

CAN A SCREENING ALGORITHM FOR OBSTRUCTIVE SLEEP
APNEA BE FORMULATED FROM MAXIMAL
EXERCISE TEST VARIABLES?

by

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ABSTRACT

CAN A SCREENING ALGORITHM FOR OBSTRUCTIVE SLEEP
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Purpose: The primary purpose of this study was to compare the cardiopulmonary and electrocardiography exercise testing responses of overweight individuals between one group, at low-risk (LR) for developing OSA, versus another group at high-risk (HR) for developing OSA. **Methods:** Both men (N = 11) and women (N = 11) participated in the study (age 37.00 ± 12.55 yrs., BMI 35.61 ± 6.43). Each subject was assigned to one of two groups, LR (AHI ≤ 5) or HR (AHI > 5) depending upon their overnight AHI score from the ApneaLink[®] sleep report. In the LR (age 30.45 ± 8.40 yrs., BMI 34.93 ± 5.66 , AHI 1.82 ± 1.47) group, there were 2 males and 9 females and in the HR (age 43.55 ± 12.89 , BMI 36.30 ± 7.34 , AHI 26.10 ± 18.80) group there were 6 males and 5 females. Each Independent t-tests were used to analyze

difference between the LR and HR groups. Significance was set at .05. **Results:** Regression analysis revealed that the combination of neck circumference, age, and four minute recovery rate pressure product (RPP) explained 76 percent of the variance in risk indicator (RI) observed in results from the sleep recording taken from the ApneaLink. Similarly, neck circumference, age, four minute recovery RPP, and peak ventilation (VE_{pk}) explained 82 percent of the variance in apnea-hypopnea index (AHI). **Conclusion:** Exercise markers in combination with neck circumference and age, may be helpful in the initial detection of obstructive sleep apnea (OSA). This may help detect those who may benefit from an expensive polysomnography (PSG) test for OSA diagnosis. These preliminary results suggest that the value of a graded exercise test (GXT) to assess the performance of those with undiagnosed OSA.

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CHAPTER 1

INTRODUCTION

An increasing number of individuals are recognizing that changes in their sleeping habits along with daytime somnolence may be related to obstructive sleep apnea (OSA). Diagnosed OSA currently affects 2% of middle-aged women and 4% of middle-aged men.⁴ Severity of OSA is measured by an apnea-hypopnea-index (AHI) value, which is the mean number of apneas and hypopneas per hour. An $AHI \leq 5$ is within normal ranges, or not at risk for developing OSA. However, if an $AHI > 5$ is used as the sole indicator of sleep-disordered breathing, then the prevalence rises to 9% for women and 24% for men.⁴

Obstructive Sleep Apnea is characterized by periodic complete or partial upper airway obstruction during sleep, causing intermittent cessations of breathing (apneas), or reductions in airflow (hypopneas) despite ongoing respiratory effort. OSA is defined by the presence of at least 5 obstructive apneas, hypopneas, or both per hour while one is sleeping.⁴ An apnea is a cessation of airflow by 80-100% for 10 seconds or more and the apnea index is the total number of apneic episodes that occur over the course of an hour. A hypopnea is a 30-50% reduction in airflow for more than 10 seconds and the hypopnea index is the number of hypopneic episodes that occur over the course of an hour. Thus, the apnea-hypopnea index (AHI) is defined as the mean number of apneic and hypopneic episodes for every hour of sleep. OSA is divided into three categories:

mild ($AHI \geq 5$ but < 15 events per hour); moderate ($AHI = 15-30$ events per hour); and severe ($AHI > 30$ events per hour).⁴ OSA becomes clinically significant if AHI values are greater than 20 and if oxygen saturation (SaO_2) falls below 80 - 85%.

OSA is one of the most serious sleep disorders associated with an increased risk in morbidity and mortality, placing a significant burden on society. It adversely affects almost every system of the body. If not treated, OSA contributes to an increased risk to several health complications including hypertension, pulmonary hypertension, cardiac arrhythmias, cardiovascular disease, stroke and altered immune function. In addition, there are health risks associated with daytime somnolence, such as car accidents. OSA must be treated aggressively to improve one's quality of life and decrease health risks and other complications that result from this disease. Although OSA has been described for decades, its recognition still remains a problem.⁴

There are a number of clinical consequences of OSA, including abnormal gas exchange, arterial oxygen desaturation, systemic and pulmonary hypertension, abnormal autonomic nerve function, neurocognitive disorders, alveolar hypoventilation and a number of cardiac disorders. Advanced, or severe, cases of OSA are associated with cor pulmonale, chronic carbon dioxide retention and polycythemia. Cardiovascular repercussions of OSA can include cardiac arrhythmias, myocardial infarction and stroke.

OSA is typically undiagnosed or misdiagnosed due to the lack of screening tools. There are symptoms that can be observed that are suggestive of OSA, such as, poor sleep quality, snoring, and an excessive daytime somnolence.⁵ The gold standard

for the diagnosis of OSA is the overnight polysomnogram (PSG), which provides an accurate picture of sleep characteristics and the severity of OSA.⁴ However, this method is costly, timely, inconvenient, and usually catches OSA very late in its progression. Other less costly methods are needed to aid in earlier identification and treatment of OSA.

Exercise testing with ECG monitoring is currently used to screen for chronic diseases such as coronary artery disease, ischemia, abnormal heart rhythms or arrhythmias. However, there are few studies that have formulated a screening equation from physical characteristics and noninvasive exercise testing measures, which can be used to predict OSA development. By detecting OSA in early stages of development, it would help to identify those who are at high-risk for developing the disease and to then pursue additional clinical screening and testing. Exercise testing would be a cost-efficient way to screen for and help predict OSA presence and severity.

Little is known about the physiological responses and recovery to standardized maximal exercise tests, in those with an AHI above normal ranges and of those who are borderline obese. Studies have examined several variables used for predicting OSA at rest and during sleep, but few have examined variables from a maximal exercise test as a predictor. Further investigation of characteristics, including diastolic and systolic blood pressure, ventilation responses, and ECG morphology during peak exercise, is needed to help screen for the presence of OSA and to identify individuals who would benefit from further clinical testing, early detection, subsequent behavioral or medical treatment.

1.1 Purpose

The purpose of this study was to compare various maximal graded exercise test (GXT) variables in borderline obese individuals using low risk (LR) versus high risk (HR) subjects for OSA from an overnight sleep AHI score recorded by a portable sleep device. The variables compared included, resting and exercise heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), rate pressure product (RPP) and R-wave amplitude (mV). Variables measured at peak exercise included rate of perceived exertion (RPE), METs, HR, SBP, DBP, oxygen consumption (Vo_2), peak ventilation (VE_{pk}), ventilatory threshold (T_{vent}), R-wave amplitude (mV) and ST-segment depression (mm). Exercise testing recovery responses, taken at 4 minutes post exercise, included HR, SBP, DBP and RPP. Physiological responses were analyzed to determine if there was a consistency of physiological characteristics that could be used as criteria to help screen individuals who may benefit from further clinical testing, screening, or assessment for obstructive sleep apnea.

1.2 Hypotheses

Hypothesized physiological responses between the HR ($\text{AHI} > 5$) group vs. the LR ($\text{AHI} \leq 5$) group, included; 1) increased resting HR, SBP, DBP, RPP and R-wave amplitude; 2) Increased peak exercise SBP, DBP, RPP, ST-segment depression and R-wave amplitude at peak exercise; 3) Elevated 4-minute recovery HR, SBP, DBP and

RPP; 4) Lower $\dot{V}O_2$, $\dot{V}E_{pk}$ and T_{vent} during peak exercise; 5) Higher ESS scores; 6) Sleep questionnaires would not be significant predictors of OSA in the HR group.

1.3 Definition of Terms

Obstructive Sleep Apnea (OSA) – Periodic complete or partial upper airway obstruction during sleep, causing intermittent cessations of breathing (apneas) or reductions in airflow (hypopneas) despite ongoing respiratory effort.

Apnea – A reduction of airflow by 80-100% that lasts 10 seconds or longer.

Hypopnea – A 30-50% reduction of airflow that lasts 10 seconds or longer associated with 4% decrease in oxygen saturation.

Apnea-hypopnea index (AHI) – Mean number of apneas and hypopneas per hour in an evaluation period. Points calculated from AHI is as follows:

$$AHI \times 1 \text{ h}^* = \text{number of points (e.g. } AHI = 5/h \times 1 \text{ h} = 5 \text{ points)}$$

Flow-Limited Breaths Without Snoring (FL) – Percentage of all flow-limited breaths compared with the total of all breaths. Snoring events not included.

Flow-Limited Breaths With Snoring (FS) – Percentage rate of all flow-limited breaths with snoring in relation to the total sum of breaths. An FS is created if there is at least a 30% overlap between flow limitation and snoring events.

$$FL/FS \text{ Point Score} = 10 \times (0.8 \times FL + 1.2 \times FS) / Az) \text{ number of points}$$

Risk Indicator (RI) – The central message of the ApneaLink[®] report that is displayed.

Risk Indicator (RI) is calculated as follows:

$$RI = \text{point score as a sum of AHI} + \text{score of FL/FS}$$

ApneaLink[®] - A simple, cost effective sleep-screening device designed to identify patients at risk for obstructive sleep apnea. Automatically analyzes and derives AHI, flow limitation and snoring.

Hypoxia – A shortage of oxygen in the body.

Hypoxemia – Reduced amount of oxygen in the body, specifically the blood.

Hypercapnia – Higher than normal levels of carbon dioxide in the blood.

Ventilation (VE) - The circulation and exchange of gases in the lungs that is basic to respiration.

Peak Ventilation (VE_{pk})- Maximal minute ventilation (L/min, BTPS) at peak exercise.

Ventilatory Threshold (T_{vent}) - The point during graded exercise testing when ventilation increases disproportionately to oxygen uptake.

Rate Pressure Product (RPP) – An index of myocardial oxygen consumption (mVO₂).

Amplitude - The height of a wave, or the measure of a wave's magnitude of oscillation.

R wave – The initial upward deflection of the QRS complex, following the Q wave in the normal electrocardiogram and representing early depolarization of the ventricles.

ST-segment – Represents the period from the end of ventricular depolarization to the beginning of ventricular repolarization.

Continuous Positive Airway Pressure (CPAP) – CPAP is a popular noninvasive method of treatment for those with OSA, by delivering air into the airway through a specially designed nasal mask, which rates adequate pressure to keep the airway open while inhaling.

Polysomnography (PSG) – A comprehensive recording of the biophysiological changes that occur during sleep. The PSG is usually performed at night and monitors body functions during sleep, including, brain (EEG), eye movements (EOG), muscle activity or skeletal muscle activation (EMG), heart rhythm (ECG), and breathing function.

1.4 Delimitations

The delimitations of this study were twenty-two males and/or females; 1) between 20-60 years of age; 2) who were borderline obese (25-35 lbs. over ideal body weight) with a BMI ≥ 26 , subjects who did not exercise more than 2 times per week and had no known cardiovascular or metabolic disease.

1.5 Assumptions

The following assumptions were considered throughout the study; 1) the subjects filled out the health history questionnaire accurately and honestly; 2) the subjects performed the maximal graded exercise test to the best of their ability; 3) Subjects followed instructions for recording sleep using the ApneaLink®.

1.6 Limitations

Limitations of the study were subject error of using the take home sleep device, the ApneaLink®, to record sleep activity. Subject's compliance to alcohol and caffeine elimination 24 hours prior to maximal graded exercise testing (GXT) was also a

limitation. Subject's familiarity to the treadmill, level of comfort while performing a GXT, and reaching a true $\text{VO}_{2\text{max}}$ were exercise limitations in this study.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Pathophysiology of OSA

Obstructive sleep apnea originates in the site where upper airway obstruction is typically found, the pharynx. The pharyngeal muscles are used for swallowing, the maintenance of pharyngeal opening during inspiration and phonation, or the use of the larynx or voice box. Narrowing of the pharyngeal airway can be caused by several conditions, including surface adhesive forces, neck flexion, jaw opening, gravity and increased nasal resistance. Pharyngeal narrowing can occur in a few areas of the pharynx in OSA patients, including the velopharynx, oropharynx and hypopharynx. However, the most common site of occlusion in the majority of OSA patients is the velopharynx.⁴

The central nervous system controls the pharyngeal muscles by continuous stimulation from neuromuscular activation. During periods of sleep, this activation is reduced causing the upper airway to close. However, reduced neuromuscular activation in addition to either anatomic abnormalities of the pharynx, or other abnormalities such as an enlarged tongue, can contribute to the development of obstructive hypopneas and apneas in patients with OSA.⁴

When narrowing or total occlusion of the upper airway occurs, then ventilation can be significantly reduced or potentially eliminated completely. When the upper airway is completely or partially occluded, then hypoxia and hypercapnia develop. Events of hypoxia and hypercapnia lead to an increased respiratory effort and then arousal. Hypopneic and apneic events can occur repeatedly throughout the night, leading to fragmented sleep and arousal. Arousal triggers adrenergic surges with each cycle.⁴ Chronic intermittent hypoxia/asphyxia can induce long-term facilitation of central respiratory drive to upper airway muscles. This results in impaired upper airway reflex recruitment of pharyngeal dilator muscle to acute physiological stimuli. This helps to conclude that chronic intermittent hypoxia impairs neural control systems, which regulate the patency of the upper airway and through altered respiratory muscle contractile function. These events lead to a cycle of further airway obstruction, which chronically exacerbates the condition.³⁸

2.2 Risk Factors for OSA

2.2.1 Obesity

There are risk factors associated with OSA that can be modified by a person's behavior. These include weight loss through diet and exercise, avoiding sleep deprivation by taking steps to a regular sleep pattern, avoiding tobacco, alcohol, sedative hypnotics and sleep postural changes. One of the largest risk factors that can be modified is weight loss. Weight loss may not completely eliminate OSA, but can have a significant reduction in AHI.

Obesity is one of the most important risk factors for OSA. There has been a consistent association, in several studies, between increased body weight and the risk of OSA, specifically, upper body obesity and body mass index (BMI). Skinfold thickness of upper body measurements and neck fat are also greater in patients with OSA when compared to matched controls.²⁹ A protein hormone, called leptin, which helps regulate body weight and metabolism, is increased substantially in obesity and can have a significant effect on chemoreflex function and breathing control.⁵ Specific mechanisms underlying the effects of obesity on OSA need to be further investigated.

Obesity may be related to OSA just by the effects of fat deposition on airway anatomy. Shepard et al.⁴² found that a CT scan accurately classified 70 percent of obese males with OSA, by having a cross-sectional area of less than 1.0 cm of the upper airway which is significantly smaller than normal subjects. This study indicated that there are detectable differences during wakefulness that contribute to OSA development.

The effects of obesity on OSA have been strongly linked. Obstructive sleep apnea may actually predispose individuals to obesity. However, this has not previously been tested. Patients newly diagnosed with OSA have a history of recent significant weight gain, preceding the diagnosis of OSA. Phillips et al.²⁹ documented weight histories in fifty-three with newly diagnosed OSA and evaluated them for one year. There were 28 males and 25 females found to have severe OSA (AHI 33 ± 5 and 37 ± 10 respectively). The newly diagnosed OSA patients had not been treated and were compared to twenty-four matched controls without any sleep disordered breathing (AHI

2 ± 1). OSA patients had a significant ($p = 0.001$) recent weight gain (7.4 ± 1.5 kg) when compared to the weight loss of the similarly matched obese controls (0.5 ± 1.7 kg). This study showed that patients with OSA had an increase in weight preceding the diagnosis of OSA.

Schwartz et al.²⁸ and Norman et al.⁶ evaluated the effect of weight loss on those with OSA. Schwartz et al. evaluated the effect of weight loss on the collapsibility of the upper airway. The purpose of this study was to determine if weight loss caused a decrease in the collapsibility of the upper airway. This study took the measurement of critical pressure (P_{crit}) of the upper airway in thirteen patients with OSA before and after a ($17.4 \pm 3.4\%$) reduction in BMI. Weight loss was associated with decreases in upper airway collapsibility in patients with OSA along with proof that there is a correlation between the severity of sleep apnea and of the absolute level to which P_{crit} falls. Norman et al. also looked at the effects of weight loss, but through exercise training and its effects on physical and subjective measures associated with OSA. Norman exercise trained nine subjects with mild to moderate OSA and found that regular exercise training had a positive impact on AHI, even though there was not a significant change in body weight.

The effects of OSA on weight gain and obesity could also be multifactorial. Patients with OSA typically develop daytime somnolence, as a result of multiple episodes of disrupted sleep caused by apnea-hypopnea related arousals throughout the night. Daytime somnolence may predispose OSA patients to weight gain due to a

decrease in physical activity.⁵ However, OSA could be the result of weight gain, due to an inactive lifestyle.

2.2.2 Anatomical Abnormalities

Obstructive sleep apnea develops as a result of several anatomical abnormalities including, receding chin, hypertrophied tonsils, adenoids, oversized tongue, back sloping jaw, throat tumors and blocked nose. Anatomic abnormalities of the pharynx can also play a role in the development of OSA. The velopharynx, which is the most common site of occlusion in the majority of OSA patients, along with velopharyngeal closing pressure have been shown to be highly correlated with the frequency of nocturnal desaturations in those with OSA when compared to those without OSA.³⁷

Other craniofacial abnormalities have been linked to OSA. For example, achondroplasia is the combination of a short cranial face and midface hypoplasia and is the most common skeletal dysplasia in children. They typically have sleep-related respiratory disturbances that lead to hypoxemia. Anatomic features of this disease are associated with upper-airway obstruction or brain stem compression.³⁹ Some anatomical abnormalities can be resolved by surgery, such as achondroplasia can be resolved by an adenotonsillectomy.

2.2.3 Gender and Age

Prevalence of OSA may vary in different age groups and populations, but it has been estimated that the prevalence of OSA is two to threefold greater in males than females, or approximately 24% of middle-aged men and only 9% of middle-aged women.⁵ Anthropometric differences, specifically height and neck circumference may

be the reason for the difference of OSA prevalence in males vs. females. Neck circumference and neck/height ratio have been highly correlated with AHI.³⁶ Males tend to store more fat in the upper body regions, including the neck area, resulting in a greater neck circumference and a higher AHI. Women typically store fat in the lower body region, resulting in decreased neck circumferences and AHI when compared to men.

Another possible reason why OSA is more prevalent in males is that males with OSA have approximately 50% higher plasma leptin levels than matched obese control subjects without OSA. Leptin, a protein produced by adipocytes, suppresses appetite and increases energy expenditure, resulting in weight loss. However, when obese individuals have high leptin levels, such as obese males with OSA, obesity persists due to “leptin resistance” or resistance to appetite suppression and metabolic effects of leptin.⁵

There is also a high prevalence of OSA in middle aged and elderly population. Age has become an important risk factor for OSA that is independent from other risk factors. This is primarily due to the changes in oropharyngeal collapsibility, such as decreased upper airway muscle tone that occurs during sleep. However, the prevalence of OSA and increasing age is still unclear, but may be linked to either pharyngeal soft tissue characteristics or neural regulation.³⁰

2.2.4 Diseases and Disorders

Diseases and disorders, such as hypothyroidism, acromegaly, amyloidosis, vocal cord paralysis, neuromuscular disorders, Marfan’s syndrome and Down Syndrome can

all cause OSA. For example, hypothyroidism and OSA patients share several clinical signs and symptoms, such as overweight, snoring and impaired concentration.³¹

2.3 Physiological Consequences of OSA

2.3.1 OSA and Hypertension

Several studies have shown a strong association of OSA and arterial hypertension. Approximately 40% of patients with OSA have hypertension. Studies have shown that the risk of OSA patients developing hypertension is a 1.5- to – 3.0-fold increase.⁴ Repeated apneic and hypopneic events lead to possible arousals during sleep. Repeated arousals can lead to hypoxia or hypercapnia, which can result in hypoxemia over time. Hypoxia and hypercapnia increase sympathetic nerve activity or drive. A consequence of sympathetic vasoconstrictor response is an increase in blood pressure during sleep.⁴⁰ Peled et al.²² found that nocturnal hypoxia is more closely associated with the level of sympathetic activation and with daytime level of blood pressure than with sleep fragmentation.

Blood pressure, in patients with OSA, can reach up to 240/120 mmHg, during periods of sleep. Diastolic blood pressure (DBP) has been shown to be higher early in the course of OSA, such as in a study by Sharabi et al.⁸ In this investigation, a sleep study was performed on 121 of newly diagnosed patients with OSA and was compared to 229 matched control subjects. The subjects with OSA had a higher BMI (3-kg/m² difference) and a higher DBP (4 mmHg difference) without elevation in SBP. However,

this study did not examine DBP as a separate screening tool for identifying individuals with newly developed or mild OSA.

Obstructive sleep apnea patients may show daytime blood pressure as within normal ranges and without the pathology of OSA, but during sleep, repetitive episodes of apneas results in repeated hypertensive surges. The lack of blood pressure lowering, or “non-dipping”, during sleep has been associated with an adverse cardiovascular prognosis.²⁴ However, Narkiewicz et al.⁴⁰ found that increases in daytime blood pressure have also been seen in those with OSA. The increases in sympathetic nerve activity and blood pressure during sleep can tend to carry over into the daytime in those with OSA, resulting in those with OSA having an increased prevalence of hypertension. The mechanisms underlying increased sympathetic activity during the daytime is not well known. However, Brooks et al.⁴¹ induced apnea in four dogs by intermittent airway occlusion during sleep. Daytime and nighttime BP were measured before, during and after a 1-3 month period of OSA. Brooks et al. found similar results in that acute transient increases in blood pressure during sleep (13.0 ± 2.0 mm/Hg), eventually produced sustained hypertension during the daytime (15.7 ± 4.3 mm/Hg).

Baroreflex function may also be impaired in those with OSA. Monahan et al.¹⁴ tested the hypothesis that short-term exposure to repetitive hypoxic apneas (RHA) would result in prolonged impairment in baroreflex function. The results showed that the baroreflexes were shifted rightward to higher levels of systolic blood pressure (BP), and upward to higher levels of heart rate and muscle sympathetic nerve activity after

RHA. This finding showed that short-term exposure to RHA does reset the baroreflex stimulus-response curve to higher levels of BP for extended periods of time.

Treated OSA patients with hypertension typically see a decrease in daytime systemic blood pressure.⁴ Effective treatment of OSA with continuous positive airway pressure (CPAP) has resulted in a decrease in both daytime and nighttime blood pressure, indicating that there is a relationship between OSA and chronic hypertension.⁵

2.3.2. OSA and Cardiopulmonary Disorders

Chronic sympathetic activation has seemed to be the most likely mechanism linking OSA to cardiovascular disease. There are several other mechanisms that may also contribute to cardiovascular disease in those with OSA. These include inflammation, endothelial dysfunction, elevated levels of endothelin, hypercoagulability and stimulation of the renin angiotensin system. However, OSA is typically associated with hypertension and obesity, so interaction between these two other risk factors can result in several pathophysiological mechanisms and cardiovascular consequences.²⁴

In those with OSA, the metabolic demands for oxygen must be met from oxygen stores within the body. This means diminishing oxygen stores in the lungs and the rate of oxyhemoglobin desaturation increase, which can lead to alveolar hypoventilation.⁹ OSA has also been shown to cause mild pulmonary hypertension. It has been shown that hypoxia can cause pulmonary vasoconstriction and can increase pulmonary arterial pressure. Increased resting pulmonary artery pressure has been reported to affect approximately 15% of individuals with OSA. Chronic obstructive pulmonary disease

(COPD) is also linked with OSA. Approximately 10% of individuals with OSA have COPD.⁴

2.3.3 OSA and Abnormal Cardiovascular Responses

Over several decades, OSA was primarily linked to impaired cognitive function and daytime somnolence. However, the evidence that OSA is related to cardiovascular disease is increasing.²⁴ Several cardiovascular risks are associated with OSA. They include ischemic heart disease, congestive heart failure, stroke, and cardiac arrhythmias, especially atrial fibrillation.

The association of OSA and several cardiovascular diseases have been linked. However the mechanisms are not completely understood. Drager et al.³⁴ hypothesized that OSA has an affect on the functional and structural properties of the large arteries which contributes to the progression of atherosclerosis. This study used 12 healthy volunteers, 15 patients with mild to moderate OSA and 15 patients with severe OSA matched for age, sex and body mass index. None of the participants had any signs or symptoms of hypertension or diabetes, they did not smoke and were not on any medications. The findings of this study found that in middle-aged patients with OSA, who are free from cardiovascular disease, have early signs of atherosclerosis. Also, the vascular abnormalities measured showed a significant relationship with the severity of OSA, which further supports their hypothesis that OSA plays an independent role in the progression of atherosclerosis.

Another finding that supports the relationship between OSA severity and the progression of atherosclerosis is a study by Minoguchi et al.³⁵ They looked at carotid

intima-media thickness (IMT), which is a useful marker to detect early atherosclerosis along with the association of carotid IMT and increased serum levels of inflammatory markers in patients with OSA. The results showed that carotid IMT and serum levels of C-reactive protein (CRP) of patients with OSA were significantly higher than the obese control subjects. Also, the carotid IMT was significantly correlated with serum levels of CRP, duration of OSA- related hypoxia and severity of OSA. This showed that the duration of hypoxia during total sleep time was the primary factor in influencing carotid IMT.

Fung et al.³³ assessed to analyze the relationship between diastolic parameters and OSA severity in sixty-eight patients with confirmed OSA. An abnormal relaxation pattern (ARP) in diastole of 25 of the patients was noted. Also, those who had an AHI \geq 40/hour had significantly longer isovolumic relaxation times than those patients with an AHI $<$ 40/hour. Fung et al. concluded with two main findings from this study. One, that ARP was more common in patients with OSA and two, that OSA severity is associated with a higher degree of the left ventricular diastolic dysfunction.

Usui et al.²³ evaluated the prevalence of left ventricular hypertrophy, by wall thickness and greater septal thickness, of heart failure patients with nonischemic dilated cardiomyopathy, who suffer from OSA vs. patients without OSA. The results showed that the prevalence of left ventricular hypertrophy was greater in those with OSA vs. those without along with significantly greater interventricular septal thickness. These findings suggest that OSA is associated with an increased prevalence of left ventricular

hypertrophy in patients with nonischemic dilated cardiomyopathy and that the left ventricle is less eccentric in those with OSA vs. those without.

2.4 Exercise Responses to GXT in OSA and At-Risk Patients

2.4.1. Abnormal Maximal GXT Responses

There are limited studies on maximal exercise testing in individuals with OSA. Lin et al.¹ evaluated 20 subjects in one group with diagnosed moderate to severe OSA and 20 age, sex and weight matched controls without OSA. There was no significant difference in body mass index (BMI) or mean age between the two groups. A sleep study, along with a maximal cardiopulmonary exercise test, on a cycle ergometer was performed. The sleep study showed a significant difference between groups for AHI, with the OSA group having a higher AHI. The results concluded that the OSA group had lower $\text{VO}_{2\text{pk/kg}}$, workpeak, anaerobic threshold and oxygen pulse. Even though there was no difference between BMI, this study failed to examine other physiological responses to GXT that could be significantly different, including, blood pressure, ventilatory threshold (T_{vent}) and heart rate.

Kaleth et al.¹⁹ had 23 subjects with diagnosed OSA in one group and the other group had 9 control subjects. All subjects performed a GXT on a cycle ergometer to assess whether exercise testing might aid in discriminating between individuals with and without OSA. There were no differences between age, BMI, resting HR and BP between overweight subjects with OSA vs. without OSA. Results showed that there was a significant difference in peak systolic and diastolic BP in the OSA group and they

both remained high during a three minute exercise recovery. Exercise HR was lower in the OSA group than the overweight controls during peak exercise. This study did not examine the relationship of significant physiological responses to exercise, regardless of BMI, as criteria for predictors of OSA.

2.4.2. GXT and Peak Ventilation (VE_{pk})

Few studies have measured peak ventilation (VE_{pk}) and ventilatory threshold (T_{vent}) in maximal exercise testing of those with OSA. However, results have been inconsistent. Lin et al.¹ showed that there was a significant difference in VE_{pk} between groups, with the OSA group having a significantly lower VE_{pk} . This could indicate that a mechanical ventilatory limitation to exercise was not present. Ventilatory threshold was not examined in this study.

Kaleth et al.¹⁹ found that VE_{pk} was significantly higher during maximal GXT for the OSA group. The increase in VE_{pk} could be a response from peripheral and central chemosensitivity to CO_2 resulting from repetitive episodes of intermittent hypoxia during sleep. This study also did not examine ventilatory threshold (T_{vent}) during exercise testing.

2.4.3 GXT and Ventilatory Threshold (T_{vent})

Further research is needed in examining T_{vent} in those with OSA. Mabry et al.¹⁰ took 20 obese males with diagnosed OSA and 10 males with similar BMI and age without OSA. Results showed no difference between the Vo_{2pk} and Vo_2 at the T_{vent} between the two groups. However, heart rate was higher at the T_{vent} in the OSA group.

This study found that there is an association with OSA in young obese adult males and substantially higher heart rates at the T_{vent} .

2.4.4 GXT and Blood Pressure Responses

There is an increase in evidence that OSA is an independent risk factor for hypertension. However, there have been some conflicting results. Independent of BMI, age and gender, several studies have shown a significant association between AHI, SBP, DBP and the prevalence of hypertension.¹⁶ Borgel et al.¹⁶ confirmed an independent relationship between OSA severity, blood pressure and heart rate along with using blood pressure values before treatment as independent predictors of the lowering effect of Bi-/CPAP therapy on both systolic and diastolic blood pressure.

However, there are few studies that examine blood pressure during exercise as criteria of examining OSA as an independent risk factor for hypertension. Tryfon et al.¹⁷ examined the relationship between diastolic blood pressure response during exercise and the severity of OSA. During a maximal incremental exercise test on a cycle ergometer, DBP and VO_2 were taken at rest and at VO_{2pk} . The results of this study concluded that DBP was significantly higher in OSA patients than in normal subjects and that normotensive OSA patients develop DBP elevation at an earlier stage during exercise compared to normal subjects. This shows that DBP elevation could be a limiting factor of physical performance when it comes to OSA patients. Kaleth et al.¹⁹ found diastolic blood pressure to be significantly higher, in those with OSA, during maximal ramping cardiopulmonary exercise test. There was also a delayed response of

SBP during active recovery post-exercise and a trend for DBP to remain higher during active recovery as well in the OSA group.

2.4.5 GXT and R-wave Amplitude

Sleep apnea is typically accompanied by a characteristic cyclic variation in heart rate of other changes in the waveform of the ECG. The mechanism for the change, specifically looking at the R-wave amplitude of a surface ECG during exercise, is not clear. There are several conditions that affect the R-wave amplitude. The amplitude of the R-wave can be influenced by several factors, including blood conductivity, blood potassium, electrical axis, movement of the chest wall and diaphragm.²⁵ Recent studies have shown a relationship between OSA and ECG waveform changes, specifically showing the R-wave amplitude as being sensitive and specific to breathing pattern.¹² Waveform changes persisted in patients with autonomic dysfunction and possible central sleep apnea, which is a type of sleep apnea that is less frequent. Studies conclude that ECG waveform changes may be attributed to intrathoracic pressure changes that occur during OSA.¹¹

In a recent study conducted by Vijendra et al.¹² the primary variable examined on the ECG was the morphology of the R-wave amplitude in those with sleep-disordered breathing (SDB) subjects while performing a nocturnal polysomnography test (NPSG). Two groups of subjects were examined, including those with sleep-related problems and those with diagnosed OSA. This study found that Lead I would be the most suitable lead to examine during sleep because it best detects abnormal breathing

events using features from R-wave morphology of the ECG, in those with sleep disordered breathing and OSA.

Past studies have looked at R-wave amplitude during exercise and it's relation to coronary artery disease (CAD). The results of these studies have shown that R-wave amplitude, measured by surface electrocardiogram, decreased in normal patients and increased or stayed the same in patients with CAD. For example, Baron et al²⁵, looked at maximal exercise treadmill testing to discriminate patients with and without CAD and to help distinguish those who may have abnormal left ventricular function. They found that the mean R-wave amplitude decreased maximally one minute after exercise. Also, mean R-wave amplitude increased in patients with either triple vessel or left main CAD, or those with an akinetic region on the left ventriculogram. Baron et al. also found that in normal subjects, there was a decrease in the end-diastolic volume of the left ventricle during exercise along with a decrease in R-wave amplitude. This correlation indicates R-wave amplitude and intraventricular volume may be directly related.

There are only a few studies that examine R-wave amplitude during sleep and during exercise and only a couple of studies that examine R-wave amplitude in those with either diagnosed OSA or at high-risk for OSA. There has yet to be a study that examines breathing patterns, specifically R-wave amplitude, of those with sleep disordered breathing during exercise, specifically, a maximal graded exercise test.

2.4.6 GXT and ST-Segment Depression

Studies have shown that nocturnal ST-segment changes and myocardial ischemia are prevalent in most patients with OSA and coexisting coronary artery disease (CAD). Schafer et al.⁴³ found that patients with coronary heart disease (CHD) and OSA were endangered by ischemia that was apnea-associated and concluded that those with nocturnal ischemia should be screened for underlying sleep apnea. However, there are few studies that examine if OSA causes nocturnal ischemia in those without coronary artery disease. Fernandez et al.¹³ found no evidence of nocturnal ischemia in OSA patients without a history of CAD. Yet in another study, Hanly et al.¹⁵ found ST-segment depression, of a significant amount of 1 mm for the duration of 1 minute, in 30 percent of OSA patients without a history of CAD. Hanly et al. also included randomly assigned nasal continuous positive airway pressure (CPAP) to patients throughout the first half of the night during the overnight sleep study. Of the 30 percent, ST-segment depression decreased during nasal CPAP along with a decrease in arousal index and the duration of time that oxygen saturation was less than 90 percent. When patients were not on nasal CPAP, the AHI and arousal indexes were higher during periods of ST-segment depression.

From the studies that examined ST-segment changes, they have all looked at the ST-segment during sleep. None have been conducted on patients with OSA and ST-segment depression during peak exercise, specifically, a maximal GXT. To better understand ST-segment changes in patients at high risk for and/or diagnosed OSA,

exercise conditions should be observed as well. The correlation between maximal exercise testing ST-segment changes and those with OSA needs to be examined.

2.5 Existing OSA Prediction Equations and Screening Tools

2.5.1 Portable Take-Home Sleep Devices: ApneaLink® by ResMed®

The ApneaLink® is a take-home portable sleep device that measures airflow through a nasal cannula connected to a pressure transducer, providing an AHI based on recording time. It is a cost-efficient way to assess one's risk for developing a pathological sleep disorder. The validity of this device was tested for its use as a screening tool for sleep apnea in clinical practice. This study compared the AHI obtained from a home study using the ApneaLink® vs. the AHI obtained during a sleep-laboratory polysomnography study to test sensitivity and specificity of the device. Fifty-nine overweight subjects completed the study. The comparison of AHI from the home and laboratory studies demonstrated that the ApneaLink® has good sensitivity and specificity (sensitivity 76%, specificity 94%, for both respectively) at AHI levels of ≥ 15 and ≥ 20 .²⁶

2.5.2 Polysomnography

A polysomnography (PSG) is the gold standard for diagnosing OSA. It is performed during one night of sleep and monitors several functions throughout the night. The PSG is typically supervised by a technician and conducted in a sleep laboratory. An overnight PSG usually provides an accurate picture of sleep

characteristics and OSA severity. A PSG is time-consuming, complex and inconvenient.²⁷ It requires an overnight evaluation in a sleep laboratory with attending personnel. However, the primary limiting factor of the PSG is its' cost, which is approximately \$1,500 per study.¹²

2.5.3 Heart Rate Variability and Electrocardiogram

Heart rate variability (HRV) is used primarily in research by looking at the R-R intervals in an ECG over the course of several hours. To measure variability, the mean of the standard deviations of normal R-R intervals are taken during a 24 hour ECG recording. Heart rate variability is used to determine the balance between the sympathetic and parasympathetic input to the heart. An increase in sympathetic input and a decreased parasympathetic input indicates an increased risk of arrhythmias and mortality.

Heart rate variability patterns have been the primary focus for detecting sleep-disordered breathing (SDB) from an ECG until recently. In past studies, sensitivities and specificities reported have varied. Now, sensitivity and specificity values are up to 90% based on new methods using information derived from HRV and ECG morphology, primarily the amplitude of the R wave.¹² Electrocardiogram can be used in combination with HRV or can also be looked at individually. Vijendra et al.¹² specifically examined R-wave morphology in leads I, II and III to identify patterns of SDB. In this study, the amplitude of the R-wave was examined across various ECG lead configurations. This method helped to identify the lead that was the most appropriate for the detection of SDB.

Penzel et al.¹¹ assessed the ability of an overnight ECG recording only to distinguish patients with and without OSA. The first of the two parts of this study was to assess the ability of an overnight ECG recording to distinguish patients with and without apnea. The second part was to assess whether the ECG could detect apnea during each minute of the recording. Seventy overnight ECG recordings were collected for the comparison of apnea detection algorithms. Research groups were invited to access data via the world wide web and submit algorithm results to an international challenge. From this, a training set of 35 ECG recordings were made available for algorithm development. Finally, 13 different algorithms for apnea detection were compared. Four of the algorithms achieved a perfect accuracy score of 100% during the first part of the study and two algorithms achieved an accuracy score of 90% in the second part of the study. The four algorithms that had the highest accuracy, used frequency-domain parameters of heart rate variability or the ECG derived respiration signal with R-wave morphology. Three of these top four algorithms identified all apnea subjects correctly and the same three algorithms were the top-scoring algorithms used in the identification of minutes spent with sleep-disordered breathing.

2.5.4 Sleep and Non-Sleep Related Signs and Symptoms Measured by Questionnaires

Studies have shown that multiple sleep-related signs and symptoms can be useful in screening for significant OSA. Bartone et al.²¹ selected three sleep related questions to ask patients with either hypertension or heart failure to screen for the presence of significant OSA. The questions were; 1) do you snore loudly; 2) do you wake up more than once a night, and; 3) do you have AM fatigue? A PSG was then

performed on those who answered yes to two out of the three questions. This resulted in a positive predictive value of 67 percent and negative predictive value of 78 percent.

Chung et al.² used the Berlin questionnaire as a screening tool for identifying those at high risk for sleep apnea. There was a recruitment total of 305 orthopedic patients undergoing elective surgery at the Toronto Western Hospital. The questionnaire was comprised of three categories of questions, 1) questions related to snoring; 2) questions related to daytime sleepiness and drowsiness and 3) questions related to blood pressure and body mass index. The results of this study showed that the Berlin questionnaire correctly identified 24 percent of all patients as being high risk for sleep apnea.

One of the most commonly used sleep questionnaires, for those with suspected OSA, is the Epworth Sleepiness Scale (ESS). The ESS is comprised of eight questions that are all related to excessive daytime sleepiness. Dixon et al.³² used the ESS to look for clinical, anthropometric, biochemical and polysomnographic (PSG) predictors of excessive daytime sleepiness in obese patients. A total of 1,055 consecutive patients presenting for obesity surgery completed the ESS questionnaire. There were a total of 331 patients who were at high risk for OSA and those patients underwent a postoperative overnight PSG. The results of this study showed that there was not a significant relationship between ESS scores and diagnostic PSG factors, including AHI. In conclusion, this study found that in severely obese subjects, an increase in daytime sleepiness does not seem to be driven by OSA, the severity of obesity, anthropometric, metabolic, or inflammatory markers of the metabolic syndrome. However, daytime

sleepiness is associated with poor energy, symptoms of depression and symptoms of nocturnal sleep disturbance.

Sharma et al.¹⁸ examined a diagnostic model of predicting OSA in tertiary care center subjects with non-sleep related complaints. This study used BMI, male gender, relative-reporting snoring index (SI) and choking index (ChI) to predict OSA. This prediction equation method came out to be useful as a screening tool for OSA with a sensitivity and specificity of 82 percent and 90.7 percent respectively. Friedman et al.³ also looked at non-sleep related measures to predict OSA. This study measured Mallampati grade (MMP), tonsil size, BMI, measured thyroid-mental distance (TMD) and hyoid-mental distance (HMD) from 172 patients who had suggested OSA from questionnaire responses. The measures that correlated the highest in predicting respiratory disturbance index (RDI) included MMP, tonsil size and BMI.

2.6 Methods of Treating OSA

Oral devices and surgery are the most current forms of treatment for OSA patients. The most common and efficient treatment of opening up the airway during sleep is the use of continuous positive airway pressure (CPAP) therapy.²⁴ CPAP was first introduced in 1981 and has become the most effective and widely used treatment for those diagnosed with OSA. CPAP treats apnea-hypopnea episodes by providing positive air pressure through a nasal or facial mask to prevent the collapse of the pharyngeal airway. Bilevel positive pressure therapy is the continuously adjusting pressure to meet the patient's needs and reducing the overall air pressure. This will help

to improve tolerance and compliance of those with OSA. Long term CPAP treatment has been shown to improve daytime somnolence and blood pressure control during sleep.

Surgical treatments usually are not optimal for those who are obese with OSA. Surgical procedures will benefit those who have developed OSA due to discrete craniofacial abnormalities. There may be two phases to an OSA surgical procedure. Phase I includes a number of procedures or the combination of procedures, including, nasal septoplasty, turbinate reduction, tonsillectomy and adenoid resection, laser assisted uvulopalatoplasty, mandibular osteotomy with genioglossus advancement and hyoid myotomy-suspension.⁴

However, if the patient does not respond to the procedure performed in Phase I, then there must be a phase II surgery should be considered. Phase II consists of maxillomandibular advancement. The success rate of phase I and phase II have shown to be 90%. However, if phase I and phase II surgery treatments fail, then a tracheostomy can be considered as a final option, specifically in those who are obese with severe OSA, significant oxygen desaturation and/or cardiac disease.⁴

Few studies have examined maximal exercise test variables to aid in predicting OSA, or the need for further diagnostic testing. Hargens et al.²⁷ study compared the predictive performance of a PSG against simple measures used to screen those for OSA in comparison to that derived from exercise hemodynamic measures attained from clinical exercise testing. Thirty borderline obese individuals (BMI 32.2 ± 6.8) individuals underwent an overnight sleep study (AHI 17.3 ± 15.3 events/hr) and a

maximal ramped ergometer exercise test. Eleven independent variables from sleep function questionnaire, anthropometric measures and exercise test responses were used to predict AHI score from a PSG. The regression equation formulated was: $AHI = -99.1 + 0.66 (WHR) - 0.45 (BMI) + 0.36 (SBP_{peak})$. This showed a direct relationship between waist to hip ratio, body mass index and systolic blood pressure at peak exercise for predicting OSA.

Blevins et al.⁷ used graded exercise testing to reveal abnormalities of hemodynamic responses in those with OSA, particularly with respect to cardiac output (Qc), blood pressure (SBP, DBP, MAP) and total peripheral resistance and how these responses relate to polysomnographic PSG markers of OSA severity. Hemodynamic variables were correlated to PSG markers of OSA severity or lowest oxygen (SaO₂) and percent time that SaO₂ was less than 90 percent. Fifteen borderline obese (BMI 36.0 ± 5.9) patients with OSA participated in the study. Regression analysis of the data revealed that the combination of neck circumference, submaximal, exercise stroke volume (SV), and TPR explained 74 percent of the variance ($Y = 73.8 - 1.7 (BMI) + 0.53 (SubmaxSV) + 2.83 (SubmaxTPR)$) in low oxygen saturation (SaO) observed in PSG testing. Similarly neck circumference, submaximal MAP, and SV explained 79 percent of the variance relative to low SaO. ($Y = 85.67 - 2.87 (BMI) + 0.34 (SubmaxSV) + 0.78 (Submax MAP)$).

The purpose of this study was to compare various maximal graded exercise test (GXT) variables in borderline obese individuals using low risk (LR) versus high risk (HR) subjects for OSA from an overnight sleep AHI score recorded by a portable sleep

device. Physiological responses were analyzed to determine if there was a consistency of physiological characteristics that could be used as criteria to help screen individuals who may benefit from further clinical testing, screening, or assessment for OSA.

CHAPTER 3

METHODS

3.1 Study Design

A total of twenty-two subjects participated in the study. Each subject had two visits. The first visit to the exercise science research laboratory (ESRL) was initial testing. Initial testing included 1) the completion of an informed consent, health history form and a pre-screening health risk form, 2) two sleep questionnaires, including the Epworth Sleepiness Scale and the Stanford Sleep Questionnaire 3) descriptive and anthropometric measurements, including height, weight, body mass index (BMI), waist and neck circumference in centimeters (cm) and mandibular-hyoid measurement in (cm) and 4) pulmonary function test. The second visit consisted of 1) maximal graded exercise testing (GXT) on a motor-driven treadmill and 2) a one night sleep recording via a portable sleep device, the ApneaLink®.

Health history and pre-screening forms were distributed to place each subject in either a high or low risk category prior to exercise testing. This was done in order to determine which subject would need a supervising physician present during their maximal GXT. Sleep questionnaires were given to evaluate sleep habits and daytime somnolence. The Epworth Sleepiness Scale consists of eight questions that evaluate how likely one is to doze off or fall asleep during daily situations and the Stanford Sleep

Questionnaire consists of specific behavior during sleep indicating signs and symptoms of a possible sleep disorder.

Anthropometric measurements including height, weight, BMI, waist and neck circumference and mandibular-hyoid distance measurements, which are all risk factors for OSA, were taken. Pulmonary function was performed to assess lung volume, patency of the airway and screen for possible pulmonary disease, which can be either obstructive or restrictive. Obstructive includes diseases such as asthma or bronchitis and restrictive includes diseases such as emphysema. The maximal GXT treadmill test recorded cardiopulmonary exercise testing variables that were examined, including $\dot{V}O_2$, $\dot{V}E_{pk}$, T_{vent} , R-wave amplitude (mv) and ST-segment depression (mm).

Once initial testing was complete, all subjects were immediately placed into one of two groups, high risk (HR) or low risk (LR) depending on their AHI values. HR subjects had a sleep recording result of an $AHI > 5$ and LR subjects had a sleep recording result of an $AHI \leq 5$.

3.2 Subjects

Twenty-two men and women volunteered for the study. Subjects were recruited through the University of Texas at Arlington's (UTA) weekly newspaper, flyers posted around campus, UTA's Department of Kinesiology website and public announcements. The subjects had to meet specific criteria, including being between the ages of 20 and 60, either being 25-35 pounds over their ideal body weight at the time of testing, or

having a BMI ≥ 26 kg/m². Subjects agreed, after a phone interview, to volunteer for the study. Exclusion criteria consisted of subjects with known or suspected cardiovascular or metabolic disease.

Both men (N = 11) and women (N = 11) who participated in the study (age 37.00 ± 12.55 yrs., BMI 35.61 ± 6.43). Each subject was assigned to one of two groups, LR (AHI ≤ 5) or HR (AHI > 5) depending upon their overnight AHI score from the ApneaLink® sleep report. In the LR (age 30.45 ± 8.40 yrs., BMI 34.93 ± 5.66 , AHI 1.82 ± 1.47) group, there were 2 males and 9 females and in the HR (age 43.55 ± 12.89 , BMI 36.30 ± 7.34 , AHI 26.10 ± 18.80) group there were 6 males and 5 females. This study was approved by the University Institutional Review Board for Human Research.

3.3 General Procedures

Each subject participated in an initial orientation for a preliminary screening. Once subjects were cleared for participation, they underwent the following resting baseline physical measures, including HR (bpm), SBP and DBP (mm/Hg), height (in.), weight (lbs.), body mass index (ht/m²), neck and waist circumferences (cm), mandible-hyoid bone distance (cm), FVC, FEV1. During their second visit, VO_{2pk}, VE_{pk} and T_{vent} were measured from a maximal graded exercise test (GXT). Subjects considered high risk were supervised by a physician and an ACSM Program Director®. Exercise blood pressures, RPE, HR and 12-lead ECG were monitored throughout each maximal GXT.

3.4 At Home Sleep Study

Overnight sleep recordings were taken by using the portable battery operated ApneaLink® device by ResMed®. Subjects took the portable sleep device home after preliminary screening and before coming in to perform a maximal GXT. Subjects had to record a minimum of four hours of sleep for the ApneaLink® results to be reliable and accurate. Respiratory movement was monitored by a nasal cannula inserted into the nostrils during sleep.



Figure 3.1 Proper overnight ApneaLink® portable sleep device placement

The respiratory movement measured the average number of single apnea and hypopnea episodes, total snoring events and apnea-hypopnea index (AHI). The risk indicator (RI), which is the point score, was the end result that assessed the subject's risk of developing a pathological sleep disorder.

3.5 Sleep Variables

Risk indicator values of 0 to 5 were within normal ranges. RI values greater than five suggested an increased risk for a pathological breathing disorder.

RESMED

ApneaLink - Report of 07.03.2006 10:47

Treating physician		Referral to	

Patient data First name: <u>Severe Risk</u> Name: <u>Example</u> Street: <u> </u> Zip code, City: <u> </u> Phone: <u> </u>		Patient ID: <u> </u> DOB: <u>23.11.1944</u> Height: <u>172.72 cm</u> Weight: <u>95.34 kg</u> BMI: <u>32 kg/m²</u>	
Recording Date: <u>31.08.2004</u> Start: <u>23:13</u> End: <u>07:22</u> Duration: <u>6 h 8 min</u>		Evaluation Start: <u>23:23</u> End: <u>07:22</u> Duration: <u>7 h 58 min</u>	

Risk indicator

Normal range	Suspected pathological breathing disorder
<div style="border: 1px solid black; display: inline-block; padding: 5px 20px;">Result (23)</div>	

Points evaluation from AHI + points evaluation from FLPG (see Clinical Manual for more details)

Analysis			
Indexes	Normal	Result	
AHI*: 18	< 5 / h	Average breaths per minute [bpm]: 15.76	
RI*: 23	< 5	Breaths: 7539	
Apnea Index: 4	< 5 / h	Apneas: 35	
Hypopnea Index: 13	< 5 / h	Hypopneas: 107	
% Flow lim. Br. without Sn (FL): 48	< Approx. 60	Flow lim. Br. without Sn (FL): 3601	
% Flow lim. Br. with Sn (FS): 10	< Approx. 40	Flow lim. Br. with Sn (FS): 750	
		Snoring events: 1628	

Analysis status: Analyzed automatically

Analysis parameters used (Default)
Apnea [20%, 10s, 80s, 1.0s] Hypopnea [50%, 10s, 100s, 1.0s] Snoring [8.0%, 0.3s, 3.5s, 0.5s]

Comments

Figure 3.2 Example of ApneaLink® sleep report by ResMed®

3.6 Graded Exercise Test (GXT)

Upon arrival to the Exercise Science Research Laboratory (ESRL), procedures and risks were explained to each subject. Exercise testing was performed on a motor-driven treadmill (Q Stress®, Quinton, Seattle, Washington) that increased in either speed, grade and/or both in 2 minute increments. The GXT lasted approximately 4-10 minutes in duration, depending on the subjects fitness level and physical limitations. Subject's HR, BP and ECG were monitored at rest, during exercise testing and at 2 and 4 minutes of recovery in the supine position. Maximal oxygen consumption (V_{O_2}), $\text{V}_{\text{E}_{\text{pk}}}$ and other exercise responses were measured by the subject's expired air using a gas exchange system (VMax 29®, SensorMedics, Yorba Linda, CA.)

3.7 Cardiopulmonary Variables

The cardiovascular and ventilatory responses measured during maximal treadmill GXT, included peak oxygen consumption ($\text{V}_{\text{O}_{2\text{pk}}}$), peak ventilation ($\text{V}_{\text{E}_{\text{pk}}}$), ventilatory threshold (T_{vent}), which were measured by (VMax 29®, SensorMedics, Yorba Linda, CA.) Other cardiovascular measures were taken during exercise and evaluated. These variables included systolic and diastolic blood pressure (arm cuff, sphygmomanometer and stethoscope) along with maximal heart rate, R-wave amplitude (mV) and ST-segment depression (mm) recorded by ECG (Q Stress®, Quinton, Seattle, Washington).

3.8 Pilot Study Results

A small pilot study was conducted at The University of Texas at Arlington's ESRL. The study consisted of 5 healthy female and 7 healthy male subjects (age 23.88 ± 5.28 yrs, ht 68.53 ± 3.72 in., wt 172 ± 38.56 lbs) that were categorized into two separate groups. One group of six subjects had a BMI ≤ 25 (22.23 ± 1.83) and the other group of six subjects had a BMI > 25 (28.60 ± 1.85).

Each subject was provided with the ApneaLink®, which they took home and recorded a night of sleep while wearing the device. A minimum of four hours of sleep was recorded for all subjects. Results from the ApneaLink® provided the AHI value. If $AHI \leq 5$, then the subject was in normal ranges, but if $AHI > 5$, then the subject was at risk for a pathological breathing disorder.

Apnea-hypopnea index was then compared to BMI in which a trend for BMI increased with higher AHI values. The subject with the lowest BMI had the lowest AHI value and the subject with the second highest BMI had the highest AHI value. Apnea-hypopnea index was also compared to resting diastolic blood pressure (DBP). A trend for DBP to increase as AHI increased was found, even though there was no significant difference ($p = 0.68$) between them. However, there was a significant difference ($p = 0.04$) when comparing high AHI and BMI to snoring events. Those with a higher AHI and BMI had five times the amount of snoring events (476.7 ± 994.7 events) than those with lower AHI and BMI values (31.7 ± 17.2 events).

The subject with the lowest AHI value and the subject with the highest AHI value were maximally exercise tested. The subject with the lowest AHI value had a lower VE_{pk} value, lower maximal SBP and DBP, lower maximal heart rate and a higher VO_2 than the subject with the highest AHI value.

3.9 Data Reduction and Analysis

Once the subject completed one night of recorded sleep, the recording was then downloaded to a computer, from the ApneaLink[®], where the result sheet was created. The main message presented on the results sheet is the risk indicator (RI). Other analyzed data produced by the ApneaLink[®] include AHI, RI, apnea episodes, hypopnea episodes and snoring events. All data from ApneaLink[®] was recorded in a spreadsheet.

Maximal GXT variables, including HR, DBP, SBP, RPP, VE_{pk} , T_{vent} , peak exercise R-wave amplitude (mV) and ST-segment depression (mm) along with 4-minute recovery measures, including HR, DBP, SBP and RPP were recorded in a Microsoft Excel spreadsheet before being inserted into SPSS[®] for statistical analysis.

3.10 Statistical Analysis

Independent t-tests were first used to identify significant differences between resting, submaximal exercise, maximal exercise and recovery variables between the LR (n = 11) and HR (n = 11) groups. A stepwise multiple regression equation was then used to identify predictors of RI and AHI. RI and AHI were separately used as the dependent variable. The first set of independent variables included physical baseline

measurements (Age, BMI, Ht., neck and waist circumference, mandibular-hyoid distance) and other resting measures (HR, DBP, SBP, RPP, FVC, FEV1, resting R-wave amplitude). The second set of independent variables included peak GXT responses (HR, DBP, SBP, RPP, VO_2 , VE_{pk} , T_{vent} R-wave amplitude, ST segment depression). The third set of independent variables included 4-minute recovery post-exercise measures (HR, DBP, SBP, RPP). The a priori type I error rate was set at 5% and significance was set at .05. All statistical analysis was performed with SPSS 14.0.1 software (SPSS Inc., Chicago, IL).

CHAPTER 4

RESULTS

4.1 Descriptive Physical and Sleep Baseline Measures

Several descriptive characteristics and physical baseline measures (see Table 4.1) were taken for each subject in both the low-risk (LR) and high-risk (HR) groups.

Table 4.1 Descriptive Characteristics and Baseline Physical and Sleep Measures

Baseline Physical Measures	Low Risk (N = 11)	High Risk (N = 11)	P value
Age (years)	30.45 ± 8.40	43.55 ± 12.89	0.02
BMI (kg•m ²⁽⁻¹⁾)	34.93 ± 5.66	36.30 ± 7.34	0.11
Height (in)	65.86 ± 3.30	66.98 ± 2.86	0.83
Neck Circumference (cm)	36.15 ± 3.63	41.90 ± 6.42	0.06
Waist Circumference (cm)	97.05 ± 10.86	108.93 ± 17.20	0.07
Apnea-Hypopnea Index (events/h)	1.82 ± 1.47	26.10 ± 18.80	0.001
Risk Indicator (events/h)	4.73 ± 1.42	29.10 ± 19.06	0.001
Snoring Events	615.09 ± 1529.75	1330 ± 1558.56	0.25
Apnea Episodes	1.18 ± 1.16	57.60 ± 81.00	0.001
Hypopnea Episodes	9.09 ± 10.09	97.60 ± 51.61	0.01
Mandibular-Hyoid Distance (cm)	11.82 ± 2.30	11.73 ± 1.88	0.49
FVC (L/min)	3.66 ± 0.62	3.55 ± 0.74	0.47
FEV1 (L/min)	3.10 ± 0.45	3.00 ± 0.74	0.05

There was a combination of both males and females in each group. In the LR group, there were two males and nine females, versus the HR group with six males and

five females. Age was significantly different ($p = .02$) between the LR (30.45 ± 8.40 yrs.) and HR (43.55 ± 12.89 yrs.) groups. FEV1 was also significantly different ($p = .05$) between the LR (3.10 ± 0.45) and the HR (3.00 ± 0.74) groups. The remaining baseline measurements, including neck circumference, waist circumference, body mass index, height, mandibular-hyoid distance and FVC were not significantly different between groups.

4.2 Baseline Sleep Measures

Baseline sleep measures (AHI, RI, apnea episodes, hypopnea episodes, snoring events) were also measured for all subjects. The largest differences were seen in both the AHI and RI. Apnea-hypopnea index was significantly different ($p \leq 0.001$) between the LR (1.82 ± 1.47) and HR (26.10 ± 18.80) groups. Risk indicator was also significantly different ($p \leq 0.001$) between the LR (4.73 ± 1.42) and HR (29.10 ± 19.06) groups (see Figure 4.1).

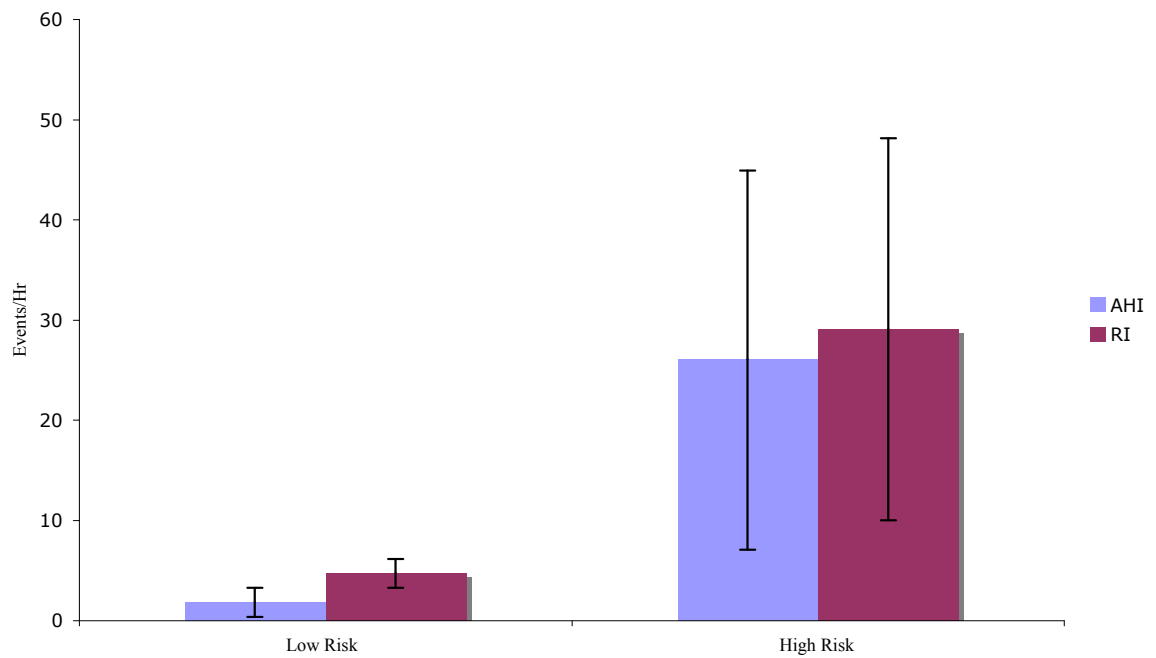


Figure 4.1 Differences in AHI and RI between groups

The ApneaLink[®] also reported the total number of apnea and hypopnea events that occurred throughout the night. The number of apnea events for the LR (1.18 ± 1.16 events) group was significantly lower ($p = .001$) than the HR (57.60 ± 81.00 events) group. The number of hypopnea events for the LR (9.09 ± 10.09 events) group was also significantly lower ($p = .01$) compared to the HR (97.60 ± 51.61 events) group.

4.3 Resting Cardiovascular and Electrocardiogram Measures

Resting cardiovascular measurements (HR, SBP, DBP, RPP) were taken prior to graded treadmill exercise testing. There was not a significant difference of HR, SBP, DBP and RPP between the LR and HR groups (see Table 4.2).

Table 4.2 Resting Cardiovascular and Electrocardiogram Measures

Resting Measures	Low Risk (N = 11)	High Risk (N = 10)	P value
Heart Rate (bts•min ⁻¹)	75.45 ± 11.02	75.40 ± 12.46	0.46
Systolic Blood Pressure (mm·Hg)	125.45 ± 12.71	133.20 ± 23.59	0.09
Diastolic Blood Pressure (mm·Hg)	85.09 ± 9.56	86.80 ± 9.62	0.76
Rate Pressure Product (mVO ₂)	94.56 ± 15.93	101.08 ± 28.37	0.20
Resting R-Wave Amplitude (mV)	0.89 ± 0.24	1.03 ± 0.52	0.01

The only resting measure that was significantly different was the electrocardiogram measure of resting R-wave amplitude in milivolts (see Figure 4.3). Finally, the R-wave amplitude of the LR (0.89 ± 0.24 mV) group was significantly lower (p = .01) than the HR (1.03 ± 0.52 mV) group.

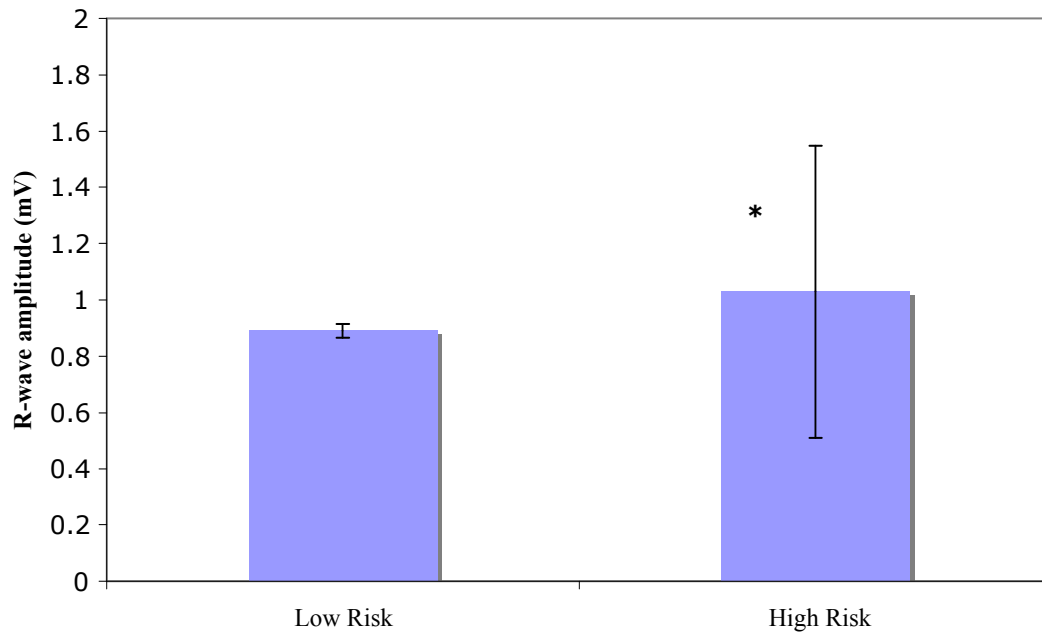


Figure 4.2 Significance of resting R-wave amplitude

4.4 Cardiovascular, Ventilatory and Electrocardiogram Responses to GXT

Exercise cardiovascular variables (VO_2 , RPE, METs, HR, SBP, DBP, RPP, VE, T_{vent}) were taken at peak exercise during the treadmill GXT (see Table 4.3). Rate of perceived exertion of the LR (17.45 ± 1.50) group was significantly different ($p = .05$) than the HR (17.10 ± 0.88) group. The remaining variables $\text{VO}_{2\text{pk}}$, METs, HR, SBP, DBP, RPP, VE, and T_{vent} at peak exercise were not significantly different between the groups.

Table 4.3 Cardiovascular, Ventilatory and Electrocardiogram responses to GXT

Exercise Measures	Low Risk, N = 11	High Risk, N = 10	P value
VO ₂ pk (ml•kg ⁻¹ min ⁻¹)	27.88 ± 7.39	22.97 ± 4.93	0.47
RPE (Borg 6-20)	17.45 ± 1.50	17.10 ± 0.88	0.05
METS	7.97 ± 2.10	6.57 ± 1.39	0.48
Peak HR (bts•min ⁻¹)	184.45 ± 9.45	161.60 ± 15.03	0.25
Peak Systolic BP (mm•Hg)	186.36 ± 23.66	185.00 ± 28.08	0.58
Peak Diastolic BP Max (mm•Hg)	84.73 ± 8.68	87.20 ± 16.44	0.28
Peak Rate Pressure Product	343.47 ± 41.30	297.65 ± 47.74	0.79
VE _{pk} (L•min ⁻¹)	73.57 ± 16.18	63.00 ± 9.98	0.09
T _{vent} (L•min ⁻¹)	1.63 ± 0.24	1.63 ± 0.47	0.95
Peak R-Wave (mV)	0.93 ± 0.28	1.33 ± 0.42	0.04
Peak Ex ST Segment (mm)	0.09 ± 0.30	0.35 ± 0.58	0.01

R-wave and ST segment depression at peak exercise were both significantly different between groups. R-wave amplitude of the LR (0.93 ± 0.28 mV) group had a significantly lower (p = .04) amplitude than the HR (1.33 ± 0.42 mV) group (see Figure 4.4). ST- segment depression was also significantly different (p = 0.01) with the LR (0.09 ± 0.30 mm) group having less depression than the HR (0.35 ± 0.58 mm) group (see Figure 4.4).

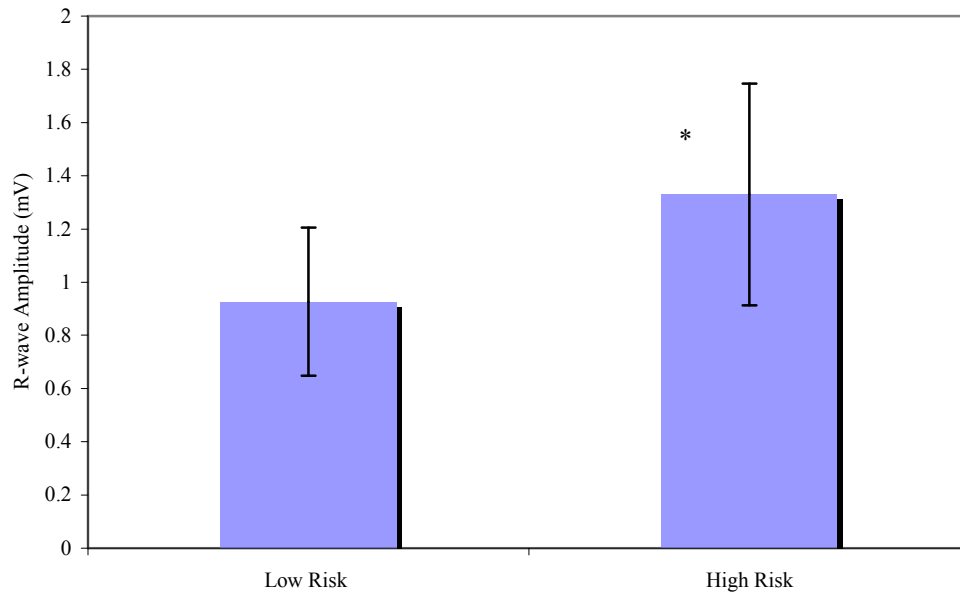


Figure 4.3 Difference in peak exercise R-wave amplitude between groups

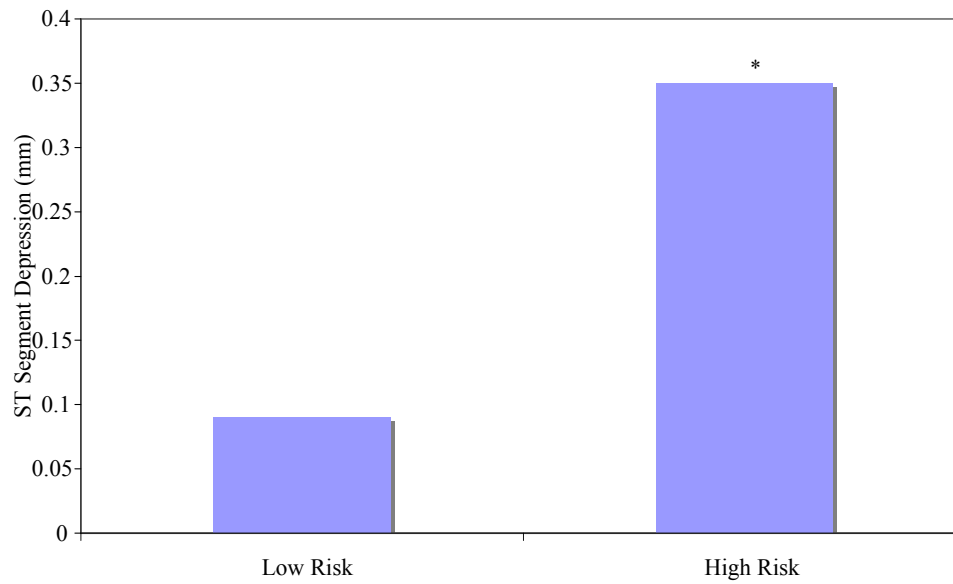


Figure 4.4 Difference in peak ST segment depression between groups

4.5 Recovery GXT Responses

Cardiovascular recovery responses (HR, SBP, DBP, RPP) were taken at four minutes post GXT in the supine position. Heart rate, SBP, DBP and RPP were not significantly different between groups (see Table 4.4), although a trend for elevated BP was noted for systolic and diastolic BP in the high-risk group.

Table 4.4 Cardiovascular Recovery Measures Post GXT (taken at 4 min.)

Exercise Recovery Measures	Low Risk N = 11	High Risk N = 10	P value
Heart Rate (bts•min ⁻¹)	108.6 ± 12.1	104.1 ± 7.3	0.15
Systolic BP (mm•Hg)	144.5 ± 15.7	148.0 ± 27.7	0.07
Diastolic BP (mm•Hg)	81.4 ± 8.3	83.8 ± 14.4	0.13
Rate Pressure Product (mVO ₂)	157.1 ± 24.7	154.2 ± 31.4	0.71

4.6 Sleep Questionnaire Scores

The two sleep questionnaires (ESS, SSQ) were given to all subjects. The ESS was significantly different ($p = 0.05$) between the LR (8.91 ± 3.14) group and HR (11.45 ± 5.44) group. Four specific questions, selected from the Stanford Sleep Questionnaire (SSQ) for the study, all resulted in significant differences between the LR and HR groups. the “hold breath” and “wake-up gasping” as being the most common symptoms of the HR group (see Table 4.5) as compared to the LR group.

Table 4.5 Questions Selected from Stanford Sleep Questionnaire Results

Questions from Stanford Sleep Questionnaire	Low Risk (N = 11)	High Risk (N = 11)	P value
Hold Breath	1	6	0.001
Wake-up Gasping	1	4	0.002
Wake-up Choking	0	1	0.04
Snore	8	10	0.03

4.7 Sleep Questionnaire Predictors of AHI and RI

All ESS scores and SSQ scores were also put into a stepwise multiple regression equation, with RI and AHI as the dependent variables. When using only AHI as the dependent variable, two specific questions from the SSQ (wake choking, hold breath) resulted as the two strongest predictors of AHI from the two sleep questionnaires. When only RI was used as the dependent variable, the exact same results were shown.

4.8 Regression Equation for Predictors of AHI and RI

All resting, exercise, and recovery variables were put into a stepwise multiple regression equation, with RI and AHI as the dependent variables. No other sleep variables were included due to the strong association of RI and AHI to the other independent sleep variables recorded by the ApneaLink[®]. Results of the regression equation formulated, using only AHI as the dependent variable, showed that the best four predictors of AHI were neck circumference, age, four-minute RPP recovery and peak ventilation during exercise. $AHI = 1.822 (\text{neck}) + 0.559 (\text{age}) - 0.24 (\text{RPP4}) - 0.307 (VE_{pk}) - 21.047$; $R^2 = 0.82$, (SEE = 8.69). Similar results were shown for the

regression equation formulated, using only RI as the dependent variable, which showed that the best three predictors of RI were neck circumference, age and four-minute RPP recovery. Risk indicator (RI) = $1.837 (\text{neck}) + 0.655 (\text{age}) - 0.232 (\text{RPP4}) - 44.809$; $R^2 = 0.76$, (SEE = 9.96).

4.9 Algorithm for Predicting OSA in the Undiagnosed Population

The information found in the present study was combined to formulate an algorithm, which could be practically applied by physicians. The algorithm presented could be used as a screening tool to help detect and predict OSA in those who have signs and symptoms of the disease, but who have not been formally diagnosed. This algorithm would indicate if further clinical testing, such as a polysomnography would be needed for any given patient.

The algorithm starts with the three best predictors of OSA found in the present study. These three predictors are gender (male), age (≥ 43 yrs.), and neck circumference (≥ 40 cm). If these three factors are present, in addition to waist circumference (≥ 108 cm) and elevated resting systolic blood pressure (≥ 133 mm/Hg), which were clinically important, then the physician should give that patient an ApneaLink[®] to take home and record a night of sleep. If the patient has either of the above combinations, then more resting measures should be assessed, such as resting R-wave amplitude (≥ 1.3 mV) taken by an ECG recording along with asking them the top two predicting questions from the Stanford Sleep Questionnaire of 1) “hold breath”

during sleep, or if they ever 2) “wake-up gasping” for air during the night. These two questions both strong predictors of AHI and RI, from the sleep questionnaire results. If these two other resting measures are present during a physician evaluation, then a graded exercise test should be performed to evaluate other variables that may be present. If the additional resting measures are not present, then an ApneaLink[®] should be taken home with the patient, for one night, to assess their risk of developing a pathological sleep disorder.

During graded exercise testing, specific variables should be examined such as low ventilation (≤ 63 L/min) at peak exercise along with elevated systolic blood pressure (≥ 144 mm/Hg) after four minutes of recovery post exercise. If these two are present, then the physician could insert the values for age (yrs.), neck circumference (cm), rate pressure product at four minutes of recovery (RPP4) along with ventilation during peak exercise (VE_{pk}) into one of the regression equations for AHI or RI, which were formulated from this study. If the patient has any ECG abnormalities, such as an elevated R-wave (≥ 1.3 mV), or ST-segment depression (≥ 0.35 mm) during peak exercise in combination with low peak ventilation and elevated systolic blood pressure, then this could mean that the patient may suffer underlying cardiovascular disease. This is when the physician could prescribe that a polysomnography (PSG) should be performed as the preferred OSA screening tool for the patient.

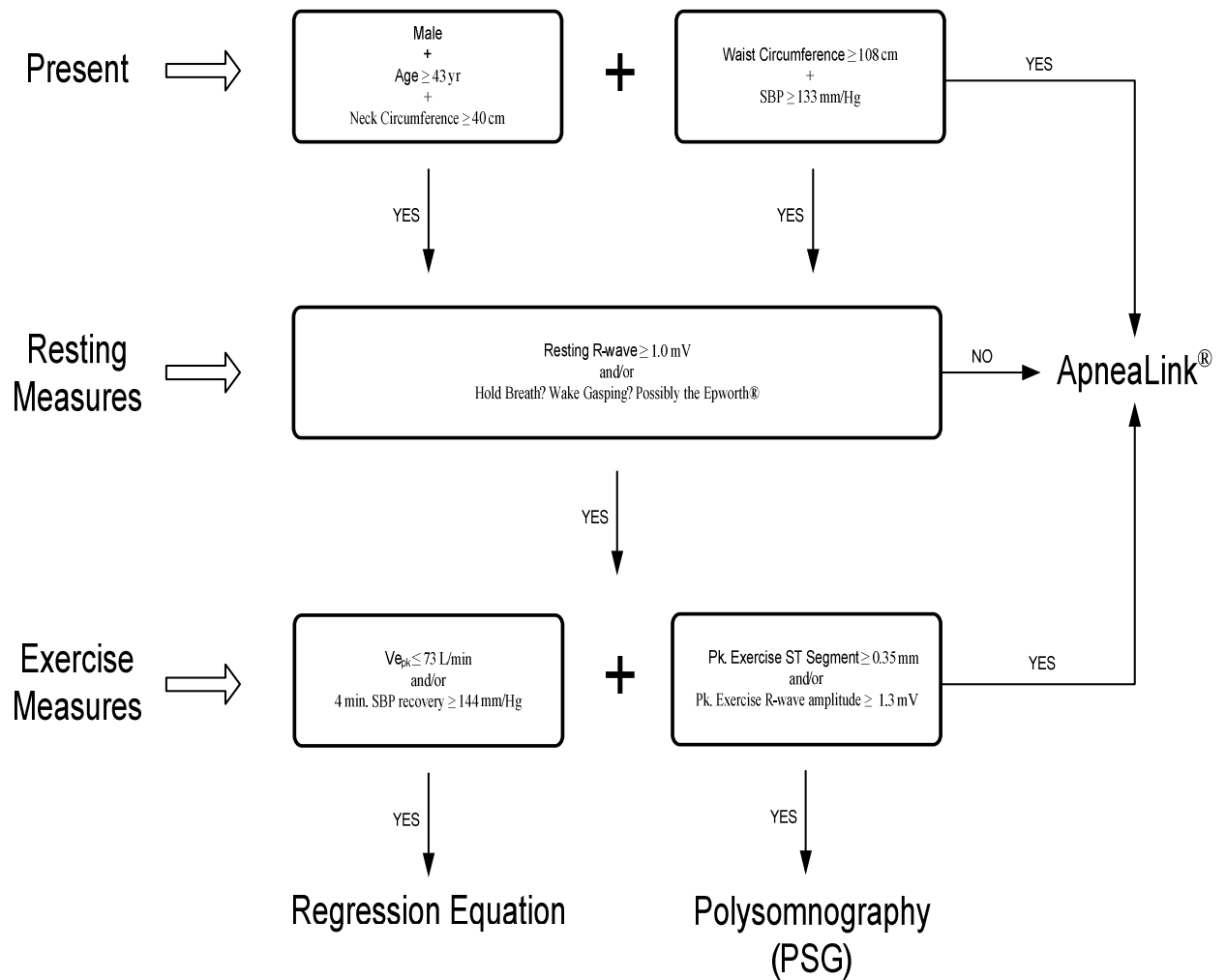


Figure 4.5 Algorithm for Predicting OSA

CHAPTER 5

DISCUSSION

The primary purpose of this study was to compare the cardiopulmonary and electrocardiography exercise testing responses between one group, at low-risk (LR) for developing OSA, versus another group at high-risk (HR) for developing OSA. Since there is an estimated 9% of middle-aged females and 24% of middle-aged males, of the U.S. population, who suffer from OSA, but approximately only 2% of middle-aged females and 4% of middle-aged males have been accurately diagnosed⁴. This means that a large percentage of people who suffer from OSA and are unaware of its presence and severity. Due to the lack of proper screening, OSA risk factors and symptoms are going unrecognized or misdiagnosed. The importance of this study is that it predicts one's risk of developing OSA, from a combination of exercise testing variables and physical measures. The hope is that unrecognized individuals will properly be treated for OSA before it advances to a greater level of severity and becomes detrimental to one's health and mortality.

Twenty-two subjects participated in the study, but only twenty-one subjects performed a maximal exercise test and completed all of the criteria for the study. One HR subject did not comply with coming back into the exercise science research laboratory for exercise testing, but performed all other testing for the study.

From the descriptive characteristics and baseline physical measures, there was no difference between BMI of the LR vs. the HR group. However, there was a trend for both neck and waist circumference measurements to be higher in the HR group. There was a trend for neck circumference in the LR (36.15 ± 3.63 cm) to be lower ($p = 0.06$) than the HR (41.90 ± 6.42 cm) group. There was a 15.9% difference from LR to HR (see Figure 5.1). Neck circumference was also the top predictor in the regression equation predicting both RI and AHI.

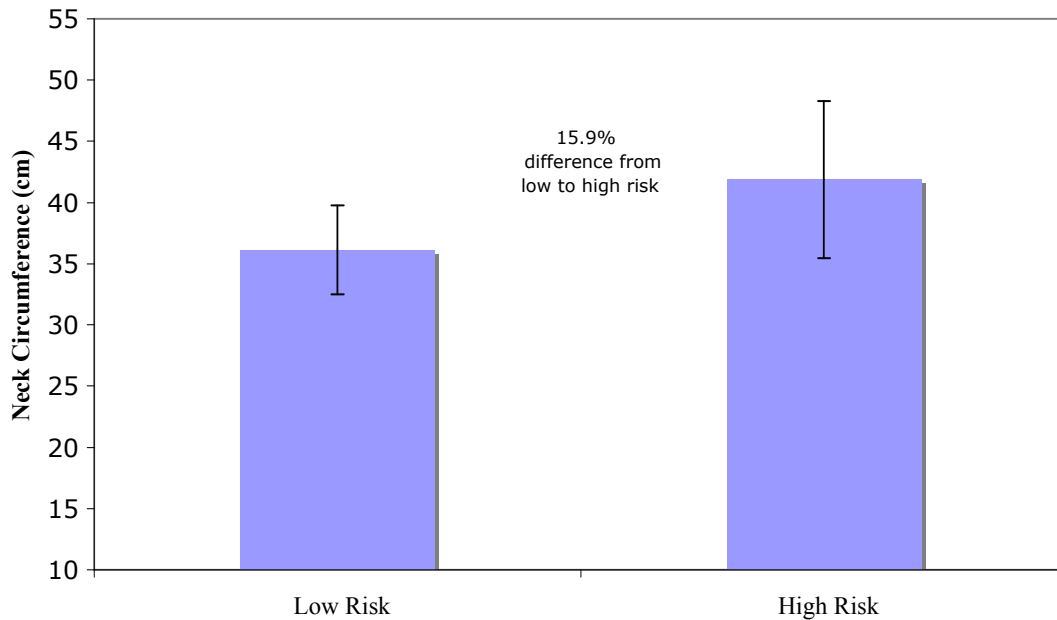


Figure 5.1 Clinical importance of neck circumference

There was also a trend for waist circumference in the LR (Mean \pm SD: 97.05 ± 10.86) group to be lower ($p = .07$) than the HR (108.93 ± 17.20 cm) group and with a 12.2% difference from the LR to HR group (see Figure 5.2). The differences of neck

and waist circumference measurements between the two groups were not significant, but could be considered clinically important in predicting OSA. The weight in pounds that someone in the LR group would have to gain to equal the neck and waist circumference of the HR group could be a large enough amount to make someone at low-risk for OSA become at an increased risk for OSA.

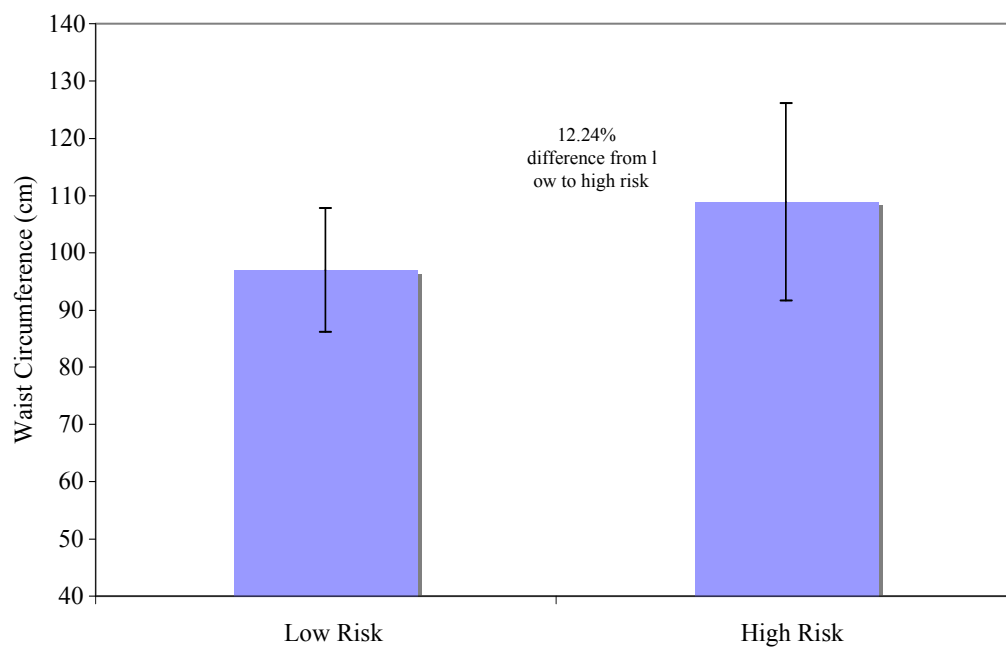


Figure 5.2 Clinical importance of waist circumference

Kaleth et al.¹⁹ found a significant difference ($p < .05$) in neck and waist circumference of the OSA group vs. the group without OSA. Neck circumference for OSA (40.4 ± 3.0 cm) group was significantly higher vs. the group without OSA (36.0 ± 3.4 cm) and waist circumference for the OSA (108.7 ± 10.5 cm) group was significantly higher vs. the group without OSA (91.7 ± 14.3 cm). This could be the result of there

being more males in the OSA group than females (M = 10, F = 7) and less males in the control group than females (M = 7, F = 8). Males hold more of their weight in the neck and abdominal area and have more central obesity than females. Lin et al.¹, Ozturk et al.²⁰ and Hargens et al.²⁷ did not examine neck and waist circumference measurements.

Out of the variables measured and evaluated, the variable that was consistently different from low risk (LR) to high-risk (HR) group, and what was hypothesized to happen, was that there was a trend for systolic blood pressure (SBP) to be higher in the HR group during resting and recovery from exercise. Arterial pressure was hypothesized to be higher, especially during resting conditions. Daytime hypertension has been documented in those with OSA with approximately 40 percent of OSA patients suffering from hypertension⁴. Resting standing SBP was higher in the HR compared to the LR group during resting conditions prior to exercise testing (see Figure 5.3). There was a 6.17% SBP difference between resting SBP from the low to high-risk group. Even though this is not statistically significant, it could be considered clinically important when examining those at high-risk for OSA due to the impact that modestly elevated blood pressure has on cardiovascular morbidity and mortality.⁵

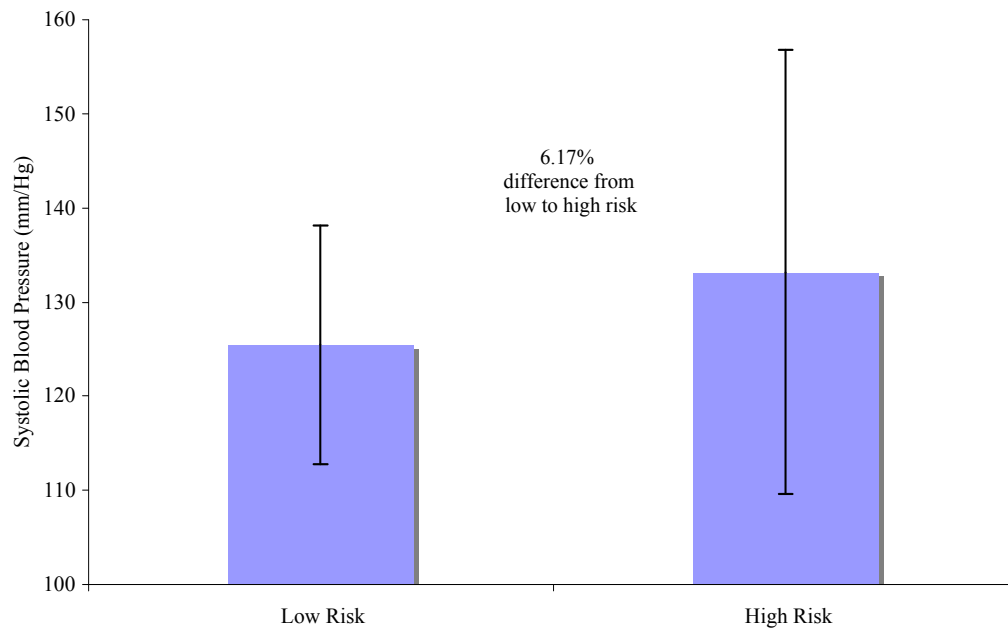


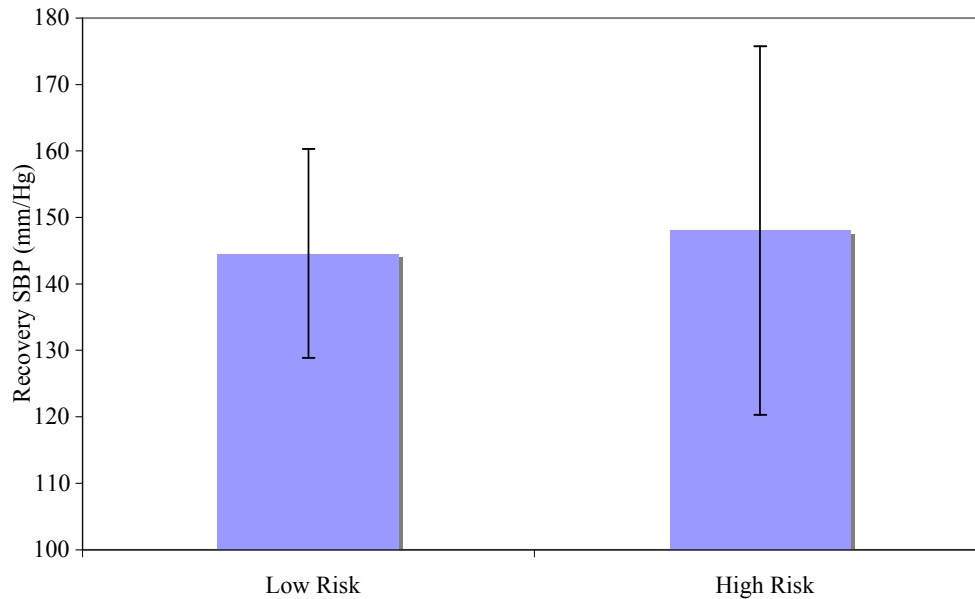
Figure 5.3 Clinical importance of resting systolic blood pressure

Lin et al.¹, Ozturk et al.²⁰ and Hargens et al.²⁷ did not evaluate baseline SBP measures, however, Kaleth et al.¹⁹ found that resting SBP was significantly higher ($p < .05$) in those with OSA (126.2 ± 12.7) when compared to controls (115.1 ± 14.7). This finding agrees with the present study of the trend for resting systolic blood pressure to be elevated in those at high-risk for OSA. This means that effects of OSA, such as nocturnal hypertension can affect daytime blood pressure by staying elevated.

Kaleth et al.¹⁹, found that DBP of those with OSA (91.7 ± 2.7) had a significantly higher ($p < .05$) DBP at peak exercise than the control group (81.8 ± 2.5), but no difference in SBP at peak exercise. In the present study, there was not a significant difference in SBP or DBP at peak exercise between the LR and HR group.

However, sub-maximal SBP of the LR (131.4 ± 17.4) group was lower than the HR (148.8 ± 16.9) group. There was also a significant difference ($p = .05$) of sub-maximal RPP between the LR (167.29 ± 35.76) group and HR (176.04 ± 18.76) group. An elevated RPP at sub-maximal exercise can be explained by the HR group having an elevated sub-maximal SBP, since RPP is directly related to heart rate and systolic blood pressure.

During the four minute recovery, post exercise testing, there was another trend for SBP to be elevated in the HR group. The recovery SBP in the HR (148.0 ± 27.7 mm/Hg) group was higher ($p = .07$) than the LR (144.5 ± 15.72 mm/Hg) group (see Figure 5.4). This is also an instance where the difference was not statistically significant, but could be considered clinically important. However, there were no differences in four minute DBP between the LR and HR groups. Elevated recovery SBP also correlates with the predicted regression equation for those at risk with OSA. Systolic blood pressure is a key factor in the calculation of rate pressure product (RPP). Along with neck circumference and age, RPP at 4-minute recovery, was a strong predictor in the regression equation for predicting both risk indicator (RI) and apnea-hypopnea index (AHI).



5.4 Clinical importance of recovery systolic blood pressure

These findings agreed with Kaleth et al.¹⁹ who found the similar result in another study with a significantly higher ($p < .05$) SBP at two minutes post exercise between the OSA (203.4 ± 5.2) group vs. the group without OSA (183.3 ± 6.1). Kaleth et al. also found a trend for recovery DBP to remain higher in the OSA group vs. the group without OSA. This finding was helpful in predicting those at high-risk for OSA. Since those who have diagnosed OSA are more likely to suffer from hypertension, then elevated SBP at rest and during exercise recovery can serve as a useful marker to help identify one's risk of developing OSA in the undiagnosed or misdiagnosed populations.

Hypertension has been shown to be an independent risk factor for OSA by the use of effective treatment for OSA, such as CPAP, which leads to improved daytime

and nighttime blood pressures.⁵ The reason why arterial blood pressure was hypothesized to be higher in the HR group is due to the repetitive apnea episodes during sleep that lead to adrenergic surges and increases nighttime BP levels. This chronic rise in BP during sleep can affect daytime measures as well by chronic sympathetic activity.

Ventilatory responses, including ventilation (VE_{pk}) and ventilatory threshold (T_{vent}) at peak exercise were analyzed. There was not a significant difference of T_{vent} between the LR ($1.63 \pm .24$ L/min) group and HR ($1.63 \pm .47$ L/min) group. However, there was a trend for VE_{pk} to be higher in the LR vs. HR group and was shown to be a strong predictor of OSA from the regression equation formulated from the present study. Even though there was not a significant difference ($p = .09$) of VE_{pk} between the LR (73.5 ± 16.1 L/min) and HR (63.0 ± 9.9) group, it could be considered to be clinically important with a 14.4% difference (see Figure 5.5).

This difference in VE_{pk} could be considered clinically important due to the fact that the HR group's VE_{pk} was more than 10 L/min lower than the LR group. This could be a result of airway obstruction in the HR group. Airway obstruction could be due to a smaller minimum upper airway cross-sectional area, which could be attributed to anatomical abnormalities. Also, nocturnal hypoventilation could also be a contributing factor. The development of alveolar hypoventilation during wakefulness is based on the balance between central ventilatory drives to breathe and mechanical loads placed on the respiratory system.⁹

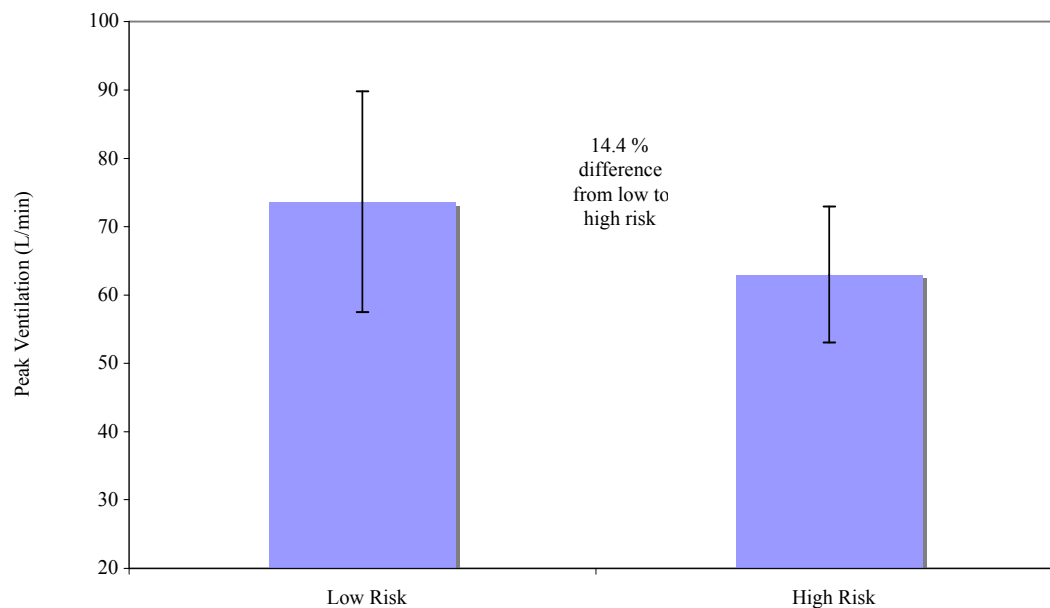


Figure 5.5 Clinical importance of peak ventilation

Another primary finding in the present study were the electrocardiography results and the significant differences of both R-wave amplitude and ST segment depression between the groups. The hypothesis was that the R-wave amplitude would be lower in the LR group and elevated in the HR group in both resting and peak exercise conditions. The reasoning for the increased R-wave amplitude is unclear. It's difficult to understand the normal ranges of R-wave amplitude, since there is currently not an existing criteria for R-wave height or size. However, it could be concluded that taller R-waves in the HR group could be the result of possible ventricular hypertrophy. Taller R-waves could also be the result of axis deviation of the heart. For example, right axis deviation is equal to an axis of 90 – 180 degrees. This type of axis deviation can

occur in any condition that may increase pulmonary pressures and cause right ventricular hypertrophy, such as cor pulmonale or pulmonary hypertension.

R-wave amplitude was significantly different between the groups, but did not result as one of the strongest indicators of RI or AHI. This may be something to consider when exercise testing someone at risk for OSA. Several factors affect the R-wave, such as blood conductivity, blood potassium, electrical axis, movement of the chest wall and diaphragm. It may be hard to really know the underlying cause of the amplitude during rest and exercise ECG tracings. However, if these factors were to be controlled for, then R-wave amplitude could be linked to ventricular hypertrophy resulting from high pulmonary pressures that are prevalent in those with OSA.

ST segment depression was also significantly different between the groups. There was more ST segment depression in the HR group, which agreed with the hypothesis. The HR group may suffer from more ST segment depression due to some myocardial ischemia, occurring from coronary artery disease, which is common in those with OSA¹⁵. However, it's been shown that ST segment depression does not have to be related to CAD to occur in significant amounts of 1 mm or more. It's been shown that ST segment depression can occur in those without CAD but with severe OSA¹⁵. This means that ST segment depression could be a symptom in severe cases ($AHI \geq 30$) of OSA.

The present study showed that a maximal exercise test was a practical way to functionally examine individuals who have signs, symptoms and/or risk factors for

OSA. The main findings of this study were that, regardless of BMI, physical indicators for those at high risk for OSA are age, neck circumference and waist circumference. Also, regardless of BMI, exercise test indicators for those at high risk can also be evaluated to predict OSA such as a lower Vo_{2pk} , elevated resting, sub-maximal, and recovery blood pressures and/or rate pressure product, and lower ventilation. Electrocardiogram measures can also be used as markers to help predict OSA in those at high-risk, including an elevated R-wave amplitude (mV) at rest and during peak exercise and more ST-segment depression (mm) during peak exercise.

In conclusion, simple baseline and exercise testing measures can be used as markers for those with underlying obstructive sleep apnea in order to decide if a PSG is needed. Key physiological variables that should be analyzed during resting, exercise, and recovery states include blood pressure responses, ECG morphology, and ventilation.

APPENDIX A
STATEMENT OF INFORMED CONSENT



THE UNIVERSITY OF TEXAS AT ARLINGTON

INFORMED CONSENT

PRINCIPAL INVESTIGATOR: Jennifer S. Blevins, Ph.D.

TITLE OF PROJECT: The effects of weight loss on sleep quality on borderline obese subjects at risk for the development of obstructive sleep apnea

This Informed Consent will explain about being a research subject in an experiment. It is important that you read this material carefully and then decide if you wish to be a volunteer.

PURPOSE:

The purpose(s) of this research study is/are as follows:

- Determine sleep quantity and quality in borderline obese subjects at baseline and after six months of exercise and diet intervention against age, weight, and gender matched controls
- Determine aerobic capacity and cardiovascular exercise performance in borderline obese subjects at baseline and after six months of exercise and diet intervention against age, weight, and gender matched controls.
- Evaluate the extent to which poor sleep quantity and quality may affect exercise performance as well as adherence to an exercise and diet intervention.

Obstructive sleep apnea is a disorder that affects two to five percent of the population. However, it is estimated that 93 percent of women and 82 percent of men who have the disorder, have not been diagnosed. Early, simpler detection tools may not only help to identify

these individuals, but may also help to identify those at risk. The information gathered in this study will help to establish the efficacy of using behavioral treatments, such as weight loss, in the prevention or delay of onset or prevention of OSA. Baseline screening and physical assessments, like the ones proposed in this investigation will help educate primary care physicians and health care providers the educational tools for early identification and referral for further diagnosis and treatment

DURATION

The duration of this project is six months. The duration of preliminary and post exercise testing will be approximately 1 to 2 hours. All testing will be conducted at University of Texas at Arlington.

PROCEDURES

The primary purpose this project is to determine if simple techniques including exercise testing, morphological measurements, and questionnaires can be used as a means to identify those at high risk for future development of a breathing disorder that occurs during sleep. The investigators will also determine if weight loss through exercise training and caloric intake reduction will have an effect on sleep quantity and quality.

PRINCIPAL INVESTIGATOR: Jennifer S. Blevins, Ph.D.

TITLE OF PROJECT: The effects of weight loss on sleep quality on borderline obese subjects at risk for the development of obstructive sleep apnea

In order to meet the goals of this research project, you are voluntarily agreeing to engage in tests used to determine your heart and lung function at rest and during exercise. You understand that you will be asked to answer verbal and written questions before undergoing testing that concern your health and sleep function. You will be asked to take an at home sleep monitoring device home once in the beginning of the study and again after 6 months. The device will be used to measure snoring, total sleep

time, and breathing during sleep. You will be asked to return the device to the principal investigator on the morning after you record your sleep. On the day immediately following this, you will come to the Exercise Science Research Laboratories in room 153 of the Activities Bldg on the UT of Arlington campus to have your height, weight, and girth measurements of your neck, waist, jaw, and hip areas. At this time, you will also be asked to complete a lung function test while seated in a chair. Finally, you will also be asked to complete one maximal exercise test at the beginning of the study and one at the end of the six month period. During the exercise test, that will last approximately 10 minutes, you will be asked to exercise to a point (only lasting a few seconds) that you feel that is difficult in terms of effort (most likely the hardest exercise that you have probably done). During this test samples of your exhaled air will be taken to measure the amount of oxygen and carbon dioxide you are consuming and producing, which will give you and the investigator information about your maximal effort and heart fitness level. This test will be performed on a motor driven treadmill with the amount of effort gradually increasing. The increase in effort will continue until you verbally report to the operator any symptoms such as fatigue or shortness of breath which may appear. It is your right to request that the test be stopped at any point if you feel unusual discomfort or fatigue. You should immediately upon experiencing any such symptoms inform the operator that you wish to stop the test at that or any other point. Your stated wish in this regard will be absolutely carried out.

Before an attending physician to conduct a basic examination, which will include listening to your lung and chest sounds. You will be interviewed by a program

staff member prior to undergoing any testing. Consequently, please understand that it is important that you provide complete and accurate responses to the interview and recognize that your failure to do so could lead to possible unnecessary injury during the test. It is further my understanding that prior to beginning the test. You will be connected by electrodes and cables to an electrocardiographic recorder, which will enable the program personnel to monitor your cardiac (heart) activity. A physician or his/her trained observer will monitor your responses continuously and take frequent readings of blood pressure, the electrocardiogram, and your expressed feelings of discomfort or effort. Once the test has been completed, but before you are released from the test area, you will be given special instructions about showering and recognition of certain symptoms that may appear within the first 24 hours after the test. You agree to follow these instructions and promptly contact the program personnel or your medical providers if such symptoms develop.

After initial testing is completed you will be randomized to either an exercise and diet intervention group or a control group. If you are selected for the intervention group, you will be prescribed a specific diet and exercise regimen for a period not to exceed 6 months. You will be asked at least 2 times per week to meet with an exercise science trainer for exercise sessions that will last 30 to 45 minutes. You will also be asked to exercise at home if you are in the intervention group. You will be provided with a diet plan at the beginning of the 6 month intervention. If you are in the control group, you agree to continue with your regular exercise and diet regimen for at least 6

months after initial testing. At that time, you will be provided with a home exercise and diet prescription.

POSSIBLE RISKS/DISCOMFORTS

You have been informed that there exists the possibility of adverse changes during any physical activity or exercise that may start as a result of this program. You have been informed that these changes could include abnormal blood pressure, fainting, disorders of heart rhythm, and very rare instances, heart attack (6 in 10,000) or death. Every effort will be made to minimize these occurrences by preliminary assessment and by precautions and instructions given prior to initiating any changes in physical activity. You have also been informed that if you experience any negative symptoms, you should contact emergency medical services for immediate assistance. I also understand that I may experience a dry mouth and/or throat during the exercise test while a mouthpiece and nose clip are placed on me during the test.

POSSIBLE BENEFITS

Potential benefits related mainly to your personal motives for participating in this study, (i.e. understanding your sleep quality and how this relates to your daytime functioning, using the information from this test to evaluate your current health status, knowing your exercise capacity in relation to the general population, weight loss, understanding your fitness level for certain recreational activities, planning your physical conditioning program, or evaluating the effects of recent physical activity habits). Although your health and fitness might also be evaluated by alternative means, (e.g. a bench step test, an outdoor running test, or a physical exam), such tests do not provide as accurate a fitness assessment as the treadmill or bike test nor do those options allow equally effective monitoring of your responses.

ALTERNATIVE PROCEDURES / TREATMENTS

There are no alternative procedures/ treatments available if you decide not to participate.

CONFIDENTIALITY

Every attempt will be made to see that your study results are kept confidential. A copy of the records from this study will be stored in (name the specific location where records will be kept) for at least three (3) years after the end of this research. The results of this study may be published and/or presented at meetings without naming you as a subject. Although your rights and privacy will be maintained, the Secretary of the Department of Health and Human Services, the UTA IRB, the FDA (if applicable), and personnel particular to this research (individual or department) have access to the study records. Your (e.g., student, medical) records will be kept completely confidential according to current legal requirements. They will not be revealed unless required by law, or as noted above.

COMPENSATION FOR MEDICAL TREATMENT:

The University of Texas at Arlington (UTA) will pay the cost of emergency first aid for any injury that occurs as a result of your participation in this study. UTA will not pay for any other medical treatment. Claims against UTA or any of its agents or employees may be submitted according to the Texas Tort Claims Act (TTCA). These claims may be settled to the extent allowable by state law as provided under the TTCA, (Tex. Civ. Prac. & Rem. Code, secs. 101.001, et seq.). For more information about claims, you may contact the Chairman of the Institutional Review Board of UTA at 817/272-1235.

FINANCIAL COSTS:

The possible financial costs to you as a participant in this research study are:

- Cost involved with traveling to UTA for testing and exercise training.
- Cost involved with purchasing proper attire and shoes for activity.

CONTACT FOR QUESTIONS

If you have any questions, problems or research-related medical problems at any time, you may call Dr. Jennifer Blevins at 817-272-5783, or Stacy Lueking at 817-272-7017. You may call the Chairman of the Institutional Review Board at 817/272-1235 for any questions you may have about your rights as a research subject.

VOLUNTARY PARTICIPATION

Participation in this research experiment is voluntary. You may refuse to participate or quit at any time. If you quit or refuse to participate, the benefits (or treatment) to which you are otherwise entitled will not be affected. You may quit by calling Dr. Jennifer S. Blevins whose phone number is 817-272-5783. You will be told immediately if any of the results of the study should reasonably be expected to make you change your mind about staying in the study.

By signing below, you confirm that you have read or had this document read to you. You will be given a signed copy of this informed consent document. You have been and will continue to be given the chance to ask questions and to discuss your participation with the investigator.

You freely and voluntarily choose to be in this research project.

PRINCIPAL INVESTIGATOR: _____ DATE _____

SIGNATURE OF VOLUNTEER _____ DATE _____

SIGNATURE OF PATIENT/LEGAL GUARDIAN (if applicable) _____ DATE _____

SIGNATURE OF WITNESS (if applicable) _____

APPENDIX B

HEALTH HISTORY QUESTIONNAIRE

Health History Form – University of Texas at Arlington
Exercise Science Research Laboratories

Date: _____

Name: _____ Age: _____ Weight: _____ pounds Height: _____ inches Sex: M F

Physician: _____ Last Medical Exam: _____

Marital Status: ☐ Married ☐ Divorced Children ☐ Yes If yes, list ages: _____
☐ Widowed ☐ Single ☐ No

Occupation: _____ Tobacco Use: ☐ Yes ☐ No

Medications: _____

Allergies: _____

Currently Exercising: ☐ Yes ☐ No If YES, specify (frequency, duration, intensity, type of activities): _____

Do you have or have you had any of the following conditions:

Anxiety/depression	<input type="checkbox"/> Yes <input type="checkbox"/> No	High Blood Pressure	<input type="checkbox"/> Yes <input type="checkbox"/> No
Asthma	<input type="checkbox"/> Yes <input type="checkbox"/> No	High Cholesterol	<input type="checkbox"/> Yes <input type="checkbox"/> No
Cancer	<input type="checkbox"/> Yes <input type="checkbox"/> No	HIV, AIDs, Hepatitis	<input type="checkbox"/> Yes <input type="checkbox"/> No
Chest Pain	<input type="checkbox"/> Yes <input type="checkbox"/> No	Indigestion/heartburn	<input type="checkbox"/> Yes <input type="checkbox"/> No
Depression	<input type="checkbox"/> Yes <input type="checkbox"/> No	Low Back Problems	<input type="checkbox"/> Yes <input type="checkbox"/> No
Diabetes	<input type="checkbox"/> Yes <input type="checkbox"/> No	Metabolic Disease	<input type="checkbox"/> Yes <input type="checkbox"/> No
If YES, type _____		Orthopedic Problems	<input type="checkbox"/> Yes <input type="checkbox"/> No
Difficulty urinating	<input type="checkbox"/> Yes <input type="checkbox"/> No	Osteoporosis	<input type="checkbox"/> Yes <input type="checkbox"/> No
Eating Disorder	<input type="checkbox"/> Yes <input type="checkbox"/> No	Pulmonary Problems	<input type="checkbox"/> Yes <input type="checkbox"/> No
Gastrointestinal Problems	<input type="checkbox"/> Yes <input type="checkbox"/> No	Skin Diseases	<input type="checkbox"/> Yes <input type="checkbox"/> No
Heart Disease	<input type="checkbox"/> Yes <input type="checkbox"/> No	Snoring	<input type="checkbox"/> Yes <input type="checkbox"/> No
Heart Valve Problem	<input type="checkbox"/> Yes <input type="checkbox"/> No	Urine Infections	<input type="checkbox"/> Yes <input type="checkbox"/> No
Hernia	<input type="checkbox"/> Yes <input type="checkbox"/> No		

If you answered YES to any of the above questions, please explain: _____

Do you have any other conditions not addressed above? _____

Family history of heart attack, cardiac procedure, or sudden death: ☐ Yes ☐ No

If YES, specify relationship(s), type of event, and age at time of event: _____

Are you pregnant? ☐ Yes ☐ No How many months? _____ Lactating: ☐ Yes ☐ No

Have you had any type of surgery: ☐ Yes ☐ No

If YES, list dates and types of surgery: _____

What are your exercise goals? _____

What activities do you enjoy? _____

Health Main

When was last (where appropriate)

Pap smear: _____

Mammogram: _____

Breast exam: _____

Cholesterol check: _____

Stool checked for blood _____

Colonoscopy/Flex Sigmoidoscopy: _____

Prostate exam: _____

Prevention

Do you wear seatbelts? ☐ Yes ☐ No

Do you wear? a) bicycle helmet ☐ Yes ☐ No b) motorcycle helmet ☐ Yes ☐ No

Do you drink alcohol? ☐ Yes ☐ No

Do you use drugs? (Marijuana, cocaine, . . .) ☐ Yes ☐ No

Do you engage in any behaviors which would increase your risk of AIDS? (IV drug use, unprotected intercourse, same sex relationship)?

☐ Yes ☐ No

Have you ever worked with chemicals, paints, asbestos, or other hazardous materials? ☐ Yes ☐ No

Female Health History

Age of start periods: _____ years old

Frequency: _____ Length of period: _____ days

Pregnancies: _____ Births: _____ Miscarriages: _____

Method of birth control: _____

Prolonged or abnormal bleeding: ☐ Yes ☐ No

Abnormal discharge: ☐ Yes ☐ No

Sexually Transmitted Disease: ☐ Yes ☐ No

Male Health History

Testicular masses ☐ Yes ☐ No

Discharge from penis ☐ Yes ☐ No

Sexually Transmitted Disease ☐ Yes ☐ No

Difficulty urinating ☐ Yes ☐ No

Problem with erection ☐ Yes ☐ No

Vaccination History

Hepatitis B ☐ Yes ☐ No

Tetanus ☐ Yes ☐ No

Flu ☐ Yes ☐ No

Pneumonia ☐ Yes ☐ No

Other: _____

Exercise Science Research Laboratories
Progress Record Physical Exam

Date: _____

Name: _____

Age: _____

Gender: ☐ Female ☐ Male

EXAMINATION:

Appearance:

Skin: ☐ normal

Head: ☐ normal

Eyes: ☐ normal

Ears: ☐ normal

Nose: ☐ normal

Mouth: ☐ normal

Neck: ☐ normal

Breasts: ☐ normal

Lungs: ☐ normal

Heart: ☐ normal

Abd: ☐ normal

Back: ☐ normal

Genitalia: ☐ normal

Ext: ☐ normal

Neuro: ☐ normal

Other: ☐ normal

APPENDIX C
GRADED EXERCISE TESTING SHEET

Exercise Testing Sheet

Name: _____ Age: _____ Date: _____ Supervising MD: _____
Medication: _____ Referring MD: _____

Previous Test Results: Date: _____ Pk METs _____ ST Δ _____ Pk RPP⁽⁻¹⁰⁾ _____ SxS _____

Resting: Supine HR: _____ Supine BP: _____ Standing HR: _____ Standing BP: _____

Exercise Test: Age-pred. peak HR _____ 85% age-pred max HR: _____

Time	(mph/%grd)	METs	HR (bts•min ⁻¹)	BP (mmHg)	RPP ⁽⁻¹⁰⁾	RPE	Signs/Symptoms
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

Total Test Time: _____ Est. Peak METs _____ Peak RPP⁽⁻¹⁰⁾ _____

Reason for Termination: _____

Recovery:

Time	HR	BP	Signs/Symptoms
IPE			
1			
2			
4			
6			
8			

Time	HR	BP	Signs/Symptoms

Physician Interpretation:

Resting ECG: _____ NORM _____ BDLN _____ ABNORM _____ INTERPRET: _____

Exercise ECG: _____ NORM _____ BDLN _____ ABNORM _____ INTERPRET: _____

Post-Exercise ECG: _____ NORM _____ BDLN _____ ABNORM _____ INTERPRET: _____

Conclusion: _____ NORM _____ BDLN _____ ABNORM _____ INTERPRET: _____

Supervising MD: _____
Signature

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BIOGRAPHICAL INFORMATION

Stacy M. Lueking was born in Bryan, TX on February 13th, 1980. Her family then moved to the upper peninsula of Michigan in 1985. She grew up in Houghton, MI, which is a small town in the northern part of the Upper Peninsula. She graduated from Houghton High School in May of 1998 and then attended Western Michigan University in the fall of 1998. She received her B.S. in Exercise Science in December of 2002 and then moved to Fort Worth, TX where she started a career in corporate fitness. After four years of working, she decided to apply to graduate school at the University of Texas at Arlington in 2006. She worked as a graduate research assistant at UTA while attaining her master's degree. She then received her M.S. in Kinesiology in December of 2007.

Stacy is undecided on her immediate professional plans post graduation, but she intends on advancing her career in exercise physiology and to possibly continuing on to a Ph.D. program someday. Her future interests are to teach at the collegiate level, conduct research and attain experience in conditioning and training elite athletes.