CHAPTER 1

Introduction

Obstructive sleep apnea (OSA) is estimated to affect 2 to 4 percent of the adult population (Young T 1993, Skomro and Kryger 1999). However, an estimated 80 to 90 percent of adults with moderate to severe OSA may be clinically undiagnosed. Annual medical costs associated with undiagnosed sleep apnea have been reported to be double that of age and gender matched controls (Kapur, Blough et al. 1999). Identification of those at risk and their subsequent diagnosis is, obviously, of great concern to clinicians. Risk factors associated with development of the disorder have helped physicians to understand the clinical presentation of the OSA patient. Middle-aged, males with upper torso obesity and cranio-facial abnormalities who snore loudly are at highest risk for developing OSA. Furthermore, the prevalence of OSA is relatively high in those with co-morbidities of hypertension (50%), myocardial infarction, stroke, neuropsychiatric problems, coronary artery disease (20%), congestive heart failure, ventricular arrhythmias (13%), angina, and obesity (Brooks D. 1997,Hla, K.M. 1994, Hall and Bradley 1995, Naughton M. 1998, Schafer H. 1997). Of these co-morbidities, the extent to which OSA may contribute to or be a consequence of cardiovascular pathology is at the forefront of clinical and diagnostic research as well as subsequent patient management. Easier, less costly, but accurate screening and diagnostic techniques are needed in order to understand this complex disorder

The current gold standard for diagnosing OSA is polysomnography (PSG)(AHCPR, 1998). Patients are required to sleep and are observed overnight in a clinically based sleep laboratory under the supervision of a board certified sleep

physician. Electroencephalography (EEG), electroculography (EOG), and electromyography (EMG) are the standard assessment tools used during the PSG for sleep staging by monitoring brain wave activity, eye movement, and muscular activity, respectively. Additional assessment methods are used in order to identify those individuals who are suspected of sleep disordered breathing including nasal/oral airflow, abdominal/chest wall movement (respiratory effort), and blood oxygen saturation levels. The primary marker used to diagnose OSA is the respiratory disturbance index (RDI), equivalent to the apnea/hypopnea index (AHI) used by some authors (McNicholas, 1997). The RDI is defined as the hourly average number of apneas (complete cessation in airflow) and hypopneas (~50% reduction in airflow) calculated over each hour of sleep. An average of five episodes per hour is classified as mild OSA, 20 – 39 is considered moderate OSA, and ≥ 40 is severe. Respiratory disturbance indices greater than 100 are not uncommon. Other markers include the amount of time during sleep that oxygen saturation levels are below 89 percent saturation (% O_2 desat), rapid eye movement sleep (REM), and sleep efficiency (time in bed/ time spent in stage 2, 3, or 4 sleep). In most cases, appropriate treatment is nasal continuous positive airway pressure (nCPAP), which provides a non-invasive means of maintaining an open airway during sleep. The patient must be observed while using nCPAP during a PSG study. Often both diagnosis of OSA can be made and nCPAP treatment started in the same night.

The development of newer technologies and methods for assessing OSA is of critical interest today for clinicians and those who fund health care. In addition to PSG, the use of portable and home monitoring devices as diagnostic tools have increased over the past several years in an effort to increase accessibility and decrease costs. The

American Sleep Disorders Association has published practice parameters regarding portable devices (Association 1994; Association 1994). Sensitivity for these devices ranges from 33 to 100 percent depending on the level monitoring of respiratory and sleep variables. Similarly, specificity ranges from 30 to 93 percent (AHCPR, 1998). The largest problem with using portable devices including portable channel devices and oximetry lies in the identification of milder as opposed to more severe cases of OSA. More study is needed to determine which recording systems may be the most useful for accomplishing this goal. It may be that additional markers of OSA taken during routine examination or functional measures of daytime physiological performance would increase the sensitivity and specificity of portable monitoring devices. Functional measures of physiological performance would also aid in determining which PSG markers best demarcate the severity of OSA.

Clinicians have attempted to determine methods that may be used to establish those clinical diagnostic criteria that are most important in characterizing clinical presentation and disease severity of the OSA patient. Controversy exists among clinicians as to an optimal set of criteria primarily due to the varying effects OSA has on day time functioning (Epstein LJ 1998; Jenkinson C 1998; Research 1998; Gottlieb, Whitney et al. 1999, Min, 1977, Sajkov, 1999). Obstructive sleep apnea is linked to excessive daytime somnolence (EDS), psychosocial dysfunction and impaired neurocognitive performance, and abnormal physiological daytime functioning. Daytime cardiovascular and hemodynamic states that may be used to describe the severity of the disorder, including arrythmias, myocardial infarction, hypertension, ischemic heart disease, and congestive heart failure, have not been firmly established as being causally linked to OSA (Weiss

JW, 1999). Given closely related risk factors associated with all of these disorders, it is sometimes difficult to control for confounding variables including male gender, age, trunk obesity, and inactivity. Moreover, physiological states are most often studied only under resting conditions. In general, the best picture of daytime cardiorespiratory and hemodynamic functioning is most often revealed under conditions of physiological stress, specifically exercise. Methods to investigate daytime cardiovascular function of OSA under acute exercise stress are limited.

Considerable potential exists to investigate the extent of OSA's effect on cardiovascular function during exercise via several causal theories. Etiological theories linking OSA to hypertension, ischemic heart disease, and congestive heart failure include the following; (1) increased sympathetic drive associated with apnea and desaturation that may spill over to daytime functioning (Narkiewicz and Somers 1997;Brooks D 1997; Silverberg and Oksenberg 1997; Narkiewicz K 1998), (2) attenuated endothelium-dependent vascular relaxation (Carlson, Rangemark, *et al*. 1996, Hedner, 1996; Saarelainen, Seppala et al. 1997) (3) increased peripheral vascular resistance (Remsburg, Launois et al. 1999; Schnall, Shlitner et al. 1999), (4) exaggerated negative intrathoracic pressure, and (5) decreased chemosensitivity to carbon dioxide (Hall and Bradley, 1995). With regards to exercise testing, obstructive sleep apnea patients show evidence of reduced functional capacity compared to their age and gender matched controls (Aguillard, Riedel *et al*., 1998). Cardiorespiratory and hemodynamic investigations during exercise have determined that OSA patients exhibit systemic and pulmonary hypertension (Hawrylkiewicz, Cieslicki et al., 1996, Schafer, Ehlenz et al. 1999), increased left ventricular wall stress (Levy, Guilleminault et al. 1991), low fibrinolytic

activity (Rangemark, Hedner et al. 1995), and abnormal ventilatory compensation (Bittencourt, Moura et al. 1998) (Greenberg and Scharf 1993). Additionally, arterial blood gas values have also been used during exercise to differentiate OSA from other types of sleep apnea, including central sleep apnea and obesity-hypoventilation syndrome (Schonhofer, Rosenbluh et al. 1997; Schafer, Ewig et al. 1998). Of these investigations, the extent to which the severity OSA may effect or be detected during standard exercise evaluations is limited.

Clinically relevant PSG markers for disease severity that have been linked to functional measures during exercise include percentage of sleep time spent in REM sleep, RDI scores, and abnormal blood gas levels carbon dioxide and oxygen. Aguillard *et al* (1998) investigated daytime functioning in 32 newly diagnosed OSA patients. Patients with higher amounts of REM sleep tended to reach higher percent-predicted VO_2 max values as determined by cycle ergometer test ($R^2 = 0.19$). In addition, a higher REM percentage (percentage of sleep spent in REM sleep), longer REM latency (time to onset of REM sleep), smaller awake percentage, and shorter total sleep time were significantly correlated with percent of predicted maximum HR achieved ($R^2 = 0.70$). Neither VO_2 max or HR achieved were significantly correlated with RDI. Tremel *et al* (1999) recently completed a prospective study investigating the association of central sleep apnea and OSA to daytime markers of disease severity in 34 congestive heart failure patients. In this investigation, peak exercise oxygen consumption was negatively correlated with apnea/hypopnea index (equivalent to RDI) ($r = -0.73$). The extent to which hemodynamic function during exercise may have been to linked to PSG parameters was not reported by these authors.

With the exception of excessive daytime somnolence (EDS) and impaired neurocognitive performance, little is understood about the daytime, dynamic physiological functioning of the OSA patient. However, considerable potential exists to investigate the extent of OSA's effect on cardiovascular function during exercise. Investigations of daytime functional parameters obtained during exercise would help clinicians in understanding the complex pathophysiological state of the OSA patient as well as determining which diagnostic criteria may be more sensitive indicators of disease severity. The present study has provided a methodological means to understand hemodynamic functioning of OSA patients. Moreover, from the results of this study, BMI and exercise hemodynamic measures taken during a standard GXT, including MAP and SV, may be sensitive indicators of hypoxic PSG markers of OSA severity.

Statement of the Problem

The purpose of this investigation was to describe the extent to which graded exercise testing may reveal abnormalities of hemodynamic response in OSA patients, particularly with respect to cardiac output, blood pressure, and total peripheral resistance.

Significance of the Study

While current prevalence estimates for OSA range from 2 – 4% for the general population, clinical presentation and identification of the undiagnosed patient remains an issue (Redline and Strohl, 1998). An estimated 93% of women and 82% of men in the general population have not been clinically diagnosed (Young T, 1997). In a recent report by the Agency for Health Care Policy and Research (AHCPR), alternatives to costly PSG or additional, simple screening tools are needed in an effort to increase diagnostic

capabilities to a larger population base. Simpler screening tools would also allow for timely follow-up and evaluation of treatment including nasal continuous positive airway pressure (nCPAP) and oral surgery. For example, baseline screening and physical exam assessments could be used indefinitely to evaluate patient prognosis. Currently, determining an optimal combination of clinical diagnostic PSG criteria which best describes the severity of the disease is an issue for many clinicians. Given the high rate of cardiovascular morbidity associated with OSA (Weiss JW, 1999, Hall and Bradley, 1995), cardiopulmonary responses obtained during standard exercise testing would be a useful means of evaluating disease severity as well as treatment outcomes.

In addition, the mechanisms underlying the association between daytime hypertension and OSA are still Exercise testing could also be used in the context exercise prescription to promote safe and effective exercise training and to improve overall health outcomes. Very little is known about the chronic effects of exercise in OSA patients. Physical activity may be an effective adjunctive treatment for patients who have been successfully treated with CPAP or surgical interventions, but the potential effectiveness of this approach has not been investigated. In particular, a multiple intervention strategy involving nCPAP and exercise may facilitate restoration of normal cardiovascular regulation and retard further weight gain over time, both of which might further increases risks for recurrent OSA and cardiovascular morbidity (Weiss JW, 1999, Hall and Bradley, 1995). The literature regarding the functional improvements in OSA patients as assessed by maximal oxygen consumption are few and have focused on improvements primarily to due nCPAP treatment. Only one published study that evaluated effects of exercise training on symptoms and severity of OSA (Netzer N, 1997). These investigators

trained eleven patients 2 hr/session, two sessions/wk, for 6 months. They reported significant reductions in the respiratory disturbance index (RDI) by polysomnography (PSG) after training, but reported no effect on PSG indicators of sleep efficiency and blood oxygen saturation. Subjective ratings of patients quality of life after the 6 months were not reported by the authors. Clearly, additional lead-up investigations are warranted with respect to how the untreated OSA patient responds to exercise in contrast to those who have been treated.

Research Aims

(1): In order to establish reliability of hemodynamic measures to be used during exercise testing, a reliability study on the acetylene single-breath cardiac output (Qc) technique in 15 healthy subjects. This study (Chapter IIIa) was conducted in order to establish reliability of exercise Q_c and total peripheral resistance (TPR), these responses could be investigated acutely in the context of evaluating the relation of these measures to markers of disease in OSA patients.

(2): The second aim of this investigation was to profile cardiorespiratory and hemodynamic responses during graded exercise testing (GXT) in OSA patients in an effort to better understand relationships between these exercise variables and PSG markers of OSA severity. This aim will be included as Chapter IIIb. Cardiorespiratory and hemodynamic responses that will be evaluated include the following: peak oxygen consumption (VO_2pk), end-tidal carbon dioxide production ($P_{ET}CO_2$), end-tidal oxygen pressure ($P_{ET}O_2$), heart rate (HR), blood pressure (systolic = SBP and diastolic = DBP), rate pressure product (RPP), peripheral vascular resistance (TPR) and its derivatives including mean arterial pressure (MAP), cardiac output (Q_c),) in OSA patients. A globalt

biochemical marker of vascular function, 24 hour urinary nitric oxide metabolite production (nitrate/nitrite) was analyzed for each patient.

(3): Chapter IIIc was included in order to provide qualitative information concerning treatment, subjective sleep and daytime function, and physical activity levels of the OSA patients in this investigation and give insights into the special challenges and potential for doing trials involving nCPAP and physical exercise with OSA patients

Assumptions

1. Subjects accurately answered the medical/health history questionnaire and, in particular, correctly reported their current physical activity regimen prior to the study.
2. Subjects exhibited a maximal effort during all maximal exercise test protocols
3. Subjects complied with all pre-testing instructions.
4. The testing bicycle ergometer was accurately calibrated and maintained throughout the study period.
5. The SensorMedics metabolic cart accurately measured all cardiopulmonary variables.
6. The sample make-up (gender, age, clinical status) increased generalizability to gender, subjects of different age, and in OSA patients with comorbid conditions (i.e. cardiovascular and/or metabolic disorders).

Limitations

1. Due to the inability of a few subjects to complete the Qc measurements during incremental exercise testing, Qc measurements were not obtained for all individuals for all trials.
2. Due to equipment malfunction, it was necessary to estimate functional capacity based on workload in two subjects for baseline testing only.

3. Two patients were required to change medications through out the course of the study that was consistent with the patients standard medical management plan.
4. Baseline urine samples were not analyzed in four OSA subjects due to accidental thawing of samples.

Delimitation's

1. Subjects were volunteers who were referred to the Allergy and Sleep Disorder Center in Christiansburg for evaluation of a suspected sleeping disorder.
2. Subjects had not been involved in any cardiovascular training defined as (> 2 day/wk) for at least 6 months prior to the study.
3. Obstructive sleep apnea subjects could not have been previously diagnosed with congestive heart failure or moderate to severe chronic obstructive pulmonary disease or have any severe orthopedic limitations that would limit activity.

Definitions of Symbols and Terms

1. Apnea – Complete cessation of airflow for longer than 10 seconds as recorded during an overnight polysomnography (Redline and Strohl 1998).
2. Carbon dioxide output (VCO_2) - The amount of carbon dioxide exhaled from the body, usually expressed per unit time in milliliters or liters per min.
3. Cardiac output (Qc) - The flow of blood from the heart in a particular period, usually expressed as liters per minute. It can be defined as the product of the stroke volume per beat and the heart rate per minute. In addition, by the Fick equation, it can be defined as oxygen uptake divided by arterial-venous oxygen difference. Cardiac output was measured using the acetylene single-breath technique (Zenger M, 1993).

4. Continuous Positive Airway Pressure (nCPAP) – This pressure device blows air into the airway to keep the airway open during sleep. Continuous positive airway pressure treats snoring and obstructive sleep apnea and is the most common means of treatment (American Sleep Disorders Association 1995; Hudgel and Auckley, 1999). All OSA patients using CPAP in this study, used devices manufactured by the same company.
5. End-tidal carbon dioxide pressure ($P_{ET}CO_2$) – Partial pressure of exhaled carbon dioxide obtained during exercise testing.
6. Exercise Test –An incremental exercise test performed on an electronically braked cycle ergometer that designed to provide gradual stress to the subject. The work rate in watts (W) was increased over 90 second periods. After a brief 2 min warm-up at 25 W, work rate increased by 12, 17 or 22 W every 90 seconds, depending on a predicted level of peak capacity for each subject. Subjects with limited capacity lower W increases were used.
7. Functional aerobic impairment (FAI) – An expression of an individuals aerobic capacity (as a percentage) relative to normal for age and gender.
8. Hypopnea – Thirty to 50 percent reduction in airflow as recorded during an overnight polysomnography study (Redline and Strohl, 1998)
9. Maximal – Determined as the highest VO_2 reached during exercise testing.
10. Minute ventilation (V_E) – The amount of air exhaled from the lungs in one minute. Expressed in $l \bullet min^{-1}$.
11. Non-Rapid eye movement sleep (NREM) – Sleep characterized by a decrease in metabolic activity in four distinct types of brain wave activity (Stage one, two, three,

and four). Non-REM sleep is characterized by low frequency waves with spindles present in stage four and large delta waves present in stages three and four.

12. Nitric oxide (NO) – Endothelial-derived substance released in response to stress stimuli including increased blood flow and shear stress to the vascular wall that causes local vasodilation (Opie 1998). In the presence of a normal endothelium, more NO is released in response to a stimulus. Nitric oxide was measured in this study by analyzing 24 h urine production of nitric oxide metabolite, nitrate.
13. Obstructive Sleep Apnea (OSA) – A syndrome, usually seen in snorers, characterized by repetitive episodes of sleep-related upper airway obstruction (Redline and Strohl 1998). This syndrome occurs when the upper airway collapses during inhalation while sleeping. Complications include chronic sleepiness and fatigue as well as a significantly increased death rate due to heart attacks and strokes. Clinically significant OSA for this investigation was defined as an RDI score greater than 10 episodes per hour (Redline and Strohl, 1998).
14. Oxygen consumption (VO_2) – The amount or rate at which oxygen can be consumed per minute. Expressed in $l \bullet min^{-1}$ or $ml \bullet kg^{-1} \bullet min^{-1}$.
15. Oxygen desaturation (SaO_2) – A lowering of the level of blood oxygen concentration that is below 89 percent. Low oxygen saturation often corresponds to apneic and hypopnic events recorded during a PSG as the percent of sleep time spent below 89 percent oxygen saturation.
16. Peak oxygen uptake (VO_{2pk}) - The highest oxygen uptake attainable during incremental exercise testing.

17. Polysomnography (PSG) – Gold standard diagnostic method for obstructive sleep apnea. A standard PSG typically consists of electroencephalogram (EEG), submental electromyogram (EMG), electrooculogram (EOG), respiratory airflow, respiratory effort (rib cage and abdominal movement), and oxygen saturation levels (Redline and Strohl 1998). Body position and electrocardiography are also monitored in most sleep lab as part of the standard work up (Redline and Strohl 1998). All PSG studies were conducted at Allergy and Asthma Associates of Southwest Virginia in Christiansburg.
18. Rapid eye movement sleep (REM) – Sleep characterized by active brain waves, flitting motion of the eye, a paralysis of the muscles; most dreaming occurs in this stage, which accounts for about 20% of total sleep time in adults.
19. Rate pressure product (RPP) – Product of HR and systolic blood pressure (SBP). Rate pressure product is an indirect indicator of myocardial oxygen consumption.
20. Recovery – All recovery measurements were analyzed at four min of recovery in the seated position.
21. Respiratory Disturbance Index (RDI) –. The total number of apneas and hypopneas per hour of sleep and is synonymous as the apnea-hypopnea index (AHI) (Redline and Strohl, 1998).
22. Respiratory rate (f) – Breathing frequency in breaths per minute.
23. Sleep efficiency – Time spent awake divided by total sleep time during PSG.
24. Slow wave sleep (SWS) - Sleep that is characterized by large delta waves (EEG). Slow wave sleep is thought to be the deepest stage of sleep (HR, BP, respiration, and body temperature are all decreased compared to other stages of sleep). Slow wave

sleep is often reduced as we age. Exercise has been shown to increase slow wave sleep in some individuals.

25. Stroke Volume (SV) – The amount of blood (ml) pumped from the left ventricle into the aorta in one cardiac cycle.
26. Submaximal – Submaximal measurements were analyzed at ~ 60% of each patients VO_{2pk}
27. Tidal volume (VT) – Volume of air inspired or expired per breath.
28. Total Peripheral Resistance (TPR) – The sum of all forces that oppose blood flow. Total peripheral resistance was determined by dividing mean arterial pressure by Q and expressed as $mmHg \bullet l \bullet min^{-1}$.
29. Ventilatory threshold (T_{vent}) – The point during progressive exercise in which ventilation increases disproportionately to oxygen uptake.

Summary

Obstructive sleep apnea is a greatly under-diagnosed and economically burdensome disorder with respect to health status, mortality, and annual medical costs. Middle-aged, males with upper torso obesity and cranio-facial abnormalities who snore loudly are at highest risk for developing OSA. The pathological consequences of sleep apnea include cardiovascular related diseases, reduced neuropsychological functioning, psychosocial dysfunction, and increased mortality. Annual medical costs associated with undiagnosed sleep apnea have been reported to be double that of age and gender matched controls. Cardiovascular and hemodynamic states that may be used to describe the severity of the disorder, including arrythmias, myocardial infarction, hypertension, ischemic heart disease, and congestive heart failure, yet these conditions have not been

firmly established as being causally linked to OSA. Exercise testing has not been adequately utilized by clinicians and researchers. Using exercise testing to monitor ventilatory, cardiovascular, hemodynamic functioning would help clinicians to better understand the complex pathophysiological state of the OSA patient as well as determining which diagnostic PSG criteria may be more sensitive indicators of disease severity. Therefore, this investigation was conducted as a means to understand cardiovascular responses during exercise in OSA patients.

CHAPTER II

REVIEW OF LITERATURE

Introduction

The following chapter provides fundamental information on recent research related to the cardiovascular pathophysiology of Obstructive Sleep Apnea (OSA). First, this section focuses on associated morbidity and mortality to give better understanding of the scope and health implications of OSA. Next, this chapter discusses the pathogenesis of the disorder with respect to the patients clinical presentation, anatomical features, and resulting pathophysiology. With in this context, special attention is given to the cardiovascular consequences of OSA during sleep and wakefulness. Most of evidence linking OSA to cardiovascular disease is through the sequel of events that lead to daytime hypertension and related increased peripheral resistance. Finally, a limited amount of information is available concerning how the OSA patient responds to physical activity. However, the physiological responses to exercise in OSA patients is discussed in some detail as this information has direct bearing on the objectives for this investigation.

Morbidity and Mortality

Regardless of the underlying mechanism, fifty percent of those with OSA also have daytime hypertension independent of other confounding factors including obesity, age, and sex (Hla, K.M., 1994). Peppard et al (2000) recently conducted a prospective study of the association between sleep-disordered breathing and hypertension in 709 participants of the Wisconsin Sleep Cohort Study. All participants completed PSG studies at baseline and at four year follow-up. The odds ratios for the presence of hypertension at

follow-up were 1.42 (95 % C.I.: 1.13 to 1.78) for those with an apnea-hypopnea index (AHI) of zero events per hour at base line. Those with the highest AHI at baseline (more than 15.0 events per hour) also had the highest presence of hypertension at the four year follow-up at 2.89 (95 % C.I.: 1.46 to 5.64). While a clear association between OSA and hypertension has been established, physiological mechanisms for its occurrence in OSA patients have yet to be determined.

Although a causal link has not been established between OSA and specific cardiovascular diseases (i.e. left ventricular dysfunction and coronary artery disease), a recent report from the Agency for Health Care Policy and Research estimates that 20.3 percent of those with diagnosed OSA have also been diagnosed with coronary artery disease (AHCPR, 1998). Obstructive sleep apnea is one of a spectrum of sleep-disordered breathing syndromes (Anstead and Phillips, 1999), which can lead to daytime hypertension and increased risk of death due to heart attack and stroke (Shepard 1992; Fletcher 1996; Marrone, Bonsignore et al. 1998; Skomro and Kryger 1999). Obstructive sleep apnea is a health concern not only from the standpoint of related morbidity but morality as well. However, mortality rates due to OSA alone have only been investigated retrospectively and most studies are less than 10 years in length. Of 198 OSA patients diagnosed between 1972 and 1980 at the Stanford Sleep Disorders Clinic, the age adjusted odds ratio for vascular mortality at 5 years was 4.7 (Partinen M, 1988) among those conservatively treated with weight loss only. In a similar study of 385 OSA patients from 1978 to 1986 (He, Kryger et al., 1988), the eight year overall mortality rate was 2.1 percent for those with an apnea index less than 20 and 10.6 for those above 20. While one cause of death in those with OSA seems to be related to cardiovascular co-morbidities

including hypertension and congestive heart failure, the other primary cause is related to traffic fatalities associated with excessive daytime sleepiness (Redline S 1993; George and Smiley 1999). Individuals with diagnosed OSA are seven times more likely to have a traffic related accidents than their non-OSA counterparts (Redline and Strohl, 1998). However, most mortality studies are retrospective in nature so that the quantification of risk is approximate. Clearly, more prospective investigations with long-term follow-up are needed to truly specify mortality rates associated with OSA.

Mortality estimates attributable to OSA also are limited due to prevalence estimates as well as the high probability that many with this disorder go undiagnosed OSA. While a relatively low percentage of the population has been diagnosed with OSA, a recent report states that more than 80 percent of those with the disorder may go undiagnosed (Young T, 1993). Improved techniques for evaluation and treatment are rapidly being developed. In addition, clinicians (primarily physicians and nurses) are slowly being educated about ways to optimize medical management and improve health care outcomes in patients with sleep disordered breathing. Very few if any clinical exercise physiologists, however, are trained or even minimally educated about sleep disordered breathing and how to incorporate physical activity into the lives of these patients' lives. This is an important issues, since there is a high association of OSA with obesity and cardiovascular disease. More clinicians should be informed of the risk factors for OSA. These include middle-aged males with upper torso obesity, excessive snoring, witnessed gasping or cessations in breathing during sleep, excessive daytime sleepiness, and reduced neuropsychological functioning. Prompt diagnosis and effective medical management may then greatly improve treatment outcomes in those with OSA.

Pathogenesis of Obstructive Sleep Apnea

Patients with OSA report snoring, nocturnal choking, excessive sleepiness, impaired neuropsychological performance, and morning headaches. However, most patients may be unaware of the origins of their problem and seek help as a result of noticeable impairments in daytime functioning or at the request of a bed partner. Obstructive sleep apnea is a complex disorder with its manifestations involving mechanical obstruction in the upper airway, neuromuscular factors, and arousals (Strollo PJ, 1996). The disorder causes a complex interplay between factors that compromise upper airway patency. Anatomical factors include obesity, nasal obstruction, enlarged tonsils, and micrognathia. Additionally, upper airway patency may be decreased by neurochemical drive, upper airway reflexes, and load compensation capabilities (McNicholas 1997; Badr 1999). Ironically, the very factors that attempt to restore a collapsed airway contribute to apneic and hypopneic events and subsequent arousals.

A progressive narrowing of the upper airway (UA) associated with OSA in and of itself may be due to several factors. Pharyngeal narrowing associated with non-rapid eye movement (NREM) sleep and exacerbated negative transmural pressure causes the UA to collapse. In addition, extraluminal pressure may also contribute to a collapse of the airway. Several anatomical states contribute to reduced UA patency (Badr, 1999). For example, in the obese OSA patient, UA patency is compromised by increased adipose in the pharyngeal area, and in those with a normal BMI, UA caliber may be caused by retrognathia and or craniofacial abnormalities. Cephalometric data show that in general, OSA patients tend to have high-grade mallampati (large tongue), and large soft palate and tonsil size (Lowe 1990). Lowe reported that forty-percent of the variation in apnea

frequency could be accounted for by a combination of tongue and soft palate volume, ANB, SNB, OB, and body mass index.

Neuromuscular factors that contribute to apneic events are related to load compensation, upper airway reactivity, and reduced chemoreceptor sensitivity. Normally, a dilator reflex activated during inspiration causes primarily the genioglossus muscle to maintain upper airway patency (Badr 1999). In OSA patients, the airway is unstable and often collapses given the same inspiratory pressure (increased airway reactivity). Moreover, habitual snorers and OSA patients alike exhibit reduced ability of the UA dilating muscles to respond to negative pressure during NREM. This phenomenon is not fully understood but is thought to be related to epithelial damage to the UA incurred during apneic and hypopneic events (Nandwani, Caranza et al., 1998). Inflammatory responses are thought to causes sensors in the pharyngeal mucosa to be less sensitive to decreases in intramural pressure. Thus, dilator muscles in this area do not respond as readily to reduced pressure and the UA is allowed to collapse. Nandwani *et al* showed that three months of nCPAP treatment significantly decreased upper airway reactivity in response to UA irritants (ammonia vapor). Subjects in this study breathed low concentrations of ammonia. Upper airway reactivity is measured as the concentration required to cause a 25 percent reduction in airflow (glottic closure) in parts per million (ppm). For example, at baseline 738 ppm on ammonia was required for glottic closure compared to 1386 ppm after three months of nCPAP treatment in OSA subjects ($P < 0.01$). In addition, at baseline, the glottic closure value for a reference group of controls of similar age without OSA was 1255 ppm. Thus, altered sensitivity in the UA of OSA subjects is a contributing factor to the disorder.

While the initiation of apnea and hypopnea may be difficult to determine, recurrence of these episodes is actually perpetuated due to subsequent arousal from hypoventilation or asphyxia. Arousal from sleep may not be the culminating factor but rather a change in sleep stage. Chemoreceptor stimuli (PaO_2 and $PaCO_2$) are important controls of hypoventilation, hyperventilation, and central apnea. Presumably, a cycle of events is initiated in which after an apneic event has occurred, arousal follows restoring UA patency. However, arousal triggers a brief period of hyperventilation followed by hypocapnia (reduced $PaCO_2$) and increased arterial oxygen saturation (SaO_2) (McNicholas, 1997). This hypocapnic period leads to subsequent apnea or hypopnea due to reduce ventilatory drive (Badr, 1999). Thus, the distinction between central sleep apnea (CSA) and OSA may not be clear-cut.

Some discrepancy exists in the literature with regards daytime hypocapnic versus hypercapnic states in those with various sub-types of sleep apnea, including OSA, central sleep apnea (CSA), and obesity-hypoventilation syndrome (OHS) (Badr MS, Skatrud JB et al. 1991). While many OSA patients are in a normoxic state during the daytime, chemoresponsiveness in sleep apnea patients largely depends on the etiology of the disorder. For example, congestive heart failure patients develop CSA primarily from Cheyne-Stokes respiration causing daytime hypocapnia without associated hypoxemia (Naughton M 1998). Several theories for this state exist including, enhanced pulmonary vagal stimuli and chronically elevated levels of circulating catecholamines. On the other hand, various subgroups of OSA patients may be in a hypercapnic state during the day. OSA patients with a high body mass index (OHS) are in physiological state of daytime hypercapnia and hypoxemia at rest and during exercise (Schonhofer, Rosenbluh et al.

1997; Schafer, Ewig et al. 1998; Sin D.D., Jones R.L. et al. 2000). Often called Pickwickian syndrome, OHS exacerbates hypopnic and apneic episodes during sleep due to mechanical impedance to breathing exerted by thoracic and abdominal fat and a ventilation-perfusion mismatch (Kopelman 1984). All of the aforementioned subgroups can usually be treated with CPAP. However, the clinician must be diligent to monitor these various altered blood gas states throughout all stages of treatment.

Cardiovascular Consequences of OSA

Hemodynamic changes during sleep in OSA patients

Obstructive sleep apnea causes severe oscillations in heart rate, cardiac output, and arterial blood pressure during sleep. Negative intrathoracic pressures (as low as –75 mmHg), hypoxia (>3% desaturation), and arousal associated with apneic and hypopneic events all contribute to these hemodynamic oscillations. The following sequence of events occurs with respect to hemodynamic consequences of OSA (Naughton and Bradley, 1998). Negative intrathoracic pressures during obstruction prevent left ventricular filling and stimulate vagal efferent parasympathetic activity responsible for the cyclical reductions in heart rate during apnea (Shepard 1992). Reduced ventricular filling and heart rate contribute to decreased stroke volume and cardiac output. Negative pressure also causes a leftward shift of the intraventricular septum furthering the decrement in left ventricular filling. Hypoxia associated with apnea or hypopnea stimulates a baroreflex response and thus increases sympathetic nervous system output. This in turn leads to increases in arterial blood pressure and tachycardia upon arousal. After arousal, a resultant restoration of ventilation occurs as well as a subsequent increase in cardiac output (Q = SV x HR). Furthermore, the highest heart rate and arterial

pressures occur five to seven seconds after apnea termination (Weiss JW, 1999). Table 1 characterizes these cardiovascular and hemodynamic changes that occur during and after an apneic event proposed by Weiss (1996) in further detail.

Table I. Cardiovascular and hemodynamic consequences of apneic and hypopneic events during sleep.

During apnea	Arousal
Increased left ventricular afterload due to negative intrathoracic pressure	Decreased left ventricular afterload due to increased intrathoracic pressure (leading to increased LV filling)
Systemic vasodilation at the beginning of apneic period due to baroreflex activation (as a result of previous arterial pressure increase)	Left ventricular wall distortion due to lung inflation
Increased venous return as a result of negative intrathoracic pressures	Increase in right ventricular afterload as a result of increased pulmonary vascular resistance
Decrease in heart rate at the beginning of the apnea episode due to baroreflex activation (as a result of previous arterial pressure increase)	Further increase in both tachycardic response as well as arterial blood pressure from arousal (CNS activation)
Tachycardia at the end of the apnea episode due to chemoreflex activation (hypercapnic hypoxia)	
Systemic vasoconstriction at the end of the apnea period due to hypoxic apnea	

It should be mentioned that great variability exists from patient to patient. For example, one patient may have a slowing of heart rate as the apnea progresses while another may have more of an acceleratory response (as noted above). Researchers are not sure why there is a drastic difference in responses among individuals. The differences are thought to be related to not only oxygen desaturation and arousals but also which stage of sleep the apnea or hypopnea occurs (REM or NREM). Heart rate slowing seems to be more prominent in REM sleep. Similarly, oxygen desaturation and arousal contribute to systemic hypertension but the etiology of this increase in blood pressure is not known. Some investigators (Weiss JW, 1999) (Ringler, Basner et al. 1990; Garpestad, Parker et al. 1994) are proponents of the arousal theory as patients treated with nCPAP may still have increased blood pressure when arousals are induced by acoustic stimuli. However, contradictory evidence of this theory has been provided in a canine model by Brooks *et al* (1997). Clearly, still more investigation is needed as to the primary mechanism(s) which cause drastic hemodynamic oscillations and exactly how this carries over to day time cardiovascular functioning.

Daytime cardiovascular abnormalities associated with OSA

Left ventricular dysfunction and ischemic heart disease. Reduced intrathoracic pressure, hypoxia, and frequent arousals resulting in increased sympathetic nervous system activity and reduced baroreceptor sensitivity contribute to the development of daytime hypertension, left ventricular dysfunction, and possibly coronary heart disease. To few studies are available to provide estimates of the association between OSA and left ventricular dysfunction. However, increased sympathetic activity while in awake in OSA patients may contribute to several adverse hemodynamic consequences including

increased peripheral vascular resistance, hypertension, and impaired ventricular function (Hall and Bradley 1995). Several authors have investigated this link. Schafer *et al* (Schafer H 1997), for example, determined that in patients diagnosed with ischemic heart disease and OSA vs. those with OSA only, 85.4% of ischemic episodes were also accompanied by apnea. In addition, sustained release nitroglycerine did not prevent ischemia during apnea episodes.

Similarly, Naughton (Naughton M 1998; Naughton and Bradley 1998) has elucidated the hemodynamic consequences of OSA that may lead to heart failure or may otherwise be associated. This link is made primarily based on an impaired filling of the left ventricle in association with the reduced intrathoracic pressures during apneic and hypopneic events (see Table 1). Exaggerated negative intrathoracic pressures may also contribute to left ventricular diastolic dysfunction (impaired ventricular filling), which exists in approximately 33 percent of those with CHF. In addition, congestive heart failure patients by way of increased pulmonary vascular volume, hypocapnia, and reduced respiratory muscle strength often develop central sleep apnea. Increase pulmonary vascular volume may also contribute to right ventricular dysfunction. More prospective investigations are needed in order to completely understand ischemic heart disease and left-ventricular dysfunction in OSA patients.

Hypertension. Obstructive sleep apnea's contribution to daytime hypertension has been given a considerable amount of attention both from a pathophysiological standpoint and as a national health concern. One the best documented links between OSA and hypertension was in a canine model in which episodes of apnea were induced in 4 bulldogs causing arousal and later the authors contrasted this to arterial blood pressure

responses to arousal only (Brooks D, 1997). Over the course of a three month period, arterial blood pressure rose an average of 15 mmHg in contrast to no increase noted in the arousal only model. Mechanisms related to this increase were not explored by these authors.

One mechanism supported by investigators, is that of increased sympathetic nervous system activity during sleep has been proposed to spillover into daytime hours as manifested by an increase in plasma norepinephrine as well as decreased sensitivity of the baroreceptors to changes in arterial blood pressure (Shepard 1992; Hall and Bradley 1995; Morgan 1996; Zwillich 1999; Fletcher 2000; Garcia-Rio, Racionero et al. 2000), (Jennum P, Wildschiodtz G et al. 1989). Narkiewicz *et al* (Narkiewicz and Somers 1997, Narkiewicz K, van de Borne et al.,1998) has done extensive work in the human model in attempt to explain the ANS derangement present in those with OSA and how it may be linked to daytime hypertension. This group works out of the model that ANS dysfunction in those with OSA is a result of increased muscle sympathetic nervous system activity (MSNA) due to hypercapnia, hypoxia, and apnea regardless of confounding variable such as obesity. For example, these investigators (Narkiewicz K, 1998) measured MSNA in 25 healthy normal-weight and 30 healthy sedentary obese subjects screened for OSA via PSG studies. Nine obese subjects and were subsequently diagnosed with OSA and found to have significantly higher amounts of MSNA (61 ± 8 bursts per 100 heart beats) compared to normal-weight (41 ± 3 bursts per 100 heart beats) or obese subjects without OSA (42 ± 3 bursts per 100 beats). Systolic blood pressure was not found to be significantly different between the groups.

In a series of prospective, randomized trials, Narkiewicz *et al* hypothesized that OSA patients have an increase in MSNA and a corresponding decrease in baroreceptor sensitivity (Narkiewicz K, van de Borne et al. 1998). Knowing that the administration of 100% oxygen in normals results in a decrease in MSNA, a double-blind administration of either 100% oxygen or room air was administered to 14 untreated OSA patients and in 12 controls (matched for age and body mass index) in the supine position for approximately 15 min. The OSA patients had significantly elevated MSNA (44 ± 4 burst per minute) compared to controls (30 ± 3 burst per minute). Both groups had a resultant decrease in heart rate, MSNA (bursts per sec), and in mean arterial pressure (MAP) with 100% oxygen administration. However, when room air changes were compared to 100% oxygen, OSA group had greater reductions in MAP (98 ± 4 mmHg to 94 ± 3 mmHg) and MSNA (43 ± 4 bursts per minute to 37 ± 4 bursts per minute) breathing 100% oxygen when compared to controls (MAP=89 ± 3 mmHg to 86 ± 3 mmHg; MSNA = 30 ± 3 to 26 ± 3 bursts per minute). Wreathing room air, controls subjects had a non-significant decrease in MAP and MSNA while the OSA patients did not. This difference was attributed to increased sympathetic nervous system activity in the OSA patient. The authors concluded that due to enhanced activation of chemoreflex afferents augmented efferent sympathetic activity. Thus, in both the human and in the animal model, recurrent hypoxic events lead to increased SNA and decreased baroreceptor sensitivity and have been shown to contribute to the development of daytime hypertension.

Total peripheral resistance and vascular function in OSA patients.

While investigators agree that OSA patients appear to have augmented SNA during the daytime, this alone cannot explain why some patients exhibit daytime hypertension and others do not. Several investigators have determined that many OSA patients do not have daytime hypertension even with higher amounts of MSNA and increased levels of circulating nor-epinephrine and epinephrine levels (Lapinski M, Przybylowski T et al. 1993; Marrone O, Riccobono L et al. 1993; Hedner J, Darpo B et al. 1995), both of which are postulated to be a result of recurrent episodes of hypoxia. In addition to these autonomic controls of vascular tone, endothelium-dependent controls of vascular tone may also be involved in the development of hypertension (Hedner, 1996). In particular is that of endothelium-derived nitric oxide. Nitric oxide (NO) is an important substance involved in the regulation of vascular tone and blood pressure, and in the presence of an intact, undamaged endothelial wall, serves as a potent vasodilator. Investigation of vascular endothelial vasodilation as demonstrated by forearm plethysmography or the dorsal hand vein technique, indicates that impairment of endothelium-dependent vasodilation during daytime is associated with sleep-disordered breathing (Guilleminault and Robinson 1997). In addition, evidence also exists concluding that hypertensive patients have reduced NO bioavailablity (plasma and urinary) compared to their healthy counterparts (Hishikawa, Nakaki et al. 1993; Kelly, Tam et al. 1998). The following sections will explain the biosynthesis, mechanism of action, and the potential role that may lead to abnormal regulation of NO-dependent vasodilation in OSA patients.

Biosynthesis of NO. Nitric oxide, along with L-citrulline, is a co-product derived from L-arginine's conversion to N-hydroxy-L-arginine by calcium-dependent and independent NO synthase (NOS) enzymes (see Figure 1). Nitric oxide enzymes exist in two primary forms, constitutive and inducible (Toutouzas PC, 1998, Dusting 1996). The constitutive form (eNOS) is released within seconds of a stimulus, such as shear stress to the vessel wall, Ach, bradykinin, substance P, thrombin, and serotonin. The inducible form (iNOS) takes longer to activate and is present in immune cells, endothelium, vascular smooth muscle, cardiac myocyctes, and astrocytoma cells in the brain. Unlike, other types of neurotransmitters, NO does not seem to be contained within a synaptic vesicle, may actually by produced on demand or on a chronic basis, and does not have a specific receptor for which is binds (Synder SH and DS, 1992).

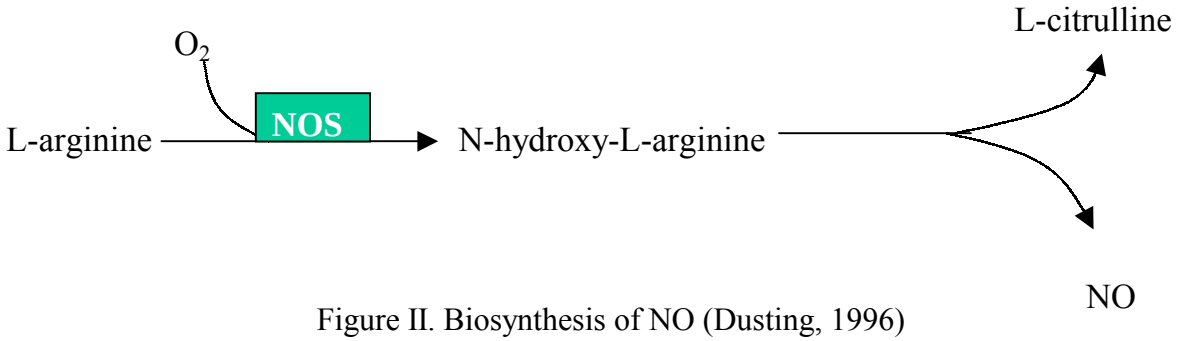

Figure II. Biosynthesis of NO (Dusting, 1996)

Mechanisms of action relative to the endothelium. Nitric oxide is a major regulator of blood flow primarily through its involvement in vascular smooth muscle relaxation, cytotoxicity, and in the inflammatory process. NO may even have a protective role by actually preventing the adhesion of platelets to damaged vessel walls (Dusting 1996; Noiri E 1997; Ikeda U 1998; Goligorsky M 1999). A simplified version of the

mechanism of action of NO within the context of ischemic heart disease and arteriosclerosis has been depicted by Furchgott (Furchgott, 1996) and later by Sabatine *et al* (1998) (see Figure 2). As stated previously, the action of NO depends largely on the state of the endothelium. With an intact endothelium, Ach induces relaxation by first binding to its respective endothelial receptor. This activates NOS to produce NO. Nitric oxide then diffuses into the smooth muscle cell where it activates guanyl cyclase that forms cyclic GMP (cGMP). Cyclic GMP then induces relaxation. Although the mechanisms by which this relaxation occurs have not been completely elucidated, it has been proposed, that cGMP activates protein dependent kinases that in turn may activate Ca^{++} dependent membrane pumps to cause a decrease in cytosolic calcium. In addition, NO may also directly relax smooth muscle by opening K^{+}-channels, there by, hyperpolarizing the cell.

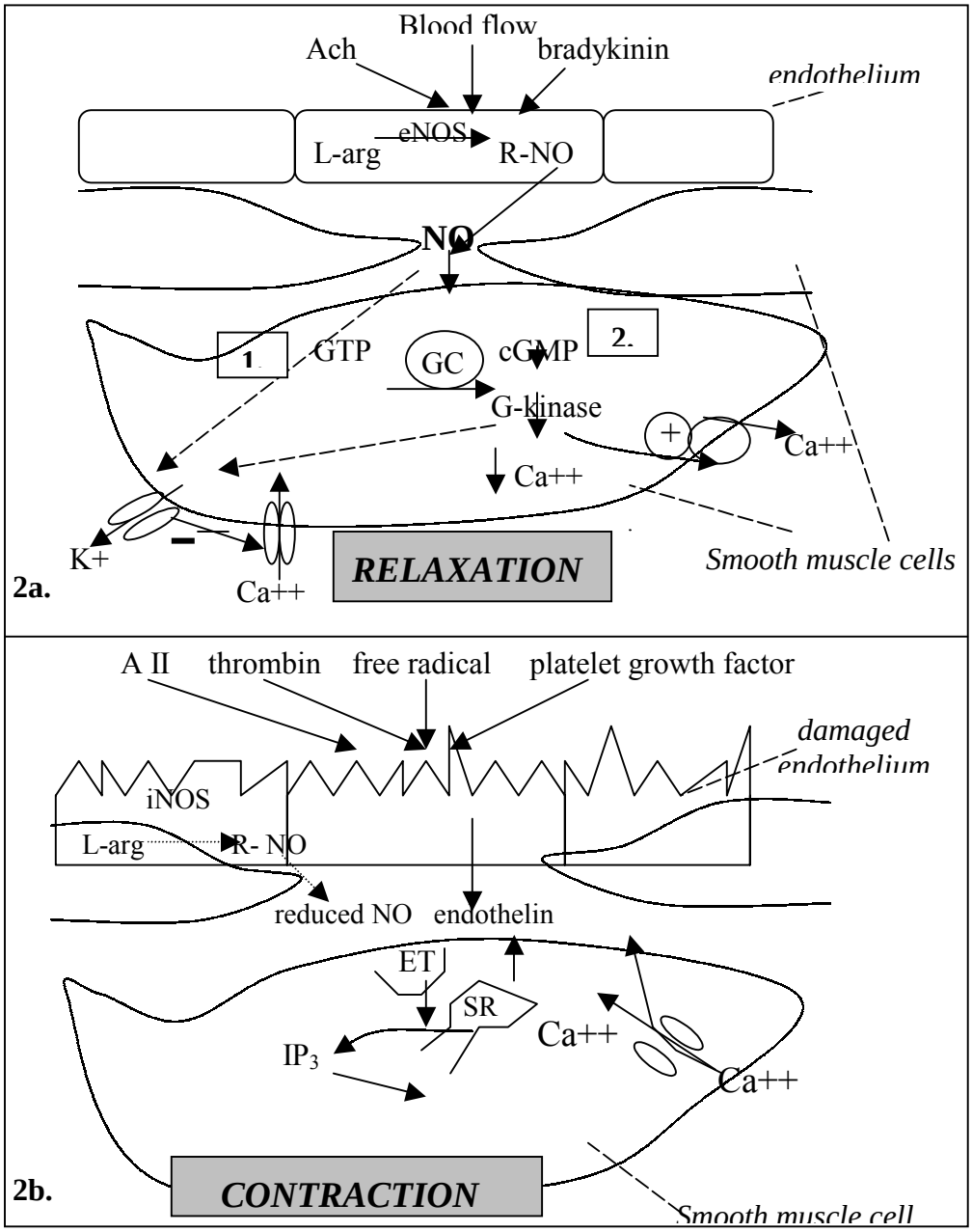

Figure II**.** Mechanism of action of NO on vascular smooth muscle in the intact endothelium (IIa). Physiologic stimuli to release NO include acetylcholine (Ach), increased blood flow, and bradykinin. Nitric oxide causes relaxation through (1) direct action on potassium channels (K+) or (2) by activating the cyclic GMP pathway (cGMP). In the damaged endothelium (IIb), free radicals and thrombin cause less NO and more endothelin (ET) to be released. Endothelin activates the inositol triphosphate pathway that promotes the release of Ca++ from the sarcoplasmic reticulum resulting in contraction (Dusting 1996; Opie 1998),(Sabatine MS, O'Gara PT et al. 1998).

A much different scenario exists within the damaged endothelium. In this case, substances (thromboxane and serotonin), which normally produce relaxation instead, produce contraction (Sabatine MS, O'Gara PT et al. 1998) (see Figure 2b). Both prostacyclin and NO serve as antithrombotics in this case. In the normal endothelium, both act synergistically to allow for appropriate distribution of blood flow, which is especially important in the coronary arteries (Dusting, 1996). However, in the damaged endothelium, less NO and prostacyclin are released in response to shear stress and platelets, and thus have less influence on vasodilatory responses and more platelets are allowed to aggregate. Chronically, this process has been postulated to contribute to the development to hypertension, atherosclerosis, and eventually coronary artery disease.

Several isozymes of NOS have been identified which each contribute to the atherosclerotic and ischemic process in their own way. The constitutive, eNOS, (isoform III) and inducible NOS (isoform II) have been discussed previously. The first isoform, nNOS, is neuronal in form and does not appear to be an integral part of the disease process (Dusting 1996; Ikeda U 1998; Wever R 1998). The importance of eNOS and iNOS is in their differing actions within different environments, with eNOS being calcium-dependent and immediate activator of NO. This critical environment between the endothelial cell and vascular smooth muscle is dependent on the expression of cytokines produced by infiltrating macrophages.

Dusting has proposed a model for a decrease in the bioavailability of NO dependent vasodilatory responses in atherosclerotic lesions. In response to injury or shear stress in a lesioned artery macrophages and T-cells migrate to the area followed by smooth muscle cell proliferation in the intima. Macrophages release cytokines, which, in

turn, activate iNOS. This inducible from of NOS may then use any available L-arginine in the endothelial cell, and in essence, "steal" L-arginine substrate from eNOS. In addition, the expression of iNOS may actually be increased within the macrophage, which would make less NO available within the endothelial cell.

The role of these various isozymes of NOS is far from solved. For example, others have proposed that NO dependent vasodilatory responses may be concentration dependent (Wever R 1998, Czubryt MP 1996). Wever *et al* proposes that eNOS produces low concentrations NO and peroxynitrite (oxidant which behaves similar to NO) as in the anti-atherosclerotic environment. However, in lesioned areas eNOS may produce not only an over abundance of NO but also superoxide, which then may deactivate NO. Similarly, Czubryt *et al* suggests that damaged endothelial cells may produce a surplus of free radicals. This production in both smooth muscle cells and cardiomyocytes which includes the oxidized low-density form of cholesterol (ox-LDL) and superoxide dismutase may be another source to cause the inactivation of NO through the second messenger system (cGMP). Clearly, more research is needed in this area to determine the exact roles of the NOS isozymes in the normal and atherosclerotic state.

Altered function of the NO pathway has recently been verified in the human model in healthy individuals and in those with congestive heart failure (CHF) and coronary artery disease (CAD). Urinary excretion of NO metabolites (nitrate) were used to evaluate NO production, as urinary levels mirror NO production *in vivo*. Significantly higher basal levels of NO were found in a group of marathon runners compared to those with coronary artery disease, 10.10 mmol/g creatinine vs. 0.35 mmol/g creatinine, respectively (Rodriguez-Plaza LG, 1998). Furthermore, 12-weeks of cardiac

rehabilitation significantly increased urinary excretion of NO metabolites by 157%, and the relationship between increases in functional capacity and NO excretion was significant. Similar findings after 8-weeks of exercise training in a group of CHF patients were also noted by Callaerts-Vegh *et al* (Callaerts-Vegh Z, 1998). Thus, in both the animal and in the human model, the cardio-protective effect of exercise training may at least be partially explained by endothelial vasodilation induced by NO production.

Role of NO-dependent vasodilation in OSA. Evidence of reduced peripheral circulation or increased peripheral vascular resistance in OSA patients is limited. While at least two investigations (Olopade, Christon et al. 1997; Agusti, Barbe et al. 1999) examining exhaled levels of NO have been conducted, to date there have been no studies which have specifically evaluated the role of endothelial NO in OSA patients. However, some evidence exists that OSA patients exhibit increased vascular resistance. Recently, Schnall *et al* (Schnall, Shlitner et al., 1999) examined the extent to which peripheral vasoconstriction may be used as a marker of disease severity. Using fingertip plethysmography in 42 untreated OSA patients (age = 47.6 ± 9.9 years; BMI = 29.7 ± 5.2 years), these authors were able to show that episodes of apnea and hypopnea were significantly correlated to increases in peripheral resistance during a standard PSG study. The authors concluded that the number of episodes of increased resistance that occurred per night could be used in the same way apnea and hypopnea indices are used as markers of disease. In another investigation, Phillips *et al* reported increased nighttime levels of circulating endothelin-1 (powerful vasoconstrictor) in 22 OSA patients (AHI = 74 ± 22 per hour) that was significantly correlated with mean arterial pressure ($r=0.44$, $P<0.02$).

Finally, two groups of investigators (Carlson, Rangemark et al. 1996; Remsburg, Launois et al. 1999) have also found that OSA patients have increased peripheral vasoconstriction during the daytime, which was due to endothelium-dependent mechanisms. In particular, Carlson *et al* found that after acetylcholine infusion (NO release stimulator), forearm blood flow was significantly reduced in OSA patients (6.0 ± 0.7 ml/min for 100g) compared with controls (9.8 ± 1.5 ml/min for 100g) ($P < 0.05$) due to higher forearm vascular resistance in the patient group. These authors did not evaluate NO levels in this study. Thus, the extent to which NO may be altered in OSA patients has not been investigated.

Physiological Responses to Exercise in OSA Patients

Ventilatory and hemodynamic responses to exercise testing.

Limited information is available concerning how the OSA patient responds during exercise (Hawrylkiewicz, Cieslicki et al. 1996; Konermann, Sanner et al. 1996; Schonhofer, Rosenbluh et al. 1997) (Levy, Guilleminault et al. 1991; Davies, Harrington et al. 1993; Marrone O. and M. 1997; Netzer N 1997; Taguchi, Hida et al. 1997; Vanuxem D 1997; Bittencourt, Moura et al. 1998; Schafer, Ewig et al. 1998; Schafer, Ehlenz et al. 1999; Tremel, Pepin et al. 1999). Much of the information regarding exercise in the OSA patient is in languages other than English (Hawrylkiewicz, Cieslicki et al. 1996; Konermann, Sanner et al. 1996; Schonhofer, Rosenbluh et al. 1997) (Netzer N, 1997) so that only the abstract form of the investigation is available. Various reasons may explain why the literature is limited considerably in terms of the functional status of the OSA patient. Simply put, the disorder is in its infancy in terms of understanding physiological functioning during not only sleep but also how the disorder may effect

daytime functioning at rest. In addition, barriers to subject recruitment for scientific investigations are a plausible reason as well. This population has well documented impairments in psychological functioning that may interfere with the patients self-efficacy for physical activity. Driving an automobile alone is a life threatening event when one considers that OSA patients are seven times more likely to be involved in a car accident than those who are legally drunk (George and Smiley, 1999). Thus, more effort should be invested to determine specific barriers to physical activity in the OSA patients.

Much of the research to date focuses on the ability to distinguish OSA patients from other groups of age matched healthy adults and if the exercise test can be used to provide an improved clinical profile of disease severity in terms of polysomnography (PSG) scoring. Aguillard *et al* (Aguillard, Riedel et al., 1998) attempted to profile some of these changes by evaluating objective and subjective measures of sleepiness with objective measures of sleep and physiological functioning in 32 OSA patients (27 males, 5 females; age = 47.1 ± 10.1; BMI = 35.2 ± 7.2). As an objective measure of fatigue, they used a maximal exercise test and used the multiple sleep latency test ("nap study") as an objective measure of sleepiness. The Fatigue Severity Scale evaluated subjective ratings of fatigue. Exercise testing on a bicycle ergometer was done one week after the PSG/MSLT study but preceding any treatment. Maximal oxygen consumption achieved during the exercise test was used a criterion measure for fatigue. The mean apnea/hypopnea index for the group was moderate to high in severity (AHI = 53.1 ± 34.2). Patients achieved 91% of age-predicted max VO_2. While AHI was poorly correlated with VO_2 max achieved ($r = 0.07$), patients with more percentage time spent in REM sleep, tended to have higher work capacities ($R^2 = 0.19$; $P < 0.05$) and higher

percentage of maximum heart rates ($R^2 = 0.18$; $P < 0.05$). However, neither VO2 max or max HR achieved were related to objective measure of fatigue (AHI or MSLT scores).

The most comprehensive investigation concerning exercise in OSA patients compares and contrasts central versus peripheral limits to exercise tolerance in OSA patients (Vanuxem D, 1997). While Vanuxem's group was primarily interested in muscle metabolism, they also profiled cardiopulmonary responses in eleven OSA patients and nine sedentary controls matched for age (OSA = 41.9 ± 3.1 years; controls = 47.8 ± 4.1 years) and BMI (OSA = 26.4 ± 1.2 kg/m^2; controls = 26.6 ± 1.0 kg/m^2). All subjects completed a maximal exercise test on a cycle ergometer. Resting and exercise arterial blood gases (PaO_2 and $PaCO_2$, mmHg), blood pressure (BP, mmHg), and heart rate (bts•min^{-1}. Blood lactate levels at rest, and during exercise and recovery were also determined as indicators of energy metabolism. Controls achieved a higher VO_2 peak (33.2 ± (SE) 1.4 ml•kg^{-1}•min^{-1}) than did the OSA patients (26.4 ± 1.2 ml•kg^{-1}•min^{-1}; $P<0.005$). In addition, lower VO_2 peak values were significantly correlated with the apnea index (total number of apneic events during sleep) ($r = -0.687$; $P < 0.05$) and minimum oxygen saturation during sleep ($r = 0.654$; $P < 0.05$). Systolic (SBP) and diastolic (DBP) blood pressures were significantly higher in the OSA group (143/99 mmHg) versus controls (132/83 mmHg) ($P < 0.05$). While SBP responses during exercise were similar for the two groups, OSA patients reached a significantly higher maximal diastolic BP (104 ± 5 mmHg) than did controls (92 ± 4 mmHg; $P < 0.05$). Arterial blood oxygen pressure was significantly higher at peak exercise in patients (95 mmHg) than controls (88 mmHg), while $PaCO_2$ levels decreased from rest to peak exercise, the difference was not statistically different between the two groups. Finally, maximal blood

lactate concentrations were significantly lower in the OSA patients, and lactate elimination rate during recovery was slower after 30 minutes of recovery than controls. The authors concluded that, for the OSA patient, peak functional capacity seems to be limited by abnormal energy metabolism rather than central mechanisms. They postulated that this group of OSA patients had impaired glycolytic metabolism as well as oxidative, due to reduced peak lactate concentrations and eliminations rates, respectively. Abnormal DBP responses at peak exercise could mean that a central component may also be a limiting factor. However, neither cardiac output (Qc) nor measurements of total peripheral resistance (TPR) were measured in these patients. These measures could have given more or less credence to the postulated limits in peak capacity in OSA patients.

Many investigators focus on the abnormalities in ventilation, neuromuscular drive, or load compensation. They are especially concerned about the extent to which abnormal ventilatory load compensation may be a cause or consequence of OSA. Only two authors have investigated this phenomenon during exercise. One found that OSA patients had abnormal load compensation at rest and during steady state exercise that was normalized after 4 weeks of nCPAP treatment (Greenberg and Scharf, 1993). It was concluded that abnormal load compensation is a consequence rather that a cause of OSA. However, Bittencourt (Bittencourt, Moura et al., 1998) studied 22 OSA patients (17 males, 5 females; mean age = 47 yrs; BMI = 32 $kg \bullet m^2$; AHI = 48) and 10 male controls (age range = 23 to 32 yrs) by assessing ventilatory response (VE), inspiratory occlusion pressure, and ventilatory patterns at rest and during exercise. All ventilatory values were within normal limits compared to controls. The only significant correlation was between inspiratory occlusion pressure and weight for the OSA group ($r = 0.48$; $P = 0.02$). These

authors postulated that since ventilatory mechanics were similar in the obese-OSA subjects in this group compared to non-OSA, obese subjects, that OSA patients may have altered chemoresponsiveness causing abnormal load compensation. Clearly, more investigation is needed in this area to determine the extent to which hypocapnia or hypercapnia may be a marker of disease severity in OSA patients.

Other investigators have used exercise to evaluate diagnostic and prognostic issues related to chemoreceptor function during exercise, particularly to evaluate differences between OSA and OHS. Cycle ergometry in at least two studies has shown promise not only for differential diagnosis between the two subgroups, but also predictive factors associated with treatment. Fourteen patients with OHS (age = 53.2, BMI = 41.7, $PaCO_2$= 50.7) and 28 patients with severe OSA (age = 54.5, BMI = 35.7, $PaCO_2$ = 37.3) completed a 4 minute exercise test on a cycle ergometer at baseline and after 3 months of positive pressure ventilation (Schonhofer, Rosenbluh et al., 1997). Obesity-hypoventilation patients exercise load was significantly lower (81 ± 26 W) than OSA patients (112 ± 20 W) at a load calculated to equal 66 percent of predicted maximal workload in the OSA group ($P < 0.0001$). Additionally, the OHS group had an exercise induced increase in $PaCO_2$ from minute one to four both before (50.7 to 56.6 mmHg) and after treatment (39.1 to 45.6 mmHg), while the OSA group did not show abnormal $PaCO_2$ before or after treatment (values not given).

Similarly, Schafer *et al* (Schafer, Ewig et al. 1998) studied blood gas and exercise responses in 13 patients who failed to respond to CPAP in a 15 month period (age = 57 years; AHI = 44.4) compared to an age and AHI matched control group (age = 56 years; AHI = 38.0). The failure group weighed more (BMI = 44.4 $kg \bullet m^2$) and reported more

difficulty breathing (92.3 percent) than did controls (BMI = 30.8 $kg \bullet m^2$; 23.0 percent). Both groups had the same types of apnea and hypopnea during PSG analysis. The mean nocturnal oxygen saturation and time spent below 90 percent were significantly different. The failure group had a mean oxygen saturation of 86 percent and spent 82 percent of sleep time below a 90 percent oxygen saturation level. The control group was 92 percent and 15 percent, respectively. At baseline, the failure group was hypercapnic and hypoxemic compared to controls at rest and after 4 minutes of steady state exercise at 50 Watts (Resting: failure group PaO_2 = 58.5 mmHg, $PaCO_2$ = 44.7 mmHg; control group PaO_2 = 71.3 mmHg, $PaCO_2$ = 38.3 mmHg, Exercise: failure group PaO_2 = 68.7 mmHg, $PaCO_2$ = 47.3 mmHg; control group PaO_2 = 86.4 mmHg, $PaCO_2$ = 36.9 mmHg) ($P < 0.05$). After 3 months of treatment with bilevel positive airway pressure (BiPAP) in the failure group, both blood oxygen and carbon dioxide levels normalized at rest and during exercise. The patients in the failure group could clearly be categorized in the obesity-hypoventilation subgroup due to obesity, hypercapnia, and hypoxemia. As stated previously, the Pickwickian syndrome creates abnormalities in ventilatory control that are a consequence of mechanical loading, abnormal chest wall mechanics, impaired neuromuscular coupling, and impaired ventilatory control. These authors have demonstrated that this subgroup can be separated and treated accordingly given a light to moderate exercise challenge. However, no one has yet to determine if similar differences exist with regards to hemodynamic responses during exercise.

Cardiovascular functioning during exercise in OSA patients is limited to primarily systemic and pulmonary blood pressure responses and cardiopulmonary changes associated with nCPAP treatment. Only one investigation conducted in Germany (Netzer

N 1997) (mentioned previously) regarding exercise alone as a treatment is available. In another German study, Balabanski *et al* (Balabanski L., Polonov K. et al. 1991) was able to show that cardiovascular profiles (blood pressure and blood lipid profiles) significantly improved in a forced 26-day weight loss program but exercise was not included in this study. The following investigations are the only exercise related studies to date regarding cardiovascular function during exercise in OSA and CSA.

Obstructive sleep apnea has been shown to cause abnormalities in pulmonary circulation during exercise. Investigators report that post-capillary pulmonary pressure is often elevated in patients with OSA (Hawrylkiewicz, Cieslicki et al. 1996) (Marrone O. and M. 1997). Schafer *et al* (Schafer, Ehlenz et al. 1999) recently investigated atrial natriuretic peptide levels (ANP, released in response to increased right atrial distention) and pulmonary artery pressure in six male patients (age = 54.7 years; BMI = 31.7 $kg \bullet m^2$) with moderate to severe OSA during daytime resting and exercise as well as sleep. All patients were required to stop antihypertensive medications and diuretics 72 hours before the study and those with diagnosed CHF or coronary artery disease were excluded. The highest levels of ANP were found during exercise (0.334 ± 0.170 $nmol \bullet L^{-1}$) when compared to awake $0.207 \pm 0.057 nmol \bullet L^{-1}$ or sleep values (0.235 ± 0.088 $nmol \bullet L^{-1}$). However, this difference could not be investigated more due to low subject number and the lack of a comparison group.

One noteworthy prospective investigation concerned with the prevalence of CSA and OSA in 34 patients admitted to a cardiac care unit 1 month after their admittance with acute left ventricular failure (Tremel, Pepin et al. 1999). Twenty-eight of these had patients had sleep apnea (82%), 21 were CSA and 7 were OSA (mean age = 62 years;

BMI = 27; left ventricular ejection fraction = 30%). Blood gases, peak VO_2,and AHI were measured at baseline (one month post acute failure) and after two months of medical treatment. Arterial blood carbon dioxide pressure was lowest in the CSA group ($PaCO_2$ = 33 mmHg; OSA = 37mmHg) ($P < 0.005$). Predicted VO_2 max reached was also lowest in the CSA group (66% of predicted maximum). However, the OSA group was also lower (72% of predicted maximum VO_2) than non-sleep disorder patients (92% of predicted maximum VO_2) ($P < 0.009$). There was also a significant correlation between AHI and percent VO_2 max but was mainly a function of CSA ($r = -0.73$) ($P < 0.01$). No relationships between sleep function and exercise capacity was found in the OSA group. Also, neither cardiac output nor blood pressure responses were given for this investigation.

Effects of treatment on cardiovascular responses during exercise.

In general, the published literature indicates that CPAP treatment is associated with improved exercise capacity. Davies *et al* (Davies, Harrington et al. 1993) conducted a randomized control trial investigating changes in exercise tolerance and left ventricular function after two weeks of nCPAP treatment in six male CHF patients with a baseline ejection fraction of 18 percent. They determined that exercise tolerance, symptom scores, and the severity of sleep apnea were similar on active nCPAP compared with placebo. Taguchi *et al.* (Taguchi, Hida et al. 1997) showed a significant improvement (15.4% increase) in the maximal oxygen uptake after only 7 days of CPAP therapy ($P < 0.05$). Konermann *et al*. (Konermann, Sanner et al. 1996) used cycle ergometry to evaluate the effectiveness of a 6-month trial of CPAP therapy in a group of 30 OSA patients. In their study, the patients' work rate at maximal effort increased by 27.5% after the treatment

period ($P < 0.01$). Konermann *et al*. expressed cardiovascular efficiency in exercise by calculating ratios of heart rate or blood pressures at the 100-Watt workload divided by the corresponding value for these measures, taken the resting state before exercise. After 6 months of CPAP therapy, the patients' exercise heart rate and systolic blood pressure ratios indicated 15-20% greater efficiency (lower values). These improvements coincided with a 44.5% improvement in self-reports of "well-being," as assessed by psychometric questionnaire.

One published study, i.e. Netzer *et al.* (1997), has evaluated the effects of exercise training on symptoms and severity of OSA. These investigators trained 11 patients 2 hr/session, 2 sessions/wk, for 6 months. They reported significant reductions in the respiratory distress index (RDI) by polysomnography (PSG) after training, but did not find any improvements in PSG indicators of sleep efficiency and SaO_2. Unfortunately, their study did not include information on the physical training regimen, functional capacity outcomes resulting from the training, nor the extent to which reported improvements in RDI might have been due to CPAP treatment Vs physical training.

Summary

Obstructive sleep apnea is a disorder that has severe health implications for daytime functioning including increased cardiovascular morbidity and mortality, reduced neuropsychological functioning, and increased risk of traffic related accidents. Without treatment, the odds ratio for vascular mortality is approximately six five years after initial diagnosis for all ranges of OSA severity. Special attention should be given to prompt diagnosis and effective medical management in order to improve treatment outcomes in those with OSA. The disorder causes a complex interplay between factors that

compromise UA patency, including obesity, nasal obstruction, enlarged tonsils, and micrognathia, and factors the restore upper airway patency, including impaired neurochemical drive, upper airway reflexes, and load compensation capabilities. Moreover, different anatomical features between normal weight and obese patients may cause various subtypes of OSA with differing degrees of severity. Neuromuscular factors that contribute to apneic events are related to load compensation, upper airway reactivity, and reduced chemoreceptor sensitivity. Reduced intrathoracic pressure, hypoxia, and frequent arousals resulting in increased sympathetic nervous system activity and reduced baroreceptor sensitivity contribute to the development of daytime hypertension, left ventricular dysfunction, and possibly ischemic heart disease. Other factors that help to control vascular tone such as endothelium-dependent controls may be implicated in the development of increased peripheral resistance. Links between OSA and cardiovascular disease are sometimes contradictory, however, due to confounding comorbitities and various sub-types of sleep disordered breathing. Consequently, exercise testing and training would contribute to not only the understanding of the underlying cardiovascular pathophysiology related to OSA, but may also help to improve daytime treatment outcomes. Only 15 studies have either used exercise to evaluate functional capacity in OSA patients. While some of this information has been able to distinguish, for example, degrees of OSA severity, the extent to which the disorder may be distinctly recognizable due to abnormal cardiovascular responses to exercise is not known. Current evidence exists that treatment alone (nCPAP only) may improve daytime cardiovascular profiles during exercise.

CHAPTER IIIA

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RELIABILITY OF ACETYLENE SINGLE-BREATH CARDIAC OUTPUT IN EXERCISE

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ABSTRACT

Reliability of acetylene single-breath cardiac output in exercise. JS. Blevins, WG. Herbert, FACSM, DE. Zedalis. Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA. **Purpose**: A new automated single-breath technology (SensorMedics 229TM, Yorba Linda, CA) has been developed in which cardiac output (Q_c) is determined based on the diffusion rate for acetylene gas into the pulmonary capillary blood. This study measured the reliability for Q_c, when repeated on the same day (intra-trial) and on different days (inter-trial) during ramp-load (RL) and two different fixed-load (FL) cycle exercise conditions. **Methods:** Fifteen healthy volunteers (7 male and 8 female) completed two different exercises on the same day. First, RL was performed to ~80% of estimated VO_2pk, followed by the FL exercises on an electronically braked cycle ergometer. These exercises were repeated in the same order on a separate day. **Results:** Ramp Load trials demonstrated high reproducibility for inter-trial Q_c measures (r^2 = 0.82, P = 0.01). Repeated measures ANOVA revealed no significant differences for intra- or inter-trial FL Q_c measures. Intra-trial Q_c measures for FL were highly reproducible (range, r^2 = 0.92 – 0.98, P = 0.001). Inter-trial reliability for the FL trials was somewhat lower (range, r^2 = 0.59 – 0.90). No systematic bias in variability of Q_c values was noted across the range of exercise intensities that were evaluated, as determined using modified Bland-Altman plots, that included both the RL or FL type exercise bouts. Mean responses and 95 percent confidence limits of Q_c measurements were 6.06 ± 1.08 l•min^{-1}, 15.88 ± 1.51 l•min^{-1}, and 14.84 ± 1.27 l•min^{-1}, for resting, RL and FL exercises, respectively. **Conclusion:** Thus, the new automated single-breath acetylene system for non-invasive Q_c determination provides reliable

measures of cardiac output at rest and in different modes of aerobic exercise for cycle ergometry with apparently healthy adults.

Key words: cardiac output, acetylene, single-breath, ramp exercise

INTRODUCTION

Valid and reliable**,** non-invasive measurements of cardiac output are important for hemodynamic evaluation of individuals in both clinical and research settings. Recently, SensorMedics® Corporation (Yorba Linda, CA) developed an automated device for rapid measurement of cardiac output using the single-breath acetylene uptake method. The new device is incorporated into the SensorMedics, Vmax Series Model 229® system, an existing technology pulmonary function assessment and cardiopulmonary gas exchange exercise testing. Zenger et al and Sadeh et al (19,15). have validated prototypes of this device While those investigators reported a high correlation between automated single-breath technique (acetylene) and direct Fick and thermodilution methods (r = 0.90 and 0.92, respectively), their studies were restricted to measurements of cardiac output (Q_c) under resting metabolic conditions in cardiovascular disease patients. Others (10,16) have validated the acetylene rebreathing technique using similar devices during exercise, reporting correlations of 0.87 to 0.91 for the acetylene methods vs. thermodilution and Fick methods, respectively. Thus, there is a clear need to establish the validity and reliability of the single-breath acetylene Q_c technique under exercise conditions appropriate to evaluation of cardiac function in research and clinical settings.

Since the late 1920's, a number of other non-invasive methods have been developed for cardiac output using inert gases. The techniques that utilize acetylene (C_2H_2) may be performed either with re-breathing or single-breath methods (3,5,11). The

C_2H_2 gas does not bind to hemoglobin and yet is both highly diffusible and soluble in blood (18). When inhaled, it moves rapidly into the pulmonary capillaries at a rate highly dependent upon the rate of pulmonary capillary blood flow. Therefore, measurements at the mouth that allow rapid and accurate estimations of alveolar gas concentrations for C_2H_2 provide an index of the pulmonary blood flow. The rate of disappearance for alveolar C_2H_2, assessed concurrently with changes in a carbon monoxide reference marker, provides a mathematical basis for calculation of Q_c via the Fick relationship (17). Several investigators have demonstrated that measurements of cardiac output are highly correlated when the acetylene method and direct Fick methods ("gold standard") are compared. In fact, some recent studies have demonstrated the C_2H_2 method to be even more accurate than other noninvasive methods for patients with frequently encountered cardiac and pulmonary diseases (provided that $FEV_1 > 60\%$). In contrast, thermodilution, which is a widely used invasive procedure in clinical settings, appears not to perform as well in some pulmonary disease conditions (4,7,8,13). Carbon dioxide rebreathing has traditionally been the method of choice for non-invasive cardiac output assessment for exercise but, this technique has questionable reliability when exercise is non- state or the intensity is greater than ~ 60 % VO_2pk (12). The single-breath acetylene method is very comfortable, easy for subjects to learn, and has potential for measuring Q in a wider range of exercise conditions as a consequence of the rapid single-breath technique.

This particular study evaluated measurement reliability with repeated trials on the same test day and on different test days with healthy adults. Two very different cycle ergometer exercise protocols, frequently used in contemporary laboratory protocols, were examined on each day of testing. The first objective was to determine measurement

reliability for Q_c, for two different types of exercise loading conditions, i.e. fixed loads (FL) and ramp loading (RL). The second objective was to assess the reliability of the single-breath technique in the same FL conditions, with either brief (1 min) long (5 min) Q_c measurement intervals.

METHODS

Subjects: After pre-screening by interview, fifteen men and women volunteers (age 18 - 35 years) were subjects. The exclusion criteria established on the basis of medical history and/or physician diagnoses were: coronary artery disease; uncontrolled hypertension; chronic obstructive pulmonary disease; carotid vascular disease; diabetes mellitus; and orthopedic or musculoskeletal limitations that would preclude moderate-vigorous exercise. The protocol was approved by Institutional Review Board at Virginia Tech. All subjects gave informed consent to participate in the study. Prospective subjects reported to the Allergy and Sleep Disorders Center of Southwest Virginia for a first practice trial, at which time each gave informed consent and a health history.

Measures: *Practice session*. The Q_c procedure was explained in detail and then each subject practiced the breathing technique under resting conditions, using only the breathing mask and bag set-up. Subjects then practiced with the breathing apparatus to simulate Q_c measurements while performing exercise on a low intensity fixed load protocol on an electrically braked cycle ergometer for 10 min ($CardioO_2$, MedGraphics, St. Paul, MN). Heart rate and perceived exertion were measured every 2 min. The goal of practice sessions was to obtain Q_c values for two successive trials at rest and during a light intensity fixed load of exercise that differed by < 10%. If an individual subject had variations in Qc at rest or in exercise that were greater than 10 percent in the first two

days of preliminary testing, then those subjects returned to the lab to perform additional practice trials until this stability criterion was met. Only four of the 15 subjects needed to return for an additional third day of practice to satisfy this requirement.

Exercise sessions. Within one week of completing the practice sessions, each subject returned to the lab for their day one trial (D1), first performing a ramp loading (RL) exercise test and then a fixed load (FL) exercise test on the electronic cycle ergometer. First, Q_c was measured under seated resting conditions, and then the cycling tests exercise tests were performed. For RL exercise was continued to an intensity of ~80% of the predicted maximal aerobic capacity (based upon estimates derived from age-adjusted predicted maximal heart rates. The ergometer allowed application of ramp rates of 10-20 Watts•min^{-1}, pre-selected according to each subject's body weight and activity habits so that the target exercise intensity endpoint was reached within 20 min (12). All subjects were monitored continuously throughout exercise for possible signs of myocardial ischemia and heart rhythm disturbances via a 12-lead ECG. Test termination criteria were used to limit exercise endpoints, as recommended by the ACSM *Guidelines for Exercise Testing and Prescription* (1). Subjects rested ~ 30 min and then Q_c was measured at and then two fixed loads that were performed for 10 min each; without interruption. The FL intensities corresponded to ~25 % and ~75 % of each subject's aerobic capacity. Within one week of completing the D1 trials, subjects returned to the lab for D2 to perform procedures identical to those in D1. Time of testing in D1 Vs. D2 varied less than $\pm$ 3 hours for each subject.

Expired gases and Q_c procedure. In each trial, the Vmax® metabolic cart was used to collect expired respiratory gases for oxygen uptake and for Q_c determinations.

This methodology is described by Zenger et al (19) and was performed in accordance with the manufacturer's protocol for the device using proprietary computer software. For the Q_c measurements taken at rest, subjects breathed through the valve and mouthpiece assembly for 10-min to promote normalization of ventilation, before expired respiratory gases were collected. Following a 5-min rest, subjects then completed duplicate Q_c measurements that were separated by 5 min to allow for washout of the inert gas. For the RL, Q_c measurements were done singularly at minutes 5, 10, 15, and 20. In the FL tests on D1, measurements were done at the 5 minute mark of the given exercise load, followed by a 5 minute washout period then again at 10 minutes, for both intensities of exercise.

On D2, expired gases in and Q_c measurements were completed in the same way, except that end-tidal carbon dioxide values ($P_{ET}CO_2$) were used to estimate the minimum of washout time necessary before proceeding to the next measurement of Q_c. at rest or during FL exercise. Thus, for all resting trials and for FL measurements, the first Q_c trial was taken after 5 min of rest or exercise. The second Q_c trial was taken as soon as $P_{ET}CO_2$ values were within 1 mmHg of the preceding value. This resulted in the intra-trial measurement interval being reduced to 1-2 min. The primary purpose for this procedure was to determine the shortest interval between Q_c trials that would still be reliable. The ramping exercise trials were conducted in the same manner as on D1.

Data Analyses: Q values determined through Q_c for comparable conditions, within and between days of testing, were evaluated using repeated measures ANOVA. Coefficients of determination were calculated to estimate the precision of measurements for Q_c, and the analytic method of Bland-Altman (2) was used to detect possible

responses bias related to magnitude of Q_c. Significance was set at 0.05 level of significance.

RESULTS

Resting Q_c**:** Of the 15 subjects aged 25 ± 8 years (Mean ± SD) , 7 were male and 8 female. Height and weight values for the group were 173.5 ± 11.2 cm and 69.1 ± 13.0 kg, respectively. No differences were present between trials for any of the Q_c measurements taken under resting conditions. Table 1 shows stability of Q_c responses for sitting resting conditions in eight trials over two days of testing. Mean values for Q_c differed by less than 14% across all trials and the maximum variation in CI was ~1 l•min^{-1}. Inter-trial coefficients of determination for Q_c at rest ranged between 0.87 – 0.98, indicating highly consistent responses among subjects.

Exercise Q_c**:** *Ramp exercise*. Ramp exercise results for Q_c were evaluated only in terms of D1 Vs D2 test-retest reproducibility. Linear regression of Q_c/VO_2 was utilized from D1 and D2 test results for all subjects in order to examine linearity of Q_c responses. The Q_c/VO_2 regression values were $r^2 = 0.83$, $Y = 4.54 + 5.97x$, ($P < .001$) for D1. Day 2 Q_c/VO_2 regression analyses were comparable to D1 with $r^2 = 0.83$ and $Y = 3.96 + 6.50x$, ($P < 0.0001$). Similarly, Figure 1 illustrates a high correspondence of Q_c responses for the same time points in the ramp exercise tests on D1 and D2 ($r^2 = 0.82$). Between-trial variations in oxygen consumption and heart rate also were evaluated to determine if instability in these measures might have reduced the inter-trial estimates of Q_c reproducibility for this exercise condition. However, such effects were not evident, as the inter-trial coefficient of determination for heart rate and VO_2 were high on both days and similar in magnitude to calculated values for Q_c, i.e. $r^2 \geq 0.90$.

Fixed-load exercise: Cardiac output responses for the two exercise intensities (~25% and ~70% VO_2pk) were not significantly different in the FL exercise tests, either for duplicate determinations within the same test or between days (see Table 2). The intra-trial reliability coefficients exceeded $r^2 = 0.82$ ($P = 0.01$) for duplicate comparisons with the FL exercise. Table 2 also shows inter-trial reliability coefficients for Q_c measures between the two test days. Reproducibility of Q_c in FL exercise between D1 and D2 was somewhat lower ($r^2 = 0.59 - 0.90$) than what was found for duplicate determinations within the same test day. Inter-trial reproducibility of HR and VO_2 was also somewhat lower in the FL exercise tests (r^2 values = 0.66 – 0.84). However, intra-trial coefficients of determination for both of these variables were very high ($r^2 = 0.95$), suggesting that variations in these measures had little influence on of intra-trial exercise Q_c in the FL tests, but most likely influenced low reliability estimates for inter-trial measures.

DISCUSSION

This study was concerned with the reliability of the acetylene single-breath technique developed by Grollman in 1929 (6). Our aim was to evaluate intra- and inter-trial reproducibility of this method using a new proprietary computer-controlled measurement module developed by SensorMedics® Corporation that is integrated within their Vmax220® exercise metabolic gas exchange system. These results demonstrate that intra-trial reproducibility with this unit is high, regardless of the metabolic state of the subjects or the wide range of testing protocols that were evaluated. Lower reproducibility exhibited for between day Q_c for this study was most likely due to variations in HR and VO_2 between days. Our comparisons, for which this high reproducibility was

demonstrated, included seated resting Vs cycle ergometer exercise conditions, intra- and inter-trial comparisons, a wide range of exercise intensities that approximated 25-80% of VO_2pk, and fixed-load Vs ramping workload applications.

Exercise Measures: There is a need to establish the performance of the acetylene technique relative to its reproducibility for determining cardiac output within the context of exercise testing conditions appropriate for clinical assessment. To this end, we chose to analyze not only the linear response of Q_c measurements relative to increases in oxygen consumption and exercise intensity during ramping exercise, but also the reproducibility of measurements at two different levels of fixed-load exercise. We also evaluated the reasonableness of these values compared to other published data on Q_c for similar exercise situations. For example, the computed a-v O_2diff based on our observed VO_2 at the low (x = 0.97 L•min^{-1}) and high (2.25 L•min^{-1}) exercise intensities would be approximately 9.1 ml•100ml^{-1} and 11.7 ml•100ml^{-1}**,** respectively. Using calculations reported by Rowell (14), the estimated a-vO_2diff at corresponding exercise oxygen uptakes would be = 1.00 and 2.25 L•min^{-1} should be ~10.0 ml•100ml^{-1} and ~12.0 ml•100ml^{-1}**,** respectively. With the method of carbon dioxide rebreathing, it is not technically possible to measure exercise Q at intensities higher than 65% of peak capacity due to increasing carbon dioxide levels that interfere with the rebreathing procedure (9). With the C_2H_2 single-breath methodology, we have demonstrated that Qc can be assessed reliably within the same testing environment at loads up to ~75% of peak power, whether by fixed-load or ramp protocols.

Most non-invasive Qc measurement techniques do not offer a reliable and valid means to obtain Q_c measurements during high intensity exercise. Q_c measurements at

exercise $VO_2 \geq 3$ L•min^{-1} were observed in our study only within the ramping protocol. Measurements of higher intensities tend to be more difficult for subjects to perform. In a rebreathing study by Liu et al (10), exercise Q_c measurements were reported to be highly reproducible up to a heart rate of 190 bt•min^{-1}. However, even the single-breath technique that we evaluated presented difficulties for our subjects in terms of their reported problems in sustaining a controlled exhalation when breathing frequency exceeded 40 per minute.

Figure 2 gives evidence of stability of exercise Q_c responses between ramping and fixed-load exercise conditions, when comparisons are made at equivalent workloads and oxygen uptake levels. Regression analysis was used to establish a means to estimate Q_c for specific workloads during the ramping trials. This was done to provide a basis for comparing Q_c in RL exercise at the same workloads used for the FL trials. These comparisons indicate that Q_c values were very similar for both FL and RL exercise, at the low (26 W) and high (130 W) intensities. Similarly, we determined Q_c differences based on the same oxygen consumption at a low intensity and a high intensity equivalent to ~ 1.00 l•min^{-1} and 2.00 l•min^{-1}, respectively (see Figure 2). Again, no appreciable differences were found between Qc values the low (VO_2 = 0.98 l•min^{-1}) and high (VO_2 = 2.33 l•min^{-1}) exercise intensities.

Subject to much controversy in the literature when using the acetylene technique is the amount of time required before a duplicate measurement can be taken. This is because the level of residual acetylene gas in the subject cannot be determined once it has been inhaled to perform a Q_c measurement. Other studies have suggested using a 10-min interval between measures to allow approximately 5 min for acetylene to washout of the

circulation (4,13). However, Sadeh et al (15) reported a high correlation (r = 0.89) when comparing Q_c with thermodilution measures even when trials were performed consecutively, within an interval as brief as 10 min. No investigations to date have determined the acetylene washout time required to optimize reliability of Q_c measurement at rest or during exercise.

A graphic representation of reproducibility between measures is illustrated in Figure 3. We demonstrated reproducibility that was high for duplicate measures were taken 5 min apart (D1: $r^2 = 0.92 – 0.94$) and when this interval was shortened to 1 min (D2: $r^2 = 0.92$-0.98). In this study, we did not repeat a Q_c measurement until the $P_{ET}CO_2$ values stabilized to within 1 mmHg of the previous trial. It may be that some alternative markers, such as heart rate or RER, might function just as well in this regard. Our data suggest that a brief one minute period between trials was adequate time to produce reliable intra-trial Qc estimates.

As stated previously, Qc reliability between days for FL trials was somewhat lower than for intra-trial measures. This finding may have been attributable to the reproducibility in the applied workload in the trial, as well as inter-trial variability in subject related factors that affected HR and VO_2 responses, i.e. inter-trial biological variability. Measurements of responses for low and high intensities in both D1 and D2 were obtained at the same absolute power (W) for each subject. Coefficients of determination for between day measures of HR were 0.71 and 0.70 for the low and high intensity, respectively. Coefficients for VO_2 for the same were 0.48 and 0.50. While these coefficients are somewhat disappointing, reliability estimates for HR and VO2 for intra-trial measures are considerably higher at $r^2 = 0.87 – 0.93$ for HR and $r^2 = 0.87$ - 0.98 for

VO2. These coefficients are consistent with high coefficients for intra-trial Q_c measures (see Table 2).

Inter-trial VO_2, HR, and Q_c differences may have been affected by testing order, i.e. RL followed by FL. All FL trails were performed approximately ~ 30 min to 1 h after the RL trials and after subjects were allowed to drink water ad libdum and rest before the FL trial. In addition, responses during FL trials may be a result of physiological variation on the given day. Thus, while intra-trial Q_c measures were highly reproducible for both measures taken 5 min and 1 min apart, this technique may have influenced somewhat the estimate of between-day Q_c reliability.

To determine if bias were present in Q_c responses across different exercise intensities, a modified version of the Bland - Altman analysis was applied to individual Q_c trials (2). This analysis was designed to determine estimates of response bias, which may be present between some reference standard value and a new measurement. However, these bias plots also will work well when evaluating reproducibility and distribution around a mean (computed) value. A modified Bland-Altman plot was used in this study, to determine uniformity of response variability at different levels of cardiac output, e.g. if unexplained response variation may occur when the expected Q_c level is high. For the analysis, we computed a mean score for each individual for all respective time periods or workloads. This mean value is represented as a "zero" point for each person. Subsequently, each individual Q_c trial was plotted as a difference from that trial's mean. No systematic bias was present between resting and exercise values or ramping or fixed load exercise (Figure 4 and Figure 5.) For all resting measurements, the 95% CI were 6.06 ± 1.08 $l \bullet min^{-1}$. This spread is similar to an analysis recently published by

Warburton et al (18) using the acetylene rebreathe technique. For ramping and the fixed load, CI bands were 15.88 ± 1.51 $l \bullet min^{-1}$ and 14.84 ± 1.27 $l \bullet min^{-1}$, respectively. The potential to detect any experimental intervention or clinical effect is promising during exercise given these CI bands (<10% of the mean difference.)

CONCLUSIONS

This new proprietary automated single-breath acetylene system reliably measures cardiac output in apparently healthy adults. This technique was reproducible not only at rest and during fixed-load exercise in which a stable physiological environment was established (intra-trial), but also during ramping exercise. Further investigations should focus on the reproducibility of the single-breath technique within ramping exercise protocols, using shorter measurement intervals (~3 min) between trials. Finally, a study should be done to contrast Q_c responses for apparently healthy subjects with patients who have specific cardiovascular diseases, e.g., CHF patients.

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Table 1. Cardiac output values measured under resting conditions in eight different trials over two days (N=15;mean ± SD).

Trial	Mean Qc ($l \cdot min^{-1}$)	CI for Qc ($l \cdot min^{-1}$)
Rest1 D1	5.9 ± 1.7	0.88
Rest2 D1	5.7 ± 1.6	0.79
Rest3 D1	6.3 ± 1.8	0.90
Rest4 D1	6.5 ± 2.1	1.06
Rest5 D2	5.8 ± 1.5	0.77
Rest6 D2	5.9 ± 1.9	0.94
Rest7 D2	6.4 ± 2.4	1.20
Rest8 D2	6.2 ± 2.0	0.96

CI is 95% confidence interval.

Table 2. Exercise responses and coefficients of determination cardiac output at two different fixed-load intensities during cycle ergometry exercise on Day 1 and Day 2.

Fixed-Load (FL) Trial	**Power (Watts)**	**HR ($bt \cdot min^{-1}$)**	**VO_2 ($l \bullet min^{-1}$)**	**Qc ($l \bullet min^{-1}$)**	**Intra-trial r^2 values**	**Inter-trial r^2 values**
FL1- LOW	26 ± 8	92.1 ± 8.4	0.97 ± 0.30	10.4 ± 2.9		
FL1- LOW	26 ± 8	94.9 ± 11.4	0.94 ± 0.25	10.6 ± 3.3	0.94	
FL1- HIGH	130 ± 7	144.7 ± 15.1	2.22 ± 0.50	18.9 ± 4.2		
FL1- HIGH	130 ± 7	152.4 ± 17.4	2.28 ± 0.55	18.7 ± 4.5	0.92	
FL2- LOW	26 ± 8	97.3 ± 10.4	1.10 ± 0.47	10.8 ± 3.4		0.69
FL2- LOW	26 ± 8	101.8 ± 7.2	1.08 ± 0.42	10.7 ± 3.5	0.98	0.72
FL2- HIGH	130 ± 7	150.7 ± 13.0	2.37 ± 0.71	19.2 ± 4.4		0.90
FL2- HIGH	130 ± 7	152.7 ± 22.1	2.47 ± 0.71	18.6 ± 4.0	0.92	0.59

Values are Means ± SD; Intra- and inter-trial coefficients of determination for corresponding trials, e.g. $r^2 = 0.94$, show reproducibility for duplicate measurements of Q_c at the low load on day 1. Similarly, $r^2 = 0.69$ shows Q_c reproducibility for the low load exercise level between Day 1 and Day 2 (inter-trial reproducibility).

List of Captions for Figures 1-4 (figures follow)

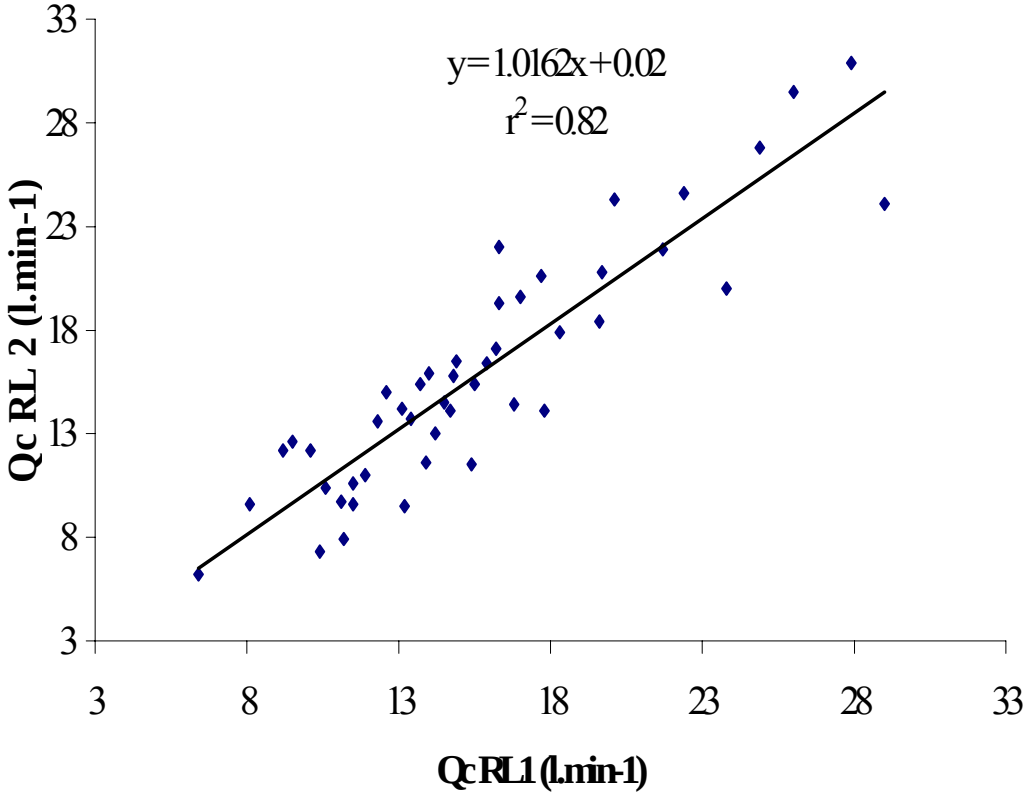
Figure 1. Inter-trial reproducibility for acetylene single-breath cardiac output measurements for ramping cycle ergometer exercise in apparently healthy adults (N=15).

Figure 2. Comparative values between the ramp and fixed-load exercise test for acetylene single-breath cardiac output measurements at the same power output and oxygen consumption (N=15).

Figure 3. Acetylene single-breath cardiac output responses during low-intensity and high-intensity fixed-load exercises. Vertical bars show stability of cardiac output responses, when repeated determinations are made, using either 1- or 5-min intervals (N=15; values are Mean ± SD).

Figure 4. Individual differences from mean acetylene single-breath cardiac output Qc for fixed-load exercise. Each data point represents an individual Qc measure relative to that persons mean Qc values for four FL trials over the two day period. The mean Qc value is represented as the "0" point on the vertical axis (N = 15; CI = 14.84 ± 1.27 $l \bullet min^{-1}$).

Figure 5. Individual differences from mean acetylene single-breath cardiac output Qc for ramp exercise. Each data point represents an individual Qc measure relative to that persons mean Qc values for the two RL trials. The mean Qc value is represented as the "0" point on the vertical axis (N = 15; CI = 15.88 ± 1.51 $l \bullet min^{-1}$).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8
13
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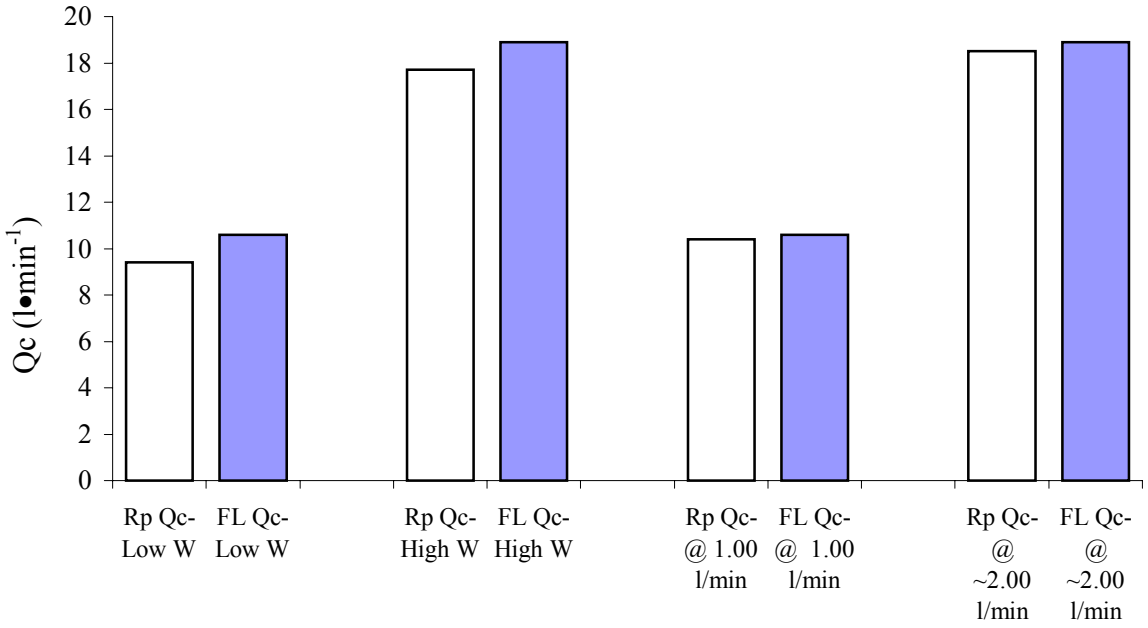
28
33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18
16
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12
10
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6
4
2
0
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FL Qc- Low W
Rp Qc- High W
FL Qc- High W
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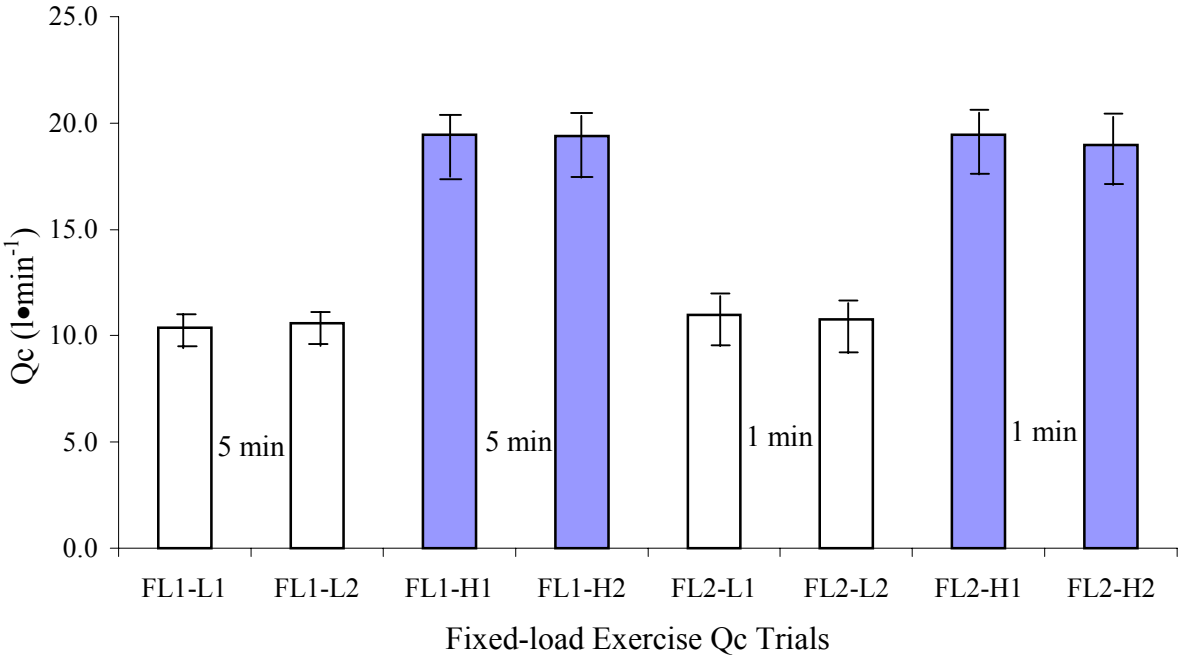
Rp Qc- @ ~2.00 l/min
FL Qc- @ ~2.00 l/min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5 min
1 min
1 min
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FL2-L1
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FL2-H2
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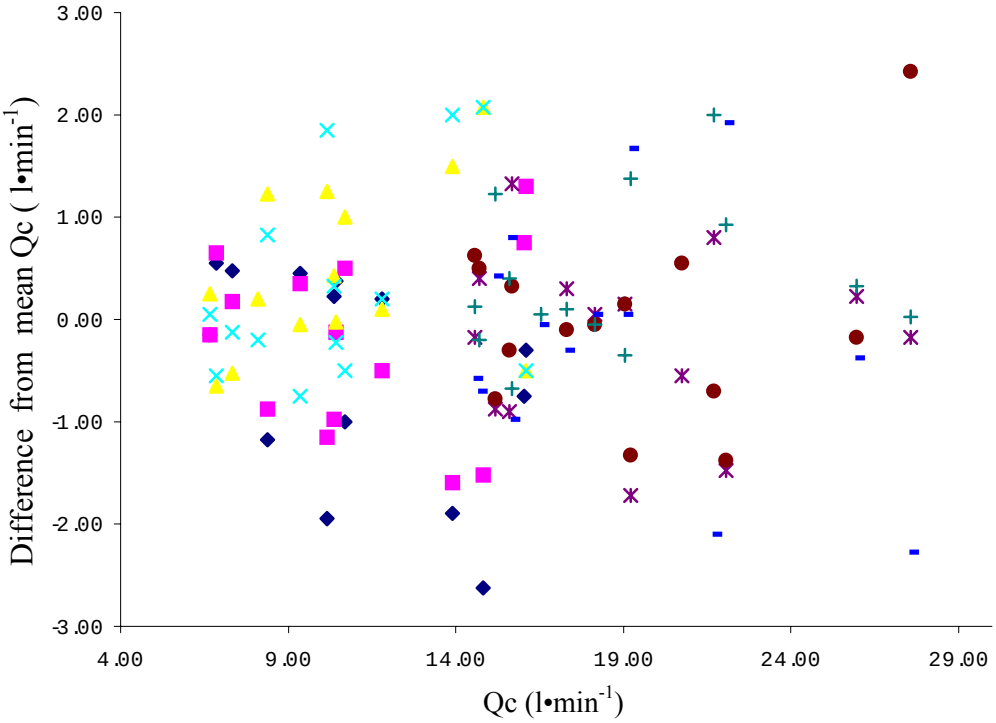
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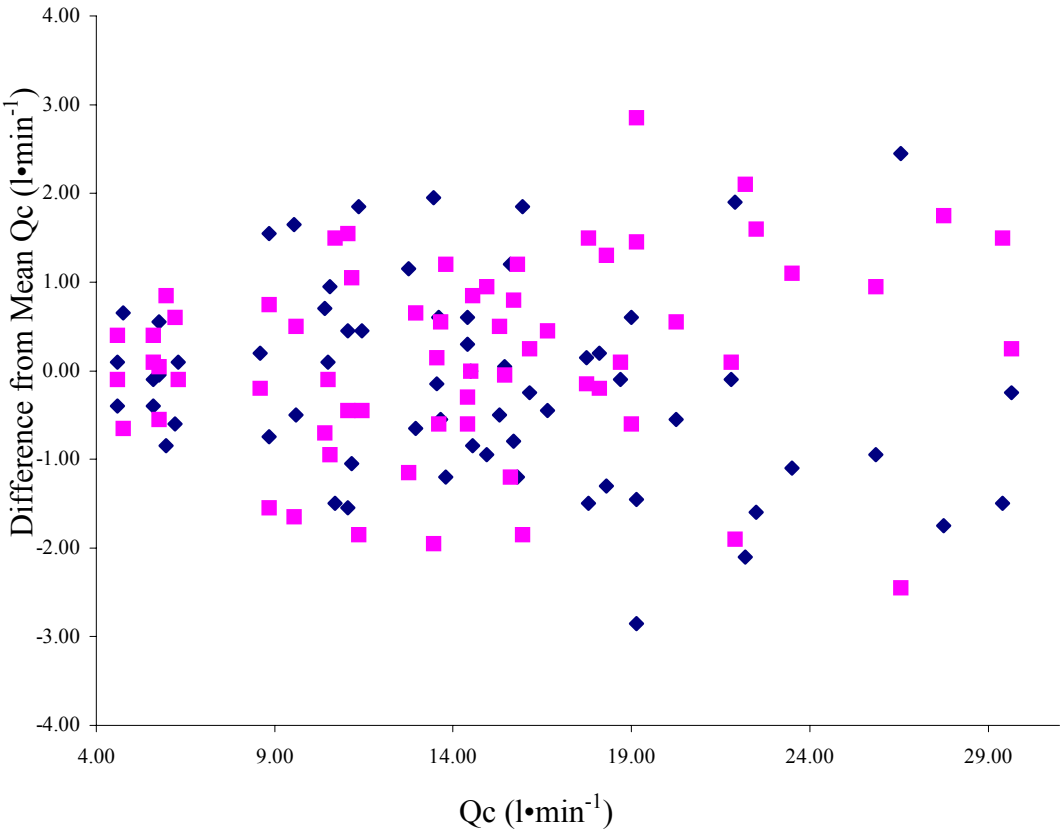
Qc (l•min-1)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Difference from Mean Qc (l•min-1)
4.00
9.00
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19.00
24.00
29.00
Qc (l•min-1)

CHAPTER IIIB

Journal Manuscript II

THE RELATIONSHIP BETWEEN MARKERS OF DISEASE SEVERITY IN OBSTRUCTIVE SLEEP APNEA PATIENTS TO HEMODYNAMIC AND RESPIRATORY FUNCTION DURING GRADED EXERCISE

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ABSTRACT

The Relationship Between Markers Of Disease Severity In Obstructive Sleep Apnea Patients To Hemodynamic And Respiratory Function During Graded Exercise JS. Blevins, DE. Zedalis, J Gregg, L Cross, H Ballentine, R Bos, WG. Herbert,FACSM. Department of Human Nutrition, Foods, and Exercise, Virginia Tech, Blacksburg, VA. **Purpose**: The purpose of this investigation was to describe the extent to which graded exercise testing may reveal abnormalities of hemodynamic response in obstructive sleep apnea (OSA) patients, particularly with respect to cardiac output (Qc), blood pressure (SBP, DBP, MAP), and total peripheral resistance (TPR) that may be related to polysomnography markers of OSA severity. **Methods:** Eleven, newly diagnosed OSA patients (6 male and 5 female) a maximal graded exercise test (GXT) an electronically braked cycle ergometer. Hemodynamic measures were taken during sitting resting and at a submaximal exercise intensity (64.7 ± 6.3 % VO_2pk). Hemodynamic variables of interest were then compared to polysomnography (PSG) markers of OSA severity (respiratory disturbance index (RDI), lowest SaO2 during sleep (lowSaO2), and percent time that SaO_2 < 90 percent during sleep using Pearson product moment correlation and multiple regression analysis. Twenty-four hour urinary nitrite/nitrate elimination was also performed as a biological marker of vascular function. **Results:** Peak oxygen consumption for the group was 2.10 ± 0.70 l•min^{-1} (range = 1.33 - 3.27). Average age predicted max heart rate achieved was 0.87 ± 0.07 bt•min^{-1} (range = 0.78 – 1.01). subjects tended to be middle-aged (45.3 ± 11.7 yr) with borderline obesity (BMI: 35.8 ± 6.4). Regression analysis revealed that body mass index (BMI) and submaximal exercise stroke volume (SV) were able to explain 88 percent of the variance relative to low the

lowest SaO_2 during sleep (P = 0.009). Moreover, BMI, SV, and mean arterial pressure were able to explain 97 percent of the variance relative to the lowest SaO_2 during sleep (P = 0.002). **Conclusion:** This study was conducted, in part, to explore circulatory function in OSA patients during exercise and to examine the potential relationships between exercise hemodynamics and clinical markers of disease severity in OSA that may explain the occurrence of daytime hypertension. A hypoxic marker of disease severity in OSA , SaO_2, was related to abnormal responses during submaximal exercise while the number of apneic events that occurred during sleep was not significantly related with any exercise cardiorespiratory or hemodynamic measures in this group of OSA patients.

Key words: obstructive sleep apnea, cardiac output, stroke volume, nitrite/nitrate, incremental exercise test

INTRODUCTION

Limited information is available concerning how obstructive sleep apnea OSA) patients respond to exercise. The present study has provided a methodological means to understand hemodynamic functioning of OSA patients. Moreover, from the results of this study, body mass index BMI) and exercise hemodynamic measures taken during a standard graded exercise test GXT), including mean arterial pressure MAP) and stroke volume SV), may be sensitive indicators of hypoxic polysomnography PSG) markers of OSA severity.

Obstructive sleep apnea OSA) is estimated to affect 2 to 4 percent of the adult population (1), (2). However, an estimated 80 to 90 percent of adults with moderate to severe OSA may be clinically undiagnosed. Annual medical costs associated with undiagnosed sleep apnea have been reported to be double that of age and gender matched controls (3)) Identification of those at risk and their subsequent diagnosis is, obviously, of great concern to clinicians. Risk factors associated with development of the disorder have helped physicians to understand the clinical presentation of the OSA patient. Middle-aged, males with upper torso obesity and cranio-facial abnormalities who snore loudly are at highest risk for developing OSA. Furthermore, the prevalence of OSA is relatively high in those with co-morbidities of hypertension 50%), myocardial infarction, stroke, neuropsychiatric problems, coronary artery disease 20%), congestive heart failure, ventricular arrhythmias 13%), angina, and obesity (4-8)) Of these co-morbidities, the extent to which OSA may contribute to or be a consequence of cardiovascular pathology is at the forefront of clinical and diagnostic research as well as subsequent patient

management. Easier, less costly, but accurate screening and diagnostic techniques are needed in order to understand this complex disorder.

The disorder causes a complex interplay between factors that together compromise upper airway patency. These factors include obesity, nasal obstruction, enlarged tonsils, and micrognathia (9-11),(12). Also are factors that restore upper airway patency, including impaired neurochemical drive, upper airway reflexes, and load compensation capabilities (13-16). Moreover, different anatomical features between normal weight and obese patients may cause various subtypes of OSA with differing degrees of severity (17, 18).

Considerable potential exists to investigate the extent of OSA's effect on cardiovascular function during exercise via several causal theories. Etiological theories linking OSA to hypertension, ischemic heart disease, and congestive heart failure include the following; a) increased sympathetic drive associated with apnea and desaturation that may spill over to daytime functioning (4, 19-22); b) attenuated endothelium-dependent vascular relaxation (23-25), c) increased peripheral vascular resistance (26, 27), d) exaggerated negative intrathoracic pressure' and 5) decreased chemosensitivity (6). With regards to exercise testing, obstructive sleep apnea patients show evidence of reduced functional capacity compared to their age and gender matched controls (28). Cardiorespiratory and hemodynamic investigations during exercise have determined that OSA patients exhibit systemic and pulmonary hypertension (29, 30), increased left ventricular wall stress (31), low fibrinolytic activity (32), and abnormal ventilatory compensation (33, 34). Additionally, arterial blood gas values have also been evaluated during exercise to differentiate OSA from other types of sleep apnea, including central

sleep apnea and obesity-hypoventilation syndrome (17, 18). Of these investigations, the extent to which the severity of OSA may effect or be detected during standard exercise evaluations is limited.

Clinicians have attempted to determine methods that may be used to establish those clinical diagnostic criteria polysomnography information, PSG) that are most important in characterizing disease severity in the OSA patient. Controversy exists among clinicians as to an optimal set of criteria primarily because of the varying effects OSA has on daytime functioning (12, 35-37)). Moreover, physiological states are most often studied only under resting conditions.

The purpose of this investigation was to describe the extent to which graded exercise testing may reveal abnormalities of hemodynamic response in OSA patients, particularly with respect to cardiac output, blood pressure, and total peripheral resistance.

METHODS

Subjects

Patients in the OSA group were recruited from a group of volunteers who had been previously referred to the Southwest Virginia Sleep Disorders Center SVSDC) in Christiansburg. The protocol was approved by Institutional Review Board at Virginia Tech. All referred patients were given an informative flyer explaining the general protocol and benefits of the study. Interested individuals, who signed the recruitment flyer, were called about the specifics of the study. Screening for exclusion criteria and further willingness to participate was also conducted at this time. Exclusion criteria for all OSA subjects included; recent complicated myocardial infarction, recent episode of uncontrolled or increasing angina pectoris, recent revascularization, moderate to severe

chronic obstructive pulmonary disease, congestive heart failure, uncontrolled hypertension, uncontrolled diabetes mellitus, orthopedic and musculoskeletal disabilities, history of regular participation in moderately vigorous physical activity.

Baseline Characteristic Measures

Interested OSA candidates were interviewed the morning immediately following their diagnostic PSG in order to disclose the purpose of the clinical treatment trial in detail, determine eligibility based on exclusion criteria, sign the informed consent questionnaire, administer appropriate questionnaires, and obtain demographic and baseline characteristic measures. The questionnaires included in this investigation were medical history questionnaire and the Veterans Specific Activity Questionnaire (VSAQ) to predict peak-MET capacity. Height in), weight kg), and neck, waist, hip circumference cm), and BMI (body weight (kg) / height (m^2) were taken at this time. Patients subsequently reported to either the Health and Exercise Science Lab (HESL) at Virginia Tech or the Southwest Virginia Sleep Disorders Clinic in the morning, but before the initiation of nCPAP, to complete baseline resting and the graded exercise test (GXT).

Exercise testing

Resting Measures. Resting measures were taken while subjects were seated on the bicycle to be used during the GXT. The Vmax 229® (SensorMedics, Yorba Linda, Ca.) metabolic cart was used to collect expired respiratory gases for oxygen uptake and for single-breath acetylene cardiac output (Q_c) determinations. Subjects were fitted to the breathing apparatus after which data were collected for a period of 5 min of quiet breathing were collected. Methodology used for the Q_c procedure is described by Zenger et al (38) and was performed in accordance with the manufacturer's protocol for the

device using proprietary computer software (see below). For the Q_c measurements taken at rest, subjects breathed through a valve and mouthpiece assembly for 5 min to promote normalization of ventilation, before expired respiratory gases were collected. End-tidal carbon dioxide values $P_{ET}CO_2$) were used to estimate the minimum washout time necessary before proceeding to the next measurement of Q_c. A second Q_c trial was taken as soon as $P_{ET}CO_2$ values were within 1 mmHg of the preceding value. This resulted in the intra-trial measurement interval being reduced to 1-2 min. A minimum of three measurements was taken before the GXT.

Blood pressure BP) was assessed indirectly with a standard mercury sphygmomanometer and stethoscope. Heart rate HR) was assessed using the Schiller AT-10® ECG recorder (Switzerland). Both were taken at rest immediately preceding the GXT, as well as immediately before each Q_c measurement.

Exercise Measures. A graded exercise test (GXT) was completed on an electronically, braked bicycle ($CardioO_2$, MedGraphics, St. Paul, MN). Subjects began at an initial work rate of 25 Watts and load were continuously ramped every 90 sec. The ergometer allowed application of ramp rates of 12, 17, and 22 Watts•$90sec^{-1}$, pre-selected according to each subject's body weight and activity habits so that the target exercise intensity endpoint was reached within 20 min 14,(39). Activity habits were assessed using the Veterans Specific Activity Questionnaire. Subjects were asked to give "maximal" effort in order to achieve peak (RPE> 17). The Vmax 229® (SensorMedics, Yorba Linda, Ca.) metabolic cart was used to collect expired respiratory gases for oxygen uptake (VO_2), carbon dioxide production VCO_2), and respiratory exchange ratio

(VCO_2/VO_2). The highest VO_2 reached during the last min of exercise was used as the peak oxygen consumption (VO_2 pk).

A trained physician as well as an ACSM Certified Exercise Specialist supervised the test. All subjects were monitored continuously throughout exercise for possible signs of myocardial ischemia and heart rhythm disturbances via a 12-lead ECG. Test termination criteria were used to limit exercise endpoints, as recommended by the ACSM *Guidelines for Exercise Testing and Prescription* (40)). Blood pressures, Qc, rating of perceived exertion (RPE), were taken every three minutes while and heart rate (HR) was taken the last 10 sec of every 90 sec stage.

Cardiac output, total peripheral resistance, and stroke volume determination. The Q_c procedure was explained in detail and then each subject practiced the breathing technique under resting conditions during the interview process. The Vmax 229® (SensorMedics, Yorba Linda, CA.) metabolic cart was used to determine Q_c determinations. This methodology is described by Zenger *et al* (38) and was performed in accordance with the manufacturer's protocol for the device, using proprietary computer software. Subjects breathed through the valve and mouthpiece assembly for 5 min while seated on the bike to promote normalization of ventilation, before expired respiratory gases were collected. Before the single-breath Q_c expiratory maneuver, subjects first exhaled to near residual volume. At that time, the Vmax 229® automatically switched to a test gas mixture containing 0.03% acetylene, methane, and carbon monoxide, and balance nitrogen, which the subject inhaled to near maximal lung capacity for a breath hold of 1 to 2 sec. Finally, the subject slowly exhaled for a period lasting 5 to 8 sec. End-tidal carbon dioxide values ($P_{ET}CO_2$) were used to estimate the minimum of washout

time necessary before proceeding to the next measurement of Q_c at rest. At rest, the second Q_c trial was taken as soon as $P_{ET}CO_2$ values were within 1 mmHg of the preceding value. This resulted in the intra-trial measurement interval of 1-2 min (intra-trial r^2 =0.92 –0.98). Due to the nature of the GXT, only one Q_c measurement was taken at 3 min intervals. Cardiac index (CI), relative total peripheral resistance (TPR), and stroke volume (SV), were calculated manually from Q_c determinations.

Urinary nitrate/nitrite determination.

Twenty-four hour urine samples were collected from each subject prior to exercise testing. For storage, each 24 hour sample was measured for volume and then ~100 ml of the sample was stored at –70 degrees Celsius until the time of analysis.

Nitrate (NO_3-) and nitrite (NO_2-) were determined using high performance liquid chromatography HPLC). A Beckman "Gold" Model HPLC system (San Ramon, CA) was connected to a Wescan Silica-based anion and cation exchanger (column 10 x 4 mm: Alltech, Deerfield, IL). On the day of determination urine samples were thawed in cool water, centrifuged at 4000 rpm for 20 minutes and filtered through YMT ultrafiltration membranes (Amicon, Inc., Beverly, MA). Urine was diluted with distilled water. The mobile phase was 1.5 mM sulfuric acid. Nitrate and nitrite standards (LabChem, Inc., Pittsburgh, PA) were injected first at a flow rate of 3 min. Retention times for NO2- and NO3- were 3.67 min and 16.4 min, respectively. For aqueous standards within the concentration interval the regression coefficients for the standard curves were : r^2 = 0.999 (NO2-) and r^2 = 0..998 (NO3-).

Nitrate production was calculated mmol/24 hours and normalized to individual renal function creatinine clearance estimated according to eh equation):

$$\frac{150 - \text{age} * \text{body weight in kg k)}}{\text{Ccr}} = \text{creatinine clearance ml/min)}$$

in which Ccr = creatinine serum concentration in mmol/l; k = 1.1 and 0.9 for males and females, respectively (41). Total urinary nitrate/nitrite excretion was reported as U_{NOx} (*u*mol/mmol creatinine).

Statistical Analysis

Values are reported as mean ± SD. Pearson product moment correlation coefficients were calculated to explore potential relationships between hemodynamic variables (HR, SBP, DBP, MAP, Qc, SV, and TPR) and polysomnography (PSG) markers of sleep function. Polysomnography markers included respiratory disturbance index (RDI), total sleep time (TST), awake time (AWAKE), slow wave sleep time (SWS), rapid eye movement sleep time (REM), lowest SaO_2 during sleep ($lowSaO_2$) and percent of total sleep time below SaO_2 of 90 percent PTless90).

Multiple linear regression was used to investigate PSG markers of OSA severity. Descriptive and hemodynamic exercise variables were entered as predictor variables in subsets of three clustered by observer choice, using "enter" selection method in SPSS statistical software package. These clusters were then matched to three of the most common criterion PSG markers of OSA severity used in clinical practice; RDI, $lowSaO_2$, and PTless90. The regression equations included were those with the highest multiple correlation coefficients and for which beta coefficients were statistically significant at P level of .05.

RESULTS

Descriptive characteristics including the physical characteristics of the eleven newly diagnosed OSA patients 6 male, 5 female) are presented in Table 1. In general,

subjects tended to be middle-aged 45.3 ± 11.7 yr) with borderline obesity BMI: 35.8 ± 6.4). The average respiratory disturbance index RDI) for the group was 30.8 ± 30.5 events per hour of sleep and ranged from 10.6 to 120.0 Table 2). The lowSaO_2 for the group was 84.1 ± 8.4 percent range = 63.0 - 96.0) and the percent time of sleep that SaO_2 was less than 90 percent PTless90) was 20.6 ± 37.1 percent range = 0.3 - 99.1). Subjects medical histories and various medications used are included in Table 3a and 3b. For the group, high comorbid prevalence rates were present with respect to cardiovascular disease n = 4), orthopedic diseases and disabilities n = 6), and psychological diagnoses n=5). In addition, four patients were diagnosed with periodic leg movement disorder for which they were being pharmacologically treated Table 3b).

Rest and exercise hemodynamic and respiratory responses

Resting hemodynamic measures, including cardiac output Q_c), stroke volume SV), mean arterial pressure MAP), and total peripheral resistance TPR) are presented in Table 4. End-tidal oxygen pressure $P_{ET}O_2$) and end-tidal carbon dioxide pressure $P_{ET}CO_2$) were 94.8 ± 7.0 mmHg range = 84.6 – 104.0) and 34.1 ± 5.0 mmHg range = 27.3 – 41.3), respectively.

Exercise responses represented in Table 5 correspond to hemodynamic and respiratory responses at a submaximal load corresponding to moderately vigorous exercise intensity equal to 64.7 ± 6.3 percent range = 55.0 - 78.0) for this patient sample. Eight subjects were able to complete Q_c measures during exercise so that Qc, SV, and TPR means, standard deviations, and ranges are reported for these eight only. Peak oxygen consumption for the group was 2.10 ± 0.70 $l \bullet min^{-1}$ N= 11: range = 1.33 - 3.27). Average age-adjusted predicted maximal heart rate achieved was 0.87 ± 0.07 range =

0.78 – 1.01) and peak rating of perceived exertion was 16.7 ± 0.91 range = 15 – 18). Ten subjects stopped exercise due to general fatigue and one stopped due to a peak limit imposed by the electronic bicycle ergometer. Symptoms, which occurred during the graded exercise, test included lightheadedness, dry mouth, and slight headache.

Relationship between PSG markers of disease severity and hemodynamic variables.

Pearson correlations for resting and submaximal exercise are presented in Table 6-8. Rapid eye movement REM) sleep time was significantly correlated with resting see Table 6) diastolic blood pressure DBP) r = -0.69; P = 0.02) and MAP r = -0.60; P = 0.05). Lowest SaO2 was significantly correlated with resting HR r = -0.62; P = 0.02). Relationships see Table 7) were observed between total sleep time TST) and exercise SV r = 0.70; P = 0.05) and slow wave sleep time and SV r = 0.69; P = 0.05). Additionally, reserve calculations for submaximal work were determined in order to account for any differences in resting measures. The reserve was calculated as the percent of a given variable remaining between submaximal and peak exercise reserve = peak – submaximal / peak – resting)). A low percentage meant that the patient only had a small amount of reserve left before reaching peak exercise. A high percentage meant that the patient had a large amount of reserve of a given variable before reaching peak exercise. Only HR, SBP, DBP, and MAP were calculated as Q_c, SV, and TPR measures were not obtainable during peak exercise. No significant relationships were present for any of these variables N = 10: range r = -0.02 – 0.65). Neither RDI nor PTless90 were significant criterion variables with any selected cluster of predictor variables.

DISCUSSION

In OSA patients, reduced intrathoracic pressure, hypoxia, and frequent arousals during sleep in increased sympathetic nervous system activity and reduced baroreceptor sensitivity and contribute to the development of daytime hypertension, left ventricular dysfunction, and possibly coronary heart disease (9),(7, 42-46). Additionally, treatment of the disorder using nasal continuous positive airway pressure nCPAP) has been evaluated for its ability to improve cardiovascular and systemic function by reducing daytime blood pressure after short-term treatment (47), Shifflet *et al*, 1999, in review). However, to our knowledge hemodynamic function during exercise, specifically Q_c, SV, and TPR have not been investigated. In the present study, an automated technique (38, 48, 49) for the non-invasive measurement of cardiac output was used to evaluate exercise hemodynamic function in this group of OSA patients.

Several aspects of this group of patients are note worthy with regard to physical characteristics, comorbid conditions, and disease severity. Risk factors for the development of OSA include being middle-aged, male, upper-torso obesity, loud snoring, witnessed nocturnal choking or gasping, and craniofacial abnormalities (2, 50, 51),(52). While these patients were middle-aged and borderline obese, 45 percent of the sample n = 5) were females. Much of the published literature has focused on males. Certainly, the subject recruitment process volunteer) as well as a the small number of patients in this investigation are an important consideration, especially when compared to large epidemiological population studies. The National Institutes of Health classifies a BMI above 30 as being obese and above 34.9 as being morbidly obese. Similarly, women with waist circumferences greater that 88 cm and males greater than 100 cm have been

demonstrated to be at increased risk for cardiovascular disease and diabetes. All males and females in this sample had waist circumferences greater than 95 cm see Table 1). Relative to OSA patients, Redline and Strohl (53) report that patients with BMIs greater than 29 are 8 to 12 times more likely to be at risk for OSA than non-obese individuals. Only two subjects had BMI values below 30 and six were above 35. Body mass index was an important predictor of OSA severity lowest SaO_2 as criterion variable) in this sample of patients. Finally, seven of the eleven patients 64 percent) had additional cardiovascular or metabolic related disorders see Table 3a) whereas five 54 percent) had orthopedic limitations. Obstructive sleep apnea recently has been linked and reported as being a significant risk factor for the development of chronic hypertension (5, 54, 55). Twenty-seven percent (n = 3) of this sample had diagnosed hypertension. However, given the high prevalence of obesity in this group, these comorbid conditions should not be considered as being solely related to or a consequence of OSA.

Functional Capacity.

The relationship of disease severity in OSA patients to subjective and objective measures of daytime function is of considerable interested to many clinicians. One objective measure used to evaluate fatigue in OSA patients is peak oxygen consumption. The mean level of peak oxygen consumption achieved by this group (2.10 ± 0.70 l•min^{-1}) was higher than reported by Taguchi et al. (1.84 ± 0.35 l•min^{-1}) (47) but similar to that reported by Vanuxem et al. (2.15 ± 0.81 l•min^{-1}) (56). However, according to the American College of Sports Medicine (57), the age-adjusted predicted VO_2pk for this group of patients, averaged for sedentary males and females of similar age is expected to be close to 30.6 ml•kg^{-1}•min^{-1}. The VO_2 pk achieved by this group (20.6 ml•kg-1•min-1)

equates to 67 percent of the age predicted max value or a functional aerobic impairment (FAI) equal to 33%, mild impairment (57). While bicycle ergometry tends to under-estimate VO_2 pk by approximately 12%, this group of males and females would still be well below average.

The extent to which reduced work capacity may be related to objective measures of OSA has been evaluated by several investigators. Vanuxem et al (56) reported that lower VO_2 peak values were significantly correlated with the apnea index total number of apneic events during a night of sleep) ($r = -0.69$; $P < 0.05$) and minimum oxygen saturation during sleep ($r = 0.65$; $P < 0.05$). Tremmel *et al* (58) studied the prevalence of CSA and OSA in 34 patients admitted to a cardiac care unit 1 month after their diagnosis with acute left ventricular failure . In this study, predicted VO_2pk reached also was lowest in the CSA sub-group (n = 21: 66 percent of predicted maximum). However, the OSA group was also reduced at 72 percent of predicted VO_2pk than were non-sleep disorder patients without sleep disorders (92 percent of predicted VO_2pk) $P < 0.009$). There also was a significant correlation between AHI and percent VO_2 max, but this was observed mainly in the CSA patient subset ($r = -0.73$) ($P < 0.01$). Tremmel et al found no relationships between sleep function and exercise capacity were found in the OSA group.

In a prospective investigation, Aguillard et al (28) evaluated a group patients who were of similar age (47.1 yr) and RDI scores (N = 32:AHI = 30.8 ± 31.8 # of apneas + hypopneas/ hr of sleep) to those in the present study. All were tested on an electronic bicycle ergometer and obtained a measured VO_2max equivalent to 91.3 percent of age-adjusted maximal values for their gender. While they found that predicted max was significantly different from achieved VO_2max for the group, VO_2max was poorly

correlated with the AHI (r = 0.07), but was significantly correlated with REM percentage of sleep (r = 0.44). Additionally, a subjective rating of fatigue (Fatigue Severity Scale) was not significantly correlated with apnea scores. In this group of patients reported in our study, VO_2 pk was not significantly related to RDI scores (r = -0.02, P = 0.95) or REM sleep time (r = 0.25, P = 0.49). The fact that reduced aerobic fitness or work capacity an objective marker of exercise limits was not significantly correlated with RDI should not be mistakenly interpreted. Investigators have reported that daytime subjective indicators of fatigue rather than sleepiness, may not reflect objective measures of sleep function (PSG) (36, 59). This is of clinical importance for both the newly diagnosed OSA patient and for patients who have been medically treated for OSA. For example, OSA patients may report daytime subjective feelings of fatigue that are related to reduced physical fitness or mental fatigue and not related to OSA. If this is the case, measures more likely can be taken by the patient to adopt positive lifestyle behaviors (weight loss, physical activity) in order to reduce daytime fatigue.

Carbon dioxide and ventilatory responsiveness

Several investigators (17),(60) have stated that OSA patients may present either with daytime hypercapnia or hypocapnia with accompanying hypoxia. Some discrepancy exists in the literature with regards daytime hypocapnic versus hypercapnic states in those with various sub-types of sleep apnea, including OSA, central sleep apnea (CSA), and obesity-hypoventilation syndrome (OHS) (61). Chemoresponsiveness in sleep apnea patients largely depends on the etiology of the disorder. For example, congestive heart failure patients develop CSA primarily from Cheyne-Stokes respiration that is partly

related to sluggish pulmonary circulation secondary to right ventricular decompensation causing daytime hypocapnia without associated hypoxemia (7).

End-tidal carbon dioxide and oxygen pressures ($P_{ET}CO_2$ and $P_{ET}O_2$, respectively) were used as non-invasive indicators of arterial blood gas pressures see (Table 4 and 5) Patients in this study were normocapnic without hypoxia. Correlation coefficients were also calculated for end-tidal gas pressures (not reported). Neither resting or exercise gas pressures were significantly correlated with any PSG markers of OSA severity (RDI, PTless90, lowSaO_2), nor was the difference between rest to peak exercise values. This was a somewhat surprising considering the high BMI values for the patients in the study. Others (16),(17),(18)) have reported that OSA patients with a high BMI may frequently exhibit daytime hypercapnia, with hypoxemia at rest and during exercise. These investigators (18),(30)) used a steady state exercise load, unlike the GXT used in the present study, to evaluate blood gas pressures. Vanuxem *et al* (56), on the other hand, reported an increase in arterial blood oxygen pressure (PaO_2) from rest to peak exercise in OSA patients compared to controls. They interpreted that the increase observed in the patients was significantly higher at peak exercise (95 mmHg) than in control subjects (88 mmHg). While arterial blood carbon dioxide pressure ($PaCO_2$) decreased from rest to peak exercise in Vanuxem's group, the difference was not statistically different between the two groups. A trend for an increase in $P_{ET}O_2$ during exercise was noted in the present study. However, this difference was not found to be significant using dependent t-test analysis. It is plausible, however, that OSA may cause mechanical impedance to breathing, which is related to thoracic and abdominal fat (obesity-hypoventilation syndrome) or retrognathia; this may exacerbate ventilation-perfusion mismatching during

exercise stress (62). Further investigation regarding mechanisms of reduced chemosensitivity and ventilation-perfusion mismatching should be explored in the future.

Relationships between exercise hemodynamic responses and PSG markers of OSA severity

While exercise did not result in any appreciable abnormal hemodynamic responses in this group of OSA patients, several hemodynamic and descriptive variables were related to PSG markers of sleep function and seem to explain some of the variance in at least one important PSG marker of disease severity in OSA. As stated previously, lowest SaO_2, PTless90, and RDI were used as criterion PSG indices of OSA severity. Of these three variables, lowest SaO_2 during sleep was found to have the highest relationship to any descriptive and hemodynamic exercise variables. Most remarkable are for that of submaximal SV responses (see Table 8). In this limited sample, BMI and submaximal SV accounted for 88 percent of the variance relative to lowSaO_2 P = 0.009). Moreover, BMI, SV, and MAP explained 97 percent of the variance relative to lowSaO_2 P = 0.002). As noted previously, a high BMI is known to be important predictor of the presence of OSA (53, 63). Friedman et al (10) recently reported that BMI alone was significantly correlated with RDI severity correlation coefficient not given, (P = 0.003) and that BMI, mallampati grade and tonsil size together, significantly predicted RDI severity. However, as noted by Skomro and Kryger (2), obesity alone should not be considered a reliable predictor of the presence of OSA nor severity of the disorder. In this study, easily measured markers of cardiovascular function SV and BP) obtained at a submaximal level were able to explain additional variance with regard to a hypoxemic marker of OSA severity.

Nitrite/ nitrate elimination

In the present study, U_{NOx} excretion was similar to that reported in the literature 231.6 ± 277.2 *u*mol/mmol creatinine)(41). However, considerable variability existed among the eight subjects 23.8 – 757.4 *u*mol/mmol creatinine). This biological marker was used as a global indicator of impaired vascular function reduced release) which may affect vascular resistance. Evidence of reduced peripheral circulation or increased peripheral vascular resistance in OSA patients is limited. While at least two investigations (64, 65) examining exhaled levels of NO have been conducted, to date there have been no studies which have specifically evaluated the role of endothelial NO in OSA patients. However, some evidence exists that OSA patients exhibit increased vascular resistance. Recently, Schnall *et al* (27) examined the extent to which peripheral vasoconstriction may be used as a marker of disease severity. Using fingertip plethysmography in 42 untreated OSA patients age = 47.6 ± 9.9 years; BMI = 29.7 ± 5.2 years), these authors were able to show that episodes of apnea and hypopnea were significantly correlated to increases in peripheral resistance during a standard PSG study. The authors concluded that the number of episodes of increased resistance that occurred per night could be used in the same way apnea and hypopnea indices are used as markers of disease. In another investigation, Phillips *et al* reported increased nighttime levels of circulating endothelin-1 in 22 OSA patients AHI = 74 ± 22 per hour) that was significantly correlated with mean arterial pressure $r = 0.44$, $P<0.02$).

Finally, two groups of investigators (23, 26) have also found that OSA patients have increased peripheral vasoconstriction during the daytime, which was due to endothelium-dependent mechanisms. In particular, Carlson *et al* found that after

acetylcholine infusion (NO release stimulator), forearm blood flow was significantly reduced in OSA patients (6.0 ± 0.7 ml/min for 100g) compared with controls (9.8 ± 1.5 ml/min for 100g: $P < 0.05$) due to higher forearm vascular resistance in the patient group. These authors did not evaluate NO levels. Thus, the extent to which NO may be altered and possibly related to peripheral vascular resistance should be a topic of future investigation in OSA patients.

CONCLUSION

This study was conducted, in part, to explore circulatory function in OSA patients during exercise and to examine the potential relationships between exercise hemodynamics and clinical markers of disease severity in OSA that may explain the occurrence of daytime hypertension. A hypoxic marker of disease severity in OSA, SaO_2, was related to abnormal responses during submaximal exercise while the number of apneic events that occurred during sleep was not significantly related with any exercise cardiorespiratory or hemodynamic measures in this group of OSA patients.

Future investigations should focus on the degree to which PSG markers of severity including RDI, number of arousals, and degree of hypoxemia are predictors of hemodynamic function using more subjects with a wider range of disease severity. In addition, sensitivity and specificity of these markers could be further evaluated in a large randomized, prospective trial. Finally, barriers to participation in the OSA patient should be investigated further in order to improve clinical investigations (sample size) as well as patient outcomes.

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Table 1. Selected descriptive and physical characteristics of OSA patients (N = 11)

Physical Measures	**Mean ± SD**	**Range**
Age (yr)	45.3 ± 11.7	28.0 - 66.0
Weight (kg)	102.9 ± 20.8	67.8 - 143.0
BMI($kg \bullet m^{2(-1)}$)	35.8 ± 6.4	24.9 - 46.6
Neck circumference (cm)	41.2 ± 5.1	31.4 - 49.0
Waist Circumference (cm)	112.3 ± 13.8	95.5 - 145.0
Hip Circumference (cm)	119.8 ± 9.3	105.0 - 131.4
Waist to Hip Ratio	0.94 ± 0.10	0.78 - 1.11

Table 2. Polysomnography measures of sleep function in OSA patients (N = 11)

Clinical Measures	**Mean ± SD**	**Range**
RDI (apneas + hypopneas/ hr)	30.8 ± 30.5	10.6 - 120.0
Time in bed (min)	324.6 ± 96.7	93.0 - 379.0
Total sleep time (min)	263.8 ± 81.6	77.0 - 348.0
Awake (min)	41.9 ± 36.1	4.5 - 115.0
Stage 1(min)	11.1 ± 5.6	3.0 - 21.0
Stage 2 (min)	175.3 ± 55.0	72.0 - 266.5
Slow wave sleep (min)	39.6 ± 42.8	0.0 - 137.5
Rapid eye movement sleep (min)	36.3 ± 26.9	0.0 - 77.0
Baseline SaO2 (%)	96.9 ± 1.9	93.0 - 99.0
Lowest SaO2 (%)	84.1 ± 8.4	63.0 - 96.0
Percent time SaO2 < 90% (%)	20.6 ± 37.1	0.3 - 99.1

Table 3a. Comorbid conditions among all OSA patients (N = 11)

Medical Condition	**Incidence #**
Cardiovascular disease	
Myocardial Infarction	1
Hypertension	3
Metabolic disorders	
Hyperlipidemia	2
Diabetes	1
Asthma	3
Hypothyroidism	1
Allergy	4
Orthopedic diseases and disabilities	
Low back pain	4
Osteoporosis	1
Arthritis	1
Psychological diagnoses	
Depression	4
Generalized anxiety	1
Sleep Disorders	
OSA	11
Periodic leg movement disorder	4

Table 3b. Medication use separated by disease category among all OSA patients (N = 11) NEED TO COMMENT ON IF THESE MEDS AFFECT SLEEP

Medication	**Number of patients per category**
Cardiovascular Disease	
Calcium channel blockers	1
Alpha-1 blockers	1
ACE-inhibitors	2
Antihyperlipidemic	1
Antithrombotics/platelet	2
Hypoglycemic agents	
Insulin	1
Bronchodilators	
Inhalers	3
Allergy Relief	1
Antihistamines	4
Prilosec	2
Hormone replacement	
Synthroid	1
Estrogen replacement	5
Psychotropic medications	
Antidepressant / antianxiety	4
Anti-inflammatory	1
Anticonvulsants	4
Other	Fosamax, Meridia, Acyclovir

Table 4. Cardiorespiratory responses taken at rest while subjects were seated on a stationary bicycle ergometer before exercise testing (N = 11)

Resting Measures	**Mean ± SD**	**Range**
Hemodynamic measures		
Heart rate (bts•min^{-1})	85.4 ± 10.9	73 – 103
Systolic blood pressure (mmHg)	124 ± 13.6	106 – 144
Diastolic blood pressure (mmHg)	84.9 ± 7.6	70 – 96
Mean arterial pressure (mmHg)	97.8 ± 7.8	84.5 – 109.2
Cardiac output (l•min^{-1})	6.2 ± 1.3	4.0 – 8.4
Stroke volume (ml•bt^{-1})	74.1 ± 7.8	84.5 - 109.2
Total peripheral resistance (mmHg/l•min^{-1})	16.3 ± 3.3	12.6 – 22.1
Respiratory Metabolic Measures		
End-tidal oxygen pressure (mmHg)	94.8 ± 7.0	84.6 – 104.0
End-tidal carbon dioxide pressure (mmHg)	34.1 ± 5.0	27.3 – 41.3

Table 5. Hemodynamic and ventilatory responses to graded bicycle ergometer exercise testing (N = 11)

Exercise Measures	Mean ± SD	Range
Submaximal Exercise		
Power (Watts)	59.9 ± 26.4	25 - 115
Percent Peak (WATTS)	66.5 ± 8.6	55.0 – 85.0
VO_2 ($l \bullet min^{-1}$)	1.46 ± 0.60	0.81 – 2.73
V_E ($l \bullet min^{-1}$)	26.3 ± 6.7	19.1 – 40.8
Heart rate ($bt \bullet min^{-1}$)	123.5 ± 11.7	105 – 134
Systolic blood pressure (mmHg)	159.6 ± 21.8	120 – 192
Diastolic blood pressure (mmHg)	85.4 ± 7.4	70.0 – 94
Rate Pressure Product (10^{-2})	196.3 ± 36.0	129.6 – 238.5
Mean arterial pressure (mmHg)	109.9 ± 9.7	95.9 – 125.0
Cardiac output ($l \bullet min^{-1}$)	12.3 ± 2.5	8.0 - 15.7
Stroke volume ($ml \bullet bt^{-1}$)	101.2 ± 19.8	74.1 - 128.6
Total peripheral resistance ($mmHg/l \bullet min^{-1}$)	9.1 ± 1.8	6.9 – 12.0
RER	0.92 ± 0.12	0.78 – 1.12
Peak Exercise		
Power (Watts)	120.0 ± 18.4	49 - 250
VO_2 ($l \bullet min^{-1}$)	2.10 ± 0.70	1.33 - 3.27
V_E ($l \bullet min^{-1}$)	52.2 ± 18.9	33.8 - 88.3
Heart rate ($bts \bullet min^{-1}$)	152.4 ± 18.9	129 - 193
Systolic blood pressure (mmHg)	186.5 ± 21.8	156 - 212
Diastolic blood pressure (mmHg)	86.7 ± 9.0	70 - 98
Rate Pressure Product (10^{-2})	284.8 ± 53.6	220.0 - 393.7
Mean arterial pressure (mmHg)	119.7 ± 10.3	107.8 - 134.3
RER	1.12 ± 0.13	0.89 -1.28
End-tidal oxygen pressure (mmHg)	100.1 ± 8.9	79.0 – 108.2
End-tidal carbon dioxide pressure (mmHg0	38.6 ± 5.2	31.0 – 49.0

Table 6. Relationships between resting (*r*) hemodynamic measures and polysomnography markers of disease severity (N = 8).

Sleep Measure	***r*HR**	***r*SBP**	***r*DBP**	***r*MAP**	***r*TPR**	***r*SV**	***r*Q_c**
RDI	0.49	-0.13	0.5	0.25	0.01	-0.24	0.04
TST	-0.58	-0.09	-0.51	-0.38	0.31	0.00	-0.32
Awake	-0.11	0.09	-0.58	-0.32	-0.31	0.18	0.21
SWS	-0.53	0.43	-0.08	0.19	-0.28	0.58	0.36
REM	-0.40	-0.27	-0.69†	-0.60*	0.21	-0.14	-0.35
LowSaO2	-0.62*	0.09	-0.530	-0.29	0.21	0.09	-0.31
PTless90	0.11	0.03	0.150	0.12	-0.29	0.16	0.26

***** = $P \leq 0.05$; **†** = $P < 0.01$

Table 7. Relationships between submaximal exercise (s = 64.7 % of VO_2pk) hemodynamic measures and polysomnography markers of disease severity (N=8).

Sleep Measure	***s*HR**	***s*SBP**	***s*DBP**	***s*MAP**	***s*TPR**	***s*SV**	***s*Q_c**
RDI	0.35	0.09	0.39	0.26	0.54	-0.57	-0.36
TST	-0.39	0.10	-0.45	-0.15	-0.66	0.70*	0.48
Awake	-0.21	-0.02	-0.37	-0.21	0.24	-0.31	-0.28
SWS	-0.43	0.44	-0.16	0.24	-0.38	0.69*	0.35
REM	-0.17	-0.08	-0.47	-0.30	0.03	0.01	-0.08
LowSaO2	-0.44	-0.34	-0.13	-0.31	-0.21	0.31	0.05
PTless90	-0.02	-0.03	-0.27	-0.16	0.23	-0.29	-0.30

*****= P = 0.05

Table 8. Predictor variables significantly correlated with lowest SaO_2 as the criterion variable (N = 8).

Predictors	Multiple R^2	Regression Equation	SEE	Significance
BMI SubmaxSV	0.85	Y = 122.13 – 1.64(BMI) + 0.29 (SubmaxSV)	3.85	F ratio = 14.2 P = 0.009
BMI SubmaxSV SubmaxMAP	0.97	Y = 85.67 – 2.87(BMI) + 0.34 (SubmaxSV) + 0.78 (Submax MAP)	2.30	F ratio = 39.2 P = 0.002
BMI, SubmaxSV SubmaxTPR	0.91	Y = 73.8 – 1.7 (BMI) + 0.53 (SubmaxSV) + 2.83 (SubmaxTPR)	4.49	F ratio = 13.1 P = 0.02

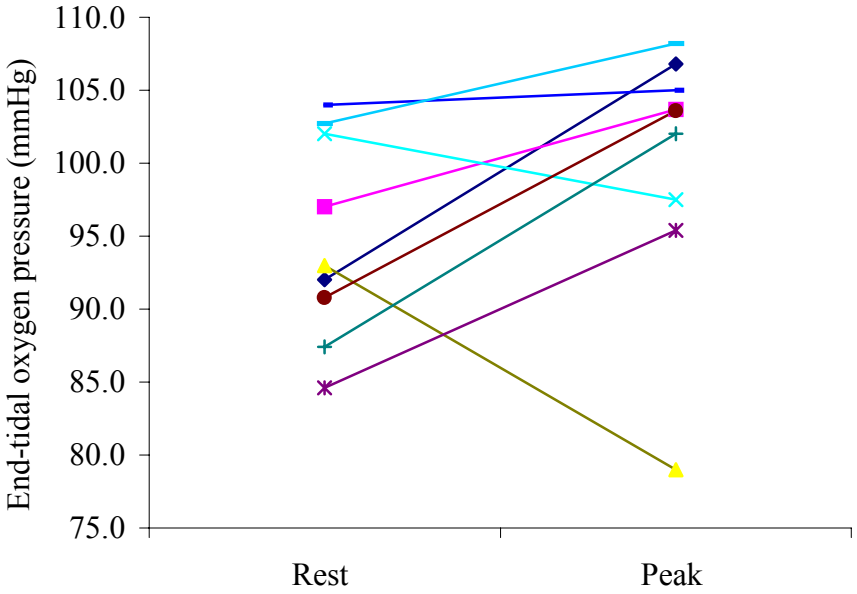

Figure IIIb-1. Changes in $P_{ET}O_2$ from rest to peak exercise plotted for each OSA patient response (N = 11).

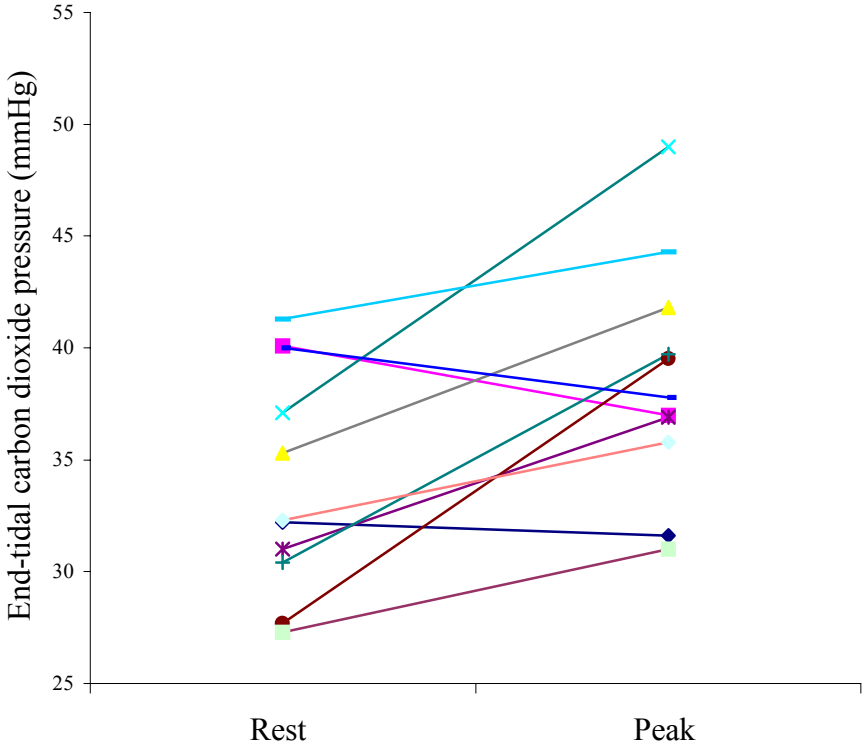

Figure IIIb-2. Changes in $P_{ET}CO_2$ from rest to peak exercise plotted according to each OSA patient response (N = 11).

CHAPTER IIIc

QUALITATIVE INVESTIGATION REGARDING TREATMENT AND PHYSICAL ACTIVITY AFTER SHORT TERM CPAP TREATMENT

Treatment of obstructive sleep apnea involves aggressive management on behalf of the health care professional. Treatment options depend on the severity of the disorder, magnitude of clinical complications, and the predominant type of apnea (central, obstructive, or mixed). Therapy for OSA has many options, including behavioral, medical, and surgical strategies, and is often not limited to only one form of treatment. Obese patients should be encouraged to loose weight since obesity is associated with an increase in soft tissue in the lateral pharyngeal area [Henderson JH, 1999 #7; Phillips, 1999 #23]. The means by which effective and permanent weight loss is achieved is of growing importance to health care professionals. Exercise may be a viable means to increase daily energy expenditure as well as reducing secondary risk factors although only one clinically based study, without the addition of other forms of treatment, has been conducted among patients with OSA [Netzer N, 1997 #51]. In all patients with moderate to severe OSA and in most with mild OSA, the usual initial treatment prescribed is NCPAP. Nasal CPAP reduces the negative pressure generated in the throat during inspiration and acts as a "pneumatic splint" pushing the soft palate and tongue forward and away from the posterior oropharangeal wall. In addition to the treatment of nocturnal apneic and hypopnic events, long term NCPAP use has been shown to be effective in reversing daytime OSA related hypertension, EDS, and in weight loss [Lobe D.I., 1997 #35] [Fletcher, 1996 #28]. Ancillary treatments may also be used in conjunction with NCPAP including oxygen therapy if significant nocturnal desaturation is present despite adequate NCPAP levels. Humidification devices may reduce irritation of the airway and

improve compliance with NCPAP. Current estimated patient compliance with CPAP are approximately 40%[Loube, 1999 #34]. Discomfort experienced during exhalation while on NCPAP, negatively effects compliance rates. Bilevel positive airway pressure, which provides a lower exhalation pressure, may be indicated in those patients who do not tolerate standard NCPAP.

Within the context of this study, the eleven subjects initially starting the study were randomly assigned to NCPAP treatment only or NCPAP plus exercise training. At this time subjects in both groups are being given follow-up evaluations (physical characteristics, exercise testing, subjective questionnaires, and urinary nitrate/nitrite analysis) at 8 weeks and 6 months. The purpose of this research aim was to give insight into the treatment of OSA, especially with regard to compliance and adherence to NCPAP and exercise training as well as unique characteristics of treatment in this population. The follow-up pages will present objective information pertaining to compliance and adherence to NCPAP and exercise training and subjective, patient feelings and ratings of treatment.

Phone interviews (~ 20 minutes per person) were conducted with eight of the eleven patients. Five to six open-ended questions were asked concerning treatment, sleep, and daily functioning. Currently, each subject is in a different phase of the 6 month treatment period. Of the initial 11, 6 patients have completed 8 week follow-up evaluations (3 exercise training, 3 NCPAP only) and 2 have completed 6 month follow-up evaluations. Two patients who started in the exercise training group had to drop out, one due to chronic shoulder pain that was treated with arthoscopic surgery and the other was sick (cold/flu) two different periods at the time of his 8 week evaluation and between

the 8 week and 6 month follow-up. The latter was given an exercise test at 6 months due to a high level of compliance with NCPAP. Two patients in the NCPAP only group did not return for exercise testing, one at 8 weeks, the other at 6 month. Compliance reports were available for nine of the patients. Average use of NCPAP (days/month) was 80 percent for these patients ranging from reports taken from one to four months. Adherence to NCPAP was also high at 5.7 hours per night use. One patient for whom compliance data was not available reported only using NCPAP about two to three hours per night.

Seven of eight patients interviewed reported that NCPAP treatment has made a vast improvement in their daily functioning. The following are some quotes from various patients and family members regarding treatment:

- "He is his old self again."
- "…could not live with out it."
- "I use my CPAP all the time and wouldn't be able to live without it."
- "I feel like doing more with my children and even going shopping more now."

In addition, patients also report that they feel much better in terms of their mood. This also seemed to carry over into their attitude to do recreational activities, including house and yard work and extracurricular activities with their families for the people on NCPAP only and in the exercise training group. Also, the one patient who did not feel that she was benefiting from NCPAP, was enjoying exercise and felt that it made her better able to do daily activities while at work (pastry chef).

The following paragraphs contain information concerning each patients response in no particular order to questions and background information that aids in the

understanding of the special challenges in doing research in patients with sleeping disorders.

Control group – This patient was not able to drive to sleep center for fear of falling asleep. He reports excellent sleep now and his wife also reports noticing significant mood changes.

Exercise group – This patient had high adherence and compliance to exercise (35 days of exercise out of possible 40 exercise sessions in 2.5 months). She uses CPAP average of 6.8 hours per night with only 2 nights missed the first month. She is exercising 3 to 4 days per week either walking or biking. She is able to keep her heart rate in her prescribed exercise target heart rate range while exercising at least 30 of the 40 minutes at each session. At her second exercise test however, she had a cold two weeks before. Her exercise results were only slightly "better" than initial. She reports that NCPAP has improved her sleep considerably. She feels more alert at work and is able to concentrate better. She also enjoys exercise training. Her husband does not like the sound of the machine, so he does not like her to wear it. They live in separate towns, so when she goes to see him, she sleeps in a separate room. He has tried wearing earplugs, but this felt uncomfortable to him.

Exercise group. This patient has lost weight, from 232 to 224 lbs. She a moderate compliance to exercise, 34 days of exercise out of 45 in 3 months. She uses CPAP an average of 2.5 hours per night, when she uses it. She reports waking up in the middle of the night and "ripping" the CPAP off. She only used NCPAP 15 days out of the first month one and 17 days out of month 2 due to illness. Both her and her husband use NCPAP. She is sometimes frustrated about using the device and reports that her husband

is able to wear the device comfortably all night and reports feeling much better during the day.

Exercise group initially, due to shoulder problems she had to go the physical therapy and could not continue program. She reports using it 5 to 6 hours per night and would not be with out it.

Control group – This patient had gained weight, 224 to 230 lbs in 3 months. He feels he is less active overall and is more "fatigued" when walking around campus. However, he reports using NCPAP 5 or 6 hours every night (No compliance reports). He reports that his sleep is excellent, a rating of 8.5 out of 10 with NCPAP. He feels that he has gained more weight since 8 week follow-up.

Control group – This patients compliance to NCPAP is excellent, 4.6 hours per night for first month with no missed days, 4.2 hours per night for second month with no days missed, 3.5 hours for 3rd month with 7 days missed, 2.8 hours for 4th month with 13 days missed, reports that she is not as sleepy during the day. She definitely feels that her sleep is better now with CPAP. She feels like doing more with her children and she goes shopping more now. She also feels that her mood is better.

Control – This patient had poor compliance for first month 2.8 hours per night use with 11 days missed, second month 3.7 hours use with 8 days missed. This patient initially started exercise training group but only showed up for 2 sessions, he then would not return any calls. He worked in a machine shop until 6:30 and then moonlighted as a mechanic in his own garage until 10 pm at night. This may have been one barrier to exercise participation.

Exercise group – This patient had excellent compliance for entire six months only missed 3 exercise sessions out of a possible 88 sessions (3x /wk for first 2 months and 4x/wk for last 4 months. She exercised slightly below prescription HR of 109-120 (usually 105 to 110 bt/min). She lost 5 pounds from the 8 week to 6 month evaluation. Her NCPAP compliance is excellent, 9.0 hours per night for first 3 months, missed 9 days in 3 month only. She feels much better since she has been using NCPAP.

Exercise group - This patient was chronically sick, 3 times for at least 2 weeks each time over the course of the training. He could not maintain his exercise program from the 3rd month to 6th month due to illness. He was compliant with his exercise before this and peaked at 3 x /week of walking and biking. He has excellent compliance to NCPAP, 6.4 hours per night for first 3 months with 1 missed day. He was switched from NCPAP to nasal pillow to keep airway open. He had a claustrophobic feeling while using the mask and reported much better sleep with the nasal pillow. He reports that sleep is a 9 on a 1 to 10 scale.

Control – This patient had good compliance to NCPAP for first 2 months, 4.1 hours month one with 6 days missed first and 6 days missed second month

Control – This patient had good NCPAP compliance, 8 days missed first month with 6.7 hours per night. This patient was sick a lot (cold and flu), so that we were unable to her at her six month evaluation.

CHAPTER IV

SUMMARY AND CONCLUSIONS

Exercise testing and exercise training has long been used to evaluated functional capacity and cardiovascular function in healthy individuals and in those with cardiovascular, metabolic, and pulmonary disease. To date, no clinical trials investigating hemodynamic function, namely cardiac output, stroke volume, and total peripheral resistance, have been evaluated during exercise in OSA patients. While it is difficult to isolate those patients without coexisting cardiovascular disease, this does not negate the usefulness of exercise testing in this population. For example, several researchers have shown that obstructive sleep apnea patients have reduced functional capacity (Schonhofer, Rosenbluh et al. 1997; Taguchi, Hida et al. 1997; Vanuxem D 1997; Aguillard, Riedel et al. 1998; Schafer, Ewig et al. 1998; Tremel, Pepin et al. 1999), pulmonary and systemic hypertension during exercise (Hawrylkiewicz, Cieslicki et al. 1996; Vanuxem D, 1997), and altered blood gas regulation during steady state exercise (Schonhofer, Rosenbluh et al. 1997; Schafer, Ewig et al. 1998). However, little attention has been given to functional measures of peripheral vascular resistance during exercise. Augmented vascular resistance could help to explain the high prevalence of daytime hypertension in OSA patients. In addition, mechanisms underlying these pathophysiological states are needed. This study was conducted, in part, to explore circulatory function in OSA patients during exercise and to examine the potential relationships between exercise hemodynamics and clinical markers of OSA severity that may explain the occurrence of daytime hypertension.

OSA patients in this study showed reduced functional capacity compared when compared to age-predicted values. This finding is in agreement with others (Taguchi, Hida et al. 1997; Aguillard, Riedel et al. 1998; Tremel, Pepin et al. 1999). While resting and exercise hemodynamic responses were not found to be abnormal compared to age and gender matched counterparts in this study, pharmacological treatment for cardiovascular and metabolic disorders may have masked any effects OSA would have on these measures alone. This means that hemodynamic changes during exercise may have been blunted due to the effects of antihypertensive or neural and vascular pharmacological agents (i.e. anticonvulsants or antidepressants) The only published exercise study conducted in which OSA patients were free from cardiorespiratory diseases or medications was by Taguchi *et al* (1997). Before CPAP treatment, diastolic blood pressure increased 21 percent from rest to peak exercise. This is compared to a negligible 2 percent increase in the present study. However, the finding that stroke volume and mean arterial pressure were able to explain additional variance associated with a hypoxic marker of OSA severity, lowest SaO_2 recorded during a PSG study, is encouraging.

In addition to exercise responses, this study also examined mechanisms that may be linked to underlying hypertension and increased peripheral vascular resistance in OSA patients. Obstructive sleep apnea patients suffer severe oscillations in hemodynamic function during sleep due to repetitive apneic and hypopneic events occurring as many as 100 times per hour. These dramatic swings in hemodynamic function have led many clinicians and researchers to investigate the causal link between OSA and cardiovascular morbidity and mortality (Weiss JW, 1999). Furthermore, a strong association of sleep-

disordered breathing and systemic hypertension has recently been established in both animal and epidemiological investigations (Brooks D 1997; Peppard, Young et al. 2000).

The link between OSA and hypertension has been evidenced by increased daytime sympathetic activity evidenced by increased circulating catecholamines levels and muscle sympathetic nervous system activity. However, several investigators have determined that many OSA patients do not have daytime hypertension even with higher amounts of MSNA and increased levels of circulating nor-epinephrine and epinephrine levels (Lapinski M, Przybylowski T et al. 1993; Marrone O, Riccobono L et al. 1993; Hedner J, Darpo B et al. 1995), both of which are postulated to be a result of recurrent episodes of hypoxia. In addition to these autonomic controls of vascular tone, endothelium-dependent controls of vascular tone may also be involved in the development of hypertension (Carlson, Rangemark et al. 1996; Hedner 1996). However, repeated apnea induced hypoxic events experienced by OSA patients may attenuate nitric oxide release and contribute to increased systemic resistance.

This study investigated a global biological marker of endothelial function, nitric oxide, by evaluating urinary production of nitrate and nitrite production, NOx. In the presence of an intact endothelium and the presence of oxygen, nitric oxide is a potent vasodilator. Methods and standards of reporting of NO metabolites vary greatly (Wenmalm *et al* 1993; Leone and Kelm *et al*, 1996; Forte et al, 1997) used in the literature to measure NOx vary greatly. Renal nitrate and nitrate elimination are end products of nitric oxide formation in the endothelial cell which is taken up by hemoglobin the red blood cell and metabolized as to nitrate or nitrite in the kidney (Wenmalm el al, 1993) and excreted in urine. Estimates for excretion of nitrate and NOx ranges from 400

to 2,334 *u*mol/day in health subjects (Boger et al, 1997; [Callaerts-Vegh Z, 1998 #24], Forte et al, 1997) and 100 to 400 *u*mol/mmol creatinine (U_{NOx}) as reported in the literature. In the present study, U_{NOx} excretion was similar to that reported in the literature (231.6 ± 277.2 *u*mol/mmol creatinine). However, considerable variability existed among the eight subjects (23.8 – 757.4 *u*mol/mmol creatinine). Nitrate elimination was not significantly related to any sleep measures or hemodynamic variables during exercise.

While plasma and urinary metabolites of NO are transient, 24 hr urinary excretion of NOx with correction for renal function is a more sensitive parameter for the detection of interindividual differences in NO formation. One aspect of the present study is noteworthy with regard to NOx elimination. While subjects were required to fast to 8 to 12 hours and to reduce activity before reporting for their exercise test, they were not required to consume a low nitrate diet before (< 100 umoles nitrate) urine collection (Forte et al, 1997). Clearly, nitrate rich foods could have affected U_{NOx} excretion rates (Surdacki et al, 1998). Additionally, while NOx levels compared to that reported in the literature, nitrate elimination was low for this group of patients (51.8 ± 52.8 *u*mol/mmol creatinine). For future studies, low nitrate diets (diets low in spinach, beets, radishes, eggplants, and cabbages) or calculation of nitrate intake should be accounted for before 24 urine collection.

Practical and Clinical Applications

Along with the need to understand pathophysiological mechanisms associated with cardiovascular morbidity, is the need for the clinician, especially those not trained in sleep disorders, to be able to recognize and characterize individuals presenting with

undiagnosed OSA. Several physical characteristics including obesity, mallampati grade, and retrognathia together with witnessed nocturnal choking or gasping, have been shown to be moderately sensitive to determining those individuals presenting with OSA (Redline and Strohl 1998; Friedman, Tanyeri et al. 1999; Phillips, Hisel et al. 1999). These characteristics are not always the best measures to be able to distinguish the severity of the disease. In this study, submaximal exercise hemodynamic variables, stroke volume and mean arterial pressure were able to explain additional variance in a marker of OSA severity, SaO_2. Clinically, this is important because it can be used as flag to recognize those individuals who may have mild to moderate RDI scores but drastic drops in oxygen saturation levels. Clearly, more investigation is needed in order to better characterize the meaning of this finding. These findings are not only important from a clinical stand point, but a from a mechanistic stand point as well.

Recommendations for Future Research

Based on the findings of the present study and relevant literature, the following studies seem warranted:

1. There is a need to increase subject number in studies involving OSA subjects. An improved means of recruiting subjects is the most logical place to start. In this study, subjects are given $100.00 dollars compensation at the completion of a 6 month observation or exercise training period. Increasing this amount along with a schedule of payments throughout a 6 month period could improve both recruitment and adherence. Also, future investigations should focus on a wide range of OSA patients along all stages of medical management. For example,

generalizability may be increased by recruiting and randomly assigning subjects to exercise or traditional treatment, after 6 months of initial nCPAP therapy.

2. A more thorough understanding is needed of the mechanisms underlying the link between OSA and cardiovascular disease. Exercise echocardiography could be used to investigate ventricular systolic and diastolic function. In addition, acetylcholine infusion could be used to evaluate vascular resistance in newly diagnosed, untreated OSA patients compared to age, gender, and BMI matched controls. *In vivo*, animal studies, especially in the dog model, could be used to isolate the effects of induced apnea and hypopnea on exercise hemodynamic function. In addition, mechanisms of endothelial-dependent vascular function could also be conducted in *vitro* studies in the a rat model.
3. More investigation is needed on all subtypes of sleep-disordered breathing including OSA, central sleep apnea, and obesity-hypoventilation syndrome. For example, short-duration, steady state exercise tests conducted at moderate-intensity may be able to identify and distinguish OSA compared to obesity-hypoventilation syndrome by using end-tidal gas pressure responses.
4. Exercise training and weight loss trials are needed in pre-clinical OSA patients. This would be the best ethical means of evaluating these tools as treatment options in individuals having risk factors for OSA or who do not meet PSG criteria at the time of diagnosis. Additionally, this would improve the subject recruitment process.
5. Future studies examining hemodynamic function in OSA patients could be strengthened by considering the following modifications to the present study:

a. Exclude subjects with diagnosed cardiovascular, metabolic, and pulmonary disease.
b. Use a functional method to evaluate peripheral vascular resistance, such as plethysmography.

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APPENDIX A

List of Abbreviations of Terms and Units of Measure

LIST OF ABBREVIATIONS

Abbreviations of Terms

CSA	central sleep apnea
DBP	diastolic blood pressure
GXT	graded exercise test
HPLC	high performance liquid chromatography
HR	heart rate, bts•min^{-1}
MAP	mean arterial pressure, mmHg
MET	metabolic equivalent of oxygen consumption
nCPAP	continuous positive airway pressure
NO	nitric oxide
NREM	non-rapid eye movement sleep
OSA	obstructive sleep apnea
$P_{ET}CO_2$	end-tidal carbon dioxide pressure, mmHg
$P_{ET}O_2$	end-tidal oxygen pressure, mmHg
PLMS	periodic limb movement of sleep
pk	peak exercise
PSG	polysomnography study
Q_c	cardiac output, l•min^{-1}
r	resting measurement
RDI	respiratory disturbance index, apnea + hypopnea/ hr of sleep
REM	rapid eye movement sleep
RPP	rate pressure product
s	submaximal exercise
$\%SaO_2$	percent saturation of hemoglobin with oxygen
SBP	systolic blood pressure, mmHg
SV	stroke volume, ml•min^{-1}
SWS	slow wave sleep
TPR	total peripheral resistance, mmHg•l^{-1}•min^{-1}
VO_2	oxygen consumption, l•min^{-1}
W	power, watts

Abbreviations of Units of Measure

Bt	beats
°C	degree centrigrade
hr	hour
kg	kilogram
l	liter
min	minutes
ml	milliliter
mmHg	millimeters of mercury
mmol	millimole
mg	milligram
*u*g	microgram

APPENDIX B

Informed Consent

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Informed Consent for Patients Who Perform

Sleep Lab Study at The Sleep Disorders Network

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

Principal Investigators: Jennifer Blevins, MA, Howard Ballentine, Don Zedalis, MD, John Gregg, DDS, Ph.D., Ron Boss, Ph.D., Richard Lock, MD, Lawrence Cross, Ph.D., and William G. Herbert, Ph.D.

I. Purpose of This Research

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, how these conditions and treatment interventions may affect your day-to-day life.

II. Procedures

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

- Allow us to use certain physical and health history information from the medical records available to your doctor at the Sleep Center.
- Complete questionnaires that request your opinion about the quality of your sleep, about your current quality of life, mood, and physical activity status.
- Allow us to complete baseline measurements including height, weight, and circumferences.
- You will also be asked to practice a few of the breathing techniques which will you will be asked to perform the day of your exercise test here at the Sleep Disorders Center in Christiansburg, VA.

In the event that your initial overnight sleep study shows that you have sleep apnea, on a different morning (between 7:30 and 10:00), you will be asked to report to the Sleep Disorders Center and complete the following:

- Allow us to initially obtain certain physical measurements from you at rest, including your blood pressure, heart rate, and cardiac output.
- Allow us to obtain a 24 hour urine sample immediately before each exercise test in order to measure the ability of your vessels to relax as well as how your nervous system functions.
- Allow us obtain a non-invasive measurement of your heart rate immediately before your exercise test in order to assess the nervous system control of your heart.
- Complete an 8 to 12 minute bicycle test and allow us to obtain your maximal functional capacity, heart rate, blood pressure, cardiac output, and various measurements of your breathing.

- 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 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. You must also perform several exercise cardiac output measures that require you to slowly exhale in a controlled manner for approximately 5 to 6 seconds. You may experience more difficulty completing this procedure during higher intensities of exercise.

After completion of the initial exercise test, you will be randomly assigned to one of the following:

- a usual care group, which will receive CPAP therapy only.
- an exercise training and CPAP therapy group, which will participate in a moderate level exercise program (60 to 85% of each individuals maximal exercise capacity) for at least 8 weeks in conjunction with CPAP therapy.
- a non-treatment group which will be comprised of individuals for whom CPAP therapy is unsuccessful or are in line for surgical intervention at a later date

Exercise training will last for at least 8 weeks. At the end of this period, you will be given the option to continue for an additional 4 months in a home exercise training program. For the first 8 weeks, exercise sessions will be held at the Health and Exercise Science Laboratory (H&ESL) on the Virginia Tech campus. Exercise training will consist of bicycle exercise training, 3-5 days/week, for approximately 1 hour. Only 8 weeks of your exercise training will be supervised. After this time, you will log all exercise

sessions for the remainder of the study in an exercise diary. Your exercise level will be based on your initial exercise test.

After completion of the first 8 weeks and at 6 months, all participants will be asked to return for a second and third exercise test, respectively.

III. Extent of Anonymity and Confidentiality

The results of this study will be kept strictly confidential. At not 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 12 minutes. At first it will be very easy and then become harder; during the last few minutes, the work will become very intense and will represent a maximal effort on your part. It may be as hard as any exercise that you remember doing.

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. Emergency equipment and defibrillation are available at this facility, and a physician and

Registered Nurse will be onsite for all exercise testing. I understand that there is a risk of injury, heart attack, or death as a result of my performance of this test and participation in exercise training but knowing those risks, it is my desire to proceed to take the test and, if chosen, exercise training 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 can expected the following compensation for my participation in the study:

- I understand that upon successful completion of the 6 month study, I will receive 3 free maximal exercise tests and resting and exercise cardiovascular assessments (blood pressure, ECG, heart rate, etc). These tests typically cost from $150 to $200 per test.
- I will also receive 3 nutrition analysis profiles over the course of the study. These profiles typically cost from $15 to $20 per analysis.
- Provided I complete the above testing procedures, I will also receive $50 at the completion of the 6 month period.
- If I am in the exercise training group, I will receive 16 hours of exercise training in a supervised setting. These sessions typically cost from $15 to $20 per session.

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.

VII. Subject's Responsibilities

I know of no reason I cannot participate in this study. I accept that it is my responsibility to:

1. Accurately report medical history.
2. Arrive to the testing lab at least 4 hours after eating for any of the exercise trials and exercise training sessions.
2. Refrain from caffeine, and nicotine products for 24 hours prior to the exercise trials.
3. Remain in the testing and/or exercise area 30 minutes after the exercise trials.
4. Attend all exercise sessions for the duration of the study.
5. Inform the investigators if I am not able to attend an exercise session at least one day prior to the session.
6. Refrain from vigorous physical activity for 12 hours on all testing days.

Report any adverse effects that might occur outside the lab during the period of testing, even if I feel it is not related to the testing to: Jennifer Blevins (231-8209/961-4812) or Dr. William Herbert (231-6565/951-0974).

VIII. Subject's Permission

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

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

Questions/Response: _____

_____

_____

_____

_____ _____

Signature Date

_____ _____

Witness Date

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

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

Jennifer Blevins 231-8209

Investigator

William Herbert, Ph.D. 231-6565

Faculty Advisor

Human Nutrition, Foods, & Exercise

Howard Ballentine 951-9612

Investigator

Tom Hurd 231-6077

Chair, IRB, Research Division

APPENDIX C

Recruitment Flyer

Virginia Tech Lab for Health & Exercise
in cooperation with the Sleep Disorders Network

NOTICE OF OPPORTUNITY FOR SLEEP CENTER PATIENTS TO PARTICIPATE IN EXERCISE RESEARCH

The Virginia Tech Lab for Health and Exercise (VT lab) is conducting a research project to better understand the effects of CPAP therapy and exercise training on heart and lung performance in individuals with obstructive sleep apnea. If eligible, you will be asked to complete an exercise test and several questionnaires about your sleep quality, quality of life, dietary habits, medical history and physical activity levels. You will also be asked to complete the above on three occasions at the VT lab during the study. In addition, you may be randomly assigned to a group that participates in exercise training. You may also be eligible, even if you are not treated with CPAP. The study is described below in further detail.

Exercise Test. As a study participant, you will be asked to perform a 15-minute exercise test on a stationary bicycle at the VT lab on a different morning following your initial sleep study. The second and third tests are performed 8 weeks and 6 months after either CPAP therapy or CPAP therapy plus exercise training, as arranged by the VT Lab. The exercise test measures your blood pressure, heart rate, heart function, and respiratory function. We also request a 24-hour urine collection the day preceding each of these tests, in order to assess your nervous system and cardiovascular function. Per your request, a copy of your exercise report can be forwarded to your primary physician. Typically, such testing costs between $200-$250 each time tested. There will be no cost to you for any of the testing.

Questionnaires. You also will be asked to complete several questionnaires during each of your visits, which should take no more than a few minutes each to complete.

Exercise Training. If you are assigned to an exercise training group, you will be asked to participate in an aerobic exercise-training program for at least 8 weeks. Training sessions will be conducted on a stationary bicycle in a supervised exercise setting at the VT lab for the first 2 weeks. As a participant, you will exercise 3 days per week for 20-40 minutes per session at a moderate rate. Sessions will include a 5 - 10 minute warm-up and cool down. The aim of the exercise training is to allow you to gradually be able to exercise on your own at a local community activity center. The cost of supervised exercise sessions would cost between $15 – $20 per session, although there is no cost to you for any of the sessions.

Our research may lead to improvements in treatments for patients who have certain sleep disorders. Therefore, we would greatly appreciate your participation in this study. If you are interested in participating in this study, please inform the staff of the Sleep Disorders Network during today's visit.

APPENDIX D

Screening Questionnaires

Preliminary Screening Form

Medical history:_____

_____

_____

_____

_____

Risk factors:

____Lipids _____HBP _____Smoking ___IDDM or NIDDM _____Early Fm. Hx. _
Sedentary _____Stress
Other:_____

_____

_____

Current Physical Activity Status:_____

_____

_____

_____

Symptoms with exertion			Elaborate
Pain or discomfort in chest or surrounding area?	Y	N	_____
Unaccustomed shortness of breath or with mild exertion?	Y	N	_____
Dizziness or syncope?	Y	N	_____
Palpitations or tachycardia?	Y	N	_____
Claudication?	Y	N	_____

Other_____

Medications:

Have you taken any medication this morning?_____

What medications do you take/action?

1)_____Action:_____ 5)_____Action:_____
2)_____Action:_____ 6)_____Action:_____
3)_____Action:_____ 7)_____Action:_____
4)_____Action:_____ 8)_____Action:_____

Do you use tobacco products?_____Time elapsed since you last smoked?_____

Sleep:

How well did you sleep last night?_____

_____

Can you rate your sleep from 1 to 10 with 1 being the worst sleep you ever remember and 10 being the best?_____

Baseline Measurements:

Height____in____cm Neck circumference_____Hip circumference_____
Weight____lb____kg Waist circumference_____Abdominal circum_____

MEDICAL and HEALTH HISTORY

Demographic Information

Name: _____ Age: ____ Date of Birth: _____
Address: _____
Phone number: Home: _____ Work: _____
Person to contact in case of emergency: _____
Relationship: _____ Phone: _____
Primary Care Physician: _____ Phone: _____
Marital Status: _____single_____divorced_____married_____widow/er
Children: Y N Number living at home:_____

Medical History

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

	Yes	No
Heart disease or any heart problems:	_____	_____
Rheumatic fever:	_____	_____
Respiratory disease or breathing problems:	_____	_____
Circulation problems:	_____	_____
Kidney disease or problems:	_____	_____
Urinary problems:	_____	_____
Reproductive problems:	_____	_____
Musculoskeletal problems:	_____	_____
Fainting or Dizziness:	_____	_____
High Cholesterol:	_____	_____
Diabetes:	_____	_____
Thyroid problems:	_____	_____
Allergies:	_____	_____

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

_____
_____
_____

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

	Yes	No
Have you ever been diagnosed as having high blood pressure?	_____	_____
Date: _____		
Are you currently being treated for high blood pressure?	_____	_____

If "yes" please explain: _____

_____

If you are female, make sure to answer the following 3 questions:

Do you use birth control? Yes _____ No _____ N/A_____

If "yes" what form of birth control: _____

Date of last menses: _____

Medications

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

Drug_____Dose_____Reason Taking_____
Drug_____Dose_____Reason Taking_____
Drug_____Dose_____Reason Taking_____
Drug_____Dose_____Reason Taking_____
Drug_____Dose_____Reason Taking_____
Drug_____Dose_____Reason Taking_____
Drug_____Dose_____Reason Taking_____

Health Habits

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

If "yes" please describe _____

_____

Do you drink caffeinated beverages? _____ _____

How many cups per day? _____

Do you drink alcoholic beverages? _____ _____

How many drinks per week? ____

Do you smoke cigarettes? _____ _____

Packs per day: _____

Exercise Habits

	Yes	No
Do you engage in regular exercise?	_____	_____

If "yes" please list:

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

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

Are there any orthopedic limitations you have that may restrict your ability to perform exercise on a stationary cycle? Yes _____ No _____

If "yes" please explain: _____
_____

Family History

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

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

Please sign to indicate the above information is correct:

_____ _____
Print Name Signature

VSAQ

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

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

APPENDIX E

Data Collection Work sheets

FAX MEMO REQUEST FOR PSG RESULTS

Health and Exercise Science Lab to

Allergy and Sleep Disorders Network in Christiansburg:

Please provide the following information for _____,who has recently been diagnosed with OSA:

1. RDI_____
2. Time in bed (min)_____
3. Total sleep time (min)_____
4. Awake (min)_____
5. Stage 1 (min)_____
6. Stage 2 (min)_____
7. Slow wave sleep (min)_____
8. REM (min)_____
9. Baseline SaO2_____
10. Lowest SaO2_____
11. % of time SaO2 <89%_____

If possible, please fill in the treatment plan and date for follow-up (i.e. CPAP titration, surgery, etc) below:

T*x* plan and date of follow-up:_____ _____

Exercise Testing Sheet

OSA Exercise Testing Data

Name			Baseline /	8 week /	6 month	Date
Seat Ht		Ramp rate		Age		F/M
Height	cm	BMI		Abd circ		Waist circ
Weight	kg			Neck circ		Hip circ

Resting:

	Hemo (Seated)			
BP	mmHg	BP	mmHg	
HR	bpm	HR	bpm	
Q	l/min	Q	l/min	

Exercise: (2 min warm-up @ 25W)

Time:	W	HR	BP	Q	RPE	SxS
1:30						
3:00						
4:30						
6:00						
7:30						
9:00						
10:30						
12:00						
13:30						
15:00						

Exercise Time: _____

Reason for termination:

Recovery:

Time:	HR	BP	SxS
IPE			
1:00			
2:00			
4:00			
6:00			

Comments: _____

QUESTIONS CONCERNING CPAP TREATMENT AND PHYSICAL ACTIVITY

Could you tell me how your CPAP treatment is progressing? (i.e. How is the cpap device?).

How often do you use your CPAP?

Tell me about your sleep now compared to before you were being treated with CPAP?

How good or bad would you say your sleep is on a scale of 1 to 10 with 10 being the best ever?

Tell me how your daily functioning is now compared to before you started using CPAP?

Do you do any additional recreational activities now that you did not do before treatment ?

Tell me if your emotional or psychological well being has changed since you started using CPAP.

APPENDIX F

Detailed Methodology

Subjects

Patients in the OSA group were recruited from a group of volunteers who had been previously referred to the Southwest Virginia Sleep Disorders Center (SVSDC) in Christiansburg. All referred patients were given an informative flyer explaining the general protocol and benefits of the study. Interested individuals, who signed the recruitment flyer, were called about the specifics of the study. The protocol was approved by Institutional Review Board at Virginia Tech. Several trial runs for improving recruitment were initiated in order to increase recruitment capabilities spanning a period of ~ one year. For example, mid-way into the subject recruitment process, subjects were allowed to ask questions about the study on the day of their physical exam by having a Virginia Tech representative present at the SVSDC. Additionally, after 8 months, all metabolic and electrocardiographic equipment was moved to the SVSDC in order to decrease barriers to participation due to location of test. Based on a conservative estimate of 250 to 300 referrals, specifically seen at the Christiansburg center, 11 subjects successfully entered the study. Approximately, 20 patients who initially signed the form, and who were eligible declined due to various reasons. The amount of time required to participate and their physical location relative to Virginia Tech were the most common reasons. Another 5 to 10 patients did not follow-up with scheduling their PSG study or had insurance problems getting the study covered. Approximately, five patients who agreed to participate had to be scheduled to for CPAP titration studies for ethical concerns before exercise testing could be scheduled. Three patients who were completed PSG studies were not subsequently diagnosed with OSA.

Screening for exclusion criteria and further willingness to participate was also conducted through phone interview or face-to-face contact. Exclusion criteria for all OSA subjects will included; recent complicated myocardial infarction, recent episode of uncontrolled or increasing angina pectoris, recent revascularization, moderate to severe chronic obstructive pulmonary disease, congestive heart failure, uncontrolled hypertension, uncontrolled diabetes mellitus, orthopedic and musculoskeletal disabilities, history of regular participation in moderately vigorous physical activity. The level of moderate to severe chronic obstructive pulmonary disease was included to allow those with mild asthma only. Those with mild orthopedic problems that did not interfere with physical activity were allowed to participate in the study.

Baseline Characteristic Measures

Interested OSA candidates were interviewed the morning immediately following their diagnostic PSG in order to disclose the purpose of the clinical treatment trial in detail, determine eligibility based on exclusion criteria, sign the informed consent questionnaire, administer appropriate questionnaires, and obtain demographic and baseline characteristic measures. The questionnaires included in this investigation were medical history questionnaire and the Veterans Specific Activity Questionnaire (VSAQ) to predict peak-MET capacity. Height (in), weight (kg), and neck, waist, and hip circumference (cm) were taken at this time. Body mass index [(body weight (kg) / height (m^2)]. Patients subsequently reported to either the Health and Exercise Science Lab (HESL) at Virginia Tech or the SVSDC on in the morning, but before the initiation of nCPAP, to complete baseline resting and the graded exercise test (GXT).

Exercise testing

Resting Measures. Resting measures were taken while subjects were seated on the bicycle to be used during the GXT. The Vmax 229® (SensorMedics, Yorba Linda, Ca.) metabolic cart was used to collect expired respiratory gases for oxygen uptake and for Q_c determinations. Subjects were fitted to the breathing apparatus after which time five minutes of quiet breathing were collected. Methodology used for the Q_c procedure is described by Zenger et al (40) and was performed in accordance with the manufacturer's protocol for the device using proprietary computer software (see below). For the Q_c measurements taken at rest, subjects breathed through a valve and mouthpiece assembly for 5-min to promote normalization of ventilation, before expired respiratory gases were collected. End-tidal carbon dioxide values ($P_{ET}CO_2$) were used to estimate the minimum of washout time necessary before proceeding to the next measurement of Q_c. A second Q_c trial was taken as soon as $P_{ET}CO_2$ values were within 1 mmHg of the preceding value. This resulted in the intra-trial measurement interval being reduced to 1-2 min. A minimum of three measurements was taken before the GXT.

Blood pressure (BP) was assessed with a standard sphygmomanometer and stethoscope. Heart rate (HR) was assessed using the Schiller AT-10® ECG and pulmonary function system. Both were taken immediately preceding the GXT. Both BP and HR were taken immediately before each Q_c measurement.

Exercise Measures. A graded exercise test (GXT) was completed on an electronically, braked bicycle ($CardioO_2$, MedGraphics, St. Paul, MN). Subjects began at an initial work rate of 25 Watts and were then ramped every 90 sec. The ergometer allowed application of ramp rates of 12, 17, and 22 Watts•90sec^{-1}, pre-selected according to each subject's body weight and activity habits so that the target exercise intensity

endpoint was reached within 20 min (14,47). Activity habits were assessed using the Veterans Specific Activity Questionnaire. Subjects were asked to give "maximal" effort in order to achieve peak (RPE> 17). The Vmax 229® (SensorMedics, Yorba Linda, Ca.) metabolic cart was used to collect expired respiratory gases for oxygen uptake (VO_2), carbon dioxide production (VCO_2), and respiratory exchange ratio (VCO_2/VO_2). The highest VO2 reached during the last min of exercise was used as the peak oxygen consumption (VO_2 pk).

A trained physician as well as an ACSM Certified Exercise Specialist supervised the test. All subjects were monitored continuously throughout exercise for possible signs of myocardial ischemia and heart rhythm disturbances via a 12-lead ECG. Test termination criteria were used to limit exercise endpoints, as recommended by the ACSM *Guidelines for Exercise Testing and Prescription* (48). Blood pressures, Qc, rating of perceived exertion (RPE), were taken every three minutes while and heart rate (HR) was taken the last 10 sec of every 90 sec stage.

Cardiac output, total peripheral resistance, and stroke volume determination. The Q_c procedure was explained in detail and then each subject practiced the breathing technique under resting conditions during the interview process. The Vmax 229® (SensorMedics, Yorba Linda, CA.) metabolic cart was used to determine Q_c determinations. This methodology is described by Zenger *et al* (40) and was performed in accordance with the manufacturer's protocol for the device, using proprietary computer software. Subjects breathed through the valve and mouthpiece assembly for 5-min while seated on the bike to promote normalization of ventilation, before expired respiratory gases were collected. For the actual maneuver, subjects exhaled to near residual volume.

At that time, the Vmax 229® automatically switched to a test gas mixture containing 0.03% acetylene, methane, and carbon monoxide, and balance nitrogen, which the subject inhaled to near maximal lung capacity for a breath hold of 1 to 2 sec. Finally, the subject slowly exhaled for a period lasting 5 to 8 sec. End-tidal carbon dioxide values ($P_{ET}CO_2$) were used to estimate the minimum of washout time necessary before proceeding to the next measurement of Q_c at rest. At rest, the second Q_c trial was taken as soon as $P_{ET}CO_2$ values were within 1 mmHg of the preceding value. This resulted in the intra-trial measurement interval of 1-2 min. Due to the nature of the GXT, only one Q_c measurement was taken at 3 min intervals. Cardiac index (CI), relative total peripheral resistance (TPR), and stroke volume (SV), were calculated manually from Q_c determinations.

Urinary nitrate/nitrite determination.

Twenty-four hour urine samples were collected from each subject prior to exercise testing. For storage, each 24 hour sample was measured for volume and then ~100 ml of the sample was stored at –70 degrees Celsius until the time of analysis.

Nitrate (NO_3-) and nitrite (NO_2-) were determined using high performance liquid chromatography (HPLC). A Beckman "Gold" HPLC system (San Ramon, CA) was connected to a Wescan Silica-based anion and cation exchanger column (10 x 4 mm) (Alltech, Deerfield, IL). On the day of determination urine samples were thawed in cool water, centrifuged at 4000 rpm for 20 minutes and filtered through YMT ultrafiltration membranes (Amicon, Inc., Beverly, MA). Urine was diluted with distilled water. The mobile phase was 1.5 mM sulfuric acid. Nitrate and nitrite standards (LabChem, Inc., Pittsburgh, PA) were injected first at a flow rate of 3 min. Retention times for NO2- and

NO3- were 3.67 min and 16.4 min, respectively. For aqueous standards within the concentration interval the regression coefficients for the standard curves were : $r^2 = 0.999$ (NO2-) and $r^2 = 0..998$ (NO3-).

Nitrate production was calculated mmol/24 hours and normalized to individual renal function (creatinine clearance estimated according to eh equation):

$$\frac{150 - \text{age} * \text{body weight in kg (k)}}{\text{Ccr}} = \text{creatinine clearance (ml/min)}$$

in which Ccr = creatinine serum concentration in mmol/l; k = 1.1 and 0.9 for males and females, respectively.

Statistical Analysis

Values are reported as mean ± SD. Pearson product moment correlation coefficients were calculated in order to investigate relationships between hemodynamic variables (HR, SBP, DBP, MAP, Qc, SV, and TPR) and polysomnography (PSG) markers of sleep function. Polysomnography markers included respiratory disturbance index (RDI), total sleep time (TST), awake time (AWAKE), slow wave sleep time (SWS), rapid eye movement sleep time (REM), lowest SaO_2 during sleep (lowSaO_2) and percent of total sleep time below SaO_2 of 90 percent (PTless90).

Multiple linear regression was used to investigate PSG markers of OSA severity. Descriptive and hemodynamic exercise variables were entered as predictor variables in subsets of three clustered by observer choice, using “enter” selection method in SPSS statistical software package. These clusters were then matched to three of the most common criterion PSG markers of OSA severity used in clinical practice; RDI, lowSaO_2, and PTless90. The regression equations included were those with the highest multiple

correlation coefficients and for which beta coefficients were significant at or below the .05 level.

APPENDIX G

Raw Data

PSG

Subject	RDI	TinBed	TST	Awake	Stage 1	Stage 2	SWS	REM	BaseSaO2
1	32.5	172.5	151.5	10.5	3	134.5	11.5	2.5	96
2	10.6	356.5	289.5	53.5	16	188.5	52.0	33.0	98
3	28.6	370.5	325	34.5	15	249	5.0	56.0	97
4	29.2	367.5	244.5	115	21	137	38.5	48.0	96
5	14.5	371.5	348	18	11	194.5	65.5	77.0	97
6	11.1	368.0	330	23	6	149.5	137.5	37.0	95
7	25.6	367.0	274	9.5	8	266.5	0.0	0.0	99
8	21.2	362.5	274	52	12.5	157	70.0	34.5	93
9	24.8	362.5	314	43.5	13.5	209	56.0	35.5	99
10	21.0	379.0	274.0	97	13	170.5	0.0	74.0	99
11	120	93.0	77	4.5	3	72	0	2	97

Subject	LowSaO2	PTless90
1	88	17.2
2	86	0.5
3	85	2.6
4	77	12.9
5	87	1.4
6	88	0.3
7	84	2.2
8	82	99.1
9	89	0.3
10	96	0.0
11	63	90.3

Physical Characteristics

Subject	Age	Height (in)	Weight (kg)	BMI	Waist (cm)	Hip (cm)	Ratio	Neck (cm)
1	66	61	104.5	43.5	113	129.0	0.88	42
2	28	74	128.0	36.2	124	126.0	0.98	45
3	35	71	101.8	31.3	102	112.0	0.91	42
4	39	69	104.5	34.0	116	109.0	1.06	44
5	38	65	75.5	27.7	108	115.0	0.94	34
6	51	69.0	143.0	46.6	145	131.0	1.11	46
7	42	69.0	106.0	34.5	100	124.0	0.81	40
8	63	64.0	102.0	38.6	102	131.4	0.78	39.4
9	51	62	94.5	38.1	115	122.0	0.94	40
10	47	65	67.8	24.9	95.5	105.0	0.91	31.4
11	38	65.34	104.5	37.9	114.5	113.5	1.01	49

Resting

S	Qc (l•min^{-1})	Sit MAP (mmHg)	Sit TPR (mmHg)	Sit SV (l•bt^{-1})	Rest ETO2 (mmHg)	Peak ETO2 (mmHg)	delta O2	delta CO2	Rest ETCO2	Peak ETCO2
1		106.5			106	110	4.0	0.0	39	39
2	8.4	105.8	12.6	107.7	92.0	106.8	14.8	-3.1	40.1	37.0
3	4.0	88.6	22.1	44.4	97.0	103.7	6.7	6.5	35.3	41.8
4	7.3	97.2	13.3	70.9	93.0	79.0	-14.0	11.9	37.1	49.0
5	5.2	93.3	17.9	61.2	102.0	97.5	-4.5	5.9	31.0	36.9
6	7.0	98.5	14.1	94.6	84.6	95.4	10.8	11.8	27.7	39.5
7	5.7	93.9	16.5	60.6				9.3	30.4	39.7
8	6.8	94.5	13.9	90.7	90.8	103.6	12.8	-2.2	40.0	37.8
9	5.1	109.2	21.4	68.0	87.4	102.0	14.6	3.0	41.3	44.3
10	5.4	84.5	15.7	74.0	104.0	105.0	1.0	3.5	32.3	35.8
11	6.7	103.9	15.5	69.07	102.7	108.2	5.5	3.7	27.3	31.0

Submaximal

Watts	HR (bt•min^{-1})	VO2 (mL/kg/min)	VO2 L/min	VE (STPD) L/min	METs	RER	RPE	SBP (mmHg)
37	134	8.8	0.920	19.1	2.5	0.8	12	146
95	134	15.8	2.022	35	4.5	0.82	8	178
115	131	19.1	1.944	40.8	5.5	1.15	13	160
70	131	17.9	1.871	25.8	4.9	0.78	11	176
25	134	13.2	0.997	23.5	3.8	0.9		
74	105	19.1	2.731	30.0	5.4		12	168
49	120	11.3	1.198	27.4	3.2	1.04	11	138
49	110	12.6	1.285	23.9	3.6	0.81	13	150
49	118	11.0	1.040	19.8	3.1	0.98	13	192
49	108	12.0	0.814	20.6	3.6	0.96	11	120
47	134	12.1	1.264	23.3	3.4	0.91	12	168

DBP	RPP (10^{-2})	Qc (l•min^{-1})	MAP (mmHg)	TPR (mmHg/l•min^{-1})	SV (l•bt^{-1})	% of peak	Watts	HR
92	195.6		109.8			65	49	141
90	238.5	15.7	119.0	7.6	117.2	63	200	193
78	209.6	15.3	105.1	6.9	116.8	60	250	176
82	230.6	11.8	113.0	9.6	90.1	78	115	147
							62	157
86	176.4	13.5	113.1	8.4	128.6	65	150	137
86	165.6	11.9	103.2	8.7	99.2	69	74	139
70	165.0	11.8	96.4	8.2	107.3	63	97	129
92	226.6		125.0			69	87	142
84	129.6	8.0	95.9	12.0	74.1	60	100	151
94	225.12	10.3	118.42	11.497	76.9	55	137	164

PEAK

Age-pred peak HR	%pk	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	RPP (10^{-2})	VO2 (mL/kg/min)	VO2 (l/min)	METs
154	0.92	156	88	110.4	220.0	13.6	1.384	3.9
192	1.01	204	90	127.6	393.7	25.1	2.969	7.2
185	0.95	188	70	108.9	330.9	32.1	3.271	9.2
181	0.81	194	98	129.7	285.2	22.8	2.309	6.5
182	0.86	156	84	107.8	244.9	15.7	1.399	4.5
169	0.81	192	86	121.0	263.0	29.5	2.878	8.4
178	0.78	164	86	111.7	228.0	16.3	1.715	4.6
157	0.82	210	74	118.9	270.9	20	2.04	5.7
169	0.84	208	98	134.3	295.4	15.8	1.4931	4.5
173	0.87	168	84	111.7	253.7	20.1	1.334	5.7
182	0.90	212	96	134.28	347.68	22.0	2.299	6.3

VE (STPD) L/min	RPE	VE/VO2	$P_{ET}CO_2$ (mmHg)	RER
39.5	15		31.6	1.09
75	17	31	37	0.99
88.3	18	36	41.8	1.28
38.4	15	22	49	0.89
33.8	17	36	36.9	1.2
51.8	17		39.5	
44	17	34	39.7	1.14
48	17	30	37.8	0.98
34.8	17	31	44.3	1.18
43.3	17	43	35.8	1.25
76.4	17		31	1.22

Recovery

HR ($bt \bullet min^{-1}$)	SBP (mmHg)	DBP (mmHg)	RPP (10^{-2})
112	134	80	150.1
125	146	82	182.5
104	92	64	95.7
100	138	84	138.0
117	144	80	168.5
91	126	78	114.7
114	134	78	152.8
110	134	74	147.4
114	162	84	184.7
92	120	68	110.4
124	140	84	173.6