CARDIOVASCULAR RESPONSES TO EXERCISE: AN EVALUATION OF THE EFFECTIVENESS OF A BRIEF EXPOSURE TO CPAP IN OBSTRUCTIVE SLEEP APNEA PATIENTS

By

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(ABSTRACT)

Summary: In order to clarify the effects of a single night of CPAP titration on various cardiovascular, gas exchange, and perceptual measures, we conducted submaximal ramping exercise tests to an intensity of ~75% of the heart rate reserve in five male subjects. Means and standard deviation for their age and BMI were 57.0±14.7 years and 30.5±7.2, respectively. The baseline exercise test was administered immediately after the patients arose from bed, following an overnight PSG diagnostic evaluation. The exercise test was repeated within ~2 weeks of completion of an overnight CPAP evaluation trial. Patients reported experiencing improved sleep quality (50%) after the CPAP titration, based on comparison of morning questionnaire responses from the diagnostic PSG vs. CPAP titration. Statistical significance was not attained ($p>0.05$) upon analysis of the following parameters at 60% of the individuals maximum workload although there were changes in the mean values of the variables from the diagnostic PSG vs CPAP titration. The following changes were noted: heart rate increased by 6%, systolic blood pressure decreased by 6%, and the rate pressure product decreased by 5.8%. Respiratory variables changed as follows: VO_2 decreased by 5.3% and VE decreased by 8.5%. The

perceptual measure rate of perceived exertion (RPE) decreased by 17.5%. These preliminary findings demonstrate that self-reports of sleep quality in patients with diagnosed OSA improved after a single night of CPAP titration, even in a setting wherein the total time of CPAP sleep and reduction of apneas, hypopneas, and hypoxemic episodes are highly variable. Additionally, sleep structure revealed a marked increase in slow wave (53.2%) and REM (30.4%) sleep with CPAP titration in comparison to the diagnostic PSG. It was concluded that CPAP titration effectively improves sleep structure and patient ratings of sleep quality, but does not have significant effects on cardiorespiratory responses to submaximal endurance exercise.

Key Words: Obstructive sleep apnea---CPAP---exercise---physiological

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Chapter I

INTRODUCTION

Sleep disorders are among the most common medical complaints in our society, contributing to thousands of lost workdays, decreased vitality and productivity, life threatening accidents, and even fatalities. The National Commission on Sleep Disorders Research has indicated that sleep disorders constitute a significant health problem for millions of Americans (Roth, Roehrs, Conway, 1988). Common and serious sleep disorders is Obstructive Sleep Apnea (OSA). OSA is the reduction of airflow occurring during sleep as the result of upper airway narrowing. Some of the common symptoms include excessive sleepiness or fatigue, lack of motivation, mood or personality change, poor memory, and inability to concentrate. While this disorder goes undiagnosed in many adults, it has been estimated that OSA affects approximately 2 to 4 percent of middle-aged adults in the world (Young T, Palta M, Dempsey J, et al. 1993). Only a small percentage of the cases of suspected suffers have been diagnosed; this is related to insufficient awareness of sleep apnea among physicians and the public at large (Rosen R, Rosekind M, Rosevear C, et al. 1993).

During normal sleep or wakefulness, the upper airway is kept patent by the actions of specific dilator muscles surrounding the pharynx. In patients with OSA, the collapse of the upper airway during sleep leads to complete (apnea) or partial (hypopnea) closure. Apneas are defined as nearly complete cessations of breathing for 10 seconds or longer. They are considered obstructive in nature when due to mechanical upper airway closure. Central apneas are apneic episodes occurring as the result of a transient cessation in brainstem control of breathing. Hypopneas are partial airway obstructions.that do not last as long as apneas. During apneas and hypopneas, the patient's oxygen saturation (SAO_2) decreases and heart rate and blood pressure may rise. The respiratory events are ended by brief arousals from sleep usually in the form of a loud snort. Nocturnal airway obstruction arising in sleep results in arousal and awakening which serves to increase airway patency

and resolve the obstruction. Though the sufferer is usually unaware of airway obstruction, such events can occur several hundred times during the night, severely disrupting sleep continuity. OSA patients may or may not report tiredness, fatigue, sleepiness, memory and judgement problems, irritability, difficulty concentrating, and personality changes (Roth T, Roehrs T, Conway W, 1988).

OSA also affects the cardiovascular system. Systemic hypertension has been reported in up to 50 percent of patients with obstructive sleep apnea (Fletcher E, 1995). Mean morning blood pressure has been found to increase linearly with apneic episodes in both obese and nonobese individuals. (Strohl K, Novak R, Singer W, et al., 1994). Cardiac arrhythmias during sleep have also been associated with OSA. Typically bradyarrythmisas are observed (Guilleminault C, Connolly S, Winkle R, 1983), although ventricular tachycardia is noted in some cases associated with severe hypoxemia (Shepard J, Garrison M, Grither D, et al., 1985). It is also believed that OSA contributes to myocardial ischemia, and even myocardial infarction, in patients with coronary artery disease (Hung J, Whitford E, Parsons R, et al.,. 1990). If not treated, OSA may lead to high blood pressure, myocardial damage, dangerously abnormal cardiac rhythms, and even sudden death.

The diagnosis of OSA usually requires patients to undergo a sleep study called a polysomnogram (PSG). A PSG is usually an overnight study consisting of monitoring of sleep stages, cardiac functions, respiration, blood oxygen levels, and leg movements. Sensors and electrodes are attached to the patient's skin but do not interfere with normal body functions. This data is used to diagnose OSA, grade its severity, and help determine approaches to treatment.

The initial treatment of choice for Obstructive Sleep Apnea is administration of a Continuous Positive Airway Pressure device (CPAP). The CPAP therapy is normally a first choice treatment due to it being non-invasive and lack of side-effects that likely will be a concern with pharmacologic management. CPAP is more economical than various

surgical interventions, and it's effectiveness can be evaluated by the clinician after a very short trial (Strollo P, Rogers R, 1996). CPAP may also be used as temporary treatment until surgical treatment is performed or as an interim treatment to help support a weight loss plan where the treatment is expected to be discontinued at an ideal goal. For some though, CPAP is employed as the primary mode of treatment. Sullivan, Berthon-Jones, Issa et al. (1981) and others (O'Conner & Youngsted, 1995; Richman, Elliott, Burns et al., 1994) demonstrated virtual abolition of apnea with less blood oxygen desaturation on the first night and significant reduction of daytime hypersomnolence and other behavioral symptoms within one week. The development of CPAP for use as a treatment for OSA was made by Sullivan, Berthon-Jones, Issa et al. (1981) in Sydney, Australia. It consists of a small device, which introduces air into the nose through a mask or small tubes placed just inside the nostrils. CPAP acts as an internal dilator functioning by raising intraluminal pharyngeal pressures and splinting open the pharynx which prevents airway collapse. This results in reduction of both snoring and apnea. The correct pressure for the individual is determined in a second PSG test called a CPAP titration. During the CPAP titration trial, positive pressure is gradually increased until the apneic episodes are abolished and blood oxygen levels are stabilized. This method of treatment has been found to stabilize pulse and blood pressure abnormalities (Ali, Davies, Fleethman et al., 1992). Thus, it appears that the chronic physiological effects of OSA on the body are reversed by CPAP.

The most common problem with CPAP is compliance. Patients may discontinue CPAP use due to feeling claustrophobic while others find wearing the CPAP mask to be offensive. For those who cannot adjust to CPAP often approaches are used including use of certain dental appliances and various surgical interventions that remove excess soft tissue in the back of the palate or translocate the jaw to improve the upper airway function. Weight loss may reverse OSA in some cases, but it has the poorest success rate of all therapies.

Statement of the Problem

There is notable paucity of published research literature on physical activity or exercise training regarding patients with Obstructive Sleep Apnea. Yet, there clearly is an association in many patients between progressive weight gain, chronic physical inactivity, and a diagnosis of OSA (Flemons W, Whitelaw W, Brant R, et al., 1994) .

CPAP is usually the first line of treatment for OSA. It is effective in abolishing apneic episodes, thus improving the duration and quality of many PSG sleep parameters. With CPAP, many patients often report a feeling of "euphoria" soon after starting therapy. There are likely unidentified physiologic and psychogenic factors that contribute to this euphoria. If this euphoric feeling is physiologically mediated and associated with reduced cardiorespiratory demand during physical activity, this effect may lead to increased potential for the patients to engage in daytime physical activities that have potential to aid in exercise-facilitated weight loss.

Virtually no research has been published found which examines whether cardiovascular responses improve after a single night of CPAP therapy in OSA patients. In this regard, it would be most helpful to measure for change in various cardiovascular components after administration of CPAP treatment in these patients, along with information on any concurrent changes in their perceptions of sleep quality, daytime wakefullness, and health-related quality of life. Such information might be very helpful in determining the viability of aerobic physical training as an adjunct for weight control with patients who continue to be at risk for progression of OSA while maintaining CPAP therapy.

Hypotheses

Ho^{1} – Ho^{3}**:** In a group of patients diagnosed with OSA and then administered a single night's trial with CPAP, acute improvements will be observed for the following via stationary cycle ergometry:

heart rate before and after the CPAP trial;
blood pressure before and after the CPAP trial;
rate of percieved exertion before and after the CPAP trial;

Ho^4: In a group of patients undergoing two PSG studies, the first diagnostic for OSA and the second to titrate CPAP treatment, acute improvements will be observed in the following self-report indicator of status based on an overnight sleep quality questionnaire:

perceived quality of sleep.

Significance of the Study

Previous published research and the experience of clinicians indicates that CPAP, in most cases, is an effective treatment for OSA (Issa F, Sullivan C, 1986). Physical activity also has the potential to contribute to optimization of body weight in OSA patients for whom excess body fat is part of the etiology of this disorder. Eventually, some OSA patients may be able to eliminate the need for CPAP therapy by reducing the amount of body fat with a regular exercise program. In addition, even those patients who must continue to use CPAP may have an improved prognosis as a function of autonomic adaptations that tend to occur with increases in aerobic physical activity.

The information obtained from this study can be used to better understand the immediate physiological and psychological changes that occur with the initial titration of CPAP in OSA patients. The purpose of this study is to observe whether or not OSA patients who undergo short term CPAP treatment have significant improvement in heart rate, systolic blood pressure, rate pressure product, and rate of perceived exertion .

Basic Assumptions

The following assumptions were made:

1. Subjects were truthful in answering all questions in the questionnaires used in this study.
2. Subjects completed all questionnaires as instructed.

3. Blood pressure readings were accurate.
4. CPAP titrations were optimal.

Delimitations

The following delimitations were imposed by the investigator due to the nature of the study:

1. The selection of subjects was limited to OSA patients with an initial PSG test AHI reading of >10.
2. Subjects were excluded from the study if they had been diagnosed with any of the following conditions: coronary artery disease; uncontrolled hypertension, chronic obstructive pulmonary disease; carotid vascular disease, uncontrolled diabetes mellitus.
3. Subjects were also excluded for any of the following:. excessive body mass (>136 kg), musculoskeletal disorders, and a history of regular participation in moderately vigorous physical activity
4. The exercise-testing mode was limited to the stationary cycle ergometer.
5. Blood pressure was obtained manually with two trained technicians measuring simultaneously.

Limitations

The following limitations of the study are recognized:

1. All questionnaires relied on direct recall of the subject.
2. Subjects were of varying fitness levels.
3. Resting elevations in blood pressures is not due to anxiety.

Definitions and Symbols

1. Obstructive Sleep Apnea (OSA): cessation of airflow as the result of upper airway occlusion in spite of continued increasing inspiratory effort.
2. Continuous Positive Airway Pressure (CPAP): a device used in the treatment of OSA. It operates by providing a constant flow of air into a mask worn by the patient, this splinting open the upper airway to allow adequate respiration.
3. Apnea: "without breath," loss of airflow associated with oxygen desaturation.
4. Hypopnea: partial airway obstruction in which airflow continues but at a much reduced level; usually associated with oxygen desaturation.
5. Respiratory Disturbance Index (RDI): this measure may include abnormal respiratory events, beyond clinically significant apneas and hypopneas, which are felt to be significant by the sleep specialist. The RDI describes the number of abnormal respiratory events per hour, which is felt to be the most sensitive and accurate in diagnosing OSA.
6. Apnea-Hypopnea Index (AHI): scoring tool for OSA which is computed by summation of all apneic and hypopneic events occurring during sleep. Commonly reported as an average number of events per hour.
7. Hypoxia: diminished availability of oxygen to the body tissues.
8. Hypoxemia: deficient oxygenation of the blood. May eventually lead to hypoxia.
9. Pharynx - the throat, the muscular membranous tube extending form the cavity of the mouth to the esophagus.
10. REM sleep: a specific stage of sleep characterized by eye movements, skeletal muscle paralysis, and dreams. This stage of sleep accounts for 20-25% of normal sleep in adults.
11. Slow wave sleep: a synonym for stage 3 and 4 sleep

Summary

Obstructive sleep apnea (OSA) is a multifaceted problem that takes many years to evolve. Rates of occurrence of OSA have been found to range from 2% to 4% of the population, and up to 30% of snorers. This disorder in gaining in notoriety due to its contributing to lost workdays, decreased vitality and productivity, life threatening accidents, and even fatalities. The major objective of this study was to observe if OSA patients have a significant change in various cardiac, respiratory, and perceptual parameters after a single night of CPAP therapy. The knowledge gained from this study could greatly help to determine if single night improvements are either psychological or physiological in nature.

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Chapter II

REVIEW OF LITERATURE

Introduction

Sleep disorders are among the most common medical complaints in our society, contributing to thousands of lost workdays, decreased vitality and productivity, life threatening accidents, and even fatalities. The National Commission on Sleep Disorders Research has indicated that sleep disorders constitute a significant health problem for millions of Americans. One of the most common and serious sleep disorders is Obstructive Sleep Apnea (OSA). While this disorder goes undiagnosed in many adults, it has been estimated that OSA affects approximately 2% to 4%, respectively, of the adult population of the world (Young T, Palta M, Dempsey J, et al., 1993).

Epidemiology of OSA

Obstructive sleep apnea (OSA) is the most common organic disorder of excessive daytime somnolence. In cross-sectional studies the minimum prevalence of OSA among adult men is about one per cent. Prevalence is highest among men aged 40-65 years. In a study of 602 employed men and women between the ages of 30 to 60 years, it was estimated that 2% of women and 4% of men in the middle-aged work force meet the minimum sleep apnea requirements of AHI≥5 and 3 symptoms of daytime hypersomnolence (Young, Palta, Dempsey, et al., 1993). Habitual snoring is the most common symptom of OSA (70-95%). Woodhead, Davies, and Allen (1991) studied 35 patients with a history of loud snoring. Each patient underwent a PSG to diagnose for OSA. They found that 16 (46%) of the 35 subjects demonstrated OSA. The most significant risk factor for OSAS is obesity, especially involving the torso. A significant

study by Rossner, Lagerstrand, Persson, et al., (1991) utilized 34 obese male subjects referred to an obesity unit for a period of 4 years. Twenty-two men underwent a PSG and 15 (68%), were found to have significant OSA (mean AHI=46). Research has also found obesity to be a prevalent risk factor for women also. Richman, Elliott, Burns, et al. (1993) studied 86 eligible women who met the requirements of BMI>30 kg/m^2 and age >18 yr. Of the 86, 33 volunteered to undergo a PSG. Twenty-nine of the 33 had successful recordings and of those 29, it was found that 37.9% had an RDI >5. Other risk factors for snoring and for OSA include male gender, age between 40 and 65 years, cigarette smoking, use of alcohol, and poor physical fitness.

Pathophysiology of OSA

Under normal conditions, the patency of the upper airway during wakefulness and sleep is due to the morphologic design of the upper airway. The nasal passage functions to warm, humidify, and filter inspired air is surrounded by bone and cartilage. The larynx and trachea maintain their patency in large due to cartilaginous support. On the other hand, the pharynx is potentially a collapsible segment of the upper airway. This portion consist of three contiguous anatomic segments: (1) the nasopharynx, ending form the end of the nasal septum to the free margin of the soft palate; (2) the oropharynx, extending from the margin of the soft palate to the top of the epiglottis; and (3) the hypopharynx, extending from the top to the base of the epiglottis (Kuna & Sant Ambrogio, 1991). In OSA patients, upper airway obstruction during sleep often develops in the pharaynx and initially involves one centimeter length of airway (Chaban et al., 1988). Investigators have reported that the initial site of airway closure is constant in a given OSA patient, but varies among patients. (Hudgel, 1986; Launiois et al., 1990). Closure can occur in the nasopharynx, oropharaynx, and/or hypopharynx. Decreased upper airway muscle activity occurring at sleep onset is suggested as the cause of pharyngeal narrowing. An increase in subatmospheric intraluminal pressure promotes further pharyngeal narrowing. Inadequate

activation of upper airway dilator muscles in response to the increased resistive load and chemical stimulation results in pharyngeal closure. As the upper airway obstruction persists, hypercapnia and hypoxemia serve to increase output to the respiratory pump muscles and upper airway muscles, resulting in pharyngeal reopening. The restoration in airflow decreases arterial PCO_2 and increases arterial PO_2 toward normal limits. This cycle repeats itself throughout the night (Kuna & Sant Ambrogio, 1991). Certain evolving aberrations in upper airway morphology, perhaps linked to soft tissue accumulation and excess weight gain, appear to contribute to this etiology. It is believed that obesity of the neck cause static compression, leading to diurnal narrowing, as well as dynamic loading, which overwhelms the residual pharyngeal dilator activity. Additionally, a study by Rodenstein *et al* (1990) showed that this excess accumulation of fat is greater in OSA patients, and the pharyngeal airways tend to be narrowed laterally in these individuals, compared to normal non-obese subjects. Other proposed mechanisms have been postulated to contribute to OSA, including neural and/or chemoreceptor malfunction. One such mechanisms suggests that abnormal sensory function originating in airway mucosal tissue leads to disproportionate or delayed respiratory muscle contraction (Chernick , 1980). It also has been suggested that the mucosal sensory functions may be normal, but that sensory signal processing may be mishandled by malfunctioning central neural pathways and this may somehow contribute to a diminished respiratory drive. These changes in respiratory control during sleep may fail to promote normal in arterial blood gas levels which could further exacerbate disordered breathing and further alter respiratory drive (Dempsey & Skatrud, 1986). This fluctuation in breathing causes problems in that after a period of time, the brain responds to a lack of oxygen and initiates a neural flow to induce sudden arousal. Although the sufferer is unaware of it, this cycle can happen several hundred times during the night, severely disrupting sleep. As this disruption increases in severity and becomes a chronic problem, sleep deprivation effects occur during waking periods, daytime alertness is reduced and individuals complain of problems ranging from

inexplicable chronic fatigue to disabling sleepiness. Some of the common symptoms of sleep disruption include excessive tiredness, lack of motivation, mood or personality change, poor memory, and inability to concentrate. If not treated, OSA can possibly lead to high blood pressure, fluid retention, myocardial damage, dangerously abnormal cardiac rhythms, and even sudden death..

Health Related Quality Of Life

OSA has been found to significantly affect a person's quality of life. Daily activities are often interupted or made more difficult due to complications of sleep disruption and hypoxemia. Consequences often found with OSA may include memory deficits, decreased alertness, irritability, depression, headaches, or decreased ability to concentrate. These deficits can lead to impairment of work efficiency, social and relationship problems, and increased automobile accidents (Flemons and Tsai (1997) Paiva, Farinha, Martins, et al. (1997), and Wright, Johns, Watt, et al. (1997).

OSA Diagnosis

Diagnosis of OSA usually requires patients to undergo a sleep study called a polysomnogram (PSG). This overnight study consists of monitoring sleep stages, cardiac function, respiration, blood oxygen level, and leg movements. Sensors and electrodes are attached to the patient's skin but do not interfere with normal body functions. Several indices from this test are used to diagnose OSA, grade its severity, and help determine specific approaches to treatment. The most common measurement of OSA is the apnea plus hypopnea index (AHI), which is similar to the respiratory disturbance index (RDI). The AHI is calculated by dividing the number of apneas and hypopneas occurring during the night by the total sleep time. Thus, the AHI defines the number of abnormal respiratory events per sleep hour. This index is utilized to determine the severity of the OSAand the effectiveness of the treatment (Guilleminault, 1983).

CPAP Therapy

Sullivan, Issa, and Berthon-Jones (1981) first utilized the CPAP device as a possible treatment for OSA. It was used on five patients with severe OSA via providing pressurized air through a nasal mask. The authors found that low levels of pressure (range 4.5-10 cm H_2O) completely prevented upper airway occlusion during an entire night of uninterrupted sleep in all affected patients examined. The goal behind the use of CPAP is to reduce the number of respiratory disturbances during sleep and improve the patient's quality of sleep. To use CPAP, the patient is required to wear a mask over the nose, or in some cases, over both the nose and the mouth (Sanders et al., 1994). The mask is connected to an air compressor device which forces air through the nasal passages and acts as a pneumatic splint by increasing the intraluminal pressure in the oropharyngeal airway, thus reversing the transmural pressure gradient across the pahryneal airway (American Thoracic Society, 1994). This method of treatment is usually prescribed after polysomnography has first determined the level of CPAP pressure required to reduce or eliminate sleep apnea (Waldhorn & Wood, 1993).

Berthon-Jones, Lawerence, Sullivan, et al. (1996) preformed a study on 41 males and 4 females with untreated OSA with an AHI>20 (mean AHI=30.4). They found that with the use of CPAP, the mean AHI fell to 0.4 events/hr ($p<0.0001$). They also found a significant increase in the percentage of slow wave sleep (8.9% untreateed vs. 12.3% treated, $p=0.01$) and REM sleep (11.6% untreated vs. 15.5% treated, $p=0.014$). Issa and Sullivan (1986) found that patients with severe OSA demonstrate long periods of both

REM sleep and stage 4 NREM sleep after successful CPAP titration. They studied 12 severe OSA patients aged 30 to 58 with AHI's ranging from 28-83. It was found that stage 3 and 4 NREM sleep increased from 6.7% to 31.5%. REM sleep increased from 18.4% to 30.6%. CPAP has also been found to be markedly effective in reversing daytime somnolence (Lojander, Maasilta, Parinen, et al., 1996). During this study, OSA patients on CPAP were followed and contacted after 1 yr of therapy. After one year of treatment, treated patients were significantly ($p<0.05$) less somnolent. These improvements are the result of a reduction in sleep fragmentation.

The effect of CPAP on hypertension has been examined by Lies, Nabe, Pakow, et al. (1996). Their study consisted of patients diagnosed with OSA defined as an AHI>10. Ambulatory blood pressures were monitored for 24 hours before the initial diagnostic PSG, after1-3 days of CPAP, and after 4-6 months of CPAP therapy. They found a significant decrease in daytime blood pressures after short-term as well as long term CPAP therapy. A baseline blood pressure of 144.8/94.4 mmHg decreased to 138.9/89.4 mmHg after short-term use of CPAP and to 136.4/86.9 mmHg after long term use. Another study by Mayer, Becker, Brandenburg, et al. (1991) looked at the issue of the effects of long-term CPAP on hypertension in OSA patients. This study conssited of 12 men with mean BMI of 29.3 and mean AHI of 58. After 6 months of therapy, the BMI did not change and AHI significantly decreased to 2 after CPAP therapy ($p<0.01$). Mean blood pressure and heart rate were found to significantly decrease as a result of the CPAP therapy. Mean systolic blood pressure decreased from 147.1 mmHg to 126.4 mmHg and mean diastolic blood pressure decreased from 81.6 mmHg to 69.4 mmHg. Mean heart

rates also decreased from 68.8 bpm to 65.4 bpm. Statistical significance was found for all three of the above studies ($p<0.001$). From these studies, it can be inferred that hypertension in OSA patients may decrease with CPAP therapy.

CPAP effects on sympathetic stimulation due to hypertension caused by OSA was studied by Waradekar, Sinoway, Zwillich, et al. (1996) who looked at muscle sympathetic nerve activity in 7 OSA patients before CPAP therapy and after one month of therapy. Mean sympathetic nerve activity before CPAP was 69.4 bursts/min and 53.9 bursts/min ($p<0.01$) after one month of CPAP therapy.

Obstructive sleep apnea is also associated with decreased hypercapnic ventilatory response (HCVR) which is likely to be responsible for aggravating OSA (White, Douglas, Pickett, et al., 1983). Verbraecken, DeBacker, Willemen, et al. (1995) evaluated whether patients with various types of sleep apnea experience a significant decrease in HCVR. In this study, 5 groups of patients were evaluated: controls, heavy snorers, normocapnic OSA, hypercapnic OSA, and OSA patients with COPD. Each patient underwent the measurement of hypercapnic ventilatory response. All patients then underwent an overnight polysomnography study. In the second phase of the study, patients with predominately OSA were treated with CPAP if their obstructive apnea index was at least 15 and central apnea index was not greater then 5. A significant increase of the slope in the normocapnic OSA and overlap group was identified. They found that a depressed HCVR could only be observed in chronic hypercapnic OSA. Also it was found that changes in the AHI after CPAP do not parallel the HCVR. They concluded that in

eucapnic OSA patients CPAP therapy does not change CO_2 drive. They believed that increased chemical CO_2 drive contributes to its pathogenesis.

When compared with no treatment or other treatment modalities, patients treated with CPAP have a lower mortality rate (Keenan et al., 1994). Even though CPAP has been demonstrated to be effective, it is difficult for some patients to adapt to its use. Adherence to CPAP treatment varies greatly between individuals but tends to be higher in patients with severe symptoms (Kribbs et al., 1993).

Cardiac Function During Sleep

Cardiac hemodynamics significantly vary during sleep. In nomal sleep, systemic blood pressure declines on average 5 to 10 percent in stages 1 and 2 of NREM sleep and 10 to 15 percent in stages 3 and 4. Blood pressure is variable in REM sleep, but is typically higher than in NREM sleep. Pulmonary artery pressures are essentially unchanged. Heart rate usually declines by 5 to 10 percent in NREM sleep, with changes in cardiac output during REM sleep being predicted, but not documented to be variable.

In contrast to normal individuals, systemic blood pressure increases during sleep by as much as 25% in most patients with severe OSA. In a non-selected community based population, Hla, Young, Bidwell et al. (1994) found that there is an association between hypertension and sleep apnea independent of obesity, age, and sex. Their study included 147 men and women aged 30-60 yr. Mean blood pressure during wakefulness and sleep were assessed during a 24-hour period in subjects with sleep apnea (AHI≥5)

and in those without sleep apnea. During wakefulness, participants with an AHI≥5 had a mean systemic blood pressure of 131/80 mmHg compared to a reading of 122/75 mmHg for the subjects with an AHI<5($p<.05$). After controlling for obesity, sex, and age; obstructive sleep apnea was significantly associated with hypertension in a dose response relationship. Form this data, the researchers concluded that there was an association between systemic hypertension and OSA independent of age, obesity, and sex in a community based population. Also, the rise in blood pressure was proportional to the severity of oxyhemoglobin desaturation for each individual. Another study that examined the link between OSA and hypertension was conducted by Young, Peppard, Palta, et al. (1997). They evaluated a sample of 1060 employed men and women ages 30-60 yr. All subjects underwent an overnight PSG study. It was found that blood pressure, as measureed on the night of the PSG study, increased linearly with an increasing AHI ($p=0.003$ for systolic and $p=0.01$ for diastolic). The authors concluded that an increased severity of OSA results in a higher prevalence of hypertension. Interestingly, two phases to this rise in pressure are seen. The first phase is the rise in pressure observed during the later portion of the apnea; the second phase occurs after the apnea termination. It is theorized that the sympathetic nervous system plays a significant role in the cause of systemic hypertension in OSA. Carlson, Hadner, Elam, et al. (1993) studied 11 males previously diagnosed with OSA and 9 male control subjects. They found that the skeletal muscle sympathetic activity (MSA) in the OSA group was significantly higher at 60.6 bursts a minute compared to 43.0 bursts a minute in the control group ($p<0.01$).

Additionally they found that plasma norepinephrine levels between the OSA subjects and the control group were significantly different ($p<0.05$). They concluded that resting MSA was increased during awake, supine rest in OSA patients.

An increased risk of cardiovacular disease as a result of OSA has also been discovered. Mooe, Rabben, Wiklund, et al. (1996) performed a study that found men with coronary artery disease (CAD) had a much higher occurrence of OSA when compared to age matched controls. A sample of 142 men with angiographically verified CAD and 50 controls without known heart disease were studied. It was found that 37% of the CAD subjects had an AHI score of ≥10 compared to 20% of the control subjects with the same AHI. Therefore, the authors concluded that sleep disordered breathing is common in men with CAD.

Cardiac output has also been reported to decrease up to 33 percent with obstructive apneas of 35-40 second duration. Guilleminault, Motta, Mihm, et al. (1986) studied cardiac output variability in seventeen men ages 21 to 58 yr diagnosed with severe OSA for cardiac output changes. They utilized a thermodilution technique and found that regardless of age, sleep state, or the mechanism inducing OSA, the cardiac output decreased significantly from baseline during apneic events. In addition, immediately after apnea termination, there is a sudden increase in heart rate, which, in combination with arousal, contributes to an increase in cardiac output that may exceed baseline. Left ventricular stroke volume (LVSV) has been found to also decrease during apneas. Tolle, Judy, Yu et al. (1983) studied 10 patients with severe OSA in which noninvasive

electrical impedance method was used to evaluate LVSV. Their results found that LVSV, cardiac output, and heart rate decreased by 18, 27, and 11%, respectively ($p<0.01$).

Ventricular ectopy has also been reported to occur in 57 to 74 percent of patients with OSA. Ventricular ectopy has been shown to increase threefold where the SaO_2 dropped below 60%. This ectopy is believed to be the result of hypoxemia and elevated sympathetic activity.

Exercise and Obstructive Sleep Apnea

Little research has been done in the area of the effects of OSA on exercise capability. Only two studies could be found with any mention of exercise performance in OSA patients undergoing CPAP treatment. In a study completed by Konermann, Sanner, Klewer, et al. (1996) exercise cardiopulmonary parameters were examined in OSA patients after CPAP therapy. 30 patients with severe OSA were studied. The authors found that steady state exercise testing after 2 weeks of CPAP revealed a decrease in heart rate ratio 100W/rest by 13.5% ($p<0.001$), a drop in the systolic blood pressure 100W/rest by 0.8% (n.s.), but no significant change in diastolic blood pressure 100W/rest. It was also found that after 6 months of CPAP therapy, the heart rate ratio decreased by another 6.5% ($p<0.01$), with the systolic blood pressure dropping by another 14.9% ($p<0.001$). The diastolic blood again did not significantly change however. The second study was conducted by Taguchi, Hida, Okabe, et al. (1997). In this study 6 patients undergoing CPAP therapy underwent an incremental cycle ergometry test was used before CPAP therapy and 7 days after the start of CPAP therapy. The exercise test

began at 0 W and increased by 25 W every 3 minutes until maximal exhaustion occurred. In this patient population, the maximal oxygen consumption increased after 7 days of therapy (1841 mL/min v. 2125 mL/min, $p<0.05$).

Another area that has not been well researched is the concept that physical exercise could decrease symptoms and severity of OSA. A study conducted by Netzer, Lormes, Giebelhaus, et al., (1997) examined 11 patients with mild to severe OSA to determine if physical exercise would improve OSA symptoms in an open trial. The exercise program consisted of a six month period in which patients exercised twice weekly for 2 hr at a time. Measurements were performed before and after the six month period and consisted of: a full PSG without CPAP use, a bicycle exercise test with lactate profile, echocardiography, blood test, and body weight and height measurements. The study did not find any significant reduction in weight, SAO_2, or improvement in physical health status. It was also found there were no echocardiographic changes or change in blood pressure during the bicycle test. There was however, a significant decrease of the RDI ($p<0.05$), but no differences in the percent of REM. From this data, the authors concluded that there was an improvement of the sleep apnea correlated to a decrease of the RDI in the studied patients possibly due to the increase in the respiratory drive or a stabilized muscle tone in the upper airways. They believe that a physical training program should therefore included the treatment plan for patients with sleep apnea.

Questionnaires

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, which assesses sleep quality and disturbances over a 1-month interval. It consists of 19 self-rated questions and five additional questions rated by a bed partner or roommate. Buysse, Reynolds, Monk, et al. (1989) found that a global PSQI score >5 yielded a diagnostic sensitivity of 89.6% and specificity fo 86.5% in distinguishing good and poor sleepers. Their study consisted of "good" sleepers (healthy subjects, n=52) and "poor" sleepers (depressed patients, n=54; sleep-disorder patients, n=62). Acceptable measures of internal homogenity, consistency (test-retest reliability), and validity were obtained. In another study, Richman, Elliott, Bunn, et al. (1994) studied the prevalence of OSA in 29 obese females (BMI>30 kg/m^2, age >18 yr). All subjects were screened by an overnight ambulatory sleep study to rule out OSA. The PSQI was used to assess subjective sleep quality and sleep disturbances. In this study the prevalence of OSA (RDI>5) was found to be 37.9%. It was concluded that over one-third of the women had OSA, yet they did not complain of symptoms even though the PSQI questionnaire indicated that they were poor sleepers.

The Baecke Questionnaire of Habitual Physical Activity is a measurement of habitual physical activity encompassing three distinct dimensions. It consists of three sections: work activity, sports activity, and non-sports leisure activity. Each section consists of several questions scored on a five-point Likert scale. Baecke, Burema, and Frijters (1982) found that in 139 male and 167 females subjects between the ages of 20-27 yr, the relationship between first test and 3 month retest reliability of the work index, sports index, and leisure time index were .88, .81, and .74, respectively. Richardson,

Ainsworth, and Wu (1995) studied the ability of the Baecke to assess leisure physical activity in 78 men and women, age 20-59 yr. They compared it to six 48-hour physical activity records; fourteen 48 hour Caltrac accelerometer readings (Caltrac); three peak oxygen consumption (VO_2 peak) determinations; and percent body fat. The results showed that associations were evident in men and women respectively, between sport and exercise physical activity and physical activity record heavy intensity activity (r=0.73 and r=0.63); VO_2 peak (r=0.67 and r=.45); and percent body fat (r=-0.37, P=0.08 and r=-0.44). Pols, Peeters, Bueno-De-Mesquita et al. (1995) tested for reproducibility and relative validity in a population of 134 men and women aged 20-70 yr. Relative validity was determined by comparing the questionnaire to a four times repeated 3-day activity dairy. They found that reproducibility after 5 and 11 months was good with test-retest correlation coefficients between .65 and.89 for main sections of the questionnaire.

The Health Status Questionnaire (HSQ) was developed by Summit Medical Inc. It is a variation of the Medical Outcomes Study (MOS) SF-36. Content for the HSQ is identical to the MOS, but it is setup in an easier to use format. The MOS SF-36 is a 36 item short-form constructed to survey subjective health statues. It was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The questionnaire includes a one multi-item scale that assesses eight health concepts: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health; 6)

limitations in usual role activities because of emotional problems; 7) vitality; and 8) general health perceptions. Only one study could be found utilizing the MOS SF-36 for determination of quality of life in sleep apnea patients. This study by Jenkinson, Stradling, and Petersen (1997) studied the quality of life outcome in evaluation of CPAP for sleep apnea patients. The study consisted of 108 patients with OSA undergoing a therapeutic assessment of CPAP. Each subject completed the MOS SF-36 questionnaire before and 5 weeks after commencing CPAP therapy. The authors found that the SF-36 revealed substantial adverse effects on the subjective health of OSA patients and that CPAP treatment produced dramatic positive effects. The effect sizes (differences in score, divided by SD of baseline score) in the Energy/Vitality dimension was 0.98, 0.76 and 0.57, respectively for the overall Mental and Physical Component scores.

Chapter III

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CARDIOASCULAR RESPONSES TO EXERCISE: AN EVALUATION OF THE EFFECTIVENESS OF A BRIEF EXPOSURE TO CPAP IN OBSTRUCTIVE SLEEP APNEA PATIENTS

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ABSTRACT

Summary: In order to clarify the effects of a single night of CPAP titration on various cardiovascular, gas exchange, and perceptual measures, we conducted submaximal ramping exercise tests to an intensity of ~75% of the heart rate reserve in five male subjects. Means and standard deviation for their age and BMI were 57.0±14.7 years and 30.5±7.2, respectively. The baseline exercise test was administered immediately after the patients arose from bed, following an overnight PSG diagnostic evaluation. The exercise test was repeated within ~2 weeks of completion of an overnight CPAP evaluation trial. Patients reported experiencing improved sleep quality (50%) after the CPAP titration, based on comparison of morning questionnaire responses from the diagnostic PSG vs. CPAP titration. Statistical significance was not attained ($p>0.05$) upon analysis of the following parameters at 60% of the individuals maximum workload although there were changes in the mean values of the variables from the diagnostic PSG vs CPAP titration. The following changes were noted: heart rate increased by 6%, systolic blood pressure decreased by 6%, and the rate pressure product decreased by 5.8%. Respiratory variables changed as follows: VO_2 decreased by 5.3% and VE decreased by 8.5%. The perceptual measure rate of perceived exertion (RPE) decreased by 17.5%. These preliminary findings demonstrate that self-reports of sleep quality in patients with diagnosed OSA improved after a single night of CPAP titration, even in a setting wherein the total time of CPAP sleep and reduction of apneas, hypopneas, and hypoxemic episodes are highly variable. Additionally, sleep structure revealed a marked increase in slow wave (53.2%) and REM (30.4%) sleep with CPAP titration in comparison to the diagnostic PSG. It was concluded that CPAP titration effectively improves sleep structure and patient ratings of sleep quality, but does not have significant effects on cardiorespiratory responses to submaximal endurance exercise.

Key Words: Obstructive sleep apnea---CPAP---exercise---physiological

Introduction

Sleep disorders are among the most common medical complaints in our society, contributing to thousands of lost workdays, decreased vitality and productivity, life threatening accidents, and even fatalities (1). Obstructive sleep apnea (OSA) is one of the more common sleep disorders and affects 2 to 4 percent of middle-aged adults in the world (2). OSA is characterized by a temporary cessation of airflow and is a result of repeated upper airway closure during sleep. Hypoxemia and sleep fragmentation are responsible for the typical symptoms of OSA. Continuous positive airway pressure (CPAP) is the primary noninvasive therapeutic alternative used for the treatment of OSA (3). CPAP acts as a pneumatic splint by increasing the pressure in the oropharyngeal airway, thereby maintaining airway patency throughout the ventilatory cycle (4). The purpose of this study was to determine if a single night's trial of CPAP would elicit acute improvements in cardiovascular, gas exchange, and perceptual measures via stationary cycle ergometry in OSA patients.

Methods

Subjects:

Numerous patients for polysomnographic (PSG) evaluation from the Sleep Disorders Network of Southwest Virginia, Christiansburg, VA, were contacted and screened for inclusion in this study between November 1997 and February 1998. Five male subjects met the criteria for inclusion and volunteered to participate in this study. Patients were excluded for the following diagnoses or clinical conditions: excessive body mass (>300 lb.); coronary artery disease; uncontrolled hypertension, chronic obstructive pulmonary disease; carotid vascular disease; uncontrolled diabetes mellitus; or orthopedic

and musculoskeletal conditions that would prevent stationary cycling exercise. In addition, only those patients who were scheduled for a follow-up PSG study for continuous positive airway pressure (CPAP) titration were continued in the study. This method of treatment is usually prescribed after PSG results have determined the level of CPAP pressure required to reduce or eliminate sleep apnea.

Measures:

Demographic and health history variables were obtained from medical records and a structured interview. Patients were requested to complete the following questionnaires at the time just prior to their diagnostic PSG study: Health Status Questionnaire, Baecke Physical Activity questionnaire; and the Pittsburgh Sleep Quality Index (PSQI. Upon arising from the initial PSG, subjects completed the short-term PSQI on the morning after the diagnostic PSG. Each patient then was asked to complete a submaximal cycle ergometer test. The test was based on a ramping protocol that was administered up to an intensity of approximately 75% of the patient's predicted cardiac reserve (5). A MedGraphics CardiO_2 cycle ergometer allowed for controlled application of ramp rates, ranging (from 6, 9, or 12 Watts/min), according to each subject's physical activity level, so that the target exercise intensity endpoint was reached within 16 min. Respiratory gas data was continuously collected utilizing a Sensormedics VMAX 22 system (Yorba Linda, CA). Subjects were monitored continuously for possible ischemic-type ST wave, rhythm, and conduction changes during exercise via a 12-lead ECG exercise monitoring unit that was an integral part of the VMAX system. Blood pressure and rate of perceived exertion were recorded at 3-min intervals throughout the test. Specific guidelines for test termination criteria are as recommended by the ACSM.

Subjects were asked to continue in the exercise study if their initial PSG results yielded a positive diagnosis of OSA and were requested to return to the sleep center for a follow-up overnight study to titrate CPAP therapy. The short-term PSQI was

administered a second time to rate the quality of sleep after CPAP therapy. After completing the questionnaire, the cycle ergometer test procedure was repeated just as before.

Data Analysis. Cardiovascular measures consisted of heart rate (HR), systolic blood pressure (SBP), and Rate Pressure Product (RPP). Respiratory gas exchange measurement consisted of VO_2 and ventilation rate (VE). The perceptual measures used were Rate of Perceived Exertion (RPE) and a modified short-term sleep quality index. The measures were all plotted to establish linear regression for these variables on power output for each subject. Data sets for each test yielded regression slopes and intercepts that were used to quantify the subject's response. All responses were analyzed via t-test to establish if there were any differences in intercept or slope for each cardiorespiratory measure and RPE. A clinically significant level of 60% of each subject's maximum cardiac reserve was used to determine if CPAP treatment leads to a change in the dependent measures. This level has special relevance for potential to do activities that are potentially valuable for understanding the implications of such patients for following a program of cardiorespiratory activity for fitness development and weight control. Differences in dependent variables were assessed via a paired t-test. The Minitab statistical software program was used to determine the differences in data for PSG1 vs PSG2 responses. Differences for questionnaire data were analyzed via mean differences and standard deviation. Differences were considered significant at the $P<0.05$ level.

Results

Means and standard deviations for age, weight, and body mass index (BMI) were 57±14.7 yr., 93.5±6 kg, and 30.5±7.2. Statistical analyses on the regression slope/intercept data yielded no significant ($p \leq 0.05$) differences in R^2 values, analyzed

separately for individual patients between the diagnostic PSG and CPAP titration. Slopes and y-intercepts also were analyzed for these regressions and no significant differences ($p \leq 0.05$) were found for any of the physiological variables or perceived exertion between the two test conditions (Table 2).

Mean PSQI scores utilized to determine recent history of sleep quality for the group were found to be 7.6±3.8 (Table 3). The mean RDI, which is the primary index for quantifying the physiological consequences of sleep distress in OSA, improved by nine fold as evidenced by a decrease from 47.6±18.8 during the diagnostic test to 5.1±5.7 during the CPAP titration. Physiological sleep quality also improved as indicated by substantial increases in slow wave (53.2%) and REM sleep (30.4%) periods between the diagnostic and CPAP titration sleep studies (Table 1).

Concurrently, patient self-report of changes in sleep a difference was attained in the short-term PSQI data for the change in subjective sleep quality pre- and post-CPAP therapy. The mean score for the short-term PSQI improved from 4.4±0.5 to 2.2±0.8 (50%) on average.

For each subject, the calculated 60% level was individualized according to the subject's age and resting heart rates, so that findings could be reported at an exercise intensity that approximated the same fraction of their aerobic poser. The paired t-test on heart rate at the 60% level revealed no significant change ($p > 0.05$) after a single night of CPAP treatment even though there was a 8.2% increase in the mean values. No significant differences were found in the other cardiovascular measures of systolic blood pressure ($p > 0.05$) and rate pressure product ($p > 0.05$) for the trials even though SBP had a 6% improvement in mean values from 194.0 to 82.4 and RPP had a 5.8 % improvement from 254.0 to 239.2 (Table 4). Results for the gas exchange measures were also found to be non-significant ($p > 0.05$) for the ventilatory measures of VO_2 and VE at the 60% exercise

intensity level between the two test conditions, despite a5.3% reduction in VO_2 means from 1.9 l/min to 1.8 l/min and a 8.5% reduction in VE means from 56.4 to 51.6 (Table 4). Additionally, no difference ($p>0.05$) was found in perceived exertion at the 60% exercise intensity level between the two test conditions, despite a 17.5% reduction in the mean values from 16 to 13.2, i.e. a reduction from "Hard" to "Somewhat Hard" effort; this finding appears to be attributable to substantial individual response variability.

Discussion

The purpose of this study was to determine the effect of a single night of CPAP therapy on cardiovascular, gas exchange, and perceptual measures via submaximal cycle ergometry bouts in OSA. Questionnaires were used to obtain demographic data about how each subject perceived their quality of life and quality of sleep. The data from the PSQI questionnaire showed that all of the subjects subjectively felt they were experiencing poor sleep quality over the 4 weeks prior to the diagnostic study. These findings were consistent with those found by Richman, Elliott, Burn et al., (6) Data from the HSQ showed that as a group, these patients found their perception of their health to be poor and it was also shown, that they experienced extreme feelings of lack of energy and fatigue. Data from the diagnostic sleep study showed that all of the subjects utilized in this study were in the RDI range of 24.4 to 71.5, which classified them as moderate to severe obstructive sleep apnea suffers. Measures from the diagnostic sleep study also showed a decreased amount of sleep time in slow wave sleep and REM stages (Table 1). These stages are believed to be the restorative sleep stages that we all need to maintain a healthy normal life. Lack of or decreases in time of these stages of sleep have been shown to increase daytime hypersomnolence (7)

The results of this study demonstrate that a single night of CPAP titration, although therapeutic in that it decreased the physiological variables of sleep, does not have immediate significant effects on the various exercise physiological measures utilized in this study. On the other hand, the results found that subjectively, patients found their sleep quality to improve with the use of CPAP via a short-term version of the Pittsburgh Sleep Quality Index. Patients had a significant improvement in clinical sleep measurements of a decrease in average RDI and an increase in both slow wave and REM sleep with CPAP therapy. The results of this study support the widely held clinical impression that patients experience a first night "halo effect" with CPAP administration. Due to the lack of research in the area of the effects OSA has on various physiological parameters during exercise, there is little to compare findings with. In general agreement with our findings, though, Taguchi, Hida, Okabe, et al. (8) treated six patients with CPAP therapy for seven consecutive days and did not observe changes in exercise cardiorespiratory parameters, even though oxygen consumption at maximal exercise in stationary cycling increased by an average of 8.3% ($p<0.05$). Our study design did not allow for assessment of maximal responses. However, interpretation of endpoints in maximal effort exercise studies often are confounded by the influences of subject motivation and experimenter choice of variables to establish the maximal VO_2 response (9). Thus, evaluation of submaximal exercise responses actually may be a preferred means for evaluation the physiologic consequences of OSA. Reasons for this include the potential experimentally to compare physiologic responses under conditions where psychological factors have minimum influence and recognition that submaximal exercise

responses have greater direct relevancy to understanding implications for physical activities of daily living and how these may or may not be affected by CPAP administration. In another study by Konermann, Sanner, Klewer et al. (10) investigated CPAP influences on cardiopulmonary hemodynamic functions during steady-state exercise stress testing patients and expressed their results using an index that allowed for comparing responses on different days at a reference cycling load of 100W and then adjusting the exercise responses for day to day variation in resting heart rate. Using this index, Konermann, Sanner, Klewer et al. observed that the heart rate demand for a 100W decreased significantly ($p<0.001$) after only 2 wks of CPAP therapy. However, using a similar method for evaluation of exercise blood pressure responses, they observed that neither systolic nor diastolic blood pressures were affected. Additionally, Konermann, Sanner, Klewer et al. found that perceived health related quality of life increased by 14.9% ($p<0.05$). They concluded that CPAP therapy at the time points of 2 weeks and 6 months with patients with OSA improves cardiovascular responses to exercise performance and individual assessment of performance. Konermann, Sanner, Klewer et al. however, did not examine the first night effect of the CPAP titration or the differences in clinical measures of pre- and post-titration to determine clinical improvement. Differences in cardiorespiratory data found by Konermann, Sanner, Klewer et al. and the study by Taguchi, Hida, Okabe, et al. show that there is still a discrepancy in the effects of CPAP on OSA. One possible reason for the difference could be attributed to their using steady state exercise stress testing as compared to our ramping protocol. Ramping protocols are progressive with equal increments in work rate that lead to a linear increase

in cardiorespiratoy variables throughout the test, where as steady state exercise requires an initial jump in the variables and later plateaus once the body has adjusted to the workload. Finally, the difference may be due to the difference in method of assessment. Our study utilized a point that is relevant to potential use in exercise management of excess weight and is also relevant to understanding implications for upper level of sustainable occupational and recreational activities. This point was 60% of a patient's cardiac reserve.

Little research has been conducted in the area of overnight sleep quality to quantify subjective if patients improvements in sleep quality as the result of CPAP. Because of the absence of a reliable overnight sleep quality index, little is known regarding how the immediate effects CPAP treatment impacts OSA patients. Our study reported utilized a newly modified version of the Pittsburgh Sleep Quality Index for the purpose of verifying a subjective improvement in the quality of sleep after a night of CPAP treatment. The results were similar to those found by Bonsignore, Marrone, Bellia et al. (11). They studied eight patients with OSA. All patients demonstrated a significant reduction in Stage 1 and increase in REM. Along with this, patients reported marked relief of symptoms and improved sleep quality after the first night of treatment. This study was merely a preliminary test of this questionnaire to show improvement of sleep quality. More studies in the future are planned with this questionnaire to demonstrate validity and reliability.

The results of our study point out the need for more research in the area of the effects of CPAP on exercise tolerance in OSA patients. Knowledge in this area is

essential for the purpose of prescribing exercise as a possible adjunct in the treatment of OSA. It is postulated that an exercise regimen could possibly reduce the need for CPAP by eliminating the fatty tissue around the throat that often cause obstruction throughout sleep in OSA patients. This study did, if fact, show that while there is no immediate difference after CPAP treatment, there is a psychological improvement in sleep quality. This improvement in sleep quality needs to be further studied and determine in more depth why these effects occur and how they relate physiologically to the patient. With this knowledge, clinicians can better understand OSA and look to the use of exercise as a method of noninvasive treatment.

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Table 1: OSA patient characteristics and clinical measurements (N=5).

Physical measures	Mean	
Age (yr)	57.0 6.6	
Weight (kg)	93.5 2.7	
BMI (kg/m^2)	30.5 1.1	
Clinical measures	PSG 1 Mean	PSG2 Mean
RDI	47.6 9.5	5.1 2.6
Total sleep time (min)	279.4 17.4	266.4 18.2
Awake (min)	80.7 23.4	75.2 7.9
Stage 1 (min)	42.2 3.2	28.4 1.2
Stage 2 (min)	170.2 6.5	131.0 6.1
Slow wave sleep (min)	30.6 2.9	65.4 7.0
REM (min)	36.6 3.8	52.6 5.5
Baseline SaO_2	94.2 0.7	93.0 0.4
Lowest SaO_2	79.4 3.0	85.8 1.1

Values shown for each variable are means and standard errors of the mean (SEM)

Table 2: Regression parameters for exercise variables vs. power output during cycle ergometry before and after an overnight CPAP titration trial (n=5).

	Pre-r^2	Post-r^2	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept
Cardiovascular measures						
Heart rate (b/min)	0.80	0.96	0.40	0.46	89.52	84.56
	0.03	0.01	0.04	0.03	2.98	2.75
Systolic BP (mmHg)	0.90	0.95	0.62	0.46	132.21	135.42
	0.04	0.02	0.13	0.09	7.23	1.96
Rate pressure product(10^{-2})	1.00	0.97	1.53	1.29	112.23	107.61
	0.10	0.10	0.11	0.14	7.61	4.50
Respiratory gas exchange						
VO_2 (l/min)	0.90	0.97	0.01	0.01	0.61	0.56
	0.02	0.02	0.01	0.01	0.07	0.03
V_E STPD (l/min)	0.97	0.95	0.40	0.30	17.50	19.16
	0.03	0.03	0.04	0.06	3.70	0.46
Perceptual measure						
RPE (6-20)	0.94	0.96	0.10	0.09	6.03	5.14
	0.04	0.10	0.01	0.01	0.68	0.80

Values reported as means and standard errors of the mean (SEM)

Table 3: Quality of life, physical activity history, and sleep quality changes after a CPAP titration trial in OSA patients (N=5).

	PSG 1
Health Status Questionnaire	Mean
Health perception	65.6
	7.8
Physical function	85.0
	15.0
Role-physical	85.0
	6.7
Role-emotional	93.3
	12.1
Social function	82.5
	10.9
Mental health	78.4
	10.9
Bodily pain	82.5
	9.1
Energy/fatigue	57.0
	4.6
PSQI	7.6
	0.8
Short-term PSQI	
PSG 1	4.4
	0.3
PSG 2	2.2
	0.3
Baecke Physical Activity	
Work index	2.5
	0.4
Sports index	2.3
	0.3
Non-sports index	2.5
	0.3
Total index	7.2
	0.7

Values shown for each variable are means and standard error of the mean (SEM)

Table 4: Exercise test results at 60% of apparent maximal functional capacity (N=5)

Cardiovascular	PSG 1	PSG 2
Heart rate (b/min)	121.6 3.1	132.4 7.2
Systolic blood pressure (mmHg)	194.0 10.0	182.4 5.4
Rate pressure product (10^{-2})	254.0 8.3	239.2 8.0
Respiratory gas exchange		
VO_2 (l/min)	1.9 0.1	1.8 0.2
V_E STPD (L/min)	56.4 2.4	51.6 6.5
Perceptual		
RPE (6-20)	16.0 1.3	13.2 1.4

Values shown for each variable are means and standard error of the mean (SEM)

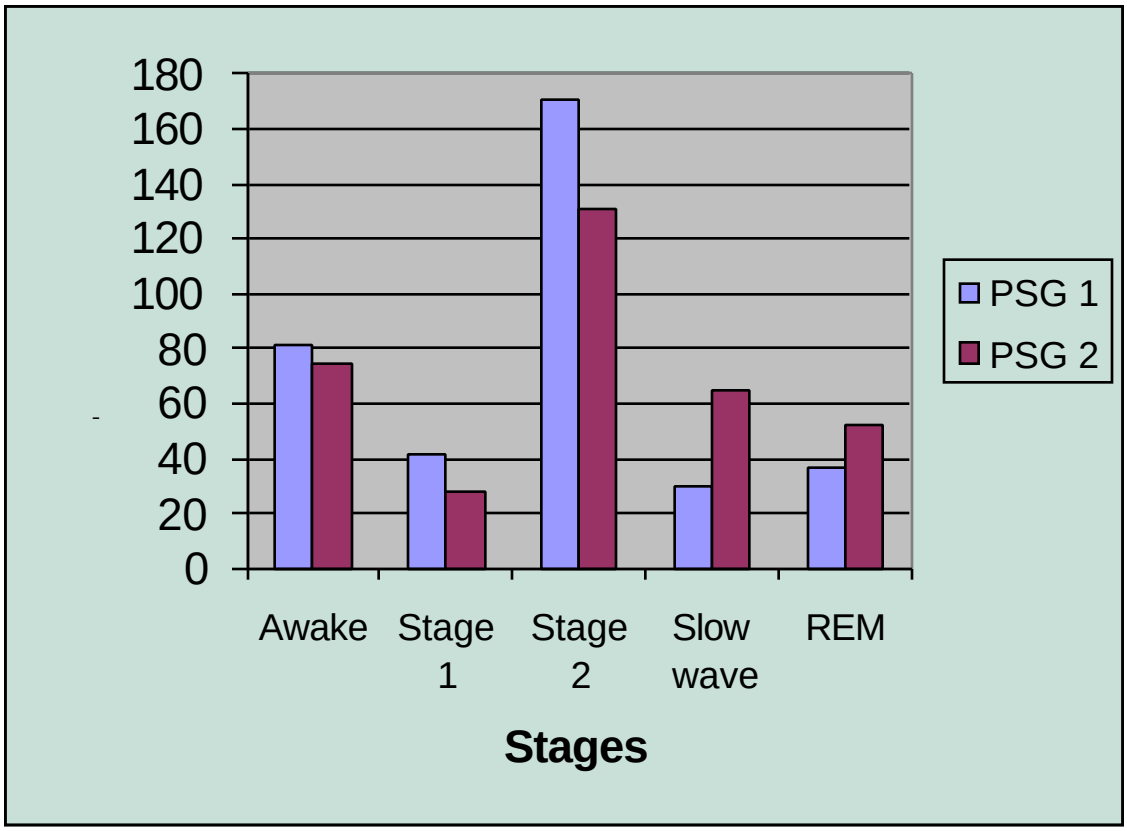

Figure 1: Comparison of sleep stages from PSG 1 and PSG 2

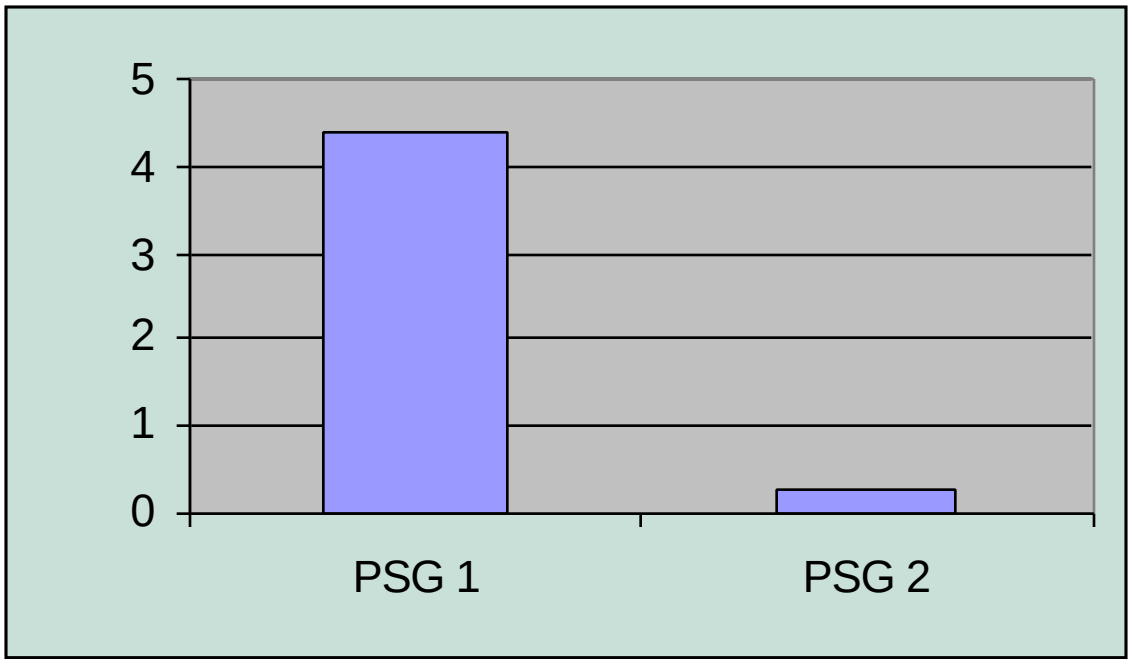

Figure 2: Changes in sleep quality via the Short-term PSQI form PSG 1 to PSG 2

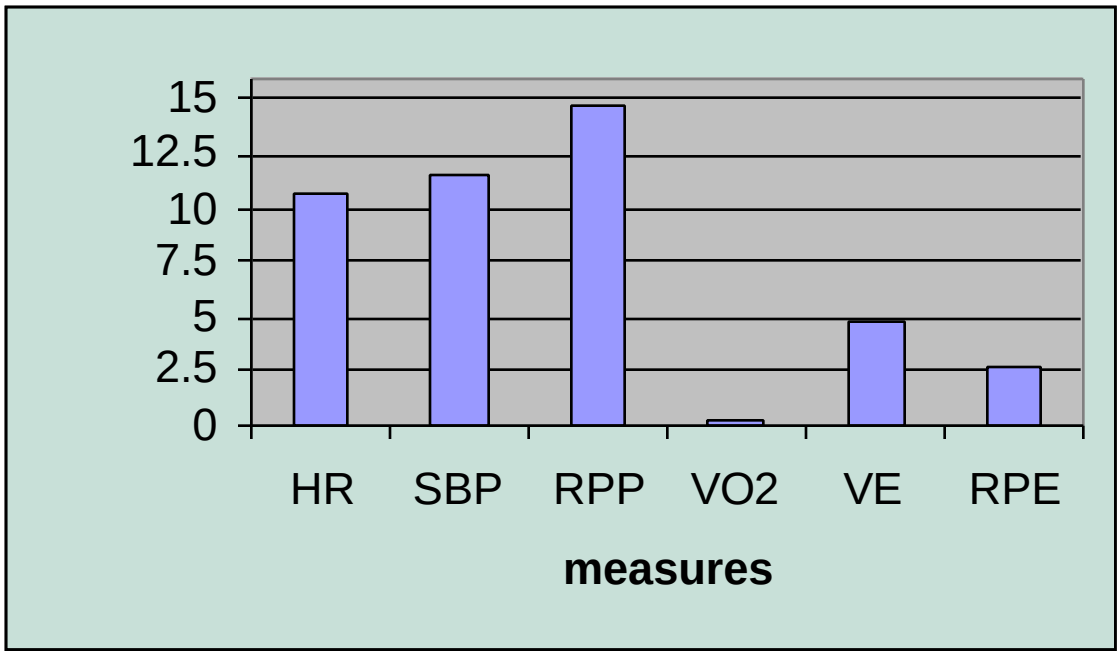

Figure 3: Changes in dependent measures at the 60% level from PSG 1 to PSG 2

Chapter IV

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

Summary

Obstructive sleep apnea is a serious and potentially life-threatening medical condition. It is a breathing disorder characterized by repeated collapse of the upper airway during sleep, with consequent cessation of airflow. Continuous positive airway pressure (CPAP) has been shown to be an effective means of treatment for obstructive sleep apnea and certain forms of central apnea. CPAP has become the major non-surgical, long-term form of treatment.

The purpose of this study was to determine the effect of a single night of CPAP therapy on cardiovascular performance, gas exchange, and perceptual measures via submaximal cycle ergometry bouts in OSA patients.

Subjects consisted of 5 males who were exercise-tested before and after CPAP titration. Subjects performed ramping cycle ergometry exercise up to an endpoint of 75% of the subjects calculated cardiac reserve. Gas exchange variables, heart rate, blood pressure, and rates of perceived exertion were obtained throughout each study. Data was analyzed at a clinically significant level of 60% of each subjects calculated cardiac reserve.

No significant changes in any of the cardiovascular or gas exchange measures were found. A majority of the mean values did decrease after CPAP use, but not to any level of significance. One of the perceptual measures was also found to be non-significant. Although the rate of perceived exertion mean values decreased, it was not significant. On the other hand, the perceptual measure of sleep quality did significantly improve.

Subjects also reported a significantly higher quality of sleep for the night of CPAP therapy compared to the diagnostic sleep study.

Issa and Sullivan (1986) found that within seconds of securing an open airway, patients with severe sleep apnea begin to have periods of REM sleep or slow wave sleep (SWS). Slow wave sleep is believed to be the most restorative sleep stage and is often decreased in OSA patients. An increase in SWS is associated with an improvement in daytime somnolence and probably results in feelings of renewed vigor and increased quality of life. This is what many clinicians have called the "halo effect" of CPAP therapy. This study has shown that even though apneas and hypopneas are eliminated, the cardiovascular and respiratory changes may lag behind. These findings are very important to the clinician in that it helps them to understand the first-night effect of CPAP therapy. With this knowledge, they will know that it is primarily an improvement in sleep quality and not physiological improvement in cardiovascular performance. Even though CPAP eliminates apneas and hypopneas, which are associated with elevated epinephrine release and oxygen desaturation during sleep, it can be postulated that this is not enough time for total improvement in cardiovascular performances. Elevated epinephrine levels and oxygen desaturations may lead to an increased heart rate fluctuation and blood pressure elevation throughout the sleep period. Over time, these physiological alterations may damage the cardiovascular system and increase the likelihood of strokes and heart disease without treatment. Due to exercise having the effect of increasing muscle tone and reducing fat masses, it is hypothesized that in the future, exercise will play a vital role in the treatment of OSA patients. Lehrhaft,

Grunstein, Sullivan et al (1991) have found that CPAP can greatly reduce the severity of OSA, but on its own does not lead to a permanent cure. For this reason, further research in this area is necessary to give the clinician another viable method of treatment.

Conclusions

The results of this study suggest that a single night of CPAP therapy does not significantly impact cardiovascular or gas exchange measures during exercise. It was found, however, that subjective sleep quality does improve with CPAP use. Research needs to clarify if CPAP treatment has any effect on cardiorespiratory variables during exercise over an extended period. Additional research needs to determine if the improvement in subjective sleep quality will lead to improvements in subjective quality of life and increased physical activity.

Recommendations for Future Research

This investigation leaves many unanswered questions that appear worthy of future investigations. There is little research regarding the effects of OSA on certain physiological variables in exercising humans. Further studies are also necessary to determine the total effect of CPAP therapy on the human body and if these effects will still remain constant over time.

One example of a recommended study would be follow-up exercise testing with this same group of patients. This study would have the ability to show if there are any changes in the physiological variables or subjective variables that occur over a longer

period. Subjects would undergo exercise testing as before and data would be analyzed and compared to both time periods. Data from this study may show whether or not any of the exercise variables may improve to a significant level and demonstrate that CPAP is much more effective therapy after a longer time period of use.

A second research project could focus on investigation of how autonomic function affects cardiovascular function in OSA patients, as well as determining the effects of surgical interventions versus exercise training on cardiovascular function, fitness and health-related quality of life. With this study, exercise could possibly be shown to be viable adjunct in the treatment of OSA. Subjects would include OSA patients who do not suffer from cardiovascular disorders or orthopedic limitations that prevent exercise. Subjects would first undergo a diagnostic sleep study and then would be maximally tested to determine the pre-training level of fitness for each subject. A mode of aerobic exercise, such as cycling, would elicit a high demand for caloric expenditure and promote muscle tone. Each subject would be prescribed an exercise program for a specified time period without any other means of treatment for OSA. After the training period, each subject would again have a diagnostic sleep study and maximal exercise test to determine if there were any noteable changes due to the exercise program. This data may show whether or not exercise is viable addition for the treatment of OSA and, if so, would give patients and clinicians a less expensive method of treatment.

Lastly, another study could measure the outcome of maximal exercise testing of OSA patients compared to non-OSA patients of similar demographic characteristics to get an idea if OSA has any effect on exercise parameters in comparison to normal

subjects. To date, there is no published research comparing exercise data from OSA patients compared to normal healthy subjects. Subjects would include non-OSA patients and clinically diagnosed suffers of OSA who do not suffer from any cardiovascular disorders or from any orthopedic limitations. Each subject would complete a maximal exercise test with cardiovascular, gas exchange, and perceptual measures taken at specific intervals during the test. Outcome data could be compared between the two groups to get a better understanding of the physiological and psychological variables of OSA patients undergoing an exercise program compared to normal healthy subjects.

Recommendatins for Clinical Usage

Results from our study may be practical to the clinician. By using the sleep quality questionnaire, clinicians will have the ability to understand how patients subjectively feel about CPAP titration and whether extra measures need to be taken to ensure compliance. It would possibly highlight those patients who may need intervention at an earlier stage to promote long-term CPAP compliance, resulting in reduced morbidity, mortality, as well as being cost effective.

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APPENDIX A: DETAILED METHODOLOGY

Detailed Methodology

Introduction

Subjects completed two stationary cycle ergometer bouts, one following an initial diagnostic polysomnography (PSG) test and the other after a second PSG test for the purpose of CPAP titration. The dependent variables of arterial pressures (BP), heart rate (HR), rate of perceived exertion (RPE), and ventilatory data were all measured during these exercise bouts to examine if there is an immediate change in the dependent variables after CPAP treatment.

Subject Screening and Selection

Subjects. Five adult men were recruited from the community to participate in this study. These subject were selected from patients referred to the Sleep Disorders Center of Southwest Virginia, Christiansburg, VA, between November 1997 and February 1998. Exclusion criteria from participation in this study included documented coronary artery disease, uncontrolled hypertension or diabetes mellitus, chronic obstructive pulmonary disease, carotid vascular disease, orthopaedic or musculoskeletal disabilities which prevented exercise, or a history of regular participation in moderate physical activity.

Methods. All prospective candidates wo were to receive a PSG study at the Sleep Disorders Center were contacted and screened for participation in the study utilizing a checklist for the above listed exclusion criteria (Appendix B). Those subjects who did not have any exclusion criteria were asked to voluntarily participate in the study.

All volunteering subjects were given an informed consent form (Appendix C) which was signed and described the procedures of the study. The informed consent was administered the evening the subject came in for their initial diagnostic PSG. In addition, each subject was asked to complete several questionnaires. These included the Pittsburgh Sleep Quality Index (PSQI) for rating sleep quality and daytime sleep related problems; the

Baecke Physical Activity Questionnaire for assessment of physical activity levels; and the Health Status Questionnaire (HSQ) for assessment of health related characteristics (Appendix B). Each subject then underwent a polysomnography for the diagnosis of obstructive sleep apnea. The morning after the PSG the following measures were recorded on each subject: height, weight, resting blood pressure, resting heart rate, and BMI, and exercise performance on a Medgraphics CardiO_2 electronically braked stationary cycle ergometer. For the exercise test, the work rate was pre-determined utilizing the subjects weight and self-reports of physical activity. The subject was placed into one of three exercising categories based upon their predicted maximal power. The three continuous ramping protocols were in increments of 6, 9, or 12 watts per minute at fifty revolutions per minute. The utilized exercise protocol enabled the patient to exercise for fifteen to twenty minutes before reaching test termination points. This amount of time was sufficient to obtain 5-7 blood pressure measurements during the exercise test.

The primary end points for the exercise test were achieving 75% of the predicted maximum heart rate or the subject reporting a perceived exertion on the Borg scale equivalent to hard exercise (RPE=16). Supportive data used as end points included a respiratory quotient >1.00 and attainment of the ventilatory threshold. The cutoff point for predicted heart rate was determined by the following steps. The first step was subtracting the subject's age from 220 to determine the subject's age predicted maximum heart rate. Then, the subject's resting heart rate was subtracted from the age-predicted maximum. Next, 75% of this value was added to the individuals resting heart rate and this final value was used to calculate on of the exercise test end points.

Exercise was monitored by at least two technicians and terminated in the event that adverse responses occur (clinical criteria of the American College of Sportsmedicine and American Heart Association). During the exercise test, blood pressure was monitored and cross validated every three minutes by 2 trained clinicians doing simultaneous ausculation. Heart rate and cardiac rhythms were monitored continuously by a 12 lead ECG throughout

the exercise test. Ratings of perceived exertion were also recorded every three minutes utilizing the Borg scale of perceived exertion. Also, during the exercise test, patients were hooked up to a Sensormedics VMAX 22 gas exchange system. This system allowed the patient to breathe through a mouthpiece while their nose was held shut by a noseclip. Expired gases were collected and analyzed on a breath by breath basis by the system. The collection of expired gases permitted a more accepted and accurate determination of workloads.

Upon completion of the initial diagnostic PSG, the subject's results were scored by a trained PSG technician at the Sleep Center. Each subject was diagnosed with OSA or not having OSA by a M.D. specializing in sleep medicine. Those with OSA, who were candidates for CPAP therapy, were asked to come back to the Sleep Center to undergo a repeat PSG for the purpose of CPAP titration. After this follow-up PSG, the patient was notified if CPAP therapy was indicated.

All subjects undergoing a CPAP titration were requested to perform a second submaximal exercise test at approximately the same time in the morning utilizing the same protocol as with the first exercise test. The Short-term PSQI was also administered to evaluate the quality of sleep during the night of the CPAP titration.

APPENDIX B: DETAILED RESULTS

Detailed Results

Subjects used in this study were of varying ages and sizes. Ages ranged from 42 to 74 years of age with a mean value of 57±14.7 years. All subjects were of similar body sizes with body mass index (BMI) ranging from 27.27 to 33.15 with a mean value of 30.5±7.2. Statistical analyses on the regression slope/intercept data yielded no significant ($p>0.05$) differences found in R^2 between the diagnostic PSG and CPAP titration. R^2 values were found to increase for HR (0.83±0.21 to 0.96±0.03), SBP (0.94±0.08 to 0.95±0.03), VO_2 (0.94±0.02 to 0.97±0.01), and RPE (0.94±0.06 to 0.96±0.03); while there was a decrease in the values for RPP (0.97±0.03 to 0.97±0.02) and VE (0.97±0.01 to 0.95±0.03). Slopes and y-intercepts were also analyzed and no significant difference ($p>0.05$) could be achieved for each variable between the two test conditions. The slope values decreased from the diagnostic PSG to the CPAP titration in the measures of SBP (0.62±0.29 to 0.46±0.13), RPP (1.53±0.22 to 1.29±0.23), VO_2 (0.01±0.01 to 0.01±0.008), VE (0.40±0.09 to 0.30±0.13), and RPE (0.10±0.04 to 0.09±0.01); while HR values were found to increase (0.40±0.08 to 0.46±0.07). Analysis of the differences in y-intercept values for all measures during the two test conditions showed a decrease in HR (89.5±6.64 to 84.56±6.26), RPP (112.2±24.1 to 107.61±17.05), VO_2 (0.61±0.18 to 0.56±0.06), and RPE (6.0±0.64 to 5.1±1.63); while there was found to be an increase in SBP (132.21±20.62 to 20.62) an VE (17.50±8.27 to 19.16±1.03).

Mean PSQI scores utilized to determine past sleep quality for the group were found to be 7.6±3.8 with a range of 4 to 9. The mean RDI, which is the primary index for quantifying the physiological consequences of sleep distress in OSA showed an

improvement (89.3%) by decreasing from 47.6±18.8 during the diagnostic test to 5.1±5.7 during the CPAP titration. RDI values for the diagnostic PSG were found to be all in the category of severe and ranged from 38.6 to 89.9. The night of CPAP titration drastically reduced the RDI values to a range of 0.8 to 15.0. Physiological sleep quality was improved by a substantial increase in slow wave sleep and REM sleep periods. Slow wave sleep values for the diagnostic PSG were found to be very low in that they ranged from 3.2% to 19.3% of total sleep time and dramatically increased in all five subjects to a much higher range of 7.7% to 50.9% (53.2% mean improvement). REM values increased for all subjects except one who had a slight decrease. The values for the diagnostic PSG ranged from 0% to 22.1% of total sleep time and increased to a range of 1.0% to 31.5% (30.4% mean improvement).

A difference was attained in the short-term PSQI data for the change in subjective sleep quality pre- and post-CPAP therapy. The mean score for the short-term PSQI improved from 4.4±0.5 to 2.2±0.8 (50%) on average. All subjects reported a dramatic improvement in sleep quality from the diagnostic PSG, which ranged from 3 to 6, to the CPAP titration ranging from 1 to 3 on a scale of 0 to 11.

For each subject, the calculated 60% level was individualized according to the subject's age and resting heart rates, so that findings could be reported at an exercise intensity that approximated the same fraction of their aerobic poser. The paired t-test on heart rate at the 60% level revealed no significant change ($p>0.05$) after a single night of CPAP treatment even though there was a 8.2% increase in the mean values. Three of the subjects were found to have decreases in HR rate at this level after the CPAP titration while two had increases in HR. No significant differences were found in the other cardiovascular measures of systolic blood pressure ($p>0.05$) and rate pressure product ($p>0.05$) for the trials even though SBP had a 6% improvement in mean values from 194.0 to 82.4 and RPP had a 5.8 % improvement from 254.0 to 239.2. SBP increased in two of the subjects

from the diagnostic to the CPAP titration, while two decreased and one remained the same. RPP also exhibited a similar trend with two of the subjects increasing and three of them decreasing after CPAP. Results for the gas exchange measures were also found to be non-significant ($p>0.05$) for the ventilatory measures of VO_2 and VE at the 60% exercise intensity level between the two test conditions, despite a 5.3% reduction in VO_2 means from 1.9 l/min to 1.8 l/min and a 8.5% reduction in VE means from 56.4 to 51.6. Three of the subjects had increases in VO_2 values from the diagnostic PSG to the CPAP titration, while two were found to have decreases. Additionally, no difference ($p>0.05$) was found in perceived exertion at the 60% exercise intensity level between the two test conditions, despite a 17.5% reduction in the mean values from 16 to 13.2, i.e. a reduction from "Hard" to "Somewhat Hard" effort. Three of the subjects reported a decrease in the rate of perceived exertion during that level of exercise, while one reported and increase and the other reported no change from the diagnostic PSG to the CPAP titration.

APPENDIX C: QUESTIONAIRES

Collaborative Project Between Virginia Tech's Lab For Exercise and Human Performance and The Sleep Disorders Center of Southwest Virginia

PATIENT CHECKLIST

Medical History

____ uncontrolled diabetes
____ uncontrolled hypertension
____ diagnosed cardiovascular disease
____ orthopedic limitations/disabilities
____ diagnosed pulmonary disease
____ previous sleep studies. If yes, results:_____
_____

____ any pain in the chest when doing physical activity?
____ any chest pain when not doing physical activity?
____ do you lose balance because of dizziness or lose consciousness?
____ any reason why you should not do physical activity?

Name _____
ID # (social security) _____
Age _____
Height _____
Weight _____
Resting Blood Pressure _____
Resting Heart Rate _____
Current Medications _____
_____
_____

This patient is/is not a candidate for participation in the study.

Collaborative Project Between Virginia Tech's Lab for Exercise and Human Performance and The Sleep Disorders Center of Southwest Virginia

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

Name: _____ Date: _____ Age: _____

Instructions:
The following questions relate to your usual sleep habits during the past 4 weeks only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past four weeks, when have you usually gone to bed at night?
Usual Bed Time _____

2. During the past four weeks, how long (in minutes) has it usually taken you to fall asleep each night?
Number of Minutes _____

3. During the past four weeks, when have you usually gotten up in the morning?
Usual Getting Up Time _____

4. During the past four weeks, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)
Hours Of Sleep Per Night _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past four weeks, how often have you had trouble sleeping because you...

(a) Cannot get to sleep within 30 minutes

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(b) Wake up in the middle of the night or early morning

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(c) Have to get up to use the bathroom

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(d) Cannot breathe comfortably

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(e) Cough or snore loudly

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(f) Feel too cold

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(g) Feel too hot

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(h) Had bad dreams

Not during the past four weeks_____	Less then once a week_____	Once or twice a week_____	Three or more times a week____

(i) Have pain

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week____

(j) Other reason(s), please describe

_____

_____

How often during the past four weeks have you had trouble sleeping because of this?

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week___

6. During the past four weeks, how would you rate your sleep quality overall?

Very good_____ Fairly good_____ Fairly bad_____

7. During the past four weeks, how often have you taken medicine (prescribed or over the counter) to help you sleep?

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past four weeks, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past four weeks_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past four weeks, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____
Only a very slight problem _____
Somewhat of a problem _____
A very big problem _____

<u>What is your usage of the following (during the past month):</u>

	Average per day # of cups/drinks/etc,)
Coffee (caffeinated only)	_____
Tea (caffeinated only)	_____
Soda (caffeinated only)	_____
Cigarettes (packs daily)	_____
Cigars	_____
Over the counter medicines(not related to sleep)	_____
Prescription medicines(not related to sleep)	_____

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Baecke Questionaire of Habitual Physical Activity

1. What is your main occupation?_____(1-3-5)

2. At work I sit
   never/seldom/sometimes/often/always_____(1-2-3-4-5)

3. At work I stand
   never/seldom/sometimes/often/always_____(1-2-3-4-5)

4. At work I walk
   never/seldom/sometimes/often/always_____(1-2-3-4-5)

5. At work I lift heavy loads
   never/seldom/sometimes/often/very often_____(1-2-3-4-5)

6. After working I am tired
   very often/often/sometimes/seldom/never_____(5-4-3-2-1)

7. At work I sweat
   very often/often/sometimes/seldom/never_____(5-4-3-2-1)

8. In comparison with others my own age I think my work is physically
   much heavier/heavier/as heavy/lighter/much lighter_____(5-4-3-2-1)

9. Do you play sport?_____ yes/no
   If yes:
   -which sport do you play most frequently?_____(Intensity 0.76-1.26-1.76)
   -how many hours a week?_____ <1/1-2/2-3/3-4/>4 (Time 0.5-1.5-2.5-3.5-4.5)
   -how many months a year?_____<1/1-3/4-6/7-9/>9 (Proportion 0.04-0.17-0.42-0.67-0.9

   If you play a second sport:
   -which sport do you play most frequently?_____(Intensity 0.76-1.26-1.76)
   -how many hours a week?_____<1/1-2/2-3/3-4/>4 (Time 0.5-1.5-2.5-3.5-4.
   -how many months a year?_____<1/1-3/4-6/7-9/>9 (Proportion 0.04-0.17-0.42-0.67-0.92)

10. In comparison with others my own age I think my physical activity during leisure time is

much more/more/the same/less/much less_____(5-4-3-2-1)

11. During leisure time I sweat
very often/often/sometimes/seldom/never_____(5-4-3-2-1)

12. During leisure time I play sport
never/seldom/sometimes/often/very often_____(1-2-3-4-5)

13. During leisure time I watch television
never/seldom/sometimes/often/very often _____(1-2-3-4-5)

14. During leisure time I walk
never/seldom/sometimes/often/very often_____(1-2-3-4-5)

15. During leisure time I cycle
never/seldom/sometimes/often/very often_____(1-2-3-4-5)

16. How many minutes do you walk and/or cycle per day to and from work, school, and shopping?
<5/5-15/15-30/30-45/>45_____(1-2-3-4-5)

Collaborative Project Between Virginia Tech's Lab for Exercise and Human Performance and The Sleep Disorders Center of Southwest Virginia

SHORT-TERM PITTSBURG SLEEP QUALITY INDEX (PSQI)

Name _____ SSN _____ Date _____ Age _____

Instructions:
The following questions relate to your sleep last night, while you were in the laboratory. Your answers should indicate the most accurate reply you are able to provide. Please answer all questions.

1. During the past night, what time did you go to bed?
   Bed Time_____

2. During the past night, how long (in minutes) did it take you to fall asleep?
   Number of Minutes_____

3. After sleeping last night, what time did you get up?
   Getting Up Time_____

For each of the remaining questions, check the one best response. Please answer all questions.

4. During the past night, did you have trouble sleeping because you...

   a. Could not get to sleep within 30 minutes
      Yes_____ No_____

   b. Wake up in the middle of the night or early morning
      Yes_____ No_____

   c. Have to get up to use the bathroom
      Yes_____ No_____

   d. Could not breathe comfortably
      Yes_____ No_____

   e. Cough or snore loudly
      Yes_____ No_____

   f. Feel too cold
      Yes_____ No_____

   g. Feel too hot
      Yes_____ No_____

   h. Had bad dreams
      Yes_____ No_____

i. Have pain
Yes_____ No_____

j. Other reason(s), please describe
_____
_____
_____

5. During the past night, how would you rate your sleep quality overall?
Very good _____
Fairly good _____
Fairly bad _____
Very bad _____

APPENDIX C: INFORMED CONSENT

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Informed Consent for Research Project: Patients Who Perform Sleep Lab Study at The Sleep Disorders Center of Southwest Virginia

Title of Research Project: Quality of Life and Physiological Responses to Exercise for Patients Completing Polysomnography Study

Investigators: Eric W. Walker, BS, D. Edward Shifflett Jr., BS, Donald Zedalis, MD, John Gregg, DDS, Ph.D., Christopher Ward, Ph.D., and William G. Herbert, Ph.D.

I. The Purpose of the Research/Project

Your doctor has asked you to come to the Sleep Center tonight and remain overnight to make measurements about the medical aspects of your sleep. He will evaluate the results of this study and inform you about whether certain treatments may be recommended. We are conducting a study to better understand the factors that cause sleep conditions like those you may be experiencing and how these conditions may affect your day-to-day life.

II. Procedures

If you agree to participate in this study, tomorrow morning when you awaken, you will be asked to do the following:

- allow us to initially obtain certain physical measurements from you at rest, including your blood pressure and heart rate.
- allow us to use certain physical and health history information from the medical records available to your doctor at the Sleep Center.
- complete a questionnaire that requests your opinion about the quality of your sleep on the night of your sleep lab study.
- complete a 15-20 minute bicycle test and allow us to obtain your heart rate and blood pressure and various measurements of your breathing.
- allow us to connect you to electrodes and wires to monitor your heart rhythms.
- allow us to measure how much oxygen you use during this exercise. To accomplish this, we will ask you to wear a light-weight rubber mouthpiece and nose clip and your exhaled air will be sampled from this device so that it can be analyzed by the machine. During exercise, you will breathe only through your mouthpiece and you may experience some dryness in your mouth. There are no other discomforts or risks for you associated with this part of the testing.

If your initial overnite sleep study shows that you have sleep apnea, then you will be asked to return to the Sleep Center to repeat the physical measurements, exercise test and questionnaires. This will be done in the early morning, immediately following a second overnight sleep study which your doctor would have you do while wearing a special positive pressure breathing device (CPAP). After this, you also will be asked to return for a third time about five weeks later, but only to do the physical measures, exercise test and questionnaires (not a third sleep study).

III. 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. 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.

IV. Risks and Benefits

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. Every effort will be made to minimize these occurrences 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 20 minutes. At first it will be very easy and then become harder; during the last few minutes, the work will feel much like jogging up a slight hill outdoors. This represents about 75% of your maximum effort, in terms of breathing and leg effort - but will be stopped before you reach a maximum effort.

I have been informed that medical personnel qualified to perform CPR and initiate 911 activation are available to deal with unusual situations should these occur. While emergency drugs and defibrillation are not available at this facility, Montgomery Regional Hospital is located approximately one mile away in the need of advanced cardiac life saving. I understand that there is a risk of injury or heart attack as a result of my performance of this test but knowing those risks, it is my desire to proceed to take the test as herein indicated.

I understand that the results of this test can be sent to my primary care physician. These results may help in determining my ability to safely do certain types of physical work or exercise.

V. Compensation

I understand that there is no monetary or other form of compensation available for participants in this project, either from the Sleep Disorders Center of Southwest Virginia, Virginia Tech, or any of the investigators listed above.

VI. Freedom to Withdraw

I understand that, if I refuse 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.

VII. 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.

VIII. Subject's Permission

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

_____ _____

Signature Date

_____ _____

Witness Date

Please check the box if you would like the information from these tests sent to your primary care physician. Physician's Name: _____

Should you have any questions about this research or its conduct. You may contact:

Eric Walker	953-3974
Investigator	Phone
Ed Shifflett	231-5056
Investigator	Phone
William Herbert, PhD	231-6565
Faculty Advisor	Phone
Tom Hurd	231-9359
Chair, IRB Research Division	Phone

APPENDIX D: STATISTICAL TABLES

Resting data

Subject	Pre HR	post HR	pre SBP	post SBP	pre RPP	post RPP	Pre VO2	post VO2	pre VE	post VE
1	85	74	112	120	126.7	120	0.465	0.648	11.5	8.2
2	88	93	118	130	103.8	136.6	0.217	0.795	7.5	15.2
3	91	82	150	144	136.5	109.6	0.686	0.08	20.5	13.5
4	79	61	130	130	102.7	102.5	0.337	0.207	9	7.4
5	83	77	136	134	112.9	122.9	0.418	0.347	11.8	11.8
p-value		0.36		0.563		0.863		0.965		0.928
mean	85.8	89.8	135.6	131.6	116.5	118.3	0.4	0.4	12.8	13.4
SD	4.8	7.3	12.4	6.8	14.7	13.1	0.2	0.3	5.2	9.2
C.I.	4.2	6.4	10.9	6	12.9	11.5	0.2	0.3	4.6	8.1

SBP: mmHg, HR: b/min, RPP: HR x SBP x 10^{-2}, VE & VO2: L/min

Values from regression equation for physiological variables at 60% of apparent functional capacity:

Subject	pre-HR	post-HR	pre-SBP	post-SBP	pre-RPE	post-RPE	pre-RPP	post-RPP
1	139	159	163	170	14	16	238	257
2	123	120	215	193	21	8	252	235
3	126	133	208	195	15	15	267	259
4	137	120	206	184	15	13	278	224
5	133	130	178	170	15	14	235	221
p-value		0.90		0.10		0.35		0.27
mean	131.60	132.40	194.00	182.40	16	13.2	254.00	239.20
SD	6.91	15.97	22.35	12.05	2.83	3.11	18.48	17.95
C.I.	6.06	14.00	19.60	10.57	2.48	2.73	16.20	15.7335

SBP: mmHg, HR: b/min, RPP: HR x SBP x 10^{-2}

Values from regression equation for ventilatory variables at 60% of apparent functional capacity:

Subject	pre-VO2	post-VO2	pre-VE	post-VE
1	2.14	2.73	59.4	76.4
2	1.41	1.57	51.4	52.3
3	1.94	1.47	64.1	43.6
4	2.03	1.67	52.3	41.6
5	1.77	1.61	54.6	44.2
p-value		0.82		0.50
mean	1.86	1.81	56.36	51.62

SD	0.28	0.52	5.32	14.44
C.I.	0.25	0.46	4.67	12.66

VE & VO2: L/min

Values for the slope from the regression equation for physiological measures:

Subject	pre-HR	post-HR	pre-SBP	post-SBP	pre-RPE	post-RPE	pre-RPP	post-RPP
1	0.39	0.53	0.36	0.28	0.06	0.08	1.07	1.13
2	0.3	0.34	1.09	0.58	0.16	0.09	1.61	1.17
3	0.36	0.52	0.56	0.6	0.11	0.09	1.45	1.67
4	0.52	0.46	0.69	0.47	0.09	0.07	1.71	1.33
5	0.43	0.45	0.41	0.38	0.09	0.1	1.17	1.15
p-value		0.21		0.18		0.37		0.43
mean	0.4	0.46	0.62	0.46	0.10	0.09	1.40	1.29
SD	0.08	0.08	0.29	0.13	0.04	0.01	0.28	0.23
C.I.	0.07	0.07	0.26	0.11	0.03	0.01	0.24	0.20

SBP: mmHg, HR: b/min, RPP: HR x SBP x 10^{-2}

Values for the slope from the regression equation for ventilatory measures:

Subject	pre-VO2	post-VO2	pre-VE	Post-VE
1	0.01	0.02	0.52	0.20
2	0.01	0.01	0.43	0.32
3	0.01	0.01	0.39	0.54
4	0.01	0.01	0.37	0.31
5	0.01	0.01	0.29	0.25
p-value		0.89		0.37
mean	0.011	0.01	0.4	0.32
SD	0.002	0.002	0.08	0.13
C.I.	0.001	0.002	0.07	0.11

VE & VO2: L/min

Values for the y-intercept taken from the regression line:

Subject	pre-HR	post-HR	pre-SBP	post-SBP	pre-RPE	post-RPE	pre-RPP	Post-RPP
1	81	82	109	120	5.5	4.5	81	91
2	96	90	117	140	7	4	106	129
3	96	91	162	146	6	7	148	122
4	85	76	138	138	6	6.5	111	94
5	89	84	135	131	5	3.7	114	102
p-value		0.04		0.69		0.34		0.65
mean	89.40	84.60	132.20	135.00	5.90	5.14	112.00	107.60
SD	6.66	6.15	20.61	9.95	0.74	1.51	23.97	17.01
C.I.	5.83	5.39	18.06	8.72	0.65	1.32	21.01	14.91

SBP: mmHg, HR: b/min, RPP: HR x SBP x 10^{-2}

Subject	pre-VO2	post-VO2	pre-VE	post-VE
1	0.41	0.59	12	19.1
2	0.47	0.59	12.4	20.2
3	0.86	0.47	32.1	18.3
4	0.72	0.63	15.6	18
5	0.59	0.53	14.7	20.2
p-value		0.66		0.697
mean	0.61	0.56	17.50	19.16
SD	0.18	0.063	8.27	1.03
C.I.	0.16	0.05	7.25	0.90

VE & VO2: L/min

APPENDIX E: RAW DATA

Table 1: OSA patient characteristics

Subject	Age	Weight	BMI
1	42	88.1	27.27
2	74	87.27	28.41
3	71	95.91	30.32
4	45	94.55	31.69
5	53	101.82	33.15

Weight in kg

Table 2: OSA patient clinical characteristics for diagnostic PSG

Subject	RDI	Sleep Time	Awake	Stage I	Stage II	SWS	REM	Base SaO_2	Low SaO_2
#1	89.9	247	116	7.1	89.7	3.2	0	95	79
#2	71.5	273	95	5.7	66.4	5.9	22.1	92	73
#3	41.8	236	126	15.3	60.2	13.3	11.2	92	81
#4	61.6	333	25	12.5	51.4	19.3	17.0	95	67
#5	38.6	249	13.5	23.7	61.2	7.7	7.4	95	84

SWS=Slow Wave Sleep, REM=Rapid Eye Movement
Sleep time and Awake values were recorded in minutes.
Stages I and II, SWS, REM, and SaO_2 values were recorded as percentagesTable 2:

Table 3: OSA patient clinical characteristics for CPAP titration

Subject	RDI	Sleep Time	Awake	Stage I	Stage II	SWS	REM	Base SaO_2	Low SaO_2
1	1.9	284.5	20.3	10.9	60.1	7.7	1.0	92	88
2	0.8	216.0	56.5	5.0	28.5	50.9	31.5	92	82
3	4.2	213.5	37.0	9.8	57.1	23.2	9.8	92	85
4	15.0	304.5	21.0	10.2	39.2	28.1	22.5	94	83
5	2.4	264.3	11.7	6.5	36.2	21.4	24.2	93	87

SWS=Slow Wave Sleep, REM=Rapid Eye Movement
Sleep time and Awake values were recorded in minutes.
Stages I and II, SWS, REM, and SaO_2 values were recorded as percentagesTable 3:

Table 4: Heart rate response to ramping exercise in OSA subjects before and after CPAP therapy

Subject	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept	Pre-r^2	Post-r^2	Pre-rest HR	Post-rest HR	Pre-pk HR	Post-pk HR
1	0.39	0.53	81	82	.89	.98	85	74	154	157
2	0.30	0.34	96	90	.48	.91	88	93	114	129
3	0.36	0.52	96	91	.81	.97	91	82	129	137
4	0.52	0.46	85	76	.98	.96	79	61	139	128
5	0.43	0.45	89	84	.99	.98	83	77	132	134

Table 5: RPE response to ramping exercise in OSA subjects before and after CPAP therapy

Subject	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept	Pre-r^2	Post-r^2	Pre 3 min RPE	Post 3 min RPE	Pre-pk RPE	Post-pk RPE
1	0.08	0.07	9	7	.96	.99	8	7	17	14
2	0.16	0.09	7	7	.94	.95	6	6	15	14
3	0.11	0.06	6	10	1.0	1.0	6	11	14	15
4	0.09	0.06	6	7	.85	.94	6	8	15	13
5	0.09	0.06	5	5	.99	.98	7	6	14	12

Table 6: RPP response to ramping exercise in OSA subjects before and after CPAP therapy

Subject	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept	Pre-r^2	Post-r^2	Pre rest RPP	Post rest RPP	Pre-pk RPP	Post-pk RPP
1	1.2	1.09	111	112	.95	.97	127	120	290	268
2	1.61	1.06	106	126	.99	.96	104	137	223	246
3	1.45	1.81	148	101	.92	.99	137	110	264	268
4	1.71	1.08	111	116	.98	.96	103	102	281	231
5	1.17	1.13	114	124	1.0	.98	113	123	218	253

Table 7: VO_2 response to ramping exercise in OSA subjects before and after CPAP therapy

Subject	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept	Pre-r^2	Post-r^2	Pre rest VO_2	Post rest VO_2	Pre-pk VO_2	Post-pk VO_2
1	.02	.01	.74	.62	.95	.99	.465	.648	3.123	2.448
2	.01	.01	.47	.58	.93	.96	.217	.795	1.207	1.749
3	.01	.02	.86	.53	.93	.96	.686	.080	2.02	1.850
4	.01	.01	.72	.63	.93	.94	.337	.207	2.144	1.963
5	.01	.01	.59	.72	.95	.85	.418	.347	1.793	1.616

Table 8: V_E response to ramping exercise in OSA subjects before and after CPAP therapy

Subject	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept	Pre-r^2	Post-r^2	Pre rest V_E	Post rest V_E	Pre-pk V_E	Post-pk V_E
1	0.53	0.19	12.7	19.1	.96	.91	15.4	19.6	97.0	50.4
2	0.43	0.31	12.4	20.2	.96	.94	7.5	26.2	43.4	57.7
3	0.39	0.51	32.1	18.3	.89	.91	20.5	4.6	69.7	64.6
4	0.37	0.23	15.6	18	.95	.89	9.0	6.2	56.9	45.7
5	0.29	0.25	14.7	20.2	.89	.87	11.8	10.3	43.3	46.9

Table 9: SBP response to ramping exercise in OSA subjects before and after CPAP therapy

Subject	Pre-slope	Post-slope	Pre-y intercept	Post-y intercept	Pre-r^2	Post-r^2	Pre rest SBP	Post rest SBP	Pre-pk SBP	Post-pk SBP
1	0.33	0.41	143	134	.99	.94	144	138	188	194
2	1.09	0.50	117	140	1.0	.98	118	138	196	192
3	0.56	0.93	162	133	.80	.99	150	132	205	214
4	0.69	0.54	138	136	.93	.88	130	122	202	188
5	0.41	0.52	135	128	.97	.93	136	128	170	186

VITA

Eric Walter Walker was born in Christiansburg, Virginia on December 7, 1972 the son of Harry and Debbie Walker. He comes from a small family with only one brother named Shawn. Eric spent the first19 years of his life in Woodstock, Virginia. He then moved to Blacksburg, Virginia and attended Radford University where he majored in Physical Education, graduating with a B.S. degree with an emphasis in Sportsmedicine. He then spent one year at home in Woodstock working at a local hospital in the physical therapy department. Eric then came to Virginia Tech in 1995, to work on a Masters Degree in Clinical Exercise Physiology and completing the requirements in May of 1998.