CHAPTER I

INTRODUCTION

Obstructive sleep apnea (OSA) is a serious health disorder which contributes to cardiovascular complications, decreased work productivity, automobile accidents, and death. This condition is characterized by a temporary and repetitious cessation of breathing resulting from repeated upper airway closure during a person's sleep. OSA is classified by several different components. Apneas, hypopneas and blood oxygen saturation (SaO_2) dips are the main constituents of this disorder. An apneic episode is a complete cessation of airflow lasting 10 sec. or more, while a hypopnea is a reduction in respiratory airflow combined with a SaO_2 decrease of $\geq$4%. Additional factors, which the sleep specialist feels are clinically significant, may also be accounted for and included when diagnosing OSA.

Excessive daytime sleepiness and fatigue are the two most common complaints of individuals with obstructive sleep apnea. According to Smolley (1990), these complaints are reported by as many as 78% of OSA patients. Flemons and Tsai (1997) and Wright, Johns, Watt et. al (1997) indicated patients with OSA have acknowledged falling asleep while performing routine activities such as watching television, reading, driving, or attending meetings. Most patients do not overtly complain about their excessive sleepiness and they may perceive it to be a "normal" state of life. What the OSA patient primarily complains about are the consequences of the excessive sleepiness and how it interferes with their social and professional aspects of life. Work performance of the OSA patient may deteriorate as the individual finds it increasingly harder to concentrate. Obstructive sleep apnea also may result in impaired memory and judgement. If called upon to make a sudden and important decision of some complexity, the individual with OSA may be unable to respond appropriately.

Additional adverse effects of OSA include a transient decrease in the SaO_2 which dramatically disturbs cardiopulmonary homeokinetics and results in acute increases in heart rate and blood pressure, ultimately leading to arousal from sleep. Research performed by He, Kryger, Zorick et. al (1988) has demonstrated OSA patients with an apnea index (AI) of greater than 20 have a significantly greater mortality rate than those

patients with an AI of less than 20. The AI is the average number of apneic episodes that a person has per hour of sleep. In addition to the increased mortality rate associated with OSA, additional health problems can be evident in these individuals regardless of their disease severity. These health problems may include hypertension, heart attacks, strokes, and a seven-fold increased risk of automobile accidents due to excessive daytime sleepiness. Currently, continuous positive airway pressure (CPAP) is the primary therapeutic alternative used for the treatment of obstructive sleep apnea. According to Mayer, Becker, Brandenburg et. al (1991) and Semple and London (1997) this form of treatment has been demonstrated to be the most effective noninvasive therapy for OSA at this point.

Sleep occupies approximately one-third of the human life span. Surprisingly, sleep experts are unable to agree upon the reason that sleep is necessary, and theories abound. What is known is that during normal sleep there is a physiologically reduced workload on the cardiovascular system. In individuals with obstructive sleep apnea there is reduced "physiological rest" and the cardiovascular system constantly is being stressed. According to Carlson, Hedner, Elam et. al (1993) and Waradekar, Sinoway, Zwillich et. al (1996) there is an increase in sympathetic activity in people with OSA. More recently, Zeigler, Nelesen, Mills, et. al (1997) have also identified an increase in sympathetic activity, as measured by norepinephrine levels, in patients with OSA. The increase in sympathetic stimulation has been implicated to be involved in the development of cardiovascular complications in OSA patients. Brooks, Horner, Kozar et. al (1997) and Dempsey (1997) have both performed studies which demonstrated OSA to be a cause of systemic hypertension. It has been estimated that approximately 58% of patients with OSA have high blood pressure. In comparison, if a group of overweight men in the same age range were evaluated, the incidence of hypertension (HTN) would be approximately 45%. Thus, those individuals with OSA have an approximately 13% higher incidence of HTN when compared to age, weight, and sex matched controls.

The prevalence of obstructive sleep apnea is much greater than once realized. Young, Palta, Dempsey et. al (1993) obtained a sample of 602 working men and women 30-60 years of age and performed a polysomnography (PSG) on each. Utilizing the

apnea-hypopnea index (AHI), any person with a value $\geq$5 was considered to have OSA. The AHI is the average number of episodes of apneas and hypopneas per hour of sleep. An apneic episode is a complete cessation of airflow lasting 10 sec. or more, while a hypopnea is a reduction in respiratory airflow combined with a SaO_2 decrease of $\geq$4%. A minimum AHI of 5 meets the minimal diagnostic criteria for OSA. Utilizing this criterion the authors estimated that 2% of women and 4% of men in the middle-aged work force meet this minimal standard. Another study performed by Mooe, Rabben, Wiklund, et. al (1994) utilized a random sample of women. Twenty percent of the women had an AHI > 5, which meets the minimal level for diagnosing OSA. It was concluded from the results of these studies that the prevalence of OSA is much higher than suspected among women and may be as high as it is among men.

While sleepiness and fatigue are the most encountered psychosocial consequences of OSA, the most observed physical indications are snoring and obesity. This disorder is most difficult to predict through any health screening process, therefore two commonly used physical measures with some predictive value include body mass index (BMI) and neck circumference (Young, Palta, Dempsey, et. al (1993) and Mooe, Rabben, Wiklund, et. al (1996).

During states of wakefulness or normal sleep, a person's upper airway is kept patent by the actions of specific muscles surrounding the pharynx. These pharyngeal muscles also coordinate the normal constriction of the upper airway during swallowing, speaking, or regurgitation. The feature of a collapsible airway is what creates the potential for upper airway narrowing and possible closure, which occurs in individuals with obstructive sleep apnea. In OSA, this complete or partial airway obstruction, or closure, may worsen over time and result in frequent and transitory cycles of asphyxiation throughout sleep. The force exerted by the inspiratory muscles to breath will increase in magnitude causing a further increase in negative pressure which then leads to further collapse of the upper airway. During this time the patient's SaO_2 decreases and the heart rate and blood pressure may rise. The apnea is usually terminated by brief arousals from sleep, or a leg twitch, breathing is restored and the muscles around the pharynx increase their tone. The patient usually does not fully awaken and returns to sleep quickly, only to

have this sequence of events repeated throughout the night, occasionally occurring at frequencies exceeding 100 times/hr in some cases. These recurrent respiratory events usually prevent the patient from attaining the deeper stages of sleep, such as stages III, IV, or rapid-eye movement (REM), for any extended period (Issa and Sullivan (1984) and Kuna and Sant'Ambrogio (1991).

The instruments used when diagnosing OSA usually require the patient to undergo a sleep study called a polysomnogram (PSG). This overnight study consists of monitoring brain electrophysiologic responses, heart rate and rhythms, respiration, blood oxygen levels, and leg movements. Electrodes are attached to the patient's skin and monitored by a sleep technician throughout the test. Data from this test is used to diagnose OSA, grade its severity, and help determine optimal therapeutic approaches.

The diagnostic scales, or indexes, which have been utilized by sleep practitioners to diagnose OSA have undergone changes as more information has become known. Originally, the apneic index was utilized. This scoring index only considered the number of apneic episodes per hour to be clinically significant. The AI was commonly used as a diagnostic tool before it was realized that hypopneas were just as clinically significant as apneas if these occur repeatedly during sleep. This led to the use of the Apnea-Hypopnea Index (AHI), which is the sum of both types of respiratory events. Estimates from clinical reports vary but the consequences of hypopneas are similar to apneas, with the exception that the drop in airflow compared to baseline is only 30-50%. Currently, another measure, the Respiratory Disturbance Index (RDI) is the most accepted diagnostic measure in clinical practice. This measure may include abnormal respiratory events, beyond clinically significant apneas and hypopneas, but are felt to be significant by the sleep specialist. The RDI is the index that is felt to be the most sensitive and accurate in diagnosing obstructive sleep apnea.

Due to its effectiveness, CPAP has become the major nonsurgical treatment for OSA. This conservative therapy operates by continuously providing positive pressure into a mask that is held firmly in place against an individuals face, thereby pneumatically "splinting" the airway open, thus preventing its collapse during inspiration. The mask is

held in place by a headgear strap, which is tightened to a firm fit with little or no air leak between the mask and the individual's face.

The optimal pressure delivered is measured in centimeters of water (cmH_20) and is determined during the course of a PSG. As the patient sleeps with the CPAP device during a PSG study, a technician adjusts CPAP until the pressure is found that best relieves the patients disordered breathing events, including snoring, hypopneas, apneas, drops in blood oxygen levels, and arousals. The ideal therapeutic pressure level can range from as low as 3-4 cmH_2O to as high as 20-22 cmH_2O, or even greater levels in rare instances (Ali, Davies, Fleetman et. al (1992) and Stradling and Davies (1997).

Several published studies have demonstrated that repeated disruptions in the OSA patient's sleep pattern are normalized when an effective level of CPAP is administered. The level of oxygen in the blood also is improved. These were some of the results as presented by Semple and London (1997) and Sforza, Krieger, Weitzenblum et. al (1990). Follow-up studies of OSA patients effectively treated in this manner also have demonstrated significant improvements in cognitive ability, memory, concentration, and psychological function (Krieger, Kurtz, Petiau et. al (1996).

For CPAP to be effective the patient must agree to accept the therapy and then continue to use it nightly in the home environment. This is one of the limitations associated with this therapy. The patient often does not truly believe CPAP will alleviate his symptoms or feels the mask and machine only make him more unable to sleep. Chervin, Theut, Bassetti et. al (1997), Likar, Panciera, Erickson et. al (1997) and Weaver, Kribbs, Pack et. al (1997) have reported the rates of compliance in the United States to range from 50%-80%. Compliance to treatment is often accepted to be nightly use of CPAP $\geq$ 4.5 hours. The concern for the patient who is non-compliant with CPAP therapy is the continued risk for health problems, as discussed previously.

Exercise may also be a useful adjunctive form of therapy for OSA. Although others have suggested this, it should be realized that exercise and weight loss therapy is not used for curing OSA, but rather to help alleviate the problems in identified individuals. Many of these patients are obese and exercise may be a useful adjunctive therapy if they are able to lose weight. The extra weight, especially in the neck region,

may add to the tissue mass that promotes upper airway collapse and exacerbates the problem. To date, there has not been a study, which has objectively evaluated a progressively increasing, aerobic, exercise tolerance test in OSA patients, either before or after they have been treated with CPAP. The study reported here was designed to compare the physiologic responses to a ramped, aerobic, exercise test in OSA patients before CPAP therapy and after 4 wk of compliance monitored CPAP therapy. The results from this study will provide useful information towards further understanding obstructive sleep apnea, the efficacy of CPAP, and clinical applications of exercise for use as an adjunctive treatment in this disorder.

STATEMENT OF PROBLEM

Given the fact that CPAP is the most frequently used treatment for obstructive sleep apnea, one would expect there to be follow-up studies examining its therapeutic effectiveness on physiological variables during exercise. However, a review of the published scientific and clinical literature revealed only two studies examining exercise and CPAP therapy. After adhering to a brief trial of CPAP therapy, those patients who subjectively report an improvement in sleep quality and daytime functioning might reasonably be expected to show improvements in exercise performance. An increased exercise tolerance would be most beneficial for the OSA patient for several reasons: the patient would be able to meet instrumental activities of daily living (IADL's) at a lower energy cost, burn more calories during an exercise session, uptake non-supervised exercise sessions, lower their risk of CAD as well as HTN, and subjectively feel better.

RESEARCH HYPOTHESES

In a group of patients diagnosed with OSA by a PSG and then submaximally exercise tested (75% of predicted HR reserve.) on a cycle ergometer there will be no differences in the following exercise test variables:

-rating of perceived exertion (RPE) at 60% of apparent maximal functional capacity

-Heart rate (HR) at 60% of apparent maximal functional capacity

-Systolic blood pressure (SBP) at 60% of apparent maximal functional capacity

-the slope HR, SBP or RPE regressed on power (W)

-the slope of SBP regressed on power (W)

SIGNIFICANCE OF THE STUDY

Obstructive sleep apnea is a condition that only in the past 15-20 years, has begun to receive serious attention in the medical world. The consequences of OSA include daytime sleepiness, fatigue, cardiovascular complications, and an increased mortality rate. Currently, continuous positive airway pressure is the primary form of treatment prescribed for those individuals diagnosed with OSA. To date, however, determination of clinical effectiveness of this treatment has been limited to subjective evaluation of the OSA patient after CPAP treatment. As mentioned previously, there has only been one documented study examining CPAP effectiveness during an exercise test. Additionally, there have only been a handful of studies that have examined the impact of CPAP on resting daytime blood pressures. Since physical functioning is a component of daily life that significantly affects a person's overall well being, health status, and ability to meet instrumental activities of daily living (IADL), it would be expected that there would be documented research on the effectiveness of this form of therapy.

This study examined the effectiveness of CPAP through objective physiological measures during a ramping, aerobic, submaximal exercise test with subjective questionnaires for added support. The questionnaires were utilized to assess subjective feelings of better sleep, decreased depression, and activity levels after CPAP therapy. This study therefore was necessary and needed to assess CPAP effectiveness on physiological variables during exercise. The results of this study could have implications in the management of OSA. It also may provide additional evidence for exercise tolerance and weight loss reduction as an adjunctive therapy for OSA management.

BASIC ASSUMPTIONS

The investigator made the following assumptions in conducting this study:

1. All subjects were truthful in recording their answers to the questionnaires

2. Volunteer subjects were representative of the population of OSA patients.

DELIMITATIONS

This study was delimitated by the investigator in the following important ways:

1. The subjects were volunteers from the community referred to the Sleep Disorders Center of Southwest Virginia for polysomnography

2. Blood pressure was determined by two trained technicians utilizing simultaneous auscultation and cross validation.

3. The aerobic exercise test was conducted on a stationary, electronic, bicycle.

LIMITATIONS

Interpretation of the results were limited by the following:

1. The period of CPAP treatment was restricted to 4 wk
2. Participants in this study were asked to refrain from undertaking additional physical activities during the study, which was evaluated though the use of activity questionaires. This was done to ensure additional physical activity was not the reason for any improvements in physiological variables.

DEFINITION OF TERMS AND SYMBOLS

1. Obstructive sleep apnea (OSA): condition characterized by repetitive periods of upper airway closure during sleep (Kuna and Sant'Ambrogio (1991).
2. 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 is the index that is felt to be the most sensitive and accurate in diagnosing OSA.
3. Apnea-Hypopnea Index (AHI): scoring tool for OSA that is computed by summation of all the apneic and hypopneic events during sleep. Commonly reported as an average number of events per hour.

4. Apnea Index (AI): scoring tool used for OSA that is computed by summation of all hypopneas occurring during sleep. Also reported as an average number of events per hour.
5. Hypoxia: diminished availability of oxygen to the body tissues.
6. Hypoxaemia: deficient oxygenation of the blood. May eventually lead to hypoxia
7. Continuous positive airway pressure (CPAP): an instrument used in the treatment of OSA. It operates by providing a constant flow of air into a mask which is worn by the patient; this pressure splints the upper airway allowing adequate respiration.

SUMMARY

Obstructive sleep apnea is a relatively newly identified disorder which health care providers are faced with treating. It is a more common disorder than once realized with reported rates of occurrence ranging from 2% to 20% of the population. The problems which medical clinicians are encountering today are not associated with understanding the etiology of the disease but the best therapeutic alternatives. Currently, continuous positive airway pressure is the most commonly used conservative therapy for OSA. In some cases, conservative treatment is not indicated and the patient must undergo some form of surgical intervention. In either form of treatment there is little patient follow-up. Thus, it is reasonable to track these patients and perform outcome assessments.

CHAPTER 2

INTRODUCTION

Obstructive sleep apnea is a relatively new condition that is beginning to gain the attention of health care professionals. This disorder has been implicated to affect up to 20% of the population and is characterized by repeated apneic episodes during sleep, which are terminated by brief arousals from sleep. These events prevent the patient from attaining the deeper stages of sleep, which are physiologically needed. The hallmarks of this disorder include snoring and excessive daytime sleepiness. Additionally, OSA may cause daytime systemic hypertension, myocardial ischemia, and other cardiovascular disorders. Currently, the preferred method of conservative treatment for OSA is continuous positive airway pressure. The outcomes for this intervention is still not well understood, as this is a relatively newly identified area of medicine.

EPIDEMIOLOGY OF OSA

The prevalence of OSA in the general population is still unclear. Several epidemiological studies have attempted to examine this issue. Epidemiological data from Young, Palta, Dempsey, et. al (1993) estimated that in a group of 602 middle aged individuals 2% of women and 4% of men meet the minimal diagnostic criteria for sleep apnea, which is an AHI $\geq$ 5 and 3 symptoms of daytime hypersomnolence. Excessive daytime sleepiness, an unrefreshed feeling after awakening, and uncontrollable daytime sleepiness which interferes with daily living, were the 3 symptoms of daytime hypersomnolence used in this study. In a more recent epidemiological study by Martin, Gascon, Carrizo, et. al (1997) the prevalence of OSA in southern Europe was examined. A total of 1222 subjects (597 males, 625 females) participated in this study. This diagnosis of OSA was established utilizing three criteria. The first criterion was loud (severe) snoring. Severe snoring was assessed, through a sleep questionnaire, by an interviewer at each subject's home. The second criterion of excessive daytime sleepiness was also assessed through this interview. The final criterion for diagnosing OSA was an abnormal, nocturnal home oximetry in the presence of repetitive short duration SaO_2 fluctuations. The diagnosis of OSA was established in 18 subjects (13 males, 5 females).

It was estimated that among southern European adults, 2.2% of men and 0.8% of women meet minimal diagnostic criteria for OSA. In another recent study the investigators opted to examine the number of sleep apnea cases which are clinically diagnosed by a M.D. versus those who have been actually screened for sleep apnea. A classification of clinical diagnosis meant that the subject had been diagnosed by a physician that they had sleep apnea. Screen detected sleep apnea meant that the subject had a combination of self-reported daytime sleepiness and the occurrence of apneas and hypopneas during sleep (AHI>5). Subjects included a sample of 4,925 men and women between the ages of 30-60 who answered a mailed questionnaire. A subsample of 1,090 subjects was studied via overnight PSG. A total of 248 subjects were found to have screen detected mild to moderate sleep apnea (AHI>5). Of this group only 16 reported they had been diagnosed with sleep apnea previously. Thus it was found that 94% of sleep apnea cases are clinically missed (Young, Evans, Finn, et. al (1997). It is obvious that OSA is a growing health concern, and we still do not know exactly how many people this disorder affects.

ETIOLOGY/PATHOPHYSIOLOGY

An understanding of the etiology and pathophysiology of OSA is essential. Patency of the upper airway is necessary for respiration to function normally. The feature of a collapsible airway is what creates the potential for upper airway narrowing and possible closure. During swallowing, speech, or regurgitation, upper airway narrowing or closure is needed for these actions to occur. In patients with OSA the collapse of the upper airway during sleep leads to apneic or hypopneic episodes. The result of this disruption in airflow includes a decrease in the SaO_2, an increase in blood pressure, increased $PaCO_2$ and metabolic alkalosis. The respiratory disturbance is usually terminated by a brief brain arousal from sleep and breathing is restored as the muscles of the upper airway increase their tone.

The specific site of upper airway occlusion varies among OSA patients. The 3 primary sites that are commonly implicated include the oropharynx, hypopharynx, and nasopharynx. The nasopharynx extends form the end of the nasal septum to the margin of the soft palate. The oropharynx begins at the margin of the soft palate and ends at the

tip of the epiglottis. Finally, the region of the hypopharynx is from the tip of the epiglottis to the vocal cords (Isoni, Feroah, Hajduk, et. al (1993).

There are many muscles which contribute to maintaining patency of the upper airway. A few of these muscles include the levator and tensor veli palatini, palotoglossus, stylopharyngeus, genioglossus, and hypoglossus. While awake the muscles of the upper airway exert high levels of tonic activity during inspiration to maintain an open airway. During sleep there is a considerable loss of tonic activity in the muscles of the upper airway which predisposes to upper airway collapse (Hudgel (1992).

The normal process of ventilation is a key to understanding the mechanisms responsible for OSA. Ventilation is dependent upon air flowing down a gradient of pressure. The inspiratory muscles, with the diaphragm being the largest contributor to inspiration, generate a negative intrapleural pressure that is transmitted to the airway. The ability of the upper airway to maintain its rigidity and stay open is dependent upon the dilator muscles to counteract the negative inspiratory pressure being generated to take air into the lungs. Therefore, the degree of obstruction in the upper airway is a balance between the collapsing forces and the dilating forces. As stated previously, there is a loss of tonic activity in the upper airway muscles during sleep and these muscles cannot maintain a patent airway against the negative inspiratory pressure. The synchronization between these forces is very important. The upper airway muscles must begin contracting and generate greater forces than the inspiratory muscles during inspiration. Under normal conditions this occurs and sleep is uninterrupted as the upper airway is stabilized. In OSA the inspiratory pressure is greater than the stabilizing forces of the upper airway and a degree of obstruction occurs (Kuna and Sant'Ambrogio (1991) and Dempsey and Skatrud (1986).

RISK FACTORS

There are several risk factors that may predispose an individual to OSA. The risk factors, which have been most frequently examined, include obesity and snoring. Several studies have reported the association between obesity and OSA. Rossner, Lagerstrand, Persson, et. al (1991) followed 34 obese men referred to an Obesity Unit for

a period of 4 years. Of the 22 men who underwent a PSG, 15 (68%) were noted to have significant OSA (mean AI=46). Nine men never attended the PSG study; 3 of who had already died. In the other 3 cases, the recordings did not allow any conclusions to be drawn. The prevalence of OSA in obese females has also been documented by Richman, Elliott, Burns, et. al (1993). In their study 33 of 86 eligible women (BMI>30kg/m^2 and age>18 yr) volunteered to undergo a PSG. Of the 33 PSG's, 29 had successful recordings. The prevalence of OSA (RDI $\geq$ 5) was 37.9%. Additionally, there was a significant, positive correlation between RDI and BMI in the group which underwent the PSG ($r=0.71$; $p<0.001$).

Snoring is another risk factor that has been examined in association with OSA. In the past, snoring was viewed as a mere annoyance. Only recently have the severe implications of snoring been realized. In one study, a total of 35 patients with a history of loud snoring were examined for OSA. Each patient underwent a sleep study to diagnose OSA. It was found that 16 (46%) of the 35 participants demonstrated OSA (Woodhead, Davies, and Allen (1991).

HEALTH RELATED QUALITY OF LIFE IN OSA

Obstructive sleep apnea has a tremendous effect on a person's quality of life. Instrumental activities of daily living are often interrupted or at least made more difficult as a result of this disorder. The consequences of OSA may include memory deficits, decreased alertness, irritability, depression, headaches, or a decrease in the ability to concentrate. These effects can result in an impairment of work efficiency, relationship and social problems, and increased automobile accidents (Flemons and Tsai (1997), Paiva, Farinha, Martins, et. al (1997), and Wright, Johns, Watt, et. al (1997).

OSA AND CARDIOVASCULAR DISEASE

Additionally, there is the increased risk of cardiovascular disease as a result of OSA. Epidemiological data has reported an association between OSA and cardiovascular disease. Mooe, Rabben, Wiklund, et. al (1996) examined the occurrence of sleep disordered breathing in women and its association with coronary artery disease (CAD). A

total of 102 women with documented CAD and 50 age-matched controls without CAD were examined for OSA. Women with CAD yielded the following percentages: AHI>5 (54%) and AHI>10 (30%). The following values were recorded from women without CAD: AHI>5 (30%) and AHI>10 (10%). A conclusion of this study was that OSA is common among women with CAD and is even a significant predictor of CAD after adjustments have been made for age, body mass index, hypertension, smoking habits, and diabetes. In another related study performed by Mooe, Rabben, Wiklund, et. al (1996) men with CAD were found to have a much higher occurrence of OSA when compared to age matched controls. This study utilized a sample of 142 men with angiographically verified CAD and 50 controls without known heart disease. Using the AHI, it was noted that 37% of men with CAD had a score of $\geq$10. In comparison, only 20% of control subjects were found to have the same AHI. The authors of this study concluded that sleep disordered breathing is common in men with CAD. Additionally, a significant association between OSA and CAD remained after adjusting for age, hypertension, BMI, and diabetes.

A few of the specific cardiovascular complications, which have been examined in research thus far, include ischemic heart disease, myocardial infarction, and systemic hypertension. The issue of ischemic heart disease has been examined by Hanly, Sasson, Zuberi, et. al (1993). In this study a total of 23 subjects (21 men and 2 women) with OSA were studied for signs of ischemia. None of the patients had a history of CAD. Of the 23 subjects, 7 presented with myocardial ischemic changes during sleep. Ischemic changes were determined by a Holter monitor with a depression in the ST segment of $\geq$ 1 mm from baseline considered to be a positive sign of ischemia. The association of myocardial infarction (MI) with sleep apnea has also been examined. Hung, Whitford, Parsons et. al (1990) demonstrated male survivors of MI have a higher incidence of apneic episodes when compared to matched controls (6.9 vs. 1.4/hr; p=0.0001). Utilizing the AHI the results showed the same trends. The mean value for the MI patients was 12.7 events/hr versus a mean of 3.7 events/hr for the controls (p=0.0001). The subjects included 101 male patients who were admitted for treatment of an acute MI. Control subjects were male volunteers from the community and did not differ in age.

HYPERTENSION AND OSA

Another aspect of the association between cardiovascular disease and OSA that has been examined is hypertension. It has been suggested that OSA and HTN are linked. Young, Peppard, Palta, et. al (1997) recognized this issue and tested the hypothesis that sleep disordered breathing is related to elevated blood pressure. A sample of 1060 employed men and women aged 30-60 yr who underwent an overnight PSG were included in this study. It was reported that blood pressure, as measured on the night of the PSG, increased linearly with an increasing AHI ($p=0.003$ for systolic and $p=0.01$ for diastolic). It was concluded that there is a dose-response relationship between sleep-disordered breathing and blood pressure independent of confounding factors. Hla, Young, Bidwell, et. al (1994) reported similar results. Participants in this study included 147 men and women aged 30-60 yr. Mean blood pressures during wakefulness and sleep were compared in those subjects with sleep apnea (AHI $\geq$ 5) and those without sleep apnea. Twenty-four hour ambulatory blood pressure monitoring assessed blood pressures during the awake period. During wakefulness, those participants with an AHI $\geq$ 5 had a mean blood pressure of 131/80 mmHg compared to a reading of 122/75 mmHg in those people with an AHI < 5 ($p<0.05$). In comparing the same groups during sleep the mean blood pressures were 113/66 mmHg compared to 104/62 mmHg ($p<0.05$). Additionally, after controlling for obesity, sex, and age, sleep apnea was significantly associated with HTN in a dose response relationship. Thus, it was concluded that there was an association between HTN and sleep apnea independent of age, obesity and sex in a community based adult population. In yet another study, the relationship between HTN and sleep-disordered breathing was examined. Coy, Dimsdale, Ancoli-Israel, et. al (1996) studied 67 men and women aged 30-60 yr and .90-1.5 times ideal body weight. Results indicated the RDI to be an independent predictor of diastolic blood pressure and accounting for 15% of the variance ($p=0.02$). In those subjects with a RDI > 30, the RDI accounted for 36% of the variance in diastolic blood pressure. Interesting to this study was that the RDI was not related to systolic blood pressure recordings. In a study performed by Brooks, Horner, Kozar, et. al (1997) a direct cause and effect relationship was shown between OSA and HTN. Their research consisted of inducing OSA in dogs

and examining nighttime and daytime blood pressures. Mean arterial blood pressures during the night progressively increased to a maximal level of 13.0 mmHg above control values ($p=0.005$). Daytime mean arterial blood pressures also progressively increased to a maximum of 15.7 mmHg above control values ($p=0.004$). Control values were taken from the animals during a 1-2 month period before OSA induction. Also, all of these responses were noted in each of the 4 dogs and occurred within 4 wk of the induction of OSA. This study provides strong evidence that there is a direct cause and effect relationship between OSA and HTN.

The prevalence of HTN in OSA patients has been well documented. It is clear that OSA does, in fact, produce hypertension even when confounding variables, such as obesity and age, are accounted for in statistical analysis. The next issue, which needs to be addressed, is the cause of HTN in this population. It is believed that the sympathetic nervous system has a major role in the cause of HTN in OSA. Muscle sympathetic activity (MSA) in awake OSA patients has been examined by Carlson, Hedner, Elam, et. al (1993). Subjects included 11 males previously diagnosed with OSA and 9 males as control subjects. The average of the MSA in the OSA group was 60.6 bursts/min compared to 43.0 bursts/min in the controls ($p<0.01$). The MSA was unrelated to disease severity and in the whole group of subjects the MSA was not correlated with body weight or BMI ($r=0.06$ and $r=0.13$, respectively). Additional results revealed a significant difference ($p<0.05$) in plasma norepinephrine (NE) levels between the OSA subjects and the control group. This was true for both arterial (0.46 pg/L and 0.26 pg/L) and venous samples (0.51 pg/L and 0.29 pg/L). The authors concluded that resting MSA is increased during awake, supine rest in OSA patients.

CPAP THERAPY FOR OSA

The basic goal in prescribing CPAP therapy is to decrease the number of disturbances during sleep and improve the quality of the patient's sleep. A few of the end results of CPAP therapy include a decrease in the AHI or RDI, increased feeling of alertness, decreased daytime sleepiness, improved sleep quality, and reduced resting blood pressures. Research by Berthon-Jones, Lawrence, Sullivan, et. al (1996) revealed a

decrease in the AHI with CPAP therapy. Subjects included 41 males and 4 women with an untreated AHI > 20 (mean AHI=30.4). With the use of a CPAP device the mean AHI fell to 0.4 events/hr ($p<0.0001$). Additionally, there was a significant increase in the percentage of slow wave sleep (8.9% untreated vs. 12.3% treated; $p=0.01$) and REM sleep (11.6% untreated vs. 15.5% treated; $p=0.014$). A decrease in somnolence was noted in a study done by Lojander, Maasilta, Partinen, et. al (1996). OSA patients on CPAP were followed and contacted after 1 yr of therapy. After 1 yr of CPAP therapy OSA patients were significantly ($p<0.05$) less somnolent. Recently, a study was done examining bed-partners assessment of CPAP in OSA. This study also showed an increase in the OSA patient's quality of life, but also revealed an increase in the bed-partners quality of life. Logically, the bed-partner of those afflicted with OSA would have a decrease in sleep quality due to the snoring, leg twitches, and arousals of the OSA patient. The OSA patient on CPAP therapy had an improvement of sleep as noted by mean values on the Epworth sleepiness score (14.3 vs. 5.2; $p<0.005$). Bed-partners of those with OSA subjectively evaluated their own improvements in sleep quality, daytime alertness, mood, and quality of life (questions 1-4) as well as the same parameters in the OSA patient (questions 5-8). The possible range for scores was -1 (worse) to +3 (marked improvement). Questions 1-4 revealed median scores of 2, 1, 1, and 2, respectively. For questions 5-8 the median scores were 3, 3, 2, 3, respectively. This data indicates that not only does the OSA patient on CPAP therapy feel improvements in sleep and quality of life, but their bed-partners also feel improvement in these areas (Kiely and McNicholas (1997).

Hypertension is commonly observed in OSA patients and this was discussed earlier. In addition, the effect of CPAP on HTN has been examined. Lies, Nabe, Pakow, et. al (1996) performed a study on the effect of CPAP on HTN in OSA patients. OSA was verified by PSG and defined as an AHI > 10. Ambulatory blood pressure was monitored for 24 hours before, after 1-3 days, and after 4-6 months of CPAP therapy. A significant decrease in daytime blood pressures was observed after short term as well as long term therapy with CPAP. The baseline blood pressure was 144.8/94.4 mmHg. After short-term therapy the blood pressure dropped to 138.9/89.4 mmHg. An additional

decrease in blood pressure, 136.4/86.9 mmHg, was noted after long term therapy. Mayer, Becker, Brandenburg et. al (1991) also examined the effects of long term CPAP therapy on blood pressure in OSA patients. Their subjects consisted of 12 men with a mean BMI of 29.3. During the therapy period of 6 months BMI did not change. The AI significantly decreased from 58 before therapy to 2 after therapy ($p<0.01$). The mean blood pressures and heart rates were also observed to significantly decrease as a result of CPAP therapy. The mean intra-arterial systolic blood pressures (SBP) and diastolic blood pressures (DBP) before and after therapy were as follows: SBP 147.1 mmHg vs. 126.4 mmHg and DBP 81.6 mmHg vs. 69.4 mmHg. Mean heart rate values also decreased from 68.8 b/min to 65.4 b/min. For all three parameters measured statistical significance was achieved ($p<0.001$). These results also showed that HTN in OSA patients is reversible through the use of CPAP therapy for OSA.

It has been shown that resting blood pressure is reduced in OSA patients after the initiation of CPAP therapy. In discussion previously it was noted that the increase in blood pressure, as seen in OSA, may be the result of an increase in sympathetic stimulation. Thus, it is reasonable to examine the effect CPAP has on sympathetic stimulation. Waradekar, Sinoway, Zwillich, et. al (1996) examined this issue. Muscle sympathetic nerve activity (MSNA) was documented in 7 OSA patients before CPAP therapy and after 1 month of therapy. At baseline, the mean MSNA was 69.4 bursts/min. After one month of CPAP therapy there was a significant decrease in the mean MSNA values (53.9 bursts/min; $p<0.01$). It should also be noted that their was a direct linear correlation between the number of hours of CPAP use per night and the decrease in mean MSNA ($r=0.87$; $p=0.01$). The effect of CPAP on autonomic stress responses in OSA patients has also been studied. Tests of autonomic stress responses included HR responses to Valsalva maneuver, deep breathing, and change of posture from lying to standing. Systolic blood pressure responses to standing and diastolic blood pressure to handgrip were also analyzed. An abnormal test (compared to published normal values) scored +1.0 and marginal test results scored +0.5. Tests were performed in the morning and the evening. Subjects included 6 males with moderate to severe OSA (median AHI=51). Five of the 6 subjects showed normalization in their test scores after 1 year of

CPAP therapy (2.0 vs. 0.2; $p<0.05$). Compliance in these 5 subjects averaged 7.8 hr/night. In one subject their was an increase in test score (1.0 vs. 1.5). It was also noted that this subject was not compliant (3 hr/night) with CPAP therapy. Thus, it was concluded that effective treatment of OSA through the use of CPAP normalizes autonomic stress responses (Veale, Pepin, Wuyam, et. al (1996).

Studies examining the effects of CPAP in OSA patients during exercise are scarce. To date, an exhaustive search has revealed only two studies that have examined exercise performance in OSA patients treated with CPAP therapy. Both of these studies have been published in foreign journals and are written in a foreign language. This does present a limitation in interpreting the studies, but also provides further evidence that research is needed in this area. The abstracts are written in English and it is from the abstracts the following details were gathered. In a study completed by Konermann, Sanner, Klewer, et. al (1996) cardiopulmonary parameters to exercise were examined in OSA patients after CPAP therapy. Subjects included 30 patients with severe OSA. Information regarding the subject's demographics is not known nor is it known what classification these authors used for determining severe OSA. After 2 wk of CPAP therapy steady state exercise testing revealed a decrease in HR ratio 100W/rest by 13.5% ($p<0.001$), a drop in the systolic blood pressure 100W/rest by 0.8% (n.s.), and no significant change in diastolic blood pressure 100W/rest. After 6 months of CPAP therapy the heart rate ratio decreased by another 6.5% ($p<0.01$), systolic blood pressure by another 14.9% ($p<0.001$) and again diastolic blood pressure did not significantly change. The other study, which has been done in this area, was by Taguchi, Hida, Okabe, et. al (1997). Their subjects included 6 patients undergoing CPAP therapy. Further information regarding the subjects is not known. An incremental exercise test was done on a bicycle ergometer before therapy and after 7 days of therapy. The exercise test was a stage protocol beginning at 0W and increasing 25W every 3 minutes until maximal exhaustion. It was noted that maximal oxygen consumption increased after 7 days of CPAP therapy (1841 mL/min vs. 2125 mL/min; $p<0.05$). In addition, other cardiorespiratory parameters did not significantly change. These parameters were not mentioned in the abstract. These 2 studies indicate that there is an interest in the exercise

performance of OSA patients after CPAP therapy. Yet, there has been no research done in this area in the United States and nothing published in any English journals.

QUESTIONNAIRES

The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month time interval. It consists of 19 self rated questions and five questions rated by the 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 of 86.5% in distinguishing good and poor sleeps. 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 homogeneity, consistency (test-retest reliability) and validity were obtained. Another study looked at the ability of the PSQI to verify OSA in an obese female population. Richman, Elliott, Bunn, et al. (1994) studied the prevalence of OSA in an obese female population (BMI>30 kg/m^2, age >18 yr). All subjects were screened by an overnight ambulatory sleep study to detect OSA. The PSQI was used to assess subjective sleep quality and sleep disturbances in 29 subjects. They found the prevalence of OSA (RDI>5) was 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 4=.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 repeatability 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 repeatability after 5 and 11 months was good with test-retest correlation coefficients between .65 and.89 for main sections of the questionnaire.

Summit Medical Inc developed the Health Status Questionnaire (HSQ). It is a variation of the Medical Outcomes Study (MOS) SF-36. Content for the HSQ is identical to the MOS, but it setup in an easier to use format. After a long exhaustive search, o published journal articles could be found on this questionnaire for reliability or validity. Due to the content for the questionnaires being the same and the lack of published research, a review on the MOS SF-36 will be used. 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 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. Jenkinson, Stradling, and Petersen (1997) studied the quality of life outcome in evaluation of CPAP for sleep apnea patients. The study consisted on 108 patients with OSA undergoing a therapeutic assessment of CPAP. Each subject completed the questionnaire before and 5 weeks after commencing treatment. They found that the SF-36 revealed substantial adverse effects on subjective health of OSA 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 and for the overall Mental and Physical Component scores, 0.76 and 0.57, respectively.

SUMMARY

Obstructive sleep apnea has been estimated to affect 2-4% of the population. There are numerous effects of this disorder, which include excessive daytime sleepiness, decreased alertness, mood swings, increased automobile accidents, and cardiovascular disease. Specifically, hypertension has been demonstrated to be linked with OSA. It is obvious that there are serious consequences of this disorder. The primary therapy that is administered for OSA is nasal continuous positive airway pressure. This form of therapy has been demonstrated to relieve OSA and subjectively increase the patients feeling of well being and quality of life. Thus far, the objective effects of CPAP therapy on exercise performance have only been published in two studies. Both studies utilized different protocols and measurements. Neither of the studies have performed an incremental exercise test and examined heart rate and blood pressure responses at a given workload. Additionally, the two studies varied in the length of CPAP therapy. The one study had a period of 7 days for CPAP therapy and the other study followed up with patients after 2 wk and 6 months of CPAP therapy.

CHAPTER 3: JOURNAL MANUSCRIPT

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PHYSIOLOGICAL RESPONSES TO RAMPING EXERCISE IN OSA PATIENTS AFTER CPAP THERAPY

D. Edward Shifflett, Jr.

Laboratory for Health and Exercise Sciences

and the Sleep Disorders Center of Southwest Virginia

Department of Human Nutrition, Foods, and Exercise

Virginia Tech, Blacksburg, VA

Summary: Continuous positive airway pressure (CPAP) is the primary therapy administered for those afflicted with obstructive sleep apnea (OSA). We examined the effects of CPAP therapy on physiological variables during a ramped exercise. The five male, OSA patients had mean values and standard deviations for RDI=60.7±19.1, BMI=29.9±2.9, and age=56±16.1 yr were examined before and after 4 wk of nCPAP therapy. After 4 wk of CPAP therapy, patient responses to exercise showed a 17.6%, ($p<0.05$) improvement in rating of perceived exertion (RPE) at identical power outputs (60% of the individual's apparent functional capacity). Statistical significance was not attained ($p>0.05$) upon analysis of the following parameters at 60% of the individuals maximum workload: heart rate, VO_2, systolic blood pressure, and rate pressure product although there was a trend showing a decrease in these variables. The data support the interpretation that the decrease in RPE during 60% of the individual's maximum predicted HR reserve corresponded with an increase in sleep quality (mean increase of 52.5%, 4.2 units) as measured by the Pittsburgh Sleep Quality Index before and after 4 wk of CPAP therapy. It was concluded that the slight, yet not significant, increase in exercise tolerance can be attributed to the subjective feelings of improved sleep quality after 4 wk of CPAP therapy. **Key Words:** Obstructive sleep apnea---CPAP---exercise---physiological responses.

Introduction: The prevalence of obstructive sleep apnea (OSA) in the general population is outstanding. This disorder has been implicated to affect 1-4% of the population (12,25). Obstructive sleep apnea is a serious health disorder which contributes to impairment in work efficiency, social dysfunction, and increased automobile accidents (5,6,16,24). Additionally, OSA has been implicated to be associated with an increased risk of cardiovascular disorders, including myocardial ischemia (7,14,15) and myocardial infarction (8). Moreover, the prevalence of hypertension (HTN) in combination with OSA has been examined. It has been demonstrated that systemic HTN in those afflicted with OSA is a direct result of the disruption in sleep (3,4,11,26). Clinical presentation of OSA includes snoring, obesity and excessive daytime sleepiness. Several studies have demonstrated that these are associated with OSA (17,18,23)

The primary therapy that is administered for OSA is continuous positive airway pressure (CPAP). This conservative form of therapy has been shown to be effective at reducing and/or eliminating the apneas, hypopneas, and other disruptions in OSA (1,2). In addition, CPAP has been evaluated subjectively, and demonstrated to be effective at eliminating the symptoms of OSA and improving the patient's quality of life (9,24). A few studies (11,13,19) have attempted to examine the effectiveness of CPAP objectively through measurements on resting blood pressure. Results from these studies have generally shown that CPAP does reduce resting blood pressures in the OSA patient (11,13,19).

Studies examining the effect of CPAP on physiological parameters during exercise have been only briefly examined. In short, two studies have examined the effects of CPAP on physiological parameters during exercise and have shown an increase in performance (10,20). What those studies have not addressed is the effect of CPAP on physiological responses during a ramping exercise. Additionally they have not accounted for individual differences in functional capacity. Thus, the aim of the present study was to evaluate the effect of CPAP on physiological parameters during a submaximal, ramping, cycling protocol. An increase in exercise tolerance would provide additional evidence for the efficacy of CPAP. Also, an improvement in exercise performance after short-term CPAP therapy would provide an indication that the treatment of OSA increases one's ability to perform activities of daily living. This is clinically important for the patient as it demonstrates an increase in an important dimension of daily living and raising possibilities for activity based-treatment interventions to curb weight gain.

Methods. *subjects*: Five adult men and women were recruited from the community to participate in this study. These subjects 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, orthopedic or

musculoskeletal disabilities which prevented the subject from doing exercise, or a history of regular participation in moderate physical activity.

procedures: All prospective candidates who 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. 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 which was signed and described the procedures of the study. Each subject completed several questionnaires. These included the Pittsburgh Sleep Quality Index (PSQI) for rating sleep quality and daytime sleep related problems; Baecke questionnaire for assessment of physical activity levels; and the Health Related Quality of Life (HRQL) questionnaire for assessment of health related characteristics. Each subject then underwent a polysomnography (PSG) for the diagnosis of obstructive sleep apnea (OSA). The morning after the PSG the following measures were recorded on each subject: height, weight, resting blood pressure, resting heart rate, BMI, and exercise performance on a Medgraphics 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 W/min at fifty RPM's. The utilized exercise protocol enabled the patient to exercise for fifteen to twenty minutes before reaching test termination points. 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 exchange ratio >1.00 and attainment of the exercise ventilatory threshold.

Exercise was monitored by at least two trained technicians and terminated in the event that adverse responses occur (clinical criteria of the American College of Sports Medicine and American Heart Association). During the exercise test, blood pressure was monitored and cross-validated every three minutes by two trained clinicians doing

simultaneous auscultation. 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 3 min utilizing the Borg scale of perceived exertion. Also, during the exercise test, patients were measured for VO_2 using a computer controlled breath-by-breath gas exchange system (Sensormedics Vmax 22, Yorba Linda, CA).

Upon completion of the initial, diagnostic PSG a trained PSG technician at the Sleep Center scored the subject's results. Each subject was diagnosed with OSA or not having OSA by a physician specializing in sleep medicine. Those with OSA who were candidates for continuous positive airway pressure therapy were asked to return 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 CPAP therapy were contacted and returned to the Sleep Center four weeks from initiation of CPAP treatment at home. Subjects were then given a second submaximal exercise test at the same time in the morning utilizing the same protocol as with the first exercise test. The same questionnaires were also given to the participants for completion and were completed prior to the exercise test.

Results from the pre-CPAP and 4 wk post-CPAP exercise tests were analyzed for physiological changes. Regression lines were completed for the following variables against workload (watts): heart rate (HR), oxygen consumption (VO_2), systolic blood pressure (SBP), ratings of perceived exertion (RPE), and rate pressure product (RPP). Utilizing the regression equations, physiological parameters at 60% of the subject's apparent maximal functional capacity were analyzed by dependent t-tests before and after 4 wk of CPAP therapy. Physiological parameters were analyzed at 60% of apparent maximal functional capacity since this is the lower end of a typical exercise prescription. This value is recommended by the American College of Sports Medicine for training and exercising in order to have beneficial effects on the skeletal muscles and cardiovascular system.

Results: Five male subjects with mean values for RDI=60.7$\pm$19.1 and BMI=29.9$\pm$2.9 participated in this study. Additional patient demographics and clinical measurements,

including mean values and standard deviations can be seen in Table 1. Cardiovascular, respiratory and perceptual measures were analyzed at 60% of each individual's apparent maximal functional capacity. Dependent t-tests on heart rate at 60% of the subject's maximum revealed no significant change ($p=0.07$) after 4 wk of CPAP therapy. There was also no significant change ($p>0.05$) in the VO_2 at 60% of the subject's maximum after 4 wk of CPAP therapy. Additionally, there was no significant change ($p>0.05$) in RPP or SBP at 60% of the subject's apparent maximal level after 4 wk of CPAP therapy (Table 2). Although statistical significance was not achieved in the 4 previously listed physiological parameters it should be noted that there was a trend for those values to decrease. The HR decreased an average of 8.0 b/min (6.0%) at 60% after 4 wk of CPAP therapy (Figure 1). The VO_2 decreased an average of 0.23 L/min (11.7%) at 60% and the SBP and RPP also decreased an average of 8.0 mmHg (4.0%) and 22.4 units (8.6%), respectively. Significance was attained in RPE at 60% of the subject's maximum after 4 wk of CPAP therapy ($p<0.05$, Figure 2). The mean RPE decreased 3.0 units on average. Additional statistical analysis was done on the slopes of the regression lines for each variable and again no significance ($p>0.05$) was achieved for HR, VO_2, SBP, or RPP. Once again, it should be noted as before that there was a trend for the slopes of these variables to decrease after 4 wk of CPAP therapy. The slope for RPE did significantly decrease ($p=0.02$) after 4 wk of CPAP therapy.

Subjective improvements in sleep were also documented. Through the use of the Pittsburgh Sleep Quality Index subjects reported an average improvement in sleep quality of 4.2 units (52.5%). Health related quality of life was also improved after 4 wk of CPAP therapy. Additionally subjects were given a questionnaire regarding physical activity levels. These values did not change after 4 wk of CPAP therapy. All data for the questionnaires can be seen in Table 3.

Discussion: These results demonstrate that objective measurements of exercise tolerance do not significantly change after 4 wk of CPAP therapy, yet subjective assessments of well-being and performance do change significantly. The lack of significant change in physiological parameters during exercise is in agreement with previous research (20).

The authors found that cardiorespiratory parameters did not change significantly in six patients treated with CPAP therapy for 7 consecutive days. The only significant change they found occurred in maximal oxygen consumption (VO_2). Since we did not perform a maximal exercise test no comparisons in VO_2 values could be made with this study. Conversely, one study has demonstrated an improvement in physiological measures during submaximal exercise after CPAP therapy (10). They reported responses for 30 severe OSA patients. It was noted that there was a significantly ($p<0.001$) decreased heart rate ratio 100 W/rest after 2 wk of CPAP therapy (10). Systolic and diastolic blood pressures did not change significantly at 100 W/rest. There are several possible reasons for the discrepancy in significant changes in comparing our study with the aforementioned study. In their abstract, there was no definition for classifying severe OSA. Another possible reason for the discrepancy in systolic blood pressure and heart rate measurements between their study and ours may be that they analyzed steady state exercise stress testing and we performed a ramping exercise. Finally, it is not listed how they performed the exercise test. Our mode of exercise was on an electronic stationary bicycle.

A subjective feeling of increased exercise tolerance was significant after 4 wk of CPAP therapy in our study. These results are in agreement with the results published by Konermann et. al. (10). The improvement in subjective ratings of exercise exertion may be a result of the improvement in sleep quality. Sleep quality, as measured by the PSQI, was improved after 4 wk of CPAP therapy. It is expected that if OSA can be reversed by CPAP and the patient attains an improvement in sleep quality then they will also report an improvement in exercise exertion.

The results from this study also point to areas that need to be further examined. There is an extremely limited amount of research on the effects of CPAP on exercise tolerance in OSA. Increased interest and research is needed in this particular area to better understand the overall effects of CPAP. Previous research has examined the effect of CPAP therapy on resting blood pressures and shown an improvement in these values (11,13,19). Additional research has been done on sympathetic stimulation in OSA. This has been completed since it is suggested that the abnormally high blood pressures in OSA

are the result of an increase in sympathetic stimulation. Again, it has been demonstrated that CPAP can decrease sympathetic stimulation in OSA (21,22).

Research needs to be completed examining exercise tolerance in OSA for several reasons. First, instrumental activities of daily living (IADL's) require mild to moderate physical exertion. The energy cost of these activities ranges from 4-6 METS. Performing various activities such as walking at the mall, carrying groceries, or performing yardwork, may be decreased in OSA patients after CPAP therapy. If this can be accomplished through CPAP therapy then those afflicted with OSA will be able to be more productive in life. Along with the subjective improvements in tolerance to IADL's those with OSA may spontaneously uptake exercise. This exercise may be as simple as performing more yardwork or even joining a regular exercise program. This would be beneficial as exercise decreases the risk of cancer, cardiovascular disorders, and improves quality of life.

Additional research should be done to examine the long-term effects of CPAP and compliance rates. One area that should be examined is a possible dose response relationship between exercise performance and the average hours of use/night of CPAP. Those who do not comply with CPAP therapy would not be expected to perform as well during an exercise test. Another suggestion for future research is the effect of a combination of CPAP therapy and a regular exercise program versus CPAP therapy alone. Again, it may be shown that exercise is beneficial in this population and further improve physiological parameters in combination with CPAP therapy. Yet another possible study which could be performed would be the effect of the severity of OSA on physiological responses to exercise after CPAP therapy. It might be that those with more severe OSA, as indicated by a higher RDI, would show a greater improvement in physiological responses after CPAP therapy. A final area that needs to be examined is the physiological adaptation that is occurring in these subjects after CPAP therapy. It is not known if there is a central adaptation or a peripheral adaptation after CPAP therapy which allows these subjects to improve in exercise performance.

The results from this study demonstrate that objective, physiological measurements during exercise show an improvement after short-term CPAP therapy in

OSA patients. Although the improvement in physiological measures did not attain significance they did approach significance and showed a trend for an improvement in exercise performance. It was further demonstrated that subjective feelings during exercise improve after therapy. This may be attributed to the improved sleep quality.

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

Physical measures	Mean	S.D.	Range
Age (yr)	56	16.1	37-74
Weight (kg)	92.6	7.2	84-102
BMI (kg/m^2)	29.9	2.9	26-33
Clinical measures			
RDI	60.7	19.1	39-90
Time in bed (min)	342.7	40.2	263-368
Total sleep time (min)	267.5	34.9	236-333
Awake (min)	92.0	34.6	24-116
Stage 1 (min)	35.9	19.4	16-69
Stage 2 (min)	173.7	27.6	142-222
Slow wave sleep (min)	25.8	20.9	8-64
REM (min)	32.3	23.0	0-60
Baseline SaO_2	60.7	1.5	92-95
Lowest SaO_2	93.8	6.1	67-84
% of time SaO_2<80%	32.6	22.0	9-71

Table 2: Exercise test results at 60% of apparent maximal functional capacity (N=5)

Cardiovascular measures	Pre-nCPAP*	Post-	p-value
Heart rate (b/min)	133	125	p<0.10
	8.8	9.1	
Systolic blood pressure (mmHg)	199	191	p>0.10
	15.8	10.8	
Rate pressure product (10^{-2})	260	238	p<0.10
	17.0	16.0	
Respiratory gas exchange			
VO_2 (L/min)	1.96	1.73	p>0.10
	0.46	0.18	
RER	1.03	0.97	p>0.10
	0.14	0.12	
V_E STPD (L/min)	58.8	47.9	p>0.10
	14.4	7.3	
Perceptual measure			
RPE (6-20)	17	14	p<0.05
	2.8	2.0	

*Values listed are means with standards deviations below each parameter.

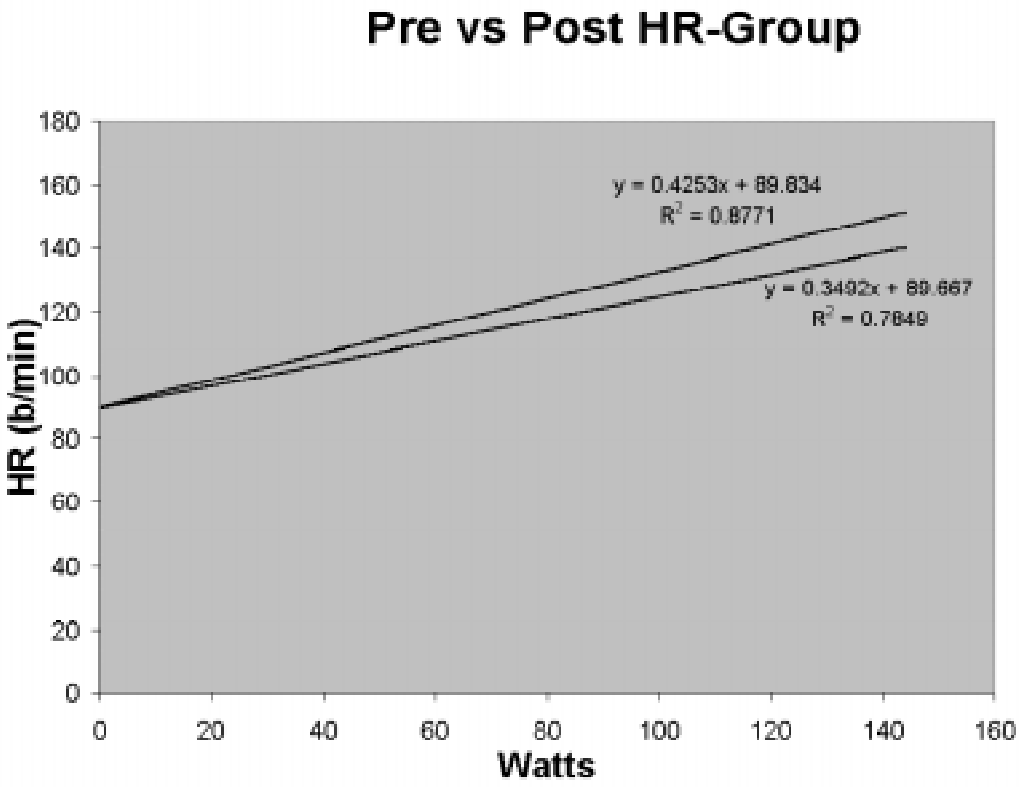

Figure 1: Comparison of change in HR in OSA before CPAP therapy and after 4 wk CPAP therapy at 60% of apparent maximal functional capacity (N=5)

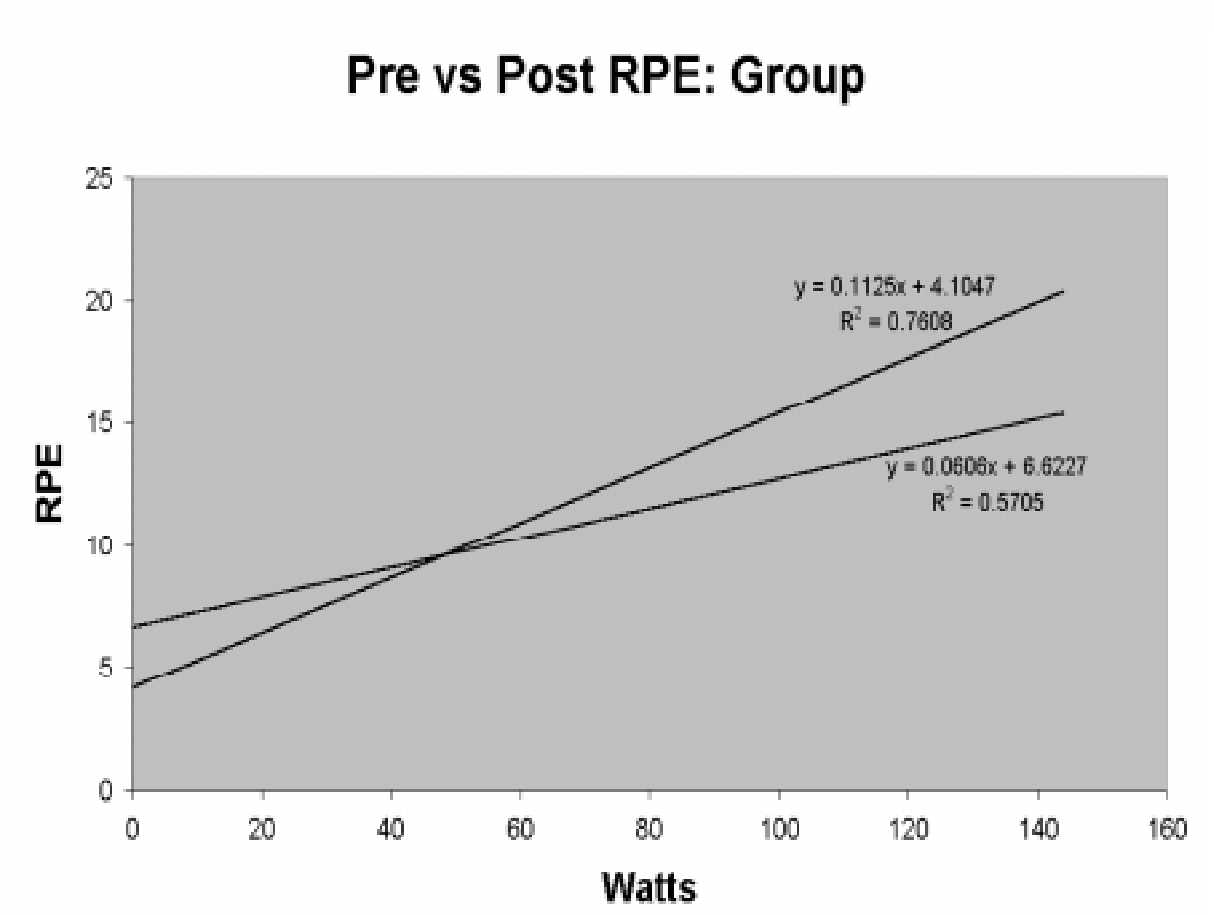

Figure 2: Comparison of change in RPE at 60% of apparent maximal functional capacity in OSA before and after CPAP therapy (N=5)

Table 3: Quality of life, physical activity history and sleep quality changes in OSA patients (N=5)

Health related quality of life	Pre-nCPAP	Post-nCPAP	Change in score
Health perception	64	82.6	18.4
Physical function	85	91	6
Role-physical	85	100	15
Role-emotional	93.3	100	6.7
Social function	82.5	86	3.5
Mental health	74.4	75.2	0.8
Bodily pain	78.5	89.5	11
Energy/fatigue	49	79.5	30.5
PSQI			
Global	8.0	4.8	3.2
Baecke			
Work index	2.6	2.6	0
Sports index	2.1	2.1	0
Non-sports index	2.3	2.4	0.1
Total index	6.9	7.1	0.2

CHAPTER 4

SUMMARY OF RESULTS AND RECOMMENDATIONS

Results: Five male subjects with mean values for RDI=60.7±19.1 and BMI=29.9±2.9 participated in this study. Additional patient demographics and clinical measurements, including mean values and standard deviations can be seen in Tables 1 and 2. Cardiovascular, respiratory and perceptual measures were analyzed at 60% of each individual's apparent maximal functional capacity. Dependent t-tests on heart rate at 60% of the subject's maximum revealed no significant change ($p=0.07$) after 4 wk of CPAP therapy. There was also no significant change ($p>0.05$) in the VO_2 at 60% of the subject's maximum after 4 wk of CPAP therapy. Additionally, there was no significant change ($p>0.05$) in RPP or SBP at 60% of the subject's apparent maximal level after 4 wk of CPAP therapy. Although statistical significance was not achieved in the 4 previously listed physiological parameters it should be noted that there was a trend for those values to decrease. The HR decreased an average of 8.0 b/min (6.0%) at 60% after 4 wk of CPAP therapy. The VO_2 decreased an average of 0.23 L/min (11.7%) at 60% and the SBP and RPP also decreased an average of 8.0 mmHg (4.0%) and 22.4 units (8.6%), respectively. Significance was attained in RPE at 60% of the subject's maximum after 4 wk of CPAP therapy ($p<0.05$). The mean RPE decreased 3.0 units on average. Additional statistical analysis was done on the slopes of the regression lines for each variable and again no significance ($p>0.05$) was achieved for HR, VO_2, SBP, or RPP. Once again, it should be noted as before that there was a trend for the slopes of these variables to decrease after 4 wk of CPAP therapy. The slope for RPE did significantly decrease ($p=0.02$) after 4 wk of CPAP therapy.

Subjective improvements in sleep were also documented. Through the use of the Pittsburgh Sleep Quality Index subjects reported an average improvement in sleep quality of 3.2 units (40%). Health related quality of life was also improved after 4 wk of CPAP therapy as measured via questionnaire. Additionally, subjects were given a questionnaire regarding physical activity levels. These values did not change after 4 wk of CPAP therapy. All data for the questionnaires can be seen in Tables 3, 4, 5.

RECOMMENDATIONS

The results from this study also point to areas that need to be further examined. There is an extremely limited amount of research on the effects of CPAP on exercise tolerance in OSA. Increased interest and research is needed in this particular area to better understand the overall effects of CPAP. Previous research has examined the effect of CPAP therapy on resting blood pressures and shown an improvement in these values (22, 26, 35). Additionally, there has been research examining sympathetic stimulation in OSA. This has been completed since it is suggested that the abnormally high blood pressures in OSA are the result of an increase in sympathetic stimulation. Again, it has been demonstrated that CPAP can decrease sympathetic stimulation in OSA (37, 38).

Research needs to be completed examining exercise tolerance in OSA for several reasons. First, instrumental activities of daily living (IADL's) require mild to moderate physical exertion. The energy cost of performing these various activities such as walking at the mall, carrying groceries, or performing yardwork, may be decreased in OSA patients after CPAP therapy. If this can be accomplished through CPAP therapy then those afflicted with OSA will be able to be more productive in life. Along with the subjective improvements in tolerance to IADL's those with OSA may spontaneously uptake exercise. This exercise may be as simple as performing more yardwork or even joining a regular exercise program. This would be beneficial as exercise decreases the risk of cancer, cardiovascular disorders, and improves quality of life.

Additional research should be done to examine the long-term effects of CPAP and compliance rates. One area that should be examined is a possible dose response relationship between exercise performance and the average hours of use/night of CPAP. Those who do not comply with CPAP therapy would not be expected to perform as well during an exercise test. Another suggestion for future research is the effect of a combination of CPAP therapy and a regular exercise program versus CPAP therapy alone.

A final recommendation, which can be offered for future research, is dealing with CPAP compliance and the degree of OSA. Research should examine the effect of disease

severity in relation to improvements after CPAP therapy. It may be seen that those with a higher RDI respond more dramatically to CPAP therapy.

The results from this study demonstrate that subjective and objective physiological measurements during exercise show an improvement after short-term CPAP therapy in OSA patients. Although the improvement in physiological measures did not attain significance they did approach significance and showed a trend for an improvement in exercise performance. It was further demonstrated that subjective feelings during exercise significantly improve after therapy. This may be attributed to an improvement in sleep quality.

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APPENDIX A: METHODOLOGY

subjects: Five adult men and women were recruited from the community to participate in this study through a selective process. Approximately 30 people referred to the Sleep Disorders Center of Southwest Virginia were screened and asked to voluntarily participate in this study. These subjects 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, orthopedic or musculoskeletal disabilities which prevented exercise, or a history of regular participation in moderate physical activity.

procedures: All prospective candidates who 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 detailed the procedures of the study. The investigators then verbally confirmed the subjects understanding of the study at which time the participant signed the informed consent. 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; Baecke questionnaire for assessment of physical activity levels; and the Health Related Quality of Life (HRQL) questionnaire 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, BMI, and exercise performance on a Medgraphics 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 w/min 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 exchange ratio >1.00 and attainment of the ventilatory threshold. The following steps determined the cutoff point for predicted heart rate. The first step was subtracting the subject's age from 220 to determine the subject's age predicted maximum heart rate. Then, the subjects 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 one of the exercise test end points.

Exercise was monitored by at least two trained technicians and terminated in the event that adverse responses occur (clinical criteria of the American College of Sports Medicine and American Heart Association). During the exercise test, blood pressure was monitored and cross-validated every three minutes by 2 trained clinicians doing simultaneous auscultation. 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 (Appendix B). Also, during the exercise test, patients breathed through a mouthpiece which transmitted expired gases to a Sensormedics gas exchange system. This system analyzed breath by breath ventilatory measures while their nose was held shut by a noseclip. Expired gases were collected and analyzed by the system. The collection of expired gases permitted a more accepted and accurate determination of workloads.

Upon completion of the initial, diagnostic PSG a trained PSG technician at the Sleep Center scored the subject's results. Each subject was then either diagnosed with OSA or not by a physician 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 CPAP therapy were asked to return to the Sleep Center in four weeks from initiation of CPAP treatment at home. Subjects were then given a second submaximal exercise test at the same time in the morning utilizing the same protocol as with the first exercise test. The same questionnaires were also given to the participants for completion and were completed prior to the exercise test.

APPENDIX B: 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 _____

What is your usage of the following (during the past month):

	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)	_____

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

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 0.04-0.17-0.42-0.67-0.92)

   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 0.5-1.5-2.5-3.5-4.5)
   -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)

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

	pre HR	post HR	pre SBP	post SBP	pre RPP	post RPP	Pre VO2	post VO2	pre VE	post VE
#1	88	87	144	138	126.7	120	0.465	0.648	15.4	19.6
#2	88	99	118	138	103.8	136.6	0.217	0.795	7.5	26.2
#3	91	83	150	132	136.5	109.6	0.686	0.08	20.5	4.6
#4	79	84	130	122	102.7	102.5	0.337	0.207	9	6.2
#5	83	96	136	128	112.9	122.9	0.418	0.347	11.8	10.3
p-value		0.360		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	6.0	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:

	pre-HR	post-HR	pre-SBP	post-SBP	pre-RPE	post-RPE	pre-RPP	post-RPP
#1	145	137	186	189	19	16	270	256
#2	123	119	215	185	21	15	252	222
#3	126	119	208	209	15	15	267	250
#4	137	117	206	189	15	13	278	221
#5	133	132	178	181	15	11	235	241
p-value		0.069		0.296		0.040		0.097
mean	132.8	124.8	198.6	190.6	17	14	260.4	238
SD	8.8	9.1	15.8	10.8	2.8	2	17.0	16.0
C.I.	7.7	8.0	13.8	9.5	2.5	1.8	14.9	14.0

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:

	pre-VO2	post-VO2	pre-RER	post-RER	pre-VE	post-VE
#1	2.66	1.98	1.1	1.1	81.4	44.5
#2	1.41	1.5	1.1	1	51.4	48.1
#3	1.94	1.79	0.91	1	64.3	59.8
#4	2.03	1.78	0.86	0.78	52.1	40.4
#5	1.77	1.62	1.2	0.95	44.9	46.5
p-value		0.145		0.295		0.184
mean	1.96	1.73	1.03	0.97	58.82	47.86
SD	0.46	0.18	0.14	0.12	14.44	7.27
C.I.	0.40	0.16	0.13	0.10	12.66	6.37

VE & VO2: L/min

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

	pre-HR	post-HR	pre-SBP	post-SBP	pre-RPE	post-RPE	pre-RPP	post-RPP
#1	0.48	0.36	0.33	0.41	0.08	0.07	1.2	1.09
#2	0.3	0.33	1.09	0.5	0.16	0.09	1.61	1.06
#3	0.36	0.5	0.56	0.93	0.11	0.06	1.45	1.81
#4	0.52	0.29	0.69	0.54	0.09	0.06	1.71	1.08
#5	0.43	0.28	0.41	0.52	0.09	0.06	1.17	1.13
p-value		0.377		0.834		0.020		0.344
mean	0.42	0.35	0.62	0.58	0.11	0.07	1.43	1.23
SD	0.09	0.09	0.30	0.20	0.03	0.01	0.24	0.32
C.I.	0.08	0.08	0.26	0.18	0.03	0.01	0.21	0.28

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

Values for the slope from the regression equation for ventilatory measures

	pre-VO2	post-VO2	pre-RER	post-RER	pre-VE	Post-VE
#1	0.015	0.01	0.002	0.002	0.53	0.19
#2	0.01	0.01	0.004	0.0003	0.43	0.31
#3	0.013	0.015	0.0009	0.0006	0.39	0.51
#4	0.013	0.012	0.001	0.0004	0.37	0.23
#5	0.012	0.009	0.003	0.003	0.29	0.25
p-value		0.311		0.261		0.236
mean	0.012	0.011	0.002	0.001	0.402	0.298
SD	0.002	0.002	0.001	0.001	0.088	0.126
C.I.	0.002	0.002	0.001	0.001	0.077	0.111

VE & VO2: L/min

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

	pre-HR	post-HR	pre-SBP	post-SBP	pre-RPE	post-RPE	pre-RPP	Post-RPP
#1	81	89	143	134	9	7	111	112
#2	96	89	117	140	7	7	106	126
#3	96	78	162	133	6	10	148	101
#4	85	89	138	136	6	7	111	116
#5	89	103	135	128	5	5	114	124
p-value		0.974		0.595		0.573		0.859
mean	89.4	89.6	139	134.2	6.6	7.2	118	115.8
SD	6.7	8.9	16.2	4.4	1.5	1.8	17.0	10.1
C.I.	5.8	7.8	14.2	3.8	1.3	1.6	14.9	8.8

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

	pre-VO2	post-VO2	pre-RER	post-RER	pre-VE	post-VE
#1	0.74	0.62	0.805	0.915	12.7	19.1
#2	0.47	0.58	0.772	0.969	12.4	20.2
#3	0.86	0.53	0.984	0.954	32.1	18.3
#4	0.72	0.63	0.766	0.737	15.6	18
#5	0.59	0.72	0.877	0.92	14.7	20.2
p-value		0.516		0.250		0.697
mean	0.68	0.62	0.84	0.90	17.50	19.16
SD	0.15	0.07	0.09	0.09	8.27	1.03
C.I.	0.13	0.06	0.08	0.08	7.25	0.90

VE & VO2: L/min

APPENDIX E: RAW DATA

Table 1: OSA patient characteristics

Subject	Age (yr)	Weight (kg)	BMI
#1	37	83.6	25.8
#2	70	87.3	28.5
#3	74	95.9	30.3
#4	45	94.6	32.0
#5	52	101.8	33.2

Table 2: OSA patient clinical characteristics

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 percentages.

Table 3: Changes in health related quality of life questionnaire after CPAP therapy

Subject	HP	PF	RP	RE	SF	MH	BP	E/F
#1	57/80	100/100	100/100	100/100	88/70	60/48	80/80	30/49
#2	77/97	90/100	100/100	100/100	88/90	88/88	100/100	55/90
#3	57/72	60/65	100/100	100/100	100/90	96/84	68/80	50/89
#4	62/67	75/90	25/100	67/100	38/90	40/76	55/88	45/80
#5	67/97	100/100	100/100	100/100	100/90	88/80	90/100	65/90

Values listed are pre/post CPAP therapy

HP=health perception, PF=physical function, RP=role-physical, RE=role-emotional, SF=social function, MH=mental health, BP=bodily pain, E/F=energy/fatigue

Table 4: Changes in the Pittsburgh Sleep Quality Index questionnaire after CPAP therapy

Subject	Pre-CPAP	Post-CPAP
#1	8	9
#2	10	4
#3	4	2
#4	13	5
#5	5	4

Table 5: Changes in the Baecke physical activity questionnaire after CPAP therapy

Subject	Work index	Sports index	Non-sport leisure	Total
#1	3.3/3.0	2.3/2.0	1.8/1.5	7.3/6.5
#2	2.1/2.3	2.0/3.0	2.3/2.5	6.4/7.7
#3	2.1/2.6	1.3/1.3	1.8/1.5	5.1/5.4
#4	3.0/2.5	2.0/1.8	2.3/3.5	7.3/7.8
#5	2.4/2.5	3.0/2.7	3.3/2.8	8.6/7.9

Values listed are pre/post CPAP therapy

Table 6: 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	0.48	0.36	81	89	.96	.98	88	87	157	145
#2	0.30	0.33	96	89	.48	.93	88	99	114	128
#3	0.36	0.50	96	78	.81	.99	91	83	129	125
#4	0.52	0.29	85	89	.98	.96	79	84	139	123
#5	0.43	0.28	89	103	.99	.92	83	96	132	136

Table 7: 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 8: 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 9: 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 10: 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 11: 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

Table 12: RER 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 RER*	*Post rest RER*	*Pre-pk RER*	*Post-pk RER*
#1	.002	.002	0.81	0.92	.82	.95	.99	.94	1.11	1.11
#2	.004	.0003	0.77	0.97	.82	.07	.79	.89	.99	1.0
#3	.0009	.0006	0.98	0.95	.13	.10	.77	1.01	.92	1.05
#4	.001	.0004	0.77	0.74	.56	.21	.75	.79	1.4	.81
#5	.003	.003	0.88	0.92	.13	.10	.86	.92	.85	.96

APPENDIX F: DETAILED RESULTS

The physiological responses to exercise were analyzed at 60% of each individual's apparent maximal functional capacity. This reference point was used for analyzing the data since this is the lower threshold that is used for common exercise prescription purposes. In all of the subjects the heart rate at 60% of apparent maximal functional capacity decreased. The largest decrease was 20 beats/min while the smallest decrease from the first test was 1 beat/min. Dependent t-tests revealed a p-value that approached significance at 0.069. This data can be seen in Figure 1. The values for SBP did not show the same trends as HR data. In 2 of the subjects there was a decrease in the SBP while in 3 of the subjects there was an increase in SBP at 60% of the individual's apparent maximal functional capacity. The largest decrease was 30 mmHg while the largest increase in SBP was 3 mmHg as noted in 2 subjects. Dependent t-tests revealed a p-value of 0.296. This can be seen in Figure 2. The values for the rate pressure product showed the same trends as the p-value approached significance at 0.097. In 4 of the 5 subjects there was a decrease in the RPP while in 1 subject there was an increase in the RPP at 60% of the individuals apparent maximal functional capacity. The data may be seen in Figure 3.

Respiratory variables did not reveal any significant changes or trends. In 4 of the 5 subjects there was a decrease in the VO_2 at 60% of the apparent maximal functional capacity while in 1 subject there was an increase in the VO_2. Dependent t-tests revealed a p-value of 0.145. The respiratory parameters of RER and V_E were much the same as VO_2. The p-values for these 2 variables were 0.295 and 0.184, respectively. The RER decreased at 60% of apparent maximal functional capacity in 4 of the 5 subjects, as did the V_E.

A subjective feeling during exercise was the only measured variable which attained significance. In 4 of the 5 subjects there was an improvement in rating of perceived exertion while in 1 subject it remained unchanged after CPAP therapy. Dependent t-tests revealed a p-value of 0.040. This data can be seen in Figure 4.

The values for the slopes taken from the regression equations were also analyzed via dependent t-tests. Again the only measured variable which attained significance was RPE. The p-value for this parameter was 0.020. For all other variables the lowest p-

value was 0.236. There was also no trend in these other variables upon examining the slopes.

APPENDIX G: FIGURES

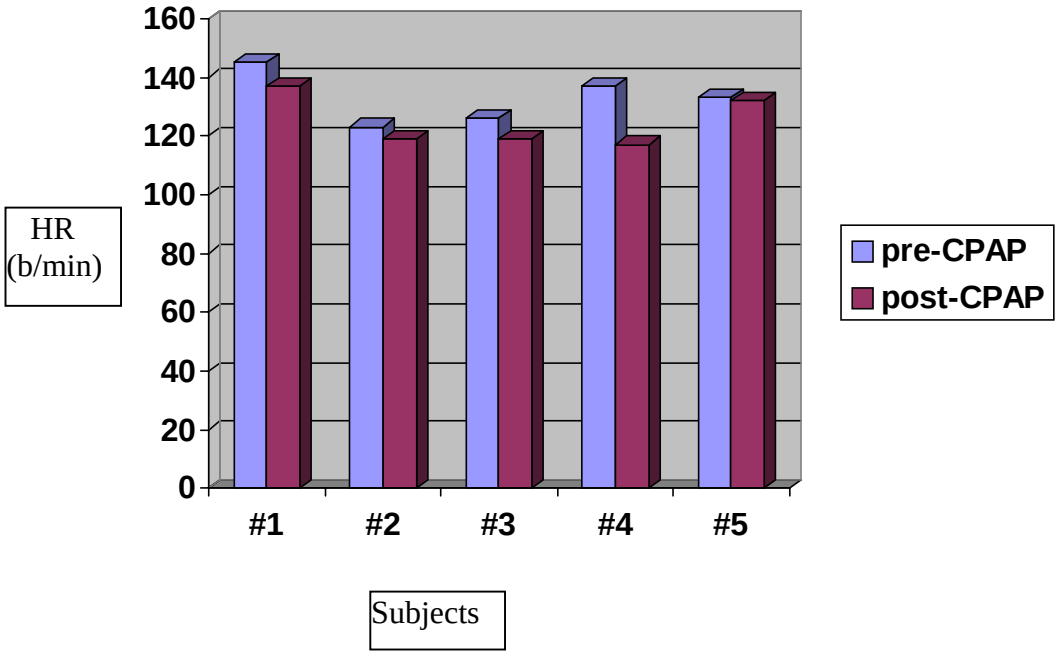

Figure 1: Change in HR for individuals at 60% of apparent maximal functional capacity

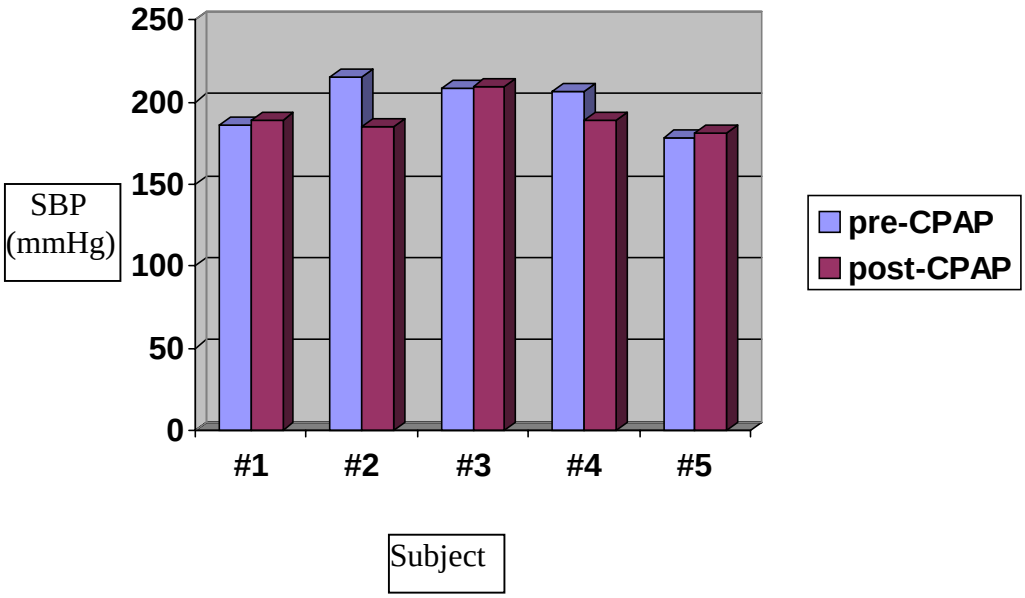

Figure 2: Change in SBP at 60% of apparent maximal functional capacity

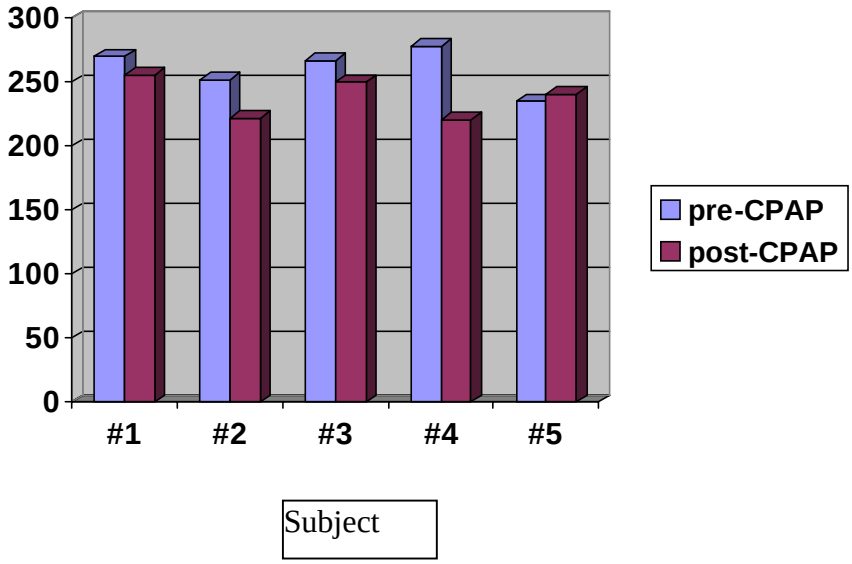

Figure 3: Change in RPP at 60% of apparent maximal functional capacity

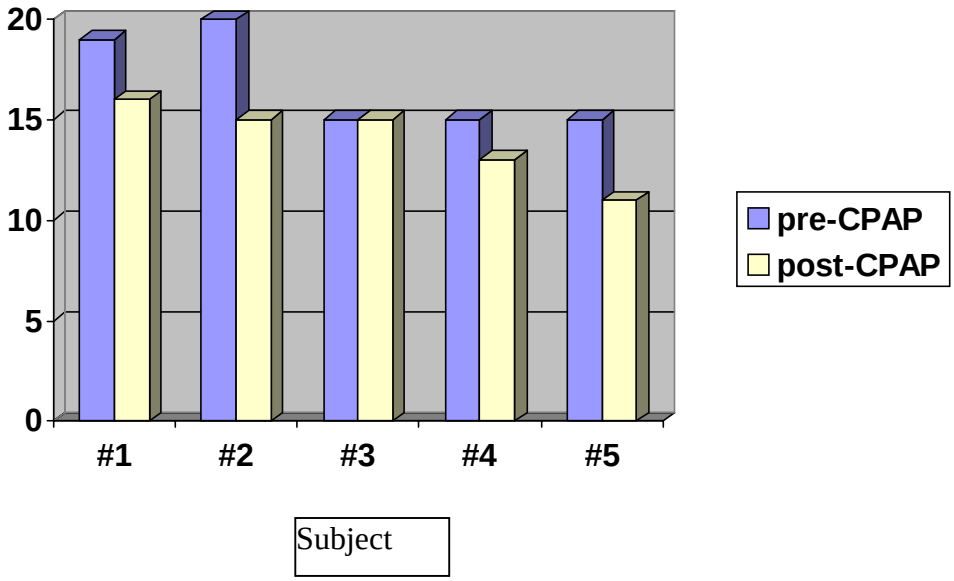

Figure 4: Change in RPE at 60% of apparent maximal functional capacity

Donnie Edward Shifflett, Jr.

Home Address
653 Valley Street
Lewistown, PA 17044
717-248-7961

Current Address
300 McDonald St. Apt 32B
Blacksburg, VA 24060
540-951-4935

Objective Obtaining a position in the field of clinical exercise physiology which requires the application of basic and advanced physiological principals in cardiac rehabilitation populations

Education Virginia Polytechnic Institute and State University (Virginia Tech)
Master of Science (thesis option), Clinical Exercise Physiology, May 1998

Lock Haven University of Pennsylvania
Bachelor of Science, Health Science, May 1996

American Heart Association BCLS certificate

American Heart Association ACLS certificate

Experience New River Community College, Dublin, VA
Adjunct Faculty member, 3/98-current
- taught fitness and wellness classes in the Health and Physical Education Department

Cardiac Therapy and Intervention Center of Virginia Tech, Blacksburg, VA
Graduate student leader, 8/96-current
- monitored and led exercise sessions during swimming, walking, biking, arm ergometry, and rowing for 80 participants, 3 times/week
- performed GXT's, ECG monitoring, patient monitoring, blood pressure assessment, case studies, PFT's and exercise prescriptions

Virginia Polytechnic Institute and State University, Blacksburg, VA
Graduate Assistant, College of Human Resources and Education 11/96-current
- assisted Dianne R. Yardley, Associate Dean-Business Office, College of Human Resources and Education with various administrativeduties
- coordinated and implemented various functions for the College including the "kick off the school year" social for all faculty and staff of the College and the annual "Excellence in Education Conference."

Geisinger Medical Group-Clinton County, Lock Haven, PA
Field Experience, Fall 1995

- shadowed and assisted Jon E. Popovich, M.D., internal medicine, with inpatients and outpatients
- observed and gained a further understanding of stress testing, interpreting lab results, echocardiograms, and prescribing medications
- received credit with honors

Lock Haven Hospital-Cardiopulmonary Dep't, Lock Haven, PA
Field Experience, Summer 1995

- observed PFT's, stress testing, arterial blood gas analysis, and echocardiograms
- performed small volume nebulizer treatments, EKG's, and ventilator monitoring in the 240 bed acute and extended care facility
- received credit with honors

Research

Exercise Performance in Obstructive Sleep Apnea Patients

- committee chairman: William G. Herbert, Ph.D., FACSM
- examined the physiological responses in OSA patients to submaximal, aerobic, exercise after one night of CPAP therapy and after 4 weeks of CPAP therapy in compliant and non-compliant CPAP patients
- received $3,500 grant from ResMed Corp (San Diego, CA)

Affiliations/ Honors

Outstanding first year graduate student of the Cardiac Therapy and Intervention Center at Virginia Tech

ACSM graduate student member

References Available Upon Request