The Utility of Bioimpedance Cardiography in Assessing the Influence of Obstructive Sleep Apnea Hypopnea Syndrome on Cardiac Function

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ABSTRACT

Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS) is a breathing disorder characterized by recurrent episodes of upper airway collapse during sleep. Measuring cardiac function in OSAHS patients may provide information to help delineate not only chronic effects of autonomic imbalance and ventricular loading in the diseases state, but also possible beneficial effects of clinical treatments. **Objectives (Study 1):** The aim of this study was to determine the reproducibility of select cardiac variables when monitoring a simulated sleep apnea event using a new improved bioimpedance cardiography system. **Methods:** Fifteen apparently healthy males were tested on three different days in a protocol requiring their performance of two 15 sec and two 30 sec forced and sustained inspiratory efforts against a closed epiglottis (Müeller Maneuver-MM). **Results:** Changes in cardiac output (CO), heart rate (HR), stroke volume (SV), myocardial contractility index (MCI) and systemic vascular resistance (SVR) were similar during 15 sec and 30 sec MM in all three days. During 30 sec MM, these changes in cardiac function were pronounced in comparison to the minimal variations observed for the 15 sec MM challenge test.

Objectives (Study 2): The aim of this study was to characterize the cardiac responses to negative intrathoracic pressure in OSAHS patients with and without hypertension versus healthy subjects. **Methods:** Two groups of 10 OSAHS patients, one without HTN and one with HTN were compared with a control group. Each subject underwent two 30 sec (MM) as previously

described. **Results:** During MM, there were similar changes in SV, HR and SVR in all three groups. CO was lower during MM in controls compared to OSAHS groups, whereas MCI decreased during MM in both controls and OSAHS+HTN groups (-7.5% and -1.7%, respectively) compared with an increase in OSAHS group (11.8%). During a Post-MM, both OSAHS groups showed return of cardiac responses toward their pre-MM baseline within 30 sec. **Conclusions**: The new bioimpedance cardiograph evaluated in this study was found to be reliable for measuring acute changes in cardiac responses to this breathing challenge test. OSAHS may cause acute changes in selected cardiac parameters during and immediately after a breathing challenge test.

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Chapter 1 – INTRODUCTION

Obstructive sleep apnea/hypopnea syndrome (OSAHS) is a complex disorder characterized by periodic complete or partial upper airway obstruction during sleep, leading to intermittent cessations of breathing (apneas), or reductions in airflow (hypopneas) despite ongoing respiratory effort. According to one study, 1 in 5 adults exhibit mild OSAHS and 1 in 15 adults have moderate OSAHS. [1] Even with all the interest generated by OSAHS in healthcare, mainly due to the recognition of associations with cardiovascular diseases, daytime sleepiness and related public safety concerns, it has recently been estimated that up to 93% of women and 82% of men with moderate to severe OSAHS still remain undiagnosed. [2]

OSAHS is one of the most serious sleep disorders and is associated with an increased risk of morbidity and mortality, placing a significant burden on society. The reported long-term sequelae associated with this disorder include various cardiovascular diseases such as hypertension, cardiac arrhythmia, myocardial infarction and congestive heart failure (CHF). [3] There are psychosocial problems that are linked with OSAHS, such as behavior changes, poor memory and impaired concentration.[4] In addition, neurobehavioral morbidity and daytime sleepiness may contribute to motor vehicle crashes and job-related accidents, which are potential risks for the patient's and others' life and pose an economic problem to the community. [5]

The main components of OSAHS are hypoxia, hypercapnia, arousals, sleep fragmentation and sleep loss, and increases in inspiratory efforts, all contributors to the physiologic changes seen in cardiovascular (CV) and pulmonary system. In most patients with OSAHS, there is a reflex increase in inspiratory effort during the obstructed periods, producing larger than normal swings in pleural pressure. These larger swings disrupt left and right ventricular outputs, as well as

systematic and pulmonary arterial pressures. The pressure gradient for blood return to the heart from the peripheral vasculature increases as the pressure in the thorax decreases, leading to an increase in venous return and consequently to a distension and a deviation of the interventricular septum. This, in turn, may alter the filling properties of the left ventricle. The high negative intrathoracic pressure can impair the relaxation of the left ventricle during diastole, lowering the ejection fraction and producing an increase in both afterload and preload to the left ventricle during systole. The overall result may be a reduction in stroke volume (SV) and cardiac output (CO).

Results in animals with normal hearts demonstrate that obstructive apnea produces a neurally-mediated stress that is specific to the left side of the circulation [6]. Adverse effects of increasing transmural pressure on SV and CO are likely to be exaggerated in patients with impaired ventricular systolic function, as their heart is more sensitive to changes in afterload than is the normal heart. [7] In these patients, apnea episodes may cause significant reductions in SV and expose the heart to increased risk of ischemia. One of the least severe forms of cardiac complications is hypertension. OSAHS has been identified as an independent risk factor for the onset of arterial hypertension. Increased sympathetic activity and endothelial dysfunction are some of the most prominent factors in the etiology of hypertension.

Cardiac function was accurately estimated during resting conditions by various techniques such as direct Fick and thermodilution. Although these methods were accurate and reliable, the use of catheters make these methods invasive and adds risk for the subjects. Also, they have to be perfomed in well-equipped and expensive environments like intensive care units and cardiac catheterization labs.

A non-invasive technique is the measurement of cardiac function from thoracic electrical bioimpedance (TEB) and combines relative simplicity of use; it permits non-invasive automated measurements of beat-to-beat CO. However, until recently the methodology proved problematic and has been criticized for lack of accuracy and reliability. Previous TEB devices have been based upon the equations that require two components: baseline thoracic impedance (Z0) and the pulsatile variation of impedance (delta Z). The Z0 depends upon accurate placement of electrodes, thorax morphology, and the measurements are affected by perspiration, subcutaneous adiposity, and poor electrical contact resulting in questionable reproducibility. More recently developed equipment, uses an alternative equation for estimation of cardiac function variables which does not rely on the measurement of Z0. This concept and methodology have been validated at rest and at exercise [8], during a maximal progressive exercise [9, 10] as well as at rest in emergency room and intensive care unit trauma patients. [11]

This bioimpedance technology can provide the tool for early identification of left ventricular dysfunction in patients with OSAHS that can warrant prompt treatment.

RESEARCH AIMS:

Research Aim 1: To determine the reproducibility of CO, SV and two additional measures of cardiac function which closely modulate variations in SV (myocardial contractility and peripheral resistance) during simulated apneas in apparently healthy subjects using a new impedance cardiography

Research Aim 2: To characterize the changes of hemodynamic responses to negative intrathoracic pressure in OSAHS patients with and without hypertension versus apparently healthy subjects at low risk of having OSAHS.

ASSUMPTIONS

1. Subjects answered correct all the health history questions.
2. Subjects provided accurate information on the Epworth and Berlin questionnaires.
3. Subjects came to their testing sessions with the same mood.
4. All laboratory equipment had been properly calibrated and maintained.
5. Subjects hold their breath at a constant intra-thoracic pressure.
6. Subjects did not alter activity patterns over the course of their inclusion in the study.

DELIMITATIONS

1. The OSAHS Subjects were patients referred to the Allergy and Sleep Disorder Center in Christiansburg for evaluation of a suspected sleeping disorder.
2. Blood pressure was taken manually in the laboratory at Virginia Tech and at the sleep clinic. Possible “white coat” effect could be present.

LIMITATIONS

1. Assessment of accuracy using the new bioimpedance cardiograph was not performed in a breath holding setting.
2. Presence of OSAHS in control group was not established with diagnostic testing, but determined based on anthropometric features and Epworth and Berlin questionnaire scores.
3. Control subjects were not selected to match with BMI of the two OSHAS groups
4. Study subjects were Caucasian males.

DEFINITIONS

Afterload - ventricular pressure at the end of systole. Ejection stops because the ventricular pressure developed by the myocardial contraction is less than the arterial pressure.

Apnea [12] - clear decrease (> 50%) in airflow from baseline lasting more than 10 seconds regardless of oxygen saturation.

Apnea/Hypopnea Index [12] – index of OSAHS severity based on total number of apneic and hypopneic events per hour of sleep

Berlin Questionnaire – easily administered questionnaire that can be used to identify individuals at risk of OSAHS

Bioimpedance cardiograph – non-invasive technology in which an alternating current is passed through the thoracic region using a tetrapolar band electrode configuration.

Cardiac output - amount of blood that is pumped from the heart in a particular period, usually expressed as liters per minute. It can be defined as the product of the stroke volume per beat and the heart rate per minute.

Continuous Positive Airway Pressure - pressure device that forces air into the nasal passages at pressures high enough to overcome obstructions in the airway and stimulate normal breathing. This treats OSAHS and snoring.

Doppler echocardiography – diagnostic test that uses ultrasound waves to create an image of the heart muscle

Epworth Sleepiness Scale – questionnaire used to determine the level of daytime sleepiness.

Fick method - involves calculating the oxygen consumed over a given period of time from measurement of the oxygen concentration of the venous blood and the arterial blood. Is invasive and requires time for the sample analysis, and accurate oxygen consumption samples are difficult to acquire.

Hypopnea [12] - thirty to 50 percent reduction in airflow associated with either an arousal or a desaturation of > 3%.

Mueller Maneuver – forced inspiration with a closed glottis after full expiration

Obstructive Sleep Apnea Hypopnea Syndrome [12] - a complex disorder characterized by periodic complete or partial upper airway obstruction during sleep, leading to intermittent cessations of breathing, or reductions in airflow despite ongoing respiratory effort.

Polysomnography (PSG) [12] - Gold standard diagnostic method for obstructive sleep apnea. A standard PSG typically consists of electroencephalogram, submental electromyogram, electrooculogram, respiratory airflow, respiratory effort (rib cage and abdominal movement), and pulse oximetry

Preload - end-diastolic volume at the beginning of systole. This is directly related to the degree of stretch of the myocardial sarcomeres.

Stroke Volume - The amount of blood (ml) pumped from the left ventricle into the aorta in one cardiac cycle.

Systemic Vascular Resistance - refers to the resistance to blood flow offered by all of the systemic vasculature, excluding the pulmonary vasculature

LIST OF ABBREVIATIONS

AHI – apnea/hypopnea Index

ANCOVA – analysis of covariance

ANOVA – analysis of variance

BP – blood pressure

BSA – body surface area

CPAP – continuous positive airway pressure

DBP – diastolic blood pressure

HTN – hypertension

LV – left ventricle

MCI – myocardial contractility

MM – Mueller maneuver

OSAHS – obstructive sleep apnea-hypopnea syndrome

SBP – systolic blood pressure

SV – stroke volume

SVR – systemic vascular resistance

TEB – thoracic electrical bioimpedance

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Chapter 2 LITERATURE REVIEW

The present study was conducted to determine reliability of a new advanced bioimpedance cardiograph in an apnea simulated setting. In addition, a population of OSAHS patients performed this simulation to determine any unique responses related to their clinical features. Various components of these variables from current research are included in this review to inform the reader about the basic understanding of this research. This chapter introduces review and interpretation of current published research related to the main variables under investigation, including physiology of cardiac output, hemodynamics measurements, obstructive sleep apnea hypopnea syndrome (OSAHS) and interaction between cardiac system and OSAHS.

Cardiac output

The main function of the heart is to supply sufficient oxygen to the tissues of the body for the current metabolic state. The measurements of CO and ventricular filling pressure have historically been used to assess the function of the heart. Cardiac output is a useful measurement of the pumping ability of the heart.

Cardiac output by definition is the amount of blood that is pumped out of the heart over a given period of time and is usually expressed in liters/minute. Its value is derived from the product of heart rate and stroke volume. Its normal value is quite variable, and changes with age, body temperature, anxiety, environmental heat and humidity, and posture.

Factors determining cardiac output

Traditionally, the regulation of CO has been discussed in terms of the factors that determine cardiac function (preload, afterload, heart rate, and myocardial contractility) and the role of the vasculature in regulating venous return. These factors can be divided into two categories, cardiac and systemic factors. Cardiac factors are those that influence heart rate and myocardial contractility. Systemic factors are those that affect the amount of blood returning to the heart from the peripheral vasculature.

Stroke volume is defined as the volume of blood that is ejected from the left ventricle with each beat. The SV is the net difference between the end diastolic and end systolic ventricular volumes. Resting SV were in the range of 70-80 mL/beat.[1] SV is determined by factors like preload, afterload and contractility.

Preload is the degree of stretch of the myocardial fibers at end-diastole and is referred to as left ventricular end-diastolic volume.[2, 3] Preload volume is dependent upon: (a) diastolic filling pressure, (b) total blood volume, (c) intrathoracic pressure, and (d) atrial systole. Changes in ventricular preload result in changes in myocardial sarcomere length, which in turn affect the force of contraction. The larger the preload, the greater is the stretch imposed on the myocardial fibers and force of contractility.

Factors affecting afterload are: (a) blood viscosity, b) radius and length of the vessels, (c) the condition of the cardiac valves, and (d) ventricular radius and wall tension. The sympathetic

nervous system, electrolyte and acid-base imbalances, oxygen level, end-diastolic volume, degree of resistance and ventricular wall tension, and positive or negative inotropic agents are factors that affect contractility.

Venous return has been identified as another factor determining cardiac output [4]. Over a period of time and given a constant circulating blood volume, the venous return must equal the CO. Venous return and ultimately CO depend on intra-thoracic pressure, blood volume and dynamic activity of skeletal muscle. Total blood volume is a minor determinant of SV as 500 mL reduction in blood volume does not impact SV and CO at rest.[5] During exercise, rhythmic skeletal muscle contractions facilitate an increase in central venous volume and pressure.[6] The process of breathing has a constant, continuous impact on venous return. Variations in the relationship between intra-abdominal and intra-thoracic pressure occur throughout the respiratory cycle. The difference between the intra-thoracic pressure and the intra-abdominal pressure facilitates the translocation of blood from the abdomen into the thoracic cavity. With inspiration, diaphragmatic excursion reduces the intra-thoracic pressure, with an associated increase in intra-abdominal pressure. The pressure gradient between the abdomen and thorax is increased, resulting in a force that promotes the flow of blood centrally. In contrast, when expiring against a closed glottis, an increase in both intra-thoracic and intra-abdominal pressure obstructs venous return, reduces SV, and ultimately decreases CO. [7]

Measurement of cardiac output

Over the years, CO was frequently measured as a fundamental descriptor of cardiovascular function. Its usage depends on accuracy and reliability. Historically, CO was first estimated by Harvey in 1628, in conjunction with the identification of a systemic blood circulation. [8] Over the years, different methods were adopted for measuring CO in humans. Adolph Fick described one of the first techniques in 1870. It was postulated that the CO could be calculated from the difference in oxygen content between the mixed venous (pulmonary artery) and arterial blood and the total body oxygen consumption. This method is considered the gold standard for measuring CO. In order to measure the difference between the arterial and venous oxygen content of the blood, right heart catheterization is required in order to obtain blood samples from the pulmonary artery and pulmonary vein. This is one of the main reasons for not using this methodology when investigating healthy subjects. Cardiac catheterization is associated with ventricular arrhythmias and fibrillation, and perforation of the pulmonary artery or the right ventricle. [9]

Stewart first introduced the indicator dilution technique known as the indirect Fick method for determination of CO in 1897 that was later modified by Hamilton in 1932.[8] Measurable indicators like inert dyes, gases, hypertonic saline and cold saline or dextrose solution of known concentration are injected into the circulation. The indicator mixes with blood and is diluted. The extent of dilution, determined by measuring the concentration, is inversely proportional to the blood flow. In the dye dilution method, a bolus of dye, usually indocyanine green is injected rapidly into the venous circulation near the right atrium and the downstream concentration of the

dye is measured from a peripheral artery. A blood sample is withdrawn continuously from the artery and passed through a densitometer that determines the concentration by spectrophotometry. A chart recorder produces a dye concentration versus time curve. The area under the curve is inversely proportional to CO. Like the Fick technique, dye dilution is not suitable for routine clinical use. Calibration of the equipment is difficult and the repeated determinations of CO are limited by the accumulation of dye in the circulation.

With the introduction of the pulmonary artery catheter, the thermodilution technique for CO measurement became famous.[10] It is similar to the indicator technique in some ways. The indicator for this technique is a cold fluid, which is cooler than the subjects' blood, usually saline solution either iced or at room temperature. The cold liquid is injected through the pulmonary artery catheter, into the right atrium, where it mixes with the venous blood and causes the blood to cool slightly. The cooled blood is ejected by the right ventricle into the pulmonary artery, where it passes a thermistor near the tip of the pulmonary artery catheter. The thermistor measures the change in blood temperature as the cooled blood travels past on the way to the lungs. The extent of cooling is inversely proportional to the CO. The thermodilution technique has undergone many modifications and is a very popular technique. It also has a few shortcomings. Errors are found in the CO reading due to the intravenous administration of fluids. This error occurs because the rapid administration of the intravenous fluid causes cooling of the thermistors, which combines with the cooling caused by the injection and results in smaller calculated CO. Another source of error may occur with the exchange of heat between the point of injection and the point of sampling. The need for easier and less painful techniques directed the development of non-invasive procedures.

These methods include the analysis of respiratory gases, echocardiography and electrical bioimpedance. Various methodologies which involve the analysis of respiratory gas exchange have been used to indirectly quantify CO via the estimation of pulmonary capillary blood flow. The fundamental assumption is that pulmonary capillary blood flow equals CO. Two types of gases, reactive and inert have been used for the estimation of the pulmonary capillary blood flow. Reactive gases are those which are normally present in respiration and that combine chemically with the blood, for example, carbon dioxide. Inert gases are those which are normally absent in respiration and which dissolve in the blood according to their relative partial pressure in the alveoli and pulmonary capillary blood, two examples being acetylene and nitrous oxide. [11]

The typical echocardiographic method of CO measurement uses Doppler to determine the velocity of systolic flow in the ascending aorta, but it can also be determined across any valve in the heart, as long as the valve is not insufficient. The principle of Doppler describes the change in frequency of sound from a moving object (blood) as compared to a stationary object (transducer). [12] Potential sources of error include the assumption that the angle between the blood flow and sound waves is zero. Usually it is not possible to identify an imaging plane with an incident angle of zero degrees, but an angle up to 20 degrees causes an error of 6%. [12] The second error involves the assumption that the aorta is circular and does not change in size. The aorta is a dynamic structure that is changing in size (diameter) and shape during the phases of cardiac cycle. Additionally, obtaining the measurement of the ascending aortic diameter is technically difficult and requires experience. Finally, the velocity of blood within the aortic column is assumed to be consistent, which is incorrect as there are changing velocities, most noted at the vessel/wall blood interface.

Thoracic electrical bioimpedance is a non-invasive technique to determine CO that analyzes changes in the thoracic cavity's resistance to an alternating current (AC) during the cardiac cycle.[10] With the transmission of AC current through the electrodes the thorax becomes a transducer whose area can be determined mathematically. Resistance associated with AC is known as impedance. A baseline value can be determined from the balance of electronically conductive blood and interstitial fluid, less conductive tissue, and nonconductive air. The change in impedance seen during each cardiac cycle is indicative of the amount of blood flowing in the aorta and therefore being ejected by the heart into the arterial tree. Greater decreases in impedance are associated with greater amounts of blood. The impedance cardiograph generates the following through the electrical signals: 1) the mean thoracic impedance between electrodes 2 and 3 (Z_0); 2) the impedance change during the cardiac cycle, delta Z (ΔZ); 3) the first derivative of ΔZ with respect to time; and 4) the electrocardiogram (EKG). When blood is ejected from the left ventricle, changes in electrical impedance can be monitored electronically to obtain a measurement of SV using the following formula derived by Kubicek et al. in 1974[13]:

$$SV = \rho \cdot (L/Z_0)^2 \cdot T \cdot (dZ/dt)min$$

where Rho (ρ) is the resistivity of blood, L is the mean distance between the two inner electrodes in cm, Z0 is the mean thoracic impedance between electrodes 2 and 3, T is the ventricular ejection time in seconds, and (dZ/dt)min is the minimum value of dZ/dt occurring during the cardiac cycle in ohms per second. Myocardial contractility is measured by the device as the first nadir after the peak of the ejection velocity and is basically the maximal rate of decrease in impedance for a given heart beat. Systemic vascular resistance is computed using the estimated CO (SV X HR) and the measured blood pressure at rest.

When comparing transthoracic impedance cardiography with direct Fick methodology, correlations range from r^2=0.69 to r^2=0.93.[14] A high correlation (r = .82) has been shown between impedance-derived SV and SV measured by nuclear ventriculography in humans. [15] However, until recently, the methodology has been problematic in terms of accuracy and reliability. Previous TEB devices have been based upon the equations that require two components: baseline thoracic impedance (Z_0) and the pulsatile variation of impedance (Δ Z). The Z_0 depends upon accurate placement of electrodes, thorax morphology, and the measurements are affected by perspiration, subcutaneous adiposity, and low electrical contact resulting in questionable reproducibility.[10] More recently developed equipment such as the PhysioFlow®, uses an alternative equation for estimation of cardiac function variables which does not rely on the measurement of Z_0. The PhysioFlow® emits high frequency (75 kHz) and low-amperage (1.8 mA) alternating electrical current via six electrodes on the thorax. This concept and methodology have been validated at rest and at exercise[16], during a maximal progressive exercise [17, 18] as well as at rest in emergency room and intensive care unit trauma patients. [19] The Physioflow was validated against the direct Fick method. Mean differences between CO values obtained by the direct Fick method and the Physioflow device (Q_{Fick} - Q_{Imp}) are not significantly different during rest (0.04 l/min)[16] , submaximal exercise (0.29 l/min)[16], or maximal incremental exercise (0.58 l/min).[17] The direct Fick method is highly correlated with the Physioflow during rest (r = 0.89, n = 40),[16] submaximal exercise (r = 0.85, n = 40),[16] and maximal exercise (r = 0.94, n = 50).[17] High correlations in the SV (r = 0.84) and Q values (r = 0.98) between the direct Fick and impedance cardiography methods have been reported during maximal cycling exercise in young, fit men (39).[20] Therefore, it seems that this impedance cardiography provides accurate CO measurements during exercise. Its simplicity and

affordability will be used at rest during a test requiring breath holding maneuvers. These types of maneuvers simulate respiratory events that represent the clinical feature of OSAHS.

Obstructive sleep apnea hypopnea syndrome

The occurrence of disordered breathing during sleep was first described more than a century ago, but the specific characteristics of OSAHS were not identified until 1965 by Gaustaut and co-workers. [21] These investigators classified the different periods of cessation of breathing observed during sleep on polysomnographic recordings into either obstructive, central or mixed apneas. [21] Over the next 2 decades, awareness of sleep-disordered breathing increased, with numerous studies being published on the pathogenesis, pathophysiology and therapeutic management of this disorder.

Obstructive sleep apnea/hypopnea syndrome is a complex disorder characterized by periodic complete or partial upper airway obstruction during sleep, leading to intermittent cessations of breathing (apneas), or reductions in airflow (hypopneas) despite ongoing respiratory effort. Severity of OSAHS is measured by an apnea/hypopnea-index (AHI) value, which is the mean number of apneas and hypopneas per hour. While an AHI < 5 is within normal ranges, the severity of this disorder can be further categorized as mild (AHI < 15), moderate (AHI >15 and < 30) and severe (AHI > 30).

According to one study, 1 in 5 adults exhibit mild OSAHS and 1 in 15 adults have moderate OSAHS. [22] Even with all the interest generated by OSAHS in healthcare, mainly due to the recognition of associations with cardiovascular diseases, daytime sleepiness and related public

safety concerns, it has recently been estimated that up to 93% of women and 82% of men with moderate to severe OSAHS still remain undiagnosed. [23]

The risk factors for OSAHS include gender, age, genetics, obesity, and alcohol intake. [24] The greater prevalence of OSAHS in males may be due to the higher pharyngeal and supraglottic resistance in normal males compared to females. [25] Similarly, pharyngeal resistance increases with age in normal men [25] and may result in greater prevalence of OSAHS in the older age group. [26] However, the association between age and OSAHS may be influenced by confounding factors such as obesity and has not been well established. [27] Conversely, the association between obesity and OSAHS has been well documented [28, 29], but the mechanisms responsible for this link remain unclear. [24] Also, some reports describe several members of a family who were afflicted with OSAHS, suggesting a genetic predisposition. [30, 31] Finally, ethanol ingestion, as little as 3 oz. before sleep, increases the severity of sleep apnea, possibly through its depressant effects on upper airway muscle tone, arousability and chemoreceptor activity. [32 33]

OSAHS is one of the most serious sleep disorders associated with an increased risk in morbidity and mortality, placing a significant burden on society. The reported long-term sequelae associated with this disorder include various cardiovascular diseases such as hypertension, cardiac arrhythmia, myocardial infarction and congestive heart failure (CHF). [34] There are psychosocial problems that are linked with OSAHS, such as behavior changes, poor memory and impaired concentration. [35] In addition, neurobehavioral morbidity and daytime sleepiness may contribute to motor vehicle crashes and job-related accidents, which are potential risks for the patient's and others' life and post an economic problem to the community. [36]

Hemodynamic changes during apneic events in OSAHS

The main components of OSAHS are hypoxia, hypercapnia, arousals, sleep fragmentation and sleep loss, and increases in inspiratory efforts, all contributors to the physiologic changes seen in cardiovascular and pulmonary system.[37] In most patients with OSAHS, there is a reflex increase in inspiratory effort during the obstructed periods, producing larger than normal swings in pleural pressure. These larger swings disrupt left and right ventricular outputs, as well as systematic and pulmonary arterial pressures. The pressure gradient for blood return to the heart from the peripheral vasculature increases as the pressure in the thorax decreases, leading to an increase in venous return and consequently to a distension and a deviation of the interventricular septum.[38] This, in turn, may alter the filling properties of the left ventricle. The high negative intrathoracic pressure can impair the relaxation of the left ventricle during diastole, lowering the ejection fraction and producing an increase in both afterload and preload to the left ventricle during systole.[39] The overall result is a reduction in SV and CO.[40]

Effects of apneas on cardiac function

During OSAHS, some authors have reported a decrease in CO with apnea as measured with thermodilution techniques and impedance cardiography. [41, 42] These reductions were the result of a decrease in HR and SV. Other authors have reported no systematic changes in CO during apneas using the same technique.[43] However, thermodilution techniques and impedance cardiography may not be sensitive enough to determine rapid changes in CO during and after apneas.[40] Nevertheless, the application of beat by beat methods by other authors has revealed no changes in CO.[44] However, late in the apnea (i.e., the last two respiratory efforts), CO decreases.[40] With arousal and resumption of breathing, despite the increase in HR, CO decreases

because of the substantial decrease in SV. Supplemental oxygen that maintains oxygen saturation above 90% does not change the response of CO to obstructive apnea suggesting that hypoxia is not the primary stimulus contributing to the changes. [38]

Performing a respiratory technique, like MM, can allow study of the hemodynamic effects of obstructive apneas without inducing confounding variables and interactions arising from hypoxia, hypercapnia, and arousals from sleep. Using Doppler echocardiography in healthy subjects performing the MM, Orban et al.[45] found that markers of LV systolic performance (SV index and cardiac index) decreased significantly from baseline (-13%, -18%, respectively). Immediately after termination of the MM, these measures increased in a compensatory fashion, intermittently exceeding baseline values. By recovery (10 minutes after the MM) all measurements had returned to baseline.

In a study by Hall et al.[46], the effects of obstructive apneas on cardiac and systemic hemodynamics were examined in patients with impaired ventricular systolic function. OSAHS is present in a substantial number of CHF patients and treatment with CPAP improved the affected left ventricular function. In these patients, MM generated an average reductions in SV index and cardiac index over the final five beats of a MM that generated an intrathoracic pressure of - 40 cmH_2O were 33% (from 27 to 18 ml/m^2) and 30% (from 2.0 to 1.4 l/min/m) below baseline, respectively.[46] Thus, MM exert adverse hemodynamic effects on patients with CHF through several mechanisms, and the intensity of these responses and their interactions vary over time. The failing myocardium is particularly susceptible to reductions in SV in response to increases in left ventricular afterload. When negative intrathoracic pressure is maintained, the influence of afterload dissipates, and additional mechanisms, such as a drop in left ventricular preload due to ventricular interaction, are engaged, then predominate. Same mechanism responsible for

exaggerated reduction in CO and SV has been observed in animal studies.[39] In instrumented pigs with pacing-induced cardiomyopathy, changes during apnea simulations seems to be explained by the combined effects of decreased LV preload and increased LV afterload.

Several studies addressed negative intrathoracic pressure effects of the MM in the context of cardiac impairment. In patients with CHF, generation of -30 cm H_2O of intrathoracic pressure lasting only 15 sec can precipitate marked reductions in BP and SV that persist beyond the release of the obstruction.[47] The reduction in cardiac index was significantly greater in CHF subjects than in healthy subjects (-0.31 ± 0.11 L/min/m^2 vs. 0.05 ± 0.09 L/min/m^2). In CHF patients, SV index fell by more than twice as much as in the healthy subjects (-8.5 ± 1.8 mL/m^2 vs -4.1 ± 2.1 mL/m^2) at the end of the MM. The authors concluded that negative intrathoracic pressure caused more profound and sustained reductions in SV and CO during the MM and following its release in treated CHF patients than in healthy subjects.

Overall, the decrease in intrathoracic pressure induced by the MM (i.e., voluntary inspiration against a closed glottis, mimicking features of a nocturnal apneic event) reduces right atrial pressure, increases venous return to the right heart and decreases left ventricular performance and outflow. [45, 48, 49] The increase in right ventricular volume may result in a shift of the intraventricular septum to the left and lead to decreased compliance and left ventricular stroke volume. [42, 50] However, the rise in venous return to the right heart is limited by collapse of the great veins at the entrance of the thoracic cavity. [51] Right ventricular afterload may increase from hypoxic pulmonary vasoconstriction. In addition, the lower intrapleural pressure during the respiratory efforts increases the transmural pressure gradient of the right and left ventricles and increases their afterload. [49, 52] Thus, the increase in afterload and the decrease in compliance of the left ventricle may lead to an increase in left ventricular end diastolic pressure and left atrial

pressure [53], as supported from evidence of increased pulmonary capillary wedge pressure during apneas. [54] These hemodynamic changes result in an increase in intra-thoracic blood volume, which in term leads to enlargement of the heart. The negative intrapleural pressure during obstructive apneas increases the preload of the right side of the heart, resulting in distention of the right atrium and the release of atrial natriuretic peptides (ANP). Mean plasma levels of ANP are correlated with the degree of hypoxemia and the negative pleural pressure generated and decrease with CPAP treatment. [55] Added together, these unique responses to apnea episodes lead to a multitude of cardiovascular abnormalities.

Potential cardiac consequences of OSAHS

Chronic sympathetic activation seemed the most likely mechanism linking OSAHS to cardiovascular disease. There are several other mechanisms that may contribute to cardiovascular disease in those with OSAHS. These include inflammation, endothelial dysfunction, elevated levels of endothelin, hypercoagulability and stimulation of the renin angiotensin system.[56] Drager et al. [57] demonstrated that OSAHS has an independent role in the progression of atherosclerosis by affecting the functional and structural properties of the large arteries. Another finding that supports the relationship between OSAHS severity and the progression of atherosclerosis is a study by Minoguchi et al.[58] Carotid intima-media thickness (IMT) was used as a marker to detect early atherosclerosis in patients with OSAHS. The results showed that OSAHS-related hypoxia was the main cause responsible for changes in carotid IMT.

Dysrhythmias and Conduction Defects

In healthy subjects, sleep is associated with the frequent presence of various types of cardiac rhythm and conduction disturbances (sinus bradycardia, sinus pause, first degree, and Mobitz I second-degree atrioventricular block). These disturbances are considered physiologic and are related to normal changes in autonomic nervous system activity typical of the different sleep stages. Various types of cardiac arrhythmias have been related to OSAHS (especially for moderate and severe forms of the disease), which may contribute to cardiovascular morbidity and probably to cardiac mortality in patients with OSAHS. [59-62] One of the most common cardiac rhythm abnormality is marked sinus arrhythmia which includes episodes of bradycardia when apnea events occur followed by tachycardia when normal breathing is restored. OSAHS patients have an increasd prevalence of atrial fibrillation and ventricular tachycardia. The prevalence of cardiac arrhythmia during sleep was 48-58% in patients with OSAHS. [63, 64] Becker et al.[65] investigated 239 consecutive OSAHS patients and reported that second- or third-degree atrioventricular (AV) blocks were common in patients with severe OSAHS and that CPAP treatment reversed these arrhythmias in 88% of the patients. Another line of evidence comes from the studies in which tracheotomy was the main treatment for OSAHS. This treatment effectively reduced cardiac arrhythmias that are related to OSAHS, specifically sinus bradycardia, sinus pauses and AV blocks. [66, 67] The prevalence of atrial fibrillation and flutter is decreased after tracheotomy possibly due to reduction in ventricular afterload and atrial distention. [68] Ventricular ectopic beats, which are associated with desaturation below 60% and ventricular tachycardia are less common after tracheotomy [69]. Occurrence of cardiac arrhythmias can be explained by the presence of structural and hemodynamic abnormalities, myocardial ischemia, neuro-hormonal activation and enhanced sympathetic activation.

Myocardial infarction

Main features of OSAHS, hypoxia, hypercapnia, and peripheral vasoconstriction are some of the stresses that can place OSAHS as a risk factor for myocardial infarction [70]. Several studies have suggested a link between these sleep-related problems and myocardial infarction (MI). A 4-year study [71] showed that complaints related to sleep, especially difficulties initiating sleep, non-refreshing sleep and chronic fatigue, were correlated to increased risk of MI. Similarly, in a study of 71,617 women, short sleep duration was associated with increased risk of nonfatal MI. [72] Habitual snoring was related to increased risk of angina and ischemic heart disease, after adjustment for confounding variables such as hypertension, age and obesity. [73, 74]

More direct evidence of an association between OSAHS and MI has been described by Hung and colleagues. [75] They studied 101 men who had suffered MI and 63 age-matched control subjects and found that an apnea index of greater than 5 carried a relative risk of 23.3 for acute MI, after controlling for hypertension, smoking, body mass, and cholesterol. Similarly, a study by Lee [76] reported that 65.7% of a sample of patients with recent MI had an apnea index of 15 or greater. Finally, in three case reports, the initial manifestations of OSAHS simulated angina or mimicked heart failure. [77]

Cerebral infarcts

Several studies have provided data to link snoring with increased risk of stroke [78-80]. Koskenvuo and colleagues [73] found an increased prevalence of stroke in habitual snorers and 35% of these patients were likely to have OSAHS. Several studies have shown that OSAHS is very common amongst stroke patients, with a prevalence exceeding 50% [81] as compared with 4% in the middle-aged adult population [27]. Moreover, a prospective cohort study provided evidence that the

OSAHS (defined as an AHI ≥ 5) significantly increased the risk of stroke or death from any cause, and this increase is independent of other risk factors, including hypertension, with a hazard ratio of 1.97. [82]

Even though a definite association between OSAHS and stroke has not been established, some of the pathophysiological changes that accompany OSAHS could possibly predispose to cerebral infarction. Possible mechanisms include acute hemodynamic changes during episodes of apnea [83, 84], decreased cerebral blood flow [85-87], paradoxical embolization [88], hypercoagulability [89, 90], hypoxia-related cerebral ischemia [91], and atherosclerosis. [92]

Mortality

In patients with OSAHS, it has been postulated that apneas at that time of the night may be longer and therefore, associated with greater degree of hypoxemia and possibly mortality. [53] The five-year mortality rate in patients with untreated OSAHS was reported between 11 and 13%.[93, 94] In the study by Partinen and co-workers [93], 57% of the deaths were the result of cardiovascular disease. The incidence of death was correlated with severity of the disease. Untreated patients with an apnea index greater than 20 had an eight year cumulative mortality of 37%, compared to 4% in those with an apnea index of less than 20 [94]. Although the time of death was not specified, Guilleminault and co-workers [63] found that death occured unexpectedly during sleep in patients with OSAHS. With effective treatment of OSAHS with nasal CPAP or tracheotomy, there were no deaths during a nine year follow-up period [94]. In a retrospective review of 198 patients with OSAHS, Partinen and Guilleminauit [95] reported lower cardiovascular morbidity and mortality in those patients who underwent definitive treatment as compared to those who were simply encouraged to lose weight. Recent data indicate that OSA is associated with an increased

incidence of both fatal and nonfatal cardiovascular events.[96] The incidence of non-fatal cardiovascular events per 100 people during 10 years' follow-up was significantly higher in patients with untreated severe OSAHS than in healthy men (2.13 vs. 0.45), as was the incidence of cardiovascular death due to fatal MI or stroke (1.06 vs. 0.3). Treatment with CPAP significantly reduced mortality in patients with severe OSAHS when compared with untreated OSAHS patients (0.64 vs. 2.13 events per 100 person year).

Several potential mechanisms could explain the higher mortality risk in OSAHS. This association may be due to the risks traditionally attributed to OSAHS. Numerous studies have shown that OSAHS is associated with hypertension, coronary artery disease, CHF, stroke and insulin resistance. There is a need for experimental data to determine whether OSAHS, per se, can be recognized as an independent predictor of mortality.

Summary

Cardiac output monitoring provides useful information about functionality of the cardiovascular system. Measuring CO should provide accurate data to ensure proper diagnosis and proper treatment. Non-invasive techniques are emerging as easy-to-use, affordable, and reliable compared to" gold standard". Thoracic bioimpedance method using a new cardiograph device overcomes some of the shortcomings demonstrated by older techniques. This device can assess cardiac hemodynamics under different circumstances; at rest, during sub-maximal exercise or at maximal effort. Using this device in a protocol entailing breath holding can find merits in the field of sleep medicine. OSAHS is a complex disorder caused by multiple apnea events over night. Simulation of apnea events using a MM can mimic the hemodynamic effects of OSAHS. This respiratory disease is associated with a multitude of cardiovascular conditions. The

cumulative effects of the failing myocardium and OSAHS could impose a greater reduction in cardiac function. Evidence from studies of OSAHS patients with preexisting hemodynamic impairments supports the relationship between OSAHS and the increase in cardiovascular morbidity. The majority of this research examined OSAHS patients with or without cardiovascular problems, although they were taking medication that could possibly interfere with their cardiac responses. To delineate just the effect of OSAHS, the current study attempted to determine the hemodynamic responses to a simulated apnea event in two groups of unmedicated OSAHS patients. Choosing a group of OSAHS patients with hypertension, helped further characterized the impact of a mild cardiovascular condition without the confounding factors represented by medication, or OSAHS treatment.

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Chapter 3

Reproducibility of cardiac monitoring in men using impedance cardiography during Mueller maneuver

Abstract

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a form of sleep-disordered breathing highlighted by recurrent episodes of upper airway collapse during sleep. OSAHS contributes to an increased risk of hypertension, cardiac arrhythmias, cardiovascular disease, stroke and altered immune function. Measuring cardiac function in OSAHS patients can provide information that can help delineate their clinical treatment efficacy. Electrical bioimpedance has been widely used to measure cardiac function. The aim of this study was to determine the reproducibility of cardiac functional parameters under dynamic conditions, in patients performing Mueller maneuver (MM). Fifteen apparently healthy males were tested on three different days in a protocol requiring their performance of forced and sustained inspiratory efforts against a closed epiglottis (Müeller Maneuver-MM). On each day, the protocol included performance of two simulated apneas of 15 seconds duration and two more of 30 seconds duration, with at least 3 minutes of normal breathing between. Changes in cardiac output (CO), heart rate (HR), stroke volume (SV), myocardial contractility (MCI) and systemic vascular resistance (SVR) were similar during both 15 seconds MM in all three days. During 30 sec MM, changes in CO, HR, SV, MCI and SVR were not different within a day or between days. However, performance of four MM within each day was associated with a constant decrease in SV and MCI and an increase in SVR. During 15 sec MM, changes from baseline were minimal, but in contrast, 30 sec MM elicited slight bradycardia and consistent reductions in CO, SV and MCI that ranged between 7-10% across trials and between days. In conclusion, the new bioimpedance cardiograph is a reliable device for measuring cardiac responses during a simulated apnea event. For clinical

purposes, a 30 sec MM test can be generated to screen OSAHS patients at high risk for cardiac dysfunction.

INTRODUCTION

OSAHS is a serious sleep disorder associated with an increased risk in morbidity and mortality, placing a significant burden on society.[1] The reported long-term sequelae associated with this disorder include various cardiovascular diseases such as hypertension, cardiac arrhythmia, myocardial infarction and congestive heart failure.[2] An increase in number of research studies is aimed at understanding the acute and chronic effects of OSAHS on different cardiac functions. [3] The most essential measure of cardiac function is SV. Most of the methods that can accurately estimate SV require catheterization and have to be perfomed in well-equipped and expensive laboratories. Some of the new, non-invasive techniques involve rebreathing techniques or usage of thoracic electrical bioimpedance (TEB). Most of the TEB devices have been based upon the equations of Kubicek and coworkers [4] which use a variable affected by perspiration, subcutaneous adiposity, and low electrical contact. In the present study, data were collected using a new cardiograph device that is supporting technology on altered equations able to overcome all the previous shortcomings presented by older equipment. The algorithm used does not utilize basal thoracic impedance measurement or the estimation of blood resistivity. Furthermore, the position of the electrodes is not critical for accuracy of the measurements. The PhysioFlow® device has been validated at rest and at exercise,[5] during a maximal progressive exercise [6,7] as well as at rest in emergency room and intensive care unit trauma patients.[8] However, no data were available on using this device in awake individuals undergoing breath holding maneuvers that simulate apnea events during sleep. This bioimpedance technology can provide the tool for early identification of left ventricular dysfunction in patients with OSAHS that can warrant prompt treatment.

The purpose of this study was to determine the reproducibility of CO, SV and two measures of cardiac function which closely modulate variations in SV [myocardial contractility (MCI) and

peripheral resistance (SVR)] during simulated apneas in apparently healthy subjects using a new impedance cardiography. Consistency in these variables can help design a simple test that can be administered to OSAHS patients to assess cardiac function in an outpatient environment.

METHODS

Sixteen apparently healthy, normal weight males were recruited for this study (Mean ± SD: age = 38.6 ± 6.3 yr.) (Table 1). Exclusion criteria consisted of: current cigarette smoking; acute respiratory infections during the previous 6 weeks; diagnosed or medically treated cardiovascular, pulmonary (including asthma), renal, inflammatory, or metabolic disorders and blood pressure higher than 130/90 mmHg. To limit the probability of OSAHS occurrence, subjects completed an Epworth Sleepiness Scale [9] and a Berlin Questionnaire [10], two widely used subjective measures of daytime sleepiness. They had their neck and waist circumference measured, as these are some of the predictors for OSAHS.[11,12] Written informed consent was obtained from all subjects and the institutional review board of the Virginia Tech authorized the study protocol.

Subjects were tested in the supine position, in the same room, on three separate days at ± 1 hour interval from the first day. Subjects refrained from physical activity for at least 8 hours prior testing. To simulate apnea episodes the Müeller Maneuver (MM) was used, which requires forced and sustained inspiratory efforts against a closed epiglottis. Previous work confirmed that the MM closely simulated changes in intrathoracic pressure produced during sleep in subjects with OSAHS.[13] On each day, the protocol included performance of two MM of 15 seconds duration and two more of 30 seconds duration, in a random order. Between apneas was at least 3 minutes of normal breathing to promote normalization of cardiac responses.

Before testing started, subjects were taught the MM technique and directed to hold their breath after a normal exhalation. They were instructed to inflate their lungs against a closed epiglottis, with an effort that achieved and maintained what they perceived to be a medium degree of negative pressure within the rib cage. Blood pressure measurements were taken on both arms before and after testing.

Cardiac variables were collected non-invasively using a TEB device (PhysioFlow PF-05 Lab1, NeuMeDx, Bristol, Pa). The PhysioFlow device and methodology have been described elsewhere. [5] In brief, the bioimpedance method of CO determination uses changes in trans-thoracic impedance during cardiac ejection to calculate SV. The PhysioFlow® emits a high-frequency (75 kHz) and low-amperage (1.8 mA) alternating electrical current via electrodes.

Cardiac output is based upon the following formula:

$$\text{Cardiac output } (\text{lmin}^{-1}) = fc\ (\text{beats} \cdot \text{min}^{-1}) \cdot \text{SVi}\ (\text{ml} \cdot \text{min}^{-2}) \cdot \text{BSA}\ (\text{m}^2)$$

where, *fc* is heart rate based on R–R interval measurement determined from the electrocardiography (ECG) first derivative dECG/d*t* which provides a more stable signal than the ECG signal itself, BSA is body surface area calculated from the Haycock [14] formula ($\text{BSA}=0.024265 \cdot \text{body mass}^{0.5378} \cdot \text{height}^{0.3964}$) and SVi is the stroke volume index (SV/BSA).

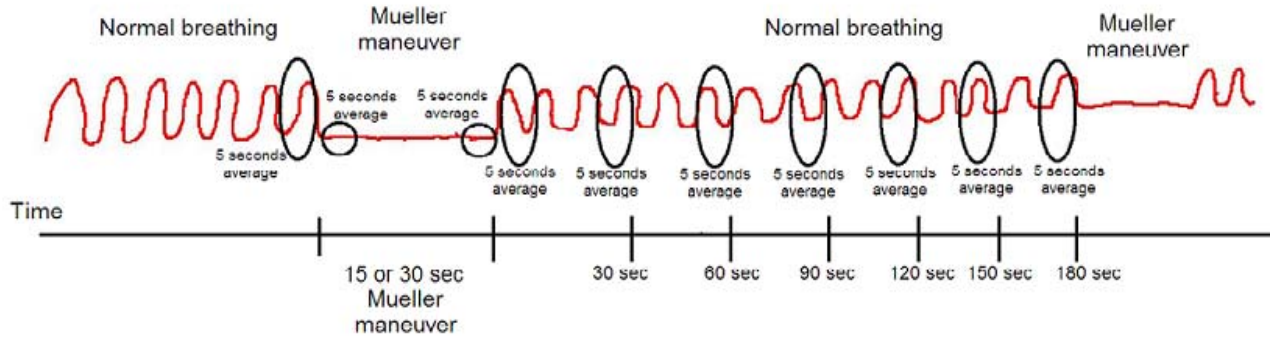
For measurement of impedance, four electrodes were placed on the subject's base of the neck and supraventricular fossa. In addition, two electrodes were used to measure a single ECG signal (positions V1 and V6). To ensure that breath holding was accomplished, thorax and abdomen movement together with oxygen saturation were monitored using Embletta (Flaga Medical Devices, Reykjavik, Iceland).

Data Analysis

Data for SV, MCI and SVR were recorded every second and analyzed during and post MM. Data were filtered to exclude outliers on different episodes corresponding to apnea or normal breathing (5 minutes of normal breathing, 30-second MM, and 3 minutes normal breathing between apneas). To identify outliers, score values generated for each beat were converted to standard scores (z-scores), using SPSS version 17 (SPSS Inc, Chicago, IL). Values representing extremes, i.e., had z-scores smaller than -2.5 or larger than 2.5, were regarded as outliers and discarded. Overall, data lost were less than 4%. To determine an individual "apnea effect" score for each measure (e.g., SV), the average value computed for the last 5 seconds of the subject's normal breathing period was subtracted from the average of the last 5 seconds of the apnea period. Thus, the effects of apnea were depicted as a temporal change between the end of normal breathing and the final 5 seconds of the apneic stress (Figure 1).

To determine if each type of MM (15 sec and 30 sec) provided stable cardiac responses within a day and between days, 2X3 [(first and second) and (day1, day2, day3)] repeated measures ANOVA was used to evaluate responses for each variable. The effect of MM type (15 sec, 30 sec), time (first, second) and day of testing (first, second or third) on each variable was studied using $2 \times 2 \times 3$ ANOVA for repeated measures. Coefficient of variation was calculated to show any differences between days. Intra-class correlation was used to generate reliability coefficients for blood pressure measurements obtained before and after the four MM. A p value < 0.05 was considered statistically significant. Data were analyzed using SPSS version 17 (Chicago, IL).

Figure 1. Example of data averaging for Mueller Maneuver and normal breathing episodes



RESULTS

Anthropometric data for the 15 healthy male volunteers are in Table 1. Mean ± SEM values from normal breathing periods are in Figure 2. SV and MCI decreased every testing day, as a function of subjects performing 4 MM. In the first day SVR was increased after 4 MM (from 1,083.1 ± 25.1 to 1,162.8 ± 33.5, P = 0.002). The same trend was seen in days two and three (P = 0.0001 and P = 0.0001, respectively).

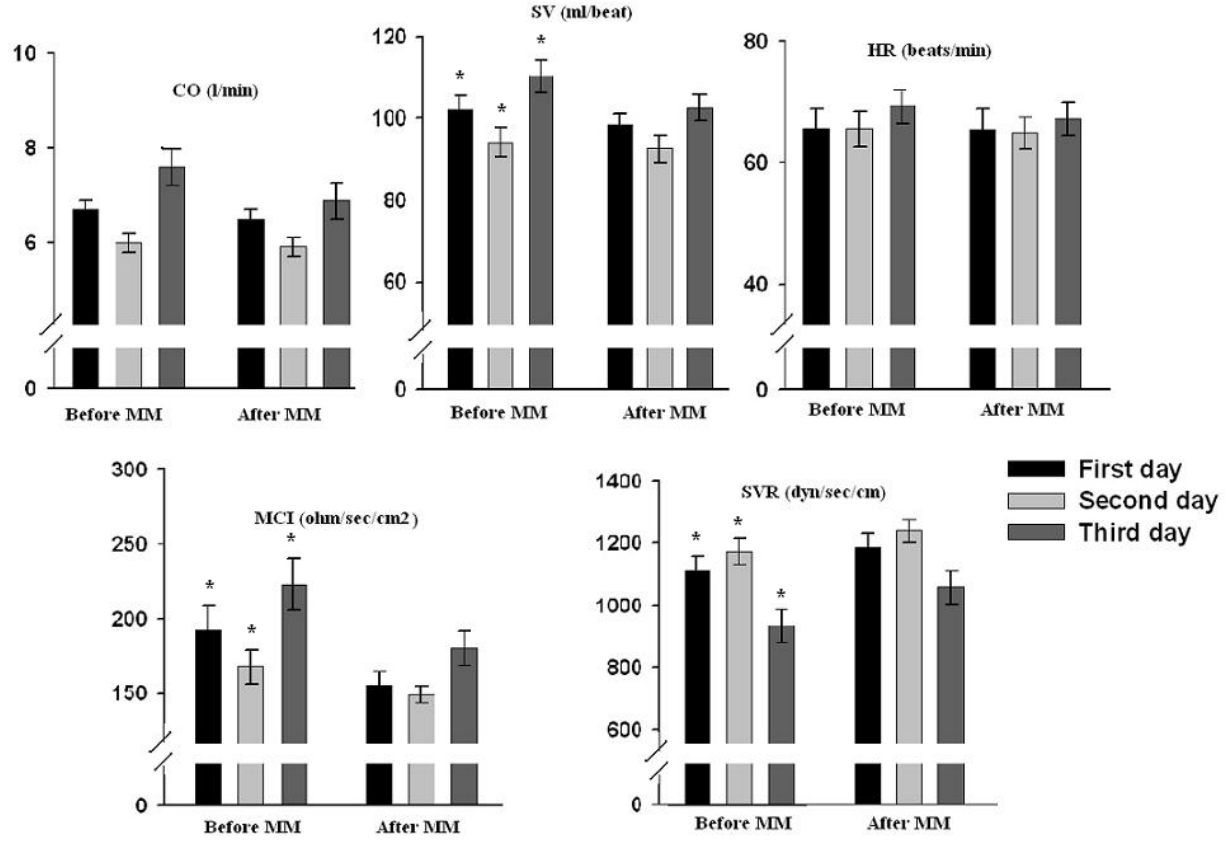
Table 1.

Subject characteristics

	Subjects (n = 15) Mean ± SD
Age, yr	37.7 ± 5.6
BMI, kg/m^2	22.8 ± 2.1
Neck circumference, cm	38.1 ± 2.1
SBP, mm Hg	117.3 ± 5.6
DBP, mmHg	76.1 ± 7.3
ESS	5.8 ± 1.8

BMI, body mass index; SBP, systolic blood pressure; ESS, Epworth Sleepiness Scale [9]

Figure 2. Cardiac variables before and after four Mueller Maneuvers



Data are presented as mean ± SEM.
CO, cardiac output, SV, stroke volume; HR, heart rate; MCI, contractility; SVR, systemic vascular resistance; MM, Mueller maneuver.
*P < 0.05 compared to after MM response.

SBP and DBP did not change after 4 MM in any of the days (Table 2).

Cardiac responses during 15 sec MM are in Figure 3. SV changes were similar within days (P = 0.54) or between days of testing (P = 0.09). The interaction between testing within a day and different days of testing failed to reach statistical significance (P = 0.8). CO, HR, MCI and SVR changed the same during 15 sec MM with no statistical significance within day or between days of testing.

Results from the 30 seconds MM are in Figure 4. Cardiac output and HR changed similarly within day or between three trials. For SV changes, there were no significant difference within

day (P = 0.8) or between days of testing (P = 0.4). The interaction between testing within a day and different days of testing was not significant (P = 0.1). MCI changes were similar within day (P = 0.1). In the first day of testing, MCI changes during MM were greater than the following two days (P = 0.05). The interaction between testing within a day and different days of testing failed to reach statistical significance (P = 0.4). During 30 sec MM, SVR changed similarly within day (P = 0.4) or between days of testing (P = 0.5).

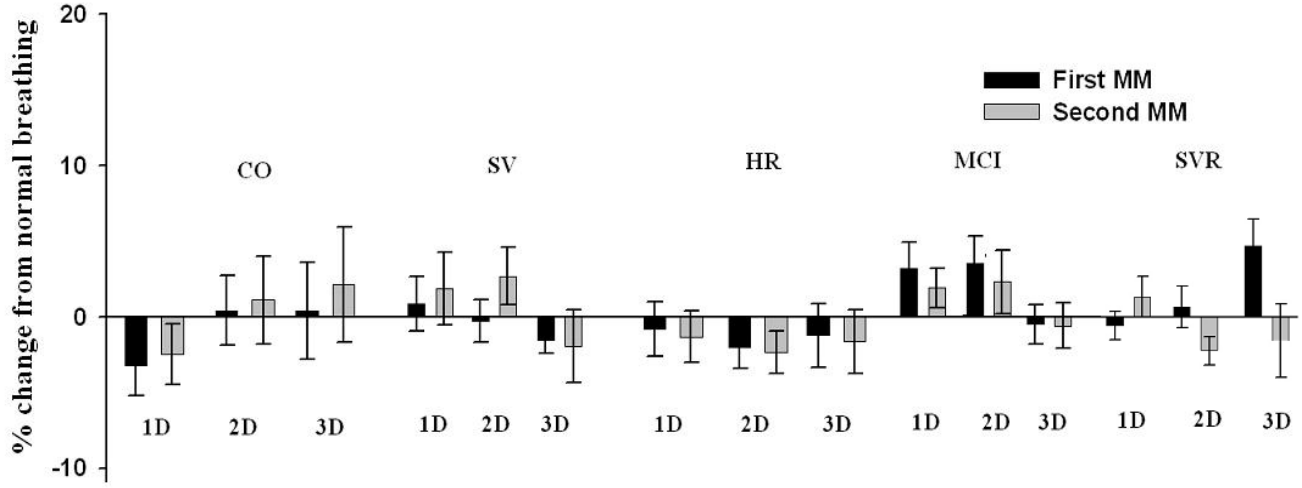
Table 2.

Intra-class reliability coefficients for systolic blood pressure and diastolic blood pressure

	r value		
	Day 1	Day 2	Day 3
SBP	0.90	0.84	0.94
DBP	0.76	0.83	0.73

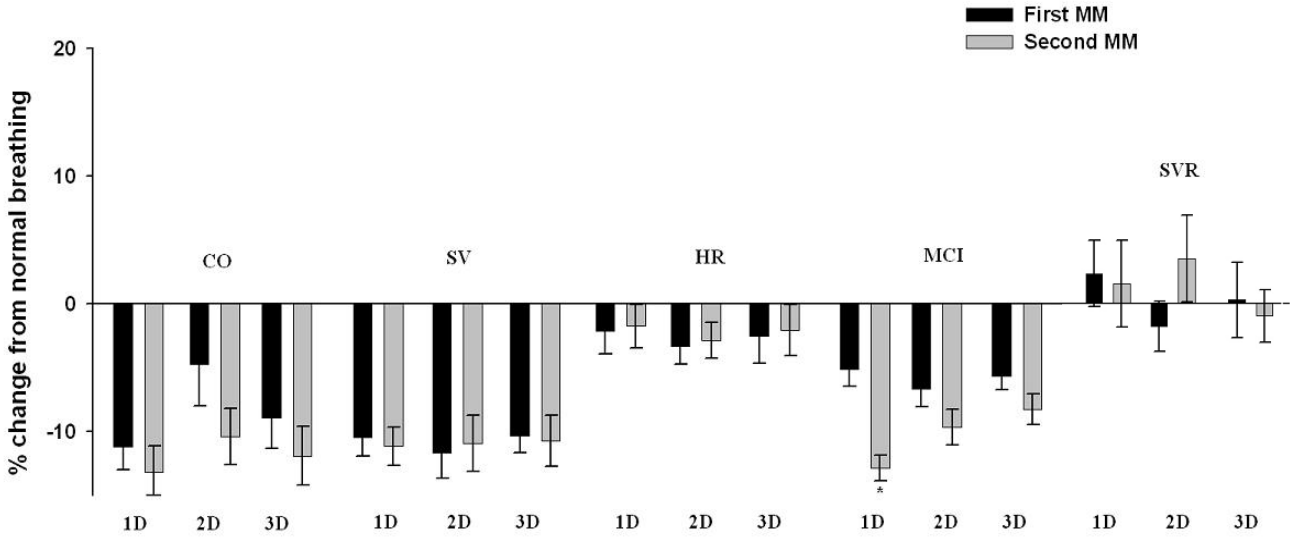
SBP, systolic blood pressure; DBP, diastolic blood pressure

Figure 3. Percent changes from normal breathing of cardiac variables during 15 seconds Mueller Maneuver



Data are presented as mean ± SEM.
CO, cardiac output, SV, stroke volume; HR, heart rate; MCI, contractility; SVR, systemic vascular resistance; MM, Mueller maneuver; D, day

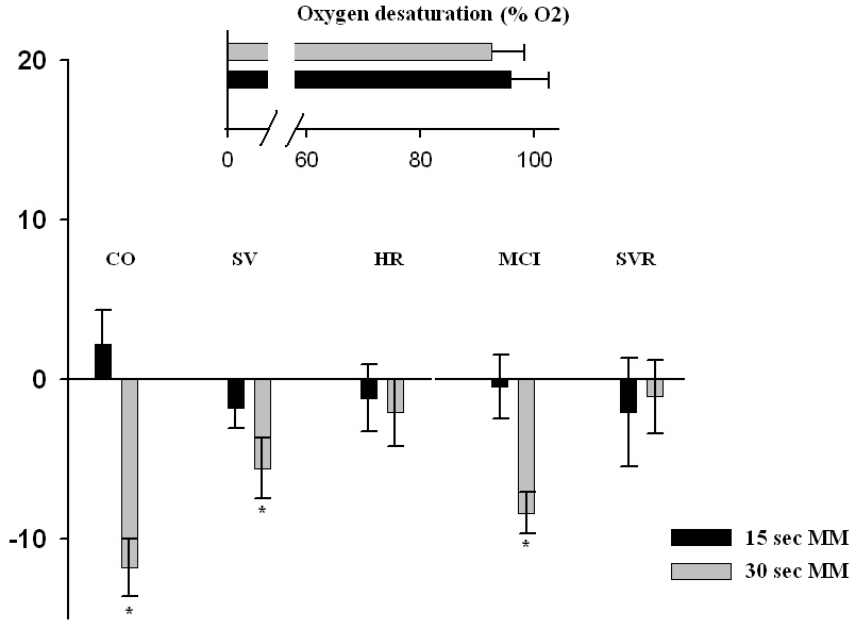
Figure 4. Percent changes from normal breathing of cardiac variables during 30 sec Mueller Maneuver



Data are presented as mean ± SEM.
CO, cardiac output, SV, stroke volume; HR, heart rate; MCI, contractility; SVR, systemic vascular resistance; MM, Mueller maneuver; D, day
*P < 0.05 compared to Days 2 and 3 for the corresponded apnea.

Comparing cardiac responses based on length of MM, a 30 sec MM produced a more pronounced and consistent change in CO, SV and MCI with no significant differences within day or between days of testing (Figure 5). After analyzing changes resulted from 30 sec MM, the coefficient of variation (CV) for the three trails had similar values on the first and second MM for all the cardiac variables with values ranging from 8.7 - 21.3% (Table 3).

Figure 5. Percent changes of cardiac variables during 30 seconds vs 15 seconds Mueller Maneuver



Data are presented as mean ± SE.
CO, cardiac output, SV, stroke volume; HR, heart rate; MCI, contractility; SVR, systemic vascular resistance; MM, Mueller maneuver; % O_2, saturation of oxygen in the blood at the end of Mueller Maneuver.
*P < 0.05 compared to 15 sec MM.

Table 3. Coefficients of Variation (CV) for cardiac output, stroke volume, heart rate, myocardial contractility and systemic vascular resistance calculated over three days. Values represent last 5 seconds period of normal breathing before MM and last 5 seconds of breath-holding during MM.

	CV (%)			
	First 30 sec MM		Second 30 sec MM	
	Start of MM	End of MM	Start of MM	End of MM
CO (l/min)	10.31	9.22	10.43	10.11
SV (ml/beat)	10.22	12.63	13.95	14.94
HR (beats/min)	9.09	8.72	10.3	9.2
MCI (ohm/sec/cm^2)	18.2	17.7	21.3	21.3
SVR (dyn/sec/cm)	12.8	11.5	14.56	11.1

CV, coefficient of variation; CO, cardiac output; SV, stroke volume; HR, heart rate; MCI, contractility; SVR, systemic vascular resistance; MM, Mueller maneuver

DISCUSSION

Trans-thoracic impedance cardiography is a non-invasive cost effective methodology used to estimate SV at rest, during steady state and non-steady state exercise conditions.[15]

There are currently more than 200 studies in the literature correlating impedance determinations of CO with some invasive criterion standard measurements. Several comprehensive meta-analyses of this literature have found overall correlations ranging from 0.82 to 0.93. [16,17]

Most of the validation studies were performed in an effort to provide high-quality intensive care hemodynamic monitoring without increasing morbidity. In a large multicenter study, the impedance cardiography provided stable signals and reliable CO estimations even under extenuating emergency conditions. That study comprised 2,081 simultaneous bioimpedance and thermodilution CO measurements in 860 critically ill patients from the emergency department, operating room, and intensive care unit. The correlation coefficient was 0.85; $r^2 = 0.73$. No instances of spurious impedance values that would have led to incorrect or untoward effects were observed.[18]

Reproducibility in stable patients without medical interventions has been demonstrated, with excellent intraday reproducibility of trans-thoracic impedance measurements ($r = 0.86$). Inter-day reproducibility was lower, but still good ($r = 0.65$).[19] These studies were designed to examine the reproducibility of bioimpedance measures alone and do not provide information about the accuracy of trans-thoracic impedance measurements.

The lack of more extensive use of this technology comes from the simplistic approach of the equations installed on the devices. [20] These use baseline impedance which is greatly affected by hydration status, chest wall configuration, distance between electrodes and resistivity of the blood. Conversely, PhysioFlow® technology is using a modified calculation method, basically relying on a Δ change in impedance.[5]

This new cardiograph was validated against the direct Fick method. Mean differences between CO values obtained by the direct Fick method and the Physioflow® device were not significant during rest (0.04 l/min),[5] sub-maximal exercise (0.29 l/min),[5] or maximal incremental exercise (0.58 l/min).[6] High correlation values between the two methods were found during rest (r = 0.89),[5] sub-maximal exercise (r = 0.85),[5] and maximal exercise (r = 0.94).[6]

The reliability of "gold standard" methods of cardiac output determination (direct Fick and dye dilution reliability) was around 5–10%. [21] Non-invasive methods for CO measurements proved as reliable as the invasive ones with CV ranging from 5 to 20%. [21] Data on the reliability of thoracic bioimpedance determinations of CO using the PhysioFlow® device are scarce and there appear to be no data on breath holding testing. During an incremental cycle test to maximum, Richard et al.[6] noted a maximum 16% variation in CO between two days of testing. Welsman et al.[7] examined the reproducibility of VO_{2max} using SV and CO obtained from PhysioFlow® in 20 subjects over three trials. Their CV was 9.3% for both CO and SV. These were comparable with values obtained for CO (10.2%) using acetylene rebreathing[21] and SV (8.5%) using Doppler-echocardiography.[22]

In the present study, the typical error expressed as a CV for CO (9.2-10.4%) and SV (10.2 – 14.9%) were in line with results reported from previous studies. These differences compared to other studies may be explained by the select sample of our participants and because our measurements were obtained in a highly relaxed stage as opposed to exercise. In addition, the present study did not consider the effects of variations in negative thoracic pressure between trials and days, due to variations in subjects' inspiratory efforts

During normal breathing, SV decreased every day, as a result of performing four MM (Figure 2). This response is supported by the decrease in MCI and the increase in SVR, two of the factors

responsible for SV alterations. Negative intrathoracic pressure, along with hypoxemia generated by the MM (Figure 5), could lead to increased sympathetic activation and alter the venous return, which is an important mechanism for maintaining a constant SV. Within MM, SV changed little during the 15-second maneuver, but consistently decreased by 10-11 % ($p < 0.05$) when the duration was 30 seconds. Even though not significantly, when subjects were exposed to 15 sec MM's, SV and its determinants, changed from positive to negative and vice versa from one MM to another in the same day, or from one day to another. In contrast, 30 sec MM induced the same response between apneas or between days, i.e., SV and MCI decreased, as SVR increased. This finding is in agreement with previous published Doppler echocardiographic studies showing that SV is reduced during simulations of OSAHS.[23] In another study, Bradley and colleagues [24] used MM to look for differences in hemodynamic responses between healthy subjects and CHF patients. Using continuous-wave echocardiographic Doppler technique, they showed a decrease of 13.8% in SV index during 15 sec MM. This decrease was near what we found in our 30 sec MM, but different from our 15 sec MM. This difference might be caused by the high negative intra-thoracic pressure that their subjects were generating during MM (- 30 cm H_2O). Also, they studied just 9 subjects and that can be an exclusive group with performances near to the higher end.

The increase in intrathoracic pressure with breath-holding is a plausible mechanism for mediating the reduction in SV observed with the 30-second maneuver. Blunting of preload due to increased intrathoracic pressure, together with the increased afterload attributable to increased SVR, may explain the diminution of the SV under these conditions. The new impedance cardiograph was able to consistently detect decreases in MCI and increases in SVR that would be linked to diminished SV during MM. Using Doppler imaging technology, Bayram et al.[25] found

that OSAHS patients had lower left ventricle diastolic and systolic functions and these improved with 6 months CPAP therapy. Furthermore, cardiac contractility assessed by isovolumic acceleration, was improved with CPAP therapy, and proved to be the most sensitive parameter of left ventricle systolic function. With CPAP therapy the upper airway tract is kept open and precludes the sympathetic over-activation, negative intrathoracic pressure and afterload increase.

Before this technology can be used in any clinical setting, any measurement should provide adequate reproducibility. A high reproducibility is not enough to guarantee accuracy, but it quantifies the degree to which the test produces the same result each time it is conducted. In the present study no differences were found in any of the cardiac variables across the three trials.

These findings should be viewed within the limitations of this study. Pressure generated during MM was not measured and we are not able to determine how differences in the negative intrathoracic pressure might alter the within and between days comparisons. In the present study the longest MM was 30 seconds and different responses could be obtained if subjects were exposed to longer MM. To control for any potential ethnic and gender cardiac influences, subjects included were Caucasian males, therefore, these results may not be applicable to other groups. Although, careful screening was performed to ensure inclusion of healthy subjects, no diagnostic test for OSAHS was undergone. Sleep questionnaires and anthropometric measurements were used to define subjects with OSAHS. The present study did not address the accuracy of this bioimpedance technique and assessed just reproducibility. As reliability of this cardiograph was previously demonstrated, current data focused on repeatability of cardiac monitoring during breath holding. In the present study, reliability of post MM responses were not assessed, and this could be of importance for more comprehensive understanding of the effects of MM on cardiac function. This new cardiograph can be used in a clinical setting to assess any

occult cardiac function dysfunctions that patients with OSAHS are prone to develop. Continuous positive airway pressure (CPAP) therapy is the treatment of choice for patients with OSAHS and is has been shown to improve left ventricular function.[25,26] In order to use this methodology as screening test for detecting any cardiac problems in OSAHS patients, we recommend incorporating a 30 seconds MM test at the beginning of their clinical pathway. We believe that patients need a practice session, a day before their test and this can be well accommodated within the required visits to the sleep clinic.

CONCLUSION

These findings support the concept that the recent advancements in impedance cardiography provide the opportunity to assess dynamic changes in cardiac function under conditions of stressful respiratory maneuver in apparently healthy males. The performance of four successive MM in one day of testing did not have any effect on the resting CO and HR responses under conditions of normal breathing in supine subjects. However, SV decreased after performance of four MM, which was consistent with simultaneous observed decreases in MCI and increase in SVR. The main factor responsible for these changes at rest could be elevated sympathetic activation triggered by the acute cumulative effect of four desaturations that accompanied these MM. The difference in level of oxygen between the 15 and 30 sec apnea was probably the factor behind the systematically, robust cardiac changes displayed by the 30 sec MM compared to 15 sec MM. A test with this new cardiograph that will monitor cardiac changes during 2 MM of 30 sec may be useful in prioritizing patients for polysomnography and CPAP therapy, facilitating expedited medical treatment in high-risk patients.

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Chapter 4

Influences of obstructive sleep apnea in adults with or without mild hypertension on acute changes in cardiac function associated with a Mueller maneuver challenge test

Abstract

Objective:

To assess dynamic cardiac functional responses to negative intrathoracic pressure (Mueller Maneuver) in obstructive sleep apnea hypopnea syndrome (OSAHS) patients with and without hypertension.

Design:

After inclusion criteria were met, cardiac monitoring was performed using a non-invasive bioimpedance device

Setting:

Private inpatient sleep clinic.

Participants:

Fifteen healthy men (37.7 ± 5.6 yr) and two groups of 10 OSAHS patients, without hypertension (HTN) (44.2 ± 10.7 yr) and with HTN (34.8 ± 6.2 yr).

Measurements and results:

Subjects underwent two 30 sec Müeller Maneuvers (MM) to assess cardiac output (CO), heart rate (HR), stroke volume (SV), myocardial contractility (MCI), and systemic vascular resistance

(SVR). During MM, there were similar changes in SV, HR, and SVR in all three groups. CO decreased by nearly 13% during MM in controls but not altered from the normal breathing values in either of the two OSAHS groups. In contrast, MCI was increased by nearly 12% above normal breathing values in the OSAHS group, but was not significantly changed in controls and OSAHS+HTN subjects. Changes in MCI were predicted by AHI and systolic blood pressure ($R^2 = 0.58$, $P < 0.03$ and $R^2 = 0.47$, $P < 0.001$, respectively). During 3 min after resumption of normal breathing following MM, in both OSAHS groups, cardiac responses rapidly returned to baseline within 30 sec, while the control group had a normal compensatory increase and returned to normal after 2 minutes.

Conclusions:

OSAHS and HTN were strong indicators of myocardial dysfunction. Increased autonomic sympathetic tone associated with chronic untreated OSAHS may be one of the mechanisms implicated in the blunted response to the respiratory challenge of MM observed in patients with OSAHS. The added HTN did not to the abnormal cardiac responses seen in OSAHS. Performing a simple cardiac monitoring test can help improve the clinical treatment algorithm of OSAHS patients.

INTRODUCTION

Obstructive sleep apnea hypopnea syndrome (OSAHS) is a chronic disorder caused by repetitive collapse of the upper airway during sleep, resulting in periods of partial and/or total airway obstruction. These respiratory events result in intermittent hypoxemia and hypercapnia, cortical arousals, and surges of sympathetic activity that lead to nocturnal hypertension.[1] Patients with OSAHS not only experience dramatic fluctuations in blood pressure (BP) during sleep, but their risk of daytime hypertension (HTN) also increases.[2,3] Large epidemiological studies have demonstrated a strong and consistent link between OSAHS and HTN.[4-6] Hypertension has been reported in 28–57% of OSAHS patients and its severity is positively related to apnea severity.[5,7-9] Pharmacological treatment of HTN in OSAHS can be effective; however, there is still a lack of robust randomized control data to establish whether treatment of OSAHS improves drug efficacy.[10] In contrast, a number of well designed studies demonstrated decreases in blood pressure (2 to 3 mmHg) following treatment of OSAHS with continuous positive airway pressure therapy (CPAP).[11] Both diseases are associated with adverse cardiac loading conditions and an elevation in sympathetic tone. Thus, exaggerated cardiovascular responses to OSAHS could be expected in patients with coexisting HTN. Negative swings in intrathoracic pressure during OSAHS may lead to a larger impact on stroke volume (SV) in the presence of HTN, mainly due to an increase in left ventricle (LV) afterload.[12] Therefore, the impact of obstructive apneas on ventricular function arising from these chronic effects might be greater in the presence of HTN. In these patients, apnea episodes may cause significant reductions in SV and expose the heart or brain to increased risk of ischemia that can trigger a cascade of cardiovascular dysfunctions. Successful treatment of OSAHS with CPAP has been shown to improve right ventricular function, LV dimensions, and contractility. Thus, early recognition of any hidden cardiac dysfunction may delineate high risk OSAHS patients that require immediate treatment.

Cardiac function was accurately estimated during resting conditions by various techniques such as direct Fick, thermodilution, or non-invasive methods involving use of inert reference gases, e.g., carbon dioxide or acetylene rebreathing.[13] Although these methods were accurate and reliable, the use of catheters make these methods invasive and adds risk for the subjects. Also, they must be perfomed in well-equipped and expensive environments like intensive care units and cardiac catheterization labs. A refined non-invasive technique is measurement of cardiac function from thoracic electrical bioimpedance (TEB).[14] This provides relative simplicity of use and permits non-invasive automated measurements of beat-to-beat SV, myocardial contractiliy (MCI) and systemic vascular resistance (SVR). The TEB method uses changes in transthoracic impedance during cardiac ejection to calculate SV. The device used in the current study does not utilize basal thoracic impedance measurement or the estimation of blood resistivity in its algorithm. Furthermore, the position of the electrodes is not critical for the accuracy of the measurements. This concept and methodology have been validated at rest and at exercise, [15] during a maximal progressive exercise [16,17] as well as at rest in emergency room and intensive care unit trauma patients.[18] The objective was to characterize the changes of hemodynamic responses to negative intrathoracic pressure in OSAHS patients with and without HTN versus healthy subjects. This could provide data to support performance of a cardiac test in patients with OSAHS and assess their risk for cardiac problems or the treatment efficacy.

METHODS

Three groups were studied performing 2 simulated apnea episodes lasting 30 seconds each. The first group consisted of OSAHS patients with HTN (n = 10), the second group included OSAHS patients without cardiac problems (n = 10), and the last group included healthy patients without OSAHS (n = 15).

Patients with OSAHS were included in the study if they were recently diagnosed with an apnea hypopnea index (AHI) > 15 and not undergoing CPAP treatment. If patients had a BP > 130/90 mmHg (pre-hypertension)[19] in two different days at the sleep clinic, they were included in the OSAHS+HTN group. Patients suffering from angina or a myocardial infarction within 3 months of the study, patients with primary valvular heart disease, and those with clinically significant Q waves or evidence of ST/T wave abnormalities were excluded. All subjects were non-smokers, free of neurological conditions (stroke, Parkinson's and peripheral neuropathy), diabetes and respiratory disease, and not taking any cardiovascular medication. The control subjects were free of cardiovascular disease as assessed by recent medical examination and confirmation/referral by primary care physician. To limit the probability of OSAHS occurrence, the control group completed an Epworth Sleepiness Scale [20] and a Berlin Questionnaire [21], two widely used subjective measures of daytime sleepiness. Subjects were excluded if they had an Epworth score > 10 and were categorized at high risk using the Berlin. Furthermore, they were excluded if their neck circumference was > 43 centimeters[22] and waist circumference higher than 102 centimeters.[23] Control patients were recruited from local area volunteers. OSAHS subjects were patients admitted to a local sleep clinic with symptoms consistent with sleep apnea, i.e., reported breath cessation, snoring, and excessive daytime sleepiness. Written informed consent was obtained from all subjects and the institutional review board of the Virginia Tech authorized the study protocol.

OSAHS subjects were those patient volunteers who were referred to the Sleep Disorders Network of Virginia to undergo attended diagnostic polysomnography studies, between June 2009 and February 2010 using a digital recording system (Alice 3 system, Respironics, Murrysville, PA). The following variables were recorded: 2-channel electrooculography, 3-

channel electroencephalography, 1-channel chin electromyography, oronasal airflow using a thermocouple, tracheal microphone, thoracic and abdominal strain gauge movement sensors, 2 leg movement sensors recorded to 1 channel, 1-channel electrocardiography, and pulse oximetry. The marking of disordered breathing events, desaturations, periodic limb movements, and sleep staging were performed according to the American Academy of Sleep Medicine recommendations.[24]

Cardiac variables were collected non-invasively using a TEB device (PhysioFlow PF-05 Lab1, NeuMeDx, Bristol, Pa). The PhysioFlow® device and methodology have been thoroughly described elsewhere. [15] In brief, the bioimpedance method of CO determination uses changes in trans-thoracic impedance during cardiac ejection to calculate SV. The PhysioFlow® emits a high-frequency (75 kHz) and low-amperage (1.8 mA) alternating electrical current via electrodes.

Cardiac output is based upon the following formula:

Cardiac output ($lmin^{-1}$) = *fc* (beats · min^{-1}) x SVi (ml · min^{-2}) x BSA (m^2)

where, *fc* is heart rate based on R–R interval measurement determined from the ECG first derivative dECG/d*t* which provides a more stable signal than the ECG signal itself, BSA is body surface area calculated from the Haycock [25] formula (BSA=0.024265 · body $mass^{0.5378}$ · $hight^{0.3964}$) and SVi is the stroke volume index (SV/BSA).

For measurement of impedance, four electrodes were placed on the subject's base of the neck and supraventricular fossa. In addition, two electrodes were used to measure a single ECG signal (positions V1 and V6). To ensure that breath holding was accomplished, thorax and abdomen

movement together with oxygen saturation were monitored using a portable somnographic system (Embletta PDS,Flaga Medical Devices, Reykjavik, Iceland).

The Müeller Maneuver (MM) is a breathing technique that requires forced and sustained inspiratory efforts against a closed epiglottis. Previous work confirmed that the MM closely simulated changes in intrathoracic pressure produced during sleep in subjects with OSAHS.[15,26] Subjects were tested supine performing two MM of 30 seconds duration with at least 3 minutes of normal breathing in between to promote normalization of cardiac responses. PhysioFow® provided reliable results when used for 30 sec MM with coefficient of variation ranging from 9.2 – 10.4% for cardiac variables measured in the present study.[27] Five minutes of normal breathing was required before and after the performance of MM. Before testing started, subjects were taught the MM technique and directed to hold their breath after a normal exhalation maintaining a mid trans-thoracic pressure. To eliminate the possibility of starting the MM in the middle of exhalation or at the beginning of inhalation, subjects were allowed to choose their MM starting points. For a correct timing, subjects learned a few command signals that were used during testing. To mark the start of the apnea, subjects showed a thumb up, without moving the arm, as soon as they begin their breath holding. After 30 sec passed, test administrator said "breath" to the subject, which let them know that they may inhale and resume regular breathing. After breath held for the specified time, all subjects were given instruction to immediately inhale.

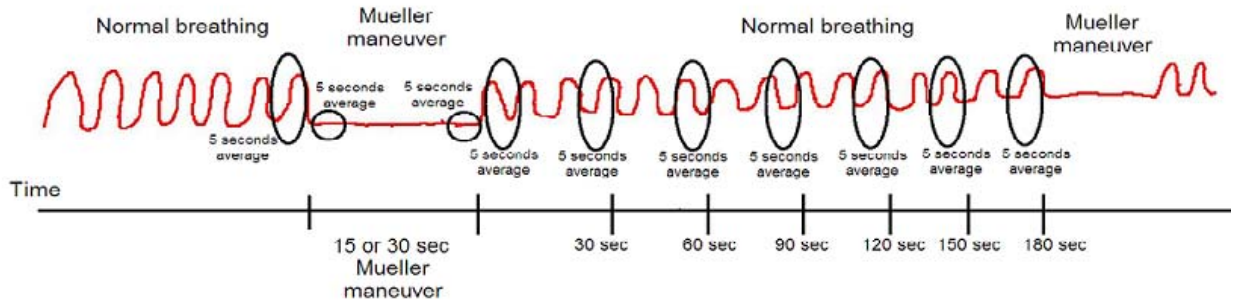
Data Analysis

Data for SV, MCI and SVR were recorded every second and analyzed during and post MM. Data were filtered to exclude outliers on different episodes corresponding to apnea or normal breathing (5 minutes of normal breathing, 30-second MM, and 3 minutes normal breathing

between apneas). To identify outliers, score values generated for each beat were converted to standard scores (z-scores) using SPSS version 17 (SPSS Inc, Chicago, IL). Values representing extremes, i.e., had z-scores smaller than -2.5 or larger than 2.5, were regarded as outliers and discarded. Overall, data lost was less than 4%. To determine an individual "apnea effect" score for each measurement (e.g., SV), the average value computed for the last 5 seconds of the subject's normal breathing period was subtracted from the average of the last 5 seconds of the apnea period. Thus, the effects of apnea were depicted as a temporal change between the end of normal breathing and the final 5 seconds of the apneic stress. For post-MM analysis, the last 5 seconds of every 30 seconds period following a MM was averaged and expressed as percentage from the normal breathing period prior to MM (Figure 1).

Data recorded for each cardiac variable were analyzed using two-way ANOVA, with repeated measures for the time factor to determine if SV, MCI and/or SVR were changed either during or after the MM and if such responses different between the three groups. To test for significant changes caused by performing 2 MM, data from the last minute of resting breathing was compared with the last minute of recovery breathing using Student's paired t-test. Additionally, one-way ANCOVA were performed to compare cardiac variables for these three groups, with OSAHS severity, BP and BMI being the covariates. If statistically significant main or interaction F ratios were found, Tukey test was performed to isolate sources of differences. A P value of 0.05 was accepted as indicating significance for all statistical tests.

Figure 1. Example of data averaging for Mueller Maneuver and normal breathing episodes



RESULTS

Characteristics of the subjects

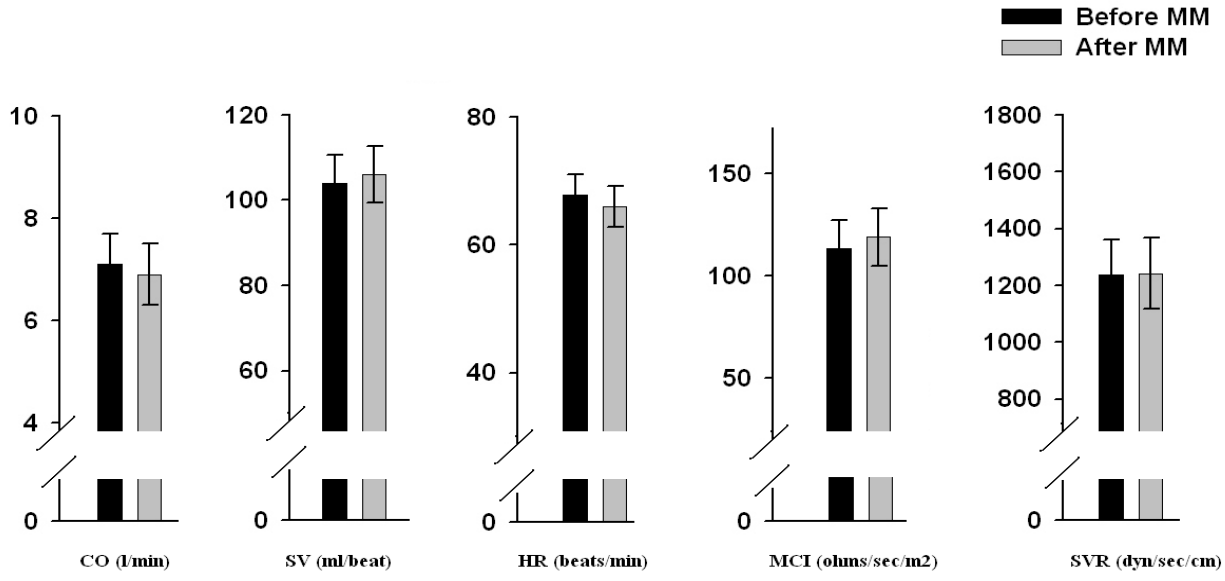
Patients' characteristics are summarized in Table 1. Age was not different between groups and, as expected, the control group did not show any of the features of OSAHS (high values for BMI, neck circumference, or ESS scores [20]). No one from the control group was categorized as high risk for OSAHS using the Berlin Questionnaire [21]. Systolic blood pressure was the lowest in the controls (117.3 ± 5.6 mmHg) compared with OSAHS patients (123.2 ± 6.2) and OSAHS+HTN patients (139.7 ± 3.2). Performing 2 MM of 30 seconds duration did not induce any changes in CO, SV and HR in any of the groups (Figures 2-4). In addition, MCI and SVR did not change following the MM. However, controls showed a higher MCI compared to all OSAHS patients and a lower SVR compared with patients with OSAHS and HTN (Figures 2-4). No differences were found when the two MM were compared with intra-class reliability coefficients ranging from 0.6 to 0.8 ($P < 0.002$). Thus, for all statistical interpretation, data obtained on the second MM was utilized.

Table 1 - Patient characteristics

	Control (n = 15)	OSAHS (n = 10)	OSAHS+HTN (n = 10)
Age, yr	37.7 ± 5.6	44.2 ± 10.7	34.8 ± 6.2
BMI, kg/m^2	22.8 ± 2.1*	33.3 ± 8.0	34.7 ± 6.2
Neck circumference, cm	38.1 ± 2.1*	42.3 ± 3.7	44.3 ± 2.9
SBP, mm Hg	117.3 ± 5.6*	123.2 ± 6.2**	139.7 ± 3.2
DBP, mm Hg	76.1 ± 7.3**	78.6 ± 4.8	84.7 ± 7.6
ESS	5.8 ± 1.8*	10.3 ± 5.0	13.4 ± 3.1
Berlin score[21], high risk-%	0	90	80
AHI	N/A	45.4 ± 37.1	36.3 ± 32.4
Lowest O_2 saturation	N/A	78.1 ± 8.5	82.8 ± 9.7
Time spent under 89% O_2	N/A	6.9 ± 7.1	9.3 ± 23.3
O_2 saturation (%)	92.7 ± 1.0	89.4 ± 1.3	89.4 ± 1.2

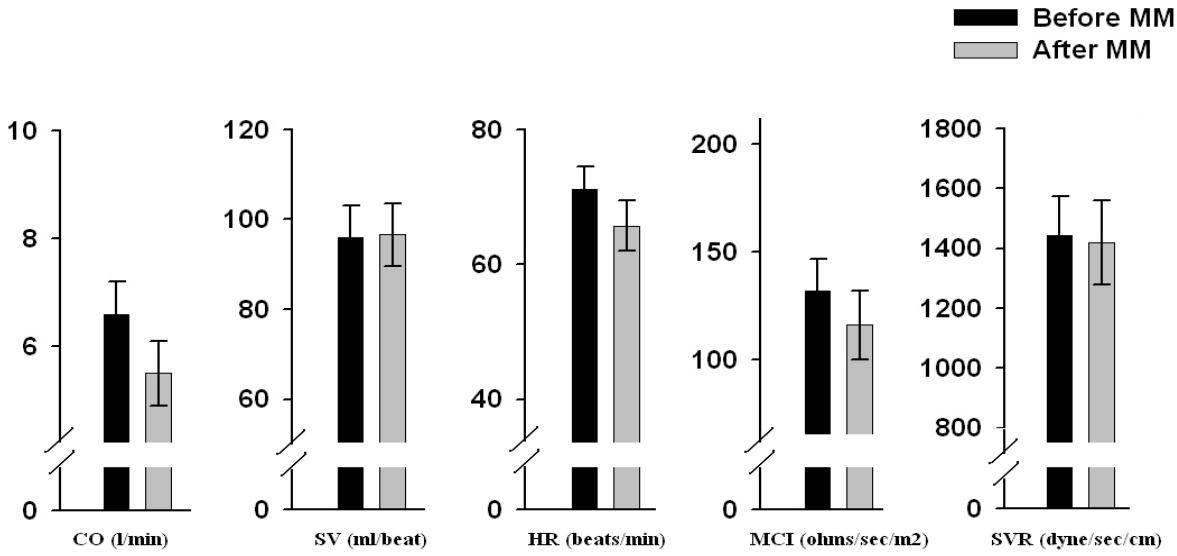
Data are presented as mean ± standard deviation. BMI refers to body mass index; ESS, Epworth Sleepiness Scale [20]; AHI, apnea hypopnea index; O_2 saturation, oxygen level at the end of 30 sec MM; Lowest O_2 saturation, lowest oxygen level during sleep test; Time spent under 89% O_2, Time spent in minutes at arterial O_2 saturation of < 89% during sleep test.
MM. *P < 0.05 compared to both OSAHS groups, **P < 0.05 compared to OSAHS+HTN.

Figure 2 - Cardiac variables before and after two Mueller Maneuvers (MM) in OSAHS patients



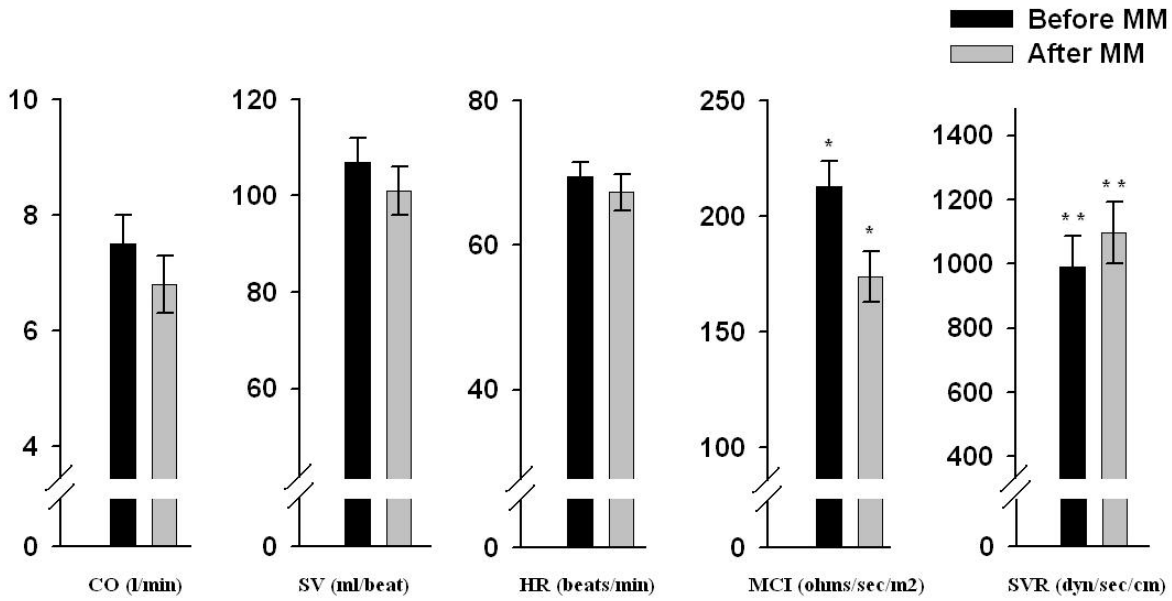
Data are presented as mean ± standard error of the mean. Abbreviations as in Table 2.

Figure 3 - Cardiac variables before and after two Mueller Maneuvers in OSAHS+HTN patients



Data are presented as mean ± standard error of the mean. Abbreviations as in table 2.

Figure 4 - Cardiac variables before and after two Mueller Maneuvers in controls

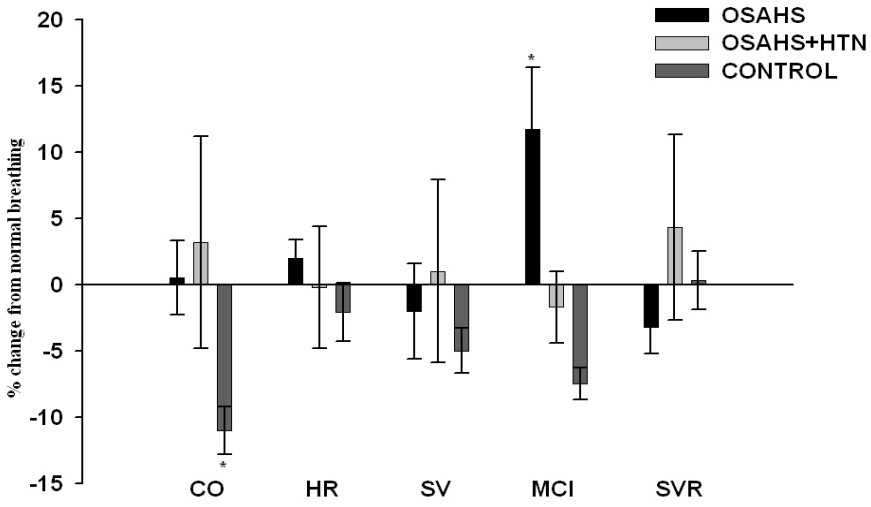


Data are presented as mean ± standard error of the mean. Abbreviations as in Table 2. *P < 0.05 compared with OSAHS and OSAHS+HTN groups; **P < 0.05 compared to OSAHS+HTN.

Responses during MM

Hemodynamic changes during MM for all three groups are illustrated in Figure 5. The control group showed a decreased CO during 30 seconds MM. All groups had the same change in HR during MM (-2.1% control, 2.1% OSAHS and -0.2% OSAHS+HTN). SV changes were not statistically significant between groups, with controls and OSAHS showing a decrease (-5.4% and -2.7% respectively) and OSAHS+HTN group an increase (1.1%). The SVR response to MM was highly variable, although not different between groups. While MCI increased in the OSAHS group (11.8%) at the end of the 30 sec MM, it decreased at this time in both the control and OSAHS+HTN groups (-7.5% and -1.7%, respectively). ANCOVA analysis showed that none of the between-group cardiac effects of MM were altered by adjusting analyses for individual differences in BMI. In contrast, OSAHS severity (AHI) and SBP were significantly related to MCI changes ($R^2 = 0.58$, $P < 0.03$, $R^2 = 0.47$, $P < 0.001$, respectively).

Figure 5 - Cardiac changes during 30 sec Mueller Maneuver

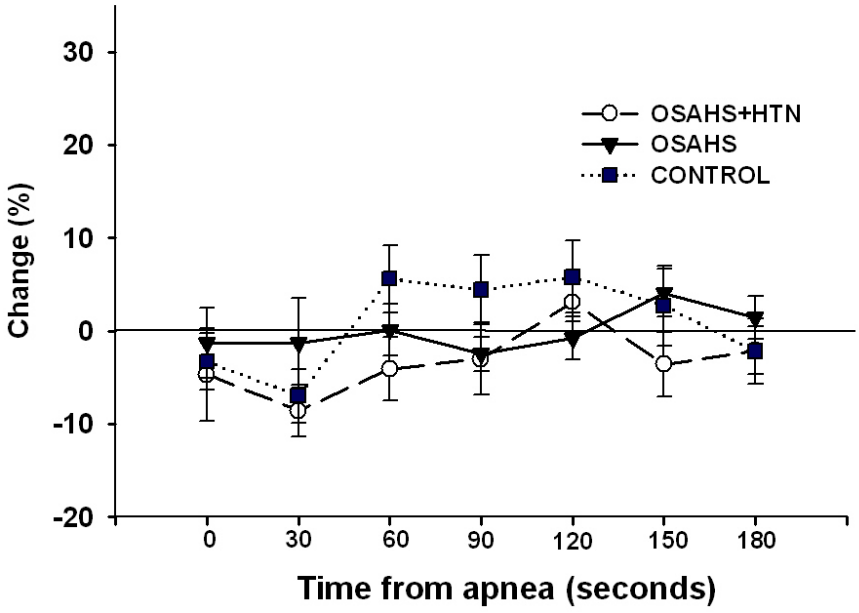


Data are presented as percentage change from normal breathing ± standard errors of the mean. Abbreviations as in Table 2. * $P < 0.05$ compared to the other groups.

Responses post MM

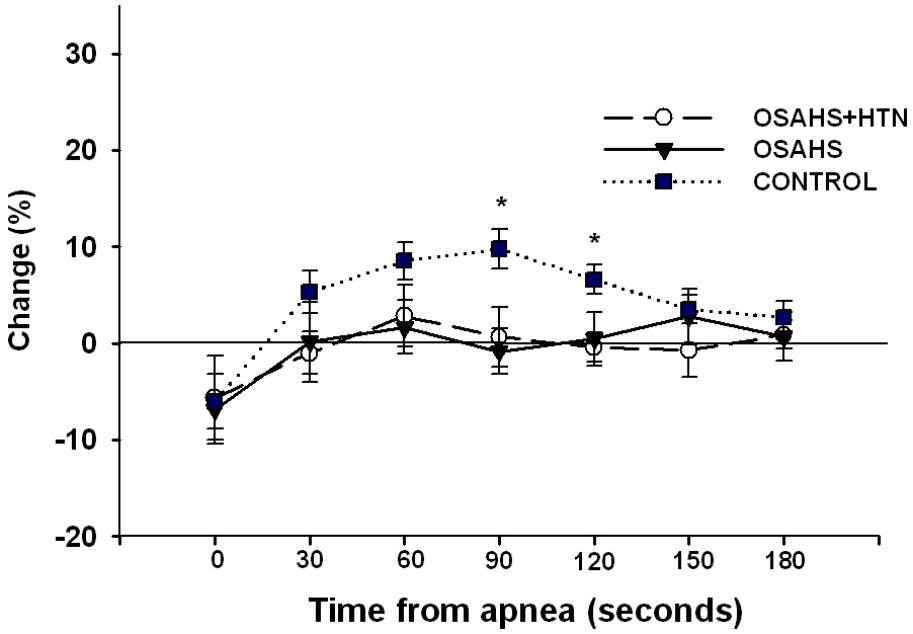
In the post-apnea period, SV in the controls increased in a compensatory fashion to maintain an unchanged CO and then returned to baseline by the end of the 3 minutes (see Figures 6 and 7). In contrast, both the OSAHS and OSAHS+HTN groups returned their SV to baseline within 30 seconds after termination of MM. The MCI was different only immediately after termination of the MM when the OSAHS group had a higher MCI than the control group (Figure 8: at time point 0 sec, difference was 18.9 ± 27.5 % versus -8.5 ± 11.9 %, $p<0.004$). The HR and SVR remained constant at 'normal breathing' baseline levels throughout the post-MM period in all three groups (Figures 9 and 10).

Figure 6 - Changes in cardiac output following 30 sec Mueller Maneuver.



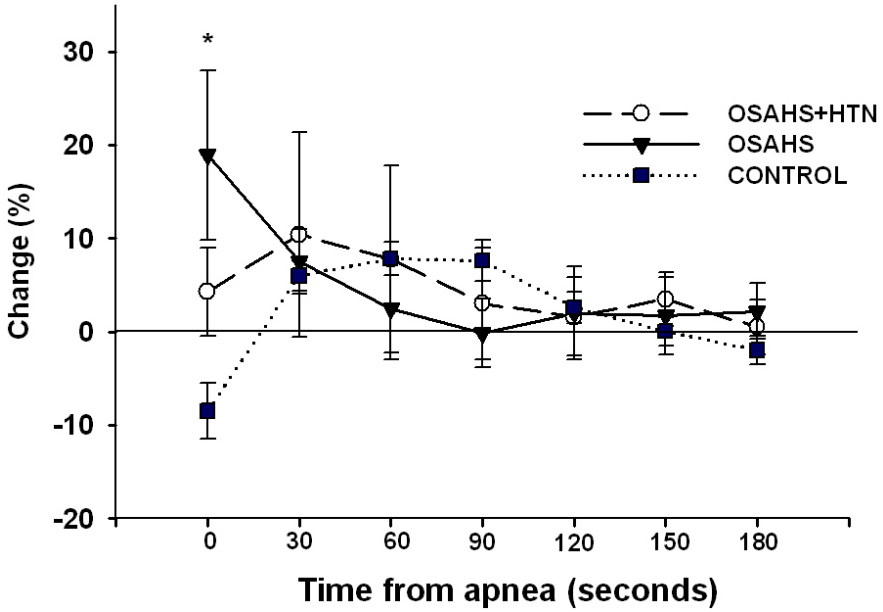
Data are presented as percentage change from normal breathing ± standard errors of the mean.

Figure 7 - Changes in stroke volume following 30 sec Mueller Maneuver.



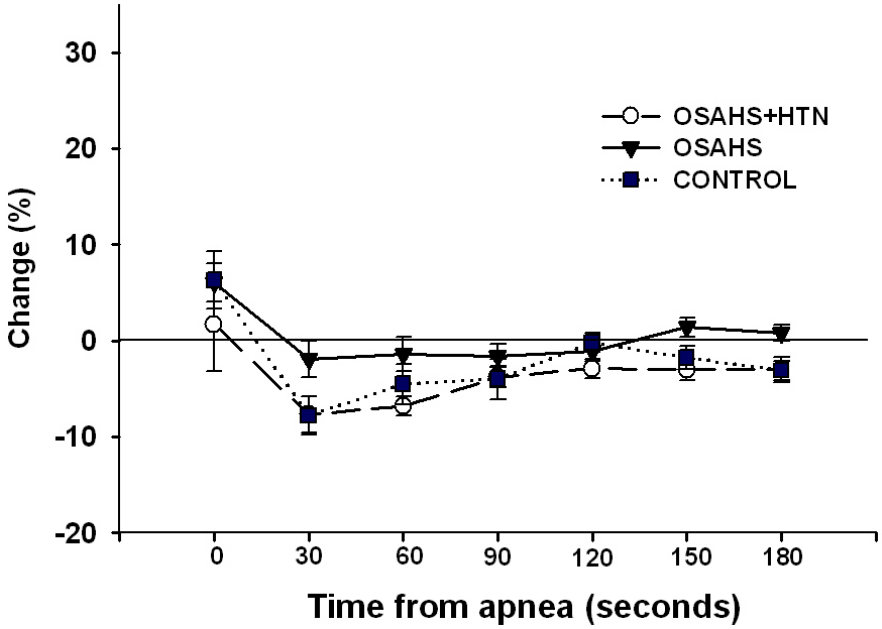
Data are presented as percentage change from normal breathing ± standard errors of the mean.
*P < 0.05 CONTROL compared to OSAHS and OSAHS+HTN groups.

Figure 8 - Changes in myocardial contractility following 30 sec Mueller Maneuver.



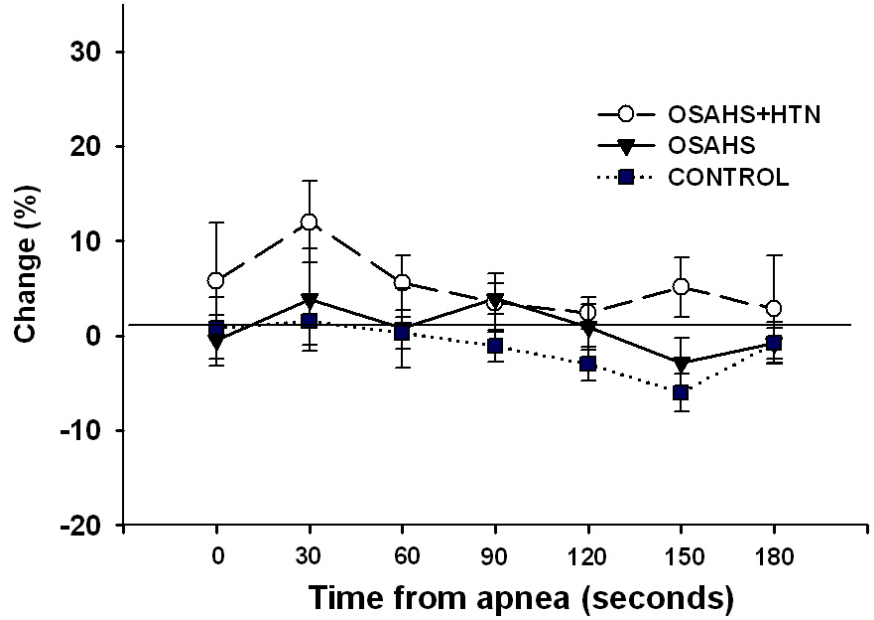
Data are presented as percentage change from normal breathing ± standard errors of the mean.*P < 0.05 OSAHS compared to CONTROL.

Figure 9 - Changes in heart rate following 30 sec Mueller Maneuver.



Data are presented as percentage change from normal breathing ± standard errors of the mean

Figure 10 - Changes in systemic vascular resistance following 30 sec Mueller Maneuver.



Data are presented as percentage change from normal breathing ± standard errors of the mean.

DISCUSSION

The objective was to determine how acute MM challenge might alter cardiac response characteristics affecting CO regulation in subjects with OSAHS or OSAHS with comorbid HTN. Changes in CO can be explained by changes in HR and/or SV. In healthy men, MM caused decreases in CO (Figure 5) that can be related to decreases in SV. Previous studies in animals and humans support the present findings of an altered SV during MM performance.[28] Bradley and colleagues [29] showed in healthy subjects a decrease of 13.8% in SV index during 15 seconds MM. Their change was higher than what current study found (-5.2%); however, this can be due to the lower number of subjects they tested (n=9) or different technology used for monitoring (echocardiographic Doppler technique). Hemodynamic mechanisms for a SV decrease include greater increases in SVR, greater decreases in LV preload and depression of MCI.[30] In the current study, healthy subjects did not display any change in SVR during MM (Figure 5). Although preload was not measured in the present study, generation of exaggerated negative intrathoracic pressure could restrict LV preload [31] by displacing the interventricular septum to the left.[32] In essence, during vigorous inspiratory effort, the left ventricle must pump blood from the lower pressure thorax into the higher pressure extrathoracic compartment. The last factor that can influence SV is MCI, one the variables measured by the present research. During MM, control subjects had decreased MCI values (Figure 5). The mechanism responsible for this decrease is most likely associated with a decreased β-receptor number and sensitivity due to elevated sympathetic activity.[33]

OSAHS patients showed a decrease in SV in apparently healthy subjects, although using a different mechanism. Their MCI was significantly higher than the other groups, while no change in SVR was displayed by any of the groups (Figure 5). While this MCI increase may seem surprising during a negative intra-thoracic pressure event, explanations may be found in the

pathophysiology of OSAHS. Structural changes in the contractile proteins of cardiac myocytes or sustained activation of cardiac sympathetic adrenergic pathways in response to intermittent hypoxia (IH) could lead to a compensatory increase in LV contractility. In an elegant study, Park and colleagues [34] demonstrated that 4 weeks of IH exposure in mice caused less cumulative myocardial injury than 1 or 2 weeks of exposure. OSA patients consistently have elevated in peripheral sympathetic nerve activity.[35] A recent study explained the augmentation of cardiac sympathetic activity as a mechanism contributing to increase cardiac contractility in response to chronic IH exposure.[36] This hypercontractile state was associated with increased cardiac cAMP levels, indicating activation of β-adrenergic signaling pathways that was attenuated with administration of the β-blocker, propranolol.

The normal response to an increase MCI would be an elevated SV, which was not shown by the OSAHS group. We speculate that negative intra-thoracic pressure may contribute to a reduced preload, resulted from impaired ventricular filling to the right side of the heart. Right heart hemodynamics are generally more affected than left side by the sustained inspiratory effort, presumably because the right heart structures are more compliant.[37]

In the present study, 3 minutes of cardiac function were recorded following resumption of breathing, from the 30 seconds MM. As soon as breathing was restored, SV continued to decrease following the trend seen during apnea (Figure 7). Two minutes into normal breathing, healthy subjects had SV values exceeding the baseline. The compensatory increase of SV following MM has been found by other studies as well.[38] During apnea, negative intrathoracic pressure draws blood into the thorax, augmenting right ventricular preload, while apnea-induced hypoxia causes pulmonary vasoconstriction, increasing right ventricular afterload.[39] These forces distend the right ventricle, causing leftward shift of the interventricular septum during

diastole that impedes left ventricular filling and decreases stroke volume. When breathing is restored, relief from intrathoracic pressure will cause a higher SV, mainly due to an increase in cardiac contractility and diastolic relaxation. [40] Apparently, this mechanism is not applicable to OSAHS patients as both OSAHS groups returned to baseline within 30 seconds suggesting a blunted sympathetic response. In addition, dysfunction of right ventricle distensibility commonly seen in these patients may diminish transpulmonary delivery of LV preload, leading to decreased SV despite intact LV contractility. The present study supports this mechanism, as all groups tested showed the same MCI change throughout the 3 minutes post MM (Figure 9), just immediately after termination of the MM, OSAHS had a higher MCI than controls. This was expected, as the measurement was taken after MM, where OSAHS group showed an increase in MCI (Figure 5).

SVR is one of the factors that can influence SV. When normal breathing is restored, O_2 saturation increases, causing a decrease in sympathetic dominance. This in turn should decrease SVR. In our study, all three groups showed a similar steady response (Figure 10)

The acute cardiac changes produced by two MM were compared between groups (Figures 2-4). Just control subjects had MCI and SVR affected by the maneuvers. The present protocol included 2 MM of 30 seconds each, and these proved sufficient for challenging the cardiovascular system. During normal breathing, before and after the 2 MM, both OSAHS groups had a lower resting MCI and a higher SVR, compared with controls (Figures 2 and 3). These can be potential markers of an occult LV dysfunction. Patients with OSAHS are exposed to chronic intermittent hypoxia, exaggerated swings of intrathoracic pressure, and arousals, all contributors to a degenerative cardiac function. One of the unique responses showed by the current study was increase MCI during 30 seconds MM in OSAHS patients. This response

proved to be a good predictor for AHI (ANCOVA, $R^2 = 0.58$, $P < 0.03$). Potentially, cardiac changes during and after 30 seconds MM can be used into a model for OSAHS screening. Post MM blunted response of SV, increase of MCI during MM, can be variables that together or alone can be tested against polysomnography for predicting OSAHS. This can provide a tool for clinical assessment of treatment effectiveness by CPAP or drug intervention. This can be of importance in HTN patients, resistant to medication, i.e., those for whom sleep disorders may be suspected. In addition, in OSAHS patients, CPAP treatment efficacy can be monitored over time to quantify normalization of cardiac function.

This study needs to be interpreted within the context of a few specific limitations. First, subjects included males only and, thus, the findings reported here may not be generalizable to women. Anatomic size of airway,[41] greater collapsibility in upper airway,[42] greater increase in upper airway resistance in men, or hormonal changes in women [43] will certainly be associated with gender-related responses to a MM. Second, the intrathoracic pressure generated during the MM was not measured. It is possible that subjects were exposed to different pressure, even though they were trained to recognize and maintain a mid pressure. Lastly, responses described in the present study may look different if patients were exposed to multiple MM with a higher negative intrathoracic pressure.

CONCLUSION

This study found that a sustained 30 second respiratory challenge with the MM has multiple effects on central hemodynamics. The CO responses were not different between groups. In controls, the main contributor for CO change was the decreased MCI that lowered SV. OSAHS patients had an increase in MCI that did not translate into a higher SV, probably due to decrease

in preload. The presence of the comorbid mild HTN did not add to the degree of acute cardiac changes seen with OSAHS when subjects were exposed to episodes of negative intrathoracic pressure by the MM.

A simple 30 seconds MM test can allow assessment of cardiac performance in OSA patients, even in the absence of comorbidies known to affect heart function. Occult cardiac dysfunction may contribute to long term progression of cardiovascular complications in untreated OSAHS patients. Monitoring patients for possible cardiac adaptive changes after CPAP may be a useful adjunct to assessing beneficial treatment outcomes. Variables like increase MCI during 30 seconds MM and blunted SV increase after 30 seconds MM could be used in a possible algorithm for OSAHS screening.

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Chapter 5 - Summary, Conclusions and Recommendations for Future Research

SUMMARY

Chronic sympathetic activation has seemed the most likely mechanism linking OSAHS to cardiovascular disease. There are several other mechanisms that may contribute to cardiovascular disease in OSAHS. These include inflammation, endothelial dysfunction, elevated levels of endothelin, hypercoagulability and stimulation of the renin angiotensin system. However, OSAHS is typically related to hypertension and obesity, so interaction between these two other risk factors can result in several cardiovascular consequences. In addition, increased aortic stiffness and rapid changes in intrathoracic pressures inducing left ventricular pressure changes may all contribute to systolic dysfunction. Successful treatment of OSAHS with CPAP improved right ventricular function, LV dimensions, and contractility. Therefore, early recognition of any hidden cardiac dysfunction may delineate high risk OSAHS patients that require immediate treatment. Currently, several technologies are available to monitor cardiac function less invasively than pulmonary artery catheterization. Thoracic electrical bioimpedance is a convenient, non-invasive technique that analyzes changes in the thoracic cavity's resistance to an alternating current during the cardiac cycle. The purpose of this study was to determine the reproducibility of CO and two measures of cardiac function which closely modulate variations in SV (MCI and SVR) during simulated apneas in apparently healthy subjects using a new impedance cardiography. Once the reliability of the device was confirmed, changes of hemodynamic responses to negative intrathoracic pressure in OSAHS patients with hypertension versus healthy subjects were assessed.

Subjects volunteering for the reproducibility study were fifteen apparently healthy, normal weight males (Mean ± SD: age = 38.6 ± 6.3 yr.). Three days cardiac monitoring was performed while in a supine position using a new bioimpedance device (PhysioFlow®). On each day, the protocol included performance of two MM of 15 seconds duration and two more of 30 seconds duration, in a random order. Between apneas was at least 3 minutes of normal breathing to promote normalization of cardiac responses.

A primary finding was that the new impedance cardiography was able to consistently detect decreases in MCI and increases in SVR that would be linked to diminished SV during MM. During 15 seconds MM, changes seen in SV ranged from -2 to 2 % from normal breathing. In contrast, during 30 sec MM, these changes were more robust, consistently decreasing within a day or between days (-8 to -12%). The same steady changes during 30 sec MM were displayed when the other cardiac factors were analyzed. The increase in intrathoracic pressure with breath-holding is a plausible mechanism for mediating the changes we observed with the 30-second MM. Blunting of preload due to increased intrathoracic pressure, together with the increased afterload attributable to increased systemic resistance, may explain the diminution of the SV under these conditions. This was better shown in 30 sec MM, probably due to higher level of hypoxemia that occurred here compared to 15 sec MM (92.5 and 95.8 SaO_2, respectively). Therefore, this new device can find its usage as a screening test for assessing myocardial dysfunction in OSAHS. A simple, two 30 seconds MM can be performed on OSAHS patients at the beginning of their sleep clinical pathway.

Second part of this study focused on cardiac responses in OSAHS patients versus healthy subjects. Subjects were male volunteers who were free of chronic cardiovascular and metabolic

disorders. They were placed into one of the following three groups based on OSAHS severity (AHI) and hypertension (HTN): 1) controls, 2) OSAHS without HTN (AHI > 15.0 and BP < 130/90 mmHg), and 3) OSAHS with HTN (AHI > 15.0 and BP > 140/90 mmHg).

Subjects were tested supine performing two MM of 30 seconds duration with at least 3 minutes of normal breathing in between and 5 minutes of normal breathing before and after the test. As a result of 30 seconds MM, HR, SV and SVR change similar in all three groups. CO was lower during MM in controls compared to OSAHS groups. The OSAHS groups showed an increase in MCI as the other two groups had a decrease ($p < 0.05$). This can be explained by an elevation in peripheral sympathetic nerve activity in response to chronic intermittent hypoxia exposure generated by multiple events witnessed every night. Post MM analysis showed that for two minutes control subjects had SV values exceeding the baseline. This compensatory increase in SV was not found in OSAHS patients, as they returned to baseline right after breathing restored. The suggested mechanism for this response may be linked to a right ventricular dysfunction commonly seen in OSAHS patients. This in turn decreased preload, one of the factors that control SV. Taken together, these findings suggest a different cardiac response in OSAHS patients compared to controls. Hypertension did not create an extra demand on the cardiac function. OSAHS can coexist with undiagnosed cardiac dysfunction, but a simple 30 seconds MM can reveal it, ensuring proper treatment.

CONCLUSIONS

In conclusion, a new bioimpedance device can be used to monitor cardiac changes during respiratory challenge involving Mueller Maneuver techniques. The work presented in chapter 3

highlights the reproducibility of CO, SV, HR, MCI and SVR over three days of testing. The present four MM protocol did not have any effect on the resting CO and HR values. However, SV decreased after performance of four MM, which was well shown by the decrease in MCI and the increase in SVR. The main factor responsible for these changes at rest could be the acute cumulative effect of four desaturations that accompanied these MM. The difference in level of oxygen between the 15 and 30 seconds apnea was probably the factor behind the systematically, robust cardiac changes displayed by the 30 seconds MM compared to 15 seconds MM. These need clarification in a study involving a higher degree of oxygen desaturation during MM. A test with this new cardiograph that will monitor cardiac changes during 2 MM of 30 seconds may be useful in prioritizing patients for polysomnography and CPAP therapy, facilitating expedited medical treatment in high-risk patients.

The results from chapter 4 show that OSAHS subjects present unique responses during and following a 30 seconds MM. Although through different mechanisms, there was no difference between groups in terms of CO responses. In controls, the main contributor for CO change was the decreased MCI that lowered SV. OSAHS patients had an increase in MCI that did not translate into a higher SV, probably due to decrease in preload. The presence of the comorbid mild HTN did not add to the severity of cardiac changes seen with OSAHS when experience episodes of negative intrathoracic pressure.

A simple 30 seconds MM test can allow assessment of cardiac performance in OSA patients, even in the absence of comorbidies known to affect heart function. Occult cardiac dysfunction may contribute to long term progression of cardiovascular complications in untreated OSAHS patients. Monitoring patients for possible cardiac adaptive changes after CPAP may be a useful

adjunct to assessing beneficial treatment outcomes. Variables like increase MCI during 30 seconds MM and blunted SV increase after 30 seconds MM could be used in a possible algorithm for OSAHS screening.

CLINICAL APPLICATION

Current findings can generate a 30 seconds MM test with potential applications to OSAHS patients. Identification of cardiac problems, in otherwise healthy patients, may be critical in preventing the advances to a greater level of cardiac severity. The tested cardiograph provided reliable data monitoring when tested on the same subjects on three different occasions. The coefficient of variation ranged from 8.7 to 21.3 % throughout the three trials. Within a day, during both MM variables tested showed similar results. Results obtained with a 30 seconds MM were more robust and compact when compared with 15 seconds MM. This information indicates that 30 seconds MM can provide consistent results, when preceded by a practice trial. Being completely noninvasive, relatively inexpensive, and easy to use, this device can entice sleep specialists to incorporate it in their clinical pathway. Cardiac variables recorded can be used to generate a screening algorithm that can be an alternative for full overnight polysomnography. Variables for this algorithm could include an increase in MCI during 30 seconds MM and a blunted SV increase after 30 seconds MM. Another feature that can be worth adding is the unchanged SV, MCI and SVR as a result of 30 seconds MM performance. Carefully monitoring these unique responses during a single testing session, a sleep physician can use bioimpedance cardiography and assess CPAP treatment efficacy on cardiac function.

FUTURE STUDIES

There are several future studies that should be considered worth conducting.

1. The present study showed reproducibility of cardiac monitoring using a new bioimpedance cardiograph during simulated apnea maneuvers. However, accuracy of this device should be assessed against Fick method, which is considered one of the gold standards in determining SV.
2. Unique features of cardiac changes were displayed by OSAHS patients. For generalizability, these findings should be expanded to women and older patients. Better screening for OSAHS and cardiac dysfunctions should be performed with all subjects.
3. Cardiac responses to 30 seconds MM were determined in newly diagnosed and untreated patients with OSAHS. Continuous positive airway pressure is the standard treatment for these patients, with proven benefits on the variables that alter cardiac function. Clinical longitudinal trials could be conducted to assess cardiac changes before and after a period of treatment compliance.
4. Distinct cardiac responses were seen in OSAHS patients during and after 30 seconds MM. These can be added into an algorithm and tested against overnight polysomnography for accuracy.
5. For better understanding of hemodynamic changes during OSAHS, overnight bioimpedance monitoring would be necessary. The MM used in the present study does not take into account the profound hypoxemia and arousals experienced by OSAHS patients.

Appendix A - PHYSIOFLOW PROTOCOL

Reliability Testing

Before testing begins:

Controlling breathing technique in test subjects

- Bring in subjects and teach breathing technique involved in apnea event
    - Be sure they know how to hold their breath just after a normal exhale
    - After breath held for specified time, all subjects immediately inhale when told to do so; do not exhale and then inhale. This should feel natural when a longer breath holding is taken place (30sec).
- Teach subjects command signals they need to know during testing
    - As soon as subject begins their breath holding, they need to show a thumb up with the hand closest to the test administrator so that the administrator knows when to mark the start of the apnea by pressing the space bar on the computer with the PhysioFlow program. Or, the time showed in the screen window will be recorded.
    - Test administrator will say "breathe" to the subject, which lets them know when they may inhale and resume regular breathing. At the same time the administrator says "breathe", he or she will also push the space bar on the computer to mark the end time of that apnea event. Or, the time showed in the screen window will be recorded.

Controlling trans-thoracic pressure in test subjects:

- Let them practice minimal and maximal efforts exerted within thoracic cavity
    - Help subjects find middle effort needed
- Teach subjects to use RPE (rate of perceived exertion) scale to define the amount of effort being exerted
- Let subjects practice using pulmonary breathing device so that they may get an idea of their expiratory capacity

Program settings on the computer:

- Should be set to measure each heart beat
- Manually average indicated apnea cycle data (after data is collected)

Day of testing:

Subject hook up:

- Shave hair from subject's chest/neck region and clean off excess skin cells from areas where electrodes will be attached (see diagram indicating where each electrode needs to go)
- Turn on all machines needed for testing and start appropriate programs
- Enter in subject data (name, date, height, weight, etc)
- Make sure all wire and cables are hooked up properly and electrode signals are registering into computer program

Calibration:

- After electrodes are appropriately hooked up to subject, have him or her lie in the supine position on test table. They should be a relaxed as possible, breathing normally, moving minimally, and not talking. When subject is as motionless as possible, test administrator can start the program clock and calibration.

Stability:

- This is to get baseline measurements from subject before testing begins; measurements will also be used to indicate or verify that subject is ready to begin next apnea test
- After calibration, subject will continue to lie in supine position as relaxed and motionless as possible for 5 minutes to achieve best resting metabolic rates
- While subject is at rest, administrator will obtain blood pressure from both arms twice
- Define a heart range where subject will be considered "stable" (50-70 bpm)
    - Subject's heart rate needs to fall back into this range before starting each apnea test

Testing:

- Testing will begin when subject is stable and at rest
- Administrator will tell subject that he or she may begin breath holding whenever he or she is ready
- Administrator will press space bar when he or she sees the subject do a thumb up, indicating the start of breath holding. Or the time showed in the screen window will be recorded.
    - Administrator will call out amount of time passed at 10 second intervals
    - Administrator must be sure to use same commands in same tone of voice for every subject; consistency between patients
- At end of specified time for apnea test, administrator will say "breathe" to subject, and subject should inhale immediately and resume normal breathing

End testing:

- Repeat procedure for stability above for 5 minutes; re-record normal breathing and resting measurements
- Obtain blood pressure for both arms again (repeat for second measurement)
- Compare start and end data
- Embletta readings
    - To show that the subject actually stops breathing, some variables from the Embletta can be used: air flow and oxygen saturation.

Appendix B - EMBLETTA PDS SET-UP

Detailed procedures

Step 1. Attach the respiratory effort sensors

1. Place the respiratory effort sensor with the yellow plug on your stomach. Center it just above your waistline and wrap the strap around you.

2. With the Velcro facing away from your body, run the free end of the respiratory effort strap through the loop on the side of the respiratory effort sensor.

3. Fasten the Velcro so the strap is snug and secure.

4. Place the respiratory effort sensor with the blue plug on your chest at the midline and tighten in the same manner.

Note: You may need to readjust the straps when you lie down.

Step 4. Attach oximeter sensor

1. Place a small piece of tape at the connection of the wire and sensor, with the sticky side placed on the same side with the two slightly elevated sensors.

2. Carefully position the tip of the index finger in the middle of the sensor, so that when folded over the finger, both sensors are in the same approximate place on the top and bottom of the finger.

3. Attach the tape to the bottom of the finger, securing the sensor in place.

4. Attach another piece of tape across the top of the sensor, completely securing both sensors to the finger in the appropriate position.

5. Attach another small piece of tape just below the middle of your index finger to secure the wire against the skin and minimize movement.

Step 5. Attaching the wires to the sensor block

1. Connect the individual sensors to the sensor plug using the color codes. Be aware of the shape of the sensor plugs and adaptors.

2. Once all sensor wires are attached, plug the sensor adaptor into the top of the Embletta PDS recorder. Be careful not to put pressure on the sensor wires or connectors. You will hear a beep and the device will power up. Recording of data begins when the sensor block is inserted. Make sure the block is completely inserted. Do not insert the block until you are ready to lie down.

3. Connect the nasal cannula to the Luer lock on top of the Embletta PDS. Twist clockwise to tighten.

Step 6. Testing procedure

1. Check that the sensors are attached correctly and that there is enough battery power to complete the study.

2. Press the test button (check) and hold until you hear a beep. The yellow lights on the front of the Embletta PDS will illuminate for 1 minute.

Status Lights

• **Yellow** means recording has not yet begun.

• **Green** means recording has started.

• **Red** means that an error has occurred

Battery light

• **Green** means that there is enough battery power to complete your study.

• **Red** means battery power is low

If the sensor lights are not lighting up properly, do the following:

1. Check the placement of the sensors.

2. Check that the sensors are firmly connected to the sensor adaptor.

Step 8. Concluding the study

1. Disconnect the sensor adaptor from the Embletta PDS. This will turn off the device.

2. Remove the sensors from your body. You do not have to disconnect the sensors from the sensor adaptor.

3. Take off the Embletta PDS strap.

4. Place all Embletta PDS components in the carry case.

Appendix C - HEALTH HISTORY QUESTIONNAIRE

MEDICAL HISTORY FORM (HEALTH SCREENING FORM)

VIRGINIA TECH

Study ID #: _____ Age: _____ yr Date of Birth: _____

Ethnicity: _____

Self-reported height: _____

Self-reported weight: _____

Medical History

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

	Yes	No
Heart disease or any heart problems:	_____	_____
Rheumatic fever:	_____	_____
Respiratory disease or breathing problems or asthma	_____	_____
Circulation problems:	_____	_____
Kidney disease or problems:	_____	_____
Urinary problems:	_____	_____
Reproductive problems:	_____	_____
Muscle problems:	_____	_____
Skeletal problems:	_____	_____
Fainting or dizziness, especially with exertion:	_____	_____
Neurological problems/disorders:	_____	_____
High blood pressure:	_____	_____

Low blood pressure: _____ _____

High blood cholesterol: _____ _____

Diabetes: _____ _____

Thyroid problems: _____ _____

Eating disorders (bulimia, anorexia): _____ _____

Crohn's disease: _____ _____

Allergies: _____ _____

Insomnia: _____ _____

Unusual sleep patterns: _____ _____

Other (Please list): _____ _____ _____

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

_____

_____

_____

_____

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

_____

_____

_____

Family Health History

Has anyone in your family (blood relatives only) been diagnosed or treated for any of the following?

	Yes	No	Relationship	Age
Heart attack	_____	_____	_____	_____
Heart disease	_____	_____	_____	_____
High blood pressure	_____	_____	_____	_____

Stroke	_____	_____	_____	_____
Kidney disease	_____	_____	_____	_____
Diabetes	_____	_____	_____	_____
Crohn's disease	_____	_____	_____	_____
Thyroid disorders	_____	_____	_____	_____
Osteoporosis	_____	_____	_____	_____
Osteopenia	_____	_____	_____	_____

Have you broken any bone(s)? Yes _____ No ____

If "yes," please list bone(s) and age(s) at time of break: _____

_____

_____

Recent Illness

Have you had a cold, or sinus or respiratory infection in the past 6 weeks? Yes _____ No _____

If yes, please describe: _____

_____

If yes, were you treated with medication for this infection? Yes _____ No _____

Health Habits

Do you add salt to your food? Yes _____ No _____

Are you on any special type of diet? Yes _____ No _____

If "yes," please describe: _____

_____

Do you drink caffeinated beverages? Yes _____ No _____ If "yes," how many cups per day? _____

Do you drink alcoholic beverages? Yes _____ No _____ If "yes," how many cups per day? _____

What is the average number of drinks that you consume on the weekend? _____

Did you use tobacco products in the past (more than 12 months ago)? Yes _____ No _____

Do you currently use tobacco products? Yes _____ No _____ If "yes," what type of tobacco products do you use, how frequently do you use them, and what number do you use per day?_____

_____

Work Schedule and Patterns

Do you engage in night-time work? YES NO

If yes, please explain: _____

_____

Sleep Habits Evaluation

Do you have episodes of parasomnias (disorders such as sleep walking, sleep talking, night terrors, body rocking, bedwetting that will cause partial or full awakening?) Yes _____ No _____

Do you show signs of sleep disturbances (such as insomnia, daytime sleepiness) when you are anxious or stressed? Yes _____ No _____

Do you have difficulties falling asleep if a certain object or a certain situation is absent such as listening to the radio, watching the television, having a teddy bear, etc.? Yes _____ No _____

Do you have difficulties falling asleep earlier or later than your usual bedtime? Yes _____ No _____

Do you wake up at night to get a snack? Yes _____ No _____

If "yes," do you think that the snack helps you to go back to sleep? Yes _____ No _____

Do you ever feel very tired or sleepy at school or work? Yes _____ No _____

Do you have hallucinations (vivid images that look like dreams occurring when you sleep) or find yourself physically weak or paralyzed for a few seconds during sleep? Yes _____ No _____

Tonsils and Adenoids Evaluation

Do you have a history of recurrent tonsillitis which is an inflammation of the tonsils (clusters of tissue that lie in bands on both sides of the back of the throat) caused by an infection? In tonsillitis, the tonsils are enlarged, red, and often coated either partly or entirely? Yes _____ No _____

Did you ever have inflammation of the adenoids (single clump of tissue in the back of the nose) causing a blockage of the back of the nose, chronic and recurrent fluid or infections of your ears, or chronic or recurrent sinus infections? Yes _____ No _____

Have you had a tonsillectomy (tonsils removed)? Yes _____ No _____

Have you had an adenoidectomy (adenoids removed)? Yes ___ No ___

Exercise Habits

Do you engage in regular exercise? Yes _____ No _____

If "yes" please list:

Activity	Frequency (times per week)	Duration (minutes)

Do you ever feel faint, short of breath, or chest discomfort with exertion? Yes _____ No _____

If “yes,” please explain: _____

_____

Are there any orthopedic limitations you have that may restrict your ability to exercise? Yes ___ No ___

If "yes" please explain: _____

_____

Medications

Please indicate any current medications that you are taking on a daily or weekly basis:

	Yes	No
Steroids (such as Prednisone):	_____	_____
Thyroid medications (such as Synthroid):	_____	_____
Bisphosphonates (such as Fosamax):	_____	_____
Anticonvulsants (such as Dilantin):	_____	_____
Glucocorticoids (such as Dexamethasone):	_____	_____
Other bone medications (such as Miacalcin):	_____	_____

Please list any nutritional supplements, herbal products, or other medications, (prescription and over-the-counter) you are currently taking on a daily or weekly basis: _____

_____

_____

_____

Weight History

What is your current weight? _____

How much did you weigh six months ago? _____

How much did you weigh one year ago? _____

During the last 2 years, how many times have you lost 5 pounds?

NEVER ONCE TWICE THREE OR MORE

During the last 2 years, how many times have you gained 5 pounds?

NEVER ONCE TWICE THREE OR MORE

BMI: _____ (For investigator use, please leave blank)

Please sign to indicate the above information is correct:

_____ _____

Print Name Signature Date

Follow Up Review and Interview by: _____

Signature of Project Staff Member Date

Results of Screening: Make certain that all questions on this form are properly completed. Query candidate, immediately after they complete this questionnaire, about any items left blank or for which clear answers are not provided. If unusual problems are present or not disclosed that may affect the candidate's safety or eligibility for the study, note this/these finding(s) below and submit to an investigator.

THIS CANDIDATE QUALIFIES FOR PARTICIPATION IN THE STUDY, SUBJECT TO VERIFICATION BY AN INVESTIGATOR. Yes: ___ No: ___.

If No, complete next section, below. Please explain reasons for which candidate is not eligible to participate in this study.

_____
_____
_____
_____

Appendix D - Data collection sheet

Screening and Measurement Data Sheet

Subject Code _____ **Date** _____ **Time**_____

Date of birth _____ **Visit**_____

Height _____ **cm** **Weight** _____ **kg** **BMI** _____ **kg/m^2**

Circumferences

Neck _____ cm Waist _____ cm Hip _____ cm

_____ _____ _____

_____ _____ _____

Blood Pressure

Left _____ Right_____ Left _____ Right_____

5 Minutes normal Breathing Start_____ End_____

First apnea Start_____ End_____

3 minutes normal breathing Start _____ End_____

Second apnea Start _____ End_____

3 minutes normal breathing Start _____ End_____

Third apnea Start _____ End_____

3 minutes normal breathing Start _____ End_____

Fourth apnea Start _____ End_____

5 Minutes normal Breathing Start_____ End_____

Blood Pressure

Left _____ Right_____ Left _____ Right_____

Appendix E - INFORMED CONSENT

Reliability study

Virginia Polytechnic Institute and State University

Informed Consent for Participants of Investigative Projects

Title of Project: Cardiac function evaluation during simulated obstructive apneas using a new impedance cardiograph device

Location of Study: 231 War Memorial Hall, Virginia Polytechnic Institute and State University, Blacksburg, Virginia

Investigators: William G. Herbert, Ph.D., Adrian Aron, MS, Ph.D Candidate

Purpose: The purpose of this study is to determine the repeatability of monitoring stroke volume and cardiac output during simulated apneas in apparently healthy subjects using an impedance cardiography. This technology is comparable with electrocardiography (ECG) and necesitate just 6 electrodes attached to the chest and neck. By demonstrating that this technology can provide reliable cardiac measurements during simulated apneas while awake, later, investigators can evaluate cardiac functions changes during sleep and assess the impact of obstructive sleep apnea hypopnea syndrome (OSAHS) on cardiovascular morbidity and mortality. OSAHS is a disorder that occurs when a person stops breathing many times during the night while asleep.

II. Procedures:

Explanation of Study, Informed Consent, and Screening

Before session 1, you will be provided a copy of this informed consent form, through either standard mailing or email. Please read this document carefully and write down any questions you may have for the research team before you report to our lab for the first meeting.

You will report to the Laboratory for Health and Exercise Science in 231 War Memorial Hall on the Virginia Tech campus. We will provide a map for you to show this location and information about parking, should you be driving to campus. Once there, a researcher will review the informed consent with you and answer any questions or concerns that you may have. If you have consented and wish to proceed as a subject in the study, you will be asked to complete a health and sleep questionnaires. Also, a researcher will measure your height, body weight, blood pressure and use a tape to measure the size of your neck, waist, and hips. If any of these values do not meet the study requirements, you will not be eligible to continue in this study. The researcher may ask you additional questions after reviewing your completed forms to clarify any aspects of your health that may affect your eligibility.

You will not be eligible to take part in the study if you currently have or have a history of any of the following:

- Heart problems, including past heart attack, chest pain that may be related to heart problems (this is called angina pectoris), surgery for your heart or its blood vessels, or heart failure;
- Blood pressure higher than 130/90 mmHg;
- Chronic lung diseases (including asthma);
- Diabetes mellitus;
- Use of medications known to affect vascular function or heart rate;
- Use of blood pressure medications or antihistamines (cold or allergy medicine);
- Use of any tobacco or nicotine products (only non-smokers can participate);
- Infectious illnesses, such as cold, sinus infection, etc. during the previous 6 weeks;
- Diagnosed or medically treated renal, inflammatory or orthopedic conditions.

If researchers are concerned by any part of your health history that may affect your eligibility and you have a personal physician, you may still qualify if you can secure documentation from your physician that clarifies the issues of concern. Only you can ask your physician to do this and he/she must secure your written permission to release this information to us. We will provide you with a fax phone number (maintained in a secured area) or mailing address for your physician to use in sending information to us, should this be needed. This will take about 60 minutes, but you may take as much time as you need to fill-out the questionnaires and forms.

Once it is determined that you are eligible, you will be asked to complete the following procedure:

Session 1 – Cardiac Monitor Test

This session will also take place in 231 War Memorial Hall on the Virginia Tech campus and will take about 55 minutes.

You will be teach the breath holding technique involved in this measurements. We want to make sure that you will learn to start holding your breath just after a normal exhale

We will teach you the command signals you need to know during testing:

- As soon as you begin your breath holding, you need to show a thumb up with the hand closest to the test administrator so that the administrator knows when to mark the start of the apnea
- Test administrator will say “breathe” to the subject, which lets them know when they may inhale and resume regular breathing. The administrator will say “breathe”, when 15 or 30 seconds will pass on the screen window

During apneas, you will continue attempting normal inspiratory and expiratory movement, except these will be against an occluded upper airway. We will allow plenty of time for exercising these breath holding maneuvers before the actual test will start.

When you are ready, we will connect you to the cardiac monitoring device. This looks like an electrocardiography machine and will use 6 small electrodes placed on your chest and side of

your neck. The electrodes are disposable and gelled on the inside; the gel very rarely may cause slight skin irritation, but if so, this should last no more than one day. To ensure breath holding, you will wear three channels of monitoring from a portable sleep test device called Embletta. The Embletta sleep test device is equipped with straps, wires, and small sensors. You will wear just two straps to detect movement of your chest wall during breathing and a small sensor to your finger, which will measure any changes in your blood oxygen level. The Embletta is a harmless, non-invasive (no needles) monitor that is sometimes used by sleep doctors to screen people who may need more medical tests for possible nighttime breathing disorders. All simulated apneas measurements will take place while you lying on you back with a pillow under your head. Before and after breath holding procedures, you will have your blood pressure measured twice on both arms.

Cardiac variables will be monitored for 5 minutes while you are breathing normally. Using the thumb signal for starting a breath holding, you will be asked to perform 2 breath holding of 15 and 30 seconds, a total of 4. After every breath holding, you will have a 3 minutes of normal breathing. After the 4^{th} breath holding, you will be monitored again for 5 minutes while breathing normally. There are no known adverse reactions of breath holding in healthy humans. If before the testing, during familiarization period, you are not able, or you feel uncomfortable performing a 15 or 30 seconds breath holding, you can withdraw from the study without any repercussions. Second and third testing session will follow the same protocol at a three to five day interval.

There will be three separate lab visits with associated activities over the course of approximately two weeks. Your participation for these three testing sessions plus the time at home filling out forms and reading the informed consent will require approximately 4 hours of your time (see attached appendix). You may require more or less time than this estimate to complete any of the procedures, and you will be given ample opportunity to complete all procedures in an unhurried manner.

III. Risks: The investigators are not aware of any specific risks associated with the portable sleep device test or the cardiac monitor. In fact, many people have this type of sleep test done to screen for sleep conditions without any problems. Cardiac monitoring is performed using a non invasive procedures, requiring 6 electrodes positioned on the chest and side of the neck. Rarely, a slight discomfort may appear when the electrodes are removed from the skin.

IV. Benefits of this Project: The investigators do not guarantee any specific benefit to you as a result of being in the study. The general public may benefit from this research as new understandings of cardiac variables dynamics during simulated obstructive apnea may be found. Later, this technique can be used on patients with OSAHS, while sleeping.

V. Extent of Anonymity and Confidentiality: Your participation in this research will not be anonymous, meaning that the researcher and the researcher' students will know your name and that you are participating in this study. In addition, other subjects who are in this study may be in the laboratory for testing at the same time as you. These subjects will know that you are participating in the study. It is possible that another subject may know your name or hear you called by your name by the investigators or the investigators' students.

Your information will be kept confidential. This means that all of your answers to questions that you are asked, measurement values, cardiac variables results will be kept confidential and shared only with you. A three-digit code number will be assigned to you. All questionnaires, data collection sheets, data analysis sheets will be identified by code number and not by your name. A master list of subjects' code numbers will be kept in a locked filing cabinet in the lead researcher's office, separate from completed data which will also be maintained in a locked office on the Virginia Tech campus. The electronic data collected from the PhysioFlow and portable sleep device will be stored in a password protected computer located in a secure area of the investigators laboratory (231 War Memorial Hall). Only the investigator and the investigators' students will be allowed access to any data.

VI. Compensation: There is no compensation for participating in this study.

VII. Freedom to Withdraw: You are free to withdraw from this study at any time, without penalty. You are free to not answer any questions or to not participate in any procedure in the study, without penalty. There may be circumstances under which the researcher may determine that you should not continue to participate in this project.

VIII. Emergency Procedure: If a minor emergency arises during your participation in any of the testing sessions of this study, you will discontinue your participation and be advised to seek care from your Primary Care Physician. If a major emergency arises during your participation in any of the testing sessions for this study, local emergency personnel will be called (911) and they will care for you. The researchers or Virginia Tech will not be responsible for any medical care or costs for same that arise directly or indirectly from of your participation in this study.

IX. Approval of Research: This research project has been reviewed, as required, by the Institutional Review Board for Research Involving Human Subjects at Virginia Polytechnic Institute and State University and by the Department of Human Nutrition, Foods and Exercise.

X. Subject's Responsibilities: You voluntarily agree to participate in this study. You have the following responsibilities throughout this study:

(1) provide written consent to complete procedures for this study;
(2) arrive at Room 231 War Memorial Hall on the Virginia Tech campus on the scheduled days and times;
(3) honestly and to the best of your knowledge complete all questionnaires, including those about health history and sleep;
(4) have your height, weight, neck, blood pressure, waist, and hip circumference measured by researchers;
(5) cooperate in performing the 4 breath holding episodes

XI. Subject's Permission: I have read the Informed Consent and conditions of this project. I have had all of my questions answered. I hereby acknowledge the above and give my voluntary consent for participation in this project. If I participate, I understand that I may withdraw at any time, without penalty. I agree to abide by the rules of this project.

Participant Signature Date

Researcher (Witness) Signature Date

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

Dr. William G. Herbert, Principal Investigator
(540) 231-5104; wgherb@vt.edu

Dr. David M. Moore, IRB Chair
(540) 231-4991; moored@vt.edu

Adrian Aron, M.S., Coordinator
Laboratory for Health & Exercise Science
(540) 231-6376; aronady@vt.edu

Appendix F - INFORMED CONSENT

Clinical study

Virginia Polytechnic Institute and State University

Informed Consent for Participants of Investigative Projects

Title of Project: Cardiac function in obstructive sleep apnea hypopnea syndrome patients during simulated obstructive apneas

Location of Study: Sleep Disorders Network of Virginia in Christiansburg, Va

Investigators: William G. Herbert, Ph.D., Donald Zedalis, MD, Adrian Aron, MS, Ph.D Candidate

Purpose: The purpose of this study will be to characterize how the heart changes in response to breath holding in OSAHS patients with hypertension versus healthy subjects. When breathing is stopped during night while someone is asleep, adverse effects are seen on heart function. These effects are likely to be exaggerated in patients with heart problems, like hypertension. If OSAHS patients with hypertension are treated for their sleep problems, their cardiovascular progression might slow down, hypertension treatment may be more effective and even incidence of non-fatal and fatal cardiac event could be reduced.

II. Procedures:

Explanation of Study, Informed Consent, and Screening

Before practice session, when you will have your first consultation with the sleep clinic, you will be provided a copy of this informed consent form. Please read this document carefully and write down any questions you may have for the research team before you come back for the first meeting. You will report to the sleep clinic, as your regular visit for the sleep test. Once there, a researcher will review the informed consent with you and answer any questions or concerns that you may have.

You will not be eligible to take part in the study if you currently have or have a history of any of the following:

- AHI score lower than 15 (for OSAHS group);
- blood pressure lower than 140/90 mmHg (for hypertension group);
- blood pressure higher than 140/90 mmHg (for OSAHS group);
- acute infection diseases;
- neurological conditions (stroke, Parkinson's and peripheral neuropathy);
- chest pain within the past 3 months before you enroll in the study or any prior heart attack;
- primary valvular heart disease;
- abnormal electrical conductivity of the heart;
- currently taking any prescriptive medicines for heart disease, high blood pressure, or diabetes;
- diabetes and respiratory disease.

If you agree to participate, your eligibility will be determined by the nurses at the sleep clinic based on your clinical evaluation and confirmation/referral by your primary care physician. All

these information will not be shared with anyone outside from the clinic or the research staff. If you have consented and wish to proceed as a subject in the study, you will be asked to complete a simple cardiac monitoring test before the sleep test will take place.

Practice Cardiac Monitor Test

You will be teach you a special breath holding technique that you need to do perform for 30 sec, so that we can measure your heart's responses with two different research machines. We want to make sure that you will learn to start holding your breath just after a normal exhalation. Then, you will try to take air in keeping your mouth and nose closed.

We will teach you the command signals you need to know during testing:

- As soon as you begin your breath holding, you need to show a thumb up with the hand closest to the test administrator so that the administrator knows when to mark the start of the apnea
- Test administrator will say "breathe" to you, which lets you know when you may inhale and resume regular breathing. The administrator will say "breathe", when 30 seconds will pass on the screen window

During apneas, you will continue attempting normal inspiratory and expiratory movement, except these will be against an occluded upper airway. We will allow plenty of time for exercising these breath holding maneuvers before the actual test will start.

When you are ready, we will connect you to the cardiac monitoring device. This looks like an electrocardiography machine and will use 6 small electrodes placed on your chest and side of your neck. The electrodes are disposable and gelled on the inside; the gel very rarely may cause slight skin irritation, but if so, this should last no more than one day. To ensure breath holding, you will wear three channels of monitoring from a portable sleep test device called Embletta. The Embletta sleep test device is equipped with straps, wires, and small sensors. You will wear just two straps to detect movement of your chest wall during breathing and a small sensor to your finger, which will measure any changes in your blood oxygen level. The Embletta is a harmless, non-invasive (no needles) monitor that is sometimes used by sleep doctors to screen people who may need more medical tests for possible nighttime breathing disorders. All simulated apneas measurements will take place while you lying on you back with a pillow under your head.

Cardiac variables will be monitored for 5 minutes while you are breathing normally. Using the thumb signal for starting a breath holding, you will be asked to perform 2 breath holdings of 30 seconds. Between breath holdings, you will have 3 minutes of normal breathing. After the second breath holding, you will be monitored again for 5 minutes while breathing normally. There are no known adverse reactions of breath holding in healthy humans. If before the testing, during familiarization period, you are not able, or you feel uncomfortable performing 30 seconds breath holding, you can withdraw from the study without any repercussions.

This test will take about 35 minutes, but you may take as much time as you need to fill-out the questionnaires.

Second testing session will follow the same protocol and will be performed when you will come for the titration visit, if diagnosed possitive for OSAHS. The overnight sleep test and the titration test are parts of the regular diagnostic and treatment procedures at the sleep clinic.

Your participation for these two testing sessions plus the time at home reading the informed consent will require approximately 1.5 hours of your time. You may require more or less time than this estimate to complete any of the procedures, and you will be given ample opportunity to complete all procedures in an unhurried manner.

III. Risks: The investigators are not aware of any specific risks associated with the portable sleep device test or the cardiac monitor. In fact, many people have this type of sleep test done to screen for sleep conditions without any problems. Cardiac monitoring is performed using a non-invasive procedures, requiring 6 electrodes positioned on the chest and side of the neck. Rarely, a slight discomfort may appear when the electrodes are removed from the skin. Regarding to the breath holding technique, you should know that this has been used for simulated apneas in many studies with no adverse reports. Oxygen content in your blood may decrease by a small and predictable amount, but this is not posing any risks since this breath holding is what you experience every night as a result of your sleep apnea, 15 or more times per hour.

IV. Benefits of this Project: The investigators do not guarantee any specific benefit to you as a result of being in the study. The general public may benefit from this research as new understandings of the changes in heart response during simulated obstructive apnea may be found. Later, this technique could possibly be used to help evaluate effects in patients with OSAHS, while sleeping, and maybe even help better determine treatments to facilitate their heart health or sleep apnea condition.

V. Extent of Anonymity and Confidentiality: Your participation in this research will not be anonymous, meaning that the researcher and the researcher' students will know your name and that you are participating in this study. In addition, other subjects who are in this study may be in the clinic for testing at the same time as you. It is possible that another subject may know your name or hear you called by your name by the investigators or the investigators' students.

Your information will be kept confidential. This means that all of your answers to questions that you are asked, measurement values, cardiac variables results will be kept confidential and shared only with you. A three-digit code number will be assigned to you. All data collection sheets, data analysis sheets will be identified by code number and not by your name. A master list of subjects' code numbers will be kept in a locked filing cabinet in the lead researcher's office, separate from completed data which will also be maintained in a locked office on the Virginia Tech campus. The electronic data collected from the PhysioFlow and portable sleep device will be stored in a password protected computer located in a secure area of the investigators laboratory (231 War Memorial Hall, at Virginia Tech). Only the investigator and the investigators' students will be allowed access to any data.

VI. Compensation: There is no compensation for participating in this study.

VII. Freedom to Withdraw: You are free to withdraw from this study at any time, without penalty. You are free to not answer any questions or to not participate in any procedure in the study, without penalty. There may be circumstances under which the researcher may determine that you should not continue to participate in this project. Your sleep testing received at the clinic is not dependent on the participation in this study.

VIII. Emergency Procedure: If a minor emergency arises during your participation in any of the testing sessions of this study, you will discontinue your participation and be advised to seek care from your Primary Care Physician. While no major emergency is expected that would affect your safety in this study, should such an emergency arise, local emergency personnel will be called (911) and they will care for you. None of the researchers conducting this project, nor Dr. Zedalis and his clinic staff, nor Virginia Tech will be responsible for any medical care or costs that may arise directly or indirectly from your participation in this study.

IX. Approval of Research: This research project has been reviewed and authorized by the Institutional Review Board for Research Involving Human Subjects at Virginia Polytechnic Institute and State University.

X. Subject's Responsibilities: You voluntarily agree to participate in this study. You have the following responsibilities throughout this study:

(6) provide written consent to complete procedures for this study;
(7) arrive at the sleep clinic for your sleep test on the scheduled days and times;
(8) cooperate in performing the 2 breath holding episodes on two different days at the Sleep Disorders Network clinic.

XI. Subject's Permission: I have read the Informed Consent and conditions of this project. I have had all of my questions answered. I hereby acknowledge the above and give my voluntary consent for participation in this project. If I participate, I understand that I may withdraw at any time, without penalty. I agree to abide by the rules of this project.

Participant Signature Date

Researcher (Witness) Signature Date

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

Dr. William G. Herbert, Principal Investigator
(540) 231-5104; wgherb@vt.edu

Dr. David M. Moore, IRB Chair
(540) 231-4991; moored@vt.edu

Adrian Aron, M.S., Co-Investigator
(540) 831-5497; aaron@radford.edu

Appendix G - IRB Approval letter

Reliability Study

VirginiaTech

Office of Research Compliance
Institutional Review Board
2000 Kraft Drive, Suite 2000 (0497)
Blacksburg, Virginia 24061
540/231-4991 Fax 540/231-0959
e-mail moored@vt.edu
www.irb.vt.edu

FWA00000572(expires 1/20/2010)
IRB # is IRB00000667

DATE: September 22, 2008

MEMORANDUM

TO: William G. Herbert
Adrian Aron
John Gregg

Approval date: 9/22/2008
Continuing Review Due Date:9/7/2009
Expiration Date: 9/21/2009

FROM: David M. Moore

SUBJECT: **IRB Expedited Approval:** "Acute Effects of Simulated Obstructive Apneas (Mueller Maneuver) on Cardiac Function in Apparently Healthy Adults Using a New Impedance Cardiograph Device" , IRB # 08-532

This memo is regarding the above-mentioned protocol. The proposed research is eligible for expedited review according to the specifications authorized by 45 CFR 46.110 and 21 CFR 56.110. As Chair of the Virginia Tech Institutional Review Board, I have granted approval to the study for a period of 12 months, effective September 22, 2008.

As an investigator of human subjects, your responsibilities include the following:

1. Report promptly proposed changes in previously approved human subject research activities to the IRB, including changes to your study forms, procedures and investigators, regardless of how minor. The proposed changes must not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.
2. Report promptly to the IRB any injuries or other unanticipated or adverse events involving risks or harms to human research subjects or others.
3. Report promptly to the IRB of the study's closing (i.e., data collecting and data analysis complete at Virginia Tech). If the study is to continue past the expiration date (listed above), investigators must submit a request for continuing review prior to the continuing review due date (listed above). It is the researcher's responsibility to obtain re-approval from the IRB before the study's expiration date.
4. If re-approval is not obtained (unless the study has been reported to the IRB as closed) prior to the expiration date, all activities involving human subjects and data analysis must cease immediately, except where necessary to eliminate apparent immediate hazards to the subjects.

Important:
If you are conducting **federally funded non-exempt research**, please send the applicable OSP/grant proposal to the IRB office, once available. OSP funds may not be released until the IRB has compared and found consistent the proposal and related IRB applicaton.

cc: File
Department Reviewer:Kevin P. Davy

Appendix H - IRB Approval letter

Clinical Study

VirginiaTech

Office of Research Compliance
Institutional Review Board
2000 Kraft Drive, Suite 2000 (0497)
Blacksburg, Virginia 24061
540/231-4991 Fax 540/231-0959
e-mail moored@vt.edu
www.irb.vt.edu

FWA00000572(expires 1/20/2010)
IRB # is IRB00000667

DATE: July 7, 2009

MEMORANDUM

TO: William G. Herbert
Adrian Aron

Approval date: 7/7/2009
Continuing Review Due Date:6/22/2010
Expiration Date: 7/6/2010

FROM: David M. Moore

SUBJECT: **IRB Expedited Approval:** "Cardiac Function In Obstructive Sleep Apnea Hypopnea Syndrome Patients" , RB # 09-587

This memo is regarding the above-mentioned protocol. The proposed research is eligible for expedited review according to the specifications authorized by 45 CFR 46.110 and 21 CFR 56.110. As Chair of the Virginia Tech Institutional Review Board, I have granted approval to the study for a period of 12 months, effective July 7, 2009.

As an investigator of human subjects, your responsibilities include the following:

1. Report promptly proposed changes in previously approved human subject research activities to the IRB, including changes to your study forms, procedures and investigators, regardless of how minor. The proposed changes must not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.
2. Report promptly to the IRB any injuries or other unanticipated or adverse events involving risks or harms to human research subjects or others.
3. Report promptly to the IRB of the study's closing (i.e., data collecting and data analysis complete at Virginia Tech). If the study is to continue past the expiration date (listed above), investigators must submit a request for continuing review prior to the continuing review due date (listed above). It is the researcher's responsibility to obtain re-approval from the IRB before the study's expiration date.
4. If re-approval is not obtained (unless the study has been reported to the IRB as closed) prior to the expiration date, all activities involving human subjects and data analysis must cease immediately, except where necessary to eliminate apparent immediate hazards to the subjects.

Important:
If you are conducting **federally funded non-exempt research**, please send the applicable OSP/grant proposal to the IRB office, once available. OSP funds may not be released until the IRB has compared and found consistent the proposal and related IRB applicaton.

cc: File

Appendix I - RAW DATA

Reliability study

Table 1. Subject characteristics of control group

Subject #	SBP	DBP	O_2desat (MM-1)	O_2desat (MM-2)	Age (Yr)	Weight (Kg)	Height (Cm)	BMI	NeckCirc (Cm)	ESS	Berlin
1	124.0	80.0	89.0	90.0	36.0	83	184	24.5	38	5	low
2	118.0	80.0	91.0	92.0	27.0	70	177	22.3	35	2	Low
4	122.0	78.0	90.0	91.0	43.0	87	184	25.7	41	8	Low
5	110.0	62.0	94.0	94.0	45.0	68	178	21.5	34	6	Low
6	120.0	80.0	92.0	93.0	30.0	87	183	25.7	39	5	Low
7	112.0	60.0	96.0	97.0	36.0	83	182	25.1	39	5	Low
8	128.0	88.0	89.0	87.0	45.0	73	184	21.6	40	4	Low
9	118.0	82.0	89.0	90.0	42.0	79	186	22.8	38	6	Low
10	108.0	76.0	97.0	95.0	38.0	76	185	22.0	37	5	Low
11	116.0	78.0	95.0	95.0	34.0	66	176	21.3	39	6	Low
12	122.0	80.0	94.0	93.0	37.0	86	189	23.8	35	7	Low
13	120.0	76.0	90.0	91.0	45.0	66	178	20.8	41	5	Low
14	112.0	70.0	96.0	97.0	40.0	70	180	21.6	38	9	Low
15	112.0	74.0	93.0	93.0	38.0	68	179	21.2	39	7	Low
Mean	117.3	76.0	92.5	92.7	38.3	75.9	181.8	22.9	38.1	5.7	Low
SD	5.8	7.6	2.9	2.8	5.6	8.1	3.8	1.8	2.2	1.7	N/A

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; O_2 desat, oxygen desaturation; AHI, Apnea Hypopnea Index; ESS, Epworth Sleepiness Scale

(-) denotes missing data

Table 2. Cardiac values during normal breathing before 4 Mueller Maneuvers

Subject #	HR4	SV4	MCI4	SVR4	HR5	SV5	MCI5	SVR5
1	64.87	109.76	227.4	1082.4	64.5	113.69	247.18	1125.34
2	88.4	85	121.9	987.6	89.29	83.79	127.06	989.91
4	75.7	101.65	130.4	953.8	76.85	100.69	138.01	946.05
5	49.3	114.5	251.3	1153.2	51.6	115.34	258.65	1132.05
6	51.3	115.8	232.8	1128.3	51.6	115.34	248.83	1139.99
7	55.2	114.23	253.8	1070.4	54.4	115.84	268.54	1058.4
8	62.8	96.3	184.2	1031.5	63.5	95.09	208.03	1075.77
9	84.5	93.5	134.1	1003.7	83.57	93.66	141.41	942.25
10	63.45	90.21	162.1	1127.5	60.8	92.03	170.4	1195.3
11	55.67	108.4	231.8	1182.5	53.4	105.22	227.5	1218.2
12	83.5	93.66	112.58	978.66	82	93.38	113.1	989.62
13	72.98	94.48	108.61	896.74	73.76	92.68	115.07	885.99
14	61.58	125.06	279.25	1131.12	61.15	127.51	295.14	1122.12
15	68.1	99.31	185.82	1186.49	65.82	101.97	195.27	1257.29
Mean	67.0	103.0	186.9	1065.3	66.6	103.3	196.7	1077.0
SD	12.5	11.7	59.1	91.1	12.5	12.5	62.5	112.7

HR4, average of 5 seconds at the end of the 4 minute during normal breathing; HR5, average of 5 seconds at the end of the 4 minute during normal breathing; SV, Stroke volume (ml/bt); MCI, myocardial contractility (ohm/sec/cm^2); SVR, systemic vascular resistance (dyn/sec/cm); SD, standard deviation.

Table 3. Cardiac changes during 15 sec Mueller Maneuver in OSAHS subjects

Subject #	HR1	HR2	HR %	SV1	SV2	SV %	MCI1	MCI2	MCI %	SVR1	SVR2	SVR %
1	56.6	53.97	-16.33	106.15	113.53	-0.14	230.17	241.78	-2.18	1063.18	1136.6	1
2	82	82.43	-7.68	88.74	81.1	-3.21	134.76	131.75	3.69	1020.9	1013	2.33
4	79.4	83.8	9.04	101.02	99.46	-1.22	135.57	132.24	-4.18	933.68	923.6	-2.37
5	53.6	53	2.71	104.39	115.65	0.27	226.46	240.85	-6.88	1207.64	1096.83	-3.11
6	53.6	53	2.71	110.98	111.65	-3.2	247.55	250.85	0.81	1152.12	1096.83	-3.79
7	52.8	53	-2.57	106.4	105.5	-8.93	224.3	238.8	-11.07	1065.5	1097.8	3.72
8	64.14	61.16	-3.69	94.2	96.42	1.4	214.12	209.31	0.62	1053.39	1076.43	0.06
9	82	83	-0.68	88.74	85.31	-8.92	140.15	144.93	2.49	990.43	1037.04	10.06
10	59.4	61.2	0.66	86.14	85.33	-7.28	169.4	166.88	-2.07	1199.3	1243.9	4.07
11	55.34	52.35	-1.97	109.22	108.32	2.95	235.56	243.12	6.87	1074.22	1090.56	-10.48
12	79.43	80.25	-2.13	101.01	97.4	4.31	123.37	120.01	6.11	937.88	922.69	-6.76
13	75.51	80.07	8.55	92.07	91.67	-1.09	113.67	111.46	-3.14	860.17	850.62	-3.99
14	60.35	60.39	-1.24	119.01	116.95	-8.28	249.86	263.24	-10.81	1142.67	1174.44	4.66
15	65.22	66.86	1.58	97.02	95.05	-6.79	193.23	189.59	-2.91	1274.74	1318.81	4.89
Mean	65.7	66.0	-0.8	100.4	100.2	-2.9	188.4	191.8	-1.6	1069.7	1077.1	0.0
SD	11.5	13.0	6.3	9.7	11.9	4.5	50.3	55.6	5.5	117.3	125.6	5.4

HR1, average of HR during first 5 sec during MM; HR2, average of HR during last 5 sec during MM; HR%, percent change in HR during MM

SV, Stroke volume (ml/bt); MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Table 4. Changes in stroke volume during 3 minutes normal breathing following 15 sec Mueller maneuver in controls

Subject #	SV0	SV30	SV60	SV90	SV120	SV150	SV180
1	114.7	111.3	108.83	109.61	109.61	108.77	110.39
2	80.29	100.1	91.17	85.86	88.44	88.73	87.33
4	97.31	92.60	96.38	95.27	93.96	92.19	91.51
5	113.1	113.8	111.65	111.17	110.58	112.68	117.42
6	117.1	113.8	111.24	112.02	112.02	111.18	112.8
7	117.5	112.1	113.4	111.2	111.6	111.8	113.2
8	93.93	93.30	95.62	94.93	95.93	95.32	96.05
9	80.29	100.1	91.17	87.73	85.88	88.72	89.95
10	86.20	85.10	91.3	92.8	91.7	92.7	90.2
11	114.1	110.3	110.32	110.32	109.79	108.36	108.43
12	97.14	96.48	95.03	95.29	93.66	92.19	95.33
13	88.91	82.71	88.02	86.28	84.17	82.85	88.99
14	129.5	125.6	125.42	123.85	125.05	124.8	125.38
15	96.53	96.92	101.59	103.72	103.42	103.97	100.65
Mean	101.9	102.4	102.2	101.4	101.1	101.0	102.0
SD	15.6	12.3	11.2	11.8	12.2	12.2	12.4

SV0, stroke volume immediately after MM; SV30, stroke volume at 30 sec.

Table 5. Changes in myocardial contractility during 3 minutes normal breathing following 15 sec Mueller maneuver in controls

Subject #	MCI0	MCI30	MCI60	MCI90	MCI120	MCI150	MCI180
1	243.03	236.91	229.62	238.36	233.25	232.39	233.39
2	129.52	149.25	142.34	114.06	125.61	133.26	124.64
4	123.85	125.64	112.99	118.71	123.82	113.8	123.53
5	237.49	242.35	235.32	240.77	232.65	251.9	235.91
6	265.44	249.32	232.03	240.77	235.66	234.8	235.8
7	265.4	244.3	240.5	240.7	235.3	239.9	237.5
8	201.99	206.89	211.82	202.06	215.41	203.86	211.53
9	132.56	155.45	142.34	146.39	135.61	133.25	124.64
10	166.5	168.4	175.3	180.6	186.8	180.6	170.6
11	260.03	243.91	226.62	235.36	230.25	229.39	230.39
12	128.05	125.97	115.69	114.88	125.11	108.94	125.99
13	101.91	104.72	91.06	98.13	103.77	91.75	102.99
14	291	268.88	266.09	264.94	259.01	265.61	261.7
15	190.37	191.25	199.16	203.11	208.78	204.58	193.07
Mean	195.5	193.8	187.2	188.5	189.4	187.4	186.5
SD	64.9	55.1	56.5	58.8	54.3	59.7	55.8

MCI0, myocardial contractility immediately after MM; MCI30, myocardial contractility at 30 sec.

Table 6. Changes in systemic vascular resistance during 3 minutes normal breathing following 15 sec Mueller maneuver in controls

Subject #	SVR0	SVR30	SVR60	SVR90	SVR120	SVR150	SVR180
1	1056.91	1046.24	1187.72	1126.5	1177.04	1042.98	1121.75
2	1141.04	799.31	985.7	916.88	995.04	1083.54	1036.23
4	996.46	902.86	972.02	978.23	929.2	930.18	955.6
5	1120.42	1044.59	1228.55	1184.91	1197.07	1031.6	1064.03
6	1059.32	1048.65	1190.13	1128.91	1179.45	1045.39	1124.16
7	1059.3	1094.92	1144.4	1184.9	1128.5	1060.4	1120.4
8	1088.17	1083.18	994.08	1103.16	1101.39	1123.52	1143.64
9	1141.04	799.31	985.7	916.88	1084.46	1083.54	1081.03
10	1169.2	1234.1	1204.4	1109.4	1089.5	1124.2	1170.7
11	1015.66	1004.99	1146.47	1085.25	1135.79	1001.73	1080.5
12	1022.12	909	969.1	973.27	911.99	930.18	968.28
13	921.5	826.81	898.12	903.22	853.17	856.19	882
14	1137.92	1174.63	1221.96	1263.57	1208.19	1138.05	1197.66
15	1246.09	1312.08	1280.23	1186.34	1167.46	1200.12	1246.23
Mean	1083.9	1020.0	1100.6	1075.8	1082.7	1046.5	1085.2
SD	82.7	158.8	126.0	117.3	115.2	93.0	99.2

SVR0, systemic vascular resistance immediately after MM; SVR30, systemic vascular resistance at 30 sec.

Table 7. Cardiac changes during second 15 sec Mueller Maneuver in OSAHS subjects

Subject #	SV1	SV2	SV %	MCI1	MCI2	MCI %	SVR1	SVR2	SVR %
1	101.36	104.33	-5.49	186.01	196.56	-15.78	1067.06	1095.04	-2.38
2	96.09	100.88	15.52	178.57	170.15	36.51	1015.18	1018.64	-1.7
4	94.65	90.63	-0.96	109.01	112.05	-9.29	1000.75	1044.34	9.29
5	100.69	113.51	-3.33	215.73	232.46	-1.46	1223.96	1170.14	9.97
6	105.65	103.51	-8.24	204.51	212.46	-9.9	1149.66	1170.14	4.09
7	100.7	113.50	0.27	204.51	212.5	-10.53	1123.9	1170.1	4.44
8	101.64	98.46	2.51	219.42	214.42	1.37	1077.71	1005.86	-12.05
9	96.08	99.88	11.04	178.59	170.15	36.51	1015.17	1018.63	-5.77
10	89.1	89.60	-0.67	162.5	159.3	-6.62	1132.9	1092.8	-6.65
11	108.63	101.32	-6.56	193.52	198.36	-13.9	1084.79	1138.45	5.36
12	93.41	91.21	-4.33	113.99	112.05	-11.07	1013.06	1037.16	7.11
13	84.75	82.04	-7.81	90.2	92.25	-10.43	923.76	965.75	9.5
14	114.26	125.75	0.3	226.98	235.96	-9.84	1204.55	1252.35	4.57
15	100.93	100.12	-0.53	183.24	181.03	-6.24	1211.82	1173.32	-5.85
Mean	99.1	101.1	-0.6	176.2	178.6	-2.2	1088.9	1096.6	1.4
SD	7.6	11.2	6.8	43.0	45.8	17.0	90.2	84.1	7.1

SV1, average of SV during first 5 sec during MM; SV2, average of SV during last 5 sec during MM; SV%, percent change in SV during MM

SV, Stroke volume (ml/bt); MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Table 8. Changes in stroke volume during 3 minutes normal breathing following second 15 sec Mueller maneuver in control subjects

Subject#	SV0	SV30	SV60	SV90	SV120	SV150	SV180
1	121.3	118.7	118.89	118.45	117.91	117.72	116.44
2	92.54	92.46	91.04	87.79	89.09	85.1	83.88
4	63.39	100.4	96.29	94.39	94.6	93.88	92.18
5	112.2	110.6	111.77	111.33	108.57	106.4	109.32
6	114.2	111.6	111.77	111.33	110.79	110.6	109.32
7	114.3	111.5	111.4	113.2	111.3	110.1	107.9
8	93.38	97.50	100.17	99.62	98.25	96.55	96.52
9	82.85	104.2	106.97	102.53	104.63	98.64	100.52
10	90.30	90.10	89.3	90.4	91.5	90.8	91.7
11	108.1	105.5	105.67	105.23	104.69	104.5	103.22
12	79.52	97.57	94.81	93.8	97.38	94.9	93.15
13	54.60	90.68	86.7	85.7	86.36	84.42	83.05
14	126.7	124.9	124.65	125.55	123.2	123.22	120.69
15	101.0	101.8	100.82	101.02	101.67	102.19	102.76
Mean	96.7	104.1	103.6	102.9	102.9	101.4	100.8
SD	21.4	10.4	11.4	12.0	10.8	11.6	11.4

SV0, stroke volume immediately after MM; SV30, stroke volume at 30 sec.

Table 9. Changes in myocardial contractility during 3 minutes normal breathing following second 15 sec Mueller maneuver in control subjects

Subject#	MCI0	MCI30	MCI60	MCI90	MCI120	MCI150	MCI180
1	244.79	238.61	237.91	234.05	236.76	241.9	234.5
2	145.97	179.68	161.52	153.01	149.71	132.2	144.37
4	78.8	148.25	113.31	113.34	112.99	117.24	119.95
5	246.07	237.49	231.79	234.82	225.64	209.05	227.38
6	237.67	231.49	230.79	226.93	229.64	234.78	227.38
7	237.7	228.4	229.8	231	221.9	233.8	216.7
8	213.78	216.17	215.48	212.87	210.16	207.48	213.34
9	179.76	182.35	182.84	184.62	179.91	164.31	155.79
10	178.8	164.2	176.4	180.9	175.7	168.9	170.3
11	226.46	220.28	219.58	215.72	218.43	223.57	216.17
12	78.89	143.08	116.9	115.33	112.46	114.85	110.42
13	56.86	127.37	93.08	93.33	92.19	95.31	95.24
14	263.3	252.94	253.69	254.67	246.36	259.39	241.07
15	202.67	187.01	198.56	202.84	198.43	192.76	192.94
Mean	185.1	197.0	190.1	189.5	186.4	185.4	183.3
SD	69.3	40.6	51.6	51.7	51.0	53.6	50.0

MCI0, myocardial contractility immediately after MM; MCI30, myocardial contractility at 30 sec.

Table 10. Changes in systemic vascular resistance during 3 minutes normal breathing following second 15 sec Mueller maneuver in control subjects

Subject#	SVR0	SVR30	SVR60	SVR90	SVR120	SVR150	SVR180
1	1121.7	1187.55	1200.68	1176.37	1193.04	1195.56	1154.97
2	1382.56	926.23	1088.28	1157.1	1165.65	1170.01	1114.85
4	1134.33	1192.22	1189.43	1163.34	1177.87	1168.94	1123.54
5	1033.52	1105.96	1193.56	1207.65	1185.92	1188.44	1147.85
6	1114.58	1180.43	1193.56	1169.25	1185.92	1188.44	1147.85
7	1114.6	1210.6	1256.5	1158.8	1121.5	1257	1263.2
8	977.84	1015.37	1075.63	1057.69	1070.92	1129.34	1073.24
9	1132.31	1210.84	1153.51	1077.93	1054.71	1013.54	1042.78
10	1193.2	1237.3	1218.5	1193.2	1153.8	1172.7	1120.7
11	1065.27	1131.12	1144.25	1119.94	1136.61	1139.13	1098.54
12	1321.41	1080.14	967.64	990.85	972.18	965.17	1005.33
13	1055.51	1112.32	1108.59	1083.86	1097.28	1090.15	1041.66
14	1197.08	1294.16	1341	1241.94	1205.75	1339.45	1348.74
15	1273.95	1319.13	1301.27	1274.61	1236.32	1253.42	1204.51
Mean	1151.3	1157.4	1173.7	1148.0	1139.8	1162.2	1134.8
SD	113.0	105.4	96.0	75.9	70.9	95.7	91.0

SVR0, systemic vascular resistance immediately after MM; SVR30, systemic vascular resistance at 30 sec.

Table 11. Cardiac changes during first 30 sec Mueller Maneuver in control subjects

Subject#	SV1	SV2	SV %	MCI1	MCI2	MCI %	SVR1	SVR2	SVR %
1	117.11	109.32	-6.11	223.71	219.36	-6.46	1004.84	1101.34	-4.64
2	91.1	73.23	-12.69	130.67	124.68	-13.64	1051.14	1112.6	-0.2
4	92.07	76.64	-16.86	110.89	108.41	-9.62	997.18	1199.31	6.74
5	109.99	111.02	1.56	227.41	241.42	6.17	1120.38	1071.94	-6.61
6	109.99	98.03	-10.33	227.41	199.42	-12.3	1120.38	1171.94	2.1
7	119.9	111.30	3.15	227.4	213.5	-1.48	1020.4	1071.4	-15.18
8	96	91.07	-5.65	209.97	195.98	-8.14	1065.77	1106.77	3.12
9	81.81	75.38	-25.01	150.67	147.04	-5.62	1125.44	1153.96	10.66
10	90.3	79.50	-13.3	171.9	152.7	-10.33	1163	1259	12.34
11	105.48	96.14	-6.86	210.14	199.31	-7.8	1160.29	1216.33	10.72
12	92.85	79.10	-15.08	111.74	104.04	-5.78	985.66	1213.69	20.73
13	83.24	68.80	-17.16	88.95	88.11	-7.49	916.28	1113.4	6.89
14	132.39	122.80	1.75	253	237.46	-1.5	1104.96	1160.97	-13.92
15	101.06	89.27	-13.13	195.77	174.93	-9.33	1245.83	1346.84	11.82
Mean	101.7	91.5	-9.7	181.4	171.9	-6.7	1077.3	1164.2	3.2
SD	14.8	17.0	8.2	53.4	51.2	5.1	87.5	77.7	10.4

SV1, average of SV during first 5 sec during MM; SV2, average of SV during last 5 sec during MM; SV%, percent change in SV during MM

SV, Stroke volume (ml/bt); MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Table 12. Changes in stroke volume during 3 minutes normal breathing following first 30 sec Mueller maneuver in control subjects

Subject#	SV0	SV30	SV60	SV90	SV120	SV150	SV180
1	91.45	112.84	112.79	114.1	111.62	111.46	111.3
2	62.86	112.94	103.47	102.53	100.8	98.64	100.52
4	75.75	77.48	92.5	80.17	81.25	81.81	85.25
5	114.44	111.5	111.45	112.76	110.28	110.12	107.96
6	90.11	111.5	111.45	112.76	110.28	110.12	109.96
7	109.2	110.1	111.7	111.3	108.5	106.4	107.8
8	90.54	98.12	99.92	98.92	98.44	101.5	101.33
9	78.99	82.46	91.04	87.91	89.09	85.09	85.6
10	77.3	82.5	90.6	91.5	86.3	85.2	86.2
11	87.2	108.59	108.54	109.85	107.37	101.21	99.05
12	82.99	85.41	90.09	92.21	91.25	96.86	89.07
13	66.92	67.68	84	70.86	71.55	73.22	76.45
14	121.69	123.56	123.86	124.27	121.86	118.65	122.26
15	88.06	94.23	101.03	102.74	97.93	95.72	96.93
Mean	88.4	98.5	102.3	100.8	99.0	98.3	98.5
SD	17.0	16.9	11.5	14.8	13.8	13.0	12.8

SV0, stroke volume immediately after MM; SV30, stroke volume at 30 sec.

Table 13. Changes in myocardial contractility during 3 minutes normal breathing following first 30 sec Mueller maneuver in control subjects

Subject#	MCI0	MCI30	MCI60	MCI90	MCI120	MCI150	MCI180
1	189.84	241.33	242.75	242.97	242.44	248.79	227.09
2	119.76	123.33	128.8	124.62	129.91	134.72	140.73
4	119.94	129.43	131.85	131.15	127.54	120.32	101.21
5	239.11	228.43	229.85	230.07	229.54	233.89	211.19
6	176.94	228.43	229.85	230.07	229.54	215.89	214.19
7	213.8	243.5	231.8	234.8	225.8	222.5	222.25
8	191.26	218.66	229.09	207.63	212.5	227.2	225.96
9	140	179.68	161.51	150.45	149.7	142.2	144.37
10	141.3	171.5	189.3	188.4	179.6	178.3	177.1
11	168.02	219.51	220.93	221.15	220.62	216.97	205.27
12	88.43	112.45	103.05	102.23	107.88	110.71	94.38
13	79.11	86.49	90.26	99.16	96.62	90.08	91.8
14	238.29	270.1	257.05	260.45	250.38	246.4	245.32
15	164.06	196.37	212.82	212.32	202.45	200.47	198.44
Mean	162.1	189.2	189.9	188.2	186.0	184.9	178.5
SD	50.5	56.8	55.9	55.5	53.3	54.6	53.8

MCI0, myocardial contractility immediately after MM; MCI30, myocardial contractility at 30 sec.

Table 14. Changes in systemic vascular resistance during 3 minutes normal breathing following first 30 sec Mueller maneuver in control subjects

Subject#	SVR0	SVR30	SVR60	SVR90	SVR120	SVR150	SVR180
1	908.9	1096.99	1158.61	1146.48	1144.16	1166.19	1124.99
2	1132.31	1129.2	1103.52	977.93	1054.72	1013.55	1042.79
4	1178.7	979.21	1035.8	1397.63	1486.67	1470.76	1349.59
5	1145.48	1210.57	1156.58	1168.99	1116.67	1257.01	1263.24
6	931.41	1119.5	1101.12	1168.99	1166.67	1188.7	1147.5
7	1083.5	1119.3	1193.5	1207.6	1187.3	1188.4	1148
8	1112.47	1017.02	1028.72	1037.25	1056.31	1034.85	1071.74
9	1382.56	1126.22	1088.28	1160.34	1138.39	1139.15	1114.85
10	1278.3	1280.5	1271.9	1230.5	1206.9	1192.5	1182.7
11	961.3	1149.39	1111.01	1198.88	1196.56	1218.59	1177.39
12	1278.7	1181.34	1024.37	920.67	1017.39	1011.66	1024.54
13	1099.77	896.27	953.86	1315.91	1405.38	1391.85	1271.09
14	1166.09	1205.9	1279.1	1292.98	1272.25	1270.97	1230.16
15	1359.16	1365.37	1355.77	1314.15	1290.12	1273.34	1263.13
Mean	1144.2	1134.1	1133.0	1181.3	1195.7	1201.3	1172.3
SD	147.2	119.1	112.2	133.1	132.4	132.1	94.7

SVR0, systemic vascular resistance immediately after MM; SVR30, systemic vascular resistance at 30 sec.

Table 15. Cardiac changes during second 30 sec Mueller Maneuver in control subjects

Subject#	SV1	SV2	SV %	MCI1	MCI2	MCI %	SVR1	SVR2	SVR %
1	111.09	101.58	-8.73	191.75	189.57	-16.52	1068.35	1127.11	0.19
2	90.17	88.88	-11.58	139.62	116.64	-17.12	1242.77	1418.72	36.05
4	97.58	73.46	-13.83	121.13	91.82	-9.28	1020.24	1147.77	-14.95
5	112.57	97.68	-9.52	204.85	183.83	-12.96	1003.09	1150.89	-8.89
6	108.78	94.68	-13.9	204.85	186.77	-12.8	1106.76	1150.89	0.3
7	108.8	94.7	-12.15	229.4	188.6	-15.14	1102.9	1143.7	-0.37
8	98.36	91.23	-9.97	224.78	190.23	-15.81	1009.5	1053.11	-1.74
9	83.01	79.7	-6.89	139.61	135.31	-6.28	1042.77	1254.49	12.53
10	85.3	78.2	-9.28	172.5	157.9	-10.84	1179.3	1284.1	8.57
11	105	92.77	-6.34	188.95	167.4	-18.45	1029.94	1103.33	-6.29
12	91.08	80.51	-9.61	120.99	88.44	-6.3	1043.71	1197.25	16.86
13	88.28	74.87	-2.07	100.35	81.87	-10.82	940.29	1064.99	-16.21
14	121.76	109.95	-10.07	253.84	212.21	-13.5	1186.51	1230.14	0
15	96.53	88.72	-8.47	195.21	179.78	-9.4	1261.18	1368.81	8.37
Mean	99.9	89.1	-9.5	177.7	155.0	-12.5	1088.4	1192.5	2.5
SD	11.7	10.6	3.1	46.5	43.9	3.9	96.1	108.0	13.6

SV1, average of SV during first 5 sec during MM; SV2, average of SV during last 5 sec during MM; SV%, percent change in SV during MM

SV, Stroke volume (ml/bt); MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Table 16. Changes in stroke volume during 3 minutes normal breathing following second 30 sec Mueller maneuver in control subjects

Subject#	SV0	SV30	SV60	SV90	SV120	SV150	SV180
1	81.46	107.95	108.1	103.89	107.5	103.61	103.59
2	66.53	102.67	111.24	109.38	104.92	102.41	102.96
4	87.43	101.54	99.75	97.92	97.49	93.92	94.78
5	82.78	108.53	110.86	106.65	110.26	106.37	99.68
6	84.22	110.71	110.86	106.65	110.26	106.37	106.35
7	88.61	108.5	104.5	109.7	99.6	103.5	107.9
8	83.1	96.42	105.1	95.79	100.54	97.13	96.98
9	66.53	102.67	111.24	109.38	104.92	102.41	102.96
10	72.1	81.8	88.9	89.3	86.3	88.2	86.4
11	82.93	109.42	109.57	105.36	108.97	105.08	105.06
12	82.24	101.8	99.12	96.06	91.04	92.79	93.16
13	79.03	91.66	90.86	89.08	87.9	85.13	86.4
14	100.67	122.04	117.05	122.2	112.85	115.95	119.94
15	82.43	93.61	99.72	100.07	97.82	98.92	96.71
Mean	81.4	102.8	104.8	103.0	101.5	100.1	100.2
SD	8.8	9.9	8.2	9.0	8.6	8.1	8.9

SV0, stroke volume immediately after MM; SV30, stroke volume at 30 sec.

Table 17. Changes in myocardial contractility during 3 minutes normal breathing following second 30 sec Mueller maneuver in control subjects

Subject#	MCI0	MCI30	MCI60	MCI90	MCI120	MCI150	MCI180
1	165.07	228.75	252.49	229.33	229.83	213.74	215.02
2	127.28	124.55	135.33	134.52	135.72	136.9	139.67
4	139.64	145.12	131.4	119.55	118.78	115.55	122.52
5	172.34	219.04	242.78	219.62	231.37	204.03	180.06
6	155.36	219.04	242.78	219.62	220.12	204.03	205.31
7	180	219	212.9	221.09	180.1	176.5	185.9
8	164.23	212.26	221	208.41	221.32	206.23	219.28
9	127.28	124.55	135.33	134.52	135.72	136.9	139.67
10	158.2	169.2	175.8	178.4	177.2	175.6	174.2
11	145.8	209.48	233.22	210.06	210.56	194.47	195.75
12	131.09	144.21	129	112.84	124.63	115.45	119.88
13	118.86	122.22	109.58	98.69	98.5	95.64	101.84
14	204.44	245.56	238.38	245.61	204.04	200.07	210.24
15	180.91	194.03	199.55	201.19	199.41	197.44	196.81
Mean	155.0	184.1	190.0	181.0	177.7	169.5	171.9
SD	24.8	44.0	51.9	50.1	46.1	40.7	39.5

MCI0, myocardial contractility immediately after MM; MCI30, myocardial contractility at 30 sec.

Table 18. Changes in systemic vascular resistance during 3 minutes normal breathing following second 30 sec Mueller maneuver in control subjects

Subject#	SVR0	SVR30	SVR60	SVR90	SVR120	SVR150	SVR180
1	957.64	1051.23	1153.66	1229.52	1125.23	1141.7	1139.43
2	1573.86	1490.57	1344.23	1145.41	1100.08	1104.64	1047.85
4	1118.45	981.75	958.83	923.24	1016.82	959.42	957.33
5	1156.29	1100.01	1172.43	1258.29	1126.43	1160.47	1094.7
6	976.41	1070	1172.43	1248.29	1144	1160.47	1158.2
7	1161.2	1100	1258.2	1130.8	1194.7	1013.2	1047.1
8	1147.81	988.12	959.26	1007.63	1042.3	1007.53	1057.52
9	1573.86	1490.57	1344.23	1145.41	1100.08	1104.64	1047.85
10	1380	1320.3	1284.2	1240.2	1210.5	1200.6	1190.5
11	1016.35	1109.94	1212.37	1288.23	1183.94	1200.41	1198.14
12	1104.86	982.42	958.14	929.85	973.04	968.23	978.27
13	1040.06	900.91	879.14	842.43	937	881.09	877.89
14	1243.25	1184.5	1341.55	1215.27	1278.18	1095.19	1130.2
15	1460.32	1403.07	1365.82	1322.94	1292.25	1280.86	1271.87
Mean	1207.9	1155.2	1171.7	1137.7	1123.2	1091.3	1085.5
SD	209.5	194.8	168.7	152.5	105.8	111.7	105.6

SVR0, systemic vascular resistance immediately after MM; SVR30, systemic vascular resistance at 30 sec.

Table 19. Cardiac values during normal breathing after 4 Mueller Maneuvers

Subject#	recSBP	recDBP	HR4	SV4	MCI4	SVR4	HR5	SV5	MCI5	SVR5
1	124	78	64.3	104.2	198.8	1210.2	63.7	102.1	188.5	1238.4
2	120	90	87.5	82.8	120.4	1009.6	89.1	88.2	127.3	999.86
4	120	78	77.1	87.2	121.5	1132.6	81.14	98.31	123.58	1099.2
5	112	68	49.1	110.4	227.8	1212.5	51	103.7	198.12	1253.33
6	122	68	51.8	112.4	210.4	1221.7	51	103.7	198.12	1253.33
7	108	68	53.2	110.2	148.2	1131.2	54.1	108.3	146.2	1142.1
8	128	90	62.77	95.9	209.1	1145.3	63.2	94.2	200.4	1162.2
9	120	78	79.3	89.5	124.6	999.2	81.3	88.1	123.9	970.3
10	110	80	62.1	88.43	151.1	1210.3	58.3	97.4	152.5	1233.6
11	116	80	52.7	99	182.3	1328.5	53.1	102.4	188.2	1302.4
12	120	78	82.39	92.63	116.35	980.13	81.64	91.67	115.34	977.34
13	122	80	76.7	78.77	102.58	1057.98	80.95	91.07	106.37	1025.47
14	112	72	57.26	122.29	170.78	1209.48	57.95	119.2	167.07	1219.49
15	110	80	64.43	98.79	171.95	1286.85	60.42	106.57	171.64	1309.26
Mean	117.4	77.7	65.8	98.0	161.1	1152.5	66.2	99.6	157.7	1156.2
SD	6.1	7.0	12.6	12.6	40.7	107.7	13.6	8.7	34.0	121.5

HR4, average of 5 seconds at the end of the 4 minute during normal breathing; HR5, average of 5 seconds at the end of the 4 minute during normal breathing; recSBP, systolic blood pressure in recovery, SV, Stroke volume (ml/bt); MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Appendix J - RAW DATA

Clinical study

Table 1. Subject characteristics of obstructive sleep apnea hypopnea syndrome population

Subject#	SBP	DBP	O_2desat (MM-1)	O_2desat (MM-2)	Age (Yr)	AHI	Baseline O_2	Under89% (Minutes)	LowestO_2	Weight (Kg)	Height (Cm)	BMI	NeckCirc (Cm)	ESS	Berlin
1.0	124.0	72.0	80.0	83.0	-	-	-	-	-	-	-	-	-	-	-
2.0	124.0	72.0	89.0	88.0	46.0	13.0	93.0	1.0	87.0	102.0	183.0	31.0	46.0	13.0	high
3.0	138.0	78.0	89.0	88.0	37.0	14.0	96.0	1.0	83.0	117.0	173.0	39.0	-	10.0	high
4.0	120.0	80.0	88.0	87.0	47.0	123.0	-	-	77.0	109.0	175.0	35.0	43.0	11.0	high
5.0	134.0	78.0	90.0	87.0	64.0	70.0	92.0	11.0	79.0	91.0	175.0	30.0	43.0	10.0	high
6.0	140.0	92.0	88.0	89.0	60.0	100.0	83.0	64.0	61.0	117.0	170.0	40.0	47.0	12.0	low
8.0	134.0	88.0	96.0	96.0	35.0	51.0	94.0	0.0	90.0	92.0	179.0	29.0	42.0	13.0	high
9.0	136.0	80.0	85.0	88.0	57.0	17.0	92.0	0.0	87.0	110.0	185.0	32.0	46.0	18.0	high
11.0	118.0	82.0	91.0	89.0	51.0	11.0	93.0	0.0	86.0	84.0	185.0	24.0	36.0	8.0	high
12.0	120.0	78.0	89.0	88.0	54.0	47.0	91.0	19.0	67.0	103.0	163.0	39.0	46.0	14.0	high
13.0	124.0	82.0	89.0	88.0	50.0	27.0	90.0	12.0	77.0	111.0	169.0	38.0	45.0	16.0	high
14.0	144.0	78.0	93.0	92.0	36.0	22.0	96.0	0.0	88.0	139.0	183.0	41.0	48.0	8.0	low
15.0	118.0	80.0	96.0	96.0	63.0	31.0	94.0	7.0	74.0	162.0	180.0	50.0	43.0	0.0	low
16.0	140.0	92.0	89.0	85.0	32.0	7.0	95.0	0.0	89.0	93.0	183.0	28.0	42.0	15.0	high
17.0	133.0	88.0	94.0	95.0	46.0	48.0	93.0	11.0	67.0	101.0	180.0	31.0	43.0	17.0	high
18.0	142.0	90.0	89.0	90.0	42.0	17.0	94.0	0.0	88.0	108.0	182.0	32.0	44.0	14.0	high
19.0	142.0	90.0	88.0	86.0	39.0	64.0	82.0	9.0	77.0	121.0	172.0	41.0	45.0	13.0	high
20.0	118.0	78.0	90.0	92.0	43.0	22.0	92.0	0.0	88.0	90.0	182.0	27.0	37.0	9.0	high
Mean	130.5	82.1	89.6	89.3	47.2	40.2	91.9	8.4	80.3	108.8	177.6	34.5	43.5	11.8	N/A
SD	9.6	6.4	3.7	3.6	10.0	33.1	4.0	16.0	8.9	19.3	6.4	6.6	3.3	4.3	N/A

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; O_2 desat, oxygen desaturation; AHI, Apnea Hypopnea Index; ESS, Epworth Sleepiness Scale

(-) denotes missing data

Table 2. Cardiac changes during 30 sec Mueller Maneuver in obstructive sleep apnea hypopnea syndrome subjects

Subject#	HR1	HR2	HR %	SV1	SV2	SV %	CO %	MCI1	MCI2	MCI %	SVR1	SVR2	SVR %
1.0	65.4	69.2	1.8	59.7	47.6	-28.2	-15.5	134.0	143.2	1.5	2095.9	2052.9	7.9
2.0	55.6	57.0	8.1	106.7	106.9	-2.0	2.7	116.8	97.3	-5.9	1232.4	1191.8	-6.0
3.0	67.0	65.3	5.0	96.6	96.5	-8.5	-2.6	75.7	81.8	2.5	1189.3	1313.5	18.3
4.0	61.4	58.3	-1.6	86.9	96.3	5.1	5.3	126.2	124.1	-11.5	1672.3	1601.9	-0.6
5.0	66.6	62.6	-5.9	96.7	89.4	-6.5	-13.1	84.5	99.3	13.4	1206.1	1216.8	-0.3
6.0	61.4	62.4	-5.7	100.7	117.6	16.3	18.8	116.2	110.2	-2.4	1457.9	1204.6	-6.3
8.0	65.2	48.5	-25.2	107.5	107.8	1.4	-25.4	175.7	168.1	-5.7	1069.2	1423.5	31.0
9.0	57.2	60.2	5.6	129.8	133.2	3.1	8.0	114.5	131.3	11.5	942.5	888.5	-7.2
11.0	63.3	68.1	2.2	115.6	115.4	-2.6	7.3	125.1	144.7	25.4	1276.9	1191.1	-9.5
12.0	82.6	81.5	4.5	107.4	116.1	10.5	6.6	132.1	145.9	21.7	927.2	887.0	-11.6
13.0	68.7	66.3	4.0	99.7	98.6	-8.4	-3.6	77.4	83.9	4.1	1192.2	1301.7	19.1
14.0	78.3	86.1	4.2	49.2	60.1	15.1	34.4	83.8	73.7	4.5	1888.2	1577.7	-19.5
15.0	84.2	81.5	1.2	106.4	115.8	1.5	5.3	73.0	85.0	13.3	837.2	793.0	0.5
16.0	84.7	94.4	18.2	122.8	77.7	-38.9	-29.6	115.4	119.4	-3.5	894.3	1171.4	30.3
17.0	66.0	68.9	6.8	135.5	127.8	-5.9	-1.6	174.0	168.2	17.7	1052.5	1083.2	-0.6
18.0	78.3	86.1	4.2	49.2	50.1	-4.1	-2.1	83.8	73.7	4.5	1888.2	1577.7	-19.5
19.0	69.9	66.5	-9.8	62.8	59.6	-7.3	-9.7	129.7	127.9	-7.2	2876.1	2751.3	6.5
20.0	61.7	65.9	1.6	112.5	113.4	3.7	7.6	115.1	134.3	30.4	1287.6	1204.0	-8.8
Mean	68.8	69.4	1.1	97.0	96.1	-3.1	-0.4	114.1	117.3	6.4	1388.1	1357.3	1.3
SD	9.1	11.9	9.0	26.0	26.6	13.5	15.1	30.5	30.7	12.0	521.9	459.2	15.0

HR1, average of HR during first 5 sec during MM; HR2, average of HR during last 5 sec during MM; HR%, percent change in HR during MM

SV, Stroke volume (ml/bt); CO, cardiac output, MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Table 3. Changes in heart rate during 3 minutes normal breathing following Mueller maneuver in obstructive sleep apnea hypopnea syndrome subjects

Subject#	HR0	HR30	HR60	HR90	HR120	HR150	HR180
1.0	67.6	65.0	64.0	64.3	67.4	66.3	66.6
2.0	59.2	46.0	48.6	48.7	53.2	56.2	53.7
3.0	56.6	53.3	59.7	58.5	62.2	61.7	63.2
4.0	62.2	57.0	56.8	59.5	61.8	59.3	59.2
5.0	78.5	63.7	63.8	65.2	65.0	67.6	69.4
6.0	66.0	66.3	61.5	66.4	63.2	64.0	64.0
8.0	53.3	56.0	57.6	62.4	63.5	61.3	60.9
9.0	62.0	53.4	51.0	54.8	55.2	54.6	54.8
11.0	69.2	69.7	69.5	65.1	62.8	68.5	68.7
12.0	76.5	80.4	84.5	78.3	78.0	79.6	75.2
13.0	57.8	54.5	60.9	59.7	63.4	62.9	64.4
14.0	90.0	79.7	77.0	77.3	78.4	74.8	74.6
15.0	85.1	77.3	76.3	80.8	80.0	83.1	80.5
16.0	101.7	70.6	76.0	81.5	81.6	81.1	80.7
17.0	70.5	67.3	63.6	67.9	63.6	61.7	64.6
18.0	90.0	79.7	77.0	77.3	78.4	74.8	74.6
19.0	66.8	72.2	68.5	68.4	70.6	72.7	70.7
20.0	66.7	67.4	66.9	62.7	62.0	67.1	67.0
Mean	71.1	65.5	65.7	66.6	67.2	67.6	67.4
SD	13.3	10.4	9.7	9.3	8.6	8.4	7.8

HR0, heart rate immediately after MM; HR30, heart rate at 30 sec.

Table 4. Changes in stroke volume during 3 minutes normal breathing following Mueller maneuver

Subject#	SV0	SV30	SV60	SV90	SV120	SV150	SV180
1.0	59.8	75.6	75.4	75.6	76.5	81.4	79.1
2.0	111.4	97.4	110.7	110.2	110.1	105.7	106.2
3.0	99.1	96.0	117.2	108.8	106.4	108.5	111.3
4.0	96.3	78.4	80.8	84.4	81.6	94.5	94.3
5.0	83.4	103.3	99.6	99.8	100.3	97.9	94.4
6.0	95.0	104.1	114.3	115.1	106.3	106.6	105.1
8.0	105.8	107.4	106.8	108.5	106.9	106.2	106.9
9.0	127.4	120.6	127.4	130.5	127.6	130.7	128.7
11.0	95.1	129.9	124.5	115.4	121.9	123.0	116.3
12.0	117.5	84.3	94.1	94.7	95.0	98.6	98.7
13.0	97.4	94.3	115.5	107.1	104.7	106.8	109.6
14.0	60.2	51.9	45.1	43.5	47.3	42.1	48.0
15.0	99.4	116.8	117.6	109.3	110.6	111.0	111.7
16.0	91.4	141.4	142.9	134.5	131.7	130.5	131.3
17.0	125.6	134.2	136.7	131.2	130.7	132.1	131.1
18.0	60.2	51.9	45.1	43.5	47.3	42.1	48.0
19.0	61.2	61.9	63.4	61.4	63.5	63.1	65.0
20.0	89.9	123.6	119.3	110.6	117.4	117.7	111.0
Mean	93.1	98.5	102.0	99.1	99.2	99.9	99.8
SD	21.5	27.1	29.1	27.4	26.2	27.2	25.2

SV0, stroke volume immediately after MM; SV30, stroke volume at 30 sec.

Table 5. Changes in myocardial contractility during 3 minutes normal breathing following Mueller maneuver

Subject#	MCI0	MCI30	MCI60	MCI90	MCI120	MCI150	MCI180
1.0	119.0	120.8	100.6	108.6	116.8	130.0	118.6
2.0	93.9	122.3	132.9	111.7	116.6	100.8	100.6
3.0	106.0	116.7	122.1	104.9	99.9	96.9	93.6
4.0	150.0	146.3	135.0	127.2	127.4	141.5	142.4
5.0	148.2	101.3	99.5	97.4	93.8	94.2	95.6
6.0	109.0	112.6	114.5	110.7	111.1	113.9	113.8
8.0	171.7	162.7	163.5	171.9	175.3	172.3	163.6
9.0	127.7	86.5	93.6	111.2	113.8	111.6	115.2
11.0	157.9	124.4	121.1	120.6	141.9	140.1	132.4
12.0	161.7	120.3	104.4	109.9	93.9	101.9	113.6
13.0	102.2	112.9	118.3	101.1	96.1	93.1	89.8
14.0	79.8	81.5	69.5	70.8	63.7	75.1	68.3
15.0	81.7	90.1	86.2	79.8	77.3	73.5	79.2
16.0	122.0	206.3	192.9	159.3	141.5	131.3	131.9
17.0	143.2	156.3	146.6	151.4	138.6	132.2	140.7
18.0	79.8	81.5	69.5	70.8	63.7	75.1	68.3
19.0	127.3	129.6	136.7	133.2	133.7	134.5	128.2
20.0	142.2	109.1	106.5	106.2	126.9	123.7	117.8
Mean	123.5	121.2	117.4	113.7	112.9	113.4	111.9
SD	29.2	31.6	31.3	27.6	29.1	26.9	26.2

MCI0, myocardial contractility immediately after MM; MCI30, myocardial contractility at 30 sec.

Table 6. Changes in systemic vascular resistance during 3 minutes normal breathing following Mueller maneuver

Subject#	SVR0	SVR30	SVR60	SVR90	SVR120	SVR150	SVR180
1.0	1923.6	1865.3	1869.5	1898.4	1761.9	1683.6	1698.7
2.0	1135.7	1586.5	1349.1	1356.3	1216.7	1252.2	1271.4
3.0	1467.6	1535.3	1094.4	1127.7	1156.3	1145.8	1111.5
4.0	1603.5	2004.5	1968.4	1749.9	1766.2	1516.0	1612.9
5.0	1162.0	1204.6	1112.8	1195.3	1198.2	1233.6	1229.8
6.0	1408.7	1350.7	1287.4	1223.0	1230.8	1343.1	1321.7
8.0	1343.5	1243.5	1208.7	1107.5	1100.9	1125.3	1115.2
9.0	874.2	1104.0	1097.4	980.9	985.6	971.5	994.5
11.0	1318.9	1084.5	1109.8	1347.6	1232.5	1146.4	1210.6
12.0	915.9	1212.8	1125.4	1117.8	1109.1	1047.7	1107.4
13.0	1489.1	1556.8	1115.9	1149.2	1177.8	1167.3	1133.0
14.0	1617.6	1971.6	2321.1	2417.6	2128.7	2470.2	2276.7
15.0	937.0	816.0	830.8	841.5	839.4	830.3	819.5
16.0	1009.5	922.5	856.6	853.6	856.2	871.9	874.9
17.0	1084.1	1072.3	1120.8	1079.6	1170.3	1164.4	1125.8
18.0	1617.6	1971.6	2321.1	2417.6	2128.7	2470.2	2276.7
19.0	2311.3	2691.2	2663.1	2689.9	2656.9	2753.1	2599.8
20.0	1325.8	1091.0	1118.6	1355.2	1238.2	1156.0	1214.3
Mean	1363.6	1460.3	1420.6	1439.4	1386.4	1408.3	1388.6
SD	371.7	483.5	551.2	560.9	495.7	571.5	509.0

SVR0, systemic vascular resistance immediately after MM; SVR30, systemic vascular resistance at 30 sec.

Table 7. Subject characteristics of control subjects

Subject#	SBP	DBP	O_2desat (MM-1)	O_2desat (MM-2)	Age (Yr)	Weight (Kg)	Height (Cm)	BMI	NeckCirc (Cm)	ESS	Berlin
1.0	124.0	80.0	89.0	90.0	36.0	83	184	24.5	38	5	low
2.0	118.0	80.0	91.0	92.0	27.0	70	177	22.3	35	2	low
4.0	122.0	78.0	90.0	91.0	43.0	87	184	25.7	41	8	low
5.0	110.0	62.0	94.0	94.0	45.0	68	178	21.5	34	6	low
6.0	120.0	80.0	92.0	93.0	30.0	87	183	25.7	39	5	low
7.0	112.0	60.0	96.0	97.0	36.0	83	182	25.1	39	5	low
8.0	128.0	88.0	89.0	87.0	45.0	73	184	21.6	40	4	low
9.0	118.0	82.0	89.0	90.0	42.0	79	186	22.8	38	6	low
10.0	108.0	76.0	97.0	95.0	38.0	76	185	22.0	37	5	low
11.0	116.0	78.0	95.0	95.0	34.0	66	176	21.3	39	6	low
12.0	122.0	80.0	94.0	93.0	37.0	86	189	23.8	35	7	low
13.0	120.0	76.0	90.0	91.0	45.0	66	178	20.8	41	5	low
14.0	112.0	70.0	96.0	97.0	40.0	70	180	21.6	38	9	low
15.0	112.0	74.0	93.0	93.0	38.0	68	179	21.2	39	7	low
16.0	118.0	78.0	90.0	89.0	32.0	77	182	23.2	38	8	low
Mean	117.3	76.1	92.3	92.5	37.9	75.9	181.8	22.9	38.1	5.9	low
SD	5.6	7.3	2.8	2.9	5.6	7.8	3.7	1.7	2.1	1.8	N/A

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; O_2 desat, oxygen desaturation; AHI, Apnea Hypopnea Index; ESS, Epworth Sleepiness Scale

Table 8. Cardiac changes during 30 sec Mueller Maneuver in control subjects

Subject#	HR1	HR2	HR %	SV1	SV2	SV %	CO %	MCI1	MCI2	MCI %	SVR1	SVR2	SVR %
1.0	72.8	60.7	-16.7	118.3	113.0	6.1	-10.6	232.3	220.6	-9.9	852.5	886.8	-7.7
2.0	73.7	61.8	6.9	91.4	78.2	-13.2	-12.5	141.4	128.4	-7.6	1092.3	1162.7	10.7
4.0	72.1	59.8	9.9	130.2	106.3	-0.8	-14.9	182.8	155.9	-9.7	669.6	880.7	2.4
5.0	74.3	63.8	6.3	115.9	110.1	2.2	-14.2	255.4	244.8	-2.8	810.9	890.6	-9.5
6.0	76.5	66.1	-13.5	120.5	112.4	3.2	-10.3	264.3	245.7	2.7	967.5	993.2	-7.5
7.0	59.7	62.8	5.3	86.3	90.5	-10.7	5.1	155.2	148.6	-9.7	1098.3	1167.2	-4.7
8.0	61.8	69.6	12.6	100.7	91.3	-8.2	-8.2	220.4	197.3	-5.2	1101.3	1183.6	8.1
9.0	78.7	53.4	-32.2	87.7	84.0	-3.7	-5.1	166.3	161.8	-1.9	1050.2	1175.3	13.0
10.0	50.2	60.3	20.1	78.9	71.3	-5.3	-6.4	178.3	158.2	-12.9	1277.2	1391.5	7.0
11.0	78.9	53.6	-32.1	112.2	100.7	-7.8	-13.6	239.5	218.4	-10.1	814.1	863.0	-14.8
12.0	55.8	61.6	10.4	123.7	100.0	-9.4	-16.7	178.8	155.9	-7.0	713.8	880.7	10.2
13.0	56.0	61.8	-14.5	135.4	110.5	-1.1	-15.4	192.6	163.1	-9.4	743.3	967.6	1.9
14.0	55.9	61.7	5.6	119.5	93.6	-18.1	-23.1	216.4	192.8	-12.5	1078.5	1239.5	-8.5
15.0	51.0	53.0	3.9	105.2	97.2	-9.7	-12.4	236.3	199.2	-15.2	1084.9	1141.8	-1.9
16.0	59.4	55.0	5.0	91.0	85.5	-5.1	-13.1	151.6	129.6	-1.9	1614.4	1874.5	4.5
Mean	65.1	60.3	-1.5	107.8	96.3	-5.4	-11.4	200.8	181.4	-7.5	997.9	1113.2	0.2
SD	10.4	4.8	16.2	17.6	13.0	6.6	6.3	39.6	38.6	4.9	246.2	266.6	8.7

HR1, average of HR during first 5 sec during MM; HR2, average of HR during last 5 sec during MM; HR%, percent change in HR during MM

SV, Stroke volume (ml/bt); CO, cardiac output, MCI, myocardial contractility (ohm/sec/cm^2), SVR, systemic vascular resistance (dyn/sec/cm)

Table 9. Changes in heart rate during 3 minutes normal breathing following Mueller maneuver in control subjects

Subject#	HR0	HR30	HR60	HR90	HR120	HR150	HR180
1.0	66.0	59.5	59.2	58.6	62.6	59.8	61.4
2.0	66.9	60.6	60.2	59.7	63.6	60.7	62.6
4.0	68.1	62.0	61.5	61.2	64.9	62.0	64.1
5.0	74.8	63.8	62.8	61.8	64.0	63.4	63.6
6.0	73.4	62.2	61.4	60.2	62.5	62.8	61.3
7.0	66.0	59.5	59.3	58.6	62.6	59.8	61.4
8.0	74.8	63.8	62.8	61.8	64.0	63.4	63.0
9.0	64.7	55.3	67.2	64.2	69.0	70.2	64.6
10.0	61.0	49.8	51.8	50.7	50.4	49.4	49.4
11.0	63.1	52.1	53.2	50.7	50.5	48.9	51.8
12.0	62.6	51.0	52.9	49.3	50.2	48.0	49.3
13.0	59.6	55.1	54.1	58.3	61.7	59.1	59.9
14.0	57.1	52.3	51.5	55.5	59.0	56.5	57.0
15.0	57.0	52.6	52.0	58.4	60.7	59.4	58.7
16.0	57.1	52.7	52.0	58.5	60.8	59.5	58.7
Mean	64.8	56.8	57.5	57.8	60.4	58.9	59.1
SD	6.1	5.0	5.2	4.4	5.7	6.1	5.1

HR0, heart rate right after MM; HR30, heart rate at 30 sec.

Table 10. Changes in stroke volume during 3 minutes normal breathing following Mueller maneuver in control subjects

Subject#	SV0	SV30	SV60	SV90	SV120	SV150	SV180
1.0	103.2	108.3	115.2	118.9	113.5	106.6	106.0
2.0	65.2	100.4	101.3	99.3	96.2	93.2	90.1
4.0	115.7	125.6	126.5	128.9	123.9	121.9	123.5
5.0	105.9	111.1	117.9	121.7	116.2	109.3	108.7
6.0	112.2	117.0	123.3	127.3	120.6	114.6	113.9
7.0	93.4	93.7	89.1	97.2	96.2	95.9	99.8
8.0	82.1	110.5	109.4	110.5	108.3	105.3	101.2
9.0	79.2	78.3	90.2	89.4	87.6	87.2	87.7
10.0	67.2	79.3	84.8	85.7	82.1	79.3	75.6
11.0	104.6	109.8	116.6	120.4	114.9	108.0	107.4
12.0	120.7	125.6	126.5	128.9	123.9	121.9	123.5
13.0	121.8	130.8	132.0	134.7	129.1	127.2	128.9
14.0	90.6	115.5	118.0	114.2	117.2	113.3	106.7
15.0	90.9	103.4	112.2	103.3	107.5	104.1	104.0
16.0	88.7	100.1	95.0	97.0	92.1	93.2	92.6
Mean	96.1	107.3	110.5	111.8	108.6	105.4	104.6
SD	18.0	15.4	15.0	15.6	14.5	13.6	14.5

SV0, stroke volume immediately after MM; SV30, stroke volume at 30 sec.

Table 11. Changes in myocardial contractility during 3 minutes normal breathing following Mueller maneuver in control subjects

Subject#	MCI0	MCI30	MCI60	MCI90	MCI120	MCI150	MCI180
1.0	248.3	254.5	288.1	283.5	254.8	263.4	225.2
2.0	110.4	153.5	150.2	149.2	148.2	143.2	140.3
4.0	192.0	194.1	190.3	209.4	177.8	156.5	171.7
5.0	238.6	244.8	258.4	253.8	245.0	253.7	245.5
6.0	249.5	254.3	287.6	281.7	253.7	261.6	223.4
7.0	129.1	179.5	154.0	155.0	139.1	143.4	144.2
8.0	187.2	227.8	228.1	220.4	221.5	220.7	198.2
9.0	159.4	167.2	166.4	165.0	163.3	164.3	165.5
10.0	149.2	189.2	190.6	190.4	186.7	179.2	179.4
11.0	229.1	235.2	268.9	264.3	235.5	244.2	235.9
12.0	138.7	184.1	180.3	179.4	186.2	176.5	171.7
13.0	202.1	204.4	198.4	217.5	186.3	164.8	179.2
14.0	184.2	231.1	252.6	229.4	241.5	214.1	189.3
15.0	176.1	224.3	230.8	218.2	231.5	216.3	228.5
16.0	114.4	152.6	142.5	149.4	145.6	146.4	145.4
Mean	180.6	206.4	212.5	211.1	201.1	196.6	189.6
SD	47.0	35.1	50.3	46.1	41.5	44.8	35.0

MCI0, myocardial contractility immediately after MM; MCI30, myocardial contractility at 30 sec.

Table 12. Changes in systemic vascular resistance during 3 minutes normal breathing following Mueller maneuver in control subjects

Subject#	SVR0	SVR30	SVR60	SVR90	SVR120	SVR150	SVR180
1.0	771.8	861.8	907.7	925.8	853.8	788.8	1033.2
2.0	1210.3	1208.4	1192.5	1189.3	1120.3	1092.5	1082.6
4.0	820.6	874.0	845.9	790.1	791.2	748.0	824.0
5.0	1090.5	1090.6	956.5	944.6	972.5	907.5	1052.0
6.0	869.9	969.1	1013.3	1032.2	962.8	894.1	1139.8
7.0	1237.9	1293.6	1237.4	1262.8	1267.6	1168.2	1160.7
8.0	1210.3	1221.5	1198.5	1178.2	1182.4	1132.8	1110.7
9.0	1266.2	1187.5	1132.0	1093.2	1080.6	1053.0	1051.9
10.0	1420.4	1387.2	1360.4	1359.2	1362.8	1371.2	1291.7
11.0	830.5	920.5	966.4	984.5	912.5	847.5	1091.9
12.0	898.4	874.0	845.9	790.1	791.2	764.1	736.8
13.0	905.8	965.0	933.8	879.2	880.6	837.0	913.5
14.0	1243.2	1192.8	1262.1	1349.2	1217.5	1251.2	1185.9
15.0	1234.8	1080.9	1048.9	1098.5	1133.4	1098.3	1148.7
16.0	1763.9	1696.7	1802.4	1580.2	1558.4	1589.0	1624.5
Mean	1118.3	1121.6	1113.6	1097.1	1072.5	1036.2	1096.5
SD	272.3	229.7	248.6	225.8	221.7	243.3	203.4

SVR0, systemic vascular resistance immediately after MM; SVR30, systemic vascular resistance at 30 sec.

Appendix K – STATISTICAL OUTPUT FOR THE SIGNIFICANT FINDINGS

Reliability study

Table 1. Repeated ANOVA for SV before and after MM for three days (see Ch 3, Fig. 2)

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
day	Pillai's Trace	.425	4.065[a]	2.000	11.000	.048
type	Pillai's Trace	.623	19.820[a]	1.000	12.000	.001
day * type	Pillai's Trace	.481	5.094[a]	2.000	11.000	.027

a. Exact statistic

Pairwise Comparisons for day effect

Measure:SV

(I) day	(J) day	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	8.662*	2.919	.035	.547	16.776
	3	-4.180	3.638	.819	-14.292	5.933
2	1	-8.662*	2.919	.035	-16.776	-.547
	3	-12.841	5.311	.097	-27.602	1.920
3	1	4.180	3.638	.819	-5.933	14.292
	2	12.841	5.311	.097	-1.920	27.602

Based on estimated marginal means

*. The mean difference is significant at the .05 level. a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons for day*type (MM duration) interaction

Measure:SV

(I) type	(J) type	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	4.261*	.957	.001	2.176	6.346
2	1	-4.261*	.957	.001	-6.346	-2.176

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 2. Repeated ANOVA for MCI before and after MM for three days (see Ch 3, Fig. 2)

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
day	Pillai's Trace	.595	8.096[a]	2.000	11.000	.007
type	Pillai's Trace	.586	16.993[a]	1.000	12.000	.001
day * type	Pillai's Trace	.329	2.699[a]	2.000	11.000	.111

a. Exact statistic

b. Design: Intercept
Within Subjects Design: day + type + day * type

Pairwise Comparisons for day effect

Measure:MEASURE_1

(I) day	(J) day	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	20.513*	6.115	.017	3.515	37.511
	3	-20.810	8.108	.074	-43.346	1.727
2	1	-20.513*	6.115	.017	-37.511	-3.515
	3	-41.323*	10.206	.005	-69.690	-12.956
3	1	20.810	8.108	.074	-1.727	43.346
	2	41.323*	10.206	.005	12.956	69.690

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons for time (before after)

Measure:MEASURE_1

(I) type	(J) type	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	34.541*	8.379	.001	16.284	52.797
2	1	-34.541*	8.379	.001	-52.797	-16.284

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 3. Repeated ANOVA for SVR before and after MM for three days (see Ch 3, Fig. 2)

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
day	Pillai's Trace	.354	3.017[a]	2.000	11.000	.090
type	Pillai's Trace	.498	11.911[a]	1.000	12.000	.005
day * type	Pillai's Trace	.507	5.648[a]	2.000	11.000	.021

a. Exact statistic

b. Design: Intercept
Within Subjects Design: day + type + day * type

Pairwise Comparisons for day effect

Measure:MEASURE_1

(I) day	(J) day	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-90.721	36.416	.085	-191.939	10.497
	3	-15.300	26.882	1.000	-90.019	59.419
2	1	90.721	36.416	.085	-10.497	191.939
	3	75.421	34.220	.143	-19.693	170.534
3	1	15.300	26.882	1.000	-59.419	90.019
	2	-75.421	34.220	.143	-170.534	19.693

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons for time (before after)

Measure:MEASURE_1

(I) type	(J) type	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-101.463*	29.399	.005	-165.517	-37.408
2	1	101.463*	29.399	.005	37.408	165.517

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 4. Repeated measure ANOVA for CO 15 sec versus 30 sec third trial (see Ch 3, Fig. 5)

Multivariate Tests[b]						
Effect		Value	F	Hypothesis df	Error df	Sig.
day	Pillai's Trace	.102	.622[a]	2.000	11.000	.555
type	Pillai's Trace	.698	27.793[a]	1.000	12.000	.000
day * type	Pillai's Trace	.154	.997[a]	2.000	11.000	.400
a. Exact statistic						
b. Design: Intercept Within Subjects Design: day + time + day * time						

Pairwise Comparisons- day

Measure:MEASURE_1

(I) day	(J) day	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-2.081	1.853	.850	-7.232	3.070
	3	-2.021	2.857	1.000	-9.963	5.921
2	1	2.081	1.853	.850	-3.070	7.232
	3	.060	2.765	1.000	-7.625	7.745
3	1	2.021	2.857	1.000	-5.921	9.963
	2	-.060	2.765	1.000	-7.745	7.625

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons – type (15 vs 30)

Measure:MEASURE_1

(I) time	(J) time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	11.481*	2.178	.000	6.736	16.226
2	1	-11.481*	2.178	.000	-16.226	-6.736

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 5. Repeated measure ANOVA for SV 15 sec versus 30 sec third trial (see Ch 3, Fig. 5)

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
day	Pillai's Trace	.433	4.202[a]	2.000	11.000	.044
type	Pillai's Trace	.738	33.863[a]	1.000	12.000	.000
day * type	Pillai's Trace	.429	4.126[a]	2.000	11.000	.046

a. Exact statistic

b. Design: Intercept
Within Subjects Design: day + type + day * type

Pairwise Comparisons - day

Measure:MEASURE_1

(I) day	(J) day	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-3.003	1.896	.418	-8.273	2.267
	3	-5.043	1.881	.060	-10.271	.185
2	1	3.003	1.896	.418	-2.267	8.273
	3	-2.040	1.002	.194	-4.825	.746
3	1	5.043	1.881	.060	-.185	10.271
	2	2.040	1.002	.194	-.746	4.825

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons – type (15 vs 30)

Measure:MEASURE_1

(I) type	(J) type	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	10.761*	1.849	.000	6.732	14.790
2	1	-10.761*	1.849	.000	-14.790	-6.732

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Table 6. Repeated measure ANOVA for SVR 15 sec versus 30 sec third trial (see Ch 3, Fig. 5)

Multivariate Tests[b]

Effect		Value	F	Hypothesis df	Error df	Sig.
day	Pillai's Trace	.102	.622[a]	2.000	11.000	.555
type	Pillai's Trace	.809	50.777[a]	1.000	12.000	.000
day * type	Pillai's Trace	.066	.389[a]	2.000	11.000	.687

a. Exact statistic

b. Design: Intercept
Within Subjects Design: day + type + day * type

Pairwise Comparisons type (15 vs 30)

Measure:MEASURE_1

(I) type	(J) type	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	10.420*	1.462	.000	7.234	13.606
2	1	-10.420*	1.462	.000	-13.606	-7.234

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

Pairwise Comparisons type (15 vs 30)

Measure:MEASURE_1

(I) type	(J) type	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	10.420*	1.462	.000	7.234	13.606
2	1	-10.420*	1.462	.000	-13.606	-7.234

Based on estimated marginal means

*. The mean difference is significant at the .05 level.

a. Adjustment for multiple comparisons: Bonferroni.

Appendix L – STATISTICAL OUTPUT FOR THE SIGNIFICANT FINDINGS

Clinical study

Table 1. Univariate ANOVA for MCI during normal breathing before and after MM in 3 groups (see Ch 4, Fig. 4)

Tests of Between-Subjects Effects

Dependent Variable:variable

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	99265.752[a]	5	19853.150	10.150	.000
Intercept	1212674.759	1	1212674.759	619.983	.000
bef_aft	3683.911	1	3683.911	1.883	.175
group	87412.248	2	43706.124	22.345	.000
bef_aft * group	5752.221	2	2876.110	1.470	.238
Error	111490.985	57	1955.982		
Total	1732567.209	63			
Corrected Total	210756.737	62			

a. R Squared = .471 (Adjusted R Squared = .425)

Pairwise Comparisons between groups (1-OSAHS+HTN, 2-OSAHS, 3-Control)

Dependent Variable:variable

(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1.00	2.00	7.943	15.481	1.000	-30.242	46.129
	3.00	-70.057*	14.006	.000	-104.607	-35.508
2.00	1.00	-7.943	15.481	1.000	-46.129	30.242
	3.00	-78.000*	13.186	.000	-110.526	-45.475
3.00	1.00	70.057*	14.006	.000	35.508	104.607
	2.00	78.000*	13.186	.000	45.475	110.526

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

*. The mean difference is significant at the .05 level.

Post-hoc Multiple Comparisons (1-OSAHS+HTN, 2-OSAHS, 3-Control)

variable

Tukey HSD

(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1.00	2.00	8.4524	15.46171	.849	-28.7549	45.6598
	3.00	-69.5480*	13.98564	.000	-103.2033	-35.8927
2.00	1.00	-8.4524	15.46171	.849	-45.6598	28.7549
	3.00	-78.0004*	13.18579	.000	-109.7310	-46.2699
3.00	1.00	69.5480*	13.98564	.000	35.8927	103.2033
	2.00	78.0004*	13.18579	.000	46.2699	109.7310

Based on observed means.

The error term is Mean Square(Error) = 1955.982.

*. The mean difference is significant at the .05 level.

Table 2. Univariate ANOVA for SVR during normal breathing before and after MM in 3 groups (see Ch 4, Fig. 4)

Tests of Between-Subjects Effects

Dependent Variable:variable

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.644E6	5	328705.149	2.331	.054
Intercept	8.856E7	1	8.856E7	628.132	.000
bef_aft	12034.939	1	12034.939	.085	.771
group	1547946.627	2	773973.314	5.490	.007
bef_aft * group	52446.261	2	26223.131	.186	.831
Error	8036510.179	57	140991.407		
Total	9.927E7	63			
Corrected Total	9680035.922	62			

a. R Squared = .170 (Adjusted R Squared = .097)

Pairwise Comparisons (1-OSAHS+HTN, 2-OSAHS, 3-Control)

Dependent Variable:variable

(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1.00	2.00	192.144	131.432	.448	-132.056	516.345
	3.00	386.809*	118.916	.006	93.480	680.139
2.00	1.00	-192.144	131.432	.448	-516.345	132.056
	3.00	194.665	111.949	.262	-81.478	470.808
3.00	1.00	-386.809*	118.916	.006	-680.139	-93.480
	2.00	-194.665	111.949	.262	-470.808	81.478

Based on estimated marginal means

a. Adjustment for multiple comparisons: Bonferroni.

*. The mean difference is significant at the .05 level.

Post-hoc Multiple Comparisons (1-OSAHS+HTN, 2-OSAHS, 3-Control)

variable

Tukey HSD

(I) group	(J) group	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
1.00	2.00	192.9653	131.27179	.313	-122.9295	508.8602
	3.00	387.6307*	118.73980	.005	101.8931	673.3683
2.00	1.00	-192.9653	131.27179	.313	-508.8602	122.9295
	3.00	194.6653	111.94896	.200	-74.7307	464.0613
3.00	1.00	-387.6307*	118.73980	.005	-673.3683	-101.8931
	2.00	-194.6653	111.94896	.200	-464.0613	74.7307

Based on observed means.

The error term is Mean Square(Error) = 140991.407.

*. The mean difference is significant at the .05 level.

Table 3. Repeated measure ANOVA for SV during normal breathing after MM for 3 groups (see Ch 4, Fig. 4)

Tests of Within-Subjects Effects						
Measure:MEASURE_1						
Source		Type III Sum of Squares	df	Mean Square	F	Sig.
group	Sphericity Assumed	1000.172	2	500.086	3.333	.059
Error(group)	Sphericity Assumed	2700.794	18	150.044		
time	Sphericity Assumed	1815.053	6	302.509	5.527	.000
Error(time)	Sphericity Assumed	2955.645	54	54.734		
group * time	Sphericity Assumed	567.599	12	47.300	1.296	.232
Error(group*time)	Sphericity Assumed	3942.637	108	36.506		

Table 4. One way ANOVA for SV during post MM normal breathing for 3 groups (see Ch 4, Fig. 7)

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
sec0	Between Groups	6.379	2	3.190	.025	.975
	Within Groups	3720.384	31	128.289		
	Total	3726.763	33			
sec30	Between Groups	263.550	2	131.775	1.508	.238
	Within Groups	2533.907	31	87.376		
	Total	2797.457	33			
sec60	Between Groups	323.658	2	161.829	2.457	.103
	Within Groups	1909.945	31	65.860		
	Total	2233.603	33			
sec90	Between Groups	791.907	2	395.953	6.268	.005
	Within Groups	1831.875	31	63.168		
	Total	2623.782	33			
sec120	Between Groups	343.008	2	171.504	4.260	.024

	Within Groups	1167.557	31	40.261		
	Total	1510.565	33			
sec150	Between Groups	97.377	2	48.688	.947	.399
	Within Groups	1490.387	31	51.393		
	Total	1587.764	33			
sec180	Between Groups	28.535	2	14.267	.356	.703
	Within Groups	1160.887	31	40.031		
	Total	1189.422	33			

Multiple Comparisons POST-HOC (1-OSAHS+HTN, 2-OSAHS, 3-Control)

Tukey HSD

Dependent Variable	(I) HTN	(J) HTN	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
sec90	1.00	2.00	1.48222	3.86195	.922	-8.0554	11.0199
		3.00	-9.12533*	3.47954	.036	-17.7186	-.5321
	2.00	1.00	-1.48222	3.86195	.922	-11.0199	8.0554
		3.00	-10.60756*	3.35110	.010	-18.8836	-2.3315
	3.00	1.00	9.12533*	3.47954	.036	.5321	17.7186
		2.00	10.60756*	3.35110	.010	2.3315	18.8836
sec120	1.00	2.00	-.83542	3.08318	.960	-8.4498	6.7789
		3.00	-6.97475*	2.77788	.046	-13.8351	-.1144
	2.00	1.00	.83542	3.08318	.960	-6.7789	8.4498
		3.00	-6.13933	2.67534	.073	-12.7465	.4678
	3.00	1.00	6.97475*	2.77788	.046	.1144	13.8351
		2.00	6.13933	2.67534	.073	-.4678	12.7465

*. The mean difference is significant at the 0.05 level.