were asked to continue exercising until they obtained a "maximal" effort (RPE > 17). Heart rate and ratings of perceived exertion (RPE) were recorded every minute. Blood pressure and Qc were taken every two minutes. A licensed physician as well as a certified Exercise Specialist™ (American College of Sports Medicine™) supervised each test. All subjects were continuously monitored during the exercise test and the immediate post-exercise recovery period for signs or symptoms suggestive of ischemia. Test termination criteria were in accordance with standards set by the American College of Sports Medicine™ (ACSM) [91]. The results from the RXT were used to design an individualized aerobic exercise program for subjects randomized to the nasal CPAP plus exercise group. Measurements of interest included submaximal and maximal: oxygen uptake (VO_2), cardiac output (Q_c), ventilatory threshold (VT), mean arterial pressure (MAP), and recovery heart rate (HR) and blood pressure (BP).

Heart Rate Variability

Heart rate variability (HRV) was measured at baseline and 6 weeks using the Polar R-R Recorder™ (Polar Electro, Kempele, Finland), which summed over the cardiac cycles for approximately 8 waking hours, i.e. 9am to 5pm. Detailed instructions for the Polar R-R Recorder™ are presented in Appendix B. To control for various heart rates between individuals, only 40,000 normal-to-normal RR intervals, or cardiac cycles, were used in the analyses. Furthermore, only time domain measures of HRV were considered for this investigation. Measures included: the mean RR interval; standard deviation of all

normal RR intervals (SDNN); percentage of all normal RR intervals greater than 50 milliseconds (pNN50); and average heart rate. All measures were calculated after manually correcting data for ECG artifact, non-physiologic readings, and extrasystoles.

Daytime Blood Pressure

Recordings of daytime blood pressure were obtained at baseline and 6 weeks using an automated digital blood pressure device (Omron HEM-705CP). The methodology used for obtaining measurements was in accordance with the manufacturer's instructions (Appendix C). Multiple recordings were taken upon awakening in the morning; mid-day, i.e. noon; early evening, i.e. 5-6 PM; and just prior to sleep. Subjects were instructed to obtain recordings in a seated position after a 5-min rest period and to abstain from caffeine and nicotine products and refrain from vigorous physical activity for a minimum of 12- and 24-hr, respectively prior to taking measurements. A minimum of 2 measurements were recorded at each specified time until 2 measurements were recorded that were $\leq$ 5 mmHg apart. In addition, subjects were asked to complete a subjective questionnaire rating their physical activity, emotional status, i.e. stress level, for that day (Appendix C).

TREATMENTS

Nasal CPAP Therapy

All OSA subjects were fitted with an auto-titrating nCPAP device (ResMed® Auto-Set® Therapeutic, ResMed Corporation, Poway, CA). This automatic titration system was designed to act preemptively by increasing pressure in response to inspiratory flow limitations and adjust pressure on a breath-by-breath basis to suit patient needs as

they varied throughout the night. As a result, the patient received the minimum pressure required for effective therapy. The lower pressures were thought to improve patient comfort, reduce pressure-related side effects, and lead to increased patient compliance throughout the study. Table 2 lists the advantages of the Auto Set® T.

Table 2. Advantages of the Auto Set® Therapeutic

- Provides effective therapy at the lowest mean pressure;
- Adapts to patients' changing pressure needs on short- and long-term basis;
- Responds to flow limitation, snore, apneas and mask leak;
- Provides greater breathing comfort through smooth, quiet pressure delivery;
- Provides visual display for quality of mask fit, including optional alert tone in presence of significant leaks.

All patients had close follow-up through appointments at approximately 1, 2, and 6 weeks (or as dictated by the SDRC staff) at the Sleep Disorders Network Center and, in addition, received regular contract from the CRC and/or research staff to encourage compliance with their respective treatment protocol, answer questions, and offer encouragement and support. In addition, all patients on nCPAP returned to the Sleep Disorders Network Center at the aforementioned intervals (or, as determined by SVSDC staff), and utilizing ResMed's proprietary AutoScan™ software, data such as mask leakage, dates and hours used, i.e. compliance, and the apnea/hypopnea index was obtained by downloading directly from a built-in memory chip of the AutoSet® T directly to a computer. This allowed the physician and researchers to get a detailed picture of patient compliance and effectiveness of treatment.

Aerobic Exercise Program

Subjects randomized to the nCPAP and aerobic exercise treatment group exercised 3 to 4 times per week for 30 to 40 minutes per session for 6 weeks. For the first two weeks, subjects performed supervised exercise training sessions on a cycle ergometer or treadmill at the Health and Exercise Science Lab (HESL) of Virginia Tech or the Town of Blacksburg Senior Citizen Exercise Center (BSCEC). Clinical exercise physiology graduate students were present to assist and monitor these sessions. During this time, patients were familiarized with aspects related to their exercise prescription, i.e. target HR, RPE, and self-monitoring, i.e. pulse monitoring and data recording. Activities in these exercise facilities included walking or cycle ergometry, in accordance with individualized plans specified by the research staff. Initially, exercise was performed 3 days/wk, 30 min/session, at an intensity range of 50-60% of VO_2pk. Exercise sessions included a 5 to 10 min warm-up and cool-down. Blood pressure, HR, and RPE were monitored and recorded for each supervised exercise session. Progression of exercise was based on the subjects' ability to maintain their target HR, i.e. at 50-60% VO_2pk and perceived effort, i.e. RPE. Increases in exercise duration preceded those of intensity until subjects were able to maintain 30-40 min of continuous exercise. Thereafter, increases in intensity were made that allowed subjects to maintain a HR at an intensity range of 50-60% VO_2pk. The goal of this training regimen was for patients to expend an additional 100 to 200 kcal/session. Two weeks after the start of the supervised exercise training program, patients were requested to transition systematically into a pattern of exercising outside of the supervised sessions on days when they are not scheduled for supervised exercise, and given the option to exercise unsupervised on one of their scheduled 3

days/wk. Exercise logs were distributed (See Appendix F) to document the additional quantity of exercise over this period and weekly contact was made to answer questions and obtain feedback on their current training program and physical activity status. By the end of the first 4 weeks, subjects were fully transitioned to a schedule of exercising 2 to 3 days/wk unsupervised and 1-day/wk supervised. See Appendix D for a detailed description of the exercise program regimen and progression.

References

1. Johns, M. W. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 14:540-545, 1991.
2. Medicine, A. C. o. S. *ACSM's Guidelines for Exercise Testing and Prescription*. 6 ed. Baltimore: Lippincott Williams & Wilkins, 2000, 368.
3. Zenger, M. R., M. Brenner, M. Haruno, D. Mahon, and A. F. Wilson. Measurement of cardiac output by automated single-breath technique, and comparison with thermodilution and Fick methods in patients with cardiac disease. *Am J Cardiol*. 71:105-109, 1993.

APPENDIX B

DETAILED POLAR R-R RECORDER™ SPECIFICATIONS AND INSTRUCTIONS

Polar R-R Recorder™ Specifications

Size	75mm x 110mm x 20mm (3.0" x 4.3" x 0.8")
Weight	146g (5.2 oz)

Polar R-R Recorder™ data storage capacity

R-R data	> 24 hours (with accuracy of 1 ms; 2000Hz)
ECG sequences	> 30 x 20s (with 100Hz sampling frequency)
Power supply	NiCd batteries (2 x 1.2V)
Charging time	< 5 hours
Operation time with fully charged battery	> 30 hours
Readiness for 24 hours operation	> 72 hours (after being fully charged)
Water resistance	The Polar R-R Recorder unit is **not** waterproof

Polar R-R Recorder™: ECG leadwires

Two pieces, length	45 cm (18")

Polar R-R Recorder™: Connectors

Flat snap connector (female) to electrode belt or disposable electrodes

Model DIN socket to R-R Recorder unit

Polar R-R Recorder™: Electrodes

Special Polar R-R Recorder electrode belt with flat snap connectors

Connector size (male) 3.9 mm (0.154")

Polar R-R Recorder™: Optical serial interface

RS-232 protocol between interface and PC

9-pin D-connector to PC (female)

Two-way IR-transfer between R-R Recorder™ and interface

General Instructions

1. **Battery Charging:** The device must be charged for ~ 3 to 4 hours prior to using. A red light will appear on the unit and will turn green when fully charged. Once fully charged, the device will operate for approximately 30 hours. If the device is not used for a period > 72 hours, charging should be repeated.

2. **Computer Interface and Setup:** The Polar RR Recorder is connected to a computer via the optical serial interface cable that connects to a port on the computer (generally in back). This interface serves two primary purposes. It allows for patient setup and data downloads.

3. **Subjects Preparation:** The electrode chest strap should be secured around the subject below the chest muscles. The adjustable strap can be modified to fit most subjects. Once the strap is secure, connect the person to the computer by connecting the red lead wire to the left electrode and black to the right electrode. The opposing ends of the lead wires connect into the recording unit.

4. **Setting Parameters**:
    a. Setting the QRS filter
        i. Define a QRS filter for a new person.
        ii. Select **New Recording**. A window with title "ECG Curve" appears.
        iii. The software displays online ECG at 4 seconds intervals.
        iv. Select **Stop** to stop the online ECG. Choose a QRS complex from the display with the vertical cursor lines. Use **Expand/Compress** to expand or compress the picture to align the lines accurately.
        v. Select **Set Recorder** to write QRS filter to the R-R Recorder.
        vi. Select **Start** to restart the online ECG display
        vii. Select **Matched Filter** from **Filter Output/Filter Type** to see the signal produced by the filter you just set. If the signal is correct, select **Close** to exit the filter setting. Otherwise, if there is no clear symmetrical pulse in the signal, select Comb Filter from **Filter Output/Filter Type** and repeat the filter setting.

    b. Setting time of day
        i. Select **Trigger Setup**.
        ii. A window with title **Recorder Parameters** appears.
        iii. Select **Time & Day;** the current time of day setting shows up on the screen. If the time is not correct specify new time, or
        iv. Select **Get Realtime** to read time and date information from the PC.
        v. Select **Set Recorder** to write Time & Day to the R-R Recorder.
        vi. Select **Close** to exit the Time & Day setting.

c. Setting the recording time
    i. Select **Trigger Setup**. A window with title **Recorder Parameters** appears. Check that the time of day of the R-R Recorder™ is correct.
    ii. Select **Recording Time**; the previous Recording Time setting shows up on the screen.
    iii. Specify **new start** and **end times** for the recording.
    iv. Select **Start button**, if you want to start recording by pressing the start button. If the **Start button** is enabled the recording can be activated by pressing (and holding) the start button for five seconds.
    v. Select **Multirec On** if you want to do more than one recording at any given time. In this mode the recording length is specified (in HH:MM:SS) instead of the recording end time. Recording is activated either by time or by pressing the start button.
    vi. Select **Set Recorder** to write Recording time to the R-R Recorder.
    vii. Select **Close** to exit the Recording time setting.

d. Setting limits for automatic ECG pickup
    i. Select **Trigger Setup**. A window with title **Recorder Parameters** appears.
    ii. Select **ECG pickup**. The previous ECG pickup setting shows up on the screen.
    iii. Specify **maximum** and **minimum** (1500 ms and 300ms, respectively for this study) R-R interval times in milliseconds (ms) for automatic pickup.
    iv. Specify **maximum** R-R variation limit in percentages (20 % for this study) for automatic pickup. A **20 seconds sequence of ECG waveform** will be saved in memory: **10 seconds before** and **10 seconds after**.
    v. Select **Set Recorder** to write ECG pickup to the R-R Recorder.
    vi. Select **Close** to exit the ECG pickup setting.

e. Once setup is complete, disconnect the Polar recording unit from the computer. The device should blink green to signal that the Recorder is ready to go. Give the subject the recording unit, wires, electrodes and chest strap.

5. **Downloading Recorded Data**
    a. Select **Read Recorder**. A window with title **Read Recorder** appears.
    b. Select **Transfer R-R and ECG Data** and **Start** to read both R-R-data and ECG data.
        i. **Important Note**: Prior to pressing start, type in the person's name, subject number, and time point (baseline, 3-week, 6-week, or 12-week) into the appropriate spaces. Then select **START**.

c. Select **Transfer R-R** and **Start** to read only R-R-data.
    i. R-R-data will be automatically saved to the disk in file XXX.RRM.prft
    ii. ECG data will be automatically saved to the disk in file XXX.ECG01.prft
d. Select Close to exit.

6. **Analysis of Heart Rate Variability in the Time Domain**
    a. To ensure accurate filtering of HRV data, all data was manually filtered using formulas entered into an excel spreadsheet. Before entering into the spreadsheet, the data must first be converted to a text (.txt) file. To do this, complete the following steps:
        i. Select a portion of the data that is to be converted. Drag the mouse over the data area while left clicking and holding the mouse button.
        ii. Select **File**, then **Export;**
        iii. Replace the ".rrm" at the end of the file with ".txt" and save again. This will allows the data to be viewed numerically.
        iv. Copy all the data and paste into the spreadsheet.

    b. Once entered into the spreadsheet, the data is filtered using the following steps:
        i. Only those numbers greater than 300 and less than 1500 are used in the final analysis. Numbers outside this range represent non-normal physiological resting heart rates or extrasystoles and were not included in the analyses.
        ii. The difference between consecutive RR intervals is calculated.
        iii. The total number of RR intervals greater than 50 milliseconds (NN50) is calculated. The percentage of NN50 to the total number of RR intervals analyzed is then calculated.
        iv. The mean, standard deviation, and average heart rate are then calculated.

APPENDIX C

DETAILED OMRON HEM-705CP MANUFACTURER OPERATING INSTRUCTIONS AND BLOOD PRESSURE GUIDELINES

How to Take a Reading (Operating Instructions provided by manufacturer)

1. The cuff should be correctly assembled when it is removed from the box. If not, pass the end of the cuff farthest from the tubing through the metal D-ring to form a loop. The smooth cloth should be on the inside of the cuff loop, and the sewn-hook material should be on the outside. The metal D-ring should not touch your skin.

2. Put your left arm through the cuff loop. The bottom edge of the cuff should be approximately 1/2" above the elbow. The cuff tab or green cuff marker (depending on your monitor) should lie over the brachial artery on the inside of your arm. Be sure the cuff tubing aligns with the center of the forearm as shown.

3. Pull on the end of the cuff to tighten it evenly around your arm. Press the sewn hook material firmly against the pile side of the cuff.

4. Place your arm on a table with the cuff at the same height as your heart. Relax your arm and turn your palm upward.

5. Press the on/off button. Wait for the Ready to Measure Symbol to appear before taking a measurement.

6. When the Deflation Indicator symbol appears on the display, press the inflation bulb's Air Release button to deflate the cuff pressure completely. Your blood pressure and pulse will display alternately.

7. Press the Start button, remain still and do not talk. Your blood pressure and pulse will alternately display.

8. Remember to record your measurement.

Omron HEM-705CP Automated
Digital Blood Pressure Device

General Instructions for Blood Pressure Measurements

1. All measurements should be taken in a quiet place and in a relaxed state.

2. All measurements should be taken in a seated position after a 5-minute rest period.

3. A total of **4 measurements** will be taken (Immediately upon awakening; mid-day, i.e. noon; early evening, i.e. 5-6pm; and just prior to sleep).

4. A minimum of 2 measurements should be taken at each time period until 2 measurements are recorded that are $\leq$ 5 mmHg (systolic or first number) apart.

5. Repeated measurements should be separated by a minimum of 2 minutes.

6. Remain still while measurement is being taken.

7. Abstain from caffeine and nicotine products for a minimum of 12 hours prior to taking measurements.

8. Abstain from vigorous exercise for 24 hours prior to taking measurements.

9. In addition to pressing the "MEMORY SET" button after each measurement, please record the time, blood pressure, and heart rate values (from blood pressure device) on the log sheet provided.

APPENDIX D

EXERCISE TRAINING PROTOCOL AND GUIDELINES

Exercise Training Protocol

Weeks 1-2: For the first two weeks, patients performed supervised exercise at the H&ESL, Town of Blacksburg Senior Citizen Exercise Center (BSCEC), or other predetermined facility. During this time, patients were familiarized with aspects related to their exercise prescription, i.e. target HR, RPE, and self-monitoring, i.e. pulse monitoring, signs and symptoms.

- Location(s): HESL and/or BSCEC
- 3 days/wk
- 30 min/session
- All sessions supervised

Weeks 3-4: Two weeks after the start of the supervised exercise training program (3 days/wk), patients were requested to transition systematically into a pattern of exercising outside of the supervised sessions on days when they were not scheduled for supervised exercise, and given the option to exercise unsupervised on one of their scheduled 3 days/wk. Exercise logs (See Appendix F) were distributed to document the additional quantity of exercise over this period and the CRC made weekly telephone calls to obtain feedback on current training and physical activity status.

- Location(s): HESL, BSCEC, other, i.e. other facility; outdoors
- 3-4 days/wk
- 30-40 min/session
- 2 days/wk supervised; 1 day/wk unsupervised (optional)

Weeks 5-6: By the end of the first 4 wk, subjects were fully transitioned to a schedule of exercising 2-3 days/wk unsupervised and 1-day/wk supervised at the H&ESL or other designated health facility.

- Location(s): HESL, BSCEC, other, i.e. other facility; outdoors
- 3-4 days/wk
- 40 min/session
- 1 day/wk supervised; 2 days/wk unsupervised (optional).

Exercise Program Guidelines

1. Do each of the stretching and warm-up exercises as instructed by the staff. You might find it easier to stretch if you walk or cycle easily for a few minutes, then stop and stretch.

2. Start your exercise slowly and gradually increase the intensity to your prescribed level (Target Heart Rate Range). Always give yourself a few minutes at each level to allow your heart rate to adjust before checking the pulse rate (See Below).

3. Check your 10-second pulse several times each session. Doing so will help you gauge the proper intensity level. Lower the intensity, for example, miles per hour (treadmill), or resistance (bike) if you're heart rate exceeds the prescribed heart rate range. Likewise, increase the intensity if your heart rate is below the prescribed intensity.

4. Gradually taper down the intensity of your exercise towards the end of the session. Take time to cool down after exercise.

5. Remain well hydrated, especially after exercise, and throughout the day. Stretching after exercise may also help prevent muscle injury and soreness.

General Exercise Guidelines

1. Wait at least 1 to 2 hours after a large meal before exercising.

2. Wear loose fitting, comfortable clothing.

3. Wear shoes specific to the activity you choose. The shoes should be comfortable and provide ample arch and heel support.

4. Use caution when exercising in hot or cold temperatures. You may have to avoid exercise altogether during these times.

5. Exercise with a partner or in a place which is supervised whenever possible.

How to Check Your Heart Rate

1. Heart rate can be determined by finding the radial pulse, near the thumb side of the wrist on the palm side of the hand.

2. Use your forefinger and index finger and exert moderate pressure over the area.

3. Using a digital watch or watch with a second hand makes taking a pulse easier.

4. Begin the count of pulses at 1 second unless the start of the clock coincides exactly with a heartbeat.

5. Counting the number of pulses in 30-second period and multiplying by 2 can calculate resting heart rate.

    a. **Example**: Resting Heart Rate- You count 35 pulses in 30 seconds then multiply by 2= You then have your heart rate 70 beats/min.

6. Exercise heart rate can be calculated by counting the number of pulses in 10 seconds and multiplying by 6 or the by counting the number of pulses in 15 seconds and multiplying by 4. You may use either method.

    a. **Example**: Exercise Heart Rate (10 second)- You count 20 pulses in 10 second period then multiply by 6= You then have your exercise heart rate 120 beats/min.

    b. **Example**: Exercise Heart Rate (15 second)- You count 20 pulses in 15 second period then multiply by 4= You then have your exercise heart rate 80 beats/min.

APPENDIX E

INFORMED CONSENTS

EXPERIMENTAL AND CONTROL GROUPS

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
Informed Consent for Participant in ResMed2 Project – Experimental Group

Title of research Project: **The short-term effects of exercise training in conjunction with CPAP therapy on cardiovascular function, exercise tolerance, and quality of life in obstructive sleep apnea patients**

Principal Investigators: William G. Herbert, Ph.D., Don Zedalis, MD, John Gregg, DDS, Ph.D., William R. Huckle, Ph.D., Sharon Nickols-Richardson, Ph.D, R.D., Thomas W. Chittenden, MA, Anthony S. Kaleth, MS, Brian J. Hawkins, MS, Lawrence Cross, Ph.D.

I. Purpose of This Research

Your doctor has asked you to come to the Sleep Disorders Center and remain overnight to obtain measurements about the medical aspects of your sleep. He will evaluate the results of this study and inform you whether certain treatments may be recommended. We are conducting a research study to determine the possible treatment advantages of 1) a new generation nighttime positive pressure-breathing device (CPAP) that is prescribed for patients who have obstructive sleep apnea and 2) a moderate exercise program that is added to treatment with the new CPAP device.

II. Procedures

If your initial overnight sleep study shows that you have sleep apnea and you agree to participate in this study, you will be asked to complete the following procedures at three different time points 1) before starting CPAP treatment; 2) after 6 weeks of CPAP treatment; and 3) after 12 weeks of CPAP treatment:

- Allow us to use certain physical and health history information from the medical records at the Sleep Disorders Center.
- Complete questionnaires that request your opinion about the quality of your sleep, your current quality of life, mood, and physical activity status.
- Allow us to complete nutrition evaluations over the course of the study.
- Allow us to complete measurements including height, weight, body circumferences blood pressure, heart rate, and cardiac output.
- You will also be asked to practice a few of the breathing techniques while wearing a special mouthpiece and nose clip; this practice will be needed during you're exercise test, which we will ask you to perform at the Sleep Disorders Center in Christiansburg, VA.
- Allow us to obtain a 24-hour urine sample the day prior to each exercise test and a small venous blood sample (10mL) immediately before and after each exercise test to measure the ability of your blood vessels to relax, as well as how your nervous and cardiovascular systems are adjusting. Part of the blood sample collected before the exercise tests, will be assayed for blood fats. Slight brushing may occur around the area of the needle stick.
- Allow us to obtain measurements of your heart rate and blood pressure collected two consecutive days before your exercise test using small portable devices and

chest electrodes that you may keep with you for this period; these measurements will help the investigators evaluate the nervous system control of your heart.

- Complete a bicycle exercise test of approximately 12 minutes and allow us to measure your maximal fitness level at your peak effort, as well as your oxygen consumption, heart rate, blood pressure, and cardiac output. To measure how much oxygen you use during this exercise, we will ask you to breathe into a lightweight rubber mouthpiece. During exercise, you will breathe only through the mouthpiece and may experience some dryness in your mouth. You will be asked to perform several exercise cardiac output measurements that require you to slowly exhale a special mixture of oxygen and tiny amounts of a harmless gas that doesn't interact with the body; the time you exhale for this measurement will last only 5 to 6 seconds. You may experience more difficulty completing this procedure during higher intensities of exercise, but the investigators will only ask that you do your best to accomplish this.

The total time involved to complete these procedures will be ~1hour and 30 minutes per session. There will be 3 sessions 1) before starting CPAP treatment; 2) after 6 weeks of CPAP treatment; and 3) after 12 weeks of CPAP treatment.

After your first exercise test, you must agree to be assigned to one of two groups for treatment; the investigators will be unable to tell you which group this will be, until after you agree to participate in the study. The groups are:

- A group that will receive CPAP therapy with the new generation device (CPAP alone).
- A group that will receive CPAP therapy with the new device and an organized moderate exercise program; the exercise program will involve physical activities such as brisk walking or similar stationary cycling for 20-40 minutes/day, 3-4 days/week.
- Appropriate use of the CPAP system is detailed in the information and explanation given to you by the sleep staff at the time of OSA diagnosis. If you have any questions regarding the proper use of this device please contact the Research Coordinator.

Details of the Exercise Program: Exercise training will last for 12 weeks. For the first 2 to 4 weeks, exercise sessions will be held at the Health and Exercise Science Laboratory (H&ESL) on the Virginia Tech campus or The Town of Blacksburg Senior Citizen Exercise Facility (TBSCF) located on Patrick Henry Drive near Blacksburg High School. Two weeks after the start of the supervised exercise training program (3 days/wk), you will be requested to increase the frequency of exercise $\geq$ 3days/wk, and be given the option to exercise unsupervised on one of your scheduled 3 days/wk. Between months 1 to 3, you will be asked to exercise at least 4 days per week and report to the H&ESL or TBSCF for at least two supervised exercise sessions/month. Exercise logs and heart rate monitors will be distributed to document the additional quantity of exercise over this period. You will be allowed to participate at the local community activity center or at the University-based adult exercise program that is held three mornings/wk in the same Virginia Tech building as the H&ESL (War Memorial Hall). Activities in the local community center will include walking/jogging or cycling, in accordance with

individualized plans specified by the research staff. To provide flexibility for exercise sessions, subjects will be offered the opportunity to participate in morning, afternoon and/or evening monitored exercise sessions at the H&ESL or TBSCF. Your exercise level will be based on your initial exercise test and will be adjusted, as necessary, after the 6-week test. After completion of the first 6 weeks and at 3 months, all participants will be asked to return for a second and third exercise test, respectively.

III. Risks

It is my understanding and I have been informed that there exists the possibility during exercise of adverse changes during the actual test and/or exercise sessions. I have been informed that these changes could include abnormal blood pressure, fainting, disorders of heart rhythm, and in very rare instances, heart attack or death (~1 death in 10,000 exercise tests). Every effort will be made to minimize these possibilities for you by preliminary examination and by precautions and observations taken during the test. The intensity of the cycling exercise will increase as you pedal, over about 12 minutes. At first it will be very easy and then become harder; during the last few minutes, the work will become very intense and will represent a maximal effort on your part. It may be as hard as any exercise that you remember doing.

Qualified medical personnel will be available to perform CPR and contact the community Emergency Medical Services by telephone to deal with unusual situations, should these occur during your exercise tests. Emergency equipment and defibrillation are available at this facility and a medical professional with training in advanced cardiac life support will be onsite for all exercise testing. However, a thorough screening for signs of active heart disease and a review of your medical records from your primary healthcare provider will be done before you are allowed to take the exercise test. This will further reduce the chance of heart problems during the exercise testing procedure.

I understand that there is a very small risk of injury, heart attack, or death as a result of my performance on this test and participation in exercise training, but knowing these risks, it is my desire to proceed to take the take and be a subject in this research project. I understand that the results of this test will be sent to my primary care physician, if I so request. These results may help to determine my ability to safely perform certain types of physical work or exercise.

I understand that my participation in this research project is voluntary and that I may withdraw at any time, without penalty of any kind. Furthermore, I also understand that there is no guarantee that I will benefit from this research project.

IV. Benefits of this Project

- Both you and your physician will be provided with your individual results from your exercise test. This test is also be used for evaluating the condition of your heart and lungs. If your physician notes a concern after reviewing the results of this procedure, you and your physician may decide that you should consult with an appropriate healthcare specialist. However, any and all costs related to such a

referral and medical care will by borne by you and not by Virginia Tech, nor any of its agents including the investigators.

- You will be provided with and allowed to keep, as a result of participating in the study, a state of art AutoSet T breathing device from the ResMed Corporation. This breathing device costs ~$4,500 and it will be supplied to you without any cost to you or your health insurance provider, other than what would be paid were you to receive the less-advanced CPAP device usually prescribed by Dr. Zedalis for patients not in this study. .
- Participation in this study will result in increased communication about your obstructive sleep apnea care between you, Dr. Zedalis' staff, and the research team. A trained medical professional will act as a research coordinator stay in contact with you to monitor and manage your progress throughout the study, usually on a weekly basis or whenever you request assistance for advice or needs related to your participation in 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 receive three such evaluations, without charge.
- By agreeing to take part in this study, physicians may gain a better understanding of how the heart and lungs function during sleep disordered breathing. This may also result in better care for all sleep apnea patients.

V. Extent of Anonymity and Confidentiality

The results of this study will be kept strictly confidential. At no time will the researchers release my results of this study to anyone other than the individuals working on the project without your written consent. However, if the need arises, I give my permission for Dr. Zedalis' office to obtain my medical records from my primary healthcare physician. Furthermore, I understand that the information I provide will have my name removed and only a subject number (excluding social security numbers) will identify me during analyses and written reports of this research.

VI. Compensation

I can expect the following compensation for my participation in this 3-month study:

- I will receive three maximal exercise tests and resting and exercise cardiovascular assessments (blood pressure, blood flow, ECG, heart rate, etc), along with reports that I may provide to my personal physician. These tests typically cost from $250 to $300 per test in a healthcare facility. This equates to ~ $600;
- I will also receive a $4,500 AutoSet T breathing device from the ResMed Corporation. The added value of this system will depend on the type of standard CPAP coverage and co-payment plan that pertains to your individual health insurance;
- I will receive three nutritional analyses over the 3-month study. This type of analysis normally costs $50 per session. This equates to ~ $150; and

- If I am in the exercise-training group, I will receive 12 hours of exercise training in a supervised setting. These sessions typically cost from $15 to $20 per session. This equates to ~$240.

VII. Freedom to Withdraw
I understand that, if I decline to participate in this research study or choose to discontinue my participation at anytime, there will be no penalties or loss of benefits in my health care that will be provided by the attending physician or physicians who are providing care for me at the Sleep Disorders Center of Southwest Virginia.

VIII. 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.

IX. Subject's Responsibilities
I know of no reason why I cannot participate in this study. I accept that it is my responsibility to:

- Accurately report my medical history;
- Consume no food during the 12-hour period before arriving at the testing lab for a scheduled exercise tests; and consume no foods during the 1-hour before an exercise training sessions;
- Refrain from caffeine, and nicotine products for 24 hours prior to the exercise tests;
- Remain in the testing and/or exercise area 30 minutes after the exercise testing period.
- Attend all exercise sessions for the duration of the study;
- Inform the investigators if I am not able to attend an exercise session at least one day prior to the session;
- Refrain from vigorous physical activity for 12 hours on all exercise testing days.

Report any physical or medical problems that might occur outside the lab during the period of testing, even if I feel it is not related to the testing to: Tony Kaleth (231-6469/951-1136), Tom Chittenden (231-6469/953-1941) or Dr. William Herbert (231-6565/951-0974).

X. Subject's Permission
I have read and understand the informed consent and conditions of this research study. I agree to undergo all screening procedures described above prior to acceptance into the study. I have had all my questions answered. I hereby acknowledge the above and give my voluntary consent for participation in this project.

If I participate, I may withdraw at any time without penalty. I agree to abide by all the rules of the project.

Questions/Response: _____

_____

_____

_____

_____

_____ _____

Signature Date

_____ _____

Witness (Research Coordinator) Date

[ ] Please check the box if you would like the information from these tests sent to your primary care physician.

Physician's Name and Telephone: _____

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

Carol Haskell, MD 382-1165
Research Coordinator

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

Tony Kaleth 231-6469
Investigator

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

Tom Chittenden 231-6469
Investigator

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
Informed Consent for Participant in ResMed2 Project – Control Subjects

Title of research Project: **The short-term effects of exercise training in conjunction with CPAP therapy on cardiovascular function, exercise tolerance, and quality of life in obstructive sleep apnea patients**

Principal Investigators: William G. Herbert, Ph.D., Don Zedalis, MD, John Gregg, DDS, Ph.D., William R. Huckle, Ph.D., Sharon Nickols-Richardson, Ph.D, R.D., Thomas W. Chittenden, MA, Anthony S. Kaleth, MS, Brian J. Hawkins, MS, Lawrence Cross, Ph.D.

I. Purpose of This Research

Your doctor has asked you to come to the Sleep Disorders Center and remain overnight to obtain measurements about the medical aspects of your sleep. He will evaluate the results of this study and inform you whether certain treatments may be recommended. We are conducting a research study to determine the possible treatment advantages of 1) a new generation nighttime positive pressure-breathing device (CPAP) that is prescribed for patients who have obstructive sleep apnea and 2) a moderate exercise program that is added to treatment with the new CPAP device.

II. Procedures

You will be asked to complete the following procedures at three different time points: 1) before starting the study; 2) 6 weeks after the start of the study; and 3) 12 weeks after the start of the study:

- Complete questionnaires that request your opinion about the quality of your sleep, your current quality of life, mood, and physical activity status;
- Allow us to complete nutrition evaluations over the course of the study;
- Allow us to complete measurements including height, weight, body circumferences blood pressure, heart rate, and cardiac output;
- You will also be asked to practice a few of the breathing techniques while wearing a special mouthpiece and nose clip; this practice will be needed during you're exercise test, which we will ask you to perform at the Sleep Disorders Center in Christiansburg, VA;
- Allow us to obtain a 24-hour urine sample the day prior to each exercise test and a small venous blood samples (10mL) immediately before and after each exercise test to measure the ability of your blood vessels to relax, as well as how your nervous and cardiovascular systems are adjusting. Part of the blood sample collected before the exercise tests, will be assayed for blood fats. Slight brushing may occur around the area of the needle stick;
- Allow us to obtain measurements of your heart rate and blood pressure collected two consecutive days before your exercise test using small portable devices and chest electrodes that you may keep with you for this period; these measurements will help the investigators evaluate the nervous system control of your heart;
- Complete a bicycle exercise test of approximately 12 minutes and allow us to measure your maximal fitness level at your peak effort, as well as your oxygen

consumption, heart rate, blood pressure, and cardiac output. To measure how much oxygen you use during this exercise, we will ask you to breathe into a lightweight rubber mouthpiece. During exercise, you will breathe only through the mouthpiece and may experience some dryness in your mouth. You will be asked to perform several exercise cardiac output measurements that require you to slowly exhale a special mixture of oxygen and tiny amounts of a harmless gas that doesn't interact with the body; the time you exhale for this measurement will last only 5 to 6 seconds. You may experience more difficulty completing this procedure during higher intensities of exercise, but the investigators will only ask that you do your best to accomplish this.

The total time involved to complete these procedures will be ~1hour and 30 minutes per session. There will be 3 sessions: 1) before starting the study; 2) 6 weeks after the start of the study; and 3) 12 weeks after the start of the study.

After your first exercise test, you must agree not to initiate any formal exercise programs. Your participation in this study will be deemed as non-exercise or sedentary control group. The initiation of vigorous exercise on your part would greatly compromise the integrity of the research data. By agreeing to participate in this study, you are also agreeing to not participate in vigorous exercise for 3 months.

III. Risks

It is my understanding and I have been informed that there exists the possibility during exercise of adverse changes during the actual test. I have been informed that these changes could include abnormal blood pressure, fainting, disorders of heart rhythm, and in very rare instances, heart attack or death (~1 death in 10,000 exercise tests). Every effort will be made to minimize these possibilities for you by preliminary examination and by precautions and observations taken during the test. The intensity of the cycling exercise will increase as you pedal, over about 12 minutes. At first it will be very easy and then become harder; during the last few minutes, the work will become very intense and will represent a maximal effort on your part. It may be as hard as any exercise that you remember doing.

Qualified medical personnel will be available to perform CPR and contact the community Emergency Medical Services by telephone to deal with unusual situations, should these occur during your exercise tests. Emergency equipment and defibrillation are available at this facility and a medical professional with training in advanced cardiac life support will be onsite for all exercise testing. However, a thorough screening for signs of active heart disease and a review of your medical records from your primary healthcare provider will be done before you are allowed to take the exercise test. This will further reduce the chance of heart problems during the exercise testing procedure.

I understand that there is a very small risk of injury, heart attack, or death as a result of my performance on this test and participation in exercise training, but knowing these risks, it is my desire to proceed to take the take and be a subject in this research project. I understand that the results of this test will be sent to my primary care physician, if I so

request. These results may help to determine my ability to safely perform certain types of physical work or exercise.

I understand that my participation in this research project is voluntary and that I may withdraw at any time, without penalty of any kind. Furthermore, I also understand that there is no guarantee that I will benefit from this research project.

IV. Benefits of this Project

- Both you and your physician will be provided with your individual results from your exercise test. This test is also be used for evaluating the condition of your heart and lungs. If your physician notes a concern after reviewing the results of this procedure, you and your physician may decide that you should consult with an appropriate healthcare specialist. However, any and all costs related to such a referral and medical care will by borne by you and not by Virginia Tech, nor any of its agents including the investigators.
- Participation in this study will result in increased communication about your obstructive sleep apnea care between you, Dr. Zedalis' staff, and the research team. A trained medical professional will act as a research coordinator stay in contact with you to monitor and manage your progress throughout the study, usually on a weekly basis or whenever you request assistance for advice or needs related to your participation in 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 receive three such evaluations, without charge.
- By agreeing to take part in this study, physicians may gain a better understanding of how the heart and lungs function during sleep disordered breathing. This may also result in better care for all sleep apnea patients.

V. Extent of Anonymity and Confidentiality

The results of this study will be kept strictly confidential. At no time will the researchers release my results of this study to anyone other than the individuals working on the project without your written consent. However, if the need arises, I give my permission for Dr. Zedalis' office to obtain my medical records from my primary healthcare physician. Furthermore, I understand that the information I provide will have my name removed and only a subject number (excluding social security numbers) will identify me during analyses and written reports of this research.

VI. Compensation
I can expect the following compensation for my participation in this 3-month study:

- I will receive three maximal exercise tests and resting and exercise cardiovascular assessments (blood pressure, blood flow, ECG, heart rate, etc), along with reports that I may provide to my personal physician. These tests typically cost from $250 to $300 per test in a healthcare facility. This equates to ~ $600; and
- I will receive three nutritional analyses over the 3-month study. This type of analysis normally costs $50 per session. This equates to ~ $150.

VII. Freedom to Withdraw
I understand that, if I decline to participate in this research study or choose to discontinue my participation at anytime, there will be no penalties or loss of benefits in my health care that will be provided by the attending physician or physicians who are providing care for me at the Sleep Disorders Center of Southwest Virginia.

VIII. 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.

IX. Subject's Responsibilities
I know of no reason why I cannot participate in this study. I accept that it is my responsibility to:

- Accurately report my medical history;
- Refrain from vigorous physical activity for 3 months.
- Consume no food during the 12-hour period before arriving at the testing lab for a scheduled exercise tests; and consume no foods during the 1-hour before an exercise training sessions;
- Refrain from caffeine, and nicotine products for 24 hours prior to the exercise tests;
- Remain in the testing and/or exercise area 30 minutes after the exercise testing period.

Report any physical or medical problems that might occur outside the lab during the period of testing, even if I feel it is not related to the testing to: Tony Kaleth (231-6469/951-1136), Tom Chittenden (231-6469/953-1941) or Dr. William Herbert (231-6565/951-0974).

X. Subject's Permission
I have read and understand the informed consent and conditions of this research study. I agree to undergo all screening procedures described above prior to acceptance into the study. I have had all my questions answered. I hereby acknowledge the above and give my voluntary consent for participation in this project.

If I participate, I may withdraw at any time without penalty. I agree to abide by all the rules of the project.
Questions/Response: _____

_____

_____

_____

_____

_____ _____
Signature Date

_____ _____
Witness (Research Coordinator) Date

[ ] Please check the box if you would like the information from these tests sent to your primary care physician.

Physician's Name and Telephone: _____

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

Carol Haskell, MD 382-1165
Research Coordinator

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

Tony Kaleth 231-6469
Investigator

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

Tom Chittenden 231-6469
Investigator

APPENDIX F

DATA COLLECTION SHEETS

DAYTIME BLOOD PRESSURE
EXERCISE LOG
GRADED EXERCISE TEST DATA COLLECTION SHEET

Blood Pressure Measurement Recording Log

Patient Name:
Date:

Upon Awakening	Time	Systolic	Diastolic	Pulse
Measurement #1				
Measurement #2				
Measurement #3				
Measurement #4				
Measurement #5				

Mid-Day	Time	Systolic	Diastolic	Pulse
Measurement #1				
Measurement #2				
Measurement #3				
Measurement #4				
Measurement #5				

Early Evening	Time	Systolic	Diastolic	Pulse
Measurement #1				
Measurement #2				
Measurement #3				
Measurement #4				
Measurement #5				

Before Sleep	Time	Systolic	Diastolic	Pulse
Measurement #1				
Measurement #2				
Measurement #3				
Measurement #4				
Measurement #5				

Please take a few moments to record what you believe to be your overall physical demands, as well as your overall emotional demands during the day. This information is important to help us understand how your daily routine today may have affected your blood pressure and heart rate.

Physical Demands (please circle)

1- Sitting most of the day and very little walking or other activity for the rest of the day.
If other activity, please explain_____

2- Sitting 2/3 of the day, with walking or other light activity at least 1/3 of the day.
If other activity, please explain_____

3- Sitting 1/3 of the day, with walking or other light physical activity 2/3 of the day.
If other activity, please explain_____

4- Little or no sitting during the day, with walking or other physical activities most of the day.
If other activities, please explain_____

I would rate this day's physical activity as: (please circle)

Less than normal Normal More than normal Much more than normal

Please explain:

_____

_____

Emotional Demands (please circle)

1- Less stress than normal
2- Normal amount of stress
3- A little more than normal amount of stress
4- Much more than normal amount of stress

Please comment about any unusual work related or non-work related events that may have happened while you were being monitored for blood pressure, heart rate and urine output.

_____

_____

_____

_____

Virginia Tech – OSA Research Project
Exercise Log

Name: _____ Target Heart Rate Range: _____ 10 sec HR: _____

Date	Time	Weight	Pre-Exercise HR/BP	Exercise Mode	Workload	Duration	RPE	Exercise HR/BP	Post-Exercise HR/BP
			/					/	/
			/					/	/
			/					/	/
			/					/	/
			/					/	/
			/					/	/
			/					/	/
			/					/	/
			/					/	/
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			/					/	/
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			/					/	/
			/					/	/
			/					/	/

OBSTRUCTIVE SLEEP APNEA: RESMED 2
GRADED EXERCISE TEST DATA SHEET

Name _____ **Age** ____ **Wt** _____ **lb/kg** **Ht** _____ **in/cm** **Date** _____

Subject # _____ **Test (circle)**: **BASELINE** **6 WEEK** **12 WEEK**

Neck Circ: _____ **Waist Circ:** _____ **Hip Circ:** _____ **BMI:** _____

MEDICATIONS:

Name	Dose	Time last taken	Name	Dose	Time last taken

Rest HR _____ / _____ **Rest BP** _____ / _____ **Rest Qc** (L/min) _____
standing / sitting standing / sitting sitting

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

Time	Watts	HR	BP	RPE	Qc	ECG Δ/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		/			
16 – 17	280		/			
17 - 18	295		/			

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

RECOVERY	HR	BP	ECG Δ/Symptoms/Comments
IPE		/	
1		/	
2		/	
3		/	
4		/	
5		/	
6		/	
7		/	
8		/	
9		/	
10		/	

Total Test Time: _____ Peak Watts: _____

REASON FOR STOPPING TEST: _____
Comments: _____
_____
_____

APPENDIX G

SCREENING QUESTIONNAIRES

EPWORTH SLEEPINESS SCALE
MEDICAL HISTORY QUESTIONNAIRE
SLEEP CONSULT QUESTIONNAIRE
VETERAN'S SPECIFIC ACTIVITY QUESTIONNAIRE

ResMed2 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	**Chances 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

Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991;14:540-545.

Medical and Health History

Demographic Information:

Name: _____ Age: _____ Date of Birth: _____
Address: _____
Phone number: Home: _____Work: _____
Occupation _____Place of employment _____
Education
(check highest level) Elementary ___ High School___ College ___ Post Graduate____
Person to contact in case of emergency: _____
Relationship: _____Phone: _____
Primary Care Physician: _____ Phone: _____
Marital Status: _____single _____divorced _____married _____widower
Have you ever had a stress test? Yes___ No ___ date_____

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:	_____	_____
High Cholesterol:	_____	_____
Diabetes:	_____	_____
Thyroid problems:	_____	_____
Allergies:	_____	_____

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

_____
_____

Other medical problems ?

_____

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

Type: _____ Date: _____
Type: _____ Date: _____
Type: _____ Date: _____

Have you ever been diagnosed as having high blood pressure? Yes _____ No _____
Are you currently being treated for high blood pressure? Yes _____ No _____
If "yes" please explain:

_____
_____

Are you currently being treated for high cholesterol or hyperlipidemia? Yes__ No __
If yes, Please list medication _____

Medications:

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

Drug _____ Dose _____ Reason Taking _____
Drug _____ Dose _____ Reason Taking _____
Drug _____ Dose _____ Reason Taking _____
Drug _____ Dose _____ Reason Taking _____
Drug _____ Dose _____ Reason Taking _____
Drug _____ Dose _____ Reason Taking _____
Drug _____ Dose _____ Reason Taking _____

Health Habits:

	Yes	No
Do you add salt to your food?	_____	_____
Are you on any special type of diet?		
If yes, how long have you been dieting ____ months		
Who prescribed the diet? Physician____ Self_____		
Please describe diet:		
_____		
_____		
Do you drink caffeinated beverages?	_____	_____
How many cups per day? _____		
Do you drink alcoholic beverages?	_____	_____
How many drinks per week? _____		
Do you smoke cigarettes?	_____	_____
Packs per day: _____		

Exercise Habits

What is your occupational activity level? sedentary____ ; light_____ ; moderate____ ; heavy_____

	Yes	No
Do you engage in regular exercise?	_____	_____

If "yes" please list:

Activity	Frequency (times per week)	Duration (minutes)

Do you ever feel faint, short of breath, or chest discomfort with exertion? _____
If "yes", please explain:

_____
_____

Do you engage in any recreational or leisure-time physical activities?
No__ Yes___ What type_____
How often?_____ times/week For how long?_____

Are there any orthopedic limitations you have that may restrict your ability to exercise on a stationary cycle? _____Yes _____No
If "yes" please explain:

_____
_____

Family History:

Has anyone in your family been diagnosed or treated for any of the following?

	Yes	No	Relationship	Age
Heart attack				
Heart disease				
High blood				
Pressure				
Stroke				
Kidney disease				
Diabetes				

Please sign to indicate the above information is correct:

_____ _____
Print Name Signature

SLEEP CONSULT QUESTIONNAIRE
(Selected relevant questions asked of all OSA patients and control subjects)

Name: _____ Age: ___ Date: _____

Referring Doctor: _____ Primary Doctor: _____

Reason for referral: _____

Accompanied: N __ Y __ Who? _____

Do you snore? Never __ Rare __ Occasional __ Frequent __ For how many years? ___

Who has witnessed your snoring? _____

Has anyone told you that you stop breathing during your sleep? N __ Y __ Who? _____

What time do you usually go to bed during the week? _____ On weekends? _____

How long does it take you to fall asleep? _____ minutes/hours

What time do you usually wake up during the week? _____ On weekends? ____

What wakes you up? Alarm clock? N ___ Y ___ Other: _____

Is your nighttime sleep refreshing? N ___ Y ___

How long does it take you to get out of bed after sleeping? _____ minutes

Do you wake up during the night? N__Y__ # of times: ___ (range) lasting: _____

Why?_____

Do you awaken with headaches? Never ___ Rare ___ Occasional ___ Frequent ___

Do you take naps during the week? N ___ Y ___ How many? __/day

Do you take naps on weekends? N ___ Y ___ How many? __/day

Are your naps refreshing? N ___ Y ___ How long are your naps? _____minutes/hours

Do you have daytime sleepiness? None ___ Slight ___ Moderate ___ Severe ___

Do you fall asleep unintentionally (driving, watching television)? N ___ Y ___

Veteran's Specific Activity Questionnaire (VSAQ)

Draw one line Below the Activities You are Able To Do Routinely With Minimal or No Symptoms, Such As Shortness of Breath, Chest Discomfort, or Fatigue

1 MET:	• Bathing, getting dressed, working at a desk
2 METs:	• Taking a shower • Walking down eight steps
3 METs:	• Walking slowly on a flat surface for one or two blocks. • A moderate amount of work around the house, like Vacuuming, sweeping the floors or carrying groceries.
4 METs:	• Light yard work i.e., raking leaves, weeding or pushing a power mower. • Painting or light carpentry.
5 METs:	• Walking briskly, i.e., four miles in one hour. • Social dancing, washing the car.
6 METs:	• Play nine holes of golf carrying your own clubs. • Heavy carpentry, mow lawn with push mower.
7 METs:	• Perform heavy outdoor work, i.e., digging, spading soil, etc. • Play tennis (singles), carry 60 pounds.
8 METs:	• Move heavy furniture. • Jog slowly, climb stairs quickly, carry 20 pounds upstairs.
9 METs:	• Bicycling at a moderate pace, sawing wood, jumping rope (slowly).
10 METs:	• Brisk swimming, bicycle up a hill, walking briskly uphill, jog six miles per hour
11 METs:	• Cross country ski. • Play basketball (full court)
12 METs:	• Running briskly, continuously (level ground, eight minutes per mile).
13 METs:	• Any competitive activity, including those which involve intermittent sprinting. • Running competitively, rowing, backpacking

APPENDIX H

RAW DATA

Control Subject Raw Data

I. Baseline Control Characteristics

OSA	GENDER	AGE (yrs)	EPWORTH (x/24)	WEIGHT (kg)	HEIGHT (m)	BMI (kg/m2)	Waist (cm)	Neck Cir (cm)
1	MALE	42.00	7.00	72.70	1.76	23.47	88.90	36.80
2	FEMALE	28.00	14.00	92.70	1.69	32.46	96.52	36.80
3	FEMALE	46.00	3.00	87.70	1.60	34.26	94.00	33.00
4	FEMALE	44.00	12.00	81.80	1.63	30.79	99.50	38.00
5	FEMALE	34.00	4.00	71.00	1.68	25.16	79.00	35.00
6	MALE	36.00	5.00	100.00	1.77	31.92	111.00	42.80
7	FEMALE	51.00	5.00	86.40	1.69	30.25	98.30	39.00
8	MALE	45.00	2.00	87.40	1.59	34.57	87.90	35.40
9	MALE	35.00	9.00	58.10	1.69	20.34	71.20	32.40
10	FEMALE	37.00	5.00	71.40	1.69	25.00	83.00	35.80

II. Baseline Time Domain Measures of Heart Rate Variability

OSA	av_rr_am	sdnn_am	pnn50_am	av_rr_n	sdnn_n	pnn50_n	av_rr_an	sdnn_an	pnn50_an	av_rr_pm	sdnn_pm	pnn50_pm	av_rr_t	sdnn_t	pnn50_t
1	759.96	80.53	2.39	809.56	100.18	4.24	826.38	92.92	4.12	824.82	71.87	3.40	805.18	91.13	3.95
2	545.62	78.02	2.46	557.52	70.40	2.23	537.40	64.04	2.26	547.84	72.79	1.02	552.43	73.10	1.95
3	537.93	27.73	0.00	584.48	7.64	0.00	607.01	5.64	0.00	625.04	5.12	0.00	593.62	37.17	0.00
4	567.40	28.94	0.00	620.23	10.32	0.00	651.05	7.75	0.00	676.06	7.02	0.00	635.19	45.80	0.00
5	686.01	72.21	6.57	651.97	77.42	3.80	612.97	81.07	3.41	742.38	85.97	6.97	664.06	115.89	4.82
6	590.83	39.68	0.00	686.30	22.06	0.00	753.01	17.61	0.00	828.25	26.09	0.00	733.06	103.17	0.00
7	608.09	56.50	0.00	718.61	22.72	0.00	800.13	25.62	0.00	922.92	61.43	0.01	760.63	122.89	0.00
8	530.89	38.94	0.00	604.37	14.49	0.00	652.61	13.34	0.00	695.18	11.37	0.00	630.91	68.84	0.00
9	575.92	32.11	0.00	621.65	7.68	0.00	646.79	7.01	0.00	670.87	7.15	0.00	634.90	41.41	0.00
10	767.08	133.52	19.01	803.71	107.28	23.71	724.65	106.39	9.12	795.71	132.41	21.52	776.03	122.17	19.03

Abbreviations: av_rr (average RR interval; milliseconds); sdnn (standard deviation of all normal RR intervals; milliseconds); pnn50 (% of all normal RR intervals > 50 milliseconds); am (morning); n (noon); an (afternoon); pm (evening); t (daytime average)

III. Baseline Measures of Systolic (SBP), Diastolic (DBP), and Mean Arterial Pressure (MAP)

OSA	AM SBP	AM DBP	AM MAP	NOON SBP	NOON DBP	NOON MAP	ANOON SBP	ANOON DBP	ANOON MAP	PM SBP	PM DBP	PM MAP	Daytime SBP	Daytime DBP	Daytime MAP
1	109.50	69.30	82.70	119.50	80.00	93.17	116.80	77.50	90.60	111.30	74.30	86.63	114.30	75.30	88.30
2	104.00	68.50	80.33	111.50	80.50	90.83	123.00	74.50	90.67	117.00	71.50	86.67	113.90	73.75	87.13
3	102.50	68.50	103.00	103.00	72.00	71.00	102.00	71.00	81.33	107.50	73.50	84.83	103.75	71.25	82.08
4	113.00	86.00	95.00	136.00	93.00	107.33	123.00	83.00	96.33	119.00	78.00	91.67	122.80	85.00	97.60
5	103.50	62.00	75.83	101.50	69.00	79.83	103.00	65.70	78.13	102.00	63.40	76.27	102.50	65.00	77.50
6	134.50	94.00	107.50	128.00	94.00	105.33	116.00	84.50	95.00	118.00	81.50	93.67	124.10	81.50	95.70
7	123.00	81.50	95.33	124.50	75.00	91.50	113.00	69.00	83.67	111.50	60.50	77.50	118.00	71.50	87.00
8	108.00	65.00	79.33	112.50	69.50	83.83	110.00	71.00	84.00	103.00	63.00	76.33	108.40	67.10	80.87
9	105.50	69.50	81.50	104.50	68.50	80.50	113.00	75.80	88.20	109.00	71.50	84.00	108.00	72.06	84.04
10	112.50	69.50	83.83	115.50	68.00	83.83	106.00	67.00	80.00	108.50	61.50	77.17	110.63	66.50	81.21

All Measurement units = mmHg

IV. Baseline Resting Measures of Cardiovascular Function

OSA	REST HR	RESTING SBP	RESTING DBP	RESTING MAP	RESTING Qc (L/min)	RESTING CI (L/min/m2)	RESTING TPR (mmHg/L/min)	RESTING SV (mL/bt)	RESTING SVI(ml/bt/m2)
1	101.00	118.00	86.00	96.67	6.00	3.17	16.11	59.41	31.40
2	90.00	128.00	88.00	101.33	4.40	2.11	23.03	48.89	23.40
3	83.00	124.00	88.00	100.00	5.50	2.79	18.18	66.27	33.60
4	76.00	142.00	92.00	108.67	4.70	2.45	23.12	61.84	32.20
5	100.00	98.00	68.00	78.00	4.10	2.25	19.02	41.00	22.50
6	62.00	132.00	90.00	104.00	6.20	2.79	16.77	100.00	45.00
7	62.00	122.00	84.00	96.67	4.40	2.19	21.97	70.97	35.30
8	73.00	130.00	88.00	102.00	5.20	2.65	19.62	71.23	36.30
9	85.00	120.00	80.00	93.33	4.20	2.55	22.22	49.41	29.90
10	79.00	132.00	74.00	93.33	5.10	2.79	18.30	64.56	35.30

V. Baseline Submaximal Exercise Measures (60 Watts)

OSA	SBP at 60 W	DBP at 60 W	MAP at 60 W	Qc at 60 W	CI at 60 W	TPR at 60 W	HR at 60 W (bpm)
1	142.00	86.00	104.67	10.20	5.40	10.26	117.00
2	150.00	86.00	107.33	9.50	4.55	11.30	138.00
3	146.00	84.00	104.67	6.10	3.10	17.16	132.00
4	164.00	94.00	117.33	10.00	5.21	11.73	117.00
5	118.00	74.00	88.67	9.50	5.22	9.33	122.00
6	142.00	90.00	107.33	7.30	3.29	14.70	97.00
7	142.00	80.00	100.67	8.40	3.63	11.98	95.00
8	162.00	80.00	107.33	9.30	4.74	11.54	112.00
9	128.00	78.00	94.67	7.90	4.79	11.98	125.00
10	150.00	78.00	102.00	6.70	3.66	15.22	96.00

OSA	RPP at 60 WW	SV at 60 W (L/bt)	SVI at 60 W	VO2 (ml/kg/min) at 60 W	VO2 (L/min) at 60 W	RPE at 60 W	VE at 60 W (L/min)	% VO2pk
1	16614.00	87.18	46.13	12.80	0.93	9.00	23.30	41.18
2	20700.00	68.84	32.93	10.00	0.92	8.00	26.10	47.73
3	19272.00	46.21	23.45	7.40	0.65	9.00	24.00	40.06
4	19188.00	85.47	44.52	10.00	0.82	11.00	24.60	47.01
5	14396.00	77.87	42.79	12.50	0.89	7.00	23.90	59.97
6	13774.00	75.26	33.90	9.10	0.91	8.00	21.70	42.36
7	13490.00	88.42	44.00	12.00	1.04	11.00	28.70	49.37
8	18144.00	83.04	42.37	10.10	0.88	7.00	25.70	57.70
9	16000.00	63.20	38.30	11.60	0.67	8.00	26.70	42.65
10	14400.00	69.79	38.23	11.30	0.80	8.00	21.60	34.48

VI. Baseline Submaximal Exercise Measures (100 Watts)

OSA	SBP at 100W	DBP at 100W	MAP at 100W	Qc- 100W	CI at 100W	TPR at 100W	HR at 100W
1	176.00	82.00	113.33	11.90	6.30	9.52	138.00
2	166.00	78.00	107.33	10.50	5.02	10.22	158.00
3	150.00	86.00	107.33	11.20	5.67	9.58	142.00
4	188.00	96.00	126.67	11.10	5.78	11.41	137.00
5	138.00	80.00	99.33	12.60	6.92	7.88	140.00
6	160.00	90.00	113.33	9.10	4.10	12.45	102.00
7	158.00	90.00	112.67	12.00	5.97	9.39	105.00
8	172.00	80.00	110.67	12.90	6.58	8.58	134.00
9	136.00	80.00	98.67	8.30	5.03	11.89	140.00
10	164.00	78.00	106.67	10.50	5.74	10.16	115.00

OSA	RPP at 100W	SV at 100W	SVI at 100 W	VO2 (ml/kg/min) at 100W	VO2 (L/min) at 100W	% pk VO2
1	24288.00	86.23	45.26	18.10	1.31	58.22
2	26228.00	66.46	31.80	11.40	1.06	54.42
3	21300.00	78.87	40.04	12.40	1.09	67.13
4	25756.00	81.02	42.20	17.80	1.45	83.68
5	19320.00	90.00	49.45	18.20	1.29	87.31
6	16320.00	89.22	40.19	13.10	1.31	60.99
7	16590.00	114.29	58.86	17.00	1.47	69.94
8	23048.00	96.27	49.12	15.50	1.35	88.54
9	19040.00	59.29	35.93	21.20	1.22	77.94
10	18860.00	91.30	49.89	18.00	1.28	54.92

VII. Baseline Submaximal Exercise Measures (Ventilatory Threshold and 50% of Peak VO_2)

OSA	VT (ml/kg/min)	VT (L/min)	HR at VT	RPE at VT	MAP at VT	WL at VT (WATTS)	HR at 50% VO2pk	VE at 50% VO2pk (L/min)	RPE at 50% VO2pk
1	16.90	1.23	138.00	11.00	113.00	100.00	138.00	30.50	10.00
2	11.40	1.06	176.00	9.00	120.00	115.00	140.00	26.40	8.00
3	13.40	1.18	147.00	10.00	107.30	100.00	132.00	24.00	9.00
4	15.80	1.30	137.00	11.00	126.70	95.00	117.00	22.00	11.00
5	12.50	0.89	122.00	9.00	88.70	70.00	124.00	28.70	9.00
6	12.90	1.29	112.00	13.00	117.30	115.00	94.00	26.70	8.00
7	18.70	1.62	112.00	13.00	123.30	120.00	95.00	28.60	11.00
8	15.10	1.32	146.00	13.00	110.70	120.00	106.00	23.50	7.00
9	21.20	1.22	140.00	13.00	98.70	100.00	125.00	26.70	11.00
10	25.90	1.85	151.00	15.00	112.70	165.00	106.00	29.20	9.00

VIII. Baseline Peak Exercise Measures

OSA	PEAK SBP	PEAK DBP	PEAK MAP	VO2pk (L/min)	VO2pk (ml/kg/min)	Peak METS
1	192.00	82.00	118.67	2.26	31.09	8.88
2	204.00	90.00	128.00	1.94	20.95	5.99
3	188.00	80.00	116.00	1.62	18.47	5.28
4	200.00	96.00	130.67	1.74	21.27	6.08
5	152.00	82.00	105.33	1.48	20.85	5.96
6	192.00	92.00	125.33	2.15	21.48	6.14
7	194.00	100.00	131.33	2.10	24.31	6.94
8	176.00	82.00	113.33	1.53	17.51	5.00
9	154.00	76.00	102.00	1.57	27.20	7.77
10	174.00	72.00	106.00	2.34	32.77	9.36

OSA	PEAK RER	TEST TIME (min)	PEAK WL (Watts)	PEAK HR	PEAK RPP	PEAK RPE
1	1.10	11.50	190.00	183.00	35136.00	15.00
2	1.22	9.00	160.00	192.00	39168.00	16.00
3	1.22	8.37	155.00	163.00	30644.00	19.00
4	1.08	7.00	130.00	170.00	34000.00	16.00
5	1.15	7.00	130.00	160.00	24320.00	15.00
6	1.07	9.00	160.00	132.00	25344.00	17.00
7	1.09	9.00	160.00	136.00	26384.00	13.00
8	1.10	7.17	135.00	153.00	26928.00	15.00
9	1.16	8.00	145.00	162.00	24948.00	19.00
10	1.11	11.00	190.00	169.00	29406.00	17.00

IX. Baseline Recovery Blood Pressure and Heart Rate

OSA	REC HR 1 min	REC SBP 1 min	REC DBP 1 min	REC MAP 1 min	REC HR 2min	REC SBP 2min	REC DBP 2 min	REC MAP 2 min
1	170.00	148.00	86.00	106.67	132.00	128.00	80.00	96.00
2	184.00	184.00	90.00	121.33	170.00	148.00	88.00	108.00
3	151.00	164.00	78.00	106.67	137.00	138.00	76.00	96.67
4	142.00	196.00	94.00	128.00	135.00	164.00	92.00	116.00
5	142.00	140.00	78.00	98.67	129.00	128.00	72.00	90.67
6	125.00	182.00	92.00	122.00	109.00	192.00	90.00	124.00
7	116.00	178.00	92.00	120.67	99.00	172.00	86.00	114.67
8	142.00	166.00	80.00	108.67	118.00	168.00	76.00	106.67
9	137.00	142.00	78.00	99.33	131.00	138.00	78.00	98.00
10	148.00	180.00	72.00	108.00	133.00	164.00	70.00	101.33

OSA	REC HR 3min	REC SBP 3 min	REC DBP 3 min	REC MAP 3 min	REC HR 4min	REC SBP 4min	REC DBP 4 min	REC MAP 4 min
1	129.00	122.00	76.00	91.33	126.00	128.00	76.00	93.33
2	157.00	146.00	88.00	107.33	150.00	142.00	88.00	106.00
3	123.00	140.00	74.00	96.00	115.00	136.00	76.00	96.00
4	127.00	160.00	88.00	112.00	129.00	156.00	88.00	110.67
5	118.00	116.00	70.00	85.33	118.00	116.00	72.00	86.67
6	100.00	142.00	90.00	107.33	91.00	128.00	84.00	98.67
7	80.00	142.00	78.00	99.33	80.00	158.00	78.00	104.67
8	92.00	158.00	76.00	103.33	83.00	140.00	76.00	97.33
9	117.00	130.00	76.00	94.00	115.00	118.00	78.00	91.33
10	127.00	152.00	70.00	97.33	115.00	140.00	76.00	97.33

OSA	REC HR 5min	REC SBP 5min	REC DBP 5 min	REC MAP 5 min	REC HR 6min	REC SBP 6min	REC DBP 6 min	REC MAP 6 min
1	125.00	112.00	74.00	86.67	123.00	112.00	74.00	86.67
2	147.00	146.00	86.00	106.00	149.00	142.00	88.00	106.00
3	113.00	130.00	78.00	95.33	110.00	122.00	80.00	94.00
4	103.00	156.00	90.00	112.00	110.00	154.00	90.00	111.33
5	108.00	120.00	70.00	86.67	99.00	118.00	72.00	87.33
6	84.00	132.00	90.00	104.00	73.00	130.00	90.00	103.33
7	71.00	124.00	78.00	93.33	75.00	126.00	78.00	94.00
8	80.00	120.00	82.00	94.67	84.00	124.00	80.00	94.67
9	111.00	116.00	76.00	89.33	104.00	114.00	76.00	88.67
10	109.00	122.00	76.00	91.33	98.00	126.00	80.00	95.33

I. Week 6 Control Characteristics

OSA	GENDER	AGE (yrs)	EPWORTH (x/24)	WEIGHT (kg)	HEIGHT (m)	BMI (kg/m2)	Waist (cm)	Neck Cir (cm)
1	MALE	42.00	.	75.80	1.76	24.47	84.70	36.10
2	FEMALE	28.00	12.00	93.10	1.69	32.60	99.10	36.90
3	FEMALE	46.00	7.00	86.70	1.60	33.87	90.20	34.90
4	FEMALE	44.00	.	.	.	.	.	.
5	FEMALE	34.00	.	.	.	.	.	.
6	MALE	36.00	7.00	103.10	1.77	32.91	108.80	42.70
7	FEMALE	51.00	5.00	88.40	1.69	30.95	102.30	39.60
8	MALE	45.00	1.00	89.10	1.59	34.06	.	34.00
9	MALE	35.00	8.00	59.40	1.69	20.80	68.80	29.00
10	FEMALE	37.00	7.00	70.00	1.69	24.51	75.90	36.50

II. Week 6 Time Domain Measures of Heart Rate Variability

OSA	av_rr_am	sdnn_am	pnn50_am	av_rr_n	sdnn_n	pnn50_n	av_rr_an	sdnn_an	pnn50_an	av_rr_pm	sdnn_pm	pnn50_pm	av_rr_t	sdnn_t	pnn50_t
1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	598.55	96.71	4.27	618.13	69.39	4.34	635.03	70.38	5.69	555.86	80.24	4.16	601.89	85.22	5.00
3	.	.	.	.	.	.	.	.	.	.	.	.	596.53	66.11	1.22
4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	691.82	88.07	2.64	528.57	179.12	1.54	508.95	227.17	1.86	680.88	115.36	2.77	602.56	182.40	2.46
7	744.88	198.41	24.64	803.71	107.28	23.71	724.65	106.39	9.12	797.07	134.45	20.94	767.26	145.63	19.82
8	671.71	88.51	1.43	668.82	56.13	1.03	671.44	60.82	1.23	620.45	75.69	0.52	658.11	74.68	1.17
9	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	672.36	172.00	13.81	793.85	110.75	20.98	880.80	142.25	36.03	791.00	115.26	17.90	784.53	155.98	22.46

Abbreviations: av_rr (average RR interval; milliseconds); sdnn (standard deviation of all normal RR intervals; milliseconds); pnn50 (% of all normal RR intervals > 50 milliseconds); am (morning); n (noon); an (afternoon); pm (evening); t (daytime average)

III. Week 6 Measures of Systolic (SBP), Diastolic (DBP), and Mean Arterial Pressure (MAP)

OSA	AM SBP	AM DBP	AM MAP	NOON SBP	NOON DBP	NOON MAP	ANOON SBP	ANOON DBP	ANOON MAP	PM SBP	PM DBP	PM MAP	Daytime SBP	Daytime DBP	Daytime MAP
1	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	110.00	77.00	88.00	124.00	80.00	94.67	103.50	75.00	84.50	105.50	66.00	79.17	110.75	74.50	86.58
3	100.00	65.50	77.00	120.00	77.50	91.67	108.00	73.00	84.67	114.50	75.00	88.17	110.60	72.75	85.37
4	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	114.00	78.00	90.00	121.00	82.50	95.33	103.50	76.50	85.50	108.50	77.50	87.83	108.50	78.63	88.59
7	114.50	70.00	84.83	136.50	84.00	101.50	121.50	71.50	88.17	107.00	68.00	81.00	119.88	73.38	88.88
8	101.00	65.50	77.33	111.00	71.00	84.33	112.50	72.50	85.83	104.50	69.00	80.83	107.25	69.50	82.08
9	103.50	64.50	77.50	101.50	61.50	74.83	100.00	63.00	75.33	97.50	63.50	74.83	100.63	63.13	75.63
10	118.30	72.70	87.90	119.00	68.00	85.00	121.00	62.00	81.67	119.00	66.70	84.13	119.33	67.35	84.68

All Measurement units = mmHg

IV. Week 6 Resting Measures of Cardiovascular Function

OSA	REST HR	RESTING SBP	RESTING DBP	RESTING MAP	RESTING Qc (L/min)	RESTING CI (L/min/m2)	RESTING TPR (mmHg/L/min)	RESTING SV (mL/bt)	RESTING SVI(ml/bt/m2)
1	91.00	112.00	74.00	86.67	4.00	2.07	21.67	43.96	22.78
2	112.00	114.00	82.00	92.67	4.40	2.11	21.06	39.29	18.80
3	104.00	116.00	84.00	94.67	5.10	2.60	18.56	49.04	25.02
4	.	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.	.
6	84.00	112.00	84.00	93.33	4.80	2.13	19.44	57.14	25.40
7	68.00	108.00	80.00	89.33	5.30	2.60	16.86	77.94	38.21
8	87.00	128.00	88.00	101.33	5.50	2.78	18.42	63.22	31.93
9	75.00	110.00	78.00	88.67	4.40	2.63	20.15	58.67	35.13
10	77.00	104.00	82.00	89.33	4.20	2.38	21.27	54.55	30.14

V. Week 6 Submaximal Exercise Measures (60 Watts)

OSA	SBP at 60 W	DBP at 60 W	MAP at 60 W	Qc at 60 W	CI at 60 W	TPR at 60 W	HR at 60 W (bpm)
1	138.00	74.00	95.33	8.60	4.46	11.09	110.00
2	162.00	92.00	115.33	9.00	4.31	12.81	148.00
3	118.00	80.00	92.67	13.70	6.99	6.76	130.00
4	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.
6	130.00	88.00	102.00	9.30	4.13	10.97	107.00
7	148.00	80.00	102.67	9.00	4.41	11.41	96.00
8	172.00	84.00	113.33	8.60	4.34	13.18	122.00
9	126.00	82.00	96.67	9.30	5.57	10.39	108.00
10	132.00	82.00	98.67	7.90	4.20	12.49	101.00

OSA	RPP at 60 WW	SV at 60 W (L/bt)	SVI at 60 W	VO2 (ml/kg/min) at 60 W	VO2 (L/min) at 60 W	RPE at 60 W	VE at 60 W (L/min)	% VO2pk
1	15180.00	78.18	40.51	16.00	1.21	8.00	23.90	49.50
2	23976.00	60.81	29.10	11.50	1.08	8.00	26.70	52.98
3	15340.00	105.38	53.77	.	.	9.00	.	.
4	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.
6	13910.00	86.92	38.63	11.70	1.21	9.00	29.70	57.77
7	14208.00	93.75	45.96	13.60	1.20	11.00	33.00	57.87
8	20984.00	70.49	35.60	11.10	0.99	9.00	31.40	57.81
9	13608.00	86.11	51.56	.	.	10.00	26.40	.
10	13332.00	78.22	43.22	13.30	0.93	7.00	26.60	37.54

VI. Week 6 Submaximal Exercise Measures (100 Watts)

OSA	SBP at 100W	DBP at 100W	MAP at 100W	Qc- 100W	CI at 100W	TPR at 100W	HR at 100W
1	150.00	76.00	100.67	8.90	4.61	11.31	126.00
2	164.00	98.00	120.00	14.20	6.79	8.45	169.00
3	134.00	78.00	96.67	13.80	5.71	7.00	140.00
4	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.
6	162.00	94.00	116.67	9.70	4.31	12.03	121.00
7	168.00	82.00	110.67	10.10	4.95	10.96	105.00
8	204.00	88.00	126.67	11.70	5.91	10.83	144.00
9	146.00	82.00	103.33	11.50	6.89	8.99	128.00
10	150.00	82.00	104.67	10.10	6.13	10.36	121.00

OSA	RPP at 100W	SV at 100W	SVI at 100 W	VO2 (ml/kg/min) at 100W	VO2 (L/min) at 100W	% pk VO2
1	18900.00	70.63	36.60	17.00	1.28	52.60
2	27716.00	84.02	40.20	12.30	1.16	56.66
3	18760.00	98.57	50.29	.	.	.
4	.	.	.	.	.	.
5	.	.	.	.	.	.
6	19602.00	80.17	35.63	13.40	1.38	66.17
7	17640.00	96.19	47.15	16.60	1.46	70.64
8	29376.00	81.25	41.04	15.20	1.35	.
9	18688.00	89.84	53.80	20.60	1.22	69.59
10	18150.00	83.47	46.12	18.90	1.32	53.35

VII. Week 6 Submaximal Exercise Measures (Ventilatory Threshold and 50% of Peak VO_2)

OSA	VT (ml/kg/min)	VT (L/min)	HR at VT	RPE at VT	MAP at VT	WL at VT (WATTS)	HR at 50% VO2pk	VE at 50% VO2pk (L/min)	RPE at 50% VO2pk
1	17.00	1.29	134.00	11.00	104.00	115.00	126.00	33.10	10.00
2	13.00	1.21	169.00	10.00	120.00	100.00	148.00	26.40	9.00
3	.	.	.	.	.	.	.	.	.
4	.	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.	.
6	14.10	1.45	114.00	114.00	102.00	85.00	109.00	31.00	9.00
7	18.60	1.64	115.00	13.00	110.67	115.00	96.00	35.00	11.00
8	15.20	1.35	144.00	13.00	126.67	100.00	122.00	25.80	9.00
9	20.60	1.23	128.00	13.00	103.30	100.00	128.00	34.00	13.00
10	23.10	1.62	134.00	12.00	108.00	135.00	109.00	30.30	8.00

VIII. Week 6 Peak Exercise Measures

OSA	PEAK SBP	PEAK DBP	PEAK MAP	VO2pk (L/min)	VO2pk (ml/kg/min)	Peak METS
1	184.00	72.00	109.33	2.45	32.32	9.23
2	196.00	100.00	132.00	2.02	21.71	6.20
3	160.00	76.00	104.00	.	.	.
4	.	.	.	.	.	.
5	.	.	.	.	.	.
6	178.00	96.00	123.33	2.09	20.25	5.79
7	208.00	86.00	126.67	2.07	23.50	6.71
8	208.00	88.00	128.00	1.71	19.20	5.49
9	164.00	80.00	108.00	1.76	29.60	8.46
10	212.00	80.00	124.00	2.48	35.43	10.12

OSA	PEAK RER	TEST TIME (min)	PEAK WL (Watts)	PEAK HR	PEAK RPP	PEAK RPE
1	1.13	12.37	205.00	180.00	33120.00	17.00
2	1.22	9.05	160.00	188.00	36848.00	17.00
3	.	8.00	145.00	161.00	25760.00	17.00
4	.	.	.	.	.	.
5	.	.	.	.	.	.
6	1.11	9.00	145.00	137.00	24386.00	19.00
7	1.11	9.00	160.00	132.00	27456.00	15.00
8	1.14	7.97	145.00	167.00	34736.00	17.00
9	1.25	9.00	160.00	164.00	26896.00	17.00
10	1.12	12.00	205.00	172.00	36464.00	18.00

IX. Week 6 Recovery Blood Pressure and Heart Rate

OSA	REC HR 1 min	REC SBP 1 min	REC DBP 1 min	REC MAP 1 min	REC HR 2min	REC SBP 2min	REC DBP 2 min	REC MAP 2 min
1	165.00	154.00	72.00	99.33	142.00	142.00	70.00	94.00
2	164.00	152.00	82.00	105.33	151.00	154.00	82.00	106.00
3	140.00	156.00	72.00	100.00	134.00	136.00	68.00	90.67
4	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.
6	115.00	154.00	84.00	107.33	107.00	142.00	80.00	100.67
7	111.00	170.00	80.00	110.00	93.00	158.00	80.00	106.00
8	152.00	200.00	88.00	125.33	128.00	172.00	82.00	112.00
9	135.00	142.00	80.00	100.67	120.00	136.00	80.00	98.67
10	155.00	178.00	80.00	112.67	134.00	170.00	74.00	106.00

OSA	REC HR 3min	REC SBP 3 min	REC DBP 3 min	REC MAP 3 min	REC HR 4min	REC SBP 4min	REC DBP 4 min	REC MAP 4 min
1	128.00	136.00	70.00	92.00	121.00	136.00	70.00	92.00
2	149.00	148.00	82.00	104.00	143.00	132.00	80.00	97.33
3	128.00	130.00	76.00	94.00	115.00	128.00	80.00	96.00
4	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.
6	102.00	138.00	86.00	103.33	94.00	124.00	88.00	100.00
7	84.00	150.00	76.00	100.67	72.00	148.00	78.00	101.33
8	98.00	176.00	84.00	114.67	93.00	152.00	86.00	108.00
9	106.00	118.00	70.00	86.00	107.00	110.00	72.00	84.67
10	119.00	150.00	74.00	99.33	117.00	132.00	74.00	93.33

OSA	REC HR 5min	REC SBP 5min	REC DBP 5 min	REC MAP 5 min	REC HR 6min	REC SBP 6min	REC DBP 6 min	REC MAP 6 min
1	118.00	134.00	70.00	91.33	111.00	124.00	72.00	89.33
2	137.00	132.00	80.00	97.33	138.00	128.00	80.00	96.00
3	113.00	122.00	80.00	94.00	118.00	112.00	78.00	89.33
4	.	.	.	.	.	.	.	.
5	.	.	.	.	.	.	.	.
6	102.00	128.00	90.00	102.67	99.00	122.00	90.00	100.67
7	87.00	138.00	82.00	100.67	76.00	126.00	80.00	95.33
8	96.00	134.00	88.00	103.33	99.00	128.00	86.00	100.00
9	104.00	122.00	72.00	88.67	102.00	112.00	72.00	85.33
10	114.00	128.00	76.00	93.33	107.00	126.00	80.00	95.33

OSA Patient Raw Data

I. Baseline OSA Patient Characteristics

OSA	GENDER	AGE (yrs)	EPWORTH (x/24)	WEIGHT (kg)	HEIGHT (m)	BMI (kg/m2)	Waist (cm)	Neck Cir (cm)
1	MALE	50.00	15.00	90.00	1.80	27.78	95.25	38.10
2	FEMALE	58.00	19.00	102.50	1.65	37.65	105.41	38.00
3	FEMALE	25.00	9.00	133.20	1.75	43.49	121.92	40.60
4	FEMALE	37.00	14.00	114.50	1.75	37.39	111.76	39.40
5	FEMALE	49.00	14.00	84.00	1.64	31.23	94.20	36.50
6	MALE	33.00	10.00	90.60	1.81	27.65	107.00	40.30
7	FEMALE	53.00	17.00	99.10	1.83	29.59	110.00	37.90
8	MALE	44.00	16.00	87.60	1.80	27.04	109.50	39.40
9	MALE	62.00	10.00	99.50	1.83	29.71	112.10	44.00
10	FEMALE	39.00	8.00	106.00	1.61	40.89	118.00	36.60
11	MALE	61.00	7.00	75.60	1.73	25.30	93.20	38.80

II. Selected Polysomnography Results

OSA	AGE (yrs)	Time in Bed (min)	TST (min)	Stage 1 (%)	Stage 2 (%)	SWS (%)	REM (%)	Baseline SaO2 (%)	RDI (events/hr)	Low SaO2 (%)	Time < 90% SaO2 (%)
1	50.00	366.50	248.50	8.00	53.50	31.60	6.80	96.00	33.80	74.00	8.20
2	58.00	368.50	290.50	5.80	56.00	5.80	14.00	96.00	11.40	80.00	8.30
3	25.00	365.00	256.50	0.50	50.20	28.70	9.30	98.00	26.00	92.00	0.00
4	37.00	362.50	347.00	4.90	50.60	15.80	25.70	97.00	29.60	92.00	0.00
5	49.00	369.50	246.50	8.10	41.20	24.10	0.40	95.00	10.50	88.00	1.60
6	33.00	361.50	281.50	7.10	46.00	8.50	18.50	96.00	32.00	82.00	7.80
7	53.00	385.00	329.50	7.00	62.70	22.80	7.60	96.00	19.10	90.00	0.00
8	44.00	369.50	321.50	6.10	50.70	26.90	16.30	94.00	55.10	90.00	0.00
9	62.00	364.50	263.00	16.90	69.60	1.70	11.80	97.00	43.60	84.00	3.00
10	39.00	359.50	336.50	2.10	55.30	24.60	18.00	97.00	20.00	79.00	10.00
11	61.00	363.00	300.00	7.30	60.50	17.50	14.70	96.00	51.00	84.00	10.00

III. Baseline Time Domain Measures of Heart Rate Variability

OSA	av_rr_am	sdnn_am	pnn50_am	av_rr_n	sdnn_n	pnn50_n	av_rr_an	sdnn_an	pnn50_an	av_rr_pm	sdnn_pm	pnn50_pm	av_rr_t	sdnn_t	pnn50_t
1	689.16	91.84	1.83	744.95	56.35	1.88	745.93	54.16	1.71	649.79	82.56	0.87	703.90	81.62	1.49
2	644.64	50.67	0.54	602.72	58.59	0.22	539.13	62.15	0.14	579.52	98.92	2.24	599.01	83.15	1.16
3	597.71	79.75	1.34	547.11	74.00	0.98	625.25	75.25	1.66	576.02	65.09	1.19	588.03	78.87	1.31
4	707.62	48.37	0.37	767.67	51.13	0.61	764.22	39.87	1.36	670.21	59.27	0.56	727.89	64.42	0.73
5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	755.08	61.84	0.06	781.83	58.89	0.11	776.43	69.32	0.30	797.36	64.50	0.06	777.16	71.18	0.45
7	547.02	170.95	20.34	613.33	73.86	5.07	649.71	74.00	5.60	698.30	120.86	5.64	636.95	127.73	8.44
8	697.68	100.04	5.12	656.98	76.82	4.44	631.57	81.76	4.28	556.53	76.83	2.56	629.34	98.14	4.07
9	833.20	111.72	1.10	807.73	90.78	1.69	842.78	56.44	1.03	782.19	96.50	1.00	792.04	117.57	1.46
10	690.09	74.92	2.21	710.31	42.96	1.02	653.33	65.51	1.38	647.82	58.44	1.03	672.99	65.27	1.32
11	743.45	102.00	5.24	700.30	74.78	2.71	760.81	79.18	2.46	721.76	54.10	0.64	709.10	143.56	2.56

Abbreviations: av_rr (average RR interval; milliseconds); sdnn (standard deviation of all normal RR intervals; milliseconds); pnn50 (% of all normal RR intervals > 50 milliseconds); am (morning); n (noon); an (afternoon); pm (evening); t (daytime average)

IV. Baseline Measures of Systolic (SBP), Diastolic (DBP), and Mean Arterial Pressure (MAP)

OSA	AM SBP	AM DBP	AM MAP	NOON SBP	NOON DBP	NOON MAP	ANOON SBP	ANOON DBP	ANOON MAP	PM SBP	PM DBP	PM MAP	Daytime SBP	Daytime DBP	Daytime MAP
1	133.00	86.50	102.00	151.50	94.50	113.50	157.00	97.50	117.33	139.50	87.00	104.50	145.30	91.40	109.37
2	135.00	79.00	97.67	120.50	74.00	89.50	117.50	75.00	89.17	122.50	79.00	93.50	123.90	76.80	92.50
3	106.50	76.50	86.50	113.50	74.00	87.17	109.50	73.00	85.17	116.50	84.00	94.83	111.50	76.90	88.43
4	125.50	79.00	94.50	112.50	74.50	87.17	126.00	86.00	99.33	130.50	86.00	100.83	123.60	81.40	95.47
5	122.00	78.50	93.00	125.50	80.50	95.50	117.50	77.50	90.83	.	.	.	121.70	78.80	93.10
6	108.00	76.00	86.67	130.00	89.00	102.67	119.00	82.00	94.33	118.00	81.00	93.33	120.50	76.90	91.43
7	129.50	86.00	100.50	133.00	99.50	110.67	139.50	86.50	104.17	106.00	76.00	86.00	127.00	87.00	100.33
8	113.70	75.00	87.90	118.40	83.50	95.13	125.30	86.70	99.57	121.60	82.20	95.33	121.60	82.20	95.33
9	171.00	103.50	126.00	175.50	95.00	121.83	161.50	91.00	114.50	169.00	90.00	116.33	169.25	94.88	119.67
10	123.00	83.00	96.33	122.00	79.00	93.33	126.00	79.00	94.67	129.00	83.00	98.33	125.00	81.00	95.67
11	84.61	134.00	87.50	103.00	129.00	81.00	97.00	131.00	88.50	102.67	124.50	77.00	92.83	129.63	83.50

All Measurement units = mmHg

V. Baseline Resting Measures of Cardiovascular Function

OSA	REST HR	RESTING SBP	RESTING DBP	RESTING MAP	RESTING Qc (L/min)	RESTING CI (L/min/m2)	RESTING TPR (mmHg/L/min)	RESTING SV (mL/bt)	RESTING SVI(ml/bt/m2)
1	80.00	160.00	108.00	125.33	.	.	.	.	.
2	86.00	138.00	94.00	108.67	.	.	.	.	.
3	85.00	138.00	90.00	106.00	8.40	3.31	12.62	98.82	38.90
4	77.00	134.00	92.00	106.00	7.40	3.14	14.32	96.10	40.70
5	78.00	148.00	98.00	114.67	5.40	2.76	21.23	69.23	35.30
6	82.00	110.00	74.00	86.00	6.10	2.86	14.10	74.39	34.90
7	87.00	146.00	106.00	119.33	3.70	1.65	32.25	42.53	20.20
8	74.00	118.00	78.00	91.33	5.90	2.82	15.48	79.73	38.10
9	68.00	158.00	94.00	115.33	5.50	2.44	20.97	80.88	35.90
10	91.00	138.00	92.00	107.33	5.90	2.71	18.19	64.84	29.70
11	98.88	132.00	82.00	98.70	4.20	2.22	23.50	54.60	28.90

VI. Baseline Submaximal Exercise Measures (60 Watts)

OSA	SBP at 60 W	DBP at 60 W	MAP at 60 W	Qc at 60 W	CI at 60 W	TPR at 60 W	HR at 60 W (bpm)
1	192.00	100.00	130.67	.	.	.	104.00
2	162.00	88.00	112.67	.	.	.	113.00
3	128.00	86.00	100.00	13.70	5.39	7.30	115.00
4	162.00	100.00	120.67	13.70	5.81	8.81	92.00
5	198.00	90.00	126.00	11.60	5.92	10.86	126.00
6	124.00	74.00	90.67	.	.	.	106.00
7	162.00	94.00	116.67	8.00	3.57	14.58	97.00
8	118.00	76.00	90.00	8.30	3.97	10.84	92.00
9	156.00	98.00	117.33	8.60	3.82	13.64	91.00
10	154.00	84.00	107.33	10.00	4.59	10.73	129.00
11	148.00	86.00	106.70	9.00	4.76	11.85	98.00

OSA	RPP at 60 WW	SV at 60 W (L/bt)	SVI at 60 W	VO2 (ml/kg/min) at 60 W	VO2 (L/min) at 60 W	RPE at 60 W	VE at 60 W (L/min)	% VO2pk
1	19968.00	.	.	11.70	1.05	7.00	22.00	56.52
2	18306.00	.	.	7.70	0.79	9.00	31.30	42.31
3	14720.00	119.13	46.90	11.60	1.54	12.00	40.50	55.77
4	14904.00	148.91	63.10	9.20	1.06	8.00	29.10	37.10
5	24948.00	92.06	47.00	7.60	0.64	13.00	18.30	46.63
6	13144.00	.	.	11.80	1.07	10.00	30.10	43.70
7	15714.00	82.47	36.80	7.10	0.70	9.00	23.10	46.10
8	10856.00	90.22	43.17	12.70	1.11	11.00	34.10	54.27
9	14196.00	94.51	42.00	11.30	1.13	7.00	37.00	48.09
10	19866.00	77.52	35.56	11.00	1.16	7.00	40.90	62.86
11	14504.00	91.84	48.59	11.30	0.85	11.00	24.80	54.59

VII. Baseline Submaximal Exercise Measures (100 Watts)

OSA	SBP at 100W	DBP at 100W	MAP at 100W	Qc- 100W	CI at 100W	TPR at 100W	HR at 100W
1	218.00	100.00	139.33	.	.	.	116.00
2	182.00	92.00	122.00	.	.	.	136.00
3	160.00	86.00	110.67	12.90	5.08	8.58	125.00
4	190.00	92.00	124.67	9.60	4.07	12.99	107.00
5	200.00	86.00	124.00	12.20	6.22	10.16	152.00
6	126.00	74.00	91.33	.	.	.	117.00
7	176.00	88.00	117.33	8.40	3.75	13.97	121.00
8	132.00	82.00	98.67	11.60	5.55	8.51	108.00
9	180.00	100.00	126.67	8.50	3.78	14.90	105.00
10	168.00	80.00	109.33	12.10	5.55	9.04	142.00
11	182.00	88.00	119.30	9.90	5.24	12.05	127.00

OSA	RPP at 100W	SV at 100W	SVI at 100 W	VO2 (ml/kg/min) at 100W	VO2 (L/min) at 100W	% pk VO2
1	25288.00	.	.	15.30	1.37	73.91
2	24752.00	.	.	14.40	1.48	79.12
3	20000.00	103.20	40.63	17.30	2.30	83.17
4	20330.00	89.72	38.02	15.50	1.77	62.50
5	30400.00	80.26	40.95	12.20	1.03	74.85
6	14742.00	.	.	15.30	1.38	56.67
7	21296.00	69.42	30.99	12.50	1.24	81.17
8	14256.00	107.41	51.39	18.00	1.58	76.92
9	18900.00	80.95	35.98	15.40	1.54	65.53
10	23856.00	85.21	39.09	12.10	1.28	69.14
11	23114.00	77.95	.	17.50	1.32	84.54

VIII. Baseline Submaximal Exercise Measures (Ventilatory Threshold and 50% of Peak VO_2)

OSA	VT (ml/kg/min)	VT (L/min)	HR at VT	RPE at VT	MAP at VT	WL at VT (WATTS)	HR at 50% VO2pk	VE at 50% VO2pk (L/min)	RPE at 50% VO2pk
1	17.20	1.55	120.00	11.00	139.30	120.00	106.00	23.60	7.00
2	13.08	1.34	138.00	11.00	122.00	100.00	123.00	26.50	9.00
3	16.60	2.22	125.00	13.00	118.70	115.00	115.00	40.50	11.00
4	19.80	2.27	109.00	12.00	124.70	145.00	101.00	39.90	10.00
5	10.40	0.87	146.00	14.00	124.00	70.00	126.00	25.40	14.00
6	15.30	1.39	115.00	12.00	91.30	100.00	115.00	37.10	12.00
7	13.40	1.33	126.00	13.00	117.30	125.00	97.00	21.80	9.00
8	19.00	1.66	117.00	17.00	98.70	120.00	97.00	25.30	12.00
9	16.30	1.63	111.00	13.00	141.30	130.00	88.00	37.80	8.00
10	12.30	1.31	135.00	11.00	109.30	90.00	129.00	32.80	7.00
11	13.10	0.99	106.00	12.00	106.70	70.00	98.00	27.20	11.00

IX. Baseline Peak Exercise Measures

OSA	PEAK SBP	PEAK DBP	PEAK MAP	VO2pk (L/min)	VO2pk (ml/kg/min)	Peak METS
1	242.00	120.00	160.67	1.86	20.70	5.91
2	204.00	94.00	130.67	1.87	18.20	5.20
3	208.00	84.00	125.33	2.77	20.80	5.94
4	230.00	86.00	134.00	2.85	24.80	7.09
5	168.00	84.00	112.00	1.37	16.30	4.66
6	158.00	74.00	102.00	2.44	27.00	7.71
7	196.00	90.00	125.33	1.53	15.40	4.40
8	190.00	100.00	130.00	2.06	23.40	6.69
9	242.00	104.00	150.00	2.34	23.50	6.71
10	188.00	78.00	114.67	1.85	17.50	5.00
11	204.00	80.00	121.33	1.57	20.70	5.91

OSA	PEAK RER	TEST TIME (min)	PEAK WL (Watts)	PEAK HR	PEAK RPP	PEAK RPE
1	1.06	9.00	160.00	144.00	34848.00	12.00
2	1.14	7.00	130.00	151.00	30804.00	13.00
3	1.08	7.48	140.00	151.00	31408.00	15.00
4	1.06	13.00	220.00	162.00	37260.00	19.00
5	1.28	6.28	120.00	171.00	28728.00	19.00
6	1.20	12.00	205.00	155.00	24490.00	18.00
7	1.09	7.00	130.00	140.00	27440.00	17.00
8	1.08	9.00	160.00	139.00	26410.00	20.00
9	1.08	10.48	185.00	135.00	32670.00	16.00
10	1.25	7.85	145.00	164.00	30832.00	14.00
11	1.15	7.33	135.00	141.00	2918.70	18.00

X. Baseline Recovery Blood Pressure and Heart Rate

OSA	REC HR 1 min	REC SBP 1 min	REC DBP 1 min	REC MAP 1 min	REC HR 2min	REC SBP 2min	REC DBP 2 min	REC MAP 2 min
1	131.00	232.00	100.00	144.00	126.00	228.00	100.00	142.67
2	136.00	194.00	88.00	123.33	126.00	178.00	86.00	116.67
3	141.00	198.00	84.00	122.00	128.00	182.00	82.00	115.33
4	162.00	220.00	86.00	130.67	128.00	192.00	86.00	121.33
5	155.00	158.00	76.00	103.33	121.00	136.00	72.00	93.33
6	152.00	152.00	72.00	98.67	132.00	136.00	70.00	92.00
7	128.00	180.00	90.00	120.00	118.00	156.00	88.00	110.67
8	110.00	180.00	74.00	109.33	106.00	140.00	78.00	98.67
9	119.00	240.00	98.00	145.33	107.00	218.00	98.00	138.00
10	163.00	.	.	.	145.00	172.00	80.00	110.67
11	123.00	204.00	80.00	121.33	106.00	192.00	80.00	117.33

OSA	REC HR 3min	REC SBP 3 min	REC DBP 3 min	REC MAP 3 min	REC HR 4min	REC SBP 4min	REC DBP 4 min	REC MAP 4 min
1	112.00	198.00	98.00	131.33	100.00	162.00	98.00	119.33
2	126.00	174.00	84.00	114.00	121.00	162.00	84.00	110.00
3	126.00	170.00	84.00	112.67	120.00	166.00	82.00	110.00
4	125.00	194.00	86.00	122.00	121.00	182.00	86.00	118.00
5	112.00	124.00	68.00	86.67	102.00	118.00	74.00	88.67
6	114.00	142.00	68.00	92.67	106.00	144.00	66.00	92.00
7	124.00	134.00	86.00	102.00	115.00	132.00	88.00	102.67
8	110.00	130.00	74.00	92.67	94.00	138.00	78.00	98.00
9	93.00	210.00	98.00	135.33	93.00	190.00	98.00	128.67
10	131.00	.	.	.	124.00	130.00	62.00	84.67
11	101.00	164.00	78.00	106.67	99.00	158.00	82.00	107.33

OSA	REC HR 5min	REC SBP 5min	REC DBP 5 min	REC MAP 5 min	REC HR 6min	REC SBP 6min	REC DBP 6 min	REC MAP 6 min
1	96.00	150.00	100.00	116.67	98.00	138.00	100.00	112.67
2	124.00	150.00	84.00	106.00	107.00	144.00	84.00	104.00
3	120.00	158.00	84.00	108.67	117.00	146.00	82.00	103.33
4	126.00	172.00	84.00	113.33	110.00	170.00	86.00	114.00
5	100.00	110.00	72.00	84.67	97.00	100.00	68.00	78.67
6	102.00	138.00	66.00	90.00	99.00	126.00	70.00	88.67
7	110.00	130.00	90.00	103.33	105.00	124.00	88.00	100.00
8	98.00	128.00	72.00	90.67	96.00	112.00	70.00	84.00
9	84.00	186.00	96.00	126.00	84.00	168.00	96.00	120.00
10	115.00	120.00	68.00	85.33	111.00	.	.	.
11	91.00	146.00	80.00	102.00	93.00	136.00	84.00	101.33

I. Week 6 OSA Patient Characteristics

OSA	GENDER	AGE (yrs)	EPWORTH (x/24)	WEIGHT (kg)	HEIGHT (m)	BMI (kg/m2)	Waist (cm)	Neck Cir (cm)
1	MALE	50.00	5.00	89.10	1.80	27.50	88.90	38.10
2	FEMALE	58.00	15.00	103.40	1.65	37.98	104.10	38.70
3	FEMALE	25.00	7.00	133.20	1.75	43.49	123.20	40.60
4	FEMALE	37.00	6.00	116.80	1.75	38.14	113.03	40.60
5	FEMALE	49.00	10.00	85.50	1.64	31.79	89.20	37.30
6	MALE	33.00	15.00	90.10	1.81	27.50	100.50	40.10
7	FEMALE	53.00	11.00	87.50	1.83	26.13	104.30	37.00
8	MALE	44.00	13.00	87.40	1.80	26.98	98.70	38.30
9	MALE	62.00	5.00	99.30	1.83	29.65	113.40	39.50
10	FEMALE	39.00	0.00	110.00	1.61	42.44	118.00	36.50
11	MALE	61.00	.	.	.	.	.	.

II. Week 6 Time Domain Measures of Heart Rate Variability

OSA	av_rr_am	sdnn_am	pnn50_am	av_rr_n	sdnn_n	pnn50_n	av_rr_an	sdnn_an	pnn50_an	av_rr_pm	sdnn_pm	pnn50_pm	av_rr_t	sdnn_t	pnn50_t
1	745.69	91.19	4.77	785.80	99.60	7.81	723.00	56.16	1.08	760.77	70.02	3.79	758.28	85.05	4.47
2	707.61	48.36	0.37	767.67	51.13	0.61	764.22	39.87	1.36	670.21	59.27	0.56	727.43	64.60	0.79
3	725.75	50.11	0.84	767.42	60.12	1.93	742.22	76.95	4.30	679.19	62.29	1.91	728.64	70.83	2.39
4	708.87	64.15	1.07	714.74	64.52	0.61	707.89	61.77	0.93	716.34	54.91	0.62	711.96	61.56	0.96
5	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	751.46	93.31	3.42	785.41	86.51	2.46	751.43	85.08	1.04	709.66	109.42	4.34	749.49	97.83	3.25
7	908.21	160.71	44.81	1073.88	180.64	59.78	1283.09	171.06	71.06	1137.95	272.42	58.56	1091.29	240.50	59.53
8	620.82	74.29	3.12	676.72	93.85	6.22	649.26	62.80	2.30	657.41	91.19	4.91	651.05	83.97	4.57
9	930.17	61.68	1.11	957.21	70.10	3.28	797.56	89.17	2.02	798.85	69.21	0.80	870.97	103.67	1.89
10	658.78	140.99	13.87	699.65	118.92	7.59	701.74	129.08	8.89	635.10	174.69	18.48	673.92	145.24	14.92
11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Abbreviations: av_rr (average RR interval; milliseconds); sdnn (standard deviation of all normal RR intervals; milliseconds); pnn50 (% of all normal RR intervals > 50 milliseconds); am (morning); n (noon); an (afternoon); pm (evening); t (daytime average)

III. Week 6 Measures of Systolic (SBP), Diastolic (DBP), and Mean Arterial Pressure (MAP)

OSA	AM SBP	AM DBP	AM MAP	NOON SBP	NOON DBP	NOON MAP	ANOON SBP	ANOON DBP	ANOON MAP	PM SBP	PM DBP	PM MAP	Daytime SBP	Daytime DBP	Daytime MAP
1	134.50	87.00	102.83	140.00	86.00	104.00	139.00	86.00	103.67	126.50	81.50	96.50	135.00	81.50	99.33
2	102.50	80.50	87.83	113.50	72.50	86.17	113.00	81.50	92.00	128.00	78.00	94.67	124.30	78.10	93.50
3	113.50	81.00	91.83	137.00	97.50	110.67	111.00	82.50	92.00	121.00	75.50	90.67	114.90	79.90	91.57
4	111.00	72.50	85.33	120.00	70.50	87.00	121.50	58.00	79.17	121.00	73.50	89.33	118.40	68.60	85.20
5	134.50	79.00	97.50	121.50	70.00	87.17	111.00	69.00	83.00	117.50	69.00	85.17	121.10	71.80	88.23
6	114.00	76.00	88.67	128.00	81.00	96.67	116.50	76.50	89.83	119.50	74.00	89.17	118.80	82.00	94.27
7	54.98	87.50	101.33	126.50	78.50	94.50	135.00	88.00	103.67	125.50	79.00	94.50	128.90	80.00	96.30
8	118.00	78.00	91.33	118.50	70.50	86.50	114.00	75.00	88.00	121.00	75.00	90.33	117.88	74.63	89.05
9	68.89	91.00	108.00	153.50	92.00	112.50	154.50	93.50	113.83	.	.	.	150.00	92.17	111.45
10	130.00	83.00	98.67	131.00	87.00	101.67	130.00	82.00	98.00	130.00	79.00	96.00	130.25	82.75	98.58
11	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

All Measurement units = mmHg

IV. Week 6 Resting Measures of Cardiovascular Function

OSA	REST HR	RESTING SBP	RESTING DBP	RESTING MAP	RESTING Qc (L/min)	RESTING CI (L/min/m2)	RESTING TPR (mmHg/L/min)	RESTING SV (mL/bt)	RESTING SVI(ml/bt/m2)
1	72.00	158.00	90.00	112.67	6.20	2.94	18.17	86.11	40.81
2	82.00	130.00	84.00	99.33	4.50	2.06	22.07	54.88	25.17
3	95.00	140.00	100.00	113.33	5.80	2.28	19.54	61.05	24.04
4	82.00	134.00	88.00	103.33	7.60	3.19	13.60	92.68	38.94
5	78.00	154.00	88.00	110.00	4.60	2.34	23.91	58.97	29.93
6	92.00	110.00	88.00	95.33	4.10	1.92	23.25	44.57	20.92
7	82.00	122.00	88.00	99.33	5.20	2.46	19.10	63.41	30.05
8	78.00	108.00	82.00	90.67	5.60	2.68	16.19	71.79	34.35
9	67.00	168.00	108.00	128.00	4.70	2.09	27.23	70.15	31.18
10	92.00	148.00	92.00	110.67	6.90	3.11	16.04	75.00	33.78
11	.	.	.	.	.	.	.	.	.

V. Week 6 Submaximal Exercise Measures (60 Watts)

OSA	SBP at 60 W	DBP at 60 W	MAP at 60 W	Qc at 60 W	CI at 60 W	TPR at 60 W	HR at 60 W (bpm)
1	192.00	98.00	129.33	10.50	4.98	12.32	105.00
2	196.00	90.00	125.33	.	.	.	135.00
3	140.00	96.00	110.67	12.80	5.04	8.65	123.00
4	152.00	88.00	109.33	13.10	5.50	8.35	96.00
5	186.00	86.00	119.33	13.20	6.70	9.04	149.00
6	118.00	90.00	99.33	9.60	4.51	10.35	109.00
7	152.00	90.00	110.67	7.70	3.65	14.37	98.00
8	132.00	82.00	98.67	10.30	4.93	9.58	99.00
9	162.00	98.00	119.33	8.70	3.87	13.72	84.00
10	168.00	78.00	108.00	11.60	5.23	9.31	120.00
11	.	.	.	.	.	.	.

OSA	RPP at 60 W	SV at 60 W (L/bt)	SVI at 60 W	VO2 (ml/kg/min) at 60 W	VO2 (L/min) at 60 W	RPE at 60 W	VE at 60 W (L/min)	% VO2pk
1	20160.00	100.00	47.39	10.10	0.90	7.00	24.50	43.53
2	26460.00	.	.	12.00	1.26	13.00	34.50	76.43
3	17220.00	104.07	40.97	12.30	1.64	9.00	34.50	65.43
4	14592.00	136.46	57.34	9.10	1.06	9.00	23.10	47.89
5	27714.00	88.59	44.97	10.80	0.92	12.00	31.80	74.48
6	12862.00	88.07	41.35	14.10	1.27	9.00	28.80	51.09
7	14896.00	78.57	37.24	.	.	8.00	21.70	.
8	13068.00	104.04	49.78	9.60	0.84	9.00	24.90	43.44
9	13608.00	103.57	46.03	11.80	1.17	9.00	33.40	48.56
10	20160.00	96.67	43.54	10.90	1.20	7.00	33.20	52.66
11	.	.	.	.	.	.	.	.

VI. Week 6 Submaximal Exercise Measures (100 Watts)

OSA	SBP at 100W	DBP at 100W	MAP at 100W	Qc- 100W	CI at 100W	TPR at 100W	HR at 100W
1	200.00	104.00	136.00	10.90	5.17	12.48	111.00
2	204.00	90.00	128.00	.	.	.	143.00
3	162.00	94.00	116.67	13.30	4.69	8.77	123.00
4	164.00	88.00	113.33	14.70	5.63	7.71	108.00
5	.	.	.	.	.	.	.
6	124.00	90.00	101.33	9.40	4.41	10.78	120.00
7	188.00	100.00	129.33	9.10	4.31	14.21	112.00
8	162.00	78.00	106.00	16.00	7.66	6.63	109.00
9	180.00	96.00	124.00	11.50	5.11	10.78	94.00
10	186.00	78.00	114.00	14.80	6.67	7.70	134.00
11	.	.	.	.	.	.	.

OSA	RPP at 100W	SV at 100W	SVI at 100 W	VO2 (ml/kg/min) at 100W	VO2 (L/min) at 100W	% pk VO2
1	22200.00	98.20	46.54	14.70	1.31	63.36
2	29172.00	.	.	14.40	1.51	91.72
3	19926.00	108.13	42.57	15.40	2.06	81.91
4	17712.00	136.11	57.19	13.30	1.55	70.00
5	.	.	.	.	.	.
6	14880.00	78.33	36.77	15.00	1.35	54.35
7	21056.00	81.25	38.51	.	.	.
8	17658.00	146.79	70.23	15.50	1.35	70.14
9	16920.00	122.34	54.37	15.90	1.59	65.43
10	24924.00	110.45	49.75	14.70	1.62	71.01
11	.	.	.	.	.	.

VII. Week 6 Submaximal Exercise Measures (Ventilatory Threshold and 50% of Peak VO_2)

OSA	VT (ml/kg/min)	VT (L/min)	HR at VT	RPE at VT	MAP at VT	WL at VT (WATTS)	HR at 50% VO2pk	VE at 50% VO2pk (L/min)	RPE at 50% VO2pk
1	17.30	1.54	120.00	12.00	136.00	120.00	126.00	28.80	9.00
2	12.40	1.28	142.00	15.00	128.00	85.00	135.00	22.70	8.00
3	16.50	2.20	136.00	14.00	118.00	115.00	123.00	34.50	9.00
4	16.80	1.96	123.00	15.00	126.70	145.00	100.00	29.50	10.00
5	10.90	0.93	146.00	12.00	119.30	50.00	135.00	22.30	11.00
6	17.10	1.54	122.00	12.00	101.30	100.00	120.00	39.40	11.00
7	.	.	.	.	.	.	.	.	.
8	14.70	1.28	109.00	14.00	106.00	105.00	99.00	24.90	9.00
9	19.50	1.94	115.00	14.00	142.00	135.00	91.00	35.00	10.00
10	14.70	1.62	134.00	9.00	114.00	100.00	120.00	35.60	7.00
11	.	.	.	.	.	.	.	.	.

VII. Week 6 Peak Exercise Measures

OSA	PEAK SBP	PEAK DBP	PEAK MAP	VO2pk (L/min)	VO2pk (ml/kg/min)	Peak METS
1	242.00	120.00	160.67	2.07	23.20	6.63
2	218.00	90.00	132.67	1.64	15.70	4.49
3	222.00	84.00	130.00	2.50	18.80	5.37
4	216.00	86.00	129.33	2.22	19.00	5.43
5	186.00	86.00	119.33	1.24	14.50	4.14
6	156.00	86.00	109.33	2.49	27.60	7.89
7	188.00	100.00	129.33	.	.	.
8	200.00	82.00	121.33	1.93	22.10	6.31
9	238.00	100.00	146.00	2.42	24.30	6.94
10	202.00	88.00	126.00	2.28	20.70	5.91
11	.	.	.	.	.	.

OSA	PEAK RER	TEST TIME (min)	PEAK WL (Watts)	PEAK HR	PEAK RPP	PEAK RPE
1	1.16	11.00	190.00	150.00	36300.00	14.00
2	1.12	6.63	125.00	146.00	31828.00	16.00
3	1.13	8.58	155.00	158.00	35076.00	17.00
4	1.01	12.00	205.00	153.00	33048.00	19.00
5	1.23	4.47	95.00	165.00	30690.00	13.00
6	1.25	11.50	200.00	164.00	25584.00	17.00
7	.	5.67	110.00	117.00	21996.00	15.00
8	1.10	9.00	160.00	140.00	28000.00	19.00
9	1.07	0.42	175.00	133.00	31654.00	17.00
10	1.20	0.38	160.00	170.00	34340.00	13.00
11	.	.	.	.	.	.

IX. Week 6 Recovery Blood Pressure and Heart Rate

OSA	REC HR 1 min	REC SBP 1 min	REC DBP 1 min	REC MAP 1 min	REC HR 2min	REC SBP 2min	REC DBP 2 min	REC MAP 2 min
1	137.00	218.00	108.00	144.67	132.00	226.00	102.00	143.33
2	128.00	214.00	86.00	128.67	107.00	160.00	82.00	108.00
3	136.00	176.00	80.00	112.00	118.00	164.00	74.00	104.00
4	138.00	188.00	86.00	120.00	122.00	184.00	84.00	117.33
5	143.00	178.00	74.00	108.67	120.00	148.00	68.00	94.67
6	152.00	144.00	80.00	101.33	142.00	150.00	78.00	102.00
7	117.00	172.00	72.00	105.33	98.00	142.00	72.00	95.33
8	120.00	176.00	72.00	106.67	91.00	140.00	70.00	93.33
9	110.00	222.00	96.00	138.00	100.00	212.00	88.00	129.33
10	150.00	192.00	78.00	116.00	142.00	152.00	72.00	98.67
11	.	.	.	.	.	.	.	.

OSA	REC HR 3min	REC SBP 3 min	REC DBP 3 min	REC MAP 3 min	REC HR 4min	REC SBP 4min	REC DBP 4 min	REC MAP 4 min
1	123.00	220.00	98.00	138.67	107.00	192.00	94.00	126.67
2	120.00	156.00	82.00	106.67	100.00	142.00	86.00	104.67
3	106.00	138.00	76.00	96.67	96.00	134.00	80.00	98.00
4	110.00	184.00	84.00	117.33	104.00	172.00	86.00	114.67
5	100.00	136.00	74.00	94.67	98.00	134.00	78.00	96.67
6	131.00	148.00	80.00	102.67	126.00	144.00	82.00	102.67
7	84.00	130.00	90.00	103.33	94.00	132.00	90.00	104.00
8	104.00	138.00	72.00	94.00	111.00	132.00	70.00	90.67
9	91.00	172.00	90.00	117.33	87.00	168.00	100.00	122.67
10	126.00	128.00	72.00	90.67	118.00	122.00	72.00	88.67
11	.	.	.	.	.	.	.	.

OSA	REC HR 5min	REC SBP 5min	REC DBP 5 min	REC MAP 5 min	REC HR 6min	REC SBP 6min	REC DBP 6 min	REC MAP 6 min
1	100.00	188.00	96.00	126.67	93.00	166.00	100.00	122.00
2	98.00	138.00	84.00	102.00	100.00	128.00	84.00	98.67
3	106.00	128.00	84.00	98.67	107.00	130.00	86.00	100.67
4	97.00	156.00	88.00	110.67	101.00	142.00	88.00	106.00
5	92.00	130.00	80.00	96.67	103.00	132.00	82.00	98.67
6	113.00	128.00	80.00	96.00	107.00	130.00	88.00	102.00
7	88.00	132.00	98.00	109.33	83.00	120.00	92.00	101.33
8	99.00	120.00	70.00	86.67	83.00	112.00	70.00	84.00
9	86.00	152.00	90.00	110.67	81.00	140.00	98.00	112.00
10	115.00	118.00	72.00	87.33	115.00	112.00	72.00	85.33
11	.	.	.	.	.	.	.	.

VITA

Anthony Scott Kaleth was raised in Valparaiso, Indiana by his parents, Dan and Yvonne. He has two brothers, Jeff and Chris. After graduating from high school in 1992, Tony spent a year at Huntington College on a baseball scholarship. Unfortunately, a knee injury ended his playing career so he returned home to attend Valparaiso University. After receiving a Bachelor of Arts degree in Psychology, he decided to attend graduate school. Being a former competitive athlete, he decided to pursue a graduate degree in sports psychology. However, Tony was never a big "fan" of school. He thought he wouldn't be satisfied with a degree in sports psychology unless he went for the Ph.D. Of course, this was just too long to be in school! Luckily, while looking for graduate programs in sports psychology, he noticed that Ball State offered a degree program in Exercise Physiology with an emphasis in adult fitness and cardiac rehabilitation. Even better, it was only for two years. At BSU, Tony was privileged enough to work with Drs. Lenny Kaminsky and Mitch Whaley. While they may exaggerate about their golf games a little, Tony learned a great deal about the clinical aspects of exercise. Furthermore, both gentlemen helped Tony prepare for the clinical work environment and assisted in his search for doctoral programs.

After graduating from Ball State in 1998, Tony started working at St. Catherine Hospital in East Chicago, Indiana. While there, Tony assisted with many aspects of the cardiac rehabilitation program and helped develop many new programs. He enjoyed what he was doing, and more importantly, he enjoyed the people he worked with. However, after about six months, Tony realized that he wouldn't be able to do this for the rest of his life. He needed a bigger challenge. He needed to go back to school and get a

Ph.D. However, before he did that, he made another big decision…he married Jennifer! Of course, Jennifer thought Tony was "nuts" for wanting to go back to school. However, she supported his decision, and in August 1999, he enrolled at Virginia Tech under the direction of Dr. William Herbert. For the past three years, Tony has continued to grow both academically and professionally. He was the Clinical Lab Coordinator for the Therapeutic Exercise and Community Health Center for 3 years. In August 2002, Tony will graduate from Virginia Tech with a degree in Clinical Exercise Physiology. He has accepted a position as an Assistant Professor with Indiana University at the Indianapolis campus and begins work mid-August 2002. Tony just can't seem to get out of school!