EFFECT OF MAXILLOMANDIBULAR ADVANCEMENT SURGERY ON BLOOD PRESSURE IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA: A PILOT STUDY.

by

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Abstract

Purpose: There is an increased prevalence of hypertension and obesity among patients with obstructive sleep apnea (OSA). Although there is evidence that treatment of OSA with continuous positive airway pressure (CPAP) improves blood pressure and other markers of cardiac risk such as C-reactive protein (CRP), this evidence is lacking in the use of maxillomandibular advancement (MMA) surgery to treat OSA. The objective of this prospective study is to determine the effect of MMA surgery for treatment of OSA on blood pressure. Secondary objectives are to look at the effects on body mass index (BMI) and CRP.

Methods: All patients undergoing MMA surgery for treatment of OSA at the QEII Health Sciences Centre between August 2009 and September 2012 were asked to participate in the study. All willing subjects gave informed consent. The Tiba Ambulo 2400 ambulatory blood pressure (BP) monitor was used. Ambulatory BP, and BMI were recorded at baseline, and at three and six months following MMA surgery. Blood samples for CRP were drawn at 3 month and 6 months.

Results: 15 patients from a potential 52 patients agreed to participate and completed the study. This included 2 females and 13 males with an average age of 48.9 years and a mean preoperative AHI of 40.8 and a mean baseline BMI of 30.8 kg/m^2. Nine of these patients had a physician diagnosis of hypertension preoperatively and 4 of these patients were on antihypertensive medications. The patients with a diagnosis of hypertension tended to be older and have more severe OSA, although this was not statistically significant. The patients with severe OSA tended to have a higher CRP, although this was not statistically significant either. The average follow-ups were at 3 and 8 months following surgery. There were no statistically significant reductions in mean systolic or diastolic blood pressure. Blood pressures tended to be more improved at 3 months than 8 months. The prevalence of non-dippers was 20 % and this remained constant throughout the study. The BMI was found to decrease on average from 30.8 kg/m^2 to 29.3 kg/m^2 at the 8 month follow up ($p = 0.01$). Using a Pearson correlation test, changes in blood pressure were not correlated with changes in BMI. The CRP showed a decrease from 2.3 to 1.5 mg/L ($p = 0.01$), no postoperative CRPs were > 3mg/L.

Discussion: Although the literature infers that treatment of OSA with CPAP may improve blood pressure, and increase the prevalence of dippers, many of these studies are short term (< 3 months), and are not based on data obtained by the use of a 24 hour ambulatory blood pressure monitoring device. This study is underpowered to detect a small change in blood pressure.

Conclusion: The prevalence of hypertension in this OSA population was 60%. Based on this small sample size, there were no significant improvements in any blood pressure parameters following MMA surgery. The biggest positive change seems to be with diastolic pressures, particularly during sleep. More dramatic changes were noted when the patients with elevated baseline blood pressures were examined separately. There were no identifiable relationships between OSA severity and BP. MMA had a positive effect on BMI and CRP, two risk factors for cardiovascular disease. Given the prevalence of OSA and it's adverse medical consequences, more studies to determine the effect of maxillomandibular advancement on blood pressure are warranted

List of Abbreviations Used

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
AHA	American Heart Association
AHI	Apnea Hypopnea Index
ARB	Angiotensin Receptor Blocker
BMI	Body Mass Index
BP	Blood Pressure
BSSO	Bilateral Sagittal Split Osteotomy
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CO	Cardiac Output
CPAP	Continuous Positive Airway Pressure
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
FG	Functional Genioplasty
HDL	High Density Lipoprotein
HF	Heart Failure
HR	Heart Rate
HTN	Hypertension
IL-6	Interleukin 6
IL-8	Interleukin 8
LDL	Low Density Lipoprotein
LF1	Lefort 1
LV	Left Ventricle
MAP	Mean Arterial Pressure

MI	Myocardial Infarction
MMA	Maxillomandibular Advancement
NE	Norepinephrine
NO	Nitric Oxide
NREM	Non-Rapid Eye-Movement
OMF	Oral and Maxillofacial
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
RCT	Randomized Controlled Trial
RDI	Respiratory Disturbance Index
REM	Rapid Eye-Movement
SBP	Systolic Blood Pressure
SNA	Sympathetic Nerve Activity
SNS	Sympathetic Nervous System
SV	Stroke Volume
UPPP	Uvulopalatopharyngoplasty
TIB	Time in Bed
TNFα	Tumor Necrosis Factor Alpha

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Chapter 1: Introduction

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a common disorder among middle-aged men and women. It affects 3-24% of adults above the age of 40 years.[1-4] Patients suffering from OSA experience repetitive apneas and hypopneas due to partial or complete airflow obstructions during sleep, leading to transient asphyxia.[5] Cessation of air flow usually results in arousal from sleep followed by hyperventilation.[6]

Etiology

OSA results from periodic collapse of the pharynx during sleep. The pharyngeal airway is a collapsible muscular tube extending from the level of the nasal turbinates to the vocal cords. The pharynx is largely unsupported by bony structures. There are a number of muscles that surround the pharyngeal airway and influence its patency. These include the genioglossus, palatal muscles, pharyngeal constrictor muscles, and supra- and infra-hyoid muscles. Airway occlusion most commonly occurs in the retropalatal and retroglossal regions (Figure 1).[7,8]

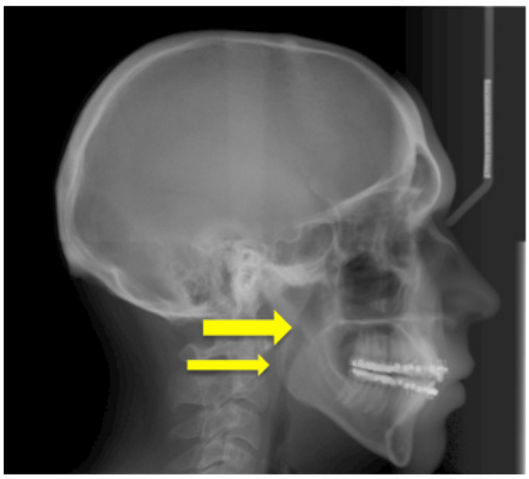

Figure 1. Narrow retropalatal (big arrow) and retroglossal (small arrow) airways.

Anatomic, neural, and mechanical factors influence the collapsibility of the airway. Anatomic factors that can increase the risk of airway obstruction include large tonsils and adenoids, and retropositioning of the maxilla and mandible. Additionally, obesity predisposes patients to OSA because of increased fat deposited in the pharyngeal tissues.[9] These factors all lead to smaller airways that are more readily occluded.

The largest upper airway dilator muscle is the genioglossus muscle, which is innervated by the hypoglossal nerve.[10] The respiratory central pattern generator and negative pressure receptors within the upper airway provide input to the hypoglossal nerve. Genioglossal activity varies during the respiratory cycle, and is typically increased during inspiration, which helps to prevent airway collapse due to negative airway pressure. The activity of upper airway dilator muscles is increased in patients with OSA, however the neural mechanisms resulting in these changes are not well understood. Many of the sleep regulating regions of the brain have neural inputs to the genioglossus and other upper airway muscles. In patients with OSA, the genioglossus muscles become more active in response to negative airway pressure and rise in carbon dioxide. Often, this increased genioglossal activity does not result in sufficient patency of airway for adequate ventilation. Once an arousal occurs and the patient is in a more wakeful state, all of the upper airway muscles become more active, ventilation is more efficient, and then the cycle repeats.[10]

Signs and Symptoms

Patients with obstructive sleep apnea suffer from a nonrefreshing sleep pattern because of sleep fragmentation and deprivation. As a result, patients feel tired in the

mornings, and may suffer from excessive daytime sleepiness (EDS) and morning headaches. The major symptom of OSA is excessive daytime sleepiness. Irritability, depression and other mood changes have also been reported.[11] Poor memory, cognitive problems and difficulty concentrating have been linked to EDS.[12] As a result, EDS can have a devastating impact on home and work life as well as interpersonal relationships. Family members or bed partners often witness loud snoring and apneas, which can be very distressing.

Epworth Sleepiness Scale

Johns first described the Epworth Sleepiness Scale (ESS) in 1993 as a tool to quantify EDS in patients with sleep apnea.[13] The ESS uses a series of eight scenarios during which people may fall asleep. Patients rate each scenario on a scale of 0 to 3 based on the likelihood that they would fall asleep or doze off in that situation. A score of 0 indicates no chance of dozing, whereas a score of 3 indicates a high probability of dozing in that scenario. A score of >10 indicates excessive daytime sleepiness, with a maximum possible score of 24. A score of ≤10 is considered to be normal (Figure 2).[13]

How likely are you to dose off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Score
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g. a theatre or meeting)	
As a passenger in a car for one hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, while stopped for a few minutes in traffic	
TOTAL	**/24**

Figure 2. The Epworth sleepiness scale.

Diagnosis

The diagnosis of OSA is based on polysomnography, which consists of an over night sleep study to monitor respiratory events. This study is most accurate if conducted in a laboratory or hospital setting. The severity of OSA is measured objectively, during polysomnography. Apnea is the cessation of airflow for a minimum of ten seconds. In contrast, a hypopnea is characterized by a reduction in airflow of 50% or greater, or a reduction in airflow associated with decrease in oxygen saturation by at least 4%.[14] Other authors also support scoring hypopneas when there is as little as a 20-30% decrease in airflow for 10 seconds and/or greater than or equal to 2-3% oxygen desaturation.[15] The number of apneas and hypopneas per hour of sleep is known as the apnea hypopnea index (AHI). This index is a measure of the severity of OSA. The diagnosis of obstructive sleep apnea is based on an AHI of at least 5 events/hour.[7,8] The severity of OSA can be categorized as mild, moderate, or severe when the AHI is between 5-15, 15-30, or greater than 30 events/hour respectively.[16]

Impact of OSA on Health

Obstructive sleep apnea is associated with significant morbidity and mortality. Excessive daytime sleepiness is dangerous to a person's health and the health of the public. Traffic and workplace accidents have been correlated with decreased performance levels because of EDS.[17]

The major associated health burden is the strong risk of cardiovascular diseases (CVD) such as hypertension (HTN), dyslipidemia, and cardiac dysrhythmias. Obesity, diabetes, and metabolic syndrome are also very prevalent among OSA patients.[18-23] Although OSA and CVD have many common risk factors, many current studies point out

that obstructive sleep apnea may be an independent risk factor for HTN as well as other cardiovascular diseases.[23,24] This paper will endeavor to provide more evidence regarding the association between OSA and hypertension.

Treatment of OSA

There are currently more than twenty reported surgical and non-surgical treatments for OSA.[25] Some examples of non-surgical treatments are: weight loss, change in sleep position, pharmacologic therapy, oral appliance therapy, and continuous positive airway pressure (CPAP).

CPAP is currently the gold standard non-surgical treatment for OSA. It acts as a pneumatic splint to the upper airway during sleep to prevent the obstruction and improve the quality of sleep.[26,27] Patient education and strong motivation are required for successful treatment with CPAP. Effective treatment is associated with less daytime sleepiness and subsequent improvement in cognitive function, less oxygen desaturations, less apneas and arousals from sleep, and overall increased chance of survival.

The patients who poorly tolerate CPAP include those with claustrophobia, abnormal nasal airways, and lack of motivation. Compliance with CPAP treatment is a major issue, and it requires nightly use, follow-up with a sleep physician, and proper pressure settings based on results from polysomnograms. Many patients do not tolerate CPAP well because of discomfort associated with wearing a poorly fitted mask, facial rash, sinusitis, nasal congestion, aerophagia and conjunctivitis.[28] The CPAP rejection rate is 18-40% among patients with OSA.[29-31] One of the biggest disincentives to CPAP use is the unaesthetic application and its psychosocial implications.

The established acceptable minimum compliance rate for CPAP, based on what is known about the need for sleep, is 4 hours per night for 70% of the nights.[32] This is significantly less than ideal use and therefore, CPAP often incompletely eliminates sleep disordered breathing.[33] An estimate of optimal CPAP use is at least 7 hours of use per 24-hour period. This optimum duration of CPAP use is based on what is known about the average daily sleep duration of middle-aged adults.[32] The acceptable level for frequency of CPAP use is stated as an average of 5 of 7 days, or greater than 70% of nights. This frequency is based on expert opinion.[32]

Kribbs *et al* undertook a study in 1993 to evaluate the CPAP compliance of 35 OSA patients.[32] The patients were given CPAP devices with a microprocessor and monitor that measured pressure at the mask for every minute of the day. The CPAP use was recorded for an average of 106 days for each patient. Patients tended to over-report their duration and frequency of CPAP use. The majority of patients declared they used CPAP nightly, however only 46% met criteria for nightly use defined as 4 hours per night for 70% of nights when the microprocessor and monitor was analyzed. Only 2 of the 35 patients used CPAP for 7 hours or more on at least 70% of nights. These authors concluded that actual CPAP use by OSA patients does not meet the therapeutic goal of providing quality sleep every night, all night. The data suggests that in fact, long duration quality sleep is a rare occurrence in the OSA population.[32]

Many surgical treatment options for OSA also exist including uvulopalatopharyngoplasty (UPPP), tonsillectomy, and tracheostomy. In the late 1970s, orthognathic surgery was introduced as a treatment for obstructive sleep apnea.[34] Over the last four decades, this became a more popular treatment option and is known as maxillomandibular advancement surgery. Although CPAP therapy has been the

cornerstone for treatment of OSA, studies show MMA has equal therapeutic efficacy. [35] Maxillomandibular advancement surgery is advantageous because it eliminates patient compliance issues that are common with CPAP.

Patients with anatomic deformities that contribute to upper airway obstruction during sleep are candidates for MMA surgery. MMA surgery is effective because the hard and soft tissue structures of the maxillomandibular complex and oropharynx become normalized.[7] MMA surgery includes advancing the maxilla via a Lefort 1 (LF1) osteotomy, advancing the mandible using a bilateral sagittal split osteotomy (BSSO). In cases of anterior mandibular deficiency, a functional genioplasty (FG) advancement is performed. All of these operations act to increase the dimensions of the pharyngeal airway.

The maxilla and mandible are directly or indirectly attached to the hyoid bone, soft palate, tongue, and associated muscles.[36] As a result of mandibular advancement, the tongue becomes more anteriorly positioned, supported by advancement of the genioglossus muscles, the anterior belly of the digastric, the mylohyoid and the geniohyoid muscles. In addition, advancing the maxilla contributes to tongue support by advancing the palatoglossal muscles. Likewise, Lefort 1 advancement surgery increases the magnitude of the oropharyngeal airway by advancing the soft palate.[7]

Maxillomandibular advancement surgery is by far the most effective single stage surgery available for treatment of OSA.[35] This surgery has very high success rates (57-100%) in the appropriate patients, and is effective at eliminating sleep apnea by reducing the number of apneas and hypopneas as well as the subjective feeling of sleepiness as measured by the Epworth sleepiness scale.[12,35,36]

Since the complete elimination of OSA is not always possible, the goal of treatment should be similar to that of treating a chronic illness: to control the symptoms and reduce severity. Surgical success is defined by a 50% reduction in the AHI, and less than 20 events per hour.[35] A recent meta-analysis including 627 patients with a mean follow up period of 5.3 months showed a high rate of surgical success, at 86%.[37] Maxillomandibular advancement surgery has also been shown to eliminate the need for use of CPAP in the majority of patients.[12]

Surgery is not without risk, however, complications of MMA surgery are infrequent. Complications include infection, non-union, malocclusion, nerve damage, velopharyngeal insufficiency, and aseptic necrosis of the maxilla.[38-41] Unfavorable changes in facial appearance have been reported by some, however, many patients feel that the esthetic changes following MMA surgery are positive.[42] The most frequent reported complication of maxillomandibular advancement surgery is sensory loss in the distribution of the mental nerve.[41]

Hypertension

Definitions

Arterial blood pressure is the pressure on the walls of the blood vessels exerted by circulating blood. It is one of the key vital signs and is an important marker of a patient's state of health. Systolic blood pressure is the highest reading, and it is the pressure exerted during contraction of the ventricles of the heart. Diastolic pressure is lower. It is the pressure in the blood vessels during diastole, or relaxation of the ventricles. Hypertension is defined as a persistently elevated blood pressure (BP) that exceeds an arbitrarily set level of normalcy.[43]

Blood pressure measurements of systolic <120 mmHg *and* diastolic <80 mmHg are considered normal. The gold standard for measurement of arterial blood pressure is with a direct intra-arterial catheter. This technique, for obvious reasons, is impractical in most instances. The classification of blood pressure (Table 1) is based on the mean of two or more properly recorded blood pressure readings on two or more office visits. Hypertension is further classified into stage 1 and stage 2 hypertension. Stage 1 is a systolic blood pressure (SBP) of 140-159 mmHg or a diastolic blood pressure (DBP) of 90-99 mmHg. If the SBP is >159 mmHg or the DBP >99 mmHg, this is known as stage 2 hypertension.[44]

Table 1. Blood Pressure Classification.

BP Classification	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	and <80
Prehypertension	120-139	or 80-89
Stage 1 HTN	140-159	or 90-99
Stage 2 HTN	≥ 160	or ≥ 100

Source: adapted from Chobanian *et al*

Mean arterial pressure (MAP), is the average blood pressure during a cardiac cycle.[45] It represents the perfusion pressure. At normal heart rates, MAP can be calculated mathematically by the formula: DBP plus one-third of the pulse pressure [MAP = DBP +(SBP-DBP)/3]. Mean arterial pressure is normally between 70-110 mmHg. Mild hypertension has been defined as a MAP of 107-113 mmHg. Moderate HTN is a MAP of 114-129 mmHg and severe HTN is a MAP ≥130 mmHg.[46]

In 15-20% of people with stage 1 hypertension, blood pressure is only elevated in the presence of a physician or nurse. When measured at home, the blood pressure is normal. This finding is known as “white coat hypertension”. It is more common in older

men and women. The difference between the office and daytime ambulatory BP is referred to as the "white coat effect".[47]

The opposite of white coat hypertension is "masked hypertension". This finding is less frequent than white coat HTN but may be more problematic to detect. Lifestyle is a significant contributor to the elevation of ambulatory BP when compared to in-office measurements.[47]

A new category of BP was designated in 2003 as "prehypertension". These are patients who have systolic blood pressure of 120-139 mmHg *or* diastolic blood pressure 80-89 mmHg.[44] Patients with prehypertension are at increased risk for progression to hypertension.

In the normal population, there is a 10-15% drop in mean arterial pressure that happens during sleep. This is phenomenon is termed "blood pressure dipping". People who do not have this decrease in nocturnal BP are referred to as "non-dippers" and are at increased risk for cardiovascular events.[44]

Epidemiology

Cardiovascular disease is now endemic worldwide and no longer restricted to economically developed countries. Hypertension is one of the biggest health issues facing the world today.[48] More than one billion individuals worldwide are affected by hypertension.[44] As the population ages, this number will increase unless effective preventive measures are realized. Canada's rate of treatment and control of blood pressure has increased five-fold in the last 15 years. Canada is now the nation with the highest reported rates of people being treated for high blood pressure.[49] It is estimated

that in the year 2025, 1.56 billion adults will have hypertension. This is almost one third of the total population.[50]

Associated Cardiovascular Events

Hypertension is largely an asymptomatic condition, which is a known risk factor for many cardiovascular complications. There is a strong relationship between blood pressure and cardiovascular events that is independent of other risk factors.[44] A substantial portion of cardiovascular disease is attributable to elevated blood pressure. In 2001, 7.6 million deaths (13.5% of all deaths) worldwide were attributed to hypertension.[51]

Coronary artery disease, congestive heart failure, stroke, peripheral vascular disease, and renal failure can all be portrayed as consequences of hypertension. A 2002 meta-analysis demonstrated that blood pressure is positively correlated with chance of stroke, myocardial infarction, heart failure, and kidney disease.[52] Epidemiological data indicates there is a higher likelihood of major cardiovascular events in patients with stage 1 hypertension (between 140/90 and 159/99 mmHg).[52]Age and hypertension are the two most powerful risk factors for stroke, and Lewington *et al* clearly demonstrated a robust and constant relation between stroke mortality and blood pressure at all ages.[52]

Recent evidence suggests that untreated obstructive sleep apnea might cause systemic hypertension and predispose patients to atherosclerosis and cardiovascular events.[23,53-57] It has been shown that for individuals aged 40 to 70 years, an increase in systolic blood BP by 20 mmHg or diastolic BP by 10 mmHg doubles the risk of cardiovascular disease events.[44,52] In patients older than 50 years of age, systolic

hypertension is a much more important cardiovascular disease risk factor than diastolic hypertension.[43,58]

Techniques for Measuring Blood Pressure

In-Office Measurement

Blood pressure should be measured by the indirect, or auscultatory, method using a properly calibrated and validated instrument.[44] The method is practical, simple, noninvasive, and inexpensive. A stethoscope and a sphygmomanometer are required for this technique, which was first described by a Russian physician, Korotkoff, in 1905.[59] When measuring BP in the office, patients should be seated comfortably and quietly with their feet and arms supported for five minutes prior to BP measurement. The cuff is placed on the upper arm, over the brachial artery. For accuracy, the cuff should be appropriately sized so that the bladder encompasses a minimum of 80% of the arm and the width of the bladder is 40% of the arm circumference. The pressure at which the first Korotkoff sound is heard is the SBP, and the DBP is the pressure at which the sounds disappear permanently. This represents the time when the artery is no longer compressed and blood flow is completely restored.[59] A minimum of two measurements should be made.[44]

Office blood pressure measurements remain the current standard for evaluation and management of hypertension. It is important to remember, however, that BP is a physiologic variable that changes in response to various stimuli. Some patients experience a pressor response in the medical setting, known as “white-coat” hypertension. In these patients, another technique of blood pressure measurement may be more accurate.

Self-Measurement

Self-measurement of BP can be performed with home measurement devices and provide useful information for patients regarding response to medications and improve patient compliance. It has become a popular measurement technique, especially among hypertensive patients. Self-measurement of BP can help with titration of antihypertensive medications while eliminating frequent trips to the doctor's office. In most hypertensive patients, the blood pressure obtained in a physician's office is higher than the pressures measured throughout the rest of the day. Home blood pressure measurement is a valuable tool in management of hypertension and has the benefit of eliminating the "white coat effect" of the physician's office.[43] Self-measurement of blood pressure should always be interpreted by a trained medical professional who can take into account the patients' overall clinical condition and cardiovascular risk factors when making important diagnostic and treatment decisions.[60]

Ambulatory Blood Pressure Measurement

Blood pressure levels normally fluctuate considerably from day to night. Casual blood pressure measurements obtained by a physician in the office, or by a patient at home, are not necessarily representative of BP readings throughout a 24-hour period.

The best way to accurately represent the blood pressure naturally occurring in daily life is to obtain multiple readings over a 24 hour period. Ambulatory blood pressure monitoring (ABPM) allows examination of BP patterns and BP variability in both awake and sleeping patients. The typical fully automated device for this ambulatory BP monitoring is battery operated and consists of an arm cuff that can be programmed to automatically inflate at specified intervals in a 24-hour period.

This type of blood pressure monitoring is especially helpful in evaluating those patients with white-coat hypertension. Blood pressure is influenced by level of activity, exercise, degree of wakefulness or sleep, temperature, mood, drugs, and a variety of emotional and psychological factors.[43] The patient is generally asked to keep a detailed diary including information about physical activity, meals, sleep, medications, and other situations during the measurement period. The diary aids in interpreting the blood pressure data.

Ambulatory blood pressure readings tend to be lower than clinic readings thus, the categories of hypertension need to be adjusted accordingly. It has been established that hypertensive individuals have a mean blood pressure of >135/85 mmHg during the awake period and >120/70 mmHg during the sleep periods.[44] A meta-analysis of 23 studies in 3476 normotensive subjects reported hypertension as mean 24-hour BP of ≥139/87 mmHg.[61]

Oscillometry is a method of recording blood pressure that has been incorporated into most ABPM because it is reliable and accurate. The oscillometric method involves a similar technique to sphygmomanometry, where a pneumatic blood pressure cuff is used. This technique uses an algorithm to convert oscillations or fluctuations in blood pressure into a blood pressure reading. The cuff is initially inflated to a pressure exceeding systolic blood pressure and then is slowly deflated. During cuff deflation, the amplitude of oscillations increases to a peak and then starts to decrease. The mean arterial pressure is the cuff pressure at which the oscillations first reach their maximum amplitude. The systolic and diastolic pressures are determined empirically as the cuff pressure at which the amplitude of pressure oscillations is approximately 0.5 or 0.6 of the maximum

amplitude (MAP) respectively. These thresholds may vary slightly depending on the manufacturer and the heart rate.[62]

The first study to evaluate the prognostic value of ABPM was in 1983 by Perloff *et al*.[63] Since the completion of his study, there have been several other reports that confirm the findings that ABPM correlates better with target-organ damage and cardiovascular events in comparison to in-office BP measurements.[63-65] Studies indicate that there is less than 5 a mmHg discrepancy between ambulatory devices and readings taken by trained healthcare professionals.[66] In addition to the monitor's accuracy, it is also provides other useful information such as the percentage of elevated blood pressure readings and the extent of nocturnal blood pressure dipping.[67]

The peak blood pressures from ABPM tend to be observed in the early morning, typically around the time of wakening. In the normotensive patient, blood pressures taper throughout the day and become lowest at night, usually reaching the lowest dip between 2 am and 4 am.[68] In most individuals, blood pressure decreases by 10-20% during the night. Non-dippers are at increased risk for cardiovascular events.[44]

Health Benefits of Lowering BP

The 2011 Canadian Hypertension Education Program recommendations[69] maintain that most patients with hypertension should be treated to achieve target in-office blood pressure levels of less than 140/90 mmHg. Patients with diabetes or chronic kidney disease should be treated to achieve a goal blood pressure of less than 130/80 mmHg. Failure to achieve these target levels results in increased cardiovascular risk.[69] It is clear

that patients with SBP greater than 160 mmHg get meaningful cardiovascular protection if the blood pressure is reduced to 140/90 mmHg.[69]

In 2009, Zanchetti *et al* discovered that for patients with uncomplicated hypertension, there were significant outcome advantages of active treatment over placebo when systolic blood pressures were reduced below 140 mmHg. [70] These results must be interpreted with caution because the baseline BP was a minimum of 160 mmHg in the studies included in this critical appraisal. The study does not draw any conclusions regarding lowering the blood pressure in patients with stage 1 hypertension.

It is now well known that antihypertensive drug therapy markedly diminishes the risk of hypertension related morbidity and mortality.[71] Clinical trials have demonstrated that antihypertensive therapy is associated with an average reduction in stroke incidence by 35-40%, myocardial infarction (MI) incidence by 25% and more than 50% reduction in heart failure incidence.[72] Investigations using conventional antihypertensive agents such as beta blockers and angiotensin converting enzyme (ACE) inhibitors indicated that a 5 mmHg decrease in diastolic blood pressure is associated with a 42% decrease in stroke and a 14% decrease in coronary artery disease within a 5 year period.[22,73] Similar longer term studies have indicated that a 31% decrease in stroke can be expected with a small drop in diastolic blood pressure.[74] Ramipril, an ACE inhibitor, has been shown to significantly reduce the rates of MI, stroke, and death in high-risk patients with no evidence of heart failure when compared to a placebo treatment.[75]

Cardiovascular Variability

Information on the clinical significance of BP variability has been accumulating over the last number of years. Recent data suggests that altered cardiovascular variability

in OSA, such as heart rate (HR) and BP variability, is associated with increased risk for end organ damage in hypertensive patients. Patients with similarly elevated mean 24-hour BP values have greater end organ damage when the 24-hour BP variability is greater.[76-78] Furthermore, some authors have indicated that greater BP variability is associated with a faster progression of end organ damage independent of the actual BP value.[78]

Blood pressure variability is estimated as the standard deviation of the blood pressure mean.[79] A BP variability that is less than or equal to the median variability for the group is considered low. High BP variability is greater than the group median variability.[80] In a 16 year follow up study of 2649 hypertensive patients, it was discovered that the rate of cardiac and cerebrovascular events was higher in patients with high BP variability. A multivariate analysis was performed to adjust for confounding factors. A high nighttime SBP variability was associated with 51% excess risk of cardiac events. The daytime blood pressure variability and the nighttime DBP variability were not found to be significant. The authors concluded that increased variability of SBP during sleep is an independent predictor of cardiac events.[80]

Some studies have demonstrated that there is a relationship between RDI and blood pressure variability, regardless of the actual blood pressure measurement.[81] It has also been suggested that BP variability is evident in OSA patients without hypertension and this has been implicated as a risk for potential development of hypertension.[78,81,82] Narkiewicz et al performed a study comparing BP variability between OSA and non OSA patients. They discovered that even though the BP was similar between groups, patients with mild-moderate OSA had more than double the BP variability of the control group.

Blood Pressure Dipping

A higher prevalence of non-dippers has been reported among subjects with obstructive sleep apnea. This means that there is a lack of normal blood pressure dipping (a decrease in MAP by 10-15%). Lack of or blunting of the nocturnal decline in blood pressure has been associated with accelerated hypertensive end organ damage as well as increased morbidity and mortality.[83,84]

A study of blood pressure dipping was performed with 44 patients with moderate to severe OSA. In hospital polysomnography and 24 hour ambulatory blood pressure monitoring was performed on these patients. They were divided into dippers and non-dippers based on a nocturnal drop in MAP > 10%. Eighty-four percent of the patients were discovered to be non-dippers. There was no difference between age, RDI, BP, or body mass index (BMI) between dippers and non-dippers. There was no statistically significant association between HTN and BP dipping.[85] These findings are consistent with those of Suzuki *et al* in 1996.[84]

Sleep Actigraphy

Actigraphy involves the use of a portable device to record movement over extended periods of time.[86] Sleep activity is higher in patients with a non-dipper blood pressure profile than in a similar group of patients with a dipper blood pressure profile. It is also known that patients with OSA are more likely to be non-dippers than normal controls.[87]

A prospective study of 52 hypertensive patients was conducted to determine the effect of activity levels during time in bed on blood pressure dipping. Prior to being enrolled in the study, the patients were screened for sleep disturbances and the study

included only patients who had no clinical evidence of sleep disordered breathing. It was determined that non-dipper patients tended to have higher body mass indices and significantly higher nighttime activity levels. The 24-hour and awake activity levels were similar in dippers and non-dippers. Both groups spent a similar amount of time in bed (about 7.5 hours). Sleep heart rate was significantly higher in the non-dipper group.[87]

Evidence Linking OSA to Hypertension

Obstructive sleep apnea has been documented to increase the risk of heart failure by 140%, the risk of stroke by 60%, and the risk of coronary artery disease by 30%.[22] For these reasons, diagnosis and treatment of sleep apnea is an important target for research aimed at reducing cardiovascular disease. Sleep disordered breathing has been linked with hypertension for over thirty years. However, confounding factors such as obesity, age and smoking have made this independent relationship difficult to assess. There is growing evidence that hypertension and sleep apnea occur together to an extent beyond what would be expected merely from the high prevalence of both disorders.[88] The association between OSA and HTN could be responsible for a substantial number of cases of hypertensive sequelae such as stroke, MI, and heart failure.

A study from 2001 suggested that the presence of uncontrolled hypertension could promote or aggravate obstructive sleep apnea.[89] In this study, 257 patients with OSA were investigated. The study found that increased severity of OSA was associated with increased difficulty in controlling hypertension, despite compliance with an antihypertensive medication regimen. When comparing patients with controlled and uncontrolled blood pressure, the nocturnal oxygen saturations were similar.[89]

There has been a lot of recent research describing the pathophysiology of the link between OSA and hypertension and other cardiovascular diseases. Acute elevation of blood pressure during apnea is a well-described phenomenon, as is the absence of nocturnal blood pressure dipping in patients with sleep apnea. A better understanding of sleep physiology as well as cardiovascular physiology can help clarify the link between these two complex medical conditions.

Evidence of a direct relationship between OSA and HTN can be demonstrated in three ways. First of all, there seems to be an **increased prevalence** of hypertension among patients with OSA. Secondly, it has been shown that there is a **dose-response effect** between OSA and hypertension, meaning that the severity of sleep apnea correlates with the severity of hypertension. Lastly, there is some evidence that treatment of OSA improves blood pressure in these patients (**treatment effect**).[6]

Daytime hypertension has been reversed or improved by effective treatment of OSA by tracheostomy or nasal CPAP.[6,90-93] This resolution of hypertension provides significant circumstantial evidence that sleep apnea caused the hypertension or at least exacerbated it.[88] On the other hand, there are also several studies that suggest treatment of sleep apnea has little or no effect on blood pressure.[94-96] The debate is ongoing.

Prevalence of Cardiovascular Disease Among OSA Patients

Recent literature regarding OSA focuses on prevalence and severity of cardiovascular disease of this population, most notably, hypertension and atherosclerosis. It is clear from epidemiological studies that cardiovascular disease is highly prevalent among patients with sleep apnea. Large cross-sectional and longitudinal studies have

confirmed an independent association between HTN and OSA in the general population as well as sleep clinic patients.[88,97-99]

Obstructive sleep apnea is a very common risk factor for hypertension. In 2003, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recognized OSA as an "identifiable cause" of hypertension and suggested that all patients suffering from OSA undergo blood pressure screening.[44] Some studies have even suggested that patients with known hypertension have a higher prevalence of OSA.

Systemic hypertension has been demonstrated to occur in 50 - 90% of patients with sleep apnea syndrome.[88,100-103] A chart review of 138 patients with OSA treated by maxillomandibular advancement (MMA) surgery in the department of Oral and Maxillofacial Surgery at the QEII Health Sciences Centre revealed 50 patients with physician diagnosed hypertension. This means that in our OSA surgical population, the prevalence of hypertension is approximately 36%. This is likely a conservative estimation of true hypertension because it is probable that some patients would have undiagnosed hypertension, thus increasing this percentage.

Sleep apnea has been reported to occur in 22-62% of patients with hypertension.[102,104-106] It has been debated in the literature whether OSA is actually an independent risk factor for hypertension; or rather the high prevalence of HTN is a result of the high prevalence of obesity and other comorbidities in this population. There is now some evidence that OSA is a significant and independent risk factor for hypertension and coronary artery disease (CAD) although this is not a universal finding.

The Sleep Heart Health Study,[107] conducted between 1995-1998, is a multiethnic prospective longitudinal epidemiological study of 6440 adults over the age of 40 years

depicted by home polysomnography. Among these subjects were 4991 adults free of self-reported CVD at baseline and were followed for incident CVD.[107] These subjects were followed-up for a median of 8.7 years. OSA was found to be a significant predictor of incident CAD in men between the ages of 40-70 years, and incident heart failure (HF) in men of all ages. In men greater than 70 years of age, or in women of any age, there was no association found between OSA and coronary heart disease.[108] Men with severe sleep apnea were 58% more likely to develop HF than those without OSA. The study concluded that OSA is associated with an increased risk of incident heart failure and CAD in men.

The strongest evidence is provided by data from a cross sectional analysis of the Sleep Heart Health Study cohort, which reported an independent association between OSA and congestive heart failure (CHF), stroke, and CAD.[97] In this very large population based study, 6132 middle-aged subjects were recruited and underwent home polysomnography and blood pressure recordings by a trained technician. The blood pressure was recorded three times at rest and the average of the second two readings were used as the true blood pressure. In this population, the mean systolic and diastolic blood pressure and the prevalence of HTN, defined as blood pressure greater than 140/90 mmHg increased significantly with increasing AHI. This study concluded that hypertension is more prevalent among individuals suffering from OSA when compared to individuals without OSA. Confounding variables were analyzed and it was determined that there is an independent association between OSA and HTN among middle-aged and older adults of different sexes and ethnic backgrounds. [97]

There is a conspicuous association between OSA and resistant hypertension, defined as blood pressure remaining above goal despite use of three different classes of

antihypertensive medications.[109] In a prospective study, 41 patients with resistant hypertension were evaluated by polysomnography and 83% of these patients had an AHI greater than 10 events/hour.[109] Another study looked at 62 consecutive patients with resistant hypertension and found that 90% of them had an AHI greater than 5 events/hour and 70% greater than 30 events/hour.[110] The ESS was also assessed in these patients and this measure of excessive daytime sleepiness was found to have a significant relationship with the frequency of the diastolic non-dipping pattern of BP. This study suggested that EDS could be a marker of pathogenetic mechanism linking OSA and hypertension.[110]

Dose-Response Effect

Many of the studies indicating an increased prevalence of hypertension in obstructive sleep apnea also found a dose-response effect, meaning that the severity of the HTN correlated well with the severity of OSA. A large population based study in Wisconsin, was among the first to implicate OSA as a causal factor in hypertension.[99,111] In this study, 1069 middle-aged people underwent overnight in-hospital polysomnography and blood pressure recordings. The Wisconsin Sleep Cohort Study[111] reported a prevalence of sleep disordered breathing of 9% for women and 24% for men. The results showed that systolic and diastolic BP increased with increasing severity of sleep disordered breathing as measured by the AHI. Multiple linear regression analysis was used to adjust for potential confounding variables such as age, sex, and body habitus. It was determined that the relationship between AHI and blood pressure decreased only slightly with increasing BMI. Therefore, in order to correctly estimate the relationship between the AHI and blood pressure, the BMI level must be specified. The relationship between blood pressure and AHI is the greatest at low to normal body weights.[111] It was

determined that an increase in the AHI of one event per hour increased the risk of having hypertension by 4%. This is a striking dose-response relationship. Overall, the authors concluded that there was an independent association between OSA and blood pressure.[111]

On the contrary, the Vitoria Sleep Cohort is a longitudinal study of a general population sample aged 30 – 70 years that did not find an association between the severity of OSA and incidence of hypertension. This was a 7.5 year follow-up study of 1557 subjects. The odds ratio (OR) for incident hypertension increased with increasing RDI in a dose-response effect, however, this finding was not true once data was adjusted for age, BMI, sex, neck circumference and other lifestyle characteristics. In the end, this prospective study did not support a causal relationship between sleep disordered breathing and hypertension.[112]

In a prospective four year follow-up cohort study of 709 of the subjects from the Wisconsin Sleep Cohort Study, it was estimated that individuals with an AHI of 5-15 events/hour at baseline have twice the risk of developing systemic hypertension after 4 years when compared to those with a baseline AHI of 0 events/hour.[99] In addition, subjects with an AHI >15 events/hour were found to be at 3 times the odds of having hypertension than those with no apneas or hypopneas. The odds ratios increased with increasing AHI, in a dose-response fashion. In this study, hypertension was defined as a resting blood pressure >140/90 mmHg *or* use of antihypertensive medications. The dose-response association between OSA at baseline and the presence of hypertension four years later was independent of known confounding variables such as body habitus, age, sex, and cigarette or alcohol use.[99]

Although it is still somewhat controversial, as determined in several population based studies like the one by Young *et al*, there seems to be an increased prevalence of

hypertension with increasing severity of OSA as measured by AHI. Even mild OSA with an AHI of 5-15 events/hour is associated with an increased risk for hypertension.[8] Whether or not the risk is even greater in patients with severe sleep apnea is unknown, because all of the studies are underpowered in the severe (AHI > 30 events/hour) category.[113]

Treatment Effect

The current gold standard treatment for obstructive sleep apnea is continuous positive airway pressure. Marin *et al* conducted a prospective cohort study that demonstrated a substantial effect of CPAP on multiple cardiovascular outcomes when compared to control groups.[114] The three groups followed in this study were: healthy men, male patients with untreated OSA, and patients with OSA treated by CPAP. The results showed that patients with untreated OSA had considerably increased risk of developing fatal (OR 2.87) and nonfatal (OR 3.17) cardiovascular disease when compared to the healthy men. This observational study also demonstrated that patients with OSA treated with CPAP therapy did not have any increased risk of cardiovascular events.[114] The results suggest that CPAP therapy eliminates the excess cardiovascular risk that is associated with OSA. One study further demonstrated that CPAP withdrawal leads to a rapid recurrence of OSA and an increase in BP.[115]

Several cohort studies, randomized controlled trials, and meta-analyses have revealed that appropriate treatment of obstructive sleep apnea using CPAP results in lowering of systemic blood pressure regardless of whether or not the patients are hypertensive at baseline.[6,73,92,93] In most cases, the reduction in blood pressure has been relatively small, but a few studies demonstrate a larger reduction in systemic blood

pressure following treatment of OSA. There are also a number of recent studies that for various reasons, were unable to show a difference in blood pressure or cardiovascular outcomes before and after treatment of OSA.[5,81,94,116-118]

Data suggests that a small reduction in nighttime or sleep blood pressure can be achieved even in normotensive patients using CPAP, and a clinically important blood pressure reduction is demonstrated in hypertensive patients. The effect of the treatment seems to be more pronounced in more severe OSA.[113]

In 2007, two meta-analyses were conducted to assess the impact of CPAP therapy on blood pressure in patients with OSA.[57,119] One of these studies included ten RCTs, and this meta-analysis showed that with pooled results, CPAP therapy resulted in a small decrease in blood pressure, which was not statistically significant. Overall, the mean compliance with CPAP was the only variable that was associated with a tendency to an increased effect of CPAP on blood pressure. Other variables such as age, BMI, Epworth sleepiness scale, AHI and use of antihypertensive medications were not found to be associated with the extent of blood pressure reduction. A subgroup analysis was conducted to include only the studies with severe sleep apnea (AHI>30). This analysis showed a greater reduction in blood pressure following treatment with CPAP. In these trials, CPAP reduced SBP on average by 3.03 mmHg and DBP by 2.03 mmHg.[119]

The second meta-analysis compiled the results of 16 randomized controlled trials and provides evidence that effective CPAP treatment does indeed reduce BP in patients with OSA.[57] There was a pooled mean net change of -2.46 mmHg, and -1.83 mmHg for SBP and DBP respectively. The nighttime MAP in the CPAP group decreased by 2.22 mmHg in comparison to the control group.[57] The duration of CPAP therapy in the

included RCTs was short, with a range between 2 and 24 weeks. It is imperative to consider that longer studies may have different results.

There are some important methodological differences between trials, including different: sample sizes, duration of follow-up, outcome measures, and percentage of patients with hypertension at baseline. Some trials used a single time point blood pressure, whereas other trials used 24-hour ambulatory blood pressure readings. Three randomized controlled trials showed a relevant reduction of mean blood pressure by 2.5mm Hg, 6mm Hg, and 9.9 mm Hg on average.[6,92,93]

In the study that showed the largest effect, 66% of the patients were hypertensive. This was a prospective randomized controlled trial involving 60 consecutive patients with moderate to severe OSA.[6] The patients were randomized to receive therapeutic or subtherapeutic CPAP for nine weeks. Overnight polysomnography and continuous noninvasive blood pressure recording for 19 hours was performed at the start of the study and again at the nine-week follow-up period. A portable, battery-operated instrument with two finger cuffs was used to monitor BP. This system yields highly reproducible results and has the advantage of not arousing the patient from sleep, which can happen when using the 24-hour ambulatory cuffs. Only 32 patients ended up completing this study, with many dropouts because of equipment malfunction, change in their antihypertensive medications, unwillingness to continue to participate, or patients were unable to tolerate the CPAP. Despite this small sample size, there was a decrease in MAP by 9.9 mmHg in the therapeutic CPAP group. In contrast, there was actually a slight increase in blood pressure in the non-therapeutic CPAP group. In the therapeutic group, the diastolic and systolic blood pressures decreased significantly by 10.3 +/- 11.4 mmHg

and 9.5 +/-15 mmHg respectively. There was a decrease in all BP outcomes during day and night in the CPAP group.[6]

Another randomized controlled trial assigned 118 men suffering from OSA to receive either therapeutic CPAP or non-therapeutic CPAP over a period of four weeks.[92] The primary outcome measure was the change in 24-hour MAP. Changes in SBP, DBP, sleep, and wake blood pressures were also documented. The study also looked for a correlation between blood pressure changes and baseline blood pressure and severity of OSA. The results illustrate a modest, but significant reduction in 24-hour MAP in those patients receiving therapeutic CPAP (2.5mmHg versus 0.8mmHg in the non-therapeutic group). It was noted that the reduction in blood pressure was more significant in those patients with more severe OSA, but there was no correlation between decline in blood pressure and baseline blood pressure reading. The study concluded that the patients with severe sleep apnea are most likely to benefit from a reduction in blood pressure.[92] In this trial, changes in blood pressure were assessed using an unpaired t-test on an intention to treat basis. According to this analysis, 10 patients that did not have follow-up blood pressure readings were analyzed as "no change". This probably makes the results of the study err on the conservative side.

In 2006, Mills *et al* published a RCT examining the effect of CPAP treatment on blood pressure and plasma NE levels.[93] This was a very short-term study, where 51 CPAP naïve patients with OSA were randomized into three groups and treated with CPAP, oxygen supplementation, or placebo CPAP for 14 days. According to the authors, the groups were evenly matched for age, BMI, gender and presence of hypertension. However, there were a few more hypertensive patients in the CPAP group. These authors discovered that effective CPAP therapy led to a decrease in plasma NE levels as well as a

decrease in BP and HR. Neither the placebo CPAP group nor the oxygen supplementation group showed a significant difference in any of these outcomes. In the CPAP group, the mean systolic blood pressure decreased from 155.2 to 145.1 mmHg and the diastolic blood pressure decreased from 84.2 to 79.5 mmHg. Both of these findings were statistically significant.[93]

In a multicenter, double blind, randomized, placebo controlled trial performed by Duran-Cantolla *et al.,* patients with untreated, newly diagnosed hypertension and OSA were assigned to receive either effective or sham CPAP therapy for three months in order to assess the effect of CPAP on 24-hour ambulatory blood pressure.[120] The ambulatory device recorded BP values every 20 minutes during the day, and every 30 minutes at night. The results showed that three months of CPAP therapy significantly improved systemic hypertension, with a mean reduction of 2 mmHg. The greatest changes were observed with SBP and nocturnal blood pressure. Any patient that withdrew from the study had their blood pressure recorded as no change from the baseline level, which underestimates the standard errors. The CPAP group showed a reduction in the percentage of non-dipping patients and in the number of patients with systemic hypertension. The results have vague clinical relevance owing to the small reduction in systemic BP, however the use of CPAP may still offer a beneficial effect to lower blood pressure. Although there was no significant relationship between changes in blood pressure and the ESS, there was a significant association between CPAP compliance and ESS improvement. Compliant patients also had a greater reduction in blood pressure over three months.[120]

A small placebo trial showed dissimilar and curious results.[95] The study included 39 patients between the ages of 30 and 65 years with sleep apnea and hypertension. The

subjects were randomized to receive either therapeutic or subtherapeutic CPAP. The duration of follow-up was only one week, so these results must be interpreted cautiously. Overall, a significant decrease in daytime blood pressure was found in both groups. This leads one to believe that there is a placebo effect of wearing subtherapeutic CPAP at night. The nocturnal blood pressure, however, decreased significantly only in the therapeutic group.[95]

Faccenda *et al* also conducted a randomized placebo-controlled trial of the effects of CPAP on blood pressure in 68 patients with sleep apnea.[96] This study was based on a cross-over design, meaning that after four weeks of being randomized to one group, the patients crossed-over to the other group and received the opposite treatment (either placebo or CPAP). The analysis of 24-hour ambulatory blood pressures revealed that the decrease in 24-hour DBP was significantly correlated with the frequency of desaturations in the baseline sleep study. The hypoxemic patients experienced a decrease in blood pressure by 5 mmHg diastolic at the completion of the four-week CPAP limb of the study. This was the only significant correlation determined by multiple regression analysis. The study also found that there was a fall in diastolic blood pressure in the CPAP groups between 2:00 am and 10:00 am. There was no significant drop in blood pressure during waking hours.[96] There were two major limitations to this study. Firstly, all of the patients were normotensive, and secondly, the placebo was actually an oral capsule that subjects believed would help make their airway musculature more active during sleep.

Effective CPAP therapy has been shown to reduce the frequency of prehypertension and masked hypertension in patients with severe obstructive sleep apnea.[55] Drager *et al* conducted a randomized trial based on in-office BP and 24-hour

ABPM for 36 male patients with prehypertension or masked hypertension and severe OSA (mean AHI 56 events/hour). The patients were assigned to either no treatment, or CPAP therapy for three months. In the control group, there were no significant changes in blood pressure detected at the three month follow up, however, there was a significant reduction in the frequency of prehypertension (94% to 55%) and masked hypertension (39% to 5%) in the CPAP group.[55]

Some short-term studies have concluded that CPAP does not have an effect on mean 24-hour ambulatory blood pressure in patients without daytime hypersomnolence.[116] However, the long-term RCT performed by Barbé *et al.* monitored nonsleepy patients for one year to assess the effectiveness of CPAP in decreasing blood pressure.[56] In this multicenter study, the Spanish cohort of 359 nonsleepy patients with OSA was randomly assigned to receive either CPAP treatment or conservative treatment consisting of dietary counseling and sleep hygiene advice. Subjects were evaluated at 3, 6, and 12 months to determine blood pressure, CPAP compliance, weight, drug and alcohol use, and ESS score. Results showed that CPAP reduced blood pressure by 2 mmHg and there was a dose-response effect relationship for systolic blood pressure. The AHI and decrease in ESS score during follow-up was directly dependent on the patient's compliance to wear CPAP for more than 5.6 hours per night. The findings are significant and clinically relevant because not only does CPAP relieve symptoms of daytime sleepiness, it also may decrease the risk for cardiovascular disease. The authors concluded that CPAP could be an effective treatment to reduce blood pressure for hypertensive patients with OSA who do not experience hypersomnolence.[56]

Barbé *et al* published another, very similar, 4-year follow up study in 2012, with a

total of 725 consecutive nonsleepy OSA patients.[5] The objective was to determine the effect of CPAP and OSA severity on the incidence of hypertension or cardiovascular events in this population. Continuous positive airway pressure was found to be ineffective in patients who used it for less than 4 hours per night. It was found that CPAP use in these nonsleepy OSA patients did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events.[5] A possible explanation for the results is that CPAP is less effective in nonsleepy patients.

Several other studies exhibited no significant drop in MAP with CPAP therapy for OSA, and a small decrease in diastolic or mean daytime blood pressure by approximately 2 mmHg.[81,94-96] In most studies that showed little or no difference in mean blood pressure, the percentage of patients with hypertension before treatment of OSA was very low, [81,94-96] or the compliance with CPAP use, as expressed in hours of use/night, was inadequate.[118]

Sixty-eight patients with sleep apnea and hypertension, on antihypertensive medications were enrolled in a parallel, randomized, placebo-controlled trial. The patients were divided into either a CPAP group or a subtherapeutic CPAP group for 4 weeks and their antihypertensive regimen was not changed.[118] At baseline, the groups were similar with respect to AHI, BP, and BMI. Objective compliance between groups was also similar (4.4 – 5 hours/night). There was a small decrease in in 24-hour mean BP in both groups, which was not statistically significant. There were no changes in systolic, diastolic, daytime, or nighttime blood pressure. The normal nocturnal BP dipping pattern was restored in more patients in the CPAP group when compared to the control, but again, this was not statistically significant.[118] Other studies have shown that CPAP

compliance needs to be greater than 5.6 hours per night in order to be effective.[56,121] The combination of very short-term follow-up, and inadequate CPAP compliance in both groups could account for the lack of significant findings.

The role of CPAP in treatment of resistant hypertension has been shown to be essential. In a randomized controlled trial of 96 patients with resistant hypertension, using 24 hour ambulatory blood pressure monitoring, a mean decrease in blood pressure of 10/7 mmHg was found following three months of CPAP treatment when compared to medical treatment alone.[121] The compliant patients (>5.8hrs of CPAP/night) in the CPAP group showed a greater reduction in daytime DBP, 24-hour SBP, and 24-hour DBP. Patients with non-dipping patterns increased in the CPAP group.[121]

In summary, the contradictory results of the RCTs may be explained by the different study designs and the small sample sizes. Recent meta-analyses have shown small but significant improvements in BP with CPAP treatment in OSA patients, especially when the compliance is high and the OSA is severe. The reduction in blood pressure demonstrated in many of the CPAP trials may seem minuscule, but it is comparable to improvements achieved through medical management with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) as demonstrated in a meta-analysis.[122] Perhaps the patients who would benefit the most from treatment of OSA are those with resistant hypertension.[121]

Pathogenesis of Cardiovascular Effects of OSA

Both the acute and long-term cardiovascular effects of OSA result from a multifactorial pathogenesis that is not yet completely identified. In order to fully appreciate the effect of OSA on the cardiovascular system, it is important to first

understand some normal sleep physiology, and how sleep relates to blood pressure in the normal situation as well as in OSA.

Several mechanisms linking sleep apnea to CVD and hypertension have been proposed in the literature. OSA is characterized by repetitive episodes of upper airway collapse, causing arousals that disrupt sleep. This causes elevations in intrathoracic pressure, intermittent hypoxia, activation of the sympathetic nervous system, and promotes oxidative stress, systemic inflammation, and endothelial dysfunction.[121] It appears that obstructive sleep apnea has effects on both awake and sleep blood pressure.

Normal Sleep Physiology

Normal nocturnal sleep displays consistent basic organization. There are two types of sleep: non-rapid eye-movement (NREM) and rapid eye-movement (REM) sleep. These two basic stages of sleep alternate cyclically throughout the period of sleep. Furthermore, normal NREM sleep progresses through four stages, which are basically a continuum of depth of sleep. Each stage has unique changes in muscle tone, eye movements, and brain activity patterns.[123]

Normal sleep begins with a short period of NREM stage 1 sleep, which progresses through stages 2-4 and then finally to REM sleep. Then sleep alternates between stages of NREM and REM sleep throughout the remainder of the night. Basically, about 80% of the time is spent in NREM sleep and the remaining 20% in REM sleep.[123] REM sleep should increase as the night continues, with most of the REM sleep being in the last third of the night. REM sleep is characterized by dreams, bursts of rapid eye movements, and decreased muscle tone with paralysis.[123]

There are well known physiologic effects of sleep on blood pressure in the normal population. The transition from wakefulness to NREM sleep is accompanied by significant alterations in respiratory and cardiovascular function.[124] For instance, the healthy patient should experience an increase in parasympathetic activity and a decrease in sympathetic nerve activity (SNA), heart rate, systemic vascular resistance, cardiac output (CO) and blood pressure during NREM sleep. Blood pressure, in the normal adult, should decrease by approximately 10-15% compared to awake measurements.[113,125] This decrease in blood pressure is known as "blood pressure dipping".[85] The decrease in CO appears to be related mainly to decrease in HR, because stroke volume (SV) remains unchanged.[125,126] Myocardial workload is reduced during this period of sleep.[124,127] It is also normal to experience a slight decrease in minute ventilation, and an increase in carbon dioxide levels and upper airway resistance.[128]

During the transition from NREM to REM sleep, there are some divergent alterations in cardiovascular and respiratory activity. Physiologic changes occurring during REM sleep as compared to NREM sleep in the normal individual include: an increase in HR and HR variability, increase in SNA, absence of muscle tone, and increased respiratory drive.[127] It is proposed that the irregular pattern of breathing during this stage of sleep is likely related to dream content.[124] Basically, the sympathetic nerve activity, BP, and HR increase to levels similar to relaxed wakefulness.[127]

Because adults spend approximately 80% of their total sleep time in NREM sleep, sleep is generally a time of cardiovascular quiescence. In obstructive sleep apnea however, this cardiovascular relaxation is disrupted.[124]

OSA Sleep Physiology

The cardiopulmonary events during sleep are critically different in the presence of OSA.[36,129] During the period of REM sleep especially, there is an increase in pharyngeal collapse and decreased muscle tone. Patients with OSA frequently experience variations in HR ranging from sinus bradycardia and arrest to tachycardia syndromes. Systemic and pulmonary hypertension and decreased cardiac output are also common findings.[129]

Typically, 5-7 seconds after apnea termination, there is an arousal from sleep which is coincident with the lowest point of oxygen saturation, and a surge in HR and BP.[130] In OSA, these apneic events and BP and HR surges are frequent and repetitive and are proposed to contribute to the adverse cardiovascular outcomes. Three pathophysiological features of sleep in OSA patients have been identified to contribute to these cardiovascular abnormalities: negative intrathoracic pressure, hypoxia, and arousals from sleep.[124,131]

During ineffective respiratory efforts against the occluded pharynx, there is an acute rise in intrathoracic pressure. This can impair relaxation and filling of the left ventricle (LV) and increase cardiac afterload. This leads to a reduction in SV during the apneas that is proportional to the negative intrathoracic pressure generated. Following termination of the apneic event, stroke volume abruptly increases. During the initial phase of increased intrathoracic pressure, there is an effect of baroreceptor activity that actually causes a brief inhibition of sympathetic outflow.[132,133] Normal lung expansion inhibits sympathetic outflow by vagal afferent feedback, whereas apnea disinhibits it.[134,135]

In the absence of airflow, hypoxic stimulation of the carotid body promotes vagal activity and causes bradycardia. However, several seconds into an apneic event, and

especially upon resumption of airflow, sympathetic vasoconstrictor activity rises in response to the hypoxia.[136] This explains why the maximum vasoconstrictor and chronotropic effects of the hypoxic event occur during the post apneic phase, when ventilation resumes. Surges in BP and HR are common during this phase.[137] The degree of desaturation during each obstructive event has been directly related to the magnitude of the increase in BP following the apnea.[124] In cases of severe OSA, despite the increase in sympathetic tone, there is usually still a nighttime physiologic drop in BP, but these blood pressure values remain much higher than normal.

Apneic events are terminated by arousal, which activates upper airway dilator muscles, and acts as a defense mechanism against asphyxiation. It is controversial whether the arousal itself also contributes to the rapid spikes in HR and BP following an apnea. In awake patients, voluntary breath holding and periodic breathing was demonstrated to cause post apneic surges in HR and BP in the absence of hypoxia.[138] Sudden lung inflation, however, causes inhibition of SNA and helps with the decrease in BP that happens before the onset of the next apnea.[137] Basically, arousals can contribute to the development of post apneic surges in BP, but don't seem to be crucial.[124]

Sympathetic Activation

The changes in blood pressure, heart rate and cardiovascular variability associated with OSA are often assumed to be a result of changes in sympathetic nervous system (SNS) activity. Sympathetic activity has been measured directly as SNA and indirectly as catecholamine levels in blood and urine. Many studies support a link between OSA and increased blood pressure, HR, and sympathetic nervous system activation as well as elevated plasma and urine norepinephrine (NE).[81] One retrospective study of 540 patients

found that nocturnal mean and maximum HR was significantly positively correlated with the AHI and the presence of hypertension.[139]

One theory is that apneic events lead to acute hypoxia and hypercapnia, large negative intrathoracic pressures, and transient arousals with hyperventilation.[113] A combination of the changes in blood gases as well as the arousal itself leads to an increase in sympathetic nervous system activation, resulting in an increase in HR and BP.[140] Patients with severe OSA may have several hundred of these apneic events each night. The increased SNA is most prominent immediately following arousal from sleep, but it is suspected that it lasts much longer.

In one study, sympathetic nerve activity was found to be higher during the day and night in 10 patients with OSA when compared to 10 normal controls.[141] It was also noted that in the 10 patients with OSA, BP and SNA did not fall during any stage of sleep. Four of the patients with OSA were treated with CPAP and the sympathetic nerve activity decreased to near normal levels in these patients.[141] They concluded that patients with OSA have higher SNS activity when awake, with further increases in BP and SNS activity during sleep. These changes seem to be improved by CPAP treatment.

Another study successfully demonstrated that in hypertensive patients with OSA, CPAP significantly reduced plasma norepinephrine levels in comparison to normotensive patients with OSA.[142] A randomized controlled trial performed by Bao *et al* in 2002, looked at the relationship between SNS activity (as inferred from 24-hour urine NE) and 24-hour BP variability measured by ABPM.[81] Twenty-four hour BP was measured on 41 patients with an RDI >12 events/hour. The subjects were then randomized to receive CPAP treatment or CPAP placebo for one week. After the first night of treatment, and after one week of treatment, 24-hour ABPM was performed. Urine NE was also collected

for a 24-hour period at these same intervals. The severity of sleep apnea (as measured by RDI) was found to have a significant positive correlation with urine NE and with nighttime BP variability, but there was no correlation with mean BP levels. Wake NE was significantly and positively related to all measures of BP variability. However, the sleep NE had a significant positive correlation only with sleep DBP. In this study, after one week of CPAP or CPAP placebo therapy, the overall BP variability decreased significantly, but equally, in both groups. These authors concluded that OSA is more related to BP variability than the blood pressure itself. Daytime urine NE, a measure of elevated SNS activity, predicts changes in BP variability during both daytime and nighttime.[81]

The proposed effects of OSA on daytime blood pressure have also been described. Multiple episodes of hypoxia during sleep in these patients, contribute to daytime hypertension which can potentially be explained by sympathetic activation lasting longer than the hypoxia itself.[143,144] A study using healthy male subjects showed that the response to combined hypoxia and hypercapnia produced a substantial increase in minute ventilation and SNA. The minute ventilation quickly returned to normal after exposure to room air, however approximately two thirds of the increase in sympathetic nerve activity persisted for the duration of the study (twenty minutes).[143] This demonstrates that brief periods of asphyxic stimulation cause substantial increases in sympathetic motor tone that outlives the stimuli. The prolonged increase of sympathetic activity seems to be the most important mechanism explaining daytime hypertension.

Systemic Inflammation

Inflammatory processes have materialized as critical in the pathogenesis of atherosclerosis. Inflammation plays a key role in all stages of atherosclerotic plaque formation.[145] The mechanisms underlying the inflammatory process in OSA remain uncertain. It is likely that intermittent hypoxia (short periods of hypoxia followed by rapid reoxygenation) plays a substantial role in the initiation of inflammation.[18]

Future cardiovascular risk has been reported to be associated with elevated levels of a multitude of circulating markers of inflammation. The most commonly implicated inflammatory markers are: tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6), interleukin 8 (IL-8), and C-reactive protein (CRP).[18] There is evidence to suggest that these inflammatory markers are elevated in patients with OSA and they decline to normal levels following treatment with CPAP.[146-148]

TNFα is a potent pro-inflammatory cytokine that has been shown to be consistently elevated in patients with OSA compared to controls. This relationship exists independent of obesity, and levels of TNFα decline with effective CPAP treatment.[149,150] One study was able to demonstrate a strong independent correlation between severity of OSA and TNFα levels.[151] IL-8 is a chemokine that plays an important role in the process by which neutrophils and monocytes adhere to the vascular endothelium. Levels of IL-8 have also been shown to be elevated in OSA patients.[151,152]

CRP is an acute phase reactant produced by hepatocytes and regulated by cytokines, including IL-6, IL-1 and TNF-α.[153] The stimuli responsible for elevations in CRP are unknown at this time; however it is produced during tissue injury, infection, and inflammation. Elevated plasma CRP level also has a clear association with both

cardiovascular disease and OSA. [18] C-reactive protein is an easily testable, sensitive marker of inflammation. Serum CRP has been shown to be elevated in a group of male patients with OSA when compared to a control group.[154]

CRP binds to the plasma membranes of damaged cells. Aggregated CRP binds low density lipoprotein (LDL) and very low density lipoprotein (VLDL), and activates complement, all of which contribute to low-grade inflammation and its association with the pathogenesis of atherothrombosis.[153] Multiple studies have demonstrated that CRP is associated with an increased risk of future cardiac events. The American Heart Association recommends using CRP in risk factor assessment in adults without known cardiovascular disease. In 2004, the recommendations from the AHA workshop were to use C-reactive protein because it has assay characteristics that are the most helpful for use in clinical practice.[155]

Mechanisms linking OSA to elevated CRP include repetitive hypoxemic stress and sleep deprivation. These events increase IL-6, which is a key regulation of CRP synthesis in the liver.[156] When measured with a high-sensitivity assay, C-reactive protein levels are broadly recognized as strong predictors of future cardiovascular events in patients with known cardiovascular disease as well as in otherwise healthy adults.[153,157] The role of CRP in OSA however is still under debate. The strong association between CRP and obesity, a well-known risk factor for cardiovascular disease and OSA, is the reason for the confusion and conflicting results regarding CRP and OSA. Visceral obesity is associated with chronic low-grade inflammation with elevated levels of CRP and IL-6.[158]

The Wisconsin Sleep Cohort Study assessed 907 adults and failed to detect an independent association between CRP and OSA after adjusting for body mass index.[111,159] Both obesity and OSA are pro-inflammatory conditions and may both heighten the progression of cardiovascular diseases.[18] A recent randomized controlled trial (RCT) showed that effective CPAP treatment had no significant effect on levels of CRP or IL-6 when compared to subtherapeutic CPAP.[160]

A newly published meta-analysis investigated the effects of CPAP on CRP levels among patients with OSA.[148] Ten studies were included in this review. The average duration of CPAP treatment was 4 months, with an average nightly use of 5.49 hours. The average BMI was 33.12 kg/m^2, and 93% of the subjects were men. At baseline, the average AHI was 55.7 events/hour with an ESS of 14.7. The mean CRP was decreased from 4.3 +/- 0.39 mg/dL to 3.5 +/- 0.46 mg/dL following CPAP therapy. This reduction in CRP was found in the absence of a change in BMI.[148]

Shamsuzzaman *et al.* found that plasma CRP levels were higher in patients with OSA compared to a control group: 0.33 mg/dL versus 0.09 mg/dL.[156] CRP levels of 22 subjects who were recently diagnosed with moderate to severe OSA (AHI ≥20) and free of comorbidities were compared to 20 control subjects (AHI ≤5) who were matched for age and BMI. Standard overnight polysomnography using a split-night protocol was used to diagnose OSA and perform a continuous positive airway pressure (CPAP) trial. Latex particle enhanced immunoturbidimetrox assay was performed to quantitatively determine high-sensitivity CRP. Age, sex, BMI, smoking, alcohol consumption, low density lipoprotein, and high density lipoprotein (HDL) were adjusted for using ANOVA to express the independent relationship between CRP and OSA severity. Not only was there

a direct association between OSA and CRP level, but as the severity of OSA increased, CRP also increased proportionally.[156]

Uvulopalatopharyngoplasty is one of the surgical treatment options for OSA. This surgical procedure has been demonstrated to decrease plasma levels of both CRP and TNFα.[161,162] There are studies that show CRP is higher in patients with OSA when compared to controls, and has a positive correlation with AHI. CRP levels in these studies decreased to a significant degree following effective treatment with CPAP.[146,147]

According to Raitakari *et al*[163] in a population-based study, the determinants of CRP level include obesity, smoking, physical activity, and oral contraceptive use. CRP concentration >3 mg/L was said to be the cut off point for high risk of cardiovascular disease. However, approximately one in three healthy women who use oral contraceptives have CRP concentrations exceeding this value.[163] The AHA stratifies risk categories as: low risk < 1.0 mg/L, average risk 1.0-3.0mg/L and high risk >3.0mg/L.[155]

The MONICA Augsburg Cohort Study[153] was used to describe cardiovascular risk factors in a random sample of a general population from 1984-1985. This study is based on 936 men between the ages of 45-64 years. The purpose of this study was to examine the association of CRP with the incidence of a first major coronary event in these men. To survey the participants, a questionnaire was completed along with recordings of blood pressure, BMI, smoking habits, alcohol consumption, duration and frequency of physical activity, and education level. Non-fasting blood samples were taken as a baseline to analyze the CRP levels. This study was performed as an 8-year follow-up to record the number of fatal and nonfatal acute myocardial infarctions, including sudden cardiac death, since the first CRP measurements. In total, 53 first major CHD events occurred. After adjusting for age and smoking behavior, there was a strong, linear correlation

between CRP and risk of a fatal or nonfatal coronary event. CRP had positive associations with age, BMI, smoking, and a history of diabetes.[153]

Although an abundance of randomized controlled trials is lacking, treatment with CPAP or UPPP appears to have an important effect on CRP in OSA patients. The debate is ongoing as to the true relationship between CRP, OSA, and hypertension. Further research including long term randomized controlled trials will help define this relationship in the future.

Endothelial Dysfunction

Endothelial dysfunction is well known as an early marker of vascular abnormality that precedes clinically detectable cardiovascular disease.[54] Evidence suggests that OSA independently impairs endothelial function. The function of intact endothelium is to regulate vascular tone and maintain homeostasis between pro-inflammatory, anti-inflammatory, and coagulation systems.[54] It has been proposed that impaired vasomotor tone and endothelial dysfunction due to chronic sympathetic activation and repetitive hypoxia may be a link between OSA and daytime hypertension and early development of atherosclerosis.[54,113]

OSA patients with no cardiovascular comorbidities have impaired endothelium-dependent vasodilation. This suggests reduced availability of the potent vasodilator, nitric oxide (NO). Endothelium dependent vasodilation can be measured by forearm blood flow following injection of acetylcholine (an endothelium-dependent vasodilator). Forearm blood flow is reduced in patients with severe OSA compared with normal controls of a similar BMI.[164,165] In more than one thousand elderly patients with OSA, flow-mediated dilation remained impaired after adjusting for BMI and heart-related comorbidities.[166]

This study presents further evidence to suggest there is a decrease in NO bioavailability in OSA patients. In addition, there have been studies to show that there is less circulating NO in the plasma of patients with OSA when compared with controls. These levels may be normalized following effective CPAP treatment.[167]

Effective CPAP treatment has improved flow-mediated vasodilation in OSA patients with no cardiovascular comorbidities.[167,168] Three months of CPAP therapy increased endothelium-dependent vasodilation in otherwise healthy OSA patients. This recent study by Lattimore *et al* would suggest that CPAP treatment induces increased NO availability.[169] Similarly, forearm vasoreactivity improved after only two weeks of CPAP therapy in normotensive and hypertensive OSA patients.[170] The effect of surgical treatments for OSA on vasomotor tone is unreported.

To add to the problem of endothelial dysfunction, patients with OSA may have higher levels of circulating endothelin-1, a potent vasoconstrictor. These findings are inconsistent and the evidence is not robust. Elevated circulating endothelin -1 is believed to cause greater systemic vasoconstriction in these patients, contributing to hypertension.[23] One very small study of nine patients with OSA and normal blood pressure showed that endothelin-1 levels are elevated when compared with healthy controls.[171] Many studies compared groups that were not appropriately matched for confounding factors such as BMI and BP. For instance, a 2006 study demonstrated higher plasma levels of endothelin-1 in the morning when compared with controls with lower BMI and lower systolic BP.[172]

Elevated Levels of Aldosterone

There is increasing evidence to link the mineralocorticoid hormone, aldosterone, with both resistant hypertension and obstructive sleep apnea.[173] An estimated 10-20% of patients being treated for hypertension have resistant hypertension.[174] Primary aldosteronism is a group of disorders that cause overproduction of aldosterone by the adrenal cortex. High levels of serum aldosterone can result in plasma renin suppression, hypertension, and sodium retention, all of which have harmful effects on the cardiovascular system.[175] A recent large study found that the prevalence of primary aldosteronism in hypertensive patients was 6%, with an even higher prevalence among patients with resistant hypertension.

A study of 71 patients with resistant hypertension showed the overall prevalence of OSA to be 85% and demonstrated a significant correlation between plasma aldosterone concentration and severity of OSA. This and other studies have suggested that aldosterone excess might be a risk factor for increased severity of OSA[173,176], and perhaps treatment with spironolactone (an aldosterone antagonist) could improve OSA symptoms and severity.[176,177] This has not been widely researched yet.

In 2010, Gonzaga *et al* evaluated 109 consecutive patients with resistant hypertension and found that 28% of these patients had hyperaldosteronism and 77% of them also suffered from OSA. The severity of OSA was correlated with excessive plasma aldosterone levels in these individuals.[178]

Obesity

Obesity is a serious public health concern and is a growing epidemic disease.[179] Height and weight are considered the most useful measures for monitoring nutritional

status and classifying individuals as underweight, normal, overweight, or obese. The BMI is calculated as the weight in kilograms divided by the height in meters squared. BMI is basically a crude measure of fatness or thinness and does not take into account whether the weight is muscle or fat.

In adults, a normal BMI is between 18.5 – 24.9Kg/m^2. Overweight is defined as a BMI of 25-29.9Kg/m^2. Mild obesity is defined as a body mass index of 30-34.9Kg/m^2, whereas moderate obesity and morbid obesity are 35-39.9Kg/m^2 and is ≥40Kg/m^2 respectively (Table 2).[179]

Table 2. Classification of Body Mass Index.

Classification	BMI (Kg/m^2)
Underweight	<18.5
Normal	18.5-24.9
Overweight	25-29.9
Mild Obesity	30-34.9
Moderate Obesity	35-39.9
Morbid Obesity	≥40

Increase in body weight over time, is a well-established risk factor for both hypertension and OSA, however not all obese individuals have OSA and hypertension.[180] OSA can occur in non-obese persons, though it is often with less severity when compared to obese individuals.[181] Obstructive sleep apnea is highly prevalent in patients with clinically significant obesity.[182] A 10% increase in body weight over four years is associated with 6 times the risk of developing OSA.[183]

In obesity, fat deposits accumulate in the parapharyngeal area, which results in reduction of airway diameter.[179,184] Dietary weight loss can result in significant improvement in severity of sleep apnea.[185] The improvement in severity of OSA has been linked to the reduction in upper airway collapsibility from pharyngeal fat deposits. A 10-15% reduction in body weight has been found to reduce the AHI by up to 50%.[185] Weight

reduction programs do not completely eliminate sleep disordered breathing and should be considered as an adjunct to other therapies.[185]

A subset of the patients from the Sleep Heart Health Study was followed-up and it was discovered that there was a 40% incidence of newly diagnosed OSA in the patients who gained weight at the 5-year follow-up.[186] They also documented that men who lost ten pounds were 5 times as likely to experience a reduction in AHI by ≥15 events/hour.[186]

There is evidence that surgically assisted weight loss, in the form of bariatric surgery, significantly improves obesity-related OSA. In a prospective study completed by 101 bariatric surgery patients, the mean preoperative RDI was 51 events/hour, and the BMI was 56 kg/m^2. Approximately 11 months following bariatric surgery, the average BMI had decreased to 38 kg/m^2, and the RDI was down to 15 events/hour.[182]

Maxillomandibular advancement surgery has also been proven to benefit patients with OSA and an elevated BMI.[187] Because of the intermaxillary fixation and the acute, but short term, change in diet, it is common that patients lose some weight during the immediate phase of healing. There have been no long-term studies to determine the effects of MMA surgery on BMI in obese patients.

Prospective studies have also demonstrated that sleep disordered breathing in all ages predisposes to obesity.[188,189] This could be related to decreased energy during the day for physical activities, leading to a more sedentary lifestyle.

Obesity is a well-established cardiac risk factor. The complex associations between OSA, obesity, and hypertension make it difficult to interpret the findings of many studies. Obesity has been directly linked to hypertension long before the association between OSA and hypertension was discovered.[88] Many studies however, analyzed the data taking into considering the confounding variable of BMI. For instance,

among 1464 male patients, obesity and apnea severity were independent risk factors for increased BP.[190] Another study with 377 subjects showed that BMI, and severity of OSA were both independent predictors of hypertension. In this study, the relative risk of hypertension associated with obesity and OSA was 2.7 and 2.1 respectively.[191]

A cross-sectional analysis of adults in the Third National Health and Nutrition Examination Survey showed that increasing BMI was associated with a significantly increased risk of hypertension. The odds ratio (OR) for hypertension for every increase in BMI by 5 was 1.58. Obesity was associated with hypertension in both sexes in all age groups.[192]

Chapter 2: Purpose

There are currently no published studies evaluating the change in blood pressure following maxillomandibular advancement surgery for correction of sleep apnea. The primary outcome measure of this prospective study is to determine the effect of maxillomandibular advancement surgery on systolic and diastolic blood pressure in patients with OSA. Secondary objectives of this study are to determine:

1. the effect of MMA surgery on body mass index.
2. the effect of MMA surgery on variability of sleep systolic blood pressure, HR, and 24 hour MAP.
3. the effect of MMA surgery on nocturnal blood pressure dipping.
4. the effect of MMA surgery on C-reactive protein levels.
5. if there is a correlation between blood pressure and:
    a. excessive daytime sleepiness (as measured by ESS)
    b. severity of OSA (as measured by AHI)
6. if there is a correlation between OSA severity and CRP

Chapter 3: Patients and Methods

Study Population

I (we) recruited patients from a teaching hospital during August 2009 to September 2012. Patients were referred to the hospital by general practitioners, dentists, otolaryngologists, and sleep physicians for an evaluation regarding their OSA. All patients were evaluated clinically and radiographically to determine their suitability for MMA surgery. All participants underwent nocturnal polysomnography. Following this complete assessment, all patients with a diagnosis of sleep apnea and a treatment plan that included MMA surgery were eligible to participate in the study. Exclusion criteria were predominantly central sleep apnea and the presence of an underlying medical condition which would render the patient unfit for surgery. An *a priori* sample size calculation determined that 51 patients should be included in the study in order to detect a difference in blood pressure of 5 mmHg. The study was approved by the Capital District Health Authority Ethics Review Board and all participants gave written informed consent.

Clinical Data

All study patients were assessed preoperatively, and then scheduled for follow up assessments at 3 months and 6 months postoperatively. A complete medication list was obtained at each time point. Height and weight were measured and body mass index was calculated as body mass in kilograms divided by height in meters squared at each of the three time intervals. Daytime somnolence was assessed using the Epworth Sleepiness Scale preoperatively and 6 months postoperatively.

Smoking and alcohol consumption were documented. Dyslipidemia was considered present if the patient was diagnosed by a physician or taking a medication for it. The presence of diabetes was documented if the patient was taking an anti-diabetic medication or given a diagnosis of diabetes by their physician. Use of CPAP was documented if the patient was consistently wearing a CPAP as prescribed by a sleep physician, for a minimum of four hours per night. Systemic hypertension was documented if a physician previously diagnosed the patient. It was then documented which patients were taking antihypertensive medications.

Procedures

Sleep Study

Polysomnography was undertaken preoperatively, and postoperatively. When possible, the sleep study was conducted in a hospital setting and scored by a trained technician according to established criteria. Because of limited availability at the sleep laboratory, an in hospital study was not always possible, and in that circumstance, a home sleep study was performed. For appropriate comparison, each patient was evaluated postoperatively with the same type of study they completed preoperatively. An apneic event was scored when there was cessation of airflow for more than 10 seconds and a hypopnea was documented as a reduction in airflow lasting a minimum of 10 seconds accompanied by at least a 4% decrease in oxygen saturation. From the total apneas and hypopneas, the AHI was calculated to determine the severity of sleep apnea.

Surgical success was qualified using the same criteria as Li in 2011.[35] If the AHI decreased by a minimum of 50% from baseline, and the postoperative AHI was less than 20 events/hour, the surgery was considered a success.

Blood Pressure Monitoring and Actigraphy

Twenty-four-hour ambulatory blood pressure was recorded by the oscillometric technique with a Tiba Ambulo 2400 ABPM. This ABPM system was validated using criteria developed by the International Standards Organization and further passed protocols published in 1993 by the British Hypertension Society.[193,194] The Tiba Ambulo 2400 also has a 3 axis accelerometer which records movement activity throughout the 24 hours to provide information on actigraphy. The accelerometer senses movement across three axes and data is sampled several times a minute and averaged and stored on a per minute basis.

The cuff was programed to inflate every 30 minutes during the day and every 60 minutes at night (between 10pm and 7am). Ambulatory blood pressure monitoring was performed at baseline and at 3 and 6 months following MMA surgery. The patients were asked to wear the device during a "normal" day and to record a diary of strenuous physical or mental activities as well as sleep time and wake time. Time in bed (TIB) was defined based on the patient-kept diary documenting the time of getting into and arising from bed.

The diagnosis of hypertension at baseline was made according to standard criteria.[44] Hypertension was defined during waking hours as systolic blood pressure 135 mmHg or above, diastolic blood pressure 85 mmHg or above, or both. During sleeping hours, hypertension was defined as systolic blood pressure of 120 mmHg or above, diastolic blood pressure 70 mmHg or above, or both.

The percentage drop in nocturnal blood pressure was calculated as follows: [(awake MAP – sleep MAP)/awake MAP] x100. Patients with a decline in sleep MAP of less than 10% were considered non-dippers.

Blood pressure variability was computed by the Tiba Ambulo 2400 software as the standard deviation of the BP. The group median value of each of these parameters was used to identify patients with high or low variability.

Maxillomandibular Advancement Surgery

Patients were informed of the risks, benefits, and alternatives to MMA surgery. All participants in the study were re-evaluated a couple of weeks prior to their scheduled surgery. Radiographs, photos, and dental models were taken at that time to aid in surgical planning. The lateral cephalometric radiograph was interpreted using the Architectural and Structural Craniofacial Analysis of Delaire.[195] The magnitude of surgical advancement of the maxilla, mandible, and chin was based on lines C3 and CF1 of this analysis (Figure 3). Model surgery was performed on the articulated dental models, and a surgical acrylic splint was fabricated for intraoperative use.

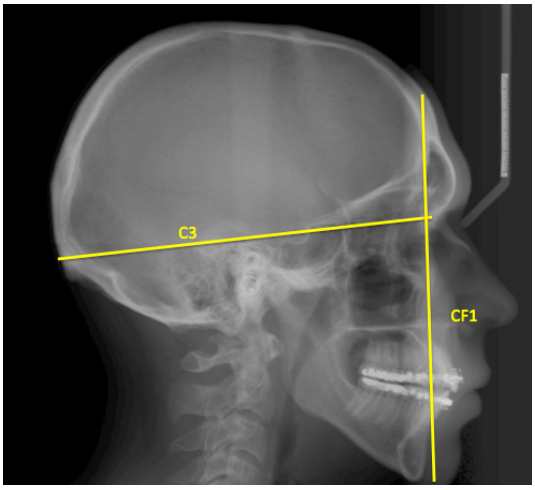

Figure 3. Lines C3 and CF1 of the Architectural and Structural Craniofacial Analysis of Delaire.

The surgery was performed at the Queen Elizabeth II Health Sciences Center in Halifax, Nova Scotia, by one of six staff Oral and Maxillofacial (OMF) Surgeons and an OMF resident. A Lefort I and BSSO were used to advance the maxilla and mandible and

a genioplasty was used to advance the chin when indicated. The maxilla, mandible, and chin were fixated with titanium plates and screws and stainless steel wires. Postoperatively, the patients were maintained in intermaxillary fixation for 2 to 4 weeks with either arch bars or orthodontic brackets and elastics.

C-Reactive Protein

To study the effect of MMA surgery on C-reactive protein, samples of peripheral venous blood were collected at baseline and at approximately 6 months following surgery. Serum levels of high sensitivity CRP were measured in a single lab, with a latex particle-enhanced immunoturbidimetric assay.

Statistical Analyses

Statistical analyses were performed with the help of a statistician, using the SPSS statistical package, version 20.0. The distribution of variables was examined for normality and wherever departures of normality were noted, nonparametric analyses were used.

Chapter 4: Results

Patient Enrollment and Follow Up

Between August 2009 and September 2012, 52 consecutive patients were asked to participate in the study. Twenty-three patients were enrolled in the study, and fifteen patients completed the study. Three patients dropped out of the study because of the inconvenience associated with wearing the blood pressure cuff for a 24 hour period. Five people were excluded from the study because of software or blood pressure cuff malfunction resulting in either a loss of data or insufficient preoperative data. The patients who did not complete the study were not different at baseline in terms of age, BMI, and severity of OSA from the rest of the study subjects.

The average follow up time for the 2 postoperative blood pressure recordings was 3 months (range 2.5 – 5.5 months) and 8 months (range 5.5 – 11.5). The blood work for the CRP levels was drawn at the second follow up (8 months on average). The ESS was also documented at that visit. The postoperative sleep study was performed at an average of 9 months following surgery (range 5 – 26 months).

Baseline Characteristics

The average age of patients completing the study was 48.9 years at the time of surgery. There were 2 female patients and 13 male patients. All patients were non-smokers and no patients reported more than 5 drinks of alcohol per week. There was one patient with type II diabetes controlled with oral antihyperglycemics, and there were 2 patients taking medications for dyslipidemia.

Table 3. Baseline characteristics of 15 study patients

Pt #	Age (yrs)	Sex	AHI (Events/ hr)	ESS	BMI (kg/m^2)	HTN§ (y/n)	Meds (y/n)	Diabetes (y/n)	Dyslipidemia (y/n)	CPAP (y/n)
1	39	M	26.4	15	25.2	N	N	N	N	N
2	33	M	87.5	1	32.4	Y	Y	N	Y	N
3	48	M	45.0	15	34.5	Y	N	N	N	Y
4	45	M	30.9	8	28.6	Y	N	N	N	N
5	27	F	23.7	12	43.2	N	N	N	N	N
6	53	M	17.7	14	29.0	N	N	N	N	N
7	57	M	128.3	8	32.4	Y	N	N	N	N
8	54	F	6.0	0	23.2	Y	N	N	N	N
9	52	M	29.3	6	35.4	Y	Y	Y	Y	Y
10	48	M	11.9	18	24.8	Y	Y	N	Y	N
11	59	M	84.9	3	37.8	Y	Y	N	N	N
12	51	M	32.2	10	26.9	N	N	N	N	N
13	37	M	15.9	16	31.9	N	N	N	N	N
14	67	M	14.9	10	27.7	Y	Y	N	N	Y
15	64	M	55.0	6	28.9	N	N	N	N	N
MEAN or TOTAL	**48.9**	**2F 13M**	**40.8**	**9.7**	**30.8**	**9**	5	1	2	3

§ HTN means a physician diagnosis of hypertension

In this study, there was a wide range of severity of OSA. The mean baseline apnea hypopnea index was 40.8 events/hour (range 6.0 to 128.3). Patients with mild to moderate OSA are compared to those with severe OSA in table 5. Three of the 15 patients used CPAP up until the time of surgery. All three of these patients had hypertension. No patients used CPAP following surgery.

Of the 15 patients who completed the study, 9 had a physician diagnosis of hypertension. Five of these 9 patients were taking at least one antihypertensive medication as prescribed by their physician. Postoperatively, only 3 of these patients continued to take blood pressure lowering medications. Patient 10 stopped his antihypertensive medications on the recommendation of his physician, because of

symptomatic hypotension, which developed approximately 10 weeks following surgery. Patient 14 is a physician, and he stopped his antihypertensive medications 8 weeks following surgery because he was feeling great, and when he checked his blood pressure daily using his home device, he felt it was significantly improved.

Table 4 provides a comparison of average baseline characteristics between the 9 patients with hypertension and the 6 patients without hypertension. Age, BMI, AHI, ESS were all examined to see if any significant differences existed between the groups.

Table 4. Mean baseline characteristics of patients with physician diagnosed hypertension compared to the rest of the study patients

Mean Baseline Characteristics	Diagnosis of HTN (n=9)	No diagnosis of HTN (n=6)	p value
Age (yrs)	51.4	45.2	0.30
BMI (kg/m^2)	30.8	30.9	0.97
AHI (events/hr)	50.7	25.6	0.22
ESS	8	12	0.14
Mean 24hr MAP (mmHg)	93.8	89.2	0.21
Mean 24hr SBP (mmHg)	122.7	117.2	0.24
Mean 24hr DBP (mmHg)	78.1	74.9	0.22
CRP (mg/L)	1.76	3.05	0.13

Independent samples t-tests were conducted and showed no statistically significant differences between groups. However, patients with hypertension were older by an average of 6.2 years. Hypertensive patients also tended to have more severe sleep apnea, but were considered less sleepy when evaluated by the Epworth Sleepiness Scale and compared to the nonhypertensive controls. The BMI between groups was essentially equal.

The CRP in the group of patients without a diagnosis of hypertension was almost double that found in the group of patients with a diagnosis of hypertension. The blood pressure was also examined and it was noted that the preoperative mean 24hr MAP, mean 24hr SBP and 24hr DBP were all elevated by 3.2 – 5.5 mmHg in the group of patients with hypertension compared to those without hypertension.

Forty-seven percent of the patients in the study (7 patients) had severe OSA at baseline. The remaining patients had mild or moderate sleep apnea (Table 5).

Table 5. Baseline comparison of patients with severe OSA (AHI ≥ 30) with patients with mild-moderate OSA (AHI < 30).

Mean Baseline Characteristic	Severe OSA AHI ≥ 30 (N=7)	Mild-mod OSA AHI < 30 (N=8)	p value
Age (yrs)	53.3	45.1	0.17
BMI (kg/m^2)	31.7	30.0	0.54
ESS	8	11	0.19
Mean 24hr MAP	93.6	90.6	0.41
Mean 24hr SBP	122.5	118.8	0.44
Mean 24hr DBP	77.3	76.4	0.72
CRP (mg/L)	2.6	2.1	0.60

Patients with severe OSA were older than those with mild to moderate OSA and had a higher BMI. The CRP in the severe OSA group was higher than in the mild-moderate OSA group. On average, the 24 hour mean blood pressures tended to be slightly elevated (0.9 – 3.5 mmHg) in the severe OSA group compared to the mild to moderate group. Independent samples T tests showed none of these differences to be significant.

Maxillomandibular Advancement Surgery

Lefort 1 and BSSO advancements were performed on all patients, with average advancements of 8 mm and 7 mm respectively. The primary surgeon made the

measurements at the osteotomy sites. Ten patients also had a functional genioplasty advancement of 7 mm on average (Table 6).

Table 6. Advancement in millimeters of Lefort 1, bilateral sagittal split osteotomy and functional genioplasty (where applicable).

Patient	LF	BSSO	FG
1	6	10	8
2	10	6	5
3	12	12	-
4	5	15	8
5	6	5	4
6	6	5	6
7	10	5	-
8	3	6	5
9	9	5	-
10	10	3	6
11	10	11	-
12	10	4	8
13	9	8	8
14	9	4	-
15	12	11	9
MEAN	8	7	7

AHI and ESS

The Epworth sleepiness scale (Table 7) decreased from 9.7 to 3.5 on average ($p = 0.01$). Preoperatively, 6 patients were considered sleepy (ESS > 10). Following surgery, only 1 patient remained sleepy (patient 10). The questionnaire was completed at 7.5 months postoperatively on average.

Table 7. Subjective and objective measures of success of maxillomandibular advancement surgery.

Patient	Preop AHI	Postop AHI	Preop ESS	Postop ESS
1	26.4	5	15	1
2	87.5	4	4	4
3	45	0.5	15	3
4	30.9	N/A	8	1
5	23.7	0.9	12	7
6	17.7	3.3	14	0
7	128.3	24.4	8	3
8	6	2.5	0	0
9	29.3	6	6	1
10	84.9	0.5	18	10
11	14.9	1	3	1
12	14.9	1	10	7
13	15.9	10.7	16	8
14	32.2	12.3	10	2
15	55	43.6	6	4
MEAN	40.8	8.3	9.7	3.5

According to the criteria outlined in the methods section, the success rate of MMA surgery in this study was 79%. All patients experienced a decrease in their AHI. The AHI decreased on average from 40.8 to 8.3 ($p<0.001$). Patient number 4 was unwilling to complete a postoperative sleep study, so his postoperative AHI is not available. Nine of the 15 patients had an in-hospital polysomnogram, and the remaining 6 patients underwent home studies for diagnosis of OSA. In all cases, postoperative sleep studies were conducted using the same study type and design as preoperatively.

Body Mass Index

A statistically significant reduction in BMI was noted at 3 months following surgery and was maintained at 8 months. Body mass index (Figure 4) decreased from an

average of 30.8 kg/m^2 to 29.0 kg/m^2 at 3 months following surgery ($p < 0.01$). The BMI then remained relatively constant and by 8 months after MMA surgery, the mean BMI was 29.3 kg/m^2 ($p = 0.01$). A complete list of BMIs can be found in appendix 1.

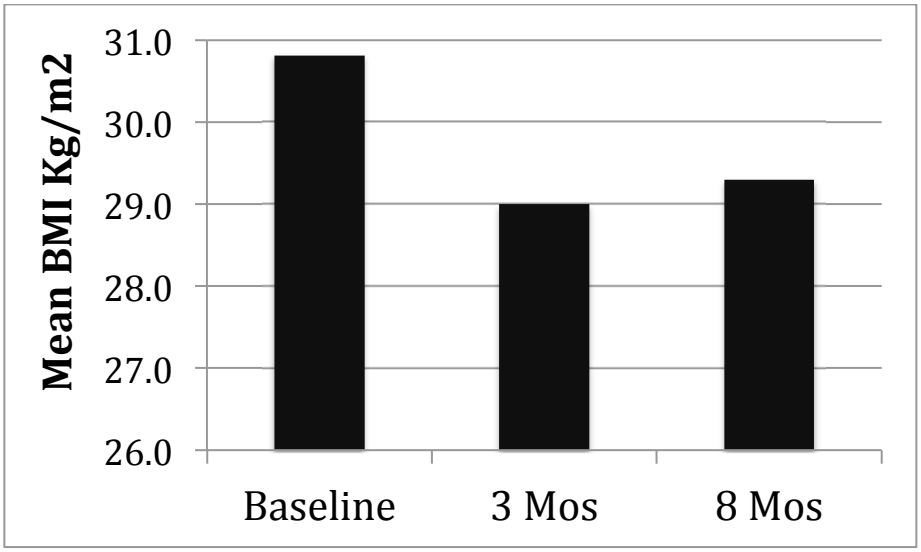

Figure 4. Mean BMI at baseline, 3 months, and 8 months following surgery.

Blood Pressure

During the baseline, 3 months, and 8 months blood pressure evaluation, patients spent an average of 8.6, 8.0, and 8.2 hours in bed, respectively. During the sleep hours, the average number of blood pressure recordings was 9 at baseline, and 8 readings at both 3 and 8 months. While awake, on average, 25 readings were obtained preoperatively and at 3 months and 23 readings at 8 months. Due to cuff malfunction, patient 14 only had 10 valid recordings throughout the 24 hour period at the 8 month follow up. Because of this, there were 4 readings during sleep and 6 throughout the day. These readings may not be an accurate representation of the 24 hour period. Patient 13 did not attend his 3 month follow up and as such, there is no blood pressure data available for him at that time. He is included in the baseline and 6 month analyses only. A more complete list of systolic and diastolic blood pressures can be found in appendices 2 and 3.

The seven patients with severe OSA were looked at independently, as were the 9 patients with a physician diagnosis of hypertension. These two patient populations did not show blood pressure results that were different from the overall study population. Patients demonstrating hypertension (not necessarily the ones with a physician diagnosis of hypertension) at baseline based on the results from the Tiba Ambulo 2400 were analyzed separately from the rest of the study patients to see if the changes in blood pressure were different. These results are presented below.

Systolic Blood Pressure

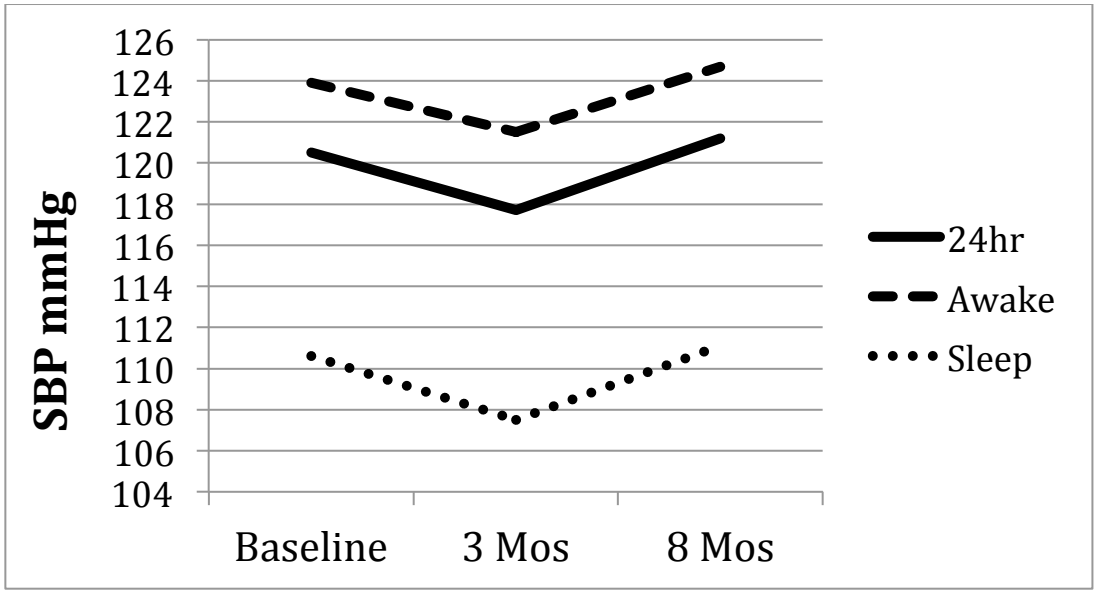

Figure 5. Systolic blood pressure.

None of the group averages of mean SBP were considered elevated at baseline. However, the group average mean systolic pressures showed improvement at 3 months following surgery (Figure 5, Table 8). By 8 months after surgery, the 24 hour SBP, sleep SBP and awake SBP all increased to just above their baseline values. Paired T-tests showed no statistical significance to any of these changes when compared with baseline. However, mean 24 hour and mean sleep SBP at 3 months are approaching significance.

Table 8. Average mean 24 hour, awake, and sleep systolic blood pressures.

	Baseline	3 Months		8 Months	
	SBP mmHg	SBP mmHg	p value vs. baseline	SBP mmHg	p value vs. baseline
Mean 24hr	120.5	117.7	0.09	121.2	0.68
Mean Awake	123.9	121.5	0.21	124.7	0.67
Mean Sleep	110.6	107.5	0.07	111.1	0.82

One patient (patient 8) had a mean baseline awake SBP > 135. A significant improvement was noted at 3 months and 8 months following surgery in this patient (Figure 6).

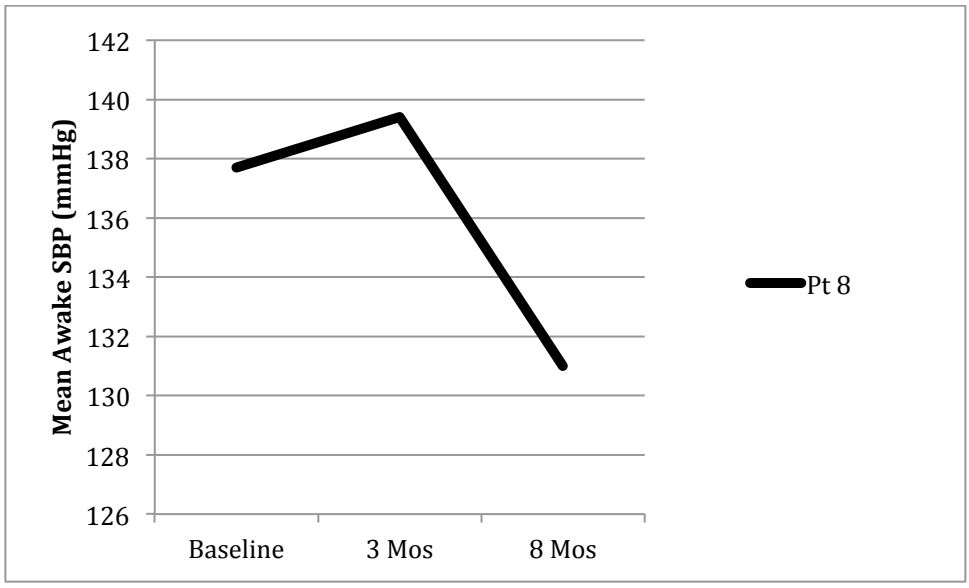

Figure 6. Patient 8, the only patient with an elevated baseline mean awake systolic blood pressure, shows a mean awake SBP in the normal range 8 months following surgery.

Two patients (patient 4 and 14) had mean sleep SBP > 120 mmHg. Patient 4 showed improvements in sleep SBP at 3 months and continued to drop at 8 months. Patient 14 demonstrated an increased blood pressure at 8 months compared to baseline.

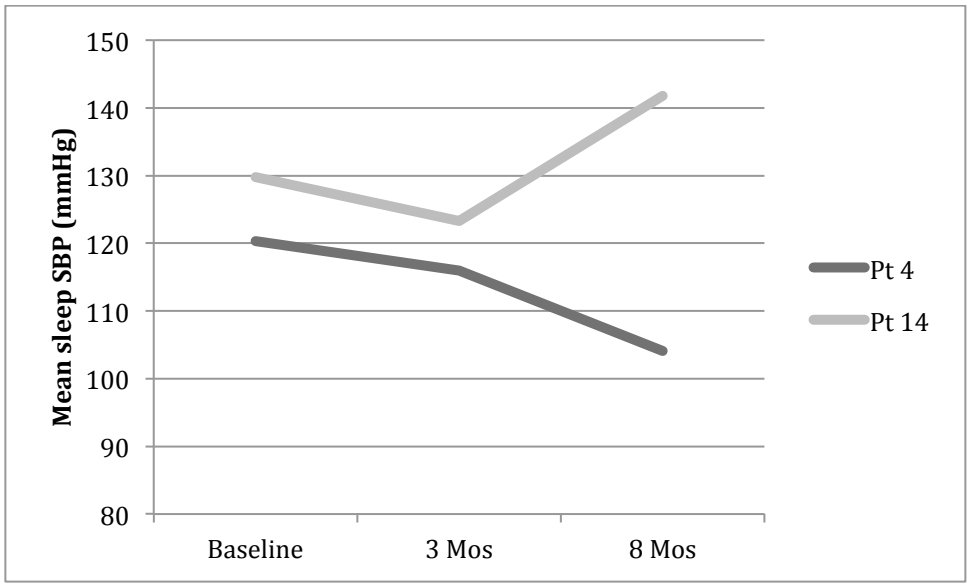

Figure 7. Sleep systolic blood pressure for patients 4 and 14.

Diastolic Blood Pressure

The average mean sleep diastolic blood pressure at baseline was in the hypertensive range (>70mmHg). The average baseline mean 24 hour and mean awake DBP were within the normal range (Figure 8, Table 9). The largest improvement was noted with mean sleep diastolic blood pressure at 3 months. The mean decrease in DBP at that time was 2.6 mmHg. A paired T-test demonstrated statistical significance (p = 0.03). By 8 months, however, the average mean sleep DBP was 69.5, and while it was still in the normal blood pressure range, the change from baseline was no longer statistically significant (p = 0.50).

Table 9. Average mean 24 hour, awake, and sleep diastolic blood pressures.

	Baseline	3 Months		8 Months	
	DBP mmHg	DBP mmHg	p value vs. baseline	DBP mmHg	p value vs. baseline
Mean 24hr	76.8	75.4	0.28	76.8	0.99
Mean Awake	79.1	78.2	0.67	79.3	0.90
Mean Sleep	70.6	67.9	**0.03**	69.5	0.50

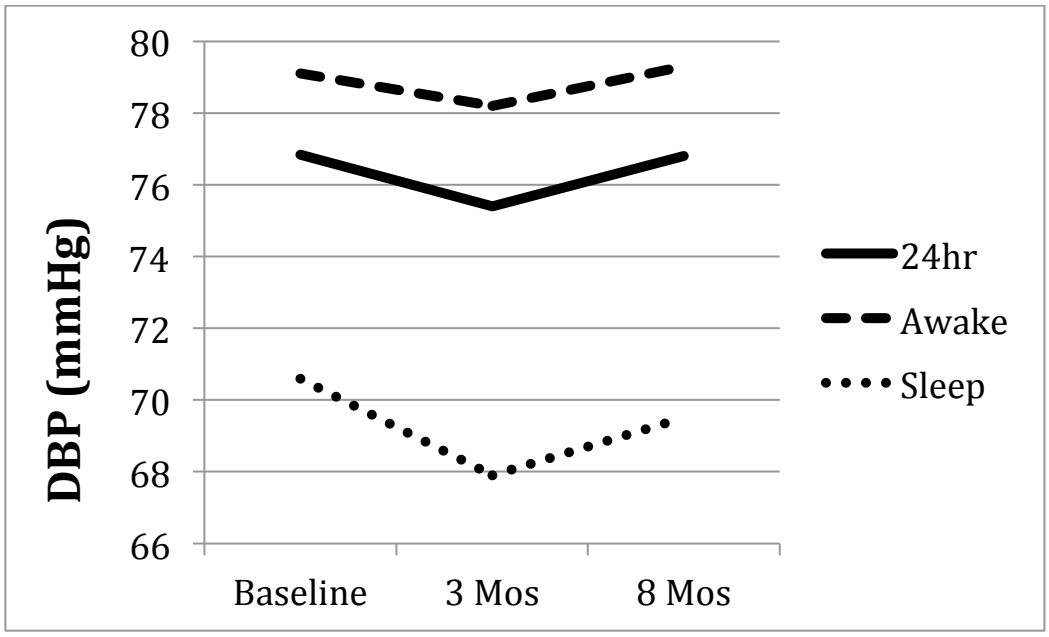

Figure 8. Diastolic blood pressure.

Patient number 4 had baseline awake and sleep diastolic blood pressures in the hypertensive range (awake > 85 mmHg, sleep > 70 mmHg). When we examined the awake DBP for this patient, it increased from 86.7 mmHg to 92.8 mmHg by 8 months (Figure 9). The sleep DBP for this patient showed improvement, and he is grouped together with 6 other patients in figure 10.

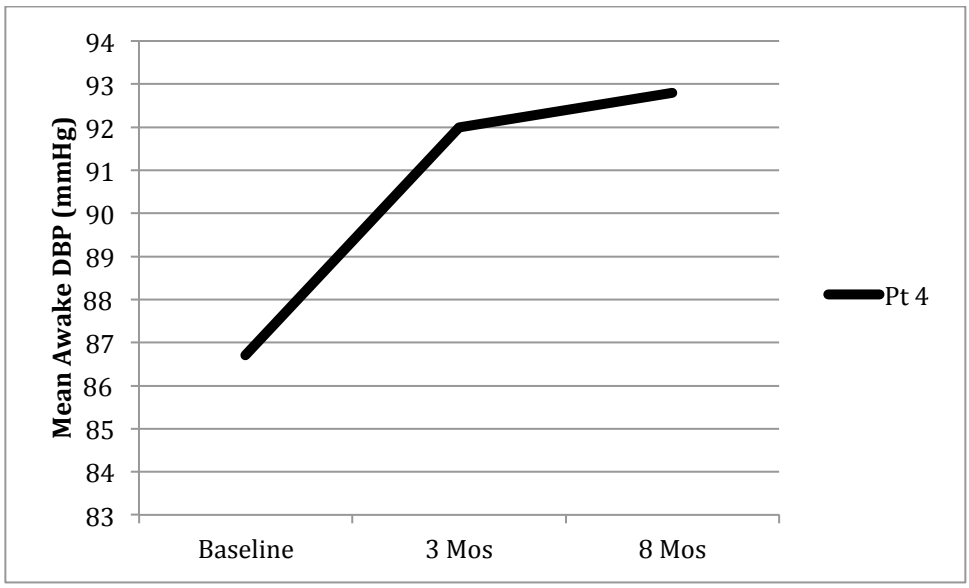

Figure 9. Patient 4 showed worsening of hypertensive mean awake DBP from baseline to 8 months.

Seven of the 15 patients had baseline mean sleep DBP > 70 mmHg (Figure 10). When we look at this population on its own, a significant improvement in sleep DBP is noted. The average mean sleep DBP decreased from 73.8 mmHg to 69.4 mmHg (p = 0.05). Each patient is indicated with a separate line in figure 10. Five of the 7 patients showed an improvement in their 8 month blood pressure.

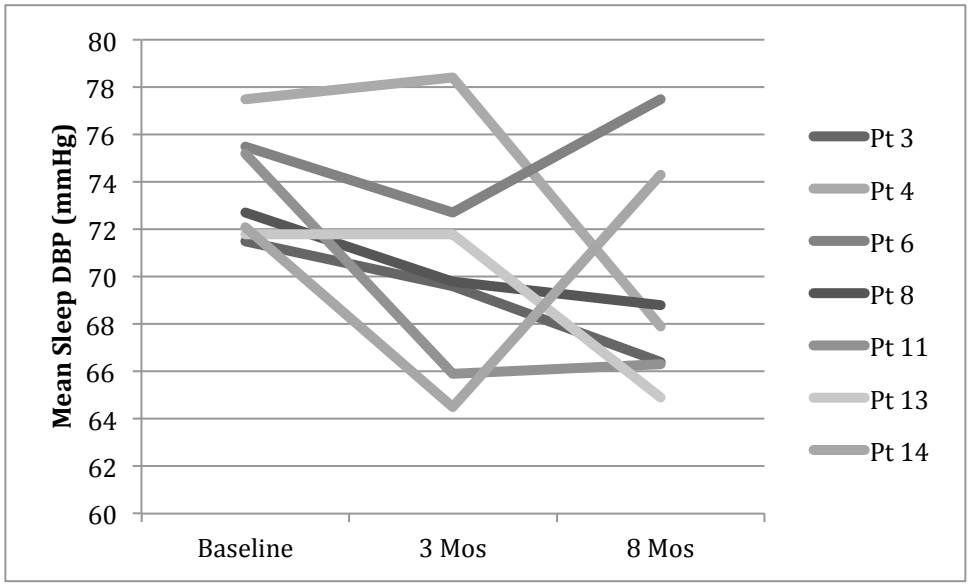

Figure 10. Mean sleep DBP for 7 patients with baseline sleep DBP > 70.

Percentage of Elevated Sleep Blood Pressures

Elevated sleep blood pressures are systolic pressures > 120 mmHg or diastolic pressures > 70 mmHg (Figure 11). The mean percent elevated sleep systolic blood pressure decreased from 22.1% to 17.8% at 3 months. By 8 months, the mean percent elevated SBP was up to 24.3%. The mean percent elevated sleep DBP sustained a small decrease at 8 months compared to baseline. None of these findings were statistically significant according to paired samples T-tests (Table 10).

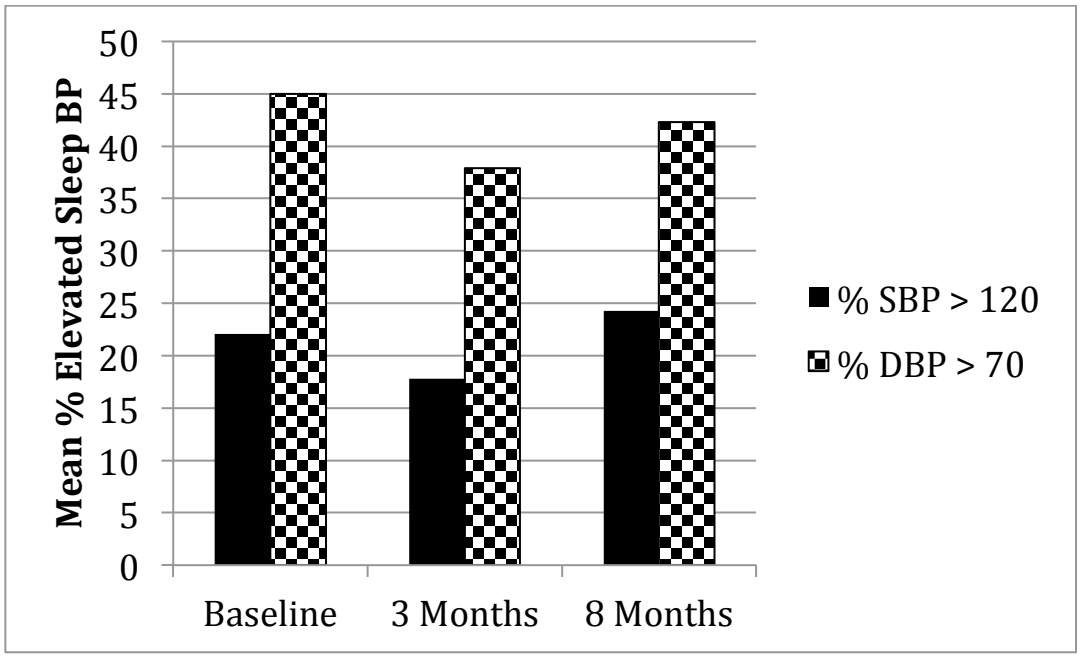

Figure 11. Mean percentage of elevated sleep blood pressures (systolic > 120 mm Hg or diastolic > 70 mmHg).

Table 10. Mean percentage of elevated sleep blood pressures.

	Baseline	3 Months		8 Months	
	%	%	p value	%	p value
% SBP > 120	22.1	17.8	0.08	24.3	0.68
% DBP > 70	45.0	37.9	0.51	42.3	0.79

Actigraphy

See appendix 4 for a full complement of actigraphy data. The changes in group average mean actigraphy over the 8 months are displayed during sleep and awake periods in Figure 12.

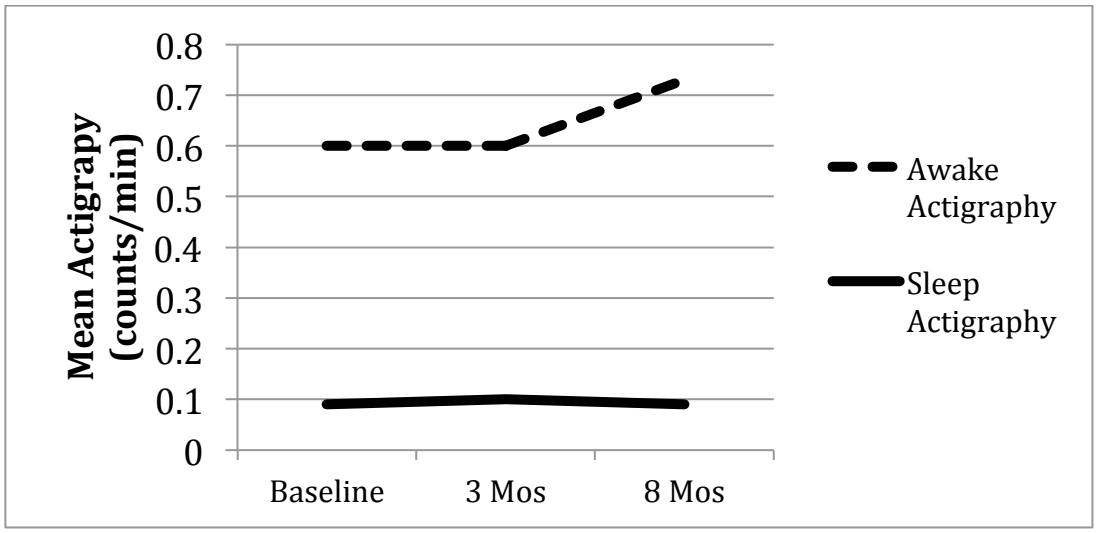

Figure 12. Mean actigraphy in counts/min as recorded by the Tiba Ambulo 2400.

Pearson correlation coefficients were calculated to determine if a relationship exists between actigraphy and blood pressure. Sleep actigraphy at the 8 month follow up was the only one showing a significant relationship (appendix 5). Sleep actigraphy at 8 months was strongly positively correlated with mean sleep SBP (0.776, sig at the 0.01 level), and moderately positively associated with mean sleep DBP (0.524, sig at the 0.05 level).

Blood Pressure Dipping

There were 3 non-dippers at baseline, 3 months, and 6 months (marked with an asterisk in table 11). Patient 6 is the only patient who was a consistent non-dipper throughout all 3 measurements. Percentage of drop in MAP at 3 months is unavailable for patient 13. Mean MAP dipping increased from 12.9% to 14.4% at 3 months ($p = 0.65$). At 8 months, mean MAP dipping was 13.0% ($p = 0.97$) (Figure 13).

Table 11. Nocturnal blood pressure dipping.

Patient	%Dip Baseline MAP	% Dip 3 Months MAP	% Dip 8 Months MAP
1	18	21	20
2	13	16	15
3	14	9*	18
4	14	15	26
5	19	12	17
6	6*	7*	1*
7	13	16	12
8	16	20	13
9	3*	20	12
10	15	21	14
11	12	20	14
12	20	10	7*
13	15	N/A	15
14	13	13	-2*
15	3*	1*	13
Mean	12.9	14.4	13.0

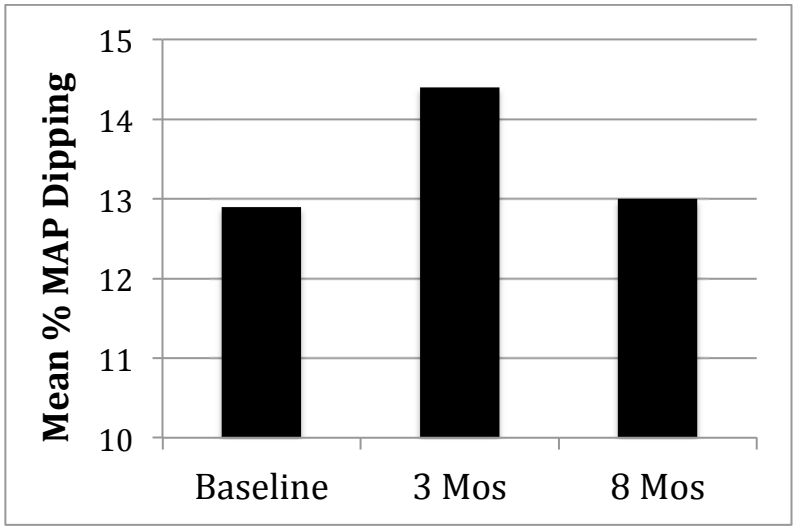

Figure 13. Mean percent MAP dipping at baseline and follow up.

Cardiovascular Variability

Data regarding variability of heart rate and blood pressure is available for all patients at baseline and 8 months. Variability data is missing for patient 8 at three months because of a software malfunction, and patient 13 at 3 months because he failed to follow up as planned. A summary of blood pressure and heart rate variability changes over time can be found in Figure 14.

The mean variability of 24 hour MAP decreased by 0.3 from baseline to 8 months postoperatively (Table 12). Patients with high variability are noted with an asterisk. They are the patients whose variability is greater than the group median variability.

Table 12. Twenty-four hour MAP variability.

Patient	Variability Baseline 24 hr MAP	Variability 3 Months 24hr MAP	Variability 8 Months 24hr MAP
1	11.3	12.5*	12*
2	9.7	10.8	13.7*
3	12.1*	8.7	10.8
4	17.4*	13.3*	20.5*
5	13.3*	9.2	10.4
6	12.2*	7.1	11.6
7	21.6*	16.1*	23.3*
8	11.7	N/A	12.7*
9	11.3	11.7	8.4
10	10.8	11.8	10
11	15.2*	12.7*	10
12	12.9*	10.6	8.5
13	10.6	N/A	13.6*
14	11.5	14*	8.9
15	10.6	12*	12.9*
MEDIAN	11.7	11.8	11.6
MEAN	12.8	11.6	12.5

The mean sleep systolic blood pressure variability decreased to a small extent from preoperative to 8 months postoperative (Table 13). A greater improvement was noted at 3 months. Again, patients with high variability are noted with an asterisk in Table 13.

Table 13. Sleep systolic blood pressure variability.

Patient	Variability Baseline Sleep SBP	Variability 3 Months Sleep SBP	Variability 8 Months Sleep SBP
1	11.8*	5	9.1*
2	13.5*	12.6*	14.9*
3	10.9	12.5*	6.1
4	12.9*	13.3*	46.2*
5	9	8.4	5.6
6	21.5*	5.6	7.9
7	18.7*	8.7	11.9*
8	12.9*	N/A	9.5*
9	8.8	7.3	8.3
10	3.7	10.3*	9.9*
11	12.5*	5.9	9.2*
12	6.9	4.4	7.6
13	8.5	N/A	7.3
14	7	10.6*	2.7
15	11.6	9.2*	8.9
MEDIAN	11.6	8.7	8.9
MEAN	11.3	8.7	11.0

Similar to the mean MAP variability and the mean sleep SBP variability, the mean heart rate variability also shows a small decrease from baseline to 8 months following surgery (Table 14).

Table 14. Twenty-four hour heart rate variability.

Patient	Variability Baseline HR	Variability 3 Months HR	Variability 8 Months HR
1	4.9	7.9	11.9*
2	13.6*	8.9*	11*
3	19.8*	5.2	9.2
4	11.4	14.6*	14.5*
5	20.1*	12.6*	12.8*
6	13.1*	8.6*	9.9
7	9.8	4.9	7.4
8	7.1	N/A	8.8
9	18.6*	9*	14*
10	7	6.7	11.3*
11	11.7	7.7	12.5*
12	16.1*	7.4	11.2*
13	6.5	N/A	8.5
14	6.4	5.6	9.5
15	12.1*	15.4*	11.1*
MEDIAN	11.7	7.9	10.9
MEAN	11.9	8.8	10.9

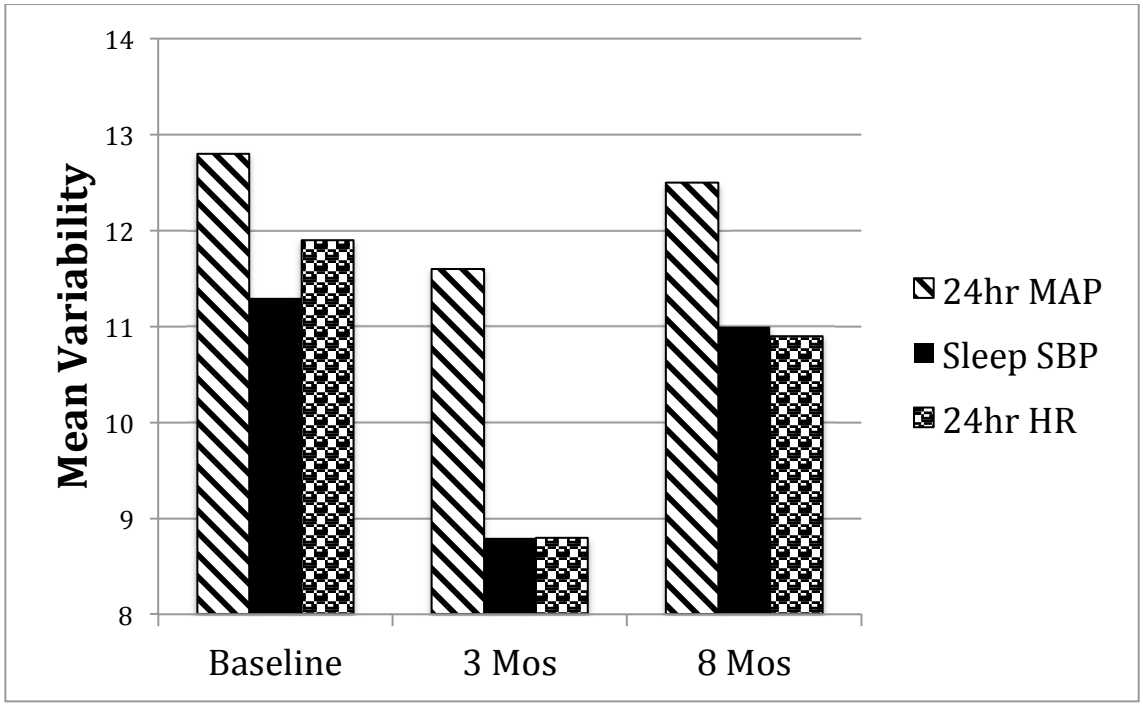

Figure 14. Summary of BP and HR variability at baseline and follow up.

C-Reactive Protein

The blood work was collected for CRP an average of 8 months following surgery. CRP values are not available for 3 of the patients because the lab test was not requested on the physician's orders sheet at time of pre-admission appointment. Figure 15 displays the pre- and post-operative CRP average values for 12 patients.

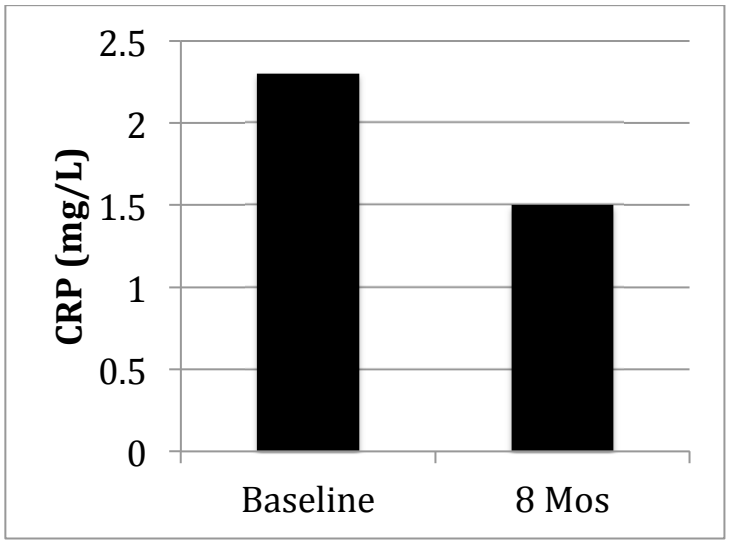

Figure 15. Mean C-reactive protein levels at baseline and 8 months following surgery.

The normal CRP according to the lab is <8mg/L. As mentioned earlier, a CRP > 3mg/L has been demonstrated as a risk factor for cardiovascular disease. In this study, no patients had a CRP > 8mg/L. The mean CRP decreased from 2.3mg/L at baseline to 1.5mg/L at 8 months postoperative. A paired T-test revealed statistical significance ($p = 0.01$). Four patients had a CRP level ≥ 3mg/L at baseline (marked with an asterisk). No patients had levels this high following surgery (Table 15).

Table 15. C-reactive protein for 12 patients at baseline and 8 months following surgery.

Patient	Baseline CRP (mg/L)	8 Month CRP (mg/L)
1	0.35	0.32
2	N/A	N/A
3	3.14*	2.52
4	N/A	N/A
5	N/A	N/A
6	5.09*	2.73
7	1.8	1.08
8	2.11	1.31
9	0.94	0.53
10	0.38	0.24
11	1.5	1.3
12	2.22	2.6
13	3.61*	0.75
14	2.43	1.15
15	3.99*	3
MEAN	2.3	1.5

Although the CRP was found to be more elevated in the patients with severe OSA (Table 5), there was no correlation between CRP and BMI or AHI. As mentioned earlier, the mean CRP for the group of patients with a diagnosis of hypertension was lower than the mean CRP for patients without hypertension (Table 4).

Chapter 5: Discussion

Hypertension and OSA

The majority of the variability in study design between previous studies looking at the effects of treatment of OSA on HTN is the number of hypertensive patients included in the study. The bulk of the studies did not use hypertension as an inclusion criterion. In most studies that showed little or no difference in mean blood pressure, the percentage of patients with hypertension before treatment of OSA was very low.[81,94,95] This study, like many of the CPAP studies discussed above, also did not use presence of hypertension as an inclusion criterion. Unfortunately, this would have limited patient enrollment to an even greater extent.

In this study, 9/15 patients had a diagnosis of hypertension at baseline, so the prevalence of cardiovascular disease in this OSA population is 60%. This is in agreement with the findings in the literature (reports of 50-90% prevalence of CVD in OSA population).

Five of the 9 patients with a diagnosis of hypertension had severe OSA and the other 4 patients had mild-moderate OSA. If more patients had been hypertensive preoperatively, perhaps a greater difference in blood pressure would have been demonstrated postoperatively. Normotensive patients would not be expected to show a dramatic drop in blood pressure following treatment of OSA.

The group of patients diagnosed with hypertension tended to be older; and age is a well-documented risk factor for hypertension. Also of note is that the patients with a

diagnosis of hypertension had more severe sleep apnea than the other patients, despite having similar mean BMIs. These were not significant findings.

Relatively healthy patients with mild OSA might be at low risk for developing hypertension or cardiovascular complications.[114] The Wisconsin Sleep Cohort Study[99] and the Sleep Heart Health Study[196] are two conflicting studies that evaluated the association between obstructive sleep apnea and the risk for incident hypertension. The former showed that the risk of incident hypertension correlated with severity of OSA, while the latter failed to show an association between OSA and the risk of incident hypertension. In these studies, 87% of patients had mild OSA, so moderate or severe OSA was infrequent.

Forty-seven percent of patients in this study suffered from severe OSA. According to CPAP studies, the effect of treatment on blood pressure seems to be more pronounced in severe OSA patients. While these patients showed dramatic improvements in the AHI following surgery, indicating successful treatment of sleep apnea, their blood pressures did not improve to a greater extent than the general study population, as might have been expected.

Studies have demonstrated that the AHI and blood pressure have a positive correlation, and tend to be most highly correlated among patients with a BMI in the normal range. In this study, there was no association found between the severity of the OSA and blood pressure. Perhaps the elevated BMI in this patient population is a contributing factor to the lack of correlation between AHI and blood pressure. Another reason for the lack of correlation between blood pressure and AHI is that the data was not collected at the same time. The baseline blood pressures were often recorded within a few weeks of the surgery, whereas the baseline sleep study was performed early in the

diagnosis and treatment planning phase. The follow up blood pressure recordings and sleep studies were also 1 month apart on average.

One study has suggested that excessive daytime sleepiness could be a marker of pathogenetic mechanism linking OSA and hypertension.[121] In this study there was no correlation between the Epworth sleepiness scale and blood pressure. The ESS significantly improved following surgery. Only one patient remained in the sleepy category following surgery.

Effects of MMA on Blood Pressure

In the entire study population, the average mean systolic and diastolic blood pressures showed minimal change from baseline to 8 months following surgery. The trend for all systolic and diastolic blood pressure parameters was to show more significant improvement at 3 months and then return to near baseline results by 8 months following surgery. The only noteworthy change in blood pressure when considering the average in all 15 patients is the decrease in average mean sleep diastolic blood pressure from the hypertensive range to the normal range. Perhaps MMA surgery has more effect on sleep blood pressure than awake blood pressure.

The obvious assumption is to jump to the conclusion that the blood pressures dropped at 3 months because the BMI dropped at three months. However, the BMI remained relatively constant between 3 and 8 months, while the blood pressure consistently became more elevated. Also, as it has been pointed out, there was no correlation between BMI and blood pressure identified.

One conceivable explanation for the drop in blood pressure at 3 months, which returns to baseline at 8 months, is an increase in activity level of patients following surgery. Most patients felt healthier and had more energy following surgery so it would make sense that they would be more active. Although there was no correlation between awake actigraphy and awake blood pressures, it is obvious from Figure 12 that the average activity level increased from 3 months to 8 months. The average mean sleep actigraphy remained fairly constant throughout the study and a positive correlation was noted between sleep actigraphy and sleep blood pressure at 8 months.

The majority of the CPAP studies were short-term studies showing small but significant improvements in blood pressure. The majority of the studies are less than 3 months in duration. From the results obtained in this study, it is clear that a shorter, 3 month study may have lead us to the conclusion that MMA surgery has a significant effect on reducing blood pressure and cardiovascular risk.

The majority of average mean blood pressures were within the normal range at baseline, which may explain why they did not change much following surgery. When the patients who had mean blood pressures elevated into the hypertensive range were analyzed independently of the patients with normal blood pressures, more significant changes were noted. The biggest drop in blood pressure again was with average mean sleep diastolic pressure. It is established that the majority of the physiologic changes associated with OSA and treatment of OSA occur during sleep. As such, following treatment of OSA, it would sense to see more profound blood pressure changes during sleep. It is unclear why the diastolic pressure seems to be affected more than the systolic pressure.

Effect of MMA on Body Mass Index

In this study, the average BMI decreased from 30.8 to 29.3, which was found to be statistically significant. The mean BMI was in the obese range preoperatively and decreased to the overweight category following surgery. There was one patient in the morbidly obese category preoperatively, and no patients in this category at 8 months. Most of the reduction of BMI happened in the first 3 months following surgery, but this weight loss was more or less maintained at 8 months following surgery.

There are currently no published studies to use as a comparison for this study to evaluate the effect of MMA surgery on BMI in the long term. It has been speculated that the weight loss immediately following surgery will be regained by most patients once they finish their healing period and return to their baseline diet. Perhaps this is not the case.

It is a well-known fact that obesity is a risk factor for hypertension. As such, it is noteworthy that the BMI in the group of patients with a diagnosis of hypertension and the group of patients without that diagnosis was essentially the same.

Effect of MMA on Cardiovascular Variability

A long-term follow up study of over 2000 hypertensive patients showed that those patients with high blood pressure variability had a higher rate of cardiac events. Specifically it was determined that the sleep SBP variability is an independent predictor of cardiac events.[80] Based on that long-term study, it was decided to focus on sleep SBP variability as one of the outcomes for this study. The mean sleep SBP variability showed only minute changes over the study period, however the median variability decreased from 11.6 to 8.9. It is the patients with variabilities above the median that are potentially

at increased risk for cardiovascular events. Neither the mean 24 hour MAP variability nor the mean HR variability showed significant changes during the study period.

The mean percentage of elevated diastolic pressures improved by 2.7 percent from baseline to 8 months. The mean percentage of elevated systolic blood pressures showed a 2.2% increase over the 8 month period. Again we see two trends recurring: the diastolic pressure is improving, whereas the systolic pressure is not, and there is a much greater improvement at 3 months when compared to 8 months.

Effect of MMA on Nocturnal BP Dipping

Lack of blood pressure dipping has been associated with increased risk of hypertensive end organ damage.[84] It was hypothesized that the proportion of dippers would increase following MMA surgery. This is based on the literature that describes OSA patients as having non-dipping blood pressure profiles. The prevalence of non-dippers in this study was 20% at baseline and follow up (3/15 patients). Two of the non-dippers at baseline became dippers at follow up and 2 patients who were dippers at baseline became non-dippers at follow up. One patient remained a non-dipper consistently.

The prevalence of non-dippers in this study significantly deviates from what is reported in the literature. A 2001 study showed a prevalence of 84% non-dippers in a group of 44 patients with moderate to severe OSA. The logical explanation for this finding is that in our study population, the majority of patients had mild-moderate OSA. However, there was only 1 non-dipper in the severe OSA group at baseline, which means that 86% of the severe OSA patients were dippers.

The mean percent drop in nocturnal blood pressure was > 10% at during all intervals. The percent MAP dipping showed improvements at 3 months and returned to baseline at 8 months.

Effect of MMA on Systemic Inflammation

Systemic inflammation is increasingly becoming linked to atherosclerosis, coronary artery disease, and cerebrovascular disease.[148] Inflammatory mediators have been identified as a risk factor for the morbidity and mortality associated with these chronic systemic conditions. In this study, CRP was chosen for analysis because it is an easily testable, sensitive biomarker for systemic inflammation. A complicating issue is that CRP has been demonstrated to vary with BMI. [197] Visceral obesity as well as hypoxemic events from OSA can contribute to chronic low grade inflammation and result in an elevated CRP.[158] In this study, there was no association found between BMI and CRP either at baseline or 8 months postoperatively. Although there was no significant correlation between CRP and AHI, the CRP was slightly elevated in the patients with severe OSA compared to those with mild or moderate OSA. This was not statistically significant.

There was no correlation between CRP and blood pressure. Interestingly, the CRP in the group of patients with a preoperative diagnosis of hypertension was only 1.76mg/L, which is nearly half that found in the patients without a diagnosis of hypertension (3.05mg/L). Although the effect of CPAP on CRP is controversial in the literature, one plausible explanation for the lower CRP in the hypertension group is that 3 of these patients were using CPAP at the time of the baseline blood work. The use of

CPAP by 3 patients during the time of the baseline blood work may have lead to an underestimation in the mean baseline CRP.

On average, there was a small but statistically significant reduction in CRP from 2.3mg/L to 1.5mg/L ($p = 0.01$). If we consider <8mg/L to be the normal range, all of the baseline CRPs were in the normal range. We wouldn't expect a normal lab value to show as much improvement as an elevated value would.

A CRP > 3mg/L has been linked with increased cardiovascular risk.[163] Four patients had a baseline CRP > 3mg/L preoperatively. All 4 of these patients were mildly-moderately obese based on their BMIs. The BMI classification postoperatively did not change in any of these patients. In fact, one of these patients actually gained weight following surgery. Despite this, no patients had an 8 month CRP > 3mg/L. This means there is potentially less risk of adverse cardiovascular outcomes in these patients at 8 months following surgery. It is also more likely that the CRP is related to sleep apnea more so than it is to obesity in these patients.

Limitations of the Study

Patient Enrollment

The 15 patients completing this study made up only 29% of total number of possible patients. Most of the patients that decided not to partake in the study chose not to because of the inconvenience associated with wearing a blood pressure cuff for 24 hours. Three other patients enrolled in the study initially but then dropped out because it was inconvenient or they found the cuff uncomfortable. Five patients were dropped from the study because of cuff malfunction during the baseline data collection, or software malfunction. These numbers are similar to Becker's study in 2003 in which only 53% of

the patients who initially enrolled completed the study because of dropouts from equipment malfunction or unwillingness to continue participation.

Because of the low enrollment rate and the high dropout rate, this study is underpowered to detect small changes in blood pressure. A post hoc power analysis shows this study to have 68% power to find a change in blood pressure of 2 mmHg to be significant.

CPAP Use

Three patients were using CPAP up until the date of surgery, including the time during which the baseline data was collected. The effect of CPAP therapy for OSA on cardiovascular outcomes is still unknown because of lack of a long-term randomized trial. Withholding CPAP treatment from patients with OSA is unethical because it could worsen the symptoms of OSA putting the patients health at risk as well as increasing the likelihood of motor vehicle accidents.[18] If these patients were, in fact, compliant with their CPAP and their OSA was being treated sufficiently, we would not expect the surgical correction of OSA to result in any significant changes in blood pressure. This could be leading to an underestimation of changes in blood pressure following MMA surgery for patients with OSA.

Antihypertensive Medications

Five patients were taking antihypertensive medications prior to enrolling in the study. Again, for ethical reasons, we could not ask patients to discontinue or change their antihypertensive regimen for purposes of the study. One patient had to stop taking his antihypertensive medications prior to the 3 month postoperative data collection because he was hypotensive and was suffering from occasional syncopal episodes. Once his

family physician discontinued his antihypertensives, the episodes resolved. A second patient, who was also on CPAP preoperatively (patient 14), stopped his blood pressure medications prior to follow up as well. This patient had been monitoring his blood pressure at home for years, and when he found his blood pressure to be significantly better following surgery, he stopped his medications. In both of these patients, the improvement in blood pressure was minimized because the antihypertensives were lowering their true preoperative blood pressure. Patient 14 showed some mild improvements in blood pressure from baseline to 8 months following surgery, even though he was on CPAP and taking antihypertensives before surgery. We would expect this improvement in blood pressure to be much more significant if he was not using CPAP and taking medications before surgery.

BMI Measurements

On occasion, the patients who did not live locally were not able to return to the clinic to collect the blood pressure monitor and have their weight documented. Under these circumstances, patients were asked to weigh themselves on their scale at home with their shoes off, wearing light-weight clothing as they would have worn to their appointments. In these patients, there may have been some inherent differences in the scales leading to some minor inaccuracies in BMI calculations.

Data Collection Days

Patients were advised to use the ABPM on a "normal day", while doing "normal daily activities". This was an attempt to make the BP recordings as true as possible to the patients usual BP. For social reasons however, many patients preferred to wear the blood pressure monitor on a day when they were not at work, or when they did not have any

important or stressful events scheduled. By choosing to wear the cuff on a day where they may be more inactive, the blood pressures recorded may not be a true representation of the patients typical blood pressures. Caffeine intake and stress levels are two variables known to be associated with fluctuations in blood pressure. These variables were not taken into account during this study.

Data Loss

Several problems are associated with ambulatory devices. These devices are more "portable" than they are "ambulatory". They are not able to accurately record blood pressure during movement of the arm. For a blood pressure reading, the patient must relax the arm at the side and keep it relatively still during cuff inflation. Any external vibrations may result in an inaccurate reading.[198] Some data loss in this study was inevitable due to the subjects' inability to cease activity and hold the arm still, or because of kinked tubing or equipment malfunction. There was significant data loss during the 8 month data collection from patient 14. This resulted in only 10 accurate blood pressure readings throughout the 24 hour period. Because of the limited data, the mean blood pressures may not be reflective of the true mean blood pressures throughout the day/night.

Interference of BP Cuff with Sleep

The ABPM may interfere with sleep and cause higher activity during the time in bed. Arousal from sleep due to the cuff inflation may have resulted in falsely elevated sleep blood pressures. The non-dippers in the study may have suffered from a higher degree of sleep interference than the dippers. In fact several patients wrote in their diary

that the cuff inflation during the night caused them to wake up and interfered with sleep quality.

The disturbance associated with cuff inflation during sleep could also result in an elevated actigraphy value. In the study that showed the largest effect of CPAP on blood pressure, a portable, battery-operated instrument with 2 finger cuffs was used to monitor blood pressure.[6] The advantage of this system is that it does not tend to arouse the patient from sleep.

Polysomnography

The scoring of the in hospital overnight sleep studies was performed in three different sleep centers throughout the Atlantic Provinces. Similar standard scoring criteria were used, however, there are likely to be inherent differences in the method of interpretation of raw data by sleep technicians and physicians. Six patients had home sleep studies, which have been shown to be less accurate for diagnosis of OSA. All patients were subjected to the same type of study postoperatively as they were postoperatively so that the results could be compared more accurately. It would have been more accurate to have all patients undergo an in hospital sleep study before and after surgery, however, this was not feasible.

Chapter 6: Conclusion

Blood pressure involves complex physiology in the healthy patient, and is cofounded further by comorbidities in the obese, sleep apnea population. As obesity, OSA, and hypertension are on the rise, this topic becomes even more crucial. This study is currently underpowered. While trends can be identified from the small sample of data, no definitive conclusions can be reached based solely on this prospective observational study.

The prevalence of hypertension in this OSA population was 60%. It would seem that patients with hypertension may have more severe OSA and patients with severe OSA may have higher blood pressure, however a cause and effect relationship cannot be more clearly defined.

There was no significant treatment effect noted with respect to blood pressure following MMA surgery in these OSA patients. The biggest positive change seems to be with diastolic pressures, particularly during sleep. More dramatic changes were noted when the patients with elevated baseline blood pressures were examined separately.

There were no identifiable dose-response relationships among EDS, AHI, and blood pressure. Maxillomandibular advancement surgery had a sustained positive effect on BMI and reduced the incidence and severity of obesity in this small population at 8 months following surgery. This change was statistically significant even in this small study. Maxillomandibular advancement surgery appeared to have little to no effect on blood pressure variability and blood pressure dipping. The prevalence of dippers was not increased following surgery.

There was a treatment effect noted with regards to C-reactive protein levels. CRP decreased significantly between baseline and 8 months follow up. More importantly, 4 patients had a reduction in their CRP at follow up, which puts them in a lower cardiovascular risk stratification (CRP < 3mg/L) than at baseline. CRP had no significant correlation with blood pressure, BMI, or AHI.

Given the prevalence of OSA and its adverse medical consequences, more studies to determine the effect of maxillomandibular advancement on blood pressure are warranted. This study will continue with the same protocol until necessary enrollment is reached to obtain sufficient power. With a larger study population, a more appropriately sized subgroup analysis of patients with OSA and hypertension can be performed. Only then will we see the true effect of maxillomandibular advancement surgery on blood pressure in patients with OSA.

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Appendix 1: BMI

Patient	BMI Baseline	BMI 3 months	BMI 8 months
1	25.2	24.4	24.5
2	32.4	31.7	31.7
3	34.5	33.7	34.5
4	28.6	25.7	25.7
5	43.2	40.4	35.5
6	29	27.1	27.8
7	32.4	30.3	30.3
8	23.2	23.1	23.2
9	35.4	32.6	33.8
10	24.8	22.8	23.7
11	37.8	37.4	36.8
12	26.9	25.2	26.3
13	31.9	N/A	32.9
14	27.7	25.4	25.9
15	28.9	26.7	27.4
MEAN	**30.8**	**29.0**	**29.3**

Appendix 2: Systolic Blood Pressure

Patient	Mean 24hr SBPpreop	Mean 24hr SBP3mos	Mean 24hr SBP8mos	Mean Awake SBPpreop	Mean Awake SBP3mos	Mean Awake SBP6mos	Mean Sleep SBPpreop	Mean Sleep SBP3mos	Mean Sleep SBP6mos
1	118.9	115.6	122.1	122.6	120.4	127.1	104.5	97.8	105.2
2	113.5	113.7	117.3	117.8	118.1	119.3	100	101.7	105
3	122.9	114.5	116.5	126.6	116.5	121.6	113.1	106.9	99.6
4	128.8	126.4	129.9	132.1	130.4	136	120.3	116	104.1
5	109.2	99.6	101	114	102.6	107.9	98.5	92.4	91.4
6	110.1	118	112	109.5	119.7	111.8	112.3	112.5	112.8
7	126.7	115.6	121.7	130.4	117.3	123	109	107.5	116.3
8	132.2	130.6	126.4	137.7	139.4	131	115.1	117.4	115
9	120	114.3	124.5	121.9	121.8	127.3	113.6	97.3	113.5
10	112.8	119.6	118.9	118	125	129	101.2	103.5	108.7
11	109.8	109	122.2	112.1	112.9	125.9	103.1	97.1	108.8
12	124.5	125.5	129.8	133	128.1	133.8	108.8	116	123.4
13	123	N/A	118.9	126.2	N/A	122.1	110.9	N/A	108.4
14	138	133	135.2	140	137.6	130.8	129.8	123.3	141.8
15	117.6	111.8	121.1	117.3	111	124.3	118.1	115.7	111.9
MEAN	**120.5**	**117.7**	**121.2**	**123.9**	**121.5**	**124.7**	**110.6**	**107.5**	**111.1**

Appendix 3: Diastolic Blood Pressure

	Mean 24hr DBPpreop	Mean 24hr DBP3mos	Mean 24hr DBP6mos	Mean Awake DBPpreop	Mean Awake DBP3mos	Mean Awake DBP6mos	Mean Sleep DBPpreop	Mean Sleep DBP3mos	MeanSleep DBP6mos
1	78.4	77.8	82.7	81.1	81.5	86.1	68.2	64.3	71.6
2	75.1	74.9	77.1	77.6	77.9	78.5	67.4	66.5	68.4
3	79	74.4	77.5	81.9	75.6	80.8	71.5	69.6	66.4
4	84.1	88.2	88.1	86.7	92	92.8	77.5	78.4	67.9
5	69.9	64.8	66.8	74.1	67.4	71.6	60.7	58.7	60.1
6	73.3	76.5	76.7	72.7	77.6	76.5	75.5	72.7	77.5
7	82.8	77.1	79.1	84.6	77.8	81.2	74	73.8	70.7
8	80.9	78.3	73.4	83.5	84.1	75.3	72.7	69.8	68.8
9	72.6	76.7	72.9	71.8	81.4	74.6	75.2	65.9	66.3
10	76.4	72.9	71.3	79.3	76.5	75.5	70	62.1	67.1
11	72.8	75.3	74.6	75	79.2	76.9	66.5	63.2	66.3
12	78.6	79.7	83.5	84.9	81.2	85.4	67.2	73.9	80.3
13	81	N/A	77.1	83.5	N/A	80.9	71.8	N/A	64.9
14	78.8	72	74.1	81.3	75.6	74	72.1	64.5	74.3
15	68.5	66.9	77.5	68.7	66.9	79.2	68.3	67.2	72.5
MEAN	**76.8**	**75.4**	**76.8**	**79.1**	**78.2**	**79.3**	**70.6**	**67.9**	**69.5**

Appendix 4: Actigraphy

	awakeACT preop	awakeACT3 mos	awakeACT 8mos	sleepACT preop	sleepACT 3mos	sleepACT 8mos
1	0.22	0.22	0.24	0.06	0.04	0.08
2	0.83	0.72	1.41	0.04	0.15	0.06
3	0.76	0.53	1	0.09	0.08	0.07
4	0.67	0.98	0.83	0.08	0.06	0.06
5	0.32	0.25	0.6	0.1	0.1	0.07
6	0.23	0.47	0.36	0.12	0.06	0.1
7	0.53	0.81	0.8	0.11	0.27	0.07
8	N/A	N/A	0.71	N/A	N/A	0.06
9	0.69	0.57	0.58	0.09	0.06	0.07
10	0.76	0.97	0.94	0.06	0.12	0.05
11	0.71	0.44	0.63	0.1	0.06	0.1
12	1.14	0.83	1.05	0.06	0.07	0.13
13	0.35	N/A	0.51	0.07	N/A	0.05
14	0.56	0.48	0.85	0.11	0.09	0.28
15	0.56	0.5	0.4	0.1	0.08	0.16
MEAN	**0.60**	**0.60**	**0.73**	**0.09**	**0.10**	**0.09**

Appendix 5: Actigraphy Correlations

Sleep Actigraphy Correlations (8 Months)

		sleepACT 8mos	Mean Sleep SBP 8mos	Mean Sleep DBP 8mos
sleepACT 8mos	Pearson Correlation	1	.776**	.524*
	Sig. (2-tailed)		.001	.045
	N	15	15	15
Mean Sleep SBP 8mos	Pearson Correlation	.776**	1	.667**
	Sig. (2-tailed)	.001		.007
	N	15	15	15
Mean Sleep DBP 8mos	Pearson Correlation	.524*	.667**	1
	Sig. (2-tailed)	.045	.007	
	N	15	15	15

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).