Relating Heart Rate Variability, Urinary Catecholamines, and Baseline Fitness to Respiratory Distress Index and Severity of Disease in Obstructive Sleep Apnea Patients

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(ABSTRACT)

Heart Rate Variability (HRV) currently is utilized when assessing the risk of mortality in individuals suffering from coronary heart disease or diabetic neuropathy. Research has shown that patients with Obstructive Sleep Apnea (OSA) also show a decrease in HRV, as well as an increase in sympathetic drive characterized by an increase in the low-frequency component of HRV. HRV, in conjunction with other indicators, may represent a non-invasive, low cost method for the confirmation of severity of OSA in some patients and therefore may represent an additional tool for the assessment of risk in these individuals. This becomes especially true when urinary catecholamines, fitness level, and quality of life (QOL) assessment are included. The purpose of this study was to determine if a correlation exists between severity of OSA as assessed by respiratory distress index (RDI) and the selected measures HRV, fitness, QOL, and catecholamine output. Subjects were 6 men and 5 women who were recently diagnosed with OSA by polysomnographic (PSG) study. HRV and blood pressure was measured during two consecutive trials consisting of 512 heartbeats. Catecholamine levels were determined by HPLC following 24-hour urine collection. Fitness levels were established following cycle ergometer testing and QOL following questionnaire completion. Subjects with lower weight, BMI, and neck circumference had significantly higher parasympathetic influence as analyzed through the amount of high frequency component of HRV ($r = .738$, .726, .789, respectively; $p<0.05$). Respiratory distress index (RDI) was negatively related to the average heart rate (HR=RR average, $r = -.610$, $p<0.05$), while the amount of total sleep ($r = .657$, $p<0.05$) and REM sleep ($r = .739$, $p<0.01$) increased as HR increased. The average HR was correlated to the predicted VO_2max ($r = .677$, $p<0.05$). When the frequency components of HRV, fitness, QOL, and catecholamines were combined, the association to RDI increased dramatically ($r = .984$, $p = .02$). The results indicate that as the severity of OSA increases, markers of fitness, QOL, and sleep decrease. There is also an inverse relationship between autonomic function and severity of OSA. It is concluded that HRV and fitness levels are inversely related to the severity of OSA, and that these measures may be developed into a risk assessment tool for use in OSA patient evaluation.

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CHAPTER 1

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a condition characterized by a collapse of the upper airway during sleep. This collapse results in the decrease of airflow, referred to as a hypoxic condition, despite persisting respiratory efforts (Figure 1). Hypoxia is typically characterized by decreasing blood oxygen saturation (SaO_2) until the episode is terminated through brief arousal and restoration of upper airway patency (Badr, 1999). Once the individual returns to the sleep state the patency of the upper airway is again compromised, resulting in another hypoxemic condition until the individual is once again forced into arousal. This continuing cycle of decreasing SaO_2 and arousal has been shown to occur hundreds of times per night (Loredo, et al., 1999). Ultimately, this could result in chronic fatigue and deterioration of health of the individual.

OSA has been shown to be associated with several cardiovascular disease states including systemic hypertension, increased cardiac arrhythmias, and congestive heart failure (CHF) (Guzzetti, et al., 1995, Marrone, et al., 1998, Peppard, et al., 2000, Skomro and Kryger, 1999). Systemic hypertension may result from an increase in sympathetic nerve activity in patients with OSA. This hypersympathetic activity results in an increase in the amounts of circulating catecholamines and therefore an increase in blood vessel tone (Hedner, et al., 1995). Acute arrhythmias associated with OSA may be a result of severe increases in vagal tone coupled with changes in oxygen saturation and lung volume (Weiss, et al., 1999). Whether OSA causes or exacerbates existing coronary artery disease (CAD) is unknown. However it has been shown that as many as 25 percent of OSA patients have CHF.

Obstructive Sleep Apnea may occur in as many as 2 percent to 4 percent of the middle-aged population (Young, et al., 1993). Those suffering with OSA are typically obese males, however an increasing number of women are now being diagnosed with the disease state. Patients may also present other physical characteristics such as a reduced chin, or clinical symptoms including excessive fatigue and systemic hypertension. Co-morbidities range from a mild increase in blood pressure to congestive heart failure.

Pharyngeal patency is a product of transmural pressure across the pharyngeal wall as well as the compliance of the wall (Badr, 1999). Patients with OSA may have reduced compliance of the pharyngeal wall and therefore reduced airflow. Increased neck size and weight associated with obese individuals may also play a role in reduced compliance. In the supine position the increased weight in the cervical region in these individuals may increase extramural pressure on the upper airway. In addition, those with abnormal craniofacial structures may compound the extramural pressure associated with a decrease in upper airway patency. An increase in extramural pressure coupled with a decrease in pharyngeal wall compliance leads to a narrowing of the airway during sleep. This in turn causes a reduction or cessation of airflow to the thoracic cavity and eventually asphyxia. An interruption in sleep is usually required to return the airway to a normal state. Once sleep is resumed, the cycle repeats.

Once diagnosed with OSA patients have several options to consider. Reduction in body mass in those individuals who are obese may result in a reduction in weight placed on the upper airway during sleep and therefore a decrease in extramural pressure. The exercise generally associated with weight reduction in obese individuals may also increase upper airway muscle tone, resulting in reduced tendency for airway obstruction.

In addition, weight loss can increase a patient's quality of life and decrease the severity of other underlying disease. The more conventional method of treatment is continuous positive airway pressure (CPAP) therapy. A mask, worn by the patient during sleep, delivers pressurized oxygen to the upper airway, increasing transmural pressure and therefore preventing the apneic event (Figure 1). Modern technology has allowed for the development of CPAP devices which sense impending airway obstruction and automatically adjust the pressure delivery to a level that eliminates airway closure (Henderson and Strollo, 1999, Sharma, et al., 1996). Patient compliance is the primary difficulty with CPAP therapy, in some cases being as low as 46 percent. Some patients do not adjust well to CPAP therapy for a variety of reasons including comfort or adaptability to the pressurized oxygen. In recent years several surgical options have also become available for those patients with OSA. In some cases the jaw is broken and moved forward to open the upper airway in those patients with craniofacial abnormalities. It is also possible to detach the soft tissue of the upper airway and reattach it to a point farther forward on the jaw, opening the upper airway and resulting in a decreased incidence of collapse. Unfortunately, surgical intervention has only proven successful in 50 percent of patients.

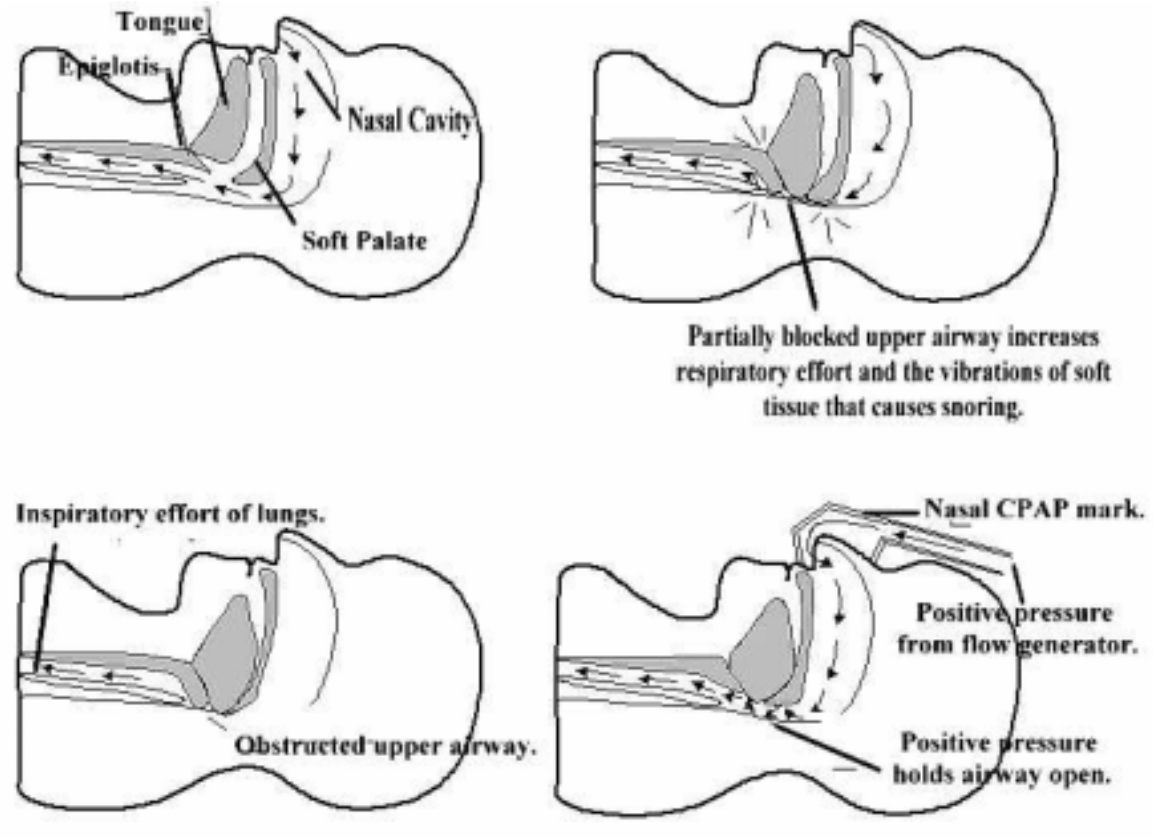

Figure 1 - Progression of Upper Airway Obstruction and use of CPAP Device

Heart Rate Variability (HRV) is a relatively new measure of autonomic function, consisting of measuring beat-to-beat variations in heart rate over a period of time. It is not the actual heart rate that is of concern when dealing with HRV, but instead the oscillation in consecutive cardiac cycles. First recognized by Hon and Lee (Hon EH, 1965) in 1965, HRV has since been associated with a decrease in autonomic nervous system control and an increased risk of mortality (Garcia-Rio, et al., 2000, Narkiewicz, et al., 1998, Salo, et al., 2000). Currently HRV has only been shown to be a clinically reliable measure in relation to increased chance of mortality in coronary heart disease

patients, or in the diagnosis of diabetic neuropathy (1996, Narkiewicz, et al., 1998, Risk M, 2001).

The physiological basis of HRV stems from the regulation of heart rate by the autonomic nervous system. The parasympathetic system sends signals to the heart via the vagus nerve. The neurotransmitter acetylcholine is released and binds with muscarinic receptors on the surface of the heart. This results in a decrease in both the heart rate and the force of cardiac contractions. Sympathetic stimulation occurs via the release of norepinephrine and epinephrine by the adrenal medullae. These neurotransmitters stimulate β-adrenergic receptors, resulting in an increase in the degree and the force of contraction. During resting condition, the parasympathetic system dominates and vessels exhibit a certain amount of vagal tone. Under these conditions changes in heart rate are dependent on vagal modulation (Goldberger, 1999). HRV monitors and records these modulations, allowing a more complete understanding of neural functioning.

HRV may be analyzed using methods of time or frequency domain. Time domain analysis is the simplest of measures and consists of variations on the average heart rate or beat-to-beat interval (RR interval). Time domain analysis may be employed using either statistical or geometric variations. Statistical variations may include mean RR interval, longest RR interval, standard deviation of RR interval, number of RR intervals exceeding 50 ms, and the standard deviation of the average RR interval. Geometric analysis may include the number of all RR intervals divided by the height of the histogram created by charting all the RR intervals (HRV triangular index), differential index, and logarithmic index.

Frequency domain analysis becomes more complicated but is perhaps the best indicator of the underlying risk of mortality. Various spectra analysis is performed to determine the variance (power) as a function of frequency (1996). The frequency spectrum may be parametric or nonparametric . Nonparametric methods result in a smoother curve and faster results, while parametric measures are used to determine the accuracy of the model. The algorithm used in most instances is known as Fast Fourier Transformation (FFT) and may vary depending on the statistical analysis desired. The result is an analysis that may be broken down into high, low, and very low frequency components. High frequency is generally associated with parasympathetic nervous system influence and the low frequency component may be considered a combination of both sympathetic and parasympathetic nervous system control (Grassi and Esler, 1999, Karemaker, 1999), although this has not been clinically established.

Advances in technology have allowed HRV to be measured using non-invasive, short-term methods. HRV can be calculated using as few as 128 consecutive cardiac cycles, or may be measured using 24-hour cardiac monitoring. Accuracy increases as the number of cardiac cycles increases, however 24-hour monitoring brings about questions of autonomic nervous system control versus neural control of the activities of daily living. Any type of arrhythmia, outside interference, missing data, ectopic beats, or changes in the respiratory cycle will change the power spectrum of the HRV measurement. Thus long-term measurements should be verified through short-term recordings during the same period, the results of which can be averaged to ensure correct estimates of autonomic nervous system modulation. The highest reproducibility of HRV measurements has come from recordings spanning either 512 or 1024 consecutive cardiac

cycles (1996). Since HRV can also be altered by the respiratory cycle, measurements should also be taken using a steady breathing pace between 12-14 breaths per minute (Amara and Wolfe, 1998, Driscoll and Dicicco, 2000). This ensures the power spectrum to be influenced solely by the autonomic nervous system and not other physiological components.

HRV is clinically accepted under a limited number of circumstances. HRV can be used to assess the risk of mortality and arrhythmic complications following an acute myocardial infarction (MI). This assessment of risk is independent of other risk factors such as left ventricular ejection fraction and increased ventricular ectopic activity. Generally it is accepted that to increase the accuracy of the risk stratification HRV measurements should be performed within one week of acute MI (Makikallio, et al., 1999). Another clinically relevant use for HRV is for the assessment of diabetic neuropathy. This is characterized by the degeneration of both parasympathetic and sympathetic nerve fibers. HRV may aid in the early detection and treatment of this condition, thereby increasing the long-term survival rate in these individuals. However, it remains to be determined as to whether HRV confirms other prognostic measures concerning diabetes. There have been numerous studies concerning HRV and it's relationship to several other cardiovascular disease states including CHF, mitral valve prolapse, heart transplantation, and ventricular arrhythmias. HRV has also been evaluated in patients with OSA for possible risk stratification properties (Roche, et al., 1999). It has been shown that patients with OSA have altered cardiovascular variability that is directly linked to the severity of the disease (Narkiewicz, et al., 1998). HRV may be shown to be useful when diagnosing the risk of cardiovascular disease in patients with

OSA. Current research also shows that cardiovascular variability is increased following exercise training. However there is currently no research concerning the effects of exercise on cardiovascular variability in OSA patients.

Initial fitness level may be a viable indicator of quality of life, and may be related to the severity of OSA. It has been shown that HRV increases with exercise (Kiilavuori, et al., 1995, Levy, et al., 1998), which may be due to an increase in vagal tone or neural control. Increases in exercise may also benefit those patients with OSA. To date, no relationship has been established between severity of OSA and fitness level. However, it stands to reason that those with more severe apnea are less likely to exercise regularly, and are more likely to score poorly on baseline fitness tests. Exercise scores have been shown to improve after treatment with CPAP in OSA patients (Shifflett DE, 2001), and reduction in weight through diet and exercise are recommended treatment options (Henderson and Strollo, 1999). Exercise may represent an important link between quality of life and severity of disease. Those who exercise may be less likely to develop cardiovascular complications associated with OSA. In addition, exercise may represent a non-invasive treatment option that could limit the progression to more severe levels of disease.

The purpose of the current research project was to confirm the link between HRV, urinary catecholamines, fitness level, and the severity of disease in OSA patients. Also evaluated was how the results of the sleep study, used to diagnose OSA patients, are related to indicators of autonomic nervous system function. It was hypothesized that patients with a more severe level of disease would show a greater reduction in HRV, lower levels of circulating urinary catecholamines, and lower levels of fitness.

This research will increase the likelihood that HRV, in combination with fitness levels and quality of life, may be used as an assessment tool for use with OSA patients. It will also assist in the promotion of exercise as an important treatment alternative. If true, this will give physicians a non-invasive method of assessing autonomic function and perhaps the risk of cardiac mortality in individuals suffering with OSA.

STATEMENT OF PROBLEM

It has been shown that HRV is an effective tool for assessing risk of cardiovascular mortality in individuals following an acute myocardial infarction. However, HRV has not been shown to be an effective tool in those individuals with OSA. In addition, while rate variability has been determined to be lower in OSA patients, few studies have been performed to determine the correlation between HRV and severity of the OSA disease state. In addition, physical fitness and its relationship to both HRV and severity of OSA have yet to be determined. Variables such as these need to be analyzed in order to determine whether HRV may be employed as an alternative to conventional sleep study sessions for potential OSA patients. It may also give physicians a preliminary screening tool to assess the neurological functioning, risk for sudden cardiac mortality, and potential success of follow-up testing by polysomnography (PSG) in OSA patients.

RESEARCH HYPOTHESIS

OSA patients, following diagnosis by sleep study, will show the following changes:

- All OSA patients will show a significantly reduced HRV level.
- All OSA patients will have a relatively low level of urinary catecholamines.

- Both HRV and circulating catecholamines will be correlated to the severity if disease as indicated by sleep study results.
- Low exercise test and questionnaire scores will be correlated to increased severity of disease.

SIGNIFICANCE OF STUDY

Successful outcomes of this study indicate HRV, catecholamine analysis, and fitness assessment as a viable additions to conventional assessment methods for individuals with OSA.

BASIC ASSUMPTIONS

The investigator made the following assumptions in conducting this study:

1. All subjects were truthful in recording their answers to the questionnaires.
2. Volunteer subjects were representative of the population of OSA patients.
3. All measurements were performed and recorded accurately by the Schiller AT-10™, and a trained technician.
4. All biochemical markers were measured and recorded accurately by HPLC and a trained technician.
5. Records obtained following polysomnography were accurate and recorded by a trained technician.
6. All results obtained through the exercise tests were measured and recorded accurately by a trained technician.

DELIMITATIONS

The investigators delimited the study through the following methods:

1. All OSA subjects were volunteers from the community referred to the Sleep Disorders Center of Southwest Virginia for polysomnography.
2. All heart rate variability measurements were performed in duplicate, using the Schiller AT-10™, to ensure accuracy.
3. Blood pressure was measured at the end of each heart rate variability trial to ensure similar patient status.
4. During the trials patients used controlled breathing (~12 breaths/min) to minimize the neural influences.
5. Fitness assessments were performed by two trained technicians to minimize error.
6. Patients were instructed on the use of equipment and were given practice trials to minimize patient error.

LIMITATIONS

Interpretation of the data was limited by the following:

1. The patients were unfamiliar with the testing procedure when undergoing the first trials. This may have resulted in skewed measurements.
2. 24-hour urine analysis used to determine catecholamine excretion might not have been performed on a day of average food consumption, which could change the excretion rate.
3. Only volunteers were used for this study and therefore the population may not be representative of the population as a whole.

4. Baseline fitness assessments were performed once, and were assumed to be representative of the patient's fitness level.
5. The patients may not have been familiar with the exercise mode and therefore achieved lower fitness scores.

DEFINITIONS OF TERMS

• Acetylcholine	Neurotransmitter released by the parasympathetic nervous system responsible for decreasing heart rate and force of contraction.
• Arousal	Action of moving from the sleep state to the awake state.
• Asphyxia	The extreme condition caused by lack of oxygen and excess of carbon dioxide in the blood, produced by interference with respiration or insufficient oxygen in the air.
• Autonomic Function	How well the system of nerves and ganglia that innervates the blood vessels, heart, smooth muscles, viscera, and glands and controls their involuntary functions, consisting of sympathetic and parasympathetic portions, is operating.
• β-adrenergic Receptors	Receptor cells in the cardiac muscle that when stimulated by the sympathetic nervous system result in an increase in the force of contraction.
• Catecholamines	Chemical markers indicating the degree of autonomic nervous system activity.
• CPAP	Continuous Positive Airway Pressure – Typical treatment for patients with Obstructive Sleep Apnea – mask worn during sleep uses pressurized oxygen to increase transmural pressure in the upper airway.
• Epinephrine	Neurotransmitter released by the sympathetic nervous system responsible in part for increasing heart rate and force of contraction.
• Extramural Pressure	Pressure originating external to the body cavity.

- FFT — Fast Fourier Transformation – Algorhythm used to statistically manipulate and analyze Heart Rate Variability.
- Frequency Domain — Analysis of Heart Rate Variability through fast fourier transformation over time.
- High-Frequency Component — Component of heart rate variability in the frequency domain that is associated with influence from the parasympathetic nervous system.
- HRV — Heart Rate Variability – Non-Invasive measure of the beat-to-beat fluctuations in heart rate analyzed in either the frequency or time domain.
- Low-Frequency Component — Component of heart rate variability in the frequency domain that is associated with influence from both the parasympathetic and sympathetic nervous system.
- Muscarinic Receptors — Cholinergic receptors on autonomic effector cells that are stimulated by muscarine, parasympathomimetic drugs and blocked by atropine.
- Norepinepherine — Neurotransmitter released by the sympathetic nervous system responsible in part for increasing heart rate and force of contraction.
- OSA — Obstructive Sleep Apnea – Disease state characterized by repeated cycles of airway collapse followed by arousal during sleep.
- Parasympathetic Nervous System — Branch of the autonomic nervous system responsible for basic function during rest as well as the slowing of heart rate.
- Patency — The condition of not being blocked or obstructed.
- RR Interval — Amount of time between consecutive ventricular contractions.
- Spectral Analysis — Analysis of heart rate variability in the frequency domain.
- Sympathetic Nervous System — Branch of the autonomic nervous system responsible for increases in heart rate.

- Time Domain — Basic manipulation of measures of heart rate variability using simple statistical analysis.
- Transmural Pressure — Pressure across a body cavity from internal sources.
- Upper Airway Compliance — Ability of the upper airway to expand or contract under pressure.
- Vagal Tone — The amount of stiffness or resting muscle patency in the vagus nerve.
- Very-Low Frequency Component — Component of heart rate variability in the frequency domain that is associated with influence from the sympathetic nervous system.

LIST OF ABBREVIATIONS

- BMI — Body Mass Index
- CAD — Coronary Artery Disease
- CHF — Congestive Heart Failure
- CPAP — Continuous Positive Airway Pressure
- E — Epinephrine
- ECG — Electrocardiograph
- FFT — Fast Fourier Transformation
- HF — High Frequency component of Heart Rate Variability
- HRV — Heart Rate Variability
- HPLC — High Powered Liquid Chromatography
- Hz — Hertz
- LF — Low Frequency component of Heart Rate Variability
- MI — Myocardial Infarction

- NE — Norepinephrine
- OSA — Obstructive Sleep Apnea
- PSG — Polysomnography
- $PaCO_2$ — Partial pressure of Carbon Dioxide in arterial blood
- QOL — Quality of Life
- REM Sleep — Rapid Eye Movement Sleep
- RDI — Respiratory Distress Index
- RPE — Rating of Perceived Exertion
- RR Average — Average interval of heart beats measured during Heart Rate variability analysis
- RR Interval — Interval of heart beats measured during Heart Rate variability analysis
- SaO_2 — Oxygen Saturation of blood
- ULF — High Frequency component of Heart Rate Variability
- VLF — High Frequency component of Heart Rate Variability
- VSAQ — Veterans Specific Activity Questionnaire
- W — Watts

SUMMARY

Obstructive Sleep Apnea is becoming a more widely known disease that could potentially affect millions of individuals in the United States alone. OSA has been shown to be correlated to many cardiovascular conditions including hypertension and congestive heart failure. While HRV has been shown to be reduced in patients with OSA, is has not been definitively shown that HRV is correlated to the severity of disease. HRV may offer a

non-invasive measure of neurological function in OSA patients. In addition, HRV may offer a less costly method to measure the severity of disease in these individuals. It is not know whether low scores on fitness questionnaires or exercise tests are a result of Obstructive Sleep Apnea, or if the severity of the disease is amplified by low cardiac fitness. More long-term research needs to be performed to determine the most appropriate measures to assess autonomic functioning and how to improve sleep, neurological and hemodynamic control, cardiovascular functioning, and quality of life.

CHAPTER 2 – LITERATURE REVIEW

INTRODUCTION

The following chapter will review the current literature pertaining to obstructive sleep apnea (OSA), specifically focusing on neuromuscular interaction. Once the pathophysiology of the disease is reviewed, the focus will shift to specifically address how heart rate variability may be altered in those suffering from OSA. The reliability and methodology of heart rate variability measurements will then be discussed. In addition, the overall functioning of the central nervous system in patients suffering from OSA will be addressed. The biochemical interaction of the central nervous system will be examined, focusing on catecholamine levels and how they are altered in OSA. Using heart rate variability, in addition to biochemical markers, as a tool in OSA patients will be covered, and fitness levels and exercise as they relate to OSA and HRV will be discussed.

PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA (OSA)

Obstructive Sleep Apnea is a condition that may affect as many as 2 to 4 percent of the adult population. However, many of these individuals are misdiagnosed. OSA is characterized by an obstruction of the upper airway during sleep. Although a reduction in muscle tone of the upper airway during sleep is normal, OSA patients suffer from a complete collapse of the airway. The result is a progressive increase in respiratory distress until arousal occurs, at which time pharyngeal patency is restored. The obstruction of the upper airway can be caused by any combination of anatomical and physiological factors, including but not limited to enlarged tonsils, craniofacial

abnormalities, increased pressure from adipose tissue in the pharyngeal area, or a decrease in upper airway muscle tone. Lowe, et al. (Lowe, 1999) showed that, in general, OSA patients present a larger tongue, tonsils, and soft palate compared to normals. Normal neuromuscular control of the upper airway must also be considered, including neurochemical factors, reflexes, and neurological control of the musculature of the upper airway. While studies have shown the typical OSA patient to be obese, middle-aged males, the above phenomenon can be commonplace in seemingly normal individuals.

Collapse of the upper airway can arise from a variety of factors. Pharyngeal patency is a determined through a combination of compliance of the pharyngeal wall and transmural pressure across the wall. It has been shown that during inspiration there is a decrease in cross-sectional area due to a reduction in intraluminal pressure. In those with sleep apnea it is thought that there is an exacerbation of the reduction in pressure due to the increase in air velocity during narrowing of the pharynx. This results in a more negative intraluminal pressure and therefore an increase in the collapse of the upper airway. The decrease in patency can also be attributed to extraluminal pressure in many instances. In the typical obese OSA patient, the collapse may be caused by an increase in adipose tissue around the upper airway. This in turn places added pressure on the pharynx, causing a reduction in the size of the airway. Reduction in airflow through the upper airway may also be caused by craniofacial abnormalities that alter the shape of the airway. During sleep, normal reduction of muscle tone in the upper airway coupled with either of these conditions is enough to cause a decrease in airflow, which in some cases leads to a total obstruction.

Compliance of the pharyngeal wall must also be considered when investigating the causes of OSA. Pharyngeal wall compliance is determined by both neuromuscular and non-neuromuscular factors. The genioglossus muscle of the upper airway is thought to be critical in preserving the patency of the upper airway. However, there is conflicting evidence regarding the role of the muscles in the upper airway and pharyngeal compliance. It has been shown that OSA patients have an increase in genioglossus muscle activity both in the awake and sleep state. In addition, Badr, et al. (Badr, 1999) reported that patients with central sleep apnea had significantly higher incidence of pharyngeal occlusion than normals despite complete inhibition of upper airway dilating muscle activity in all subjects. One explanation was presented by Rowley, et al. (Rowley, et al., 1998) who reported that vascular perfusion was increased during REM sleep and may contribute to decreased pharyngeal compliance. Therefore both neuromuscular and non-neuromuscular factors must be taken into account when investigating compliance of the pharyngeal wall.

While the direct cause of OSA in many patients may be difficult to determine, the resulting clinical symptoms are well documented. The collapse or blockage of the upper airway results in a reduction in airflow to the lungs, and therefore a decrease in oxygen saturation of the blood (SaO_2). The decrease in SaO_2 causes the central nervous system to induce hyperventilation. Because of the partially to totally closed airway, SaO_2 continues to decrease until arousal, when upper airway patency and therefore normal airflow is restored. Often following an arousal there is a period of hypocapnia (reduced $PaCO_2$) and increased SaO_2 due to hyperventilation (Figure 2). This can result in subsequent apneas or hypopneas due to a reduction in respiratory drive. Thus although

the upper airway is often only restored through arousal, a cycle of continuing apneic or hypopneic episodes may be induced.

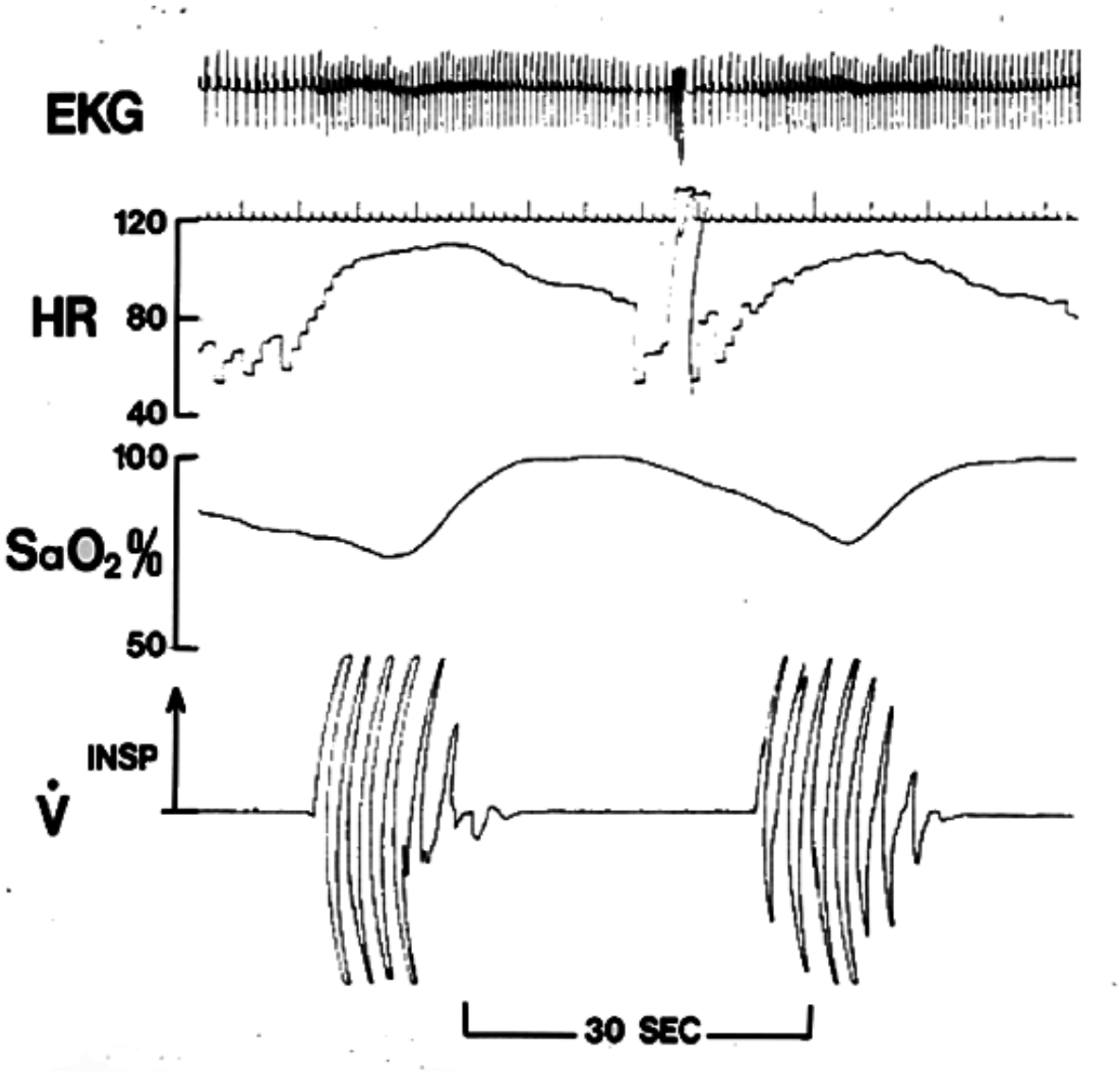

Figure 2 - Upper Airway Obstruction as Seen During Polysomnography Testing

PATHOGENESIS OF HEART RATE VARIABILITY (HRV)

Heart rate variability (HRV) refers to the spontaneous, rhythmic, fluctuations in the beat-to-beat intervals of the heart. These fluctuations represent cardiovascular system control mechanisms that compensate for environmental and physiological changes. It has been shown that there is a significant inverse relationship between time domain measures of HRV and the increased risk of sudden cardiac death. Therefore, HRV represents a possible tool in the assessment of autonomic function as well as future risk of mortality.

Under normal conditions the heart rate is controlled by the intrinsic pacemaker and modified by influence from the autonomic nervous system. The sympathetic system stimulates an increase in heart rate through release of the catecholamines norepinepherine and epinephrine by the adrenal medullae. The neurotransmitters stimulate β-adrenergic receptors, which increase the force and degree of contraction of the heart muscle. The parasympathetic influence is mediated through the vagus nerve. The neurotransmitter acetylcholine is released and binds with muscarinic receptors on the surface of the heart. This results in a decrease in both the heart rate and the force of cardiac contractions. Vagal tone is maintained at rest through the sympathetic system influence, and during this time fluctuations in heart rate are dependent on vagal modulation. The measure of HRV is a record of these modulations, allowing a more complete understanding of neural functioning.

Recently, HRV has become a relatively inexpensive commercial tool for the assessment of autonomic function. Monitors can record as few as 64 heartbeats or store data for as long as 24 hours. The stored heart beats and their intervals are then analyzed

statistically to determine the average beat-to-beat interval. The intervals may be analyzed in either the time or frequency domain. Typical time measurements include average RR (the time between consecutive R peaks on an ECG) interval, as well as median and standard deviation of the RR intervals (Figure 3). Sometimes the RR intervals are analyzed geometrically to form a pattern showing the sample distribution of adjacent intervals.

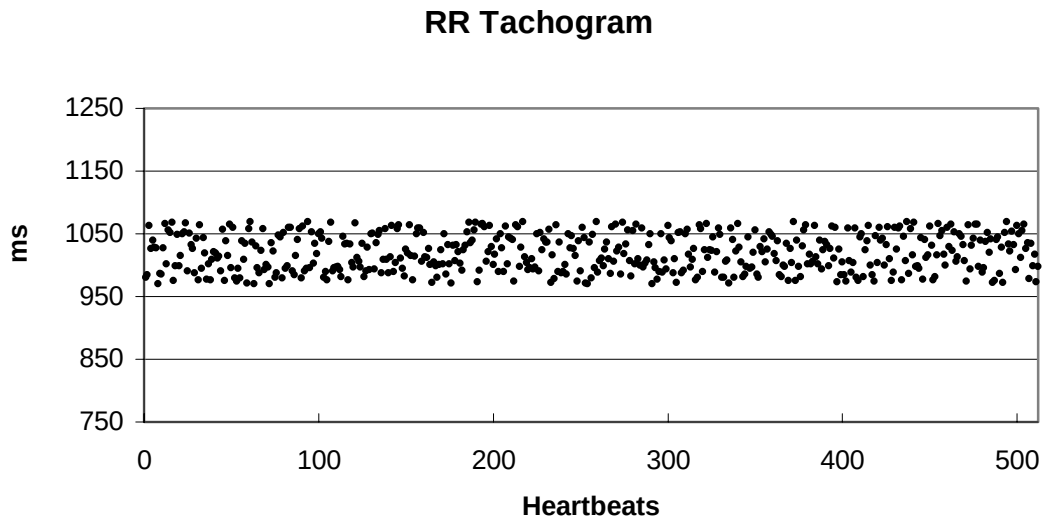

Figure 3 - Heart Rate Variability in the Time Domain

Frequency domain analysis consists of mathematical manipulation of the data, which is then broken down into components of a frequency distribution. In most cases, the algorithm used is known as fast fourier transform (FFT). Once in this form, the data are broken down into high frequency (HF), low frequency (LF), and very low frequency (VLF) components (Figure 4). It has been shown that the HF component of HRV is determined by respiration. This usually occurs between 0.15 and 0.4 Hz. Studies have also shown the low frequency component to be influenced by sympathetic modulation,

and to occur within the range of 0.04 to 0.15 Hz. The VLF component, occurring at less than 0.04 Hz, is much less understood but is thought to be a combination of thermal regulation and circulating catecholamines. Analysis of the frequency spectrum provides insight into the degree of autonomic modulation over a period of time. Since the VLF component is not fully understood, it should be avoided when analyzing autonomic modulation. Therefore, normalized units are employed when describing the influence of the HF and LF component. This allows emphasis on the controlled and balanced behavior of the two branches of the autonomic nervous system. Normalized units are achieved by removing the VLF component from the total power and dividing the remainder into either the LF or HF component. This has the effect of minimizing the changes in total power on the HF and LF components.

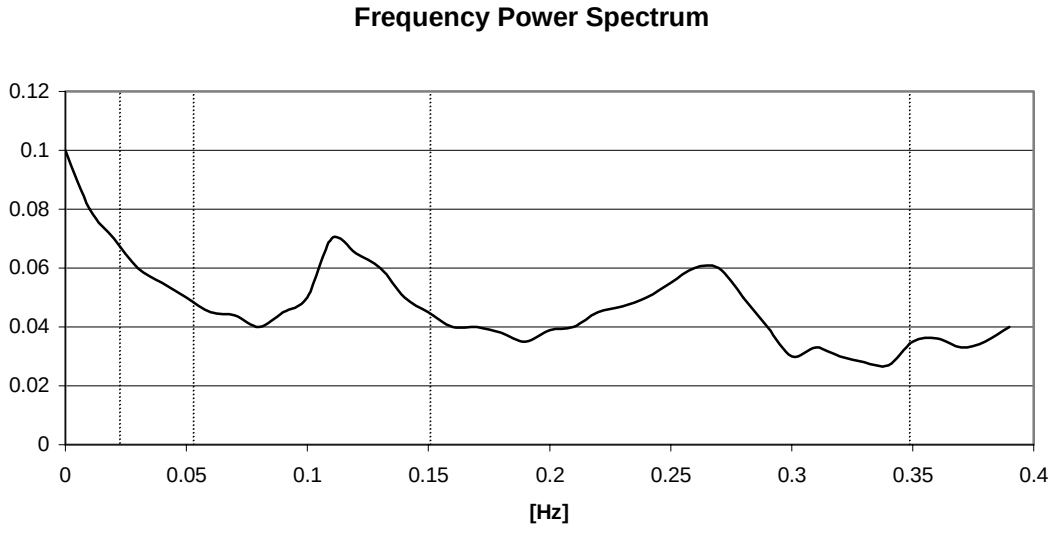

Figure 4 - Heart Rate Variability in the Frequency Domain

HRV RELIABILITY AND METHODOLOGY

HRV has been used extensively in diabetic neuropathy to track changes in autonomic function over time. HRV has also proved useful in many other areas of research. It has been shown to be highly reproducible and reliable under similar circumstances. In 1996 the European Society of Cardiology along with the North American Society of Pacing and Electrophysiology published a special report concerning the standards of measurement of HRV (1996). In that special report they pointed to several factors that can influence the reliability of HRV measurements. They concluded that short-term recordings (5 minutes) provide similar averages as 24-h recordings. In addition, they study concluded that short-term recordings may be more effective for determining the effects of short-term interventions (mild exercise, etc.) on autonomic function. The panel recommended that short-term recordings encompass no less than 512 consecutive heartbeats. Outside influences such as noise and distractions should also be limited, and each subject should be tested in similar conditions. Standard measurements include patients in the supine position, in a controlled atmospheric condition. Measurements done on separate days should include controls for temperature, pressure, noise, and other distractions.

Other studies have also confirmed the validity of short-term HRV recordings. Marks et al. (Marks and Lightfoot, 1999) compared HRV using 2.5 and 5.0-minute sampling periods from a 10-minute heart rate recording. Eight healthy active women participated in the study. ECG was recorded on two separate days within one week. The researchers controlled for physiological conditions and environment. Each subject rested in the supine position for 10 minutes, after which a 10-minute ECG was recorded. From

the recording HRV was determined from 2.5 and 5.0-minute segments. Both time and frequency domain analysis was performed.

For the time domain analysis both time segments showed significant reproducibility ($r = 0.86\text{-}0.9$, $p<0.05$). There were no significant differences between days for either the 2.5 or the 5.0-minute sampling period. The frequency domain analysis showed lower correlations ($r = 0.67\text{-}0.96$), with the highest correlation found in the low frequency to high frequency ratio. The authors concluded that there was no significant difference in the recordings on each day, but there was significant difference between the 2.5 and 5.0-minute recordings in the frequency domain.

The validity of short term HRV recording was further validated by Costa, et al. (Costa, et al., 1994), who compared 24-hour Holter recordings to shorter interval recordings. The 24-h recordings were compared to intervals of 512 beats in both the time and frequency domain. The authors found no significant difference between the two recordings. They concluded that shorter recordings provide a statistically reliable alternative to 24-h recordings for HRV analysis.

Components of respiration, environment, and other influences have been of concern when discussing HRV. It has been shown that a breathing rate of 12 breaths/minute provided significant reliability and reproducibility of HRV analysis and eliminates some of the respiratory influences on the spectral analysis. Amara et al. (Amara and Wolfe, 1998) performed a study to assess the reliability and reproducibility of HRV and systolic blood pressure at rest and during exercise. Environmental conditions were strictly controlled, and changes in breathing frequency were also investigated. Subjects were 10 healthy, active volunteers (7 women, 2 men, aged 23-35

years). Testing consisted of two, 1.5-hour sessions, 48 hours apart. Subjects abstained from caffeine and alcohol intake 6 hours prior to testing, and consumed a standard meal (350 kcal, 40% protein, 40% carbohydrate, 20% fat) 2 hours before testing. Both trials were held at the same time of day. Environmental factors were minimized, with humidity and temperature recorded for each trial. The number of testers on each day was the same, noise was limited, and interruptions were documented. Subjects performed two resting and one exercise tests on each day. The resting tests consisted of paced breathing at either 12 or 16 breaths per minute. The exercise tests were performed on a cycle ergometer and consisted of a 20 W warm-up for 2 minutes followed by a ramping protocol to approximately 80 W for women and 100 W for men. Breathing was not regulated during the exercise testing. 512 continuous cardiac cycles were collected for HRV analysis, and continuous arterial blood pressure was monitored throughout the tests. HRV data was edited to exclude those beats that were >30% of the preceding interval.

The results indicated that there was no significant difference in HRV between trials either at rest or during exercise. All reliability coefficients were significant ($p<0.05$) when breathing was controlled at 12 breaths/minute ($r = 0.55 – 0.79$), except low frequency power. At 16 breaths/minute, only fractal power, total power, and low to high frequency ratio showed significant reliability. During exercise, only high frequency ($r = 0.68$), fractal power ($r = 0.66$), percent fractal power ($r = 0.65$), and high frequency to total ratio ($r = 0.89$) showed significant reliability ($p<0.05$). The authors concluded that there is significant reproducibility and reliability when breathing is controlled at 12 breaths/minute.

Similarly, Driscoll, et al. (Driscoll and Dicicco, 2000) examined the effects of metronome breathing on the variability of autonomic activity measurements. Eight subjects (3 male, 5 Female) underwent 6 trials each. The subjects were normotensive volunteers from the student body and staff at the Parker Research Institute. Normal breathing was used for the first 3 trials, while paced breathing at a rate of 12 breaths/minute was used for the second three trials. HRV and systolic blood pressure were recorded throughout the trials. Frequency analysis was performed, with a low frequency interval of 0.04 – 0.15 Hz and a high frequency interval of 0.15 – 0.4 Hz.

The results showed that there was no significant difference in blood pressure during the controlled breathing. Controlled breathing significantly increased the high frequency power (0.25 to 0.35, $p<0.04$), and significantly decreased low to high frequency ratio (1.08 to .57, $p<0.05$). The coefficient of variation was significantly ($p<0.05$) reduced for the low frequency, high frequency, and low to high frequency ratio during the controlled breathing (47.6% vs. 23.4%, 46.2% vs. 25.8%, 50.1% vs. 23.4%, respectively). The authors concluded that controlled breathing at 12 breaths/minute reduces variation in HRV measurements but also increases high frequency components.

HEART RATE VARIABILITY IN OBSTRUCTIVE SLEEP APNEA PATIENTS

Patients suffering from OSA show an increase in sympathetic drive. This increase may be associated with increased risk of cardiovascular morbidity. Thus, if those suffering from OSA show alterations in cardiovascular variability, it may have prognostic value for risk assessment in these individuals.

Narkiewicz, et al. (Narkiewicz, et al., 1998) investigated whether OSA is accompanied by alterations in cardiovascular variability. The study used 49 subjects split into three groups (15 with moderate-to-severe OSA, 18 with mild OSA, and 16 normal controls). The OSA subjects were otherwise healthy individuals who were recently diagnosed by polysomnography. Severity of OSA was determined by the apnea-hypopnea index (AHI; mean 15 $\pm$ 1 events/h for mild group, 61 $\pm$ 8 events/h for moderate-to severe group). Simultaneous measurements of electrocardiograph (ECG), respiration (pneumograph), oxygen saturation (pulse oximeter), arterial pressure (Finapres system), and MSNA were recorded during 10 minutes of supine rest. Data was collected and analyzed using methods reported earlier. Results indicated that patients with moderate-to-severe OSA had shorter RR intervals and increased sympathetic burst compared to control subjects (793 $\pm$ 27 vs. 947 $\pm$ 42 ms; $p=0.008$ and 49 $\pm$ 4 vs. 24 $\pm$ 3 bursts/min; $p<0.001$, respectively). There was also a significant positive correlation ($r=40$; $p=0.02$) between OSA severity and blood pressure variance. The authors concluded that cardiovascular variability is altered in OSA even in the absence of other disease states, and may be linked to the severity of OSA.

In a more recent study, Wiklund, et al.(Wiklund, et al., 2000) used 51 patients with OSA and compared them to 66 controls. HRV was analyzed after supine rest, with controlled breathing as well as after tilting in each individual. HRV was performed after overnight sleep study with those individuals having an AHI greater than 20 being diagnosed as the patient group. Blood pressure, age, and BMI were also analyzed between groups. The results indicated significant decrease in indices reflecting vagal modulation, as well as those reflecting the mid-frequency component. However,

Wiklund, et al. found no correlation between vagal function and severity of OSA. They concluded there is autonomic dysfunction is those suffering from OSA, most likely involving the parasympathetic system.

Obstructive Sleep Apnea may not only affect the long-term ability of the central nervous system to control heart rate variability. Keyl, et al. (Keyl, et al., 1996) investigated how HRV is affected during an apneic episode as compared with normal breathing. Nine male subjects between the ages of 38 and 72 years participated in the study. The patients had no underlying cardiovascular disease and were not taking any medications. Each patient was monitored during two, 20-minute periods. One period was during normal breathing and the other was selected from an overnight study and included an apneic episode. Results showed a sharp peak in the VLF spectrum during the apneic episode. Also, LF and HF power increased significantly ($p<0.05$) during periodic breathing. The author's concluded that breathing abnormalities can cause marked changes in HRV.

While there is agreement concerning autonomic dysfunction in these individuals, there is no consensus as to the underlying cause. Most studies have shown that the sympathetic system is the driving factor. However some researchers content that the parasympathetic system is to blame, or in some cases show alterations in both systems.

CATACHOLAMINES AND OBSTRUCTIVE SLEEP APNEA

Patients with OSA display increases in blood pressure, both during the apneic episode and in the long term as daytime hypertension. Catecholamines have been thought to play a role in this change in blood pressure. Increases sympathetic nervous

system control could contribute to increases in epinephrine and norepinephrine release and therefore increases in blood pressure.

Marrone, et al. (Marrone, et al., 1993) investigated the release of catecholamines in normotensive patients with and without sleep apnea. Ten sleep apnea patients (9 male, 1 female; aged 48.5 $\pm$ 3.6 years) were compared to 12 control subjects (10 male, 2 female; aged 43.8 $\pm$ 3.9 years). All subjects were instructed to collect separate daytime (6 am to 10 pm) and nighttime (10 pm to 6 am) urine samples. The samples were acidified with HCl 6M and stored at -30^0C before analysis. During the night of the urine collection, OSA subjects underwent polysomnography, and blood pressure was continuously monitored. One night later the OSA subjects again underwent polysomnographic study and urine collection, with the addition of CPAP to prevent apneic episodes. Urine samples were purified with alumina and analyzed through HPLC.

Without CPAP, the systolic blood pressure decreased during the apneic episodes and increased sharply at arousal. With the CPAP device, fluctuations in blood pressure were eliminated ($p<0.01$). The subjects with sleep apnea had significantly higher levels of norepinephrine excretion during the day (75 μg/g creatinine vs. 40 μg/g creatinine; $p<0.001$) and night (55 μg/g creatinine vs. 20 μg/g creatinine; $p<0.001$). Similar results were seen with the excretion of epinephrine (12 μg/g creatinine vs. 7 μg/g creatinine; $p<0.05$ day and 11 μg/g creatinine vs. 4 μg/g creatinine; $p<0.001$ night). Levels of epinephrine excretion significantly decreased during the night collection in normal subjects (-3.6 μg/g creatinine; $p<0.025$), but not in OSA subjects. Epinephrine excretion did however significantly ($p<0.002$) decrease in OSA subjects at night during CPAP application. The study showed that catecholamine excretion levels were higher in OSA

patients than normal controls. This may be due in part to consistently elevated sympathetic activity. The authors concluded that OSA is associated with steadily increased sympathetic tone over a 24-hour period.

Garcia-Río, et al. (Garcia-Rio, et al., 2000) performed a study to examine central inspiratory drive and to determine the relationship between OSA and catecholamine excretion. Twenty-four OSA patients (22 male, 2 female) and 11 control subjects (9 male, 2 female) were included in the study. All subjects were asked not to eat for 4 hours before the study and refrain from using coffee, tea, and alcohol for $\geq$12 hours before the study. Blood pressure was monitored at 30-minute intervals over a 24-hour period. The OSA subjects were then classified according to their systolic (SBP) and diastolic (DBP) blood pressure (Type 1 = SBP <140 mmHg, DBP <90mmHg; Type 2 = progressive blood pressure elevation from the onset of sleep to the early morning; Type 3 = SBP $\geq$140 mmHg, DBP $\geq$90 mmHg). Urine samples were collected and separated according to day (7 am to 11 pm) and night (11 pm to 7 am) hours. The samples were then analyzed for catecholamines using HPLC and reported in terms of micrograms per gram of creatinine. All subjects underwent polysomnographic study during the same night as the urine collection.

After the 24-hour blood pressure monitoring, 10 patients were classified as type 1, 8 as type 2, and 6 as type 3. Apnea-hypopnea index was significantly higher in the OSA patients than controls (37.5 $\pm$ 27.9 type 1, 39.2 $\pm$ 18.2 type 2, 45.7 $\pm$ 26.7 type 3 vs. 2.4 $\pm$ 1.7; $p<0.01$). There was no significant difference in diurnal catecholamine levels across any group. However, those designated as type 2 and type 3 had a significantly higher level of nocturnal epinephrine than controls (3.5 $\pm$ 1.3 type 2, 3.8 $\pm$ 1.4 type 3 vs. 1.1 $\pm$

1.2; $p<0.05$). The authors concluded that there is a suggested relationship between peripheral chemosensitivity and nocturnal epinephrine levels, and that this relationship might serve a mediating role in OSA.

In 1999, Loredo, et al (Loredo, et al., 1999) performed a study the effects of arousals on sympathetic nervous system tone. Sixty-seven subjects (55 male, 12 female; aged 35 to 60 years) participated in the study. Of these, 24 were considered normal, 17 apneic (AHI >20), 11 hypertensive (SBP >140 mmHg and/or DBP >90 mmHg), and 15 apneic hypertensive. Subjects were admitted to the research center and immediately placed on an isocaloric diet containing 170 mEq Na^+ and 100 mEq K^+ per day. Subjects underwent polysomnographic study for two consecutive nights. Blood pressure was measured every two hours on both nights. On night 2, venous blood samples were taken hourly and centrifuged, with the plasma stored at -80^0C until analysis. Plasma norepinephrine was measured using radioenzymatic assay. On day 2, urine was collected in day (6 am to 6 pm) and night (6 pm to 6 am) samples and analyzed for norepinephrine by radioenzymatic assay.

Results indicated that apneic subjects had higher mean plasma NE than non-apneic subjects (0.470 ng/ml vs. 0.369 ng/ml; $p=0.001$). Apneic subjects also had higher 24-hour urinary norepinephrine levels (36.2 ng/ml vs. 26.0 ng/ml; $p=0.001$). Mean resting diastolic blood pressure was also related to the number of arousals from sleep ($r=0.39$; $p=0.001$). The authors concluded that the number of arousals was related to increases in plasma and urinary norepinephrine levels and may influence daytime sympathetic tone independently of RDI and nighttime saturation.

CATACHOLAMINES AND HEART RATE VARIABILITY

HRV has been projected as a non-invasive alternative to assessing sympathetic activity in humans. It has yet to be determined whether this speculation is accurate, and whether HRV is correlated to known sympathetic nervous system activity markers, such as catecholamine levels.

Kingwell, et al. (Kingwell, et al., 1994) performed a study to compare HRV to other measures of sympathetic activity such as microneurography and measurement of norepinephrine spillover. Three groups of individuals were studied against age-matched control groups drawn from a pool of 52 healthy volunteers. Group one were patients with pure autonomic failure (2 male, 2 female, aged 62 $\pm$ 6 years). Group two were orthotopic cardiac transplant recipients treated no less than 18 months previously (9 patients, aged 50 $\pm$ 3 years, matched with 30 controls). Group 3 were cardiac failure patients (10 male, 5 female, aged 49 $\pm$ 2.7 years) who were compared to the same 30 controls as group 2. HRV analysis was recorded from a 20-minute continuous ECG. The ECG was broken down into 128-beat intervals and combined into 15, 256-beat segments which overlapped by half. The frequency components were expressed as total power. Cardiac norepinephrine (NE) spillover was calculated by continuous intravenous infusion using a radiotracer and calculated by the equation $[(NE_{cs} - NE_A)+(NE_A \times NE_{EX})] \times CSPF$ where NE_{CS} is plasma NE concentration, NE_A is arterial NE concentration, NE_{EX} is the fractional extraction of titrated NE in passage through the heart, and CSPF is coronary sinus plasma flow. Microneurography was recorded from the peroneal nerve posterior to the fibula using a tungsten microelectrode. Nerve activity was analyzed manually and recorded as bursts per minute.

The patients with pure autonomic failure had significantly lower NE spillover than controls (1.2 $\pm$ 0.9 vs. 22.7 $\pm$ 3.2 ng/min; $p<0.05$). HRV in these individuals was negligible, although there were respiratory components as indicated by the power spectrum. Cardiac transplantation patients also had significantly lower NE spillover (1.9 $\pm$ 3.1 vs. 23 $\pm$ 3 ng/min; $p<0.05$) than controls. These individuals had significantly lower HRV than normals (total power, 29 $\pm$ 11 vs. 1673 $\pm$ 516 ms^2, $p<0.05$). Cardiac failure patients had a NE spillover level 2-3 times that of normals (59 $\pm$ 14 vs. 18 $\pm$ 3 ng/min, $p<0.05$). In contrast, HRV total power was significantly lower (243 $\pm$ 44 vs. 49 $\pm$17 ms^2; $p<0.05$) in cardiac failure patients. The authors concluded that there is no relationship between cardiac NE spillover rate and HRV. However, the authors indicated that HRV compliments other methods and may allow a more comprehensive assessment of neural functioning when used in conjunction with microneurography and cardiac spillover measurements.

EXERCISE AND OBSTRUCTIVE SLEEP APNEA

It is expected that people who exercise will have better sleep cycles. Exercise as an effective treatment option for those suffering from OSA has yet to be shown. It is unknown whether exercise capacity in OSA patients is reduced due to the disease, or whether a lack of activity contributes to the severity of OSA. The effects of acute exercise as well as exercise training have been examined, with mixed results.

Norman, et al. (Norman, et al., 2000) examined the effects of exercise training and weight loss on physical and subjective measures associated with OSA. Nine subjects volunteered for the study. All subjects underwent polysomnographic testing including

apnea-hypopnea index (AHI), total sleep time, sleep efficiency, number of awakenings/hour, arousals/hour, and apnea index before and after a six-month training regimen. Anthropometric measurements were also assessed before and after training. The subjects were given questionnaires including the Health Status Questionnaire, Profile of Mood Status, and Epworth Sleepiness Scale.

Results indicated that there was a significant ($p=0.002$) decrease in AHI from before to after training. There were also significant ($p<0.05$) improvements in total sleep time, sleep efficiency, number of awakenings/hour, arousals/hour, and apnea index. Significant decreases were observed in weight (mean –6.2 kg, $p<0.001$), and body mass (mean –1.6, $p<0.001$). When the Health Status Questionnaire, Profile of Mood Status, and Epworth Sleepiness Scale were analyzed, subject showed increases within sections dealing with health status, affective state, and a decrease in the section dealing with daytime somnolence. Aerobic capacity, body mass index, and quality of life indicators also had positive improvements. The authors concluded that while there were positive results, exercise training alone was not an adequate intervention strategy for most individuals but may serve as an adjunct treatment strategy for those individuals with mild to moderate OSA.

Shifflett, et al. (Shifflett DE, 2001) measured the effects of 4 weeks of CPAP therapy on exercise performance in OSA patients. Subjects were nine volunteer patients (8 male, 1 female, aged 37-74 years) referred for polysomnography (PSG) testing. Subjects were excluded for cardiovascular complications, orthopedic disabilities, or recent participation in moderately vigorous physical activity. Each subject underwent PSG testing to confirm the presence of OSA. Before treatment, all subjects performed a

cycle ergometer test, using a ramp protocol designed to achieve 75% of VO_2max in 17 $\pm$ 2 minutes. The subjects performed the same test 7 days later, and a third test after 4 weeks of CPAP therapy. Respiratory gas exchange, electrocardiograph, blood pressure, rating of perceived exertion (RPE), and heart rate were monitored.

Results indicated that after treatment, heart rates at 60% of the subject's age-adjusted maximum were significantly lower (-10.2 beats/min, p=0.043). Heart rate and systolic blood pressure at rest were not different after training. RPE was significantly lower after training for similar workloads (p=0.04). In addition, individuals with the worst scores on the PSG tests (and therefore the most severe disease) showed the greatest reduction in RPE at similar workloads after training. The authors concluded that 4 weeks of CPAP therapy significantly increases aerobic fitness, as well as improved patient perception of sleep quality and physical vitality.

EXERCISE AND HEART RATE VARIABILITY

It has been proposed that HRV is affected by aerobic exercise and that those who exercise regularly show a greater influence of the parasympathetic nervous system. These individuals have greater autonomic tone and may slow the influence of aging on HRV. The exact mechanism of action relating exercise to HRV has yet to be determined, but exercise continues to show direct relationships to increased quality of life and increased autonomic functioning.

Migliaro et al. (Migliaro, et al., 2001) performed a study to analyze the relationship between age, sedentary lifestyle, and HRV. Thirty-four healthy volunteers were divided into two groups. Group one consisted of 18 young subjects (12 men, 6

female, aged 15-20 years). Nine of the volunteers from group 1 (6 men, 3 women) performed physical activity at least five days per week and were considered non-sedentary young subjects. Group two consisted of 16 elderly sedentary subjects (2 men, 14 women, aged 39-82 years). HRV was analyzed from a 10-15 minute sampling using a standard electrocardiographic recorder. All tests were performed between 10am and 1pm, more than 2 hours since ingestion of food. Each subject in group one underwent a cycle ergometer test following HRV analysis to determine training rank. Tests were begun at a level of 50 watts (with an increase of 50 watts every 3 minutes) and continued until muscular fatigue or until maximal heart rate was achieved. Group two did not perform the stress test.

Results showed that high frequency (1418 vs. 334 ms^2/hz; p=0.0009) and low frequency (1892 vs. 467 ms^2/hz; p=0.0018) components were significantly higher in the young subjects. The non-sedentary young subjects reached a significantly higher workload (1266.7 vs. 866.7 watts; p=0.0001) than the sedentary subjects. However, there were no significant differences in HRV between sedentary and non-sedentary subjects. Resting heart rate was negatively correlated with HRV in group 1 (r = -0.68; p=0.002 vs. high frequency component; r = -0.54; p=0.02 vs. low frequency component) and group 2 (r = -0.67; p=0.004 vs. high frequency component; r = -0.66; p=0.005 vs. low frequency component). The authors concluded that age and HR are the most powerful determinants of HRV.

Levy et al. (Levy, et al., 1998) examined whether exercise training would affect the reduced HRV experienced with aging. The subjects were 13 older (mean age 68 years) and 11 younger (mean age 28 years) male volunteers. All subjects were healthy

with no contraindications, as evaluated by echocardiogram, Bruce protocol maximal exercise tests, and thallium imaging in the older subjects. All subjects underwent a six-month supervised training program consisting of 45 minutes of aerobic exercise 4-5 times per week. The training began at 50-60% of heart rate reserve and increased to 80-85% of heart rate reserve by the fourth month. Before the study and after the 6-month training, subjects performed a cycle ergometer protocol consisting of increases every 3 minutes. HRV was taken during the final 2 minutes of each stage.

Before exercise training all subjects had similar resting heart rates. However, HRV was significantly ($p=0.0002$) lower in the older subjects than the younger subjects (31 ± 2 and 58 ± 4 ms, respectively). During the exercise tests, both groups showed decreases in HRV. At peak exercise the older group had a higher HRV (17 ± 3 vs. 9 ± 1 ms, $p=0.02$). All subjects showed a significant increase in resting ($p = 0.009$), submax ($p=0.001$), and maximal ($p=0.005$) HRV after the training program. The exercise program increased maximal oxygen consumption significantly in both groups (21% older, 17% younger, $p=0.0001$). There was no significant difference in HRV increase between groups after training. The authors concluded that the decrease in heart rate was due to an increase in parasympathetic tone, and that the increases in HRV were more prominent in older subjects.

SUMMARY

The value of HRV in OSA subjects has yet to be determined. It is still unclear as to the extent that OSA may affect the autonomic nervous system. OSA has been shown to be a significant problem as new cases of the disease are diagnosed daily. Recurring

disturbances in the sleep cycle caused by interruptions in airflow leave patients debilitated both physically and mentally. The individual's quality of life is compromised, and in many cases the patient has trouble with normal daily functioning. OSA has been linked to several cardiovascular disorders, including daytime hypertension and congestive heart disease. HRV is a non-invasive assessment tool for autonomic functioning. It is used extensively in diabetic neuropathy, but has not been justified in other cases. HRV has been shown to be lower in OSA patients, and may be an indicator of decreased autonomic tone and an increased risk for cardiovascular mortality. Breathing abnormalities may affect the ability to control HRV, although the mechanism has not been established. OSA patients often show not only a decrease in HRV in the time domain, but also an increase in low frequency components of HRV in the frequency domain. This is thought to represent increases in sympathetic nervous system output, which changes the balance in the autonomic system. This decrease in balanced autonomic functioning can be demonstrated through the assessment of biochemical neural markers. Catecholamine analysis has been an accepted means of loosely assessing sympathetic and parasympathetic activity. OSA patients often show an increase in both urinary and plasma epinephrine and norepinephrine levels. There is also an increase in sympathetic nerve activity when measured by microelectrode directly on the peroneal nerve. These increases represent an increase in the sympathetic nervous system activity. This increase in activity in turn could contribute to the increase in daytime blood pressure often found in OSA patients. Catecholamines have been shown to be an important factor when analyzing HRV as well. Indicators of increased sympathetic functioning can be reinforced through increases in catecholamine output. HRV has been shown to be a

valuable addition when attempting to ascertain a complete representation of nervous system status. The value of exercise and overall fitness in the treatment of OSA has long been debated. Exercise has been shown to increase quality of life in individuals with OSA. The relationship between exercise, fitness level, and severity of OSA has yet to be determined. However, exercise has been established as a valuable tool when used in conjunction with traditional treatments for OSA. Exercise has also been shown to increase HRV measurements and perhaps enhance neural functioning. Studies indicate that exercise can retard decreases in HRV seen with aging, and may contribute to increases in autonomic tone and control. While the exact mechanisms have not been determined, it appears HRV may be a valuable tool in assessing patients with OSA. In addition, exercise training in OSA patients may provide a valuable treatment alternative while increasing individual's daily functioning and quality of life.

CHAPTER III – JOURNAL MANUSCRIPT

Relating HRV, Urinary Catecholamines, and Baseline Fitness to Respiratory Distress Index and Severity of Disease in Obstructive Sleep Apnea Patients

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ABSTRACT

Heart Rate Variability (HRV) currently is utilized when assessing the risk of mortality in individuals suffering from coronary heart disease or diabetic neuropathy. Research has shown that patients with Obstructive Sleep Apnea (OSA) also show a decrease in HRV, as well as an increase in sympathetic drive characterized by an increase in the low-frequency component of HRV. HRV, in conjunction with other indicators, may represent a non-invasive, low cost method for the confirmation of severity of OSA in some patients and therefore may represent an additional tool for the assessment of risk in these individuals. This becomes especially true when urinary catecholamines, fitness level, and quality of life (QOL) assessment are included. **Purpose:** The purpose of this study was to determine if a correlation exists between severity of OSA as assessed by respiratory distress index (RDI) and the selected measures HRV, fitness, QOL, and catecholamine output. **Methods:** Subjects were 6 men and 5 women who were recently diagnosed with OSA by polysomnographic (PSG) study. HRV and blood pressure was measured during two consecutive trials consisting of 512 heartbeats. Catecholamines levels were determined by HPLC following 24-hour urine collection. Fitness levels were established following cycle ergometer testing and QOL following questionnaire completion. **Results:** Subjects with lower weight, BMI, and neck circumference had significantly higher parasympathetic influence as analyzed through the amount of high frequency component of HRV ($r = .738, .726, .789$, respectively; $p<0.05$). Respiratory distress index (RDI) was negatively related to the average heart rate (HR=RR average, $r = -.610$, $p<0.05$), while the amount of total sleep ($r = .657$, $p<0.05$) and REM sleep ($r = .739$, $p<0.01$) increased as HR increased. The average HR was correlated to the predicted VO_2max ($r = .677$, $p<0.05$). When the frequency components of HRV, fitness, QOL, and catecholamines were combined, the association to RDI increased dramatically ($r = .984$, $p = .02$). The results indicate that as the severity of OSA increases, markers of fitness, QOL, and sleep decrease. There is also an inverse relationship between autonomic function and severity of OSA. **Conclusions:** It is concluded that HRV and fitness levels are inversely related to the severity of OSA, and that these measures may be developed into a risk assessment tool for use in OSA patient evaluation.

Keywords: Heart Rate Variability, Catecholamines, Obstructive Sleep Apnea, Polysomnography

BACKGROUND

Research has shown that Obstructive Sleep Apnea (OSA) patients show an overall decrease in HRV (1-3). Patients with OSA also typically show an increase in the sympathetic nervous system activity both while awake and asleep. Decreases in HRV have been associated with increased risk of mortality in patients with coronary heart disease and diabetic neuropathy (4-6). Increases in sympathetic activity in OSA patients has been shown to contribute to daytime hypertension through increases in circulating catecholamines as well as decreases in baroreceptor sensitivity (7, 8). OSA patients have an increased risk of the development of various cardiovascular conditions, including hypertension, congestive heart failure, and ischemic heart disease (9). Changes in autonomic nervous system function could contribute to the increased risk of cardiovascular complications. Assessment of autonomic function through HRV has been shown previously to be a useful tool in the diagnosis of OSA (10). However, whether the amount of changes in HRV parallel severity of disease has yet to be determined. Currently, OSA patients are diagnosed through overnight polysomnography (PSG) study. Using HRV to determine not only the presence of OSA but also the level of severity of disease would provide physicians with a low-cost alternative to the PSG study. In addition to a decrease in autonomic function, limited studies have shown that OSA patients experience an increase in exercise capacity following treatment (11-14). Patients often rate themselves as having low physical functioning due to the disease state. Measures of physical fitness may help explain the relationship between HRV and OSA, and may aid in the development of an early screening tool for risk of OSA. The purpose of the current study was to determine the relationship between HRV, fitness, urinary

catecholamines, PSG results, and disease severity as assessed by respiratory distress index (RDI). A secondary purpose was to determine if combined measures from each physiological area would result in a predictor of disease severity.

METHODS

Subjects: Volunteers were solicited following overnight PSG study after being referred for possible presence of OSA. Each potential subject was informed of the risks and benefits of the protocol. Subjects were excluded if their PSG results showed no sign of OSA. Subjects were also excluded if they possessed other underlying disease. Eleven subjects (6 males, 5 females) volunteered for the study. Characteristics of the subjects are given in Table 1.

Anthropometric Measurements: Before the trial, each subject was measured for height and weight. From these measurements body mass index (BMI) was determined. Neck circumference, waist circumference, hip circumference, and waist to hip ratio were also measured (Table 1).

Heart Rate Variability Measurement: Subjects were instructed to assume the prone position on a medical assessment table. All HRV measurements were recorded using the *Schiller AT-10*™. Patients were connected to a 12-lead electrocardiograph, which monitored heart rate, ECG, and beat-to-beat variability. Each subject was instructed to remain in the prone position, eyes open, during the each trial. To minimize respiratory influences on HRV, breathing was regulated using audio cues. The subjects listened to a taped metronome through headphones during each trial. The subjects were instructed to breathe in a rhythmic manner following the cues at a rate determined to be 12 breaths/minute. Subjects were acclimated before each trial through a 5-minute rest

period. During this period the subjects assumed the testing position and regulated their breathing through the audio cues. Once acclimated, 512 consecutive heartbeats were recorded and analyzed for HRV. Blood pressure was measured in the supine position by a trained technician at the end of the trial. Following completion of the first trial each subject rose to the standing position for a period of 5-minutes to simulate pre-trial conditions. To ensure accuracy, the subject then repeated the trial, including the 5-minute supine rest period.

Urinary Catecholamines: Each subject was given containers to collect 24-h urine output. Once collected, urine was pooled and total volume was determined. Approximately 100ml was then extracted from the total sample and frozen at $-40^{O}C$ for later analysis. Once all samples were collected, they were thawed and centrifuged for 20 minutes at 4000 RPM. Samples were then analyzed for creatinine coefficient using following methods outlined earlier. For catecholamine analysis, the samples were prepared by washing with silica and filtering through YMT ultrafiltration membranes (Amicon, Inc., Beverly, MA) before catecholamine analysis. Samples were then washed with alumina and analyzed using a *Beckman Gold* model HPLC system and column, following methods published previously (15).

Exercise Test Data: All tests were supervised by a physician as well as an American College of Sports Medicine (ACSM) Certified Exercise Specialist. Subjects performed exercise testing on a cycle ergometer (*Medgraphics, CardioO$_2$*) using a step-wise protocol. Initial workload was 25 watts (W) with increases every 90 seconds of either 12,17, or 22 watts dependent upon the subject's bodyweight and activity habits. Blood pressure was measured by standard mercury sphygmomanometer and stethoscope every 2

minutes, and heart rate was recorded continuously using the *Schiller AT-10*. Exercise continued until the subject reached a rating of perceived exertion (RPE) of 17 on a 20 point scale, voluntary termination, or other termination criteria as outlined in the ACSM *Guidelines for Testing and Prescription* (16). Heart rate vs. workload plots were generated from which PWC_{150} (W) was calculated and then converted to kgm/min. VO_2150 was calculated using the equation published by Myers (17):

VO_2 (ml/min) = work rate (kgm/min) x 2 ml/kgm + resting metabolic rate (ml/min)

Predicted VO_2max was calculated using the Astrand-Rhyming method (18).

Quality of Life: All subjects completed the Veterans Specific Activity Questionnaire (VSAQ) questionnaire to assess their basic fitness level and the SF-36 questionnaire to assess their quality of life (SF-36). These questionnaires were analyzed against all data to determine of a perceived quality of life change existed.

Polysomnography: PSG results were obtained following the overnight trial at the Southwest Virginia Sleep Disorders Center by a trained technician. Subjects underwent overnight PSG testing before performance of the exercise trial and HRV analysis. PSG testing included electroencephalography (EEG), electroculography (EOG), and electromyography (EMG). Results included respiratory distress index (RDI), time asleep, time awake, stages of sleep, and percentage of oxygen saturation (O_2 Sat) in the blood.

Statistics: All results were analyzed using SPSS Version 10.0 statistical software. Pearson correlations and repeated measures ANOVA were calculated, and a statistical significance level was established at $p<0.05$.

RESULTS

Anthropometric Measures: Neck circumference was significantly related to resting heart rate and diastolic blood pressure ($r = .779$, $p = 0.005$; $r = .765$, $p = 0.006$, respectively). Weight, BMI, and neck circumference were all negatively correlated ($p<0.05$) to inter-beat average (Heart rate = RR average, $r = -.638$, $-.672$, $-.695$, respectively). The same anthropometric measures were correlated to HRV in the frequency domain (see Figure 1).

Heart Rate Variability Related to Polysomnography Measures: Respiratory distress index (RDI) was negatively correlated to the HR ($r = -.610$, $p<0.05$, Figure 2). In addition, RDI was related to the amount of the very low frequency component of HRV ($r = .757$, $p<0.01$) and urinary norepinephrine ($r = .822$, $p<0.01$). Average values for urinary analysis were not outside the normal range for most subjects (Table 2) Total sleep time and REM sleep time increased as RR average increased ($r = .657$, $p<0.05$, $r = .739$, $p<0.01$, respectively). In the frequency domain, REM sleep time increased significantly ($r = .626$, $p<0.05$) as the high frequency component increased, and decreased as the percentage of very low frequency component increased ($r = -.641$, $p<0.05$).

Fitness Assessment and Questionnaire Measures: The fitness test results were not correlated to HRV or the polysomnography tests. The physical functioning section of the SF-36 questionnaire was negatively related to the RR interval ($r = -.776$, $p<0.05$). In addition, the physical functioning section was correlated with the role-physical section of the same questionnaire ($r = .814$, $p=0.026$). Predicted VO_2 Max was correlated to dRR average ($r = .677$, $p<0.05$). VO_2150 was inversely correlated to the normalized low frequency component ($r = -.615$, $p<0.05$).

ANOVA Analysis: There was a significant correlation when RDI was compared to standard markers from each category, including BMI, VSAQ, LF component, predicted VO_2max, and norepinephrine output. The analysis showed a combined correlation of r = .984, R^2 = .967, p=0.019. When analysis was run using the same variables, but substituting a time domain variable for HRV (RR average), the correlation was r = .981, R^2 = .962, p=0.024.

DISCUSSION

The relationship between Obstructive Sleep Apnea, autonomic function, and overall fitness has yet to be established. The current study was designed to determine the connection between the disease state and the physiological determinants of fitness and nervous system regulation. A secondary purpose was to assess how the patients viewed their own physical ability and quality of life. Not only was the study designed to assess each area separately, but to be able to combine standard variables and assess their validity as a predictor of disease severity.

As would be expected, increases in neck circumference, weight, and BMI resulted in a significant relationship to resting heart rate and diastolic blood pressure. Additionally, as these same indicators increased, the average RR interval decreased. It has been shown previously that individuals with lower fitness levels have lower HRV (19, 20). These individuals also have a decrease in the parasympathetic component of HRV, and an increase in sympathetic drive (21). This was demonstrated by a decrease in the high frequency component and an increase in the percentage of very low frequency component as weight, BMI, and neck circumference increased. Those individuals are

most likely less active and may have a reduced ability to regulate the balance between the sympathetic and parasympathetic nervous system.

Respiratory Distress Index (RDI) is often used as the determinant of disease severity in OSA. Individuals suffering with sleep apnea have been shown to have a lower overall HRV and an increase in sympathetic drive (22, 23). In addition, reductions in the very low frequency component of HRV have been shown following prosthetic mandibular advancement in OSA patients (24). It would follow that severity of disease should be related to HRV and it's spectral components. The results of the current study agree with these findings. RDI was inversely related to overall HRV, the individual with the highest RDI had 17% lower HRV than the subject with the lowest RDI. In addition, the low frequency component of the spectral analysis was significantly related to RDI, increasing as RDI increased. As the low frequency component is associated with sympathetic nervous system influence, it stands to reason that as the severity of disease increases, the autonomic balance is shifted towards sympathetic dominance. It is yet to be determined whether this shift is due to a lack of parasympathetic tone, or an increase in sympathetic drive as reported previously (25). In the current study, increases in sympathetic activity are further reinforced by the increase in urinary norepinephrine. Increases were correlated ($p<0.01$) to increases in RDI. However, most subjects were within normal ranges for urinary catecholamine content. It is possible that individuals with mild sleep apnea do not show as great an increase in catecholamine output. RDI was not correlated to anthropometric measures. Therefore, the decreases in HRV and increase in sympathetic nervous system influence can be viewed as being influenced greatly by the disease state rather than fitness levels alone.

Surprisingly, fitness levels were not highly correlated with HRV or disease status in the current study. However, the amount of low frequency component of HRV (in normalized units) was inversely correlated to $VO_2$150 ($p<0.05$). In addition, predicted VO_2max was correlated to the variation between individual heartbeats (dRR average, $p<0.05$). It has been shown that aerobic fitness is positively correlated with HRV and therefore it stands to reason that as HRV increases, so should overall fitness.

Psychological changes that may occur in the sleep apnea patient are also a strong consideration. How a person perceives their lifestyle and health can influence their motivation for treatment. In the current study individuals who rated themselves lower on the physical functioning section of the SF-36 questionnaire also had lower overall HRV ($p<0.05$). In addition, these individuals also had lower scores on the role-physical section of the SF-36 questionnaire. As these results were not significantly correlated to exercise test results or disease severity, it may be that the debilitating nature of OSA reduces individual's view of their quality of life.

Combining indices from each area (HRV, catecholamines, fitness, anthropometric measures, and quality of life perception) could yield significant insight into the overall link between health and severity OSA. There was a significant correlation between these indices and the severity of disease as measured by RDI. As more data is collected, the possibility exists for the development of a standard testing procedure and scale that may help determine the severity of disease and risk for mortality. The current data suggest that as severity of OSA increases, sympathetic drive increases and fitness level decreases. In addition, the perception of health and ability decreases as disease severity increases. These measures may be used in the clinical setting as a low-cost, non-invasive diagnostic

tool to assess a candidate's chances of having a high RDI. This in turn would increase efficiency in the clinical setting by allowing physicians to refer only those patients with a high risk for additional study by polysomnography.

Although RDI has been used extensively as the marker of disease severity, it may not be the definitive marker of autonomic function. Recent studies have shown that the repeated physiologic exposure to hypoxemic conditions may play a role in the increase in sympathetic drive. In the current study there was no relationship between the amount of time that SaO_2 was below 90% and sympathetic drive. However, the measure of oxygen saturation is based upon measurements in COPD patients and therefore may not represent an accurate level to determine effects on physiologic function. More research is needed to determine the level at which decreases in oxygen saturation result in changes in autonomic function.

The main drawback of the study is in the relatively limited population sample. As only volunteers were chosen for the study, they may not be representative of the OSA population as a whole. Patients were also unfamiliar with the testing procedures, which may have resulted in varied measurements. There were teaching sessions before the data collection, where extensive explanation was relayed concerning the study protocol. However, many subjects struggled with the protocol until they became acclimated to the equipment. The fitness assessment was also performed only once, and was assumed to be representative of the individuals overall fitness level. Catecholamine analysis was performed after 24-hour urine collection, and it was assumed that this period represented the normal dietary and lifestyle habits of the individuals. Other methods could include a 2-day collection to ensure normal status. Plasma measures could also be used, but would

require multiple blood draws in approximately 2-hour increments over the time period to ensure that the average 24-hour status could be assessed, rather than an instantaneous picture of sympathetic function.

The results of the current study indicate the relationship between OSA, fitness, and autonomic function. Further research should be performed to establish the link between OSA and changes in central nervous system function. It should also be determined whether baseline fitness level reduces the change in sympathetic drive in OSA patients. Fitness training is also becoming more prevalent as a treatment option for those individuals suffering with OSA. It may be shown that fitness training can help reduce changes in autonomic function that could increase risk of cardiovascular complications.

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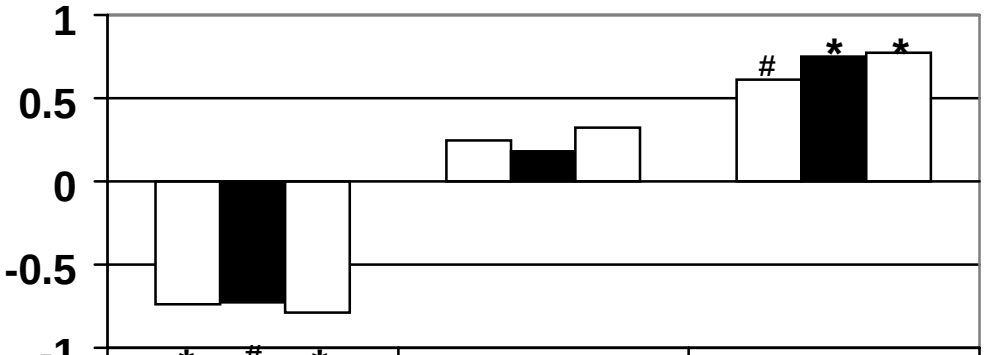
TABLE 1 – PHYSICAL CHARACTERISTICS AND POLYSOMNOGRAPHIC RESULTS

PHYSICAL MEASURES	MEAN	STDEV	RANGE
AGE (years)	45.3	11.7	28-66
HEIGHT (inches)	66.8	4.0	61-74
WEIGHT (kilograms)	102.9	20.8	68-143
BODY MASS INDEX (kg/m^2)	35.8	6.3	25-47
WAIST CIRCUMFERENCE (cm)	112.3	13.8	96-145
HIP CIRCUMFERENCE (cm)	119.8	9.3	105-131
WAIST/HIP RATIO	0.9	0.1	0.8-1.1
NECK CIRCUMFERENCE (cm)	41.2	5.1	31-49
RDI	30.8	30.5	11-120
TIME IN BED (min)	324.5	96.7	93-379
TOTAL SLEEP TIME (min)	263.8	81.6	77-348
AWAKE (min)	41.9	36.1	5-115
STAGE 1 SLEEP (min)	11.1	5.6	3-21
STAGE 2 SLEEP (min)	175.3	55.0	72-267
SLOW WAVE SLEEP	39.6	42.8	0-137
REM SLEEP (min)	36.3	26.9	0-77
BASELINE SaO_2	96.9	1.9	93-99
LOWEST SaO_2	84.1	8.4	63-96
TIME SaO_2 <89%	21.0	36.9	0-99



	HF	LF %	VLF %
□ Weight	-0.738	0.245	0.613
■ BMI	-0.726	0.179	0.749
□ Neck Circ	-0.789	0.322	0.774

 # = p<0.05
**** = p<0.01***

Figure 1 – Correlations (r-values) of Anthropometric Measures to HRV in the Frequency Domain

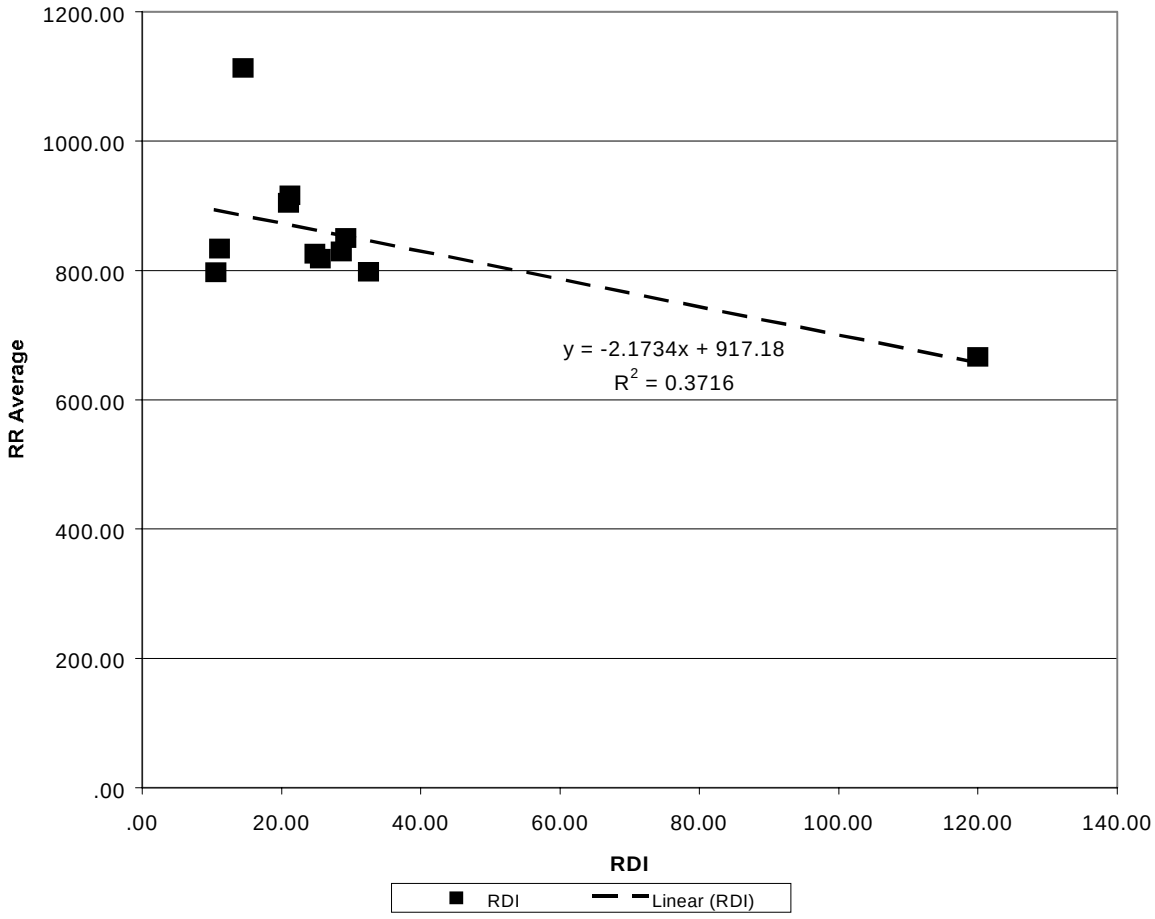


Figure 2 – Respiratory Distress Index vs. Mean Heart Rate (RR Average)

TABLE 2 – URINARY CATECHOLAMINE ANALYSIS AND NORMAL RANGES (N = 9)

CATECHOLAMINE MEASURE	MEAN	STDEV	RANGE	NORMAL RANGE
Epinephrine (ng/ml)	27.5	26.8	1.2 – 77.8	N/A
Epinephrine (μg/g creatinine)	15.4	11.5	1.2 – 35.1	0 - 20
Epinephrine (μg/day)	37.8	32.0	4.1 – 97.3	0 - 25
Norepinephrine (ng/ml)	44.6	37.5	0.9 – 90.8	N/A
Norepinephrine (μg/g creatinine)	33.9	31.3	2.4 - 107.3	0 – 45
Norepinephrine (μg/day)	68.0	59.3	3.6 – 172.2	0 - 100
Creatinine Excreted (mg/24 hrs)	2345.5	956.6	1335 - 4050	600 - 1800

CHAPTER 4 – SUMMARY, CLINICAL IMPLICATIONS, AND FUTURE RESEARCH

SUMMARY

The purpose of the current study was to relate Heart Rate Variability (HRV), fitness levels, and urinary catecholamine excretion, to respiratory distress index (RDI) and severity of disease in Obstructive Sleep Apnea (OSA) patients. Up to 10% of the population may knowingly or unknowingly suffer from OSA. Factors affecting the autonomic nervous system may be linked to cardiovascular complications often associated with OSA. It is important to determine the mechanisms involved in autonomic changes, especially increases in sympathetic drive associated with daytime hypertension, arrhythmic complications, and early cardiac mortality. It is unknown whether changes in the autonomic system are related to the severity of OSA. Also unknown is whether fitness levels in the OSA patient affect the autonomic system to help reduce changes in sympathetic drive, and therefore reduce the risk of cardiovascular complications.

The current study showed that severity of disease is correlated with overall HRV in OSA patients. Previous studies have reported that individuals with OSA have lower HRV time domain measures than normals. However the present study related time domain measures directly to RDI, showing that as disease severity increased, HRV decreased. In addition, HRV frequency domain measures also correlated with disease severity. As the RDI increased, the low-frequency component of the spectral analysis also increased. This reinforces previous studies, which have reported an increase in sympathetic nervous system drive in those with OSA. This increase is of clinical significance as it may predispose these individuals to such conditions as increased insulin

resistance, hypertension, and cardiac hypertrophy (Dimsdale, et al., 2000, Salo, et al., 2000, Wiklund, et al., 2000).

Urinary catecholamines are also an effective measure to determine the state of the autonomic nervous system. Increased sympathetic drive is often associated with an increase in the output or urinary catecholamines. OSA patients often show increased catecholamine excretion, and this may contribute to the daytime hypertension often associated with the condition. The present study supported this hypothesis. RDI was correlated to increases in urinary norepinephrine output. This increase also points to increased sympathetic drive. It has been shown that OSA patients have higher levels of norepinephrine release than normals (Marrone, et al., 1993), and that this increase could contribute to sustained hypertension in OSA patients. The present study did not find a higher than normal output of catecholamines. However, the present study did not control for diet or other outside influences that could change the excretion of urinary catecholamines.

Increased aerobic fitness has been repeatedly shown to decrease resting heart rate, blood pressure, and risk of cardiac disease. Typically, OSA occurs in middle-aged obese individuals who may not have an optimum fitness level. To date, there has been no relationship established between fitness level and severity of disease. However, the current study found that as weight, body mass index (BMI), and neck circumference increased, so did RDI. In addition, these same conditions resulted in a decrease in overall HRV and an increase in resting heart rate and diastolic blood pressure. Those individuals with higher VO_2150 levels showed lower amount of low frequency component in the HRV analysis. Other studies have confirmed that aerobic training increases HRV and

decreases sympathetic influence in the frequency domain (Hull, et al., 1994, Kiilavuori, et al., 1995, Leitch, et al., 1997, Levy, et al., 1998). It has not been established if exercise training in OSA results in a reduced increase in sympathetic drive, or a reduction in RDI. In the present study, those individuals with reduced HRV also had lower scores on the physical functioning section of the SF-36 questionnaire. Although this was not related to measured fitness values, the subjects scored themselves lower and perceived themselves as having a lower quality of life due to the effects of OSA. Increases in cardiac fitness may increase autonomic control and help return the balance between the parasympathetic and sympathetic systems. Increasing fitness may also help subjects with better sleep, decreased weight and BMI, decreased risk for cardiovascular complications, and increased quality of life.

CLINICAL IMPLICATIONS

In the clinical setting, it is increasingly important for physicians, technologists, and other staff to be able to recognize the possibility of OSA in undiagnosed individuals. These individuals have been shown to have twice the medical costs of aged-matched controls (Kapur, et al., 1999). Physical characteristics that have been shown to be associated with OSA include obesity and witnessed nocturnal choking (Friedman, et al., 1999, Phillips, et al., 1999, Redline and Strohl, 1998). The current study suggests that a relatively low cost screening including HRV, fitness assessment, BMI, catecholamine analysis, and quality of life assessment may provide a strong link to identifying patients with elevated RDI levels. This would allow clinicians to more accurately determine whether a patient is at risk for OSA and should be referred for follow-up

polysomnographic study. It may also assist the sleep specialists in determining the severity of OSA and inherent risk for further cardiovascular and autonomic complications in the future. The current evidence further solidifies the concept that OSA patients have reduced autonomic control. As exercise has been shown to increase HRV and autonomic control, it follows that exercise may continue to evolve as a cost-effective options to OSA patients in addition to conventional treatment. More research is needed to further define the relationships between these variables and OSA, as well as to determine the most appropriate course of action in the clinical setting to benefit the patient.

FUTURE RESEARCH

This study touches on several areas that are worthy of further research. HRV has been shown to be a non-invasive, effective determinant of short-term autonomic functioning. It's validity as an assessment tool in OSA patients has been shown but not widely accepted. The use of exercise as a low-cost treatment or additional assessment technique has also yet to be validated. The following research initiatives could increase the knowledge base and understanding of the links between OSA, HRV, and exercise.

1. It has been reported that HRV may be an effective tool for the screening of OSA (Roche, et al., 1999). However, long-term longitudinal data in this area has not been collected. Both short term and 24-hour recordings of HRV should be made, using a homogenous group and matched controls, to specifically compare time and frequency domain results to polysomnography and other markers of OSA. Along with this data, it should also be determined whether the increase in sympathetic drive in OSA patients is a nocturnal phenomena associated with arousals or if it sustained throughout the day as

well. Studies could focus on daytime versus nighttime collection of urine for catecholamine analysis, to assist in establishing patterns of autonomic functioning. Once data is collected, it could be determined whether those with lower RR average or more sympathetic drive (determined by low frequency component in the frequency domain and increased catecholamine output) have a decrease in sleep quality (such as amount of sleep, REM sleep, etc) or an increase in the severity of OSA.

2. Exercise, as an intervention, has been thought to be of benefit to OSA patients. Weight loss results in less transmural pressure on the esophagus and therefore fewer apneic episodes. Exercise has been shown to increase HRV in normal individuals. Few studies exist regarding the effects of exercise in OSA patients. A long-term study involving exercise, and the role it plays in managing the OSA disease state is necessary. An exercise study could focus on the role fitness plays in the reduction of symptoms correlated with OSA. Groups could include an aerobic training group, who would train exclusively using aerobic equipment at 75-80% of their maximal heart rate, a matched control group, and possibly a weight training group. The weight training group would allow comparison between the modes of exercise, as well as determining whether increasing muscular tone results in a reduction in apneic episodes. Using HRV analysis in these groups would also allow an assessment of autonomic control before and after training. This could show changes in the increase in sympathetic drive shown in OSA patients and may indicate exercise as an effective countermeasure to reductions in HRV. The same comparison could be made using normal and overweight groups as well. Studies of this nature may provide arguments for exercise as an affordable adjunct to current therapeutic procedures.

3. Another possible research opportunity stemming from these results would include long-term analysis to determine if a combination of fitness testing, HRV, biochemical analysis, and quality of life measures could result in a risk-stratification for OSA. The current study establishes a link between these factors, however additional research is needed to confirm the results. Longitudinal data in these areas would possibly allow researchers to establish "normal" values or even a global scoring system based upon standard testing measures. Physicians would then be able to use this global scoring system when assessing patients in the clinical setting. This would perhaps result in earlier detection of the disease state and therefore earlier intervention. Standard measures such as VO_2max, low frequency HRV component or low frequency to high frequency ratio, catecholamine output, and quality of life questionnaires could be combined to establish categories of risk for individuals.

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APPENDIX A

INFORMED CONSENT

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY
Informed Consent for Patients Who Perform

Sleep Lab Study at The Sleep Disorders Network

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

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

I. Purpose of This Research

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

II. Procedures

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

- Allow us to use certain physical and health history information from the medical records available to your doctor at the Sleep Center.

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

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

- Allow us to initially obtain certain physical measurements from you at rest, including your blood pressure, heart rate, and cardiac output.
- Allow us to obtain a 24 hour urine sample immediately before each exercise test in order to measure the ability of your vessels to relax as well as how your nervous system functions.
- Allow us obtain a non-invasive measurement of your heart rate immediately before your exercise test in order to assess the nervous system control of your heart.
- Complete an 8 to 12 minute bicycle test and allow us to obtain your maximal functional capacity, heart rate, blood pressure, cardiac output, and various measurements of your breathing.
- Allow us to measure how much oxygen you use during this exercise. To accomplish this, we will ask you to wear a light-weight rubber mouthpiece and your exhaled air will be sampled from this device so that it can be analyzed by the machine. During

exercise, you will breathe only through your mouthpiece and you may experience some dryness in your mouth. You must also perform several exercise cardiac output measures that require you to slowly exhale in a controlled manner for approximately 5 to 6 seconds. You may experience more difficulty completing this procedure during higher intensities of exercise.

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

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

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

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

III. Extent of Anonymity and Confidentiality

The results of this study will be kept strictly confidential. At not time will the researchers release my results of this study to anyone other than the individuals working on the project without your written consent. The information I provide will have my name removed and only a subject number (excluding social security numbers) will identify me during analyses and written reports of this research.

IV. Risks and Benefits

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

I have been informed that medical personnel qualified to perform CPR and initiate 911 activation are available to deal with unusual situations should these occur. Emergency equipment and defibrillation are available at this facility, and a physician and Registered Nurse will be onsite for all exercise testing. I understand that there is a risk of injury, heart attack, or death as a result of my performance of this test and participation in exercise training but knowing those risks, it is my desire to proceed to take the test and, if chosen, exercise training as herein indicated.

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

V. Compensation

I can expected the following compensation for my participation in the study:

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

VI. Freedom to Withdraw

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

VII. Approval of Research

This research project has been approved, as required, by the Institutional Review Board for projects involving human subjects at Virginia Polytechnic and State University and the Department of Human Nutrition, Foods, and Exercise.

VIII. Subject's Responsibilities

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

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

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

IX. Subject's Permission

If have read and understand the informed consent and conditions of this project. I have read and understand the informed consent and conditions of this research study. I agree to undergo all screening procedures described above prior to acceptance into the study. I

have had all my questions answered. I hereby acknowledge the above and give my voluntary consent for participation in this project.

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

Questions/Response:

_____

_____

_____

_____

_____

Signature: _____ Date: _____

Witness: _____ Date: _____

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

☐ Physician's Name:_____

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

Jennifer Blevins 231-8209
Investigator

Howard Ballentine 951-9612
Investigator

Tom Hurd 231-6077
Chair, IRB, Research Division

William Herbert, Ph.D. 231-6565
Faculty Advisor, Human Nutrition, Foods, & Exercise

APPENDIX B

RECRUITMENT FLYER

VIRGINIA TECH LAB FOR HEALTH & EXERCISE
IN COOPERATION WITH THE SLEEP DISORDERS NETWORK

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

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

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

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

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

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

APPENDIX C

SCREENING QUESTIONNAIRES

PRELIMINARY SCREENING FORM

Medical History:

_____
_____
_____
_____
_____

Risk Factors:

____Lipids ____HBP ____Smoking ____IDDM or NIDDM ____Early Fm. ____Hx. ____Sedentary ____Stress

Other: _____

Current Physical Activity Status:

_____
_____
_____

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

Other: _____

Medications:

Have you taken any medication this morning? _____

What medications do you take/action?

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

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

Sleep:

How well did you sleep last night? _____

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

Baseline Measurements:

Height _____ in _____ cm	Neck circumference _____	Hip circumference _____
Weight_____ lb _____ kg	Waist circumference _____	Abdominal circum _____

MEDICAL AND HEALTH HISTORY

Demographic Information:

Name: _____ Age: _____ Date of Birth: _____
Address: _____
Phone number: Home: _____Work: _____
Person to contact in case of emergency: _____
Relationship: Phone: _____
Primary Care Physician: _____ Phone: _____
Marital Status: _____single _____divorced _____married _____widower
Children: Y N Number living at home:_____

Medical History:

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

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

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

_____
_____

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

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

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

_____
_____

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

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

If "yes" what form of birth control: _____

Date of last menses: _____

Medications:

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

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

Health Habits:

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

If "yes" please describe:

_____
_____

Do you drink caffeinated beverages?	_____	_____
How many cups per day? _____		
Do you drink alcoholic beverages?	_____	_____
How many drinks per week? _____		
Do you smoke cigarettes?	_____	_____
Packs per day: _____		

Exercise Habits:

	Yes	No
Do you engage in regular exercise?	_____	_____

If "yes" please list:

Activity	Frequency (times per week)	Duration (minutes)

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

_____
_____

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

_____
_____

Family History:

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

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

Please sign to indicate the above information is correct:

_____ _____
Print Name Signature

VSAQ

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

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

APPENDIX D

DATA COLLECTION WORKSHEETS

FAX MEMO REQUEST FOR PSG RESULTS

Health and Exercise Science Lab to Allergy and Sleep Disorders Network in Christiansburg:

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

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

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

_____
_____
_____

Tx plan and date of follow-up:

_____
_____
_____

EXERCISE TESTING SHEET
OSA Exercise Testing Data

Name:_____ Baseline / 8 week / 6 month Date: _____
Seat Ht: _____Ramp rate: _____ Age:
F/M
Height: _____cm _____in BMI: _____
Abd circ: _____Waist circ:_____
Weight: _____kg Neck circ:
Hip circ:_____

Resting:

HRV (Supine T-1)		HRV (Supine T-2)		Hemo (Seated)	
dRR:		dRR:		BP (mmHg)	
%VLF		%VLF		HR (bpm)	
%LF		%LF		Q (l/min)	
%HF		%HF			
LF/HF Rat		LF/HF Rat			
BP (mmHg)		BP (mmHg)			
HR (bpm)		HR (bpm)			

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

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

Exercise Time: _____
Reason for termination:

Recovery:

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

Comments:

APPENDIX E

RAW DATA

PSG DATA

SUBJECT	RDI	TIME IN BED (MIN)	TOTAL SLEEP TIME (MIN)	AWAKE (MIN)	STAGE 1 SLEEP TIME (MIN)	STAGE 2 SLEEP TIME (MIN)	SLOW WAVE SLEEP (MIN)	REM SLEEP TIME (MIN)	BASELINE O_2 SATURATION (PERCENT)	LOWEST O_2 SATURATION (PERCENT)	PERCENTAGE OF TIME AT <90% O_2 SATURATION
1	32.5	172.5	151.5	10.5	3	134.5	11.5	2.5	96	88	17.2
2	10.6	356.5	289.5	53.5	16	188.5	52.0	33.0	98	86	0.5
3	28.6	370.5	325	34.5	15	249	5.0	56.0	97	85	2.6
4	29.2	367.5	244.5	115	21	137	38.5	48.0	96	77	12.9
5	14.5	371.5	348	18	11	194.5	65.5	77.0	97	87	1.4
6	11.1	368.0	330	23	6	149.5	137.5	37.0	95	88	0.3
7	25.6	367.0	274	9.5	8	266.5	0.0	0.0	99	84	2.2
8	21.2	362.5	274	52	12.5	157	70.0	34.5	93	82	99.1
9	24.8	362.5	314	43.5	13.5	209	56.0	35.5	99	89	0.3
10	21.0	379.0	274.0	97	13	170.5	0.0	74.0	99	96	0.0
11	120	93.0	77	4.5	3	72	0	2	97	63	90.3

PHYSICAL CHARACTERISTICS

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

HEART RATE VARIABILITY AVERAGE DATA

HEMODYNAMIC DATA

Subject	Heart Rate	SYSTOLIC BLOOD PRESSURE (MMHG)	DIASTOLIC BLOOD PRESSURE (MMHG)
1	75.5	146	79
2	75.5	129	87
3	72.5	111	77
4	70.5	136	89
5	54.0	128	90
6	72.0	130	82
7	73.5	107	74
8	65.5	138	68
9	73.0	111	76
10	66.5	109	72
11	90.0	133	90

TIME DOMAIN DATA

Subject	TACH RR	RR STDEV	RR MNDEV	RR MED	TACH DRR	DRR STDEV	DRR MNDEV	DRR PNN50	RMS STDEV
1	798.0	32.0	25.0	796.0	23.0	20.0	16.0	7.00	30.0
2	797.0	52.0	42.0	796.0	18.0	16.0	11.0	2.00	24.0
3	829.0	34.0	25.0	831.0	16.0	15.0	11.0	3.00	22.0
4	850.0	46.0	33.0	845.0	15.0	16.0	11.0	3.00	21.0
5	1113.0	81.0	69.0	1114.0	89.0	48.0	40.0	40.00	101.0
6	834.0	36.0	29.0	836.0	8.0	6.0	5.0	.00	10.0
7	818.0	37.0	30.0	819.0	16.0	14.0	10.0	3.00	21.0
8	916.0	27.0	22.0	917.0	19.0	11.0	10.0	1.00	22.0
9	826.0	47.0	37.0	827.0	18.0	14.0	11.0	2.00	23.0
10	904.0	234.0	231.5	857.0	414.0	139.0	89.5	59.5	438.0
11	666.5	44.5	43.0	660.5	18.5	15.5	10.5	3.5	21.5

FREQUENCY DOMAIN DATA

Subject	VLF	VLF PERC	LF	LF NORM	LF PERC	HF	HF NORM	HF PERC	LF/HF RATIO	PERC REJRR
1	189	26.0	96	3.93	13.0	281	1.34	39.0	0.0	0.0
2	288	19.0	350	1.71	22.0	250	2.40	16.0	1.0	0.0
3	202	28.0	122	2.27	17.0	155	1.79	22.0	1.0	0.0
4	341	21.0	233	1.35	16	81	3.88	7.0	3.0	6.0
5	84	3.0	172	13.38	7.0	2130	1.08	84.0	0.0	1.0
6	384	41.0	79	1.28	10.0	22	4.59	3.0	4.0	0.0
7	198	17.0	507	1.36	44.0	184	3.76	16.0	3.0	5.0
8	93	17.0	63	3.43	13.0	153	1.41	36.0	0.0	0.0
9	639	42.0	394	1.37	31.0	145	3.72	16.0	3.0	0.0
10	446.5	1.3	917.0	4.9	2.6	4202.5	1.3	12.5	0.3	5.0
11	961.0	39.6	827.5	1.4	22.3	379.5	3.2	15.7	1.5	3.5

URINE ANALYSIS DATA

Subject	TOTAL VOLUME EXCRETED (mL)	CREATININE EXCRETED (mg/24 hr)	EPI (ng/mL)	EPI (ug/g OF CREATININE)	NOREPI (ng/mL)	NOREPI (ug/g OF CREATININE)	DOPAMINE (ng/mL)	DOPAMINE (ug/g OF CREATININE)
1								
2	1500	4050	64.9	24.0	2.4	0.9	280.8	104.0
3	1860	1897	1.2	1.2	92.6	90.8	42.7	41.9
4	940	2086	77.8	35.1	107.1	48.3	205.4	92.5
5	1060	1335	10.1	8.0	9.3	7.4	-0.7	-0.6
6	1800	3780	24.9	11.8	14.0	6.7	258.9	123.3
7	800	1856	5.1	2.2	25.6	11.0	247.4	106.6
8	1790	1790	26.0	26.0	70.4	70.4	190.6	190.6
9	1220	1683.5	27.3	19.8	43.9	31.8	174.7	126.6
10	2800	2632	10.0	10.7	35.8	38.1	192.9	205.2
11								

FITNESS TESTING AND QUESTIONNAIRE DATA

Subject	**VSAQ**	**SF-36 PHYS FUNC**	**SF-36 ROLE PHYS**	**PWC_{150} (WATTS)**	**VO_2150 (L/min)**	**VO_2150 (mL/kg/min)**	**PREDICTED VO_2 MAX (L/min)**	**PREDICTED VO_2 MAX (mL/kg/min)**
1	4.0	60.0	100.0	64.4	1.1	10.5	2.0	19.1
2	9.0	.	.	128.7	2.0	15.5	2.7	21.1
3	9.0	.	.	156.1	2.2	21.6	3.2	31.4
4	9.0	85.0	100.0	117.9	1.8	17.2	2.6	24.9
5	8.0	0.0	25.0	54.5	0.9	11.9	1.8	23.8
6	5.0	75.0	66.7	172.0	2.6	18.2	3.4	23.8
7	4.0	.	.	88.3	1.4	13.2	2.4	22.6
8	4.0	25.0	0.0	148.8	2.1	20.6	3.4	33.3
9	4.0	50.0	50.0	104.8	1.8	19.0	2.8	29.6
10	6.0	75.0	75.0	104.8	1.5	22.1	2.7	39.8
11	7.0	.	.	95.0	1.5	14.4	2.3	22.0

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EDUCATION

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY, Blacksburg, VA.
M.S., Clinical Exercise Physiology, August 2001
- "Relating Heart Rate Variability, Urinary Catecholamines, and Baseline Fitness to Respiratory Distress Index and Severity of Disease in Obstructive Sleep Apnea Patients." – Dr. William Herbert

VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY, Blacksburg, VA.
B.S., Science of Food, Nutrition, and Exercise, May 1998
- Minors: Biology, Chemistry

PUBLICATIONS

- Chittenden TW, Kaleth AS, Blevins JS, Ballentine HM, Arner A, Gregg JM, Zedalis D, Herbert WG. Increasing physical activity in the obstructive sleep apnea patient: part 1 – clinical presentation, pathogenesis, and medical management. Am J Med Sport (Fall 2001)
- Ballentine H, Blevins J, Herbert WG. Relating heart rate variability, urinary catecholamines, and baseline fitness to respiratory distress index and severity of disease in obstructive sleep apnea patients. (in preparation)
- Blevins J, Ballentine H, Herbert WG. The relationship between polysomnography markers of disease severity to hemodynamic and respiratory function during graded exercise in obstructive sleep apnea patients. (in review)

GRANTS OBTAINED

- $9,000 – ResMed Corporation – November 1999

CERTIFICATIONS/ AFFILIATIONS/ HONORS

- Member – ACSM/SEACSM
- ASCM Certified Exercise Specialist (Fall 2001)
- Registered Clinical Exercise Physiologist (Fall 2001)
- Outstanding Graduate student – Clinical Exercise Physiology – May 1999