Association of Pulse Transit Time in Pregnancy with Obstructive Sleep Apnea Status, Blood Pressure, and Gestational Hypertensive Disorders

By

Brittany Noelle Link

Sc.B., Brown University, 2015

Thesis
Submitted in partial fulfillment of the requirements for the Degree of Master of Science in the Department of Molecular Pharmacology, Physiology and Biotechnology, and the Center of Biomedical Engineering at Brown University

PROVIDENCE, RHODE ISLAND

May 2017

AUTHORIZATION TO LEND AND REPRODUCE THESIS

As the sole author of this thesis, I authorize Brown University to lend it to other institutions or individuals for the purpose of scholarly research.

Date: _____ Signature:_____
Brittany Link, Author

I further authorize Brown University to reproduce this thesis by photocopying or other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

Date: _____ Signature:_____
Brittany Link, Author

This thesis by Brittany Noelle Link is accepted in its present form by the Department of Molecular Pharmacology, Physiology, and Biotechnology as satisfying the thesis requirements for the degree of Master of Science

Date: _____ Signature: _____

Dr. Ghada Bourjeily, Advisor

Date: _____ Signature: _____

Dr. Margaret Bublitz, Reader

Date: _____ Signature: _____

Dr. Jeffrey Morgan, Reader

Approved by the Graduate Council

Date: _____ Signature: _____

Dr. Andrew Campbell, Dean of the Graduate School

Vita

Brittany Noelle Link was born on December 19, 1992, to Charles and Diane Link in a suburb of Cleveland, Ohio. Brittany attended Brown University for her undergraduate studies. As an undergraduate student, she studied abroad on a multi-country program that traveled to Vietnam, South Africa, and Brazil, studying public health in a comparative fashion. Additionally, she took part in a research project studying obstructive sleep apnea in patients with end-stage renal disease, which was presented at the American Thoracic Society's 2016 International Conference. Brittany graduated with her Bachelor of Science degree in Biology and was inducted into the Sigma Xi Scientific Research Honor Society in May 2015.

In Fall 2016, Brittany began her graduate studies at Brown University in the Master of Science program in Biotechnology. She is currently studying the use of pulse transit time as a diagnostic and potentially predictive measurement tool for the study of obstructive sleep apnea in pregnant women. Brittany will present this research project at the American Thoracic Society's 2017 International Conference in Washington, D.C.

Upon graduation, Brittany will be entering the University of Pennsylvania School of Dental Medicine.

Acknowledgements

First, I would like to acknowledge my parents, Charles and Diane Link, for providing me with endless support throughout my academic endeavors.

I would like to thank my thesis advisor, Dr. Ghada Bourjeily. Dr. Bourjeily provided me with the opportunity to begin sleep apnea research as an undergraduate student, and to return as a graduate student to undertake my thesis research project. I am very appreciative of Dr. Bourjeily's mentorship; I have learned so much under her guidance, and I am very grateful to have had the opportunity to work with her.

I would also like to express my appreciation to Dr. Margaret Bublitz, who has provided her support and expertise throughout my research project and the writing of my thesis, and has also helped me to master the statistical analysis aspects of my project.

I would also like to thank Dr. Jeffrey Morgan, for serving as my second reader and for providing advice and support throughout my thesis-writing process and my time as a graduate student.

I would also like to express gratitude to everyone who I have worked with at the Lifespan Women's Medicine Collaborative – Tamara Sequiera, Eva Adodoadji, Zoe Livingston, Annaly Aldana, Beth Hott, Sue Martin, and Patrizia Curran – for providing a supportive environment, lending a helping hand when needed, and helping to make my research project such an enjoyable experience.

Table of Contents

List of Figures

List of Tables

Background

Respiratory Mechanics and Sleep Disordered Breathing

"Sleep-disordered breathing" is a term that encompasses a broad spectrum of conditions, all of which can affect sleep, a central aspect of a person's life. For effective respiration during sleep, a person must have an unobstructed airway so that breathing allows sufficient oxygen to be delivered into the lungs.

During inhalation, the diaphragm contacts and moves downward, increasing the intrathoracic space in the chest cavity. This allows the rib cage and the lungs to expand and also creates negative pressure in the space via Boyle's Law. The negative intrathoracic pressure drives inspiration because it draws the breath of fresh air into the lungs. When the diaphragm relaxes, the intrathoracic space decreases, which causes areas of higher pressure in the lungs. This facilitates air's exhalation from the body, as it moves from the lungs, an area of higher pressure, into the atmosphere, which has comparatively lower pressure.

When a breath of air is taken, it follows a specific pathway by which it travels into the lungs. First, air is inhaled through the nose or the mouth, and then travels through either the nasopharyx or the oropharynx into the laryngopharynx. From the laryngopharynx, the air travels down the glottis, and through the trachea, which splits into the right and left lungs. Inside the lungs, the breath of oxygenated air travels through multiple bronchi, which then branch into the bronchioles. The bronchioles terminate in clusters of alveoli, which are small air sacs with adjacent capillaries, which together allow for gas exchange. Via diffusion, the oxygen is unloaded into the blood stream through the capillaries adjacent to the alveoli, and the carbon dioxide diffuses from the

blood stream into the alveoli. During exhalation, carbon dioxide (the by-product of cellular respiration) follows the reverse of the same pathway to leave the body.

The process of breathing is essential for the human body to function. Oxygen is a requirement for cellular aerobic respiration, by which cells convert sugar to energy for the body, and carbon dioxide is produced as a byproduct. Red blood cells carry oxygen through the bloodstream to where it is needed.

Sleep-Disordered Breathing Spectrum

In instances of sleep-disordered breathing, the body struggles with a lack of adequate oxygen delivery during sleep. In the United States, 9% of women and 24% of men have sleep-disordered breathing (1). It has been estimated that 82% of men and 93% of women with sleep-disordered breathing are not diagnosed (2).

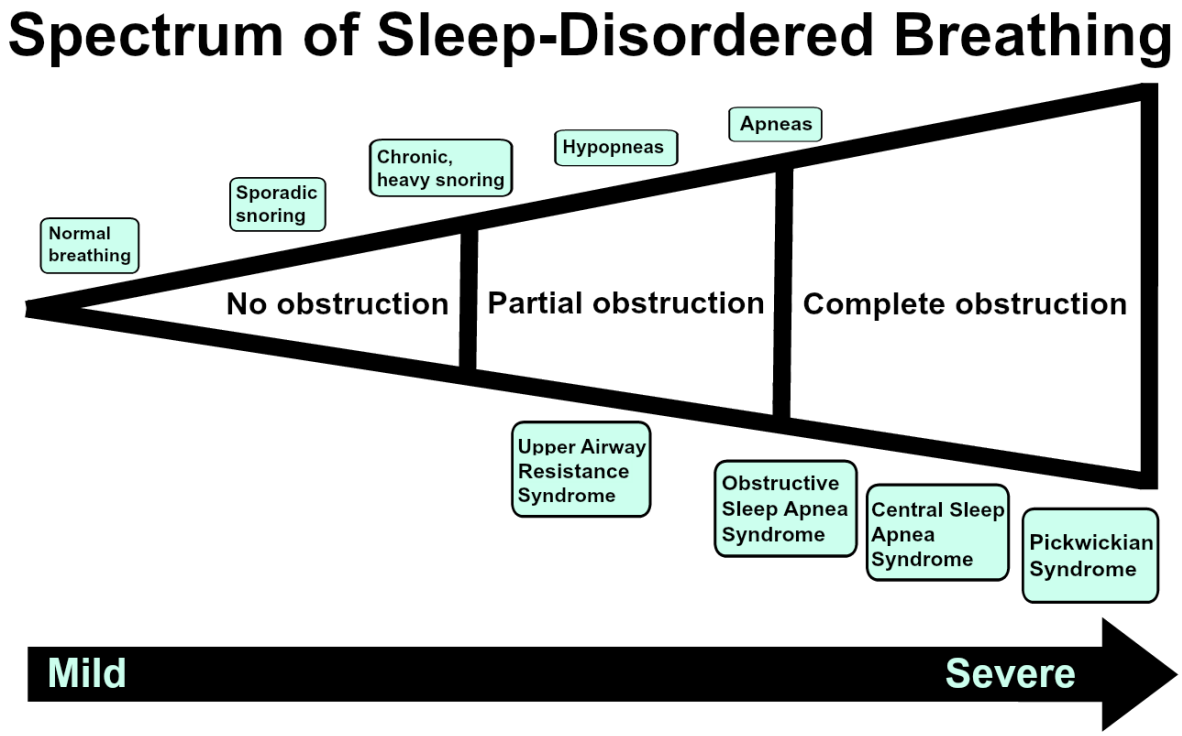


Figure 1: Spectrum of Sleep-Disordered Breathing

As seen in Figure 1, there are a wide range of issues on the sleep-disordered breathing spectrum. At the mild end of the spectrum, beyond normal breathing, is sporadic snoring. Snoring is a noise that occurs as a result of irregular airflow during sleep (Figure 2). The airflow can be irregular through the upper airway for a variety of reasons. There may be a nasal passageway obstruction. The jaw may be misaligned due to muscular tension. The upper airway may be narrowed due to an anatomic abnormality such as a large tongue, tonsils, or uvula; swollen nasal turbinates or nasal passages; compression of the airway by adjacent structures; or the existence of loose or relaxed tissue, which can be caused by aging, excess neck fat, or neuromuscular conditions that cause throat muscle weakness and excessive relaxation. The snoring sound is generated from the partially obstructed airway's loose tissue vibrations. These vibrations cause the typical snoring noise, which can range from soft to loud.

By nature, it is difficult to quantify the percentage of the population that snores. In the United States, 28% of women and 44% of men between the ages of 30 and 60 admit to regular snoring (3). Possible explanations for the discrepancy between genders include the fact that women tend to underreport snoring, and the tendency for men to gain weight in their abdomen, upper torso, and neck, while women have a tendency to gain weight in their lower body, in their hips and thighs (4).

Intermittent snoring is considered normal and typically does not have any negative effects. Primary snoring is snoring that occurs on a regular basis, but it is not fully obstructive and is not so severe that it is associated with an accompanying syndrome, such as Upper Airway Resistance Syndrome or Obstructive Sleep Apnea Syndrome. Some signs that snoring has become severe include increased snoring volume

and excessive daytime sleepiness, as normal sleep architecture has been disrupted and sleep has become more fragmented (5). Habitual snoring has also been found to increase a person's risk of developing hypertension, regardless of age or body mass index (6) (7).

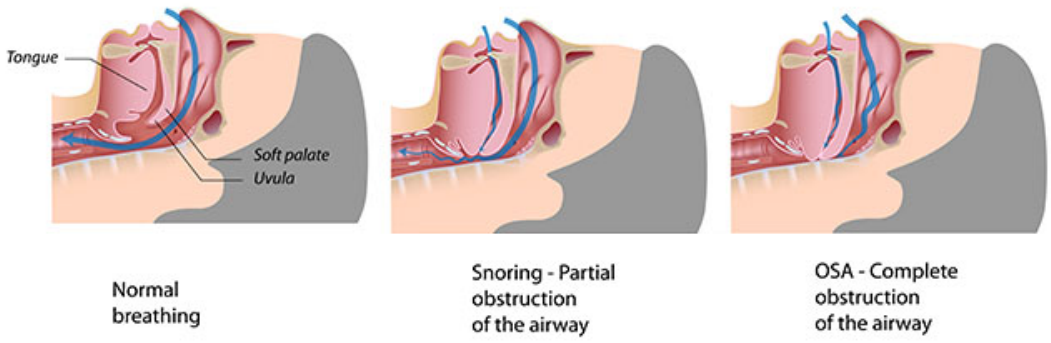


Figure 2: Mechanics of Airway Obstruction (8)

Next on the spectrum of sleep-disordered breathing is Upper Airway Resistance Syndrome, which is considered a severe form of snoring. In Upper Airway Resistance Syndrome, the airway is severely narrowed, requiring the chest muscles and diaphragm to exert extra effort to bring in breaths of air (9). The amount of airflow entering the body is similar to the amount allowed during primary snoring, but there is an increase in physical effort exerted to bring in each breath (10). When Upper Airway Resistance Syndrome patients enter periods of rapid eye movement (REM) sleep, their throat muscles relax further, requiring even more effort for each breath (11) (12). The greater the degree of narrowing, the lower the airflow, and the greater the inspiratory effort the upper airway muscles must exert to overcome the narrowing. At times, transient "snoring arousals" occur due to the large physical strain exerted by the body in an attempt to bring air into the lungs (13). It is important to note that these arousals do not occur as a result of dipping oxygen levels within the blood, because those levels remain

constant during Upper Airway Resistance Syndrome. The arousals occur only due to the excess effort the body is exerting to inhale. After the person has an arousal from sleep, they take a few deep breaths, and then return to sleep. This process disrupts their ability to have periods of REM sleep, which is critical for preventing daytime sleepiness. Consequently, Upper Airway Resistance Syndrome patients characteristically experience frequent awakenings and excessive daytime sleepiness (14).

While Upper Airway Resistance Syndrome requires extra physical effort to take breaths, the oxygen level in the bloodstream remains relatively stable. This differs for hypopnea and apnea events, which are also instances of reduced airflow, but usually result in lowered oxygen levels in the bloodstream. Therefore, patients with Upper Airway Resistance Syndrome would experience very few hypopnea and apnea events throughout a night of sleep.

Both hypopneas and apneas involve narrowed airways and increased effort exerted to take breaths, due to obstruction of the upper airway or extreme relaxation of throat muscles/tissues. Hypopneas are the less severe of the two because they are only partial blockages of the airway – they typically involve a 30-50% reduction in airflow amplitude for at least ten seconds, and either >3-4% oxygen desaturation or an arousal (15). Apneas, on the other hand, are defined as a ≥90% reduction in airflow for a minimum of ten seconds (15). Both apneas and hypopneas can cause arousals from sleep. Typically, apneas and hypopneas are also associated with an electroencephalogram arousal, as the brain responds to the lack of oxygen in the body with excessive inspiratory effort (9). Apneas and hypopneas are quantified using the "Apnea-Hypopnea Index," or the number of events that occur per hour of sleep. The

Apnea-Hypopnea Index is calculated by dividing the total number of apneas and hypopneas by total sleep time.

Obstructive sleep apnea is a condition that involves both hypopneas and apneas. The most common definition of Obstructive Sleep Apnea Syndrome is having an Apnea-Hypopnea Index of ≥5 (16). A key aspect of obstructive sleep apnea is that the sleep events that occur at night are associated with the occurrence of negative cardiovascular effects within the body that persist into the daytime (17). Obstructive sleep apnea is a chronic condition but may be exacerbated in instances of weight gain or pregnancy.

Next on the spectrum of sleep disordered breathing is Central Sleep Apnea. Central Sleep Apnea is associated with decreased airflow accompanied with a lack of breathing effort. However, the lack of inspiration is not necessarily a result of a physical airway obstruction. In Central Sleep Apnea, there are intermittent losses in respiratory drive during sleep, in which the brain does not send the proper signals to the muscles that would signal the body to breathe. Thus, the body's muscles do not make an effort to inhale air. Eventually, the lack of inspiration results in sympathetic activation and arousal from sleep. When the body has regained consciousness, inhalation resumes, and the blood stream becomes re-oxygenated. Central Sleep Apnea can be caused by a variety of factors, including severe obesity, heart failure, brainstem damage, or as a side effect of certain medications (18) (19).

On the most severe end of the sleep-disordered breathing spectrum is Pickwickian Syndrome. Pickwickian Syndrome is characterized by extreme hypoventilation during sleep, involving progressively slower and shallower breaths. Breathing motions are restricted as a result of excess fat and quickly-fatigued chest breathing muscles (20). The

hypoventilation leads to hypercapnia, a state of increased pCO_2 and lowered pO_2 in the bloodstream (21). Untreated Pickwickian Syndrome can lead to severe consequences, and it is associated with a high morbidity and mortality rate (22).

Overall, there are a wide range of issues of varying severity that are on the sleep-disordered breathing spectrum. This research project will be specifically focusing on obstructive sleep apnea.

Obstructive Sleep Apnea Epidemiology

Obstructive sleep apnea is very prevalent in the United States of America. It has been estimated that 33.9% of Americans between the ages of 30 and 70 years old have obstructive sleep apnea (23). It has also been found that men are more likely to have obstructive sleep apnea and are also more likely to be diagnosed than women. Further, 9% of men and 4% of women qualified as having moderate sleep apnea with an Apnea-Hypopnea Index ≥15 (3). Over 12 million people have undiagnosed obstructive sleep apnea (24). In one study, 93% of women and 82% of men that had moderate-severe sleep apnea syndrome had not been diagnosed (25).

A study found that a 10% body weight increase over a period of four years results in a six-fold increased risk for the development of obstructive sleep apnea (26). Other risk factors for obstructive sleep apnea include smoking, male gender, hypertension, and genetic predisposition, independent of obesity (3) (27) (28) (29) (30). Additionally, it is thought that the obesity epidemic and aging population in the United States has contributed to an increase in the prevalence of obstructive sleep apnea over the last twenty years, and it is expected to rise further in the future (23) (31).

Systemic Effects of Obstructive Sleep Apnea

Although obstructive sleep apnea is commonly thought of as a respiratory condition, it has systemic effects. When air is prevented from entering the body through the airway, it causes a subsequent bodily response that involves a cascade of events to attempt to re-oxygenate the blood. Initially, when there is an occurrence of decreased airflow entering the body, hypoxemia and hypercapnia in the bloodstream result. While inspiratory effort is typically accompanied by a slight negative pleural pressure swing, in instances of obstructive sleep apnea, the blockage of air inhalation results in large negative pleural pressure swings. When subsequent arousal and gasping for air occurs, the bloodstream is rapidly re-oxygenated.

Heart rate and blood pressure vary throughout apnea events due to sympathetic nervous system alterations (32). During the initial part of an apnea event, the heart rate decreases as the Müllerian Maneuver is performed (33). When the oxygen content of the blood remains low for a prolonged period of time due to lack of inspiration, the sympathetic nervous system becomes activated, causing arterial vasoconstriction, increased blood pressure and heart rate, and frequently culminates in sleep arousal (32) (34) (35).

As sleep is typically associated with parasympathetic system dominance, the repetitive intermittent episodes of hypoxemia and re-oxygenation associated with obstructive sleep apnea contribute to excessive daytime sleepiness and poor neurocognitive performance via sleep disruption, a lack of REM sleep, and persistent sympathetic activation (3) (36). Additionally, the presence of obstructive sleep apnea, especially when combined with hypertension, prevents the typical slight blood pressure drop during sleep due to the persistent sympathetic activation (37) (38) (39). The

absence of this blood pressure drop is associated with increased sleep fragmentation (39). Other studies attribute the daytime sleepiness observed in obstructive sleep apnea patients to the repetitive electroencephalogram arousals that correspond with apneic events (9). Sleep deprivation has also been associated with an increase in sympathetic tone, which can contribute to the development of cardiovascular disease (40).

The intermittent episodes of hypoxemia in obstructive sleep apnea also contribute to endothelial dysfunction, in which the vasculature is unable to maintain homeostasis (41). This occurs because the endothelium becomes unable to synthesize nitric oxide appropriately. Nitric oxide is necessary for growth and repair, and for allowing the vasculature to change back and forth from a restricted to a relaxed state (42). Effective obstructive sleep apnea treatment has been found to reverse endothelial dysfunction (41) (43).

High Apnea-Hypopnea Indices have also been linked with overall lowered heart rate variability (44). Heart rate variability is associated with autonomic function of the heart. During breathing, a phenomenon called "respiratory sinus arrhythmia" occurs, in which the heart rate varies consistently with each breath, increasing slightly during inhalation and decreasing slightly during exhalation (45). Due to the sympathetic stimulation associated with obstructive sleep apnea events, the heart rate is persistently increased, causing a decrease in the typical variability seen in normal breathing (46). Immediately after an apnea event, heart rate variability is especially lowered in conjunction with an increased heart rate (47). A lowered heart rate variability is linked with higher associated cardiovascular risk factors (48).

It is thought that the persistent hypoxemic stress present in obstructive sleep apnea patients may cause the release of endogenous vasoactive substances, or substances able to affect heart rate and/or blood pressure (49). They also may potentially contribute to the development of hypertension in obstructive sleep apnea patients due to persistent vasoconstriction (49).

Obstructive sleep apnea is also associated with a mild inflammatory state due to the oxidative stress from respiratory events and a lack of adequate sleep (50) (51). Pro-inflammatory cytokines become activated as part of the body's inflammatory response to the repetitive instances of hypoxemia (50) (52). Over time, prolonged inflammation, persistent sympathetic activation, and chronic vasoconstriction can cause endothelial dysfunction, which can contribute to future development of cardiovascular diseases such as hypertension, atherosclerosis, and stroke (51) (53).

Insulin resistance has also been independently associated with obstructive sleep apnea (54). It has been previously established that obesity is a primary determinant for development of insulin resistance. However, even when controlling for obesity, a study found that a patient's Apnea-Hypopnea Index and minimum oxygen saturation levels were significant determinants of their fasting insulin levels and HOMA-IR scores (Homeostatic model assessment for Insulin Resistance) (54). Multiple mechanisms may be responsible for this phenomenon, including an increase in catecholamine production as a result of persistent sympathetic activation, an increase in cortisol as a result of hypothalamic-pituitary-adrenal axis shifts, an increase in the production of reactive oxygen species as a result of oxidative stress, an increase in interleukin-6 and tumor

necrosis factor-α as a result of inflammation pathway activation, and an increase in leptin and decrease in adiponectin as a result of changes in adipokines (55).

Obstructive sleep apnea has also been found to cause greater platelet activation, increased plasma fibrinogen levels, and erythrocyte adhesiveness and aggregation (56) (57) (58). The combination of these factors can predispose obstructive sleep apnea patients to develop thrombosis (59).

Obstructive Sleep Apnea and the Cardiovascular System

Obstructive sleep apnea patients experience a large amount of negative intrathoracic pressure within the chest cavity, which creates large transmural pressure gradients across the ventricles, atria, and aorta (60) (61). These large transmural pressure gradients can have harmful effects on the functionality of the heart, including an increased afterload, systolic and diastolic dysfunction, excessive venous return to the right ventricle, left and right ventricular hypertrophy, and an increase in mass of the atria (62) (63).

While there is typically a slight decrease in blood pressure during inhalation and a slight increase in blood pressure upon exhalation, the large amount of negative intrathoracic pressure within the chest cavity during apnea events can cause "pulsus paradoxus," an excessive decrease in systolic blood pressure during inhalation and an overcompensation of raised systolic blood pressure upon arousal and gasping for air (64). The wide amplitude of blood pressure changes that repeatedly occur throughout the night in obstructive sleep apnea patients can contribute to the development of hypertension (65).

Overall, obstructive sleep apnea causes a wide variety of pathological effects, including negative intrathoracic pressure swings, persistent sympathetic nervous system stimulation, daytime sleepiness, lowered heart rate variability, chronic vasoconstriction, atrial fibrillation, inflammation, endothelial dysfunction, insulin resistance, thrombosis, and left ventricular dysfunction, which can contribute to the development of cardiovascular disease (26) (66) (67) (68) (69). A large number of studies have made the association between sleep-disordered breathing and cardiovascular disease (69) (70) (71). However, it has not yet been established whether obstructive sleep apnea independently causes cardiovascular disease. Regardless, as cardiovascular disease can have serious consequences, it is very important to address and treat obstructive sleep apnea in patients.

Hypertension frequently exists as a comorbidity to obstructive sleep apnea, and is considered a strong risk factor for the development of further cardiovascular disease. About 50% of obstructive sleep apnea patients have arterial hypertension, and 30% of all hypertensive patients also have obstructive sleep apnea syndrome (26). The severity of a patient's sleep apnea is correlated with the severity of their hypertension; specifically, their systolic, diastolic, and mean blood pressure values (72). Typically, a person's blood pressure decreases at night during sleep (39). However, many obstructive sleep apnea patients, especially those that also have hypertension, do not experience this decrease; this places them at increased risk for developing cardiovascular and vascular issues (73) (74). Over time, hypertension can cause organ damage and severe cardiovascular events, such as stroke or heart failure (75).

Obstructive sleep apnea has also been associated with myocardial ischemia and congestive heart failure (76). However, while obstructive sleep apnea is associated with

factors such as increased body mass index, heightened sympathetic activity, and hypertension, all of which can contribute to developing heart failure, a direct link has not yet been established (77). In addition, because hypertension and heart disease are both risk factors for stroke, obstructive sleep apnea as a risk factor for stroke is considered inferential (67). Some studies suggest that obstructive sleep apnea itself is a direct risk of stroke (78).

Obstructive sleep apnea is also a risk factor for coronary artery disease due to its pathophysiological mechanisms including atherosclerosis, thrombosis, and potentially myocardial ischemia (79). In one study, it was found that 37% of patients with coronary artery disease also had Apnea-Hypopnea Indices ≥10 (80). Multiple studies found a greater prevalence of coronary artery disease in both male and female patients with sleep-disordered breathing (80) (81) (82).

Obstructive sleep apnea patients have also been observed to have more frequent cardiac arrhythmias, or irregular heartbeats. A variety of types of arrhythmia are found in obstructive sleep apnea patients, and their frequency increases with both the Apnea-Hypopnea Index and with the severity of the resulting hypoxemia (83).

Another potential cardiovascular complication of obstructive sleep apnea is pulmonary arterial hypertension. Pulmonary arterial hypertension is induced by the intermittent episodes of hypoxemia, which damage the synthesis of nitric oxide (84). Nitric oxide is essential to endothelial function, and without it, vascular remodeling occurs, which can cause pulmonary vascular disease (85). It has been estimated that between 20% and 40% of obstructive sleep apnea patients also have pulmonary hypertension (86).

Last, end-stage renal disease can occur because the proteinuria and chronic blood pressure elevation that occur with obstructive sleep apnea can damage the kidneys, among other organs (87). Sixty percent of end-stage renal disease patients are also diagnosed with obstructive sleep apnea (88).

Sleep-Disordered Breathing and Pregnancy

Just over six million women become pregnant each year in the United States of America (89). Many physiological changes occur with pregnancy, some of which negatively affect a woman's quality of sleep. This is further evidenced by the fact that excessive daytime sleepiness is frequently observed during pregnancy, and worsens as the woman nears term (90).

As stated previously, a weight gain of 10% has been associated with a six-fold increase in the development of sleep-disordered breathing (91). This observation is particularly relevant, as weight gain of >10% of body weight occurs routinely in pregnancy (92). In addition, it has been found that nearly half of women of childbearing age (20-44) are either overweight or obese – 24.5% overweight, and 23.0% obese – a fact that predisposes them to the development of sleep-disordered breathing (93).

Pregnancy also severely impairs the functional residual capacity of the lungs and decreases total lung capacity (94) (95). This may affect the upper airway's patency and increase the risk of collapse (96). To compensate, pregnant women frequently exhibit increased tidal volume and minute ventilation (94).

In addition, the pharynx size becomes constricted during pregnancy. Its amount of constriction corresponds with the woman's increase in body weight (97). Upper airway edema is also common in pregnancy due to physiological alterations in the airway

mucosa (98). In cases of preeclampsia in pregnancy, excess fluid retention in the upper airway is frequently observed (96).

All of these physiological changes that occur with pregnancy can contribute to a narrowed airway and difficulty breathing at night, predisposing pregnant women to the development of sleep-disordered breathing. Additionally, many studies have found that the severity of sleep-disordered breathing increases as the pregnancy progresses (99). One study found that 4% of women reported snoring prior to becoming pregnant, and in their third trimester, 23% of women reported snoring nightly (100). Another study demonstrated that 35% of women reported snoring in the 3rd trimester and 25% reported excessive daytime sleepiness (101) (102). A different study found that almost 37% of women in their last trimester reported loud snoring, gasping, or apnea events, all symptomatic of sleep-disordered breathing (103). It has also been verified that diagnoses of obstructive sleep apnea increase in prevalence as pregnancy progresses, as well. It was found that overall obstructive sleep apnea prevalence in the first trimester is 8.4%, and the prevalence in the third trimester is 19.7% (104).

Sleep-Disordered Breathing and Pregnancy Outcomes

The presence of sleep-disordered breathing in pregnancy can cause negative outcomes for both the mother and the fetus/newborn. The frequent sleep disturbances characteristic of obstructive sleep apnea can cause sleep deprivation, which increases the risk of preterm delivery and postpartum depression (105).

It is also possible that a diagnosis of obstructive sleep apnea can be associated with abnormalities of the placenta, due to the oxidative stress and persistent sympathetic stimulation and inflammation that results from periods of airflow limitation and recurrent

hypoxia (106) (107). In addition, the poor vascularization of the placenta can cause fetal growth restriction and smaller neonatal size (108) (109). Placental effects of obstructive sleep apnea remain an active area of investigation.

New data proposes that the onset of sleep-disordered breathing during pregnancy causes increased production of red blood cells due to the instances of hypoxia; the heightened levels of nucleated red blood cells in the umbilical cord can cause uterine growth restriction and maternal hypertension (103).

Additionally, the onset of snoring during pregnancy can also confer significant risks to maternal cardiovascular health (103). A pregnant woman with sleep-disordered breathing is about two and a half times more likely to develop hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia (101). An association exists between obstructive sleep apnea and the development of gestational hypertension and preeclampsia, as well (110) (111). The development of preeclampsia has been linked to obstructive sleep apnea via pathogenic mechanisms including endothelial dysfunction, oxidative stress, inflammation, and persistent sympathetic stimulation (103) (112). These mechanisms are exacerbated by the fact that the vascular inflammatory response is very strong during pregnancy (113).

Gestational hypertension is defined as blood pressure elevation that develops after twenty weeks of gestation, and typically occurs in 10% of pregnancies (114) (115). Preeclampsia involves proteinuria along with blood pressure elevation after twenty weeks of gestation. It occurs in up to 7.5% of pregnancies, most commonly in nulliparous women in their third trimester (116) (117). Preeclampsia is thought to develop when the placenta implants irregularly, causing abnormal vascular development (103). This causes

inflammation and oxidative stress, which results in endothelial dysfunction and the release of anti-angiogenic factors (103).

Obesity is considered a major risk factor for preeclampsia and gestational hypertension (103) (115). As obesity is also a risk factor for sleep-disordered breathing, the association between gestational hypertensive disorders and obstructive sleep apnea is expected (115). Additionally, excess weight gain throughout gestation has been found to be predictive of gestational hypertension and preeclampsia development, and is also linked with the development of obstructive sleep apnea (103).

Gestational hypertension and preeclampsia are associated with a variety of negative outcomes for the mother and the fetus/newborn. Pregnant mothers with either of these conditions were found to have higher rates of neonatal intensive care unit admission, lengthier neonatal stay than normotensive pregnancies, smaller neonatal size for gestational age than normal pregnancies, and higher rates of maternal intensive care unit admission (118) (119). Gestational hypertensive disorders, including preeclampsia, are linked with maternal and infant morbidity and mortality (120) (121). In addition, preeclampsia has been found to cause increased risk of developing cardiovascular and metabolic diseases later in life (122).

When preeclampsia is present with sleep-disordered breathing, it can alter the intrauterine environment, cause fetal growth restriction, and cause impaired in-utero movement (106) (108). Studies have shown that managing sleep-disordered breathing during pregnancy can help relieve preeclampsia's symptoms (111). It is unique that the mechanisms of sleep-disordered breathing which cause cardiovascular disease in non-pregnant patients exhibit many similarities with the side effects of preeclampsia,

specifically oxidative stress, endothelial dysfunction, inflammation, and sympathetic nervous system activation (103).

Together, gestational hypertension and preeclampsia cost billions of dollars annually to treat (103). There are a variety of pharmacotherapeutic options for preeclampsia treatment. However, for diagnosis at 38 weeks of gestation or later, the only effective treatment is delivery (123). Doctors attempt to minimize the risk of preeclampsia's effect on the pregnant mother and her baby by controlling its side effects. Because obstructive sleep apnea and preeclampsia are linked, and because obstructive sleep apnea's pathogenesis is better understood and more easily prevented than preeclampsia, it may be beneficial to further explore their connection. One study suggested that, when the Population Attributable Risk is calculated, treating snoring and associated sleep-disordered breathing would relieve about 12-19% of hypertensive disorders during pregnancy (103).

Diagnosis / Screening for Obstructive Sleep Apnea

There are a multitude of reasons obstructive sleep apnea is frequently undiagnosed. First, there is a general lack of awareness surrounding obstructive sleep apnea as a disease. Many people are unaware whether they consistently snore, especially if they do not have a bed partner. Furthermore, people may assume that chronic snoring is normal. People may not know that sleep-disordered breathing could be the reason why they are tired during the day. It has also been found that medical professionals are unlikely to add patients' sleep concerns to their medical records (124). Additionally, screening for obstructive sleep apnea is inconvenient for patients and expensive due to the necessary overnight stay in a sleep facility and the time required for the interpretation

of results. It has been found that there is a lack of access to sleep testing due to a limited number of sleep facilities in existence (125). For these reasons, obstructive sleep apnea is often undiagnosed and untreated.

Presently, the gold standard method of diagnosing obstructive sleep apnea is polysomnography, which involves an in-laboratory overnight sleep analysis. The testing uses equipment that takes a variety of measures using both electrophysiological and respiratory monitoring, including brain activity, blood oxygen content, heart rate, breathing, REM latency, and leg movements (126) (127). It is useful for not only detecting obstructive sleep apnea, but a variety of other sleep disorders as well, including insomnia, narcolepsy, idiopathic hypersomnia, periodic limb movement disorder, REM behavior disorder, parasomnias, and Upper Airway Resistance Syndrome (128).

Additionally, home sleep apnea monitors are available, and are used as a first-line study in many states in the diagnosis of sleep apnea. At-home sleep apnea monitors do not typically measure sleep and cannot, therefore, measure arousals. However, these monitors can measure airflow, snoring, oxygen saturation, and body position – all essential measurements for the detection of apneas and hypopneas during later analysis by a technician.

During polysomnography testing, esophageal pressure monitoring is an additional measurement that can be done. Studies in the past have found that esophageal pressure correlates with the amount of negative pleural pressure (129). Excess negative pleural pressure, as stated previously, is correlated with airflow limitations and thus, can detect the degree of inspiratory effort.

Esophageal pressure monitoring involves the placement of a catheter into the airway, and pressure measurements are taken throughout the night. The catheter is inserted through the nostrils and ends in the lower third of the esophagus, and at its end, there can be either a small transducer or, more commonly, a balloon for recording the pressure (129) (130) (131). When pressure changes occur, they are recorded at the proximal end of the catheter with a pressure transducer (132). The intrathoracic pressure has been found to correlate with the pressure in the lower third of the esophagus (132).

The reason esophageal pressure monitoring is considered to be the gold standard method of measuring airway resistance is because it is a very sensitive measure that can identify sleep disorders, including obstructive sleep apnea and upper airway respiratory syndrome, and can also detect sleep events. While only basic equipment is needed to identify an obstructive apneic event, esophageal pressure monitoring is able to correctly identify obstructive hypopneas (which involve low degrees of airway resistance) and other instances of minor upper airway resistance, including microarousals and other events that do not necessarily qualify as an apnea/hypopnea but still elicit reactions from the sympathetic nervous system (32).

Although esophageal pressure monitoring is very precise and gives a clear picture of what is occurring, there are a few drawbacks associated with this method. First, it is very invasive and uncomfortable for patients. It also involves an overnight stay in a sleep center – it cannot be done with a home sleep test. In addition, movement during sleep can knock the esophageal pressure monitor out of place, causing inaccurate readings. Some say that esophageal pressure monitoring may modify the upper airway dynamics, affecting the polysomnography results (133). Esophageal pressure monitoring is also

expensive, so it is not frequently used during overnight sleep testing (134). Due to its invasive nature and the inconvenience of the overnight laboratory stay necessary for esophageal pressure monitoring, it is no longer routinely used in clinical laboratories.

Pulse Transit Time and Respiratory Events

Pulse transit time measurements are an alternative to esophageal pressure monitoring. "Pulse transit time" is the length of time, typically measured in milliseconds, it takes a pulse pressure wave of blood to travel from the left ventricle to an arterial site on a periphery, usually a fingertip or a toe. Each time the heart beats, there is a new pulse transit time value.

Pulse transit time is measured using electrodes and a pulse oximeter. The electrodes are necessary in order to produce an electrocardiogram, which tracks the heartbeat. In an electrocardiogram (Figure 3), the "R wave" represents the depolarization of the ventricles, which corresponds to the left ventricular ejection of oxygenated blood. Pulse transit time is measured from the peak of the R wave to a constant level within the oxygen saturation tracing from the fingertip pulse oximeter (135).

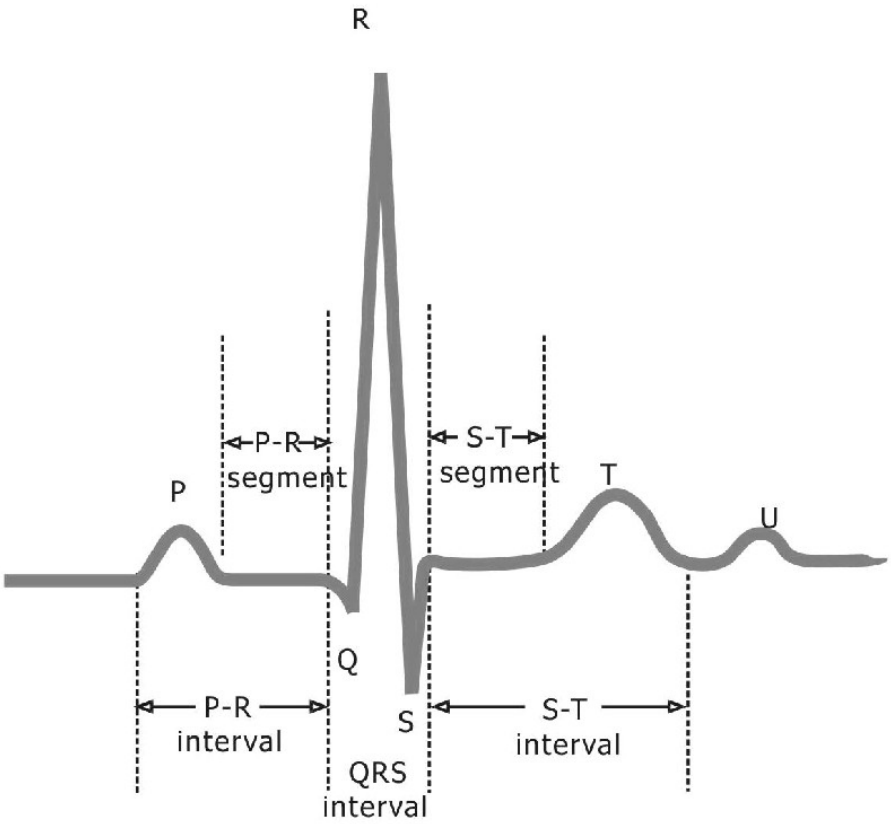


Figure 3: Electrocardiogram Waveform (136)

Pulse transit time is inversely related to blood pressure and provides continuous estimation of blood pressure changes (35) (137). A rise in blood pressure is the result of arterial wall stiffening and increased vascular tone. This increases pulse wave velocity to extremities, and hence, lowers the pulse transit time (32). While pulse transit time values, individually, are not able to predict blood pressure at a given moment, they become valuable when analyzing their changes as part of a whole. For example, at night, there is typically a blood pressure dip of 10 - 20% compared to the diurnal blood pressure (138). Pulse transit time measurements would be able to demonstrate any deviations from the baseline nocturnal blood pressure.

Pulse transit time is useful for detecting respiratory events, as well. During normal breathing, inhalation usually corresponds with a slight decrease in systolic blood

pressure of about 10 mmHg and exhalation corresponds with a slight increase in systolic blood pressure of about 10 mmHg (139). However, during sleep apnea events, the blood pressure initially dips more than 10 mmHg due inhalation against an obstructed airway (140). The negative pleural pressure becomes exaggerated as the body attempts to bring in a new breath, and the respiratory effort increases (32). Pulse transit time is able to reveal the acute blood pressure changes generated by high pleural pressure swings during these incidences of pulsus paradoxus (141). Pulse transit time oscillations during respiratory events have been found to be correlated with the degree of intensity of the negative pleural pressure swings (32). For these reasons, pulse transit time is considered a viable alternative to esophageal pressure monitoring in quantifying inspiratory effort (142) (143) (144).

During the second part of a respiratory event, as time passes and the body is unable to bring in oxygen, eventually the blood pressure increases as the sympathetic nervous system is activated (145). Ultimately, the sleep event culminates in arousal and gasping for air (140). Thee blood pressure changes associated with this part of sleep events are also accurately reflected in pulse transit time measurements.

Due to the significant blood pressure variations that occur during apnea events, patients with obstructive sleep apnea have greater blood pressure variability during sleep than patients without obstructive sleep apnea (146). Pulse transit time is able to quantify these alterations because it acts as a surrogate marker for blood pressure changes. Pulse transit time values and averages will vary between patients due to their individual blood pressures and anatomy. However, the changes in each patient's pulse transit time values throughout a night of sleep is what is helpful in scoring respiratory events.

Another aspect of respiratory events is changes in heart rate. The heart rate typically decreases with the Müllerian maneuver that occurs at the initial part of an apnea event and then increases at apnea termination when the sympathetic nervous system becomes activated (32) (33). Assessing heart rate fluctuations alone is not considered to be a sensitive measure of respiratory events, but monitoring the changes in heart rate using pulse transit time measurements is considered to be a more ideal method (35).

Pulse Transit Time versus Esophageal Pressure Monitoring

A close relationship has been demonstrated between the increase in esophageal pressure and the progressive rise in the amplitude of pulse transit time oscillations which frequently result from inhalation efforts during sleep events (141). Pulse transit time is known to be almost as accurate as esophageal pressure monitoring for distinguishing respiratory events (apneic and non-apneic) during sleep (147). Additionally, pulse transit time can distinguish between obstructive and central respiratory events (141). In one study, when differentiating between central and obstructive sleep apnea events, polysomnographers analyzing esophageal pressure monitoring measurements and pulse transit time measurements produced results that matched 94.6% of the time (141).

Unlike esophageal pressure monitoring, pulse transit time does not have to be done in a sleep lab – it can be done using a home sleep apnea test using electrodes (for electrocardiogram) and a fingertip pulse oximeter. Additionally, pulse transit time measurements are less expensive to obtain than esophageal pressure monitoring (32).

Pulse transit time is able to accurately detect microarousals, but esophageal pressure monitoring is less precise in this regard (32). Although microarousals do not necessarily result in arousal from sleep, they still cause sympathetic nervous system

activation, thus they can be sensed using pulse transit time measurements (147). This is because microarousals have associated blood pressure increases, though there may not be a significant change in the intrathoracic pressure changes (32).

During typical sleep events, there will be brain activity as part of the body's response to the lack of oxygen. Electroencephalographic arousals usually occur when there is inspiratory effort against a closed airway, even without an apnea or hypopnea event (9) (12). Electroencephalographic arousals can be detected using an electroencephalogram, and pulse transit time changes have been shown to be reflective of electroencephalogram arousal (35). Drops in pulse transit time have also been observed during subcortical arousals, when there was no evident change in the electroencephalogram (35). So, there are some subtle events that may not be disclosed by analyzing electroencephalogram measurements alone; in these instances, pulse transit time measurements are a more sensitive measure because they are able to demonstrate subcortical arousals.

In addition, pulse transit time is an especially useful measure because there are many previously established correlations between pulse transit time measurements and cardiovascular outcomes.

Pulse transit time is thought to be potentially useful as a screening tool for hypertension (148). Pulse transit time is also considered a potential useful measurement for predicting the development of preeclampsia (149). A study found a negative correlation between venous pulse transit time and hepatic vein impedance index, which is known to influence cardiac output. Both pulse transit time and hepatic vein impedance index correlate with maternal cardiac output, which correlates with neonatal birth weight

percentiles (150). Last, pulse transit time is thought of as a valuable clinical tool for assessment of vascular abnormality and autonomic nervous response (151).

Overall, pulse transit time is an ideal non-invasive method of measuring sleep apnea and events, and it can be done using a home sleep apnea test. It is especially advantageous for studying children and pregnant women, or any patient who may be reluctant to spend the night in a sleep lab.

Drawbacks of Pulse Transit Time Measurements

Although pulse transit time has many merits, it is not without drawbacks. First, there is always a possibility of motion artifact. Patient movement during sleep may disrupt the placement of the electrocardiogram leads or the pulse oximeter, which could alter the measurements taken. This could be incorrectly interpreted as a shift in amount of inspiratory effort, or a change in the baseline pulse transit time (32). Next, it is not capable of differentiating various kinds of respiratory events (apneas, hypopneas, episodes of minor upper airway resistance, etc.) by itself. An additional layer of analysis is needed, such as a nasal cannula to track airflow (32). Another disadvantage is that it may be slightly uncomfortable for the patient to sleep with a device on.

Another large problem with the use of pulse transit time measurements is the fact that REM sleep inherently involves large variations in respiratory drive (32). Therefore, the pulse transit time measurements taken during this time, in addition to esophageal pressure measurements, would make it difficult to judge whether there is a respiratory event or if the increased inspiratory effort is just a normal part of the patient's REM sleep phase (32). In these cases, it would be necessary to interpret respiratory effort separately from the arousal aspects in order to adequately assess respiratory events during this

period (32). This is a fairly significant drawback for the use of pulse transit time, because periods of REM sleep are found to have more instances of respiratory events than periods of non-REM sleep and an overall increased upper airway resistance (32).

In addition, pulse transit time is not completely accurate in assessing beat-to-beat changes in blood pressure (152). Rather, it is most useful for analyzing trends of blood pressure fluctuation throughout sleep. It must be used in conjunction with other measurements, such as those already taken by typical home sleep apnea testing devices, to give an accurate representation of changes occurring during sleep.

Last, pulse transit time is ineffective for analyzing the sleep patterns of some patients with existing cardiovascular disease (32). For example, it would be difficult to analyze patients with cardiac arrhythmias (such as atrial fibrillation), impacted isometric contraction time (such as left ventricular dysfunction or cardiac conduction defects), and those with cardiac pacemakers or on vasoactive medication. These conditions would cause changes in the pulse transit time that would be difficult to distinguish from those associated with respiratory events (32).

Presently, pulse transit time is not fully endorsed for clinical practice, though it is frequently used (32). In the future, pulse transit time has the potential to be used in conjunction with other standard home sleep apnea tests as a less expensive and less invasive option than overnight esophageal pressure monitoring in a sleep laboratory (32). Additional studies with larger populations are needed to fully elucidate the merits of pulse transit time as a tool for the study of sleep-disordered breathing in patients.

Obstructive Sleep Apnea Treatments

There are various treatment options for obstructive sleep apnea, including nasal passage dilators, myofunctional therapy, oral appliances, surgeries, or Continuous Positive Airway Pressure (CPAP) machines.

Blockages in the nasal passage have been shown to contribute to snoring and obstructive sleep apnea events (153). A variety of methods exist to dilate the nasal passages, including nasal surgery, expiratory positive airway pressure devices, and nasopharyngeal airway stenting devices (154).

Next, myofunctional therapy is also a potential treatment option for obstructive sleep apnea (155). Myofunctional therapy can consist of a range of exercises meant to strengthen or re-train the oral and oropharyngeal structures and muscles that affect breathing (156) (157).

Oral appliances can also be used as a method for treating both snoring and obstructive sleep apnea. There are a wide variety of oral appliances that can be used, with the purpose of most of them to keep the mouth only partially opened and advance the mandible to a "forward" position (158).

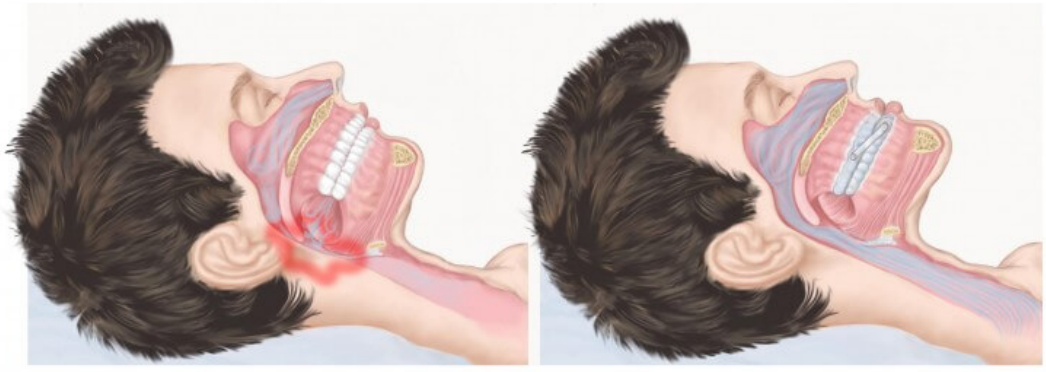


Figure 4: Mandible Forward versus Mandible Back (159)

Positioning the lower jaw in a forward position using oral appliances can help the front wall of the throat be held forward, maintaining an open airway (Figure 4). However, the use of CPAP machines has been found to be more effective than mandible-forward oral appliances (160).

Other alternative, more invasive treatment options for obstructive sleep apnea are surgeries. A variety of surgeries exist which could alter the anatomy of the airway to allow more airflow, including uvulopalatopharyngoplasty (with or without tonsillectomy), uvulopalatopharyngoglossoplasty, midline glossectomy, nasal septal reconstruction, lingualplasty, and genioglossal advancement, depending on each patient's individual circumstance (161). Other surgical remedies for obstructive sleep apnea include bariatric surgery, or an implanted "Upper Airway Stimulation" device to stimulate the breathing muscles (162) (163).

Last, Continuous Positive Airway Pressure is considered the gold standard treatment for obstructive sleep apnea (164). CPAP machines consist of a face mask placed over the mouth, attached to a machine that generates a continuous flow of oxygenated air during sleep, which helps to prevent airway collapse. It has been shown to help eliminate apnea events during sleep that occur as a result of obstruction of the upper airway (165) (166). When patients are compliant with their CPAP treatment, they show improved arterial stiffness, endothelial function, cardiovascular outcomes, and decreased insulin resistance (164) (167) (168) (169). In normotensive patients, CPAP lowered systolic blood pressure by 2-3 mmHg, and in hypertensive patients, it lowered systolic blood pressure by 6-7 mmHg (170). Overall, effective treatment of obstructive

sleep apnea can help to prevent some of the associated negative outcomes and can improve overall sleep quality for patients.

Methods

Participants and Setting

Patients were recruited from obstetric-gynecology practices throughout Rhode Island and southern Massachusetts. Inclusion criteria included a singleton pregnancy, less than fourteen weeks of gestation, acknowledging loud snoring 3-4 or more times per week, and a body mass index greater than 27 kg/m^2. These criteria correspond with risk factors for the development of obstructive sleep apnea. Women were followed until delivery. Women with atrial defibrillation were excluded due to the fact that an irregular heartbeat makes the pulse transit time measurements inaccurate.

Women with risk factors for obstructive sleep apnea were recruited because the research project tests the effectiveness of pulse transit time measurements for evaluating sleep-disordered breathing and seeks to potentially predict hypertensive outcomes of pregnancy.

Demographic information was collected from each patient at her baseline visit. Medical records were accessed after delivery to analyze medical history and gestational medical information. Patients were asked about any current medications they are taking or have taken prior to the pregnancy, any vitamins they are taking (including prenatal vitamins), and any sleep aids or medications they use. Patients were then asked specific questions about their medical history. They were asked if they have received any diagnoses or treatment for hypertension and specific cardiovascular conditions, including coronary artery disease, cardiomyopathy, congestive heart failure, and arrhythmia. The patients were also asked if they have a history of consuming alcohol or smoking cigarettes, e-cigarettes, or marijuana. Last, the patients were asked a variety of questions

about their pregnancy, including any complications they are experiencing or have experienced in the past.

As the study progressed, it was noted that some patients did not have a record for giving birth at Women and Infant's Hospital. Thus, not all relevant data and outcomes values could be collected, so they were excluded from the study.

Sample Groups

Various groupings of these patients were assembled for this study. When analyzing differences in pulse transit time variables depending on obstructive sleep apnea status, first the whole sample was analyzed, then a group of patients negative for obstructive sleep apnea, and then a group of obstructive sleep apnea positive patients. When pulse transit time measurements were correlated with blood pressure measurements, the whole sample was analyzed, and then a group of 23 patients positive for obstructive sleep apnea and 12 patients that were negative for obstructive sleep apnea were analyzed. (These were all of the patients that had completed ambulatory blood pressure monitoring testing.) When pulse transit time measurements were analyzed as a potential predictive measure for hypertensive outcomes of pregnancy, obstructive sleep apnea negative patients were studied. Last, when analyzing the ability of the pulse transit time drop index variable of predicting pregnancy-associated hypertension, the whole sample, obstructive sleep apnea positive, and obstructive sleep apnea negative groups were analyzed separately.

Pregnancy Outcomes

Gestational hypertension and preeclampsia diagnoses were arbitrated using each patient's medical record. Definitions for gestational hypertension and preeclampsia were

taken from the American College of Obstetricians and Gynecologists' Clinical Guidelines (Figure 5).

The Guidelines state that gestational hypertension is defined as having blood pressure readings of 140 mmHg or greater for the systolic measurement and 90 mmHg or greater for the diastolic measurement greater than four hours apart. The elevation in blood pressure must occur after at least 20 weeks of gestation (114).

The Guidelines state that preeclampsia has two components – a rise in blood pressure and proteinuria, which must both present after 20 weeks of gestation (114). The elevated blood pressure must include readings of 140 mmHg or greater for the systolic measurement and 90 mmHg or greater for the diastolic measurement greater than four hours apart (114). Proteinuria is defined as a protein/creatinine ratio greater than or equal to 0.3 mg/dL, a dipstick reading of 1+, or ≥300 mg/24-hour urine collection (114). If there has been a blood pressure elevation after 20 weeks of gestation, but no proteinuria, there are a few other testing options that can still allow for a diagnosis of preeclampsia, including a platelet count of less than 100,000 per microliter, liver transaminases at double the typical blood concentration, or serum creatinine concentrations >1.1 mg/dL (114).

TABLE 2-1. Diagnostic Criteria for Preeclampsia ⇦

Blood pressure	• Greater than or equal to 140 mm Hg systolic or greater than or equal to 90 mm Hg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure • Greater than or equal to 160 mm Hg systolic or greater than or equal to 110 mm Hg diastolic, hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy
and	
Proteinuria	• Greater than or equal to 300 mg per 24 hour urine collection (or this amount extrapolated from a timed collection) or • Protein/creatinine ratio greater than or equal to 0.3* • Dipstick reading of 1+ (used only if other quantitative methods not available)
Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:	
Thrombocytopenia	• Platelet count less than 100,000/microliter
Renal insufficiency	• Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
Impaired liver function	• Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema	
Cerebral or visual symptoms	

* Each measured as mg/dL.

Figure 5: Diagnostic Criteria for Preeclampsia (114)

Physical Exam Measurements

Next, a physical exam is done. Blood pressure measurements are taken using a sphygmomanometer with a cuff of appropriate size for the patient. After resting for a period of five minutes, the blood pressure measurement is taken with the patient in a seated position. Anthropometric measures are also taken, including height measurements, weight measurements, and body mass index measurements.

At-Home Sleep Apnea Monitor

All patients recruited for the study will do a home sleep apnea test using the Nox T3 Sleep Device, a level III recording device (Carefusion, San Diego, CA, USA). Studies have been done which have validated the accuracy of the Nox T3 device. It has

been found to correctly identify 100% of obstructive sleep apnea negative subjects and 88% of obstructive sleep apnea positive subjects when compared with in-laboratory polysomnography testing, and the Apnea-Hypopnea Index that the Nox T3 device calculated strongly correlated with the Apnea-Hypopnea Index that was calculated during in-laboratory polysomnography testing (r=0.93) (171).

The home sleep apnea testing device consists of two plethysmography belts that are secured around the chest and abdomen, three electrocardiogram leads, a nasal cannula, a microphone, and a fingertip pulse oximeter device. The nasal cannula records airflow, snoring, and nasal pressure using a pressure transducer. The microphone records any snoring sounds that occur. A sensor within the device is able to record bodily positioning and movements throughout the night. The plethysmography belts are able to measure thoracic and abdominal movements, and therefore inspiratory effort. The pulse oximeter measures oxygen saturation in the bloodstream, and communicates those measurements to the Nox T3 device wirelessly using Bluetooth.

The home sleep apnea test will be scored by an experienced polysomnographer, who will classify the patient's sleep events and will also determine whether to make a diagnosis of obstructive sleep apnea. Additionally, the Nox T3 device will calculate an Apnea-Hypopnea Index for each patient.

A diagnosis of obstructive sleep apnea was defined as having an Apnea-Hypopnea Index of greater than or equal to five events per hour. Definitions for apnea and hypopnea will be based on the recommendations from the American Academy of Sleep Medicine (172). The Nox T3 device is also able to allow for the identification and analysis of clinically significant airflow limitations that do not necessary meet the criteria

for being classified as an apnea or a hypopnea by using an automated method and also by allowing a visual inspection of relevant data. The automated method uses an algorithm that is able to calculate an average breath's airflow threshold on the nasal pressure signal, and records breath attempts that fall below this threshold as "airflow limitations." The European Sleep Research Society defines flattening indices in which a result of 0.3 indicates a perfect breathing pattern, while a result of 0.0 indicates a "flat" breath (173). The results from the algorithm for flattening indices will be analyzed in conjunction with a visual inspection of the results from the sleep test as a whole (174) (175).

Pulse Transit Time Measurements

The at-home sleep apnea monitor is also able to collect pulse transit time data using the fingertip pulse oximeter in combination with electrocardiogram recordings. Although a typical electrocardiogram uses ten electrodes, the at-home sleep apnea test is able to collect heartbeat information using just three. Electrodes are placed on the right shoulder, right hip, and on the left side of the body, underneath the heart. The electrodes measure the heart's electrical activity, which allows the tracking of each heartbeat and allows analysis of the function of the heart. The pulse oximeter probe is placed on the index fingertip. It is able to measure blood oxygen saturation levels using plethysmography.

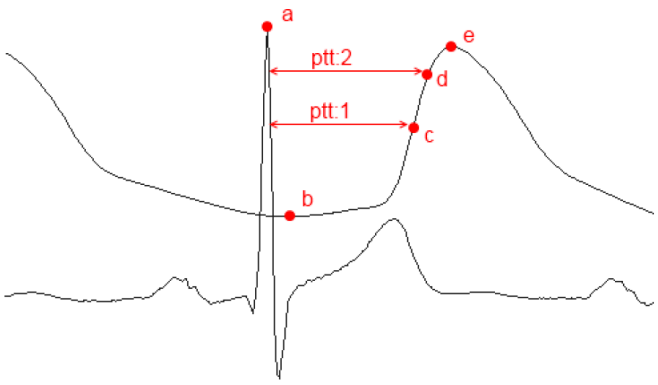
Pulse transit time measurements are taken from the peak of the R wave for each heartbeat in the electrocardiogram to the pulse wave rising 50% from nadir to its peak by plethysmograph (Figure 6, Figure 7). Using this method, the device's software is able to calculate a variety of pulse transit time variables throughout the night of sleep. These include:

- Pulse transit time drops count / index
- Pulse transit time drops with apnea count / index
- Pulse transit time drops with hypopnea count / index
- Pulse transit time drops with desaturation count / index

Pulse transit time "drops" include variables that able to be adjusted by the study administrators within the Nox T3 software. It this study, a pulse transit time "drop" was defined as a minimum of a 10 millisecond decrease of a 4 second "moving average duration" from the average pulse transit time in the 60 seconds immediately prior. For the purposes of this study, it was defined that the "drop" must remain 10 milliseconds below the background moving average for a minimum of 4 seconds. The pulse transit time drop index is defined as the number of "drops that occur per hour of sleep" (135).

PTT Measurement

The PTT value is calculated from the R-top of the EKG until the PTT has risen 50% from its lowest value. The percentage value is chosen by the user during the PTT creation. The images below show how the PTT is calculated and how this percentage value comes into play.



PTT Noxturnal - Copyright © 2012 Nox Medical 3 of 5

Figure 6: Calculating Pulse Transit Time - 1 (135)

a	R-top on the EKG
b	Pleth nadir for a single pulse
c	50% rise of the PTT from its nadir
d	80% rise of the PTT from its nadir
e	Pleth maximum for a single pulse
ptt:1	The ptt duration for measurement point a to c (50%)
ptt:2	The ptt duration for measurement point a to d (50%)

Figure 7: Calculating Pulse Transit Time - 2 (135)

Blood Pressure Measurements

Ambulatory blood pressure monitoring will also be done on all patients that were found to be positive for obstructive sleep apnea in their first trimester and on a limited number of obstructive sleep apnea negative patients. Patients will wear an ambulatory blood pressure monitor on their arm for a period of 24 hours, and blood pressure measurements will be taken at fifteen minute-intervals throughout the day. These measurements will allow quantification and comparison of nocturnal and diurnal systolic and diastolic blood pressures.

Blood pressure measurements taken by the ambulatory blood pressure monitor will allow correlation of pulse transit time measurements with nocturnal blood pressure measurements, diurnal blood pressure measurements, and whole-day blood pressure measurements. These blood pressure measurements can also be averaged to allow more straightforward analysis. These measurements are essential to this study because elevated blood pressure is linked to the outcomes studied, including gestational hypertension and preeclampsia.

Research Aims

Overall, the purpose of this study is to assess the effectiveness of pulse transit time measurements for evaluating sleep-disordered breathing and for predicting gestational hypertensive outcomes.

The specific aims of this research project were three-fold: First, pulse transit time variables will be analyzed and compared between pregnant women with obstructive sleep apnea and pregnant women without obstructive sleep apnea. Both groups include patients that exhibited risk factors for the development of obstructive sleep apnea; potentially, pulse transit time measurements can reveal differences between the patients that have obstructive sleep apnea and why some do not. Next, pulse transit time variables will be correlated with nocturnal and diurnal blood pressure in pregnant women with and without obstructive sleep apnea, all exhibiting risk factors for obstructive sleep apnea. Last, pulse transit time variables will be associated with the development of gestational hypertension in pregnant women with and without obstructive sleep apnea with risk factors for sleep apnea. In this aim, women with chronic hypertension were removed due to the fact that their pulse transit time measurements may be affected by it.

Statistical Analysis

Statistical analysis will be use to analyze differences, correlations, and associations. To compare the pulse transit time differences in pregnant women with and without obstructive sleep apnea, a t-test will be performed, and then statistically significant correlations will be analyzed. $P<0.05$ will be considered significant. In addition, Spearman correlations will be done to analyze the relationship between each patient's various pulse transit time variables and their Apnea-Hypopnea Index. Specifically, a correlation will be run between Average Pulse Transit Time Drops and

average Apnea-Hypopnea Index in the sample as a whole, in groups with obstructive sleep apnea, and in groups without obstructive sleep apnea.

Next, a Spearman correlation will be performed to analyze the relationship between each patient's pulse transit time variables and her Average Nocturnal Blood Pressure (systolic), Average Diurnal Blood Pressure (systolic and diastolic), and Average Whole-day Blood Pressure.

Last, when analyzing pulse transit time variables as a predictor of hypertensive disorders of pregnancy, a univariate analysis of variance will be done to test between-subject effects, including adjusting for height, in order to analyze the influence of each on hypertensive outcomes. The American College of Obstetricians and Gynecologists' Guidelines on Gestational Hypertension were used to adjudicate diagnoses of gestational hypertension and preeclampsia by looking at patient's medical records.

Throughout the statistical analysis, pulse transit time values were normalized for height to account for the fact that pulse transit times will be different depending on each patient's limb length.

Results

	Whole sample mean / SD	OSA+ mean / SD	OSA- mean / SD
AHI Score	2.77 ± 6.30	12.39 ± 11.58	1.23 ± 2.86
PTT Drops Count	292.42 ± 246.14	272.93 ± 250.34	295.28 ± 246.56
PTT Drops Index	43.34 ± 33.81	38.92 ± 31.74	43.99 ± 34.19
PTT Drops with Apnea Count	3.93 ± 11.63	14.5 ± 29.09	2.38 ± 4.34
PTT Drops with Apnea Index	.56 ± 1.56	2.0 ± 3.80	.35 ± .66
PTT Drops with Hypopnea Count	8.32 ± 27.92	42.19 ± 67.83	3.35 ± 7.84
PTT Drops with Hypopnea Index	1.15 ± 3.62	5.68 ± 8.59	.48 ± 1.14
PTT Drops with Desaturation Count	9.56 ± 32.02	41.94 ± 79.46	4.81 ± 11.05
PTT Drops with Desaturation Index	1.32 ± 4.19	5.55 ± 10.21	.70 ± 1.62
Average PTT Drop	227.30 ± 139.33	167.56 ± 96.31	235.42 ± 142.61
Maximum PTT Drop	726.16 ± 104.94	657.26 ± 130.89	735.53 ± 97.97
Average PTT	335.84 ± 136.60	383.06 ± 149.93	329.48 ± 134.22
Average PTT (supine)	338.05 ± 138.97	372.39 ± 147.77	333.43 ± 136.05
Average PTT (non-supine)	338.73 ± 143.42	411.36 ± 178.05	328.76 ± 136.05
Maximum PTT	838.57 ± 8.51	839.24 ± 10.82	838.48 ± 8.22
Maximum PTT (supine)	831.05 ± 13.44	831.76 ± 13.92	830.96 ± 13.44
Maximum PTT (non-supine)	834.37 ± 11.81	834.1 ± 12.03	834.41 ± 11.84
Minimum PTT	25.83 ± 29.54	30.71 ± 36.63	25.18 ± 28.60
Minimum PTT (supine)	55.18 ± 57.62	60.35 ± 59.56	54.49 ± 57.62
Minimum PTT (non-supine)	46.64 ± 56.23	97.52 ± 106.23	39.66 ± 41.70

Table 1: Pulse Transit Time Variables Collected using the Home Sleep Apnea Test in the Whole Sample, Obstructive Sleep Apnea Positive group, and Obstructive Sleep Apnea Negative Group

	OSA+ Mean / Standard Deviation
Nocturnal systolic blood pressure	117.05 ± 14.14
Nocturnal diastolic blood pressure	66.86 ± 12.22
Diurnal systolic blood pressure	124.43 ± 11.04
Diurnal diastolic blood pressure	75.00 ± 9.31
Whole-day systolic blood pressure	121.81 ± 11.35
Whole-day diastolic blood pressure	72.05 ± 9.83

Table 2: Ambulatory Blood Pressure Monitor Values in Obstructive Sleep Apnea Positive Group

Aim 1 Results: Pulse transit time differences in pregnant women with obstructive sleep apnea versus pregnant women without obstructive sleep apnea

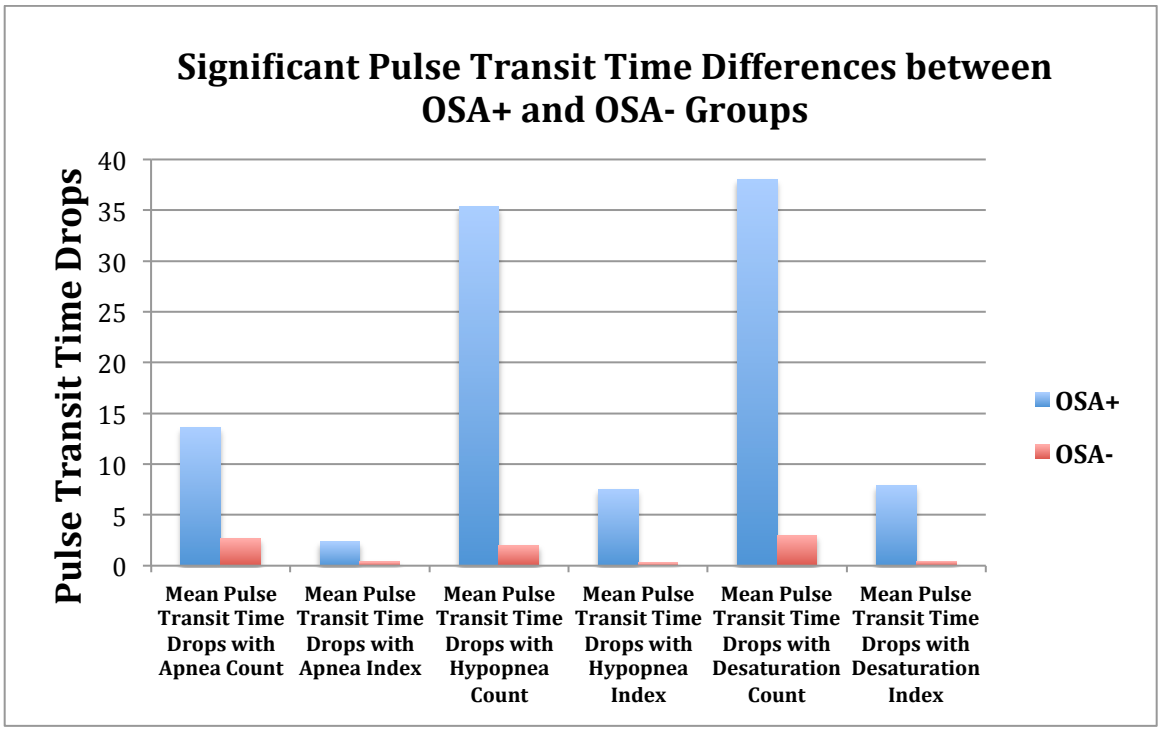
There were 128 patients in the total sample; 20 were diagnosed with obstructive sleep apnea (OSA+) and 108 were negative for obstructive sleep apnea (OSA-). Descriptive statistics are presented in Table 3. The obstructive sleep apnea positive group was slightly older, taller, and heavier than the obstructive sleep apnea negative group, with a higher body mass index, on average. All patients were studied in their first trimester when they were approximately ten weeks pregnant. A greater percentage of the obstructive sleep apnea positive group had been diagnosed with chronic hypertension outside of pregnancy (22.22%) than the non-obstructive sleep apnea group (9.48%). Similar percentages of both groups were nulliparous, about 33% for each.

	Whole sample mean (n=128)	**OSA+ mean / SD** (n=20)	**OSA- mean / SD** (n=108)
Age	29.26 years ± 6.32	33.22 years ± 5.88	28.97 years ± 5.65
Height	63.86 inches ± 3.11	64.86 inches ± 2.39	63.73 inches ± 3.19
Weight	201.55 lbs ± 47.73	229.67 lbs ± 37.00	198.93 lbs ± 47.85
BMI	34.74 kg/m^2 ± 7.98	38.46 kg/m^2 ± 6.50	34.16 kg/m^2 ± 8.06
Gestational age at study visit	10.64 weeks ± 1.90	10.26 weeks ± 2.02	10.69 weeks ± 1.89
% of women with chronic hypertension	11.19%	22.22%	9.48%
% of nulliparous women	33.58%	33.33%	33.62%
Diabetes (outside of pregnancy)	2.24%	0%	2.24%

Table 3: Demographics/Comorbidities Table for Aim 1

There were no significant differences between OSA+ and OSA- groups observed for the Average Pulse Transit Time (p=.391), Minimum Pulse Transit Time (p=.926), or Maximum Pulse Transit Time (p=.184). However, as shown in Figure 8, there were significant differences between OSA+ and OSA- groups for the following variables: Pulse Transit Time Drops with Apnea Count (p=.007), Pulse Transit Time Drops with Apnea Index (p=.007), Pulse Transit Time Drops with Hypopnea Count (p=.000), Pulse Transit Time Drops with Hypopnea Index (p=.000), and Pulse Transit Time Drops with Desaturation Count (p=.000), Pulse Transit Time Drops with Desaturation Index (p=.000). Overall, there were significantly greater numbers of pulse transit time drops associated with sleep events (apneas and hypopneas) and oxygen desaturations in the OSA+ patients. This was expected, as apneas, hypopneas, and oxygen desaturations are more common in obstructive sleep apnea positive patients, so it makes sense that they would have more pulse transit time drop measurements than obstructive sleep apnea negative patients. In addition, significant differences between OSA+ and OSA- were

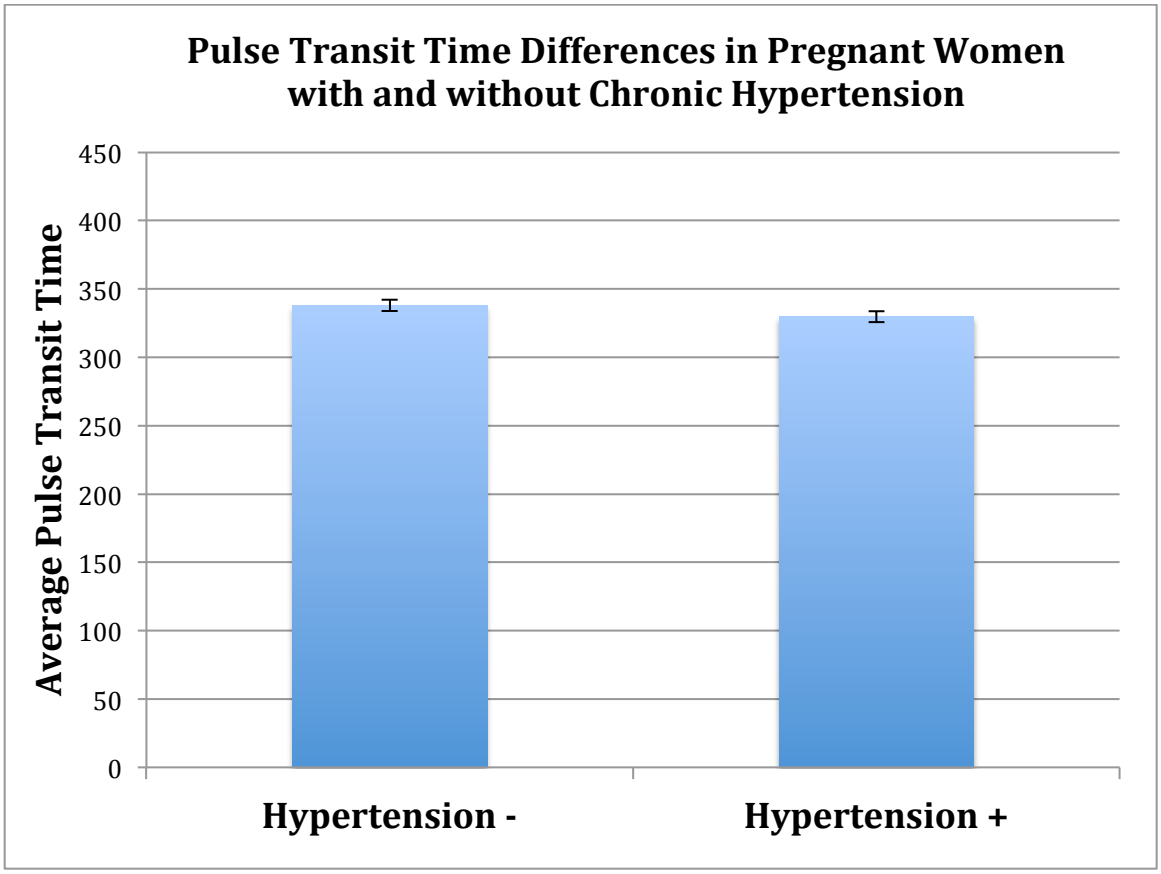
found for Average Pulse Transit Time Drop (p=.007) and Maximum Pulse Transit Time Drop (p=.008).



Sample size: 128

Figure 8: Significant Pulse Transit Time Differences between OSA+ and OSA- Groups

As shown in Figure 9, the average pulse transit time was not found to be significantly different in the hypertension positive versus the hypertension negative group (p=.924).



Sample size = 108
p=.924

Figure 9: Pulse Transit Time Differences in Pregnant Women with and without Chronic Hypertension

In addition, as shown in Figure 10, there were no significant differences between hypertension groups for maximum pulse transit time values (p=.840) or minimum pulse transit time values (.117).

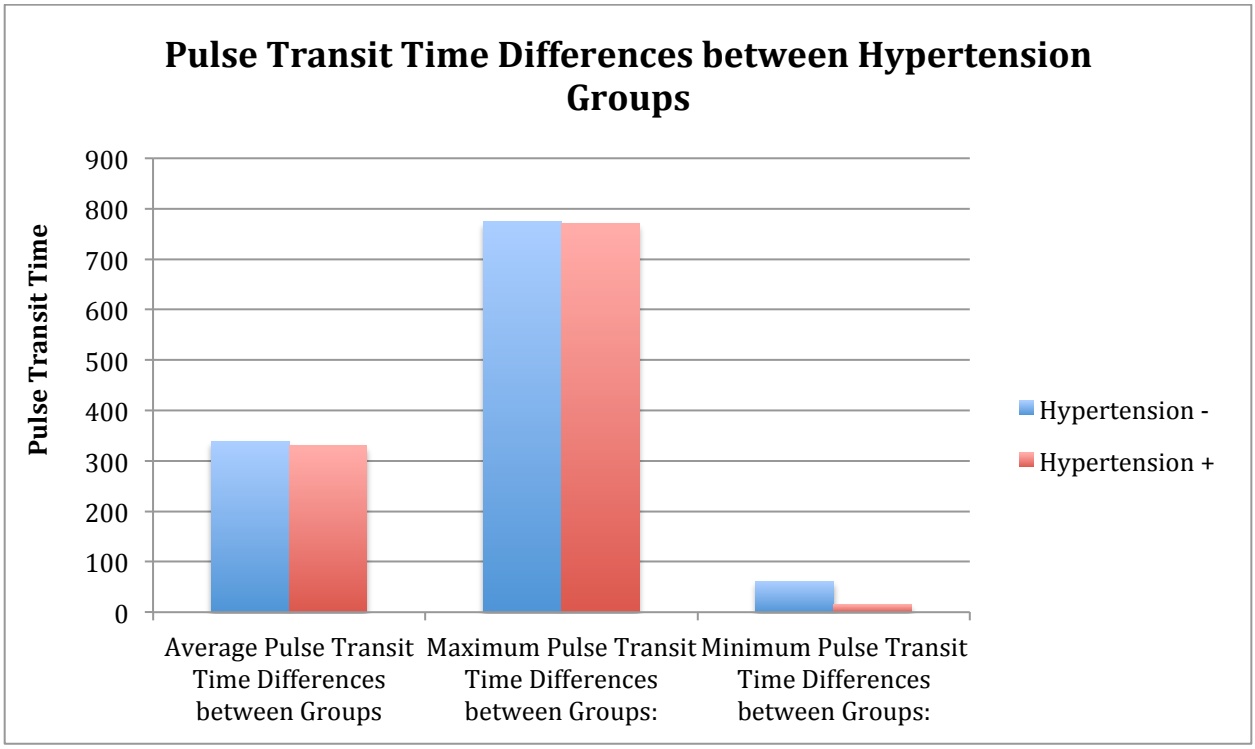
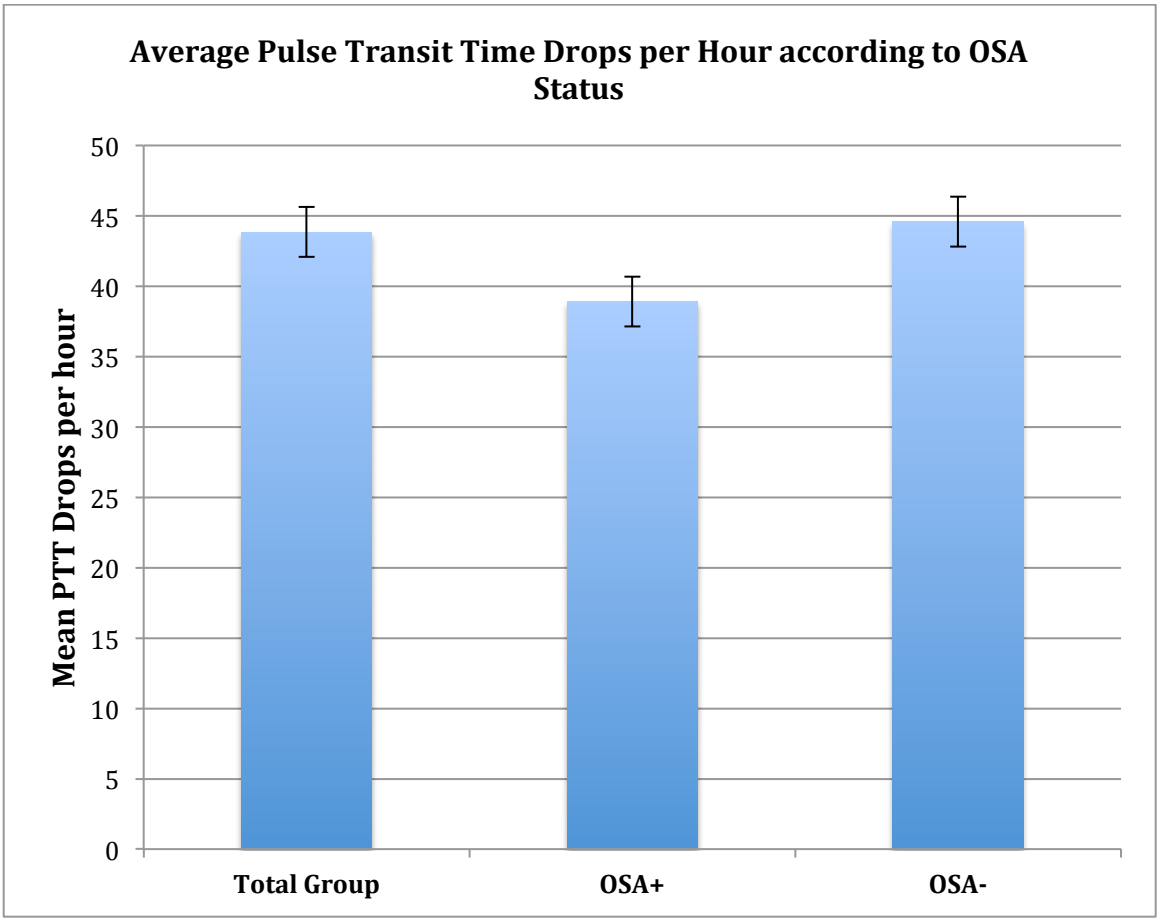


Figure 10: Pulse Transit Time Differences between Hypertension Groups

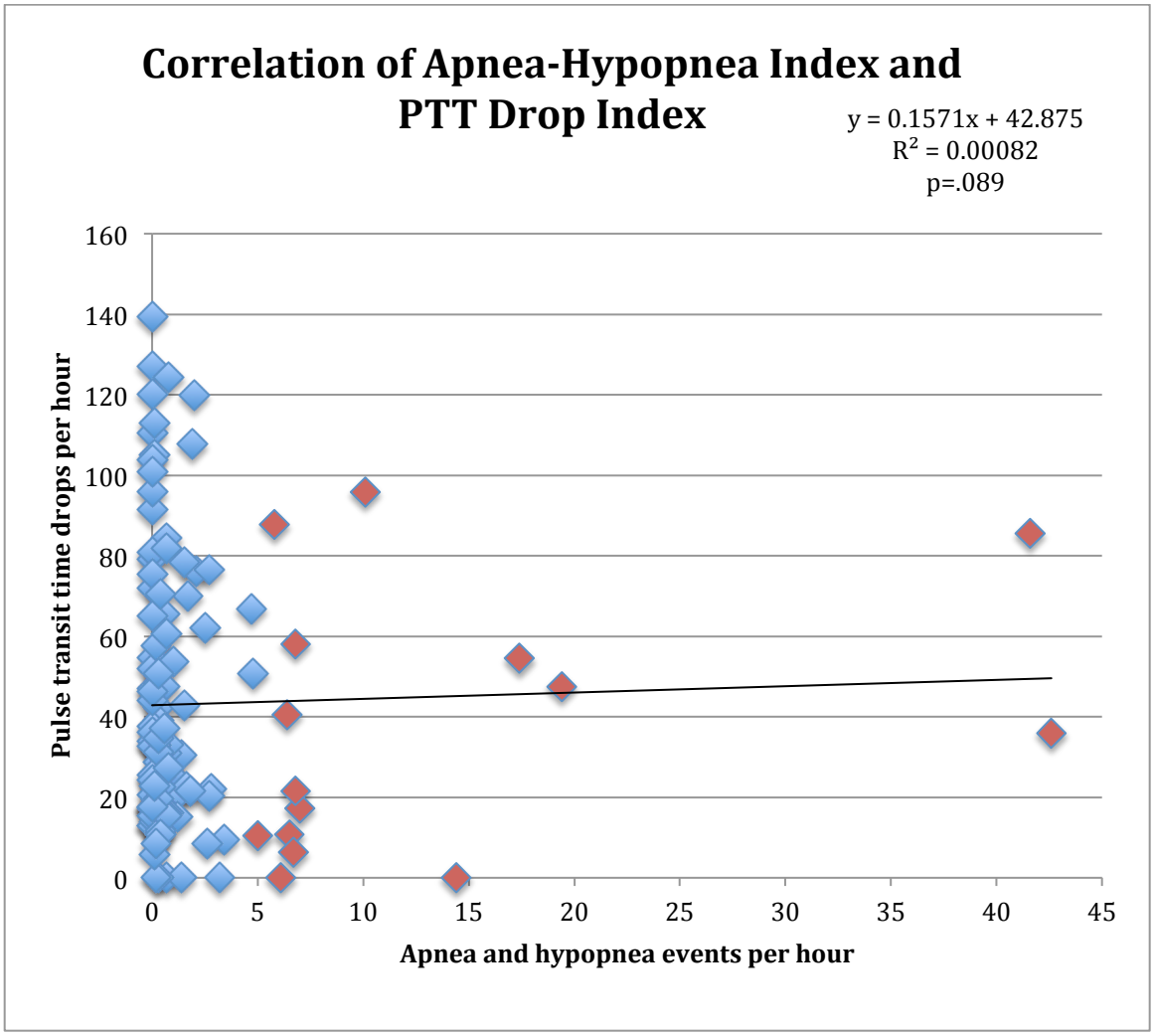
As shown in Figure 11, there was no significant correlation between obstructive sleep apnea status and average number of pulse transit time drops per hour in the total sample ($p=.089$, $r=.154$), in the obstructive sleep apnea positive group ($p=.418$, $r=.182$), or in the obstructive sleep apnea negative group ($p=.337$ and $r=-.097$).



Sample size=128
Total group p=.089
OSA+ p=.418
OSA- p=.337

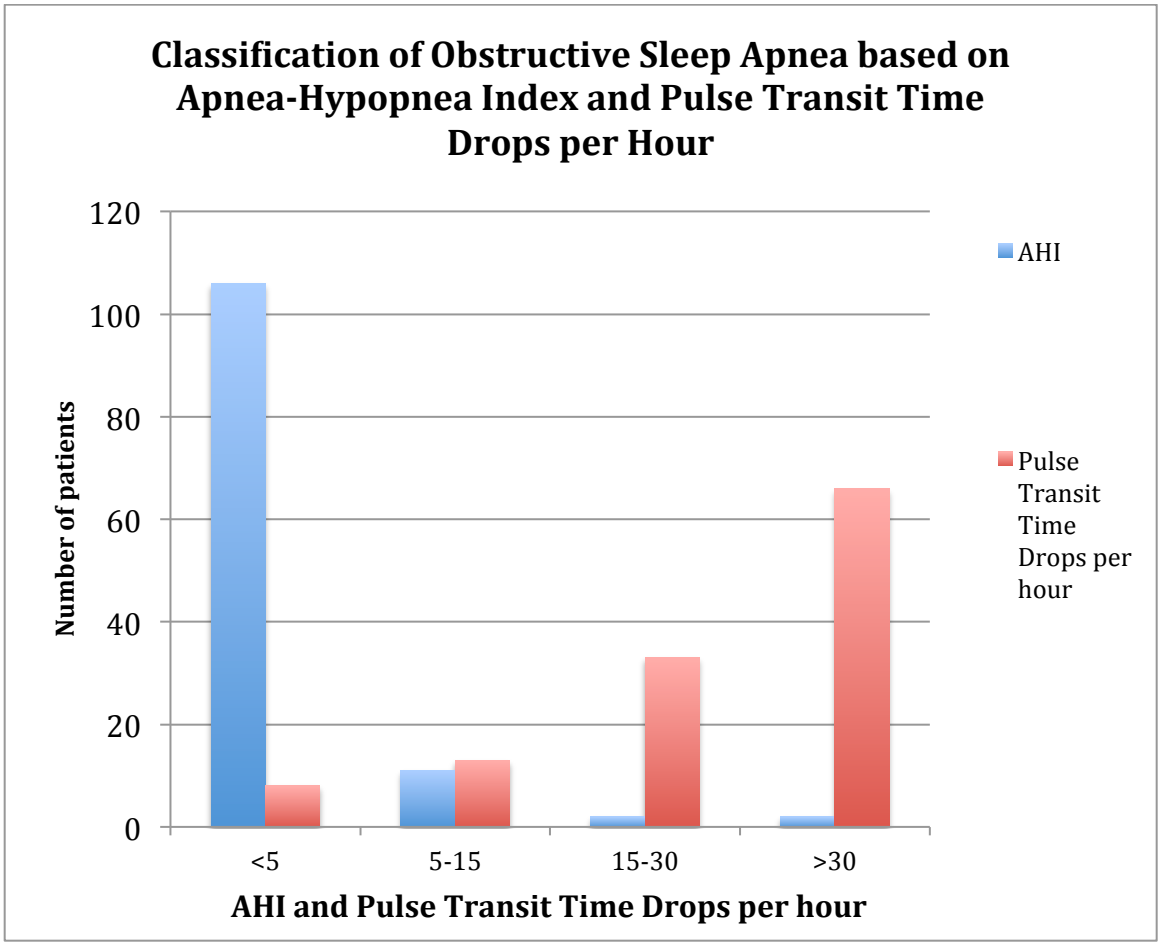
Figure 11: Average Pulse Transit Time Drops per Hour according to OSA Status

Additionally, there was no correlation of the Apnea-Hypopnea Index and the number of Pulse Transit Time Drops per hour, as demonstrated in Figure 12 (p=.089, R^2=.00082) and Figure 13.



Sample size=108

Figure 12: Correlation of Apnea-Hypopnea Index and PTT Drop Index



Sample size=108
Total group p=.089
OSA+ p=.418
OSA- p=.337

Figure 13: Classification of Obstructive Sleep Apnea based on Apnea-Hypopnea Index and Pulse Transit Time Drops per Hour

Figure 13 specifically demonstrates the large discrepancies amongst each value range, suggesting the fact that the number of pulse transit time drops per hour do not necessarily correlate with the number of apneas and hypopneas occurring per hour. This was interesting because it would be assumed that a greater number of apneas or hypopneas per hour of sleep would correspond with a greater number of pulse transit time drops.

Aim 2 Results: Correlation of pulse transit time variables with nocturnal and diurnal blood pressure in pregnant women with obstructive sleep apnea

For the second study aim, associations were examined among pulse transit time measurements and blood pressure variables. These analyses were performed in a sample of 35 women who had complete blood pressure data. Descriptive statistics for this sample are presented in Table 4. On average, women were 31.59 years old, 224.07 lbs, had a 37.63 kg/m^2 body mass index, and had a gestational age of 10.50 weeks.

	Whole sample mean (all patients who had a screening visit)	**23 Obstructive Sleep Apnea positive patients and 12 Obstructive Sleep Apnea negative patients (in the first trimester) Mean / Standard Deviations**
Age	29.26 years ± 6.32	31.59 years ± 6.22
Height	63.86 inches ± 3.11	64.90 inches ± 2.48
Weight	201.55 lbs ± 47.73	224.07 lbs ± 41.05
BMI	34.74 kg/m^2 ± 7.98	37.63 kg/m^2 ± 7.75
Gestational age at study visit	10.64 weeks ± 1.90	10.50 weeks ± 2.11
% of women with chronic hypertension	11.19%	6.06%
% of nulliparous women	33.58%	21.21%
Diabetes (outside of pregnancy)	2.24%	3.03%

Table 4: Demographics/Comorbidities Table for Aim 2

The correlation analyses that were performed revealed that there was a significant negative correlation between Maximum Pulse Transit Time and multiple blood pressure variables, including Average Diurnal Systolic (p=.003, r=-.566) and Diastolic (p=.034, r=-.426) Blood Pressure, Average Nocturnal Systolic (p=.014, r=-.484) and Diastolic

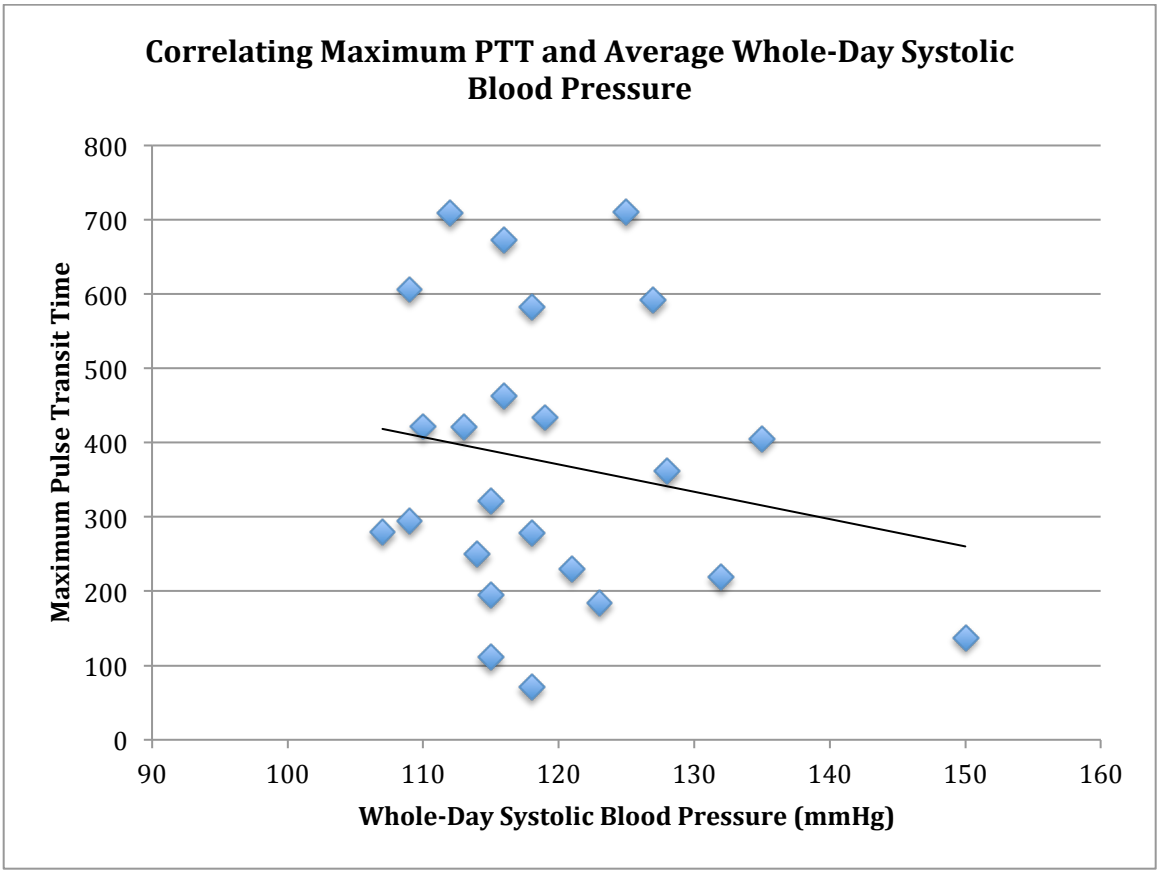
(p=.040, r=-.413) Blood Pressure, Average Whole-day Systolic (p=.007, r=-.529) and Diastolic (p=.043, r=-.408) Blood Pressure (Table 5). In addition, there was a significant negative correlation between Average Pulse Transit Time and Average Nocturnal Systolic Blood Pressure (Table 5).

	Average Pulse Transit Time	**Maximum Pulse Transit Time**	**Minimum Pulse Transit Time**
Average Diurnal Systolic Blood Pressure: Pearson Correlation	-.318	-.566	-.248
Significance (2-tailed)	.121	**.003**	.232
Average Diurnal Diastolic Blood Pressure: Pearson Correlation	.089	-.426	-.106
Significance (2-tailed)	.672	**.034**	.613
Average Nocturnal Systolic Blood Pressure: Pearson Correlation	-.479	-.484	-.141
Significance (2-tailed)	**.015**	**.014**	.501
Average Nocturnal Diastolic Blood Pressure: Pearson Correlation	-.155	-.413	-.069
Significance (2-tailed)	.460	**.040**	.743
Average Whole-Day Systolic Blood Pressure: Pearson	-.379	-.529	-.213

Correlation			
Significance (2-tailed)	.061	**.007**	.306
Average Whole-Day Diastolic Blood Pressure: Pearson Correlation	.019	-.408	-.112
Significance (2-tailed)	.928	**.043**	.593
All Day Systolic Blood Pressure: Pearson Correlation	-.039	-.061	.017
Significance (2-tailed)	.667	.500	.852
All Day Diastolic Blood Pressure: Pearson Correlation	-.012	-.048	-.036
Significance (2-tailed)	.896	.596	.695

Table 5: Correlation of Pulse Transit Time Measurements and Blood Pressure Variables

Figure 14 illustrates one of the significant correlations from Table 5, showing that Maximum Pulse Transit Time is negatively correlated with Whole-day Systolic Blood Pressure (r=-.529, p=.007). The trend line demonstrates that, in general, higher blood pressures correlate with lower maximum pulse transit times. There were no significant associations found between Whole-day Systolic or Diastolic Blood Pressure and Average, Maximum, or Minimum Pulse Transit Time.



Correlation coefficient = -.529
p = .007
Figure 14: Correlating Maximum PTT and Average Whole-Day Systolic Blood Pressure

Aim 3 Results: Association of pulse transit time variables with gestational hypertension in women without obstructive sleep apnea

For the third aim, a sample of 88 obstructive sleep apnea negative women who had given birth were studied to analyze the ability of pulse transit time measurements to predict outcomes of pregnancy including gestational hypertension of preeclampsia. Descriptive statistics are presented in Table 6.

	Whole sample mean and standard deviations	**Obstructive sleep apnea negative group means and standard deviations**
Age	29.26 years ± 6.32	28.97 years ± 5.65

Height	63.86 inches ± 3.11	63.73 inches ± 3.19
Weight	201.55 lbs ± 47.73	198.93 lbs ± 47.85
BMI	34.74 kg/m^2 ± 7.98	34.16 kg/m^2 ± 8.06
Gestational age at study visit	10.64 weeks ± 1.90	10.69 weeks ± 1.89
% of women with chronic hypertension	11.19%	9.48%
% of nulliparous women	33.58%	33.62%
Diabetes (outside of pregnancy)	2.24%	2.24%

Table 6: Demographics/Comorbidities Table for Aim 3

The results presented in Table 7 reveal that the pulse transit time variables were not able to predict the development of gestational hypertension or preeclampsia.

Pulse Transit Time Variables	df	F	Significance
Average PTT	1	.965	.330
Minimum PTT	1	1.492	.226
Maximum PTT	1	.276	.601
PTT with Apnea Count	1	.04	.258
PTT with apnea Index	1	.006	.938
PTT with Hypopnea Count	1	.423	.518
PTT with Hypopnea Index	1	.393	.533
PTT with Desaturation Count	1	.173	.679
PTT with Desaturation Index	1	.140	.709
Average PTT Drop	1	.01	.915
Maximum PTT Drop	1	.000	.984
PTT Drops Index	1	.100	.753

Table 7: Pulse Transit Time Variables as Predictors for Development of Hypertensive Disorders of Pregnancy (Gestational Hypertension and Preeclampsia)

Discussion

The main findings of the first aim of this research project were that: 1) the pulse transit time drop index may be detecting more subtle obstructive events during sleep than the more conventional parameters of obstructive sleep apnea (apneas and hypopneas); 2) pulse transit time may classify disease severity differently in women with and without obstructive sleep apnea; and 3) pulse transit time drop index may identify a significantly higher number of women with obstructive sleep apnea than the conventional scoring. In addition, Aims 2 and 3 showed that: 1) pulse transit time measures correlate with nocturnal and diurnal blood pressure numbers suggesting that the nocturnal insult carries into the daytime; and 2) pulse transit time in early pregnancy does not seem to predict the later development of hypertensive disorders of pregnancy.

Demographics/Comorbidities Table

The obstructive sleep apnea positive group is older, heavier, slightly taller, and has a higher average body mass index than the obstructive sleep apnea negative group. This was expected, as obesity is a risk factor for obstructive sleep apnea development. A much higher percentage of women in the obstructive sleep apnea positive group have hypertension than the obstructive sleep apnea negative group, most likely because hypertension and obstructive sleep apnea commonly exist as comorbidities.

Aim 1: Obstructive Sleep Apnea Status versus Pulse Transit Time Values

When comparing obstructive sleep apnea positive versus overweight and obese snorers without sleep apnea, it was found that there were no significant differences in their Average Pulse Transit Time, Minimum Pulse Transit Time, and Maximum Pulse Transit Time.

However, when comparing obstructive sleep apnea positive versus negative groups, significant differences were observed in the Pulse Transit Time Drops with Apnea Index, Pulse Transit time Drops with Hypopnea Index, and Pulse Transit Time Drops with Desaturation Index. This could be explained by the fact that obstructive sleep apnea positive patients would be experiencing more frequent respiratory events than obstructive sleep apnea negative patients, and therefore would exhibit a greater number and frequency of events during sleep. As pulse transit time drops typically correspond with respiratory events, logically there would be higher numbers of drops in obstructive sleep apnea positive than negative.

When comparing obstructive sleep apnea positive versus negative groups, it was found that the Average Pulse Transit Time Drop and Maximum Pulse Transit Time Drop values were significantly different between groups. The Mean Average Pulse Transit Time Drop in the obstructive sleep apnea negative group was much greater than the Mean Average Pulse Transit Time Drop in the obstructive sleep apnea positive group. This suggests that the obstructive sleep apnea positive patients experience less of a pulse transit time drop because their sympathetic nervous systems are chronically stimulated, thus their arterial stiffness is high all the time. So, their pulse transit time baseline is already very low; thus, there is little change in value when the sympathetic nervous system is stimulated. However, patients without obstructive sleep apnea have arteries that exist in a more "relaxed" state because their sympathetic nervous systems are not chronically activated. Thus, there is a great difference in their pulse transit time during sleep events, when their sympathetic nervous systems become activated, as compared to their normal pulse transit time values. Thus, they exhibit a larger drop value.

There were no significant findings observed when correlations of Apnea-Hypopnea Index and Average, Maximum, and Minimum Pulse Transit Time values were done. This suggests that pulse transit time is a variable that is independent from Apnea-Hypopnea Index.

Additionally, the fact that the Pulse Transit Time Drops Index values are consistently higher than the Apnea-Hypopnea Index suggests that subtle obstructive sleep events that are not defined by the conventional definition of "apnea" or "hypopnea" are occurring and resulting in either cortical arousals (detected by electroencephalography) or sub-cortical microarousals that are the result of sympathetic activation and changes in vascular tone and blood pressure. Therefore, they would not be reflected in the Apnea-Hypopnea Index, but the pulse transit time measurements are able to detect and record them through the sympathetic stimulation. These smaller flow limitations are still very important to analyze because they can cause blood pressure elevation or persistent sympathetic activation which, over time, can have a negative effect in pregnant women. These findings would be consistent with past studies where it was observed that pregnant women are prone to have subtle airflow limitations that aren't necessarily detected by typical sleep study scoring methods.

Assuming that pulse transit time measurement devices are extremely accurate and that measurements are interpreted correctly, these findings could prove very helpful in assessing clinically significant airflow limitations in pregnant women. Pregnant women may have previously been dismissed as obstructive sleep apnea negative after a sleep test returned a low Apnea-Hypopnea Index. However, perhaps with pulse transit time measurements in the future, additional subtle airflow limitations may be identified by

pulse transit time measurements beyond those recognized from a typical sleep test. This is especially relevant for the pregnant population, as diagnoses of obstructive sleep apnea are not extremely common, but the presence of sleep-disordered breathing can still cause negative outcomes in the pregnancy for both the mother and fetus.

Last, it was found that the average pulse transit time values were not significantly different between groups based on chronic hypertension status. This suggests that either average pulse transit time values are not able to differentiate between hypertension groups, or that the patients that were not diagnosed with chronic hypertension may also be at a high risk for developing chronic hypertension.

Aim 2: Pulse Transit Time Correlated with Blood Pressure Measurements

There was a significant negative correlation between the Maximum Pulse Transit Time value and a variety of blood pressure values, including Average Diurnal Systolic and Diastolic Blood Pressure, Average Nocturnal Systolic and Diastolic Blood Pressure, and Average Whole-day Systolic and Diastolic Blood Pressure. This is most likely because blood pressure values directly affect arterial stiffness, thus directly affect pulse transit time. The Maximum Pulse Transit Time variable reflects the amount of time it takes blood to travel from the heart to an extremity when the arteries are at their most relaxed state. Greater elasticity in the arteries causes a greater pulse transit time, as it takes blood longer to travel to the peripheries when the arteries are lax.

Patients with persistent sympathetic activation, high blood pressure, and chronic arterial stiffness would exhibit lower Maximum Pulse Transit Time values than patients with normal blood pressures. Thus, these results illustrate that higher blood pressure values correlate with lower Maximum Pulse Transit Time measurements.

It is also noted that blood pressure measurements that occur during the daytime correlate with pulse transit time measurements that are taken at night. This provides further evidence that changes in sympathetic activation that occur with sleep may persist into the daytime, and be reflected in higher diurnal blood pressure values.

Next, a significant negative correlation was found between Average Pulse Transit Time and Average Nocturnal Systolic Blood Pressure, and there was almost a significant correlation between Average Pulse Transit Time and Average Whole-day Systolic Blood Pressure. This signifies that higher blood pressures correspond with lower pulse transit times. This, again, is the result of persistent sympathetic activation and high blood pressures causing chronic arterial stiffness. So, a low pulse transit time is observed at night during sleep, and as seen with the close Whole-day Systolic Blood Pressure correlation, sympathetic activation may persist into the daytime in terms of heightened blood pressure. Additionally, heightened nocturnal blood pressure is known to be associated with negative cardiovascular outcomes (176).

Overall, although pulse transit time measurements are recorded during sleep, it appears that these measurements carry to the daytime and correlate with both nocturnal and daytime measurements. This implies that changes in sympathetic activation that occur with sleep may persist into the daytime.

Aim 3: Pulse Transit Time as a Predictor of a Composite Outcome of Hypertension of Pregnancy and Preeclampsia

Both preeclampsia and gestational hypertension are considered composite outcomes for this Aim. Previous studies combine preeclampsia, gestational hypertension, and reduced fetal growth. Both gestational hypertension and preeclampsia are placental syndromes.

In the results obtained in this study, it was found that pulse transit time measurements in early pregnancy were not able to determine which women would later develop hypertensive disorders of pregnancy. This may be because only 58 women were studied, and only 16 had preeclampsia. Results were limited due to the fact that many women in the total sample had not delivered at the time of data collection, so could not have their pregnancy outcomes analyzed at that time. The results may have been stronger with a greater statistical power, had more patients been studied. Or, the fact that pulse transit time measurements in early pregnancy were not able to predict later development of hypertensive disorders of pregnancy could be because obstructive sleep apnea negative women are almost as likely to develop these outcomes as positive women. Since pulse transit time drops occur quite frequently in women without obstructive sleep apnea, the high likelihood of the sleep apnea negative group developing gestational hypertensive outcomes would make it difficult to detect significant differences.

Because there are no previous studies that analyze gestational hypertension as a predictor for the development of obstructive sleep apnea, it is difficult to determine how much change should be considered significant as a predictive model.

Conclusion and Future Directions

In summary, these findings suggest that pulse transit time is capable of identifying obstructive events beyond the conventional apneas and hypopneas. This is especially relevant for pregnant women, as oxygen desaturations do not appear to play a large role in the disease, and arousals and airflow limitations are more likely, and because women who snore, but do not necessarily have obstructive sleep apnea, appear to be at risk to develop complications such as hypertensive disorders of pregnancy. This study demonstrated objective physiological alterations in women who snore but do not meet criteria for obstructive sleep apnea, setting the stage for future studies evaluating the impact of interventions in this subset of women. The correlation of pulse transit time measurements with nocturnal and diurnal blood pressure measurements further confirms the impact of these measurements on clinically measured hemodynamic variables. Future studies can examine the question of whether pulse transit time measures have the ability to predict the development of gestational hypertension outcomes in a larger sample that includes low risk controls.

References

1. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ, Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. WMJ : official publication of the State Medical Society of Wisconsin. 2009;108(5):246-9.

2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. American journal of respiratory and critical care medicine. 2002;165(9):1217-39.

3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. The New England journal of medicine. 1993;328(17):1230-5.

4. Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. Br J Nutr. 2008;99(5):931-40.

5. Svensson M, Franklin KA, Theorell-Haglow J, Lindberg E. Daytime sleepiness relates to snoring independent of the apnea-hypopnea index in women from the general population. Chest. 2008;134(5):919-24.

6. O'Brien LM, Bullough AS, Owusu JT, Tremblay KA, Brincat CA, Chames MC, et al. Pregnancy-onset habitual snoring, gestational hypertension, and preeclampsia: prospective cohort study. American journal of obstetrics and gynecology. 2012;207(6):487 e1-9.

7. Hu FB, Willett WC, Colditz GA, Ascherio A, Speizer FE, Rosner B, et al. Prospective study of snoring and risk of hypertension in women. American journal of epidemiology. 1999;150(8):806-16.

8. Miller K. Getting Enough Sleep Can Be a Matter of Life and Death: Discover Magazine; 2015 [April 2015:[Available from: http://discovermagazine.com/2015/april/17-wake-up-call.

9. Exar EN, Collop NA. The upper airway resistance syndrome. Chest. 1999;115(4):1127-39.

10. de Godoy LBM, Palombini LO, Guilleminault C, Poyares D, Tufik S, Togeiro SM. Treatment of upper airway resistance syndrome in adults: Where do we stand?(). Sleep Science. 2015;8(1):42-8.

11. Douglas NJ, White DP, Pickett CK, Weil JV, Zwillich CW. Respiration during sleep in normal man. Thorax. 1982;37(11):840-4.

12. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest. 1993;104(3):781-7.

13. Guilleminault C, Stoohs R, Clerk A, Simmons J, Labanowski M. From obstructive sleep apnea syndrome to upper airway resistance syndrome: consistency of daytime sleepiness. Sleep. 1992;15(6 Suppl):S13-6.

14. Krakow B, Romero E, Ulibarri VA, Kikta S. Prospective Assessment of Nocturnal Awakenings in a Case Series of Treatment-Seeking Chronic Insomnia Patients: A Pilot Study of Subjective and Objective Causes. Sleep.35(12):1685-92.

15. Ruehland WR, Rochford PD, O'Donoghue FJ, Pierce RJ, Singh P, Thornton AT. The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. Sleep. 2009;32(2):150-7.

16. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-89.

17. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. Journal of the American College of Cardiology. 2008;52(8):686-717.

18. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: Pathophysiology and treatment. Chest. 2007;131(2):595-607.

19. White DP. Pathogenesis of obstructive and central sleep apnea. American journal of respiratory and critical care medicine. 2005;172(11):1363-70.

20. Littleton SW, Mokhlesi B. The pickwickian syndrome-obesity hypoventilation syndrome. Clin Chest Med. 2009;30(3):467-78, vii-viii.

21. Powers MA. The obesity hypoventilation syndrome. Respir Care. 2008;53(12):1723-30.

22. Piper AJ, Grunstein RR. Current perspectives on the obesity hypoventilation syndrome. Current opinion in pulmonary medicine. 2007;13(6):490-6.

23. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. American journal of epidemiology. 2013;177(9):1006-14.

24. Bhalla V, Georgiopoulou VV, Kalogeropoulos AP, Marti CN, Cole RT, Gupta D, et al. Contemporary outcomes of optimally treated heart failure patients with sleep apnea. Case for urgency in evaluation of newer interventions? From the Atlanta Cardiomyopathy Consortium. Int J Cardiol. 2013;165(2):366-8.

25. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. Sleep. 1997;20(9):705-6.

26. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. The New England journal of medicine. 2000;342(19):1378-84.

27. Wetter DW, Young TB, Bidwell TR, Badr MS, Palta M. Smoking as a risk factor for sleep-disordered breathing. Archives of internal medicine. 1994;154(19):2219-24.

28. Dancey DR, Hanly PJ, Soong C, Lee B, Shepard J, Jr., Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. Chest. 2003;123(5):1544-50.

29. Redline S, Tosteson T, Tishler PV, Carskadon MA, Millman RP. Studies in the genetics of obstructive sleep apnea. Familial aggregation of symptoms associated with sleep-related breathing disturbances. The American review of respiratory disease. 1992;145(2 Pt 1):440-4.

30. Redline S, Tishler PV, Tosteson TD, Williamson J, Kump K, Browner I, et al. The familial aggregation of obstructive sleep apnea. American journal of respiratory and critical care medicine. 1995;151(3 Pt 1):682-7.

31. Benumof JL. Obesity, sleep apnea, the airway and anesthesia. Current opinion in anaesthesiology. 2004;17(1):21-30.

32. Smith R, Argod J, Pepin J, Levy P. Pulse transit time: an appraisal of potential clinical. Thorax. 1999;54(5):452-7.

33. Andreas S, Hajak G, von Breska B, Ruther E, Kreuzer H. Changes in heart rate during obstructive sleep apnoea. The European respiratory journal. 1992;5(7):853-7.

34. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep Apnea: Types, Mechanisms, and Clinical Cardiovascular Consequences. Journal of the American College of Cardiology. 2017;69(7):841-58.

35. Pitson D, Chhina N, Knijn S, van Herwaaden M, Stradling J. Changes in pulse transit time and pulse rate as markers of arousal from sleep in normal subjects. Clinical science (London, England : 1979). 1994;87(2):269-73.

36. Cowie MR. Sleep apnea: State of the art. Trends in cardiovascular medicine. 2016.

37. de la Sierra A, Redon J, Banegas JR, Segura J, Parati G, Gorostidi M, et al. Prevalence and factors associated with circadian blood pressure patterns in hypertensive patients. Hypertension (Dallas, Tex : 1979). 2009;53(3):466-72.

38. Zhang W, Si LY. Obstructive sleep apnea syndrome (OSAS) and hypertension: pathogenic mechanisms and possible therapeutic approaches. Ups J Med Sci. 2012;117(4):370-82.

39. Loredo JS, Nelesen R, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in normal adults. Sleep. 2004;27(6):1097-103.

40. Nagai M, Hoshide S, Kario K. Sleep duration as a risk factor for cardiovascular disease- a review of the recent literature. Curr Cardiol Rev. 2010;6(1):54-61.

41. Ip MS, Tse HF, Lam B, Tsang KW, Lam WK. Endothelial function in obstructive sleep apnea and response to treatment. American journal of respiratory and critical care medicine. 2004;169(3):348-53.

42. Tousoulis D, Kampoli AM, Tentolouris C, Papageorgiou N, Stefanadis C. The role of nitric oxide on endothelial function. Current vascular pharmacology. 2012;10(1):4-18.

43. Duchna HW, Orth M, Schultze-Werninghaus G, Guilleminault C, Stoohs RA. Long-term effects of nasal continuous positive airway pressure on vasodilatory endothelial function in obstructive sleep apnea syndrome. Sleep & breathing = Schlaf & Atmung. 2005;9(3):97-103.

44. Aeschbacher S, Bossard M, Schoen T, Schmidlin D, Muff C, Maseli A, et al. Heart Rate Variability and Sleep-Related Breathing Disorders in the General Population. The American journal of cardiology. 2016;118(6):912-7.

45. Yasuma F, Hayano J. Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? Chest. 2004;125(2):683-90.

46. Bauer T, Ewig S, Schafer H, Jelen E, Omran H, Luderitz B. Heart rate variability in patients with sleep-related breathing disorders. Cardiology. 1996;87(6):492-6.

47. Dingli K, Assimakopoulos T, Wraith PK, Fietze I, Witt C, Douglas NJ. Spectral oscillations of RR intervals in sleep apnoea/hypopnoea syndrome patients. The European respiratory journal. 2003;22(6):943-50.

48. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation. 1996;93(5):1043-65.

49. Hu X, Kang J, Xiao D, Wang W, Hou X, Yu R. [The influence of nasal continual positive airway pressure on some vasoactive substances in patients with obstructive sleep apnea syndrome]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2002;25(1):36-8.

50. Arter JL, Chi DS, M G, Fitzgerald SM, Guha B, Krishnaswamy G. Obstructive sleep apnea, inflammation, and cardiopulmonary disease. Frontiers in bioscience : a journal and virtual library. 2004;9:2892-900.

51. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep Loss and Inflammation. Best practice & research Clinical endocrinology & metabolism. 2010;24(5):775-84.

52. Yehuda S, Sredni B, Carasso RL, Kenigsbuch-Sredni D. REM sleep deprivation in rats results in inflammation and interleukin-17 elevation. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research. 2009;29(7):393-8.

53. Itzhaki S, Lavie L, Pillar G, Tal G, Lavie P. Endothelial dysfunction in obstructive sleep apnea measured by peripheral arterial tone response in the finger to reactive hyperemia. Sleep. 2005;28(5):594-600.

54. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. American journal of respiratory and critical care medicine. 2002;165(5):670-6.

55. Briançon-Marjollet A, Weiszenstein M, Henri M, Thomas A, Godin-Ribuot D, Polak J. The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms. Diabetology & Metabolic Syndrome. 2015;7.

56. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Oda N, Tanaka A, et al. Silent brain infarction and platelet activation in obstructive sleep apnea. American journal of respiratory and critical care medicine. 2007;175(6):612-7.

57. Shamsuzzaman A, Amin RS, Calvin AD, Davison D, Somers VK. Severity of Obstructive Sleep Apnea is Associated with Elevated Plasma Fibrinogen in Otherwise Healthy Patients. Sleep & breathing = Schlaf & Atmung. 2014;18(4):761-6.

58. Peled N, Kassirer M, Kramer MR, Rogowski O, Shlomi D, Fox B, et al. Increased erythrocyte adhesiveness and aggregation in obstructive sleep apnea syndrome. Thrombosis research. 2008;121(5):631-6.

59. Peng YH, Liao WC, Chung WS, Muo CH, Chu CC, Liu CJ, et al. Association between obstructive sleep apnea and deep vein thrombosis / pulmonary embolism: a population-based retrospective cohort study. Thrombosis research. 2014;134(2):340-5.

60. Buda AJ, Pinsky MR, Ingels NB, Jr., Daughters GT, 2nd, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. The New England journal of medicine. 1979;301(9):453-9.

61. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. The New England journal of medicine. 2016;375(10):919-31.

62. Otto ME, Belohlavek M, Romero-Corral A, Gami AS, Gilman G, Svatikova A, et al. Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. The American journal of cardiology. 2007;99(9):1298-302.

63. Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. Chest. 1995;107(6):1538-44.

64. Shiomi T, Guilleminault C, Stoohs R, Schnittger I. Leftward shift of the interventricular septum and pulsus paradoxus in obstructive sleep apnea syndrome. Chest. 1991;100(4):894-902.

65. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev. 2010;90(1):47-112.

66. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Archives of internal medicine. 1997;157(15):1746-52.

67. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. Jama. 2000;283(14):1829-36.

68. Nieto FJ, Peppard PE, Young TB. Sleep Disordered Breathing and Metabolic Syndrome. WMJ : official publication of the State Medical Society of Wisconsin. 2009;108(5):263-5.

69. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. American journal of respiratory and critical care medicine. 2001;163(1):19-25.

70. Caples SM, Garcia-Touchard A, Somers VK. Sleep-disordered breathing and cardiovascular risk. Sleep. 2007;30(3):291-303.

71. Newman AB, Nieto FJ, Guidry U, Lind BK, Redline S, Pickering TG, et al. Relation of sleep-disordered breathing to cardiovascular disease risk factors: the Sleep Heart Health Study. American journal of epidemiology. 2001;154(1):50-9.

72. Lavie P, Yoffe N, Berger I, Peled R. The relationship between the severity of sleep apnea syndrome and 24-h blood pressure values in patients with obstructive sleep apnea. Chest. 1993;103(3):717-21.

73. Dopp JM, Reichmuth KJ, Morgan BJ. Obstructive sleep apnea and hypertension: mechanisms, evaluation, and management. Current hypertension reports. 2007;9(6):529-34.

74. Verdecchia P, Schillaci G, Gatteschi C, Zampi I, Battistelli M, Bartoccini C, et al. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. Circulation. 1993;88(3):986-92.

75. Schmieder RE. End organ damage in hypertension. Dtsch Arztebl Int. 2010;107(49):866-73.

76. Kasai T, Floras JS, Bradley TD. Sleep apnea and cardiovascular disease: a bidirectional relationship. Circulation. 2012;126(12):1495-510.

77. Bradley TD, Floras JS. Sleep apnea and heart failure: Part I: obstructive sleep apnea. Circulation. 2003;107(12):1671-8.

78. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. The New England journal of medicine. 2005;353(19):2034-41.

79. De Torres-Alba F, Gemma D, Armada-Romero E, Rey-Blas J, López-de-Sá E, López-Sendon Jé L. Obstructive Sleep Apnea and Coronary Artery Disease: From Pathophysiology to Clinical Implications. Pulmonary medicine. 2013;2013.

80. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in men with coronary artery disease. Chest. 1996;109(3):659-63.

81. Peker Y, Kraiczi H, Hedner J, Loth S, Johansson A, Bende M. An independent association between obstructive sleep apnoea and coronary artery disease. The European respiratory journal. 1999;14(1):179-84.

82. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in women: occurrence and association with coronary artery disease. The American journal of medicine. 1996;101(3):251-6.

83. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Prevalence and significance. The American journal of medicine. 1982;73(3):317-21.

84. Giaid A, Saleh D. Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. The New England journal of medicine. 1995;333(4):214-21.

85. Ozaki M, Kawashima S, Yamashita T, Ohashi Y, Rikitake Y, Inoue N, et al. Reduced hypoxic pulmonary vascular remodeling by nitric oxide from the endothelium. Hypertension (Dallas, Tex : 1979). 2001;37(2):322-7.

86. Sajkov D, McEvoy RD. Obstructive sleep apnea and pulmonary hypertension. Prog Cardiovasc Dis. 2009;51(5):363-70.

87. Adeseun GA, Rosas SE. The Impact of Obstructive Sleep Apnea on Chronic Kidney Disease. Current hypertension reports. 2010;12(5):378-83.

88. Kraus MA, Hamburger RJ. Sleep apnea in renal failure. Advances in peritoneal dialysis Conference on Peritoneal Dialysis. 1997;13:88-92.

89. Curtin SC, Abma JC, Ventura SJ, Henshaw SK. Pregnancy rates for U.S. women continue to drop. NCHS Data Brief. 2013(136):1-8.

90. Pien GW, Fife D, Pack AI, Nkwuo JE, Schwab RJ. Changes in symptoms of sleep-disordered breathing during pregnancy. Sleep. 2005;28(10):1299-305.

91. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. Jama. 2000;284(23):3015-21.

92. Artal R, Lockwood CJ, Brown HL. Weight gain recommendations in pregnancy and the obesity epidemic. Obstetrics and gynecology. 2010;115(1):152-5.

93. Vahratian A. Prevalence of Overweight and Obesity among Women of Childbearing Age: Results from the 2002 National Survey of Family Growth. Maternal and child health journal. 2009;13(2):268-73.

94. Alaily AB, Carrol KB. Pulmonary ventilation in pregnancy. British journal of obstetrics and gynaecology. 1978;85(7):518-24.

95. Shnider SM, Levinson G. Anesthesia for obstetrics. 3rd ed. Baltimore: Williams & Wilkins; 1993. xv, 744 p. p.

96. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. Clin Chest Med. 2011;32(1):175-89, x.

97. Pilkington S, Carli F, Dakin MJ, Romney M, De Witt KA, Dore CJ, et al. Increase in Mallampati score during pregnancy. British journal of anaesthesia. 1995;74(6):638-42.

98. Camann WR, Ostheimer GW. Physiological adaptations during pregnancy. International anesthesiology clinics. 1990;28(1):2-10.

99. Izci Balserak B. Sleep disordered breathing in pregnancy. Breathe. 2015;11(4):268-77.

100. Franklin KA, Holmgren PA, Jonsson F, Poromaa N, Stenlund H, Svanborg E. Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest. 2000;117(1):137-41.

101. Bourjeily G, Raker CA, Chalhoub M, Miller MA. Pregnancy and fetal outcomes of symptoms of sleep-disordered breathing. The European respiratory journal. 2010;36(4):849-55.

102. Bourjeily G RC. Epworth Sleepiness Score in pregnancy. American Thoracic Society in Toronto. 2008.

103. O'Brien LM, Bullough AS, Owusu JT, Tremblay KA, Brincat CA, Chames MC, et al. Pregnancy-Onset Habitual Snoring, Gestational Hypertension, and Pre-eclampsia: Prospective Cohort Study. American journal of obstetrics and gynecology. 2012;207(6):487.e1-9.

104. Pien GW, Pack AI, Jackson N, Maislin G, Macones GA, Schwab RJ. Risk factors for sleep-disordered breathing in pregnancy. Thorax. 2014;69(4):371-7.

105. Chang JJ, Pien GW, Duntley SP, Macones GA. Sleep deprivation during pregnancy and maternal and fetal outcomes: is there a relationship? Sleep medicine reviews. 2010;14(2):107-14.

106. Izci-Balserak B, Pien GW. Sleep-disordered breathing and pregnancy: potential mechanisms and evidence for maternal and fetal morbidity. Current opinion in pulmonary medicine. 2010;16(6):574-82.

107. Ravishankar S, Bourjeily G, Lambert-Messerlian G, He M, De Paepe ME, Gundogan F. Evidence of Placental Hypoxia in Maternal Sleep Disordered Breathing. Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society. 2015;18(5):380-6.

108. Fung AM, Wilson DL, Lappas M, Howard M, Barnes M, O'Donoghue F, et al. Effects of maternal obstructive sleep apnoea on fetal growth: a prospective cohort study. PLoS ONE. 2013;8(7):e68057.

109. Kovo M, Schreiber L, Ben-Haroush A, Wand S, Golan A, Bar J. Placental vascular lesion differences in pregnancy-induced hypertension and normotensive fetal growth restriction. American journal of obstetrics and gynecology. 2010;202(6):561.e1-5.

110. Carnelio S, Morton A, McIntyre HD. Sleep disordered breathing in pregnancy: the maternal and fetal implications. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2016:1-9.

111. Pengo MF, Rossi GP, Steier J. Obstructive sleep apnea, gestational hypertension and preeclampsia: a review of the literature. Current opinion in pulmonary medicine. 2014;20(6):588-94.

112. Bourjeily G MJ, Paglia M. Outcomes of sleep disordered breathing in pregnancy. The Open Sleep Journal. 2013;6(Suppl 1: M4):28-36.

113. Okun ML, Roberts JM, Marsland AL, Hall M. How disturbed sleep may be a risk factor for adverse pregnancy outcomes. Obstet Gynecol Surv. 2009;64(4):273-80.

114. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstetrics and gynecology. 2013;122(5):1122-31.

115. Champagne K, Schwartzman K, Opatrny L, Barriga P, Morin L, Mallozzi A, et al. Obstructive sleep apnoea and its association with gestational hypertension. The European respiratory journal. 2009;33(3):559-65.

116. Curiel-Balsera E, Prieto-Palomino MA, Munoz-Bono J, Ruiz de Elvira MJ, Galeas JL, Quesada Garcia G. [Analysis of maternal morbidity and mortality among patients admitted to Obstetric Intensive Care with severe preeclampsia, eclampsia or HELLP syndrome]. Medicina intensiva. 2011;35(8):478-83.

117. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. Am J Hypertens. 2008;21(5):521-6.

118. Habli M, Levine RJ, Qian C, Sibai B. Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation. American journal of obstetrics and gynecology. 2007;197(4):406.e1-7.

119. Pollock W, Rose L, Dennis CL. Pregnant and postpartum admissions to the intensive care unit: a systematic review. Intensive care medicine. 2010;36(9):1465-74.

120. Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet (London, England). 1993;341(8858):1447-51.

121. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet (London, England). 2005;365(9461):785-99.

122. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet (London, England). 2010;376(9741):631-44.

123. McCoy S, Baldwin K. Pharmacotherapeutic options for the treatment of preeclampsia. Am J Health Syst Pharm. 2009;66(4):337-44.

124. Namen AM, Landry SH, Case LD, McCall WV, Dunagan DP, Haponik EF. Sleep histories are seldom documented on a general medical service. Southern medical journal. 2001;94(9):874-9.

125. Flemons WW, Douglas NJ, Kuna ST, Rodenstein DO, Wheatley J. Access to diagnosis and treatment of patients with suspected sleep apnea. American journal of respiratory and critical care medicine. 2004;169(6):668-72.

126. Douglas NJ, Thomas S, Jan MA. Clinical value of polysomnography. Lancet (London, England). 1992;339(8789):347-50.

127. Shrivastava D, Jung S, Saadat M, Sirohi R, Crewson K. How to interpret the results of a sleep study. Journal of Community Hospital Internal Medicine Perspectives. 2014;4(5).

128. Abad VC, Guilleminault C. Diagnosis and treatment of sleep disorders: a brief review for clinicians. Dialogues Clin Neurosci. 2003;5(4):371-88.

129. Cherniack RM, Farhi LE, Armstrong BW, Proctor DF. A comparison of esophageal and intrapleural pressure in man. Journal of applied physiology. 1955;8(2):203-11.

130. Gilbert R, Peppi D, Auchincloss JH, Jr. Measurement of transdiaphragmatic pressure with a single gastric-esophageal probe. Journal of applied physiology: respiratory, environmental and exercise physiology. 1979;47(3):628-30.

131. Truwit J. Lung mechanics. Comprehensive Respiratory Care. 1995:18-31.

132. Akoumianaki E, Maggiore SM, Valenza F, Bellani G, Jubran A, Loring SH, et al. The application of esophageal pressure measurement in patients with respiratory failure. American journal of respiratory and critical care medicine. 2014;189(5):520-31.

133. Woodson BT, Wooten MR. A multisensor solid-state pressure manometer to identify the level of collapse in obstructive sleep apnea. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 1992;107(5):651-6.

134. Mindell JA, Owens JA. A clinical guide to pediatric sleep : diagnosis and management of sleep problems. 2nd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010. viii, 232 p. p.

135. Nox Medical. Noxturnal PTT Customer Support Document. Reykjavik, Iceland2012.

136. National Instruments. In: http://www.ni.com/tutorial/6349/en/, editor. 2012. p. Figure 1: A typical one-cycle ECG tracing.

137. Poon CC, Zhang YT. Cuff-less and noninvasive measurements of arterial blood pressure by pulse transit time. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Annual Conference. 2005;6:5877-80.

138. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama. 2003;289(19):2560-72.

139. Hamzaoui O, Monnet X, Teboul JL. Pulsus paradoxus. The European respiratory journal. 2013;42(6):1696-705.

140. Shiomi T, Stoohs R, Guilleminault C. Aging, respiratory efforts during sleep, and pulsus paradoxus. Lung. 1993;171(4):203-11.

141. Argod J, Pepin JL, Levy P. Differentiating obstructive and central sleep respiratory events through pulse transit time. American journal of respiratory and critical care medicine. 1998;158(6):1778-83.

142. Huang H, Ye JY, Li YR, Wang XY, Zhang YH, Wang JY, et al. Pulse transit time for quantifying inspiratory effort in patients with obstructive sleep apnea. ORL; journal for oto-rhino-laryngology and its related specialties. 2011;73(1):53-60.

143. Pitson DJ, Sandell A, van den Hout R, Stradling JR. Use of pulse transit time as a measure of inspiratory effort in patients with obstructive sleep apnoea. The European respiratory journal. 1995;8(10):1669-74.

144. Brock J PD, Stradling J. Use of pulse transit time as a measure of changes in inspiratory effort. Journal of Ambulatory Monitoring. 1993;6:295-302.

145. Leas S AN, Goldman L, Loh J, Fleethham J, Strandling J. Systolic blood pressure reflect inspiratory effort during simulated obstructive sleep apnea. Sleep. 1990:178-81.

146. Leroy M, Van Surell C, Pilliere R, Hagenmuller MP, Aegerter P, Raffestin B, et al. Short-term variability of blood pressure during sleep in snorers with or without apnea. Hypertension (Dallas, Tex : 1979). 1996;28(6):937-43.

147. Argod J, Pepin JL, Smith RP, Levy P. Comparison of esophageal pressure with pulse transit time as a measure of respiratory effort for scoring obstructive nonapneic respiratory events. American journal of respiratory and critical care medicine. 2000;162(1):87-93.

148. Gomez Garcia MT, Troncoso Acevedo MF, Rodriguez Guzman M, Alegre de Montaner R, Fernandez Fernandez B, del Rio Camacho G, et al. Can pulse transit time be useful for detecting hypertension in patients in a sleep unit? Archivos de bronconeumologia. 2014;50(7):278-84.

149. Tomsin K, Mesens T, Molenberghs G, Gyselaers W. Venous pulse transit time in normal pregnancy and preeclampsia. Reproductive sciences (Thousand Oaks, Calif). 2012;19(4):431-6.

150. Vonck S, Staelens AS, Mesens T, Tomsin K, Gyselaers W. Hepatic Hemodynamics and Fetal Growth: A Relationship of Interest for Further Research. PLoS ONE. 2014;9(12).

151. Foo JY, Lim CS. Pulse transit time as an indirect marker for variations in cardiovascular related reactivity. Technology and health care : official journal of the European Society for Engineering and Medicine. 2006;14(2):97-108.

152. Payne RA, Symeonides CN, Webb DJ, Maxwell SR. Pulse transit time measured from the ECG: an unreliable marker of beat-to-beat blood pressure. Journal of applied physiology (Bethesda, Md : 1985). 2006;100(1):136-41.

153. Hsia JC, Camacho M, Capasso R. Snoring exclusively during nasal breathing: a newly described respiratory pattern during sleep. Sleep & breathing = Schlaf & Atmung. 2014;18(1):159-64.

154. Camacho M, Malu OO, Kram YA, Nigam G, Riaz M, Song SA, et al. Nasal Dilators (Breathe Right Strips and NoZovent) for Snoring and OSA: A Systematic Review and Meta-Analysis. Pulmonary medicine. 2016;2016:4841310.

155. Camacho M, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R, et al. Myofunctional Therapy to Treat Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. Sleep. 2015;38(5):669-75.

156. Guimaraes KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. American journal of respiratory and critical care medicine. 2009;179(10):962-6.

157. Guilleminault C, Huang YS, Monteyrol PJ, Sato R, Quo S, Lin CH. Critical role of myofascial reeducation in pediatric sleep-disordered breathing. Sleep medicine. 2013;14(6):518-25.

158. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep. 2006;29(2):244-62.

159. Burhenne M. How Does a Sleep Apnea Oral Device Work? [Available from: http://askthedentist.com/oral-appliance-therapy/.

160. Okuno K, Sato K, Arisaka T, Hosohama K, Gotoh M, Taga H, et al. The effect of oral appliances that advanced the mandible forward and limited mouth opening in patients with obstructive sleep apnea: a systematic review and meta-analysis of randomised controlled trials. J Oral Rehabil. 2014;41(7):542-54.

161. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. Sleep. 1996;19(2):156-77.

162. Rasheid S, Banasiak M, Gallagher SF, Lipska A, Kaba S, Ventimiglia D, et al. Gastric bypass is an effective treatment for obstructive sleep apnea in patients with clinically significant obesity. Obes Surg. 2003;13(1):58-61.

163. Van de Heyning PH, Badr MS, Baskin JZ, Cramer Bornemann MA, De Backer WA, Dotan Y, et al. Implanted upper airway stimulation device for obstructive sleep apnea. Laryngoscope. 2012;122(7):1626-33.

164. Vlachantoni IT, Dikaiakou E, Antonopoulos CN, Stefanadis C, Daskalopoulou SS, Petridou ET. Effects of continuous positive airway pressure (CPAP) treatment for obstructive sleep apnea in arterial stiffness: a meta-analysis. Sleep medicine reviews. 2013;17(1):19-28.

165. Rapoport DM, Garay SM, Goldring RM. Nasal CPAP in obstructive sleep apnea: mechanisms of action. Bulletin europeen de physiopathologie respiratoire. 1983;19(6):616-20.

166. Akashiba T, Kosaka N, Yamamoto H, Ito D, Saito O, Horie T. Optimal continuous positive airway pressure in patients with obstructive sleep apnoea: role of craniofacial structure. Respir Med. 2001;95(5):393-7.

167. Schwarz EI, Puhan MA, Schlatzer C, Stradling JR, Kohler M. Effect of CPAP therapy on endothelial function in obstructive sleep apnoea: A systematic review and meta-analysis. Respirology (Carlton, Vic). 2015;20(6):889-95.

168. Iftikhar IH, Hoyos CM, Phillips CL, Magalang UJ. Meta-analyses of the Association of Sleep Apnea with Insulin Resistance, and the Effects of CPAP on HOMA-IR, Adiponectin, and Visceral Adipose Fat. J Clin Sleep Med. 2015;11(4):475-85.

169. Kribbs NB, Pack AI, Kline LR, Smith PL, Schwartz AR, Schubert NM, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. The American review of respiratory disease. 1993;147(4):887-95.

170. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. The New England journal of medicine. 2016;375(10):919-31.

171. Cairns A, Wickwire E, Schaefer E, Nyanjom D. A pilot validation study for the NOX T3(TM) portable monitor for the detection of OSA. Sleep & breathing = Schlaf & Atmung. 2014;18(3):609-14.

172. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2012;8(5):597-619.

173. European Sleep Research Society. Glossary of Sleep-related terms. Available from http://www.esrs.eu/media/glossary-of-sleep-related-terms.html?no_cache=1.

174. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. Lancet (London, England). 2005;366(9499):1797-803.

175. Edwards N, Blyton DM, Kirjavainen T, Kesby GJ, Sullivan CE. Nasal continuous positive airway pressure reduces sleep-induced blood pressure increments in preeclampsia. American journal of respiratory and critical care medicine. 2000;162(1):252-7.

176. Friedman O, Logan AG. Can nocturnal hypertension predict cardiovascular risk? Integr Blood Press Control. 2009;2:25-37.