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Consequences of Untreated Obstructive Sleep Apnea

Binyamin S. Kanter
Touro College

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Binyamin S. Kanter will graduate with a BS in Biology in the Spring of 2018.

Abstract

Over the past few years, awareness of the prevalence of obstructive sleep apnea has significantly increased. Indeed, sleep apnea may be more common now with the increasing incidence of obesity and the growing number of elderly individuals in our population. How serious is this condition, and what are the potential long-term effects and consequences of obstructive sleep apnea if left untreated? An overlap of many serious conditions with obstructive sleep apnea has been noticed. These conditions include hypertension, heart disease and failure, stroke, diabetes, neurological diseases, depression, and a number of other serious health concerns. The purpose of this paper is to understand what the effects of untreated obstructive sleep apnea might be, and to determine if is reasonable to suggest that sleep apnea is the cause of, or at least a significant contributing factor to, the conditions it is associated with. Research shows that sleep apnea itself does inflict enormous trauma on the body. This trauma is mainly in the forms of hypoxia which leads to oxidative stress, vascular damage, and hyperstimulation of the sympathetic nervous system which can lead to high blood pressure and subsequent heart disease and failure, and by causing repeated episodes of unnatural intrathoracic pressure which can lead to a number serious health concerns and even sudden death. These findings demonstrate that sleep apnea should not be viewed as an incidental condition alongside other serious health problems nor mainly as a side effect of them. It should rather be seen as a contributing factor, if not the primary cause, of many consequential health issues.

Introduction

Untreated obstructive sleep apnea has been strongly linked to many serious diseases and early mortality. It can be the underlying cause of certain diseases, and it can cause rapid progression or early onset of others. Perhaps even more alarming, is that many incidences of sudden death, especially heart attacks, have been attributed to untreated obstructive sleep apnea. The basic understanding of its severity is that untreated obstructive sleep apnea inflicts significant and multi-faceted trauma on the body. This trauma is mainly due to nightly deprivation of oxygen in the blood, sleep deprivation, constant hyper stimulation of the sympathetic nervous system, and enormous strain on the heart. It is noteworthy that there are also secondary physical, mental, and emotional health concerns associated with untreated sleep apnea. In a random sample of several hundred individuals presenting to a sleep clinic with symptoms typical of sleep apnea, it was observed that the vast majority of the patients subsequently diagnosed with obstructive sleep apnea had at least one other serious health issue. The percentage of people with additional health problems tended to be much higher among those 40 years of age and older- i.e. in the individuals who had gone through many more years of trauma to their bodies before seeking treatment (personal observation, Chang, et.al. 2013).

It is also especially critical to explore the effects of untreated sleep apnea because it effects many more people than was previously thought (up to 24% of adult men) (Peppard, et.al. 2000) and because there has been a steady rise in the diagnosis of sleep apnea with the increased incidence of obesity. In addition to the obesity factor, it is now known that the general aging process is a major risk factor in the development of sleep apnea. Consequently, it may be prudent to study the diagnostic methods and treatment options for sleep apnea for those involved in geriatric care (Adegunsoye, Ramachandran, 2012). Several studies indicate that post-menopausal women are at increased risk for developing obstructive sleep apnea because the female sex hormones which help dilate the airway decrease after menopause (Chang, et.al. 2013). This paper will explore the question of how untreated sleep apnea effects the body and the implications of these effects.

Methods

Relevant material was scoured mainly from the web, from conversations and correspondence with a veteran pulmonologist and sleep specialist, and from personal experience observing and interviewing patients and studying polysomnography data at a sleep clinic over a period of about two months. Only materials from authoritative sources were used. An effort was made to gather information on the interaction between sleep apnea and numerous medical conditions thus broadening the scope of the paper. This was done in order get as full a picture as possible on how sleep apnea may affect the body. Material on the effectiveness of treatment of sleep apnea was also considered pertinent to understanding the mechanisms of this condition and are included in the discussion accordingly.

Definition ofTerms

Sleep apnea: Sleep apnea is defined as a cessation of breathing of ten seconds or more while asleep (Tsara, et.al. 2009). There are two main types of sleep apnea: Obstructive Sleep Apnea, and Central Sleep Apnea.

Obstructive Sleep Apnea (OSA): OSA is an anatomical condition where, while asleep, the muscles in the throat relax to an extent that the airway collapses. Specifically, there may be several different muscles responsible for this. Sleep apnea is more common in people who have a narrow airway. A narrow airway can be genetic, it can be caused by inflammation, or it can be due to obesity. (Obese individuals often have excess submucosal adipose tissue which can build up around the airway thereby causing the airway to compress.) Defects in, or damage to, the face or neck in areas which affect the airway may also be a risk factor for OSA. OSA can affect adults or children, but is more common in adults (Tsara, et.al. 2009). OSA can be a factor in determining the cause of Sudden Infantile Death Syndrome (SIDS), and a family history of OSA may be considered a risk factor in SIDS (Thach, 2008).

Central Sleep Apnea (CSA): CSA is a condition where the apneustic center in the brain stem fails to send nerve impulses necessary for breathing. CSA can occur without an obstructed airway. However, OSA and CSA are often clinically related.

When a patient who has CSA and OSA is treated just for the OSA, the CSA part of the sleep apnea is often minimized or even eliminated (Costanzo, et.al. 2015). It is possible that the disordered breathing caused by the OSA may contribute to the apneustic center malfunction- either directly or by a secondary mechanism. CSA can also be accompanied by irregular breathing patterns. For example, the Cheyne-Stokes respiration is a common symptom of primary CSA (Tsara, et.al. 2009, Costanzo, et.al. 2015). (Cheyne-Stokes respiration is a breathing pattern where there are rapid or deep breaths followed by a decrease and secession of breathing. This is usually in a cycle which can last anywhere from 30 seconds to two minutes.) CSA can also be secondary to illness or trauma, and it can be caused by certain medications and substances. It is noteworthy that if a newborn has sleep apnea, it is often CSA (Tsara, et.al. 2009) and may be a factor in determining the cause of SIDS (Thach, 2008).

Hypopnea: A hypopnea is a partial closure of the airway which is often characterized by loud snoring. (The snoring is caused by the fluttering of the air passage walls as they come in close proximity while breathing.) This partial closing is classified as a hypopnea when the obstruction is severe enough to cause oxygen desaturation in the blood.

Polysomnography: A polysomnography is a sleep study. During a sleep study, the individual is attached to electrodes and other machinery which collect information about the person's sleep. This information will include how long the patient spent in each phase of sleep, whether or not the patient has OSA or CSA, oxygen saturation or desaturation in the blood, breathing patterns, and many other items of relevance. A polysomnography can be used to diagnose sleep apnea.

Apnea-Hypopnea Index (AHI): An AHI is a score of how many events of apnea and hypopnea occur per hour. For example, if six times in the course of an hour, a patient stops breathing for ten seconds or more and/or has an oxygen desaturation, then the patient will have an AHI of 6 (or an event on average of every ten minutes).

Sleep Disordered Breathing: Sleep disordered breathing is a general term used to refer to any abnormal breathing issues or abnormal breathing patterns which can occur when one is asleep.

Continuous Positive Airway Pressure Machine (CPAP Machine): A CPAP Machine is a medical device which blows air through the nose to the back of the airway to keep it open while a person is asleep. It is currently the most effective standard treatment for sleep apnea. The machine can be adjusted to apply more or less pressure as needed, and modern machines are often self-adjusting. Other machines are available to treat more complicated cases, but they too incorporate positive pressure to treat the OSA component of any sleep disordered breathing. There are surgeries which can be performed to help eliminate OSA, but they are only about 50% effective. Some dental devices have been developed to treat OSA, but they too are often insufficient as effective treatment (Peker, et.al. 2002).

Discussion

The most obvious area of concern with sleep apnea is the fact that when breathing stops, oxygen doesn't enter the lungs. This, in turn, leads to oxygen desaturation in the blood. This hypoventilation has been linked to a number of conditions such as systemic hypertension (Peppard, et.al. 2000), pulmonary hypertension (average pressure in the pulmonary arteries greater than 25mmHg (resting)) (Adegunsoye, Ramachandran, 2012), polycythemia (high red blood cell count), heart problems, behavioral issues, emotional issues (Sheu, et.al. 2015), and birth defects (Tsara, et.al. 2009, Adegunsoye, Ramachandran, 2012). It has also been reported that early treatment is effective in eliminating these negative effects, and it is therefore of paramount importance to recognize, diagnose, and treat sleep apnea syndrome at the earliest possible opportunity (Adegunsoye, Ramachandran, 2012).

Systemic hypertension can be due to numerous factors involving OSA. One factor is that the hypoxia may lead to a pressor effect as an attempt by the body to get more oxygen (Peppard, et.al. 2000, Tkacova, et.al. 2014). Another contributing factor to hypertension is fluid and sodium retention due to sympathetic nervous system activation of the renin angiotensin aldosterone system effecting the kidneys (Bradley, Floras, 2003, Nishizaka, et.al. 2004). Many patients with untreated OSA have swelling in their legs (personal observation). It is noteworthy that administration of oxygen does not prevent the hypertensive effect of untreated OSA (Leung, Bradley, 2001).

The increased risk for developing hypertension due to untreated OSA is present even in individuals diagnosed with mild sleep apnea (AHI of approx. 5) (Peppard, et.al. 2000). The risk for developing hypertension is, however, directly related to the severity of the sleep apnea. Several studies show that individuals with more severe sleep apnea were more likely to develop hypertension than those with milder sleep apnea (Peppard, et.al. 2000, Peker, et.al. 2002, Nieto, et.al. 2000). The likelihood of developing hypertension is present regardless of gender, race, or ethnicity, and it is usually manifest in individuals middle age or older (Nieto, et.al. 2000). Severity of sleep apnea is based on AHI and on ODI (oxygen desaturation index) (Tkacova, et.al. 2014). If treatment for OSA is initiated before the onset of hypertension, then chronic hypertension as well as other cardiovascular disease may be avoided. Additionally, treatment for the OSA has a much greater impact on lowering blood pressure than does weight loss (Nieto, et.al. 2000, Tkacova, et.al. 2014, Lavie, et.al. 2000). Even in the event that hypertension has already set in, studies show that it can be minimized significantly after approximately 9 weeks of treatment (Milleron, et.al. 2004). The association between sleep apnea and hypertension is so strong that

sleep apnea should be seriously considered in the diagnosis and treatment of high blood pressure (Lavie, et.al. 2000).

Many studies have demonstrated that endothelial cells are severely damaged and impaired by hypoxic conditions, and the extent of endothelial cell damage has also been associated with the AHI index (Lui, et.al. 2013). The damage may occur in the form of apoptosis of endothelial cells, in the form of cell cycle arrest, and in a number of other ways which play a role in many of the adverse effects of untreated sleep apnea (Iida, et.al. 2002). Endothelial cell damage and dysfunction is connected to inflammation, atherosclerosis, renal damage, impaired vasodilation ability and nitric oxide production, and many other severe health issues (Bruno, et.al. 2013). Additionally, oxidative stress seems to be one of the main causes for endothelial cell damage. The extent of oxidative stress is likewise directly correlated to the severity of the sleep apnea (Del ben, et.al. 2012). It is extremely important to realize that the individual with untreated OSA is at increased risk of arterial stiffness, which can lead to heart disease and other severe health issues even if they experience very minimal symptoms (Kohler, et.al. 2008).

Hypoxia is known to cause an increase in reactive oxygen species. The mechanism for this phenomenon is not clear, but some studies suggest that this is due to the lack of a strong electron acceptor in the absence of oxygen. When there are no electron acceptors, the electrons have no place to go and therefore remain unbound as superoxide radicals or as other reactive oxygen species (ROS) (Kondoh, et.al. 2013). Compounding this problem is the reperfusion following the apneic episode which also causes an increase in ROS. Reperfusion may cause an increase in ROS for two reasons. One is that cell function has been impaired due to the lack of oxygen and is altogether not running efficiently enough to rid itself of the ROS. Second is that the sudden influx of oxygen overloads the cell which cannot process it fast enough. Studies show that hypoxia and subsequent reperfusion can cause damage to the epithelial lining of blood vessels. This damage can cause and/or contribute to atherosclerosis (Sawatari, et.al. 2016).

Aside from the ROS caused by reperfusion, there are other ROS released by a number of granular leukocytes in response to hypoxemia. The increased presence of ROS is a general danger to the body and has been linked to cancer and other illnesses. This is especially a concern for cancers which originate in endothelial cells because they are most directly affected by ROS (Kondoh, et.al. 2013). This is especially the case when the body experiences this kind of oxidative stress night after night for years on end (Adegunsoye, Ramachandran, 2012, Milleron, et.al. 2004). Proper treatment of OSA solves the problem of oxidative stress and can help reverse some or all of the damage caused by it (Del ben, et.al. 2012, Bayram, et.al. 2009).

Pulmonary hypertension in particular, is one cause for right sided heart failure and has an especially grim prognosis if left untreated. Pulmonary hypertension can be caused by a number of conditions, but its link to OSA and general sleep disordered breathing is strong enough that the American College of Chest Physicians recommends that patients presenting with pulmonary hypertension be evaluated for sleep disordered breathing. The pathophysiology of pulmonary hypertension in sleep disordered breathing is that the hypoxia caused by the breathing disorder in turn causes hypertrophy of the pulmonary arteries. This hypertrophy decreases perfusion of blood in the lungs. The situation is even more disastrous for individuals with emphysema or fibrosis of the lung. The heart tries to compensate for the decrease in perfusion by working harder, and this attempted compensation puts enormous strain on the right ventricle. This strain is unsustainable and leads to right sided heart failure and a subsequent general dyspnea even at rest. If left untreated, death typically occurs within three years of diagnosis (Adegunsoye, Ramachandran, 2012). The mechanism of how hypoxia causes the initial hypertrophy of the pulmonary arteries needs elucidation, but it seems to be related to endothelial cell dysfunction. (It is also noteworthy that obese individuals are more likely to develop pulmonary hypertension with OSA (Adegunsoye, Ramachandran, 2012).)

Aside from hypertrophy of the pulmonary arteries which can cause pulmonary hypertension, there is the direct effect of hypoxia in the form of pulmonary vasoconstriction. The reason for vasoconstriction during an hypoxic event is due to an attempt by the body to keep ventilation and perfusion in sync. In the absence of oxygen, vasoconstriction will lessen perfusion. This, however, will also cause an increase in pulmonary artery pressure. This pressure is primarily a concern while the individual is sleeping. However, about 20% of patients with elevated pulmonary artery pressure while sleeping will eventually develop pulmonary hypertension even while awake. This may be because the increased blood pressure can directly cause damage to blood vessels and result in the hardening and stenosis of those damaged vessels.

Another area of concern in untreated OSA is the effect of prolonged sympathetic nervous system stimulation. When a person with OSA has an event, the body responds to the obstructed breathing by activating the fight or flight response. This occurs for each event- all night, every night. One effect of this stimulation is vasoconstriction and an increased heart rate- both of which raise blood pressure. Eventually, this can lead to chronic systemic and pulmonary hypertension (Adegunsoye, Ramachandran, 2012).

Chronic systemic hypertension is known to negatively affect cardiovascular health and increase mortality. It has also been reported that hypertension in individuals with untreated OSA is particularly difficult to control, and that in attempting to control the high blood pressure, beta blockers are the most effective, suggesting that a major contributing factor to the high blood

pressure is sympathetic stimulation (Leung, Bradley, 2001).

Even in the absence of chronic hypertension development, there is, concern of vascular endothelial dysfunction. Over-stimulation of the sympathetic nervous system can, in of itself, lead to vascular endothelial dysfunction. The pathophysiology of the damage is, similar to what is found in patients with chronic hypertension: Vasoconstriction creates more resistance in the blood vessels. Resistance, especially if prolonged, can cause damage to the vasculature and lead to hardening of the blood vessels (Adegunsoye, Ramachandran, 2012). The damage can be quite significant because the effects of sympathetic system over-stimulation linger into the wake hours as well (Tkacova, et.al. 2014).

The constant presence of catecholamine levels also puts the untreated OSA patient at greater risk for thromboembolism because high levels of catecholamines tends to lead to platelet aggregation. This and other phenomena which can predispose an individual to thromboembolism can be reversed with effective treatment. The reversal of which suggests that the hypercoagulability in individuals with OSA is indeed caused by the OSA (Adegunsoye, Ramachandran, 2012).

There is a secondary problem associated with untreated OSA of the sleep deprived individual. The way the body clears the obstructed breathing is by jolting the person out of deep sleep long enough to return muscle tone to the airway and open it back up. This arousal from deep sleep is called a Respiratory Effort- Related Arousal or RERA. A RERA can be present even in the absence of a clinically defined apnea- for example if the breathing stops for less than 10 seconds, or if there is no significant oxygen desaturation during an event (Tsara, et.al. 2009). There are serious health risks associated with sleep deprivation as well as physiological effects and secondary risks. Psychological effects could include depression, apathy, and irritably. Secondary risks could include general fatigue or falling asleep while driving (Adegunsoye, Ramachandran, 2012).

Sleep deprivation and hypoxia are both known causes of inflammation. Inflammation is an independent factor in endothelial cell dysfunction and has also been linked to certain cancers (Lui, et.al. 2013). Several factors which cause inflammation are found in high levels in individuals with untreated OSA. Proper treatment is effective in stopping the inflammatory response (Adegunsoye, Ramachandran, 2012, Shamsuzzaman, et.al. 2003).

Another factor associated with OSA which causes sleep deprivation is nocturia. Nocturia is a condition where an individual's sleep is interrupted multiple times in order to empty the bladder. The pathophysiology of this condition is that attempting to breathe with an obstructed airway causes an enormous amount of intrathoracic pressure which results in a much larger than usual volume of blood to enter the heart. In some individuals, this overfilling causes the release of atrial nauturetic peptide (ANP). ANP in turn causes the kidneys to excrete more water. The reason this system is activated is because the overfilling of blood in the heart mimics the mechanics of increased blood volume. Increased blood volume increases blood pressure. As a result, the body, thinking that it has too much blood, will want to get rid of the excess volume by way of diuresis (Umlauf, et.al. 2004). Patients with OSA report that their nocturia subsides once they comply with effective treatment (Personal communication with patients).

In addition to the mimicking of increased blood volume which causes the release ANP, ANP excretion is also increased due to acidosis. The lack of oxygen caused by OSA can certainly lead to at least a temporary acidosis, and this may further contribute to nocturia. ANP also directly inhibits the excretion of vasopressin. Vasopressin normally plays a role in the decrease in urine production while asleep. If vasopressin is inhibited, then urine production will not decrease and the individual may experience nocturia. In one study of carefully selected individuals diagnosed with OSA, blood levels of ANP, as well as urine levels of ANP and increased urine volume were directly correlated with untreated OSA. It is also noteworthy that an elevated level of blood ANP is related to mortality rates in patients with heart problems, and a correlation between heart disease and untreated OSA has been strongly established (Umlauf, et.al. 2004).

Nocturia is often associated with aging. This association is due to the general aging process, and in men due to prostate hypertrophy, and in women due to decreased bladder volume. Aging is also a risk factor for OSA, and as such, its another possible cause of the increase in nocturia with age in both men and women. The connection between untreated OSA and nocturia is one way to explain why, in many individuals, nocturia is not resolved with the treatment for benign prostate hypertrophy. It has also been documented that the incidence of sleep apnea doubles in women post menopause- probably as a result of low estrogen levels. This correlates well with the increase in nocturia in women post menopause. Attributing nocturia in post-menopausal women to untreated OSA may be more accurate than attributing it to a simple decrease in bladder volume. The effects of over elimination of fluids and how this may affect proper hydration and general fluid management in the body also needs to be considered when evaluating the impact of nocturia (Umlauf, et.al. 2004).

Many individuals with OSA are obese. Obesity is a risk factor in OSA, but OSA can, in of itself, also cause weight gain. Weight gain can be attributed to lack of physical activity. People with OSA often experience chronic fatigue, and this can possibly cause OSA patients to limit their physical activity. However, in addition to this secondary cause for weight gain, OSA can be directly responsible for altered metabolic factors which lead to obesity. Leptin levels are often found to be at abnormally high levels in obese individuals. Patients with untreated OSA often have even higher levels of leptin than obese individuals.

The current understanding is that leptin is found at high levels because of resistance to their appetite suppressing activity. Patients with untreated OSA have sometimes been found to have high levels of leptin and gain weight in the year prior to diagnosis, and these patients tend to return to normal leptin levels and lose the weight once proper treatment is undertaken. It is also noteworthy that a high leptin level is considered a risk factor for cardiovascular disease (Adegunsoye, Ramachandran, 2012, Shamsuzzaman, et.al. 2003, Milleron, et.al. 2004).

Another metabolic factor linked to OSA is impaired glucose tolerance. Insulin resistance has been directly correlated to OSA, and several studies demonstrate that individuals with OSA are several times more likely to develop diabetes mellitus than those without OSA (Adegunsoye, Ramachandran, 2012, Gottlieb, et.al. 2010, Bayram, et.al. 2009).

One of the most extensive areas of study concerning untreated OSA is the effect it has on the heart. In fact, about 50% of patients with heart failure have OSA, and medication for heart failure seems to have little, if no effect on alleviating OSA (Bradley, Floras, 2003). In addition to the effect of pulmonary hypertension on the heart (discussed above), there are additional ways in which untreated OSA can cause cardiac health problems. When the body tries to breath while the airway is obstructed, an enormous amount of negative pressure is generated in the thoracic cavity. This negative pressure pulls large amounts of blood from the superior and inferior vena cava into the right atrium of the heart, thus effectively increasimg afterload (Shekerdemian, Bohn, 1999). The negative intrathoracic pressure increases venous return and distends the right ventricle which effectively impairs left ventricular filling (Bradley, Floras, 2003). Additionally, the negative pressure may prevent the left ventricle from relaxing and filling properly (Shamsuzzaman, et.al. 2003). These mechanisms effectively decrease cardiac output (Adegunsoye, Ramachandran, 2012, Mooe, et.al. 2001, Gottlieb, et.al. 2010). Individuals with OSA can thus have high blood pressure due to vasoconstriction from sympathetic nervous system stimulation but decreased cardiac output due to impaired left ventricular filling. Unnatural configuration of the heart and aortic stretching are also caused by this large negative pressure. This stress on the heart can cause either rapid or reduced heart rate, and even complete sudden heart failure. The longer the apneic episode the greater the risk of cardiac malfunction (Adegunsoye, Ramachandran, 2012).

Aside from rhythmic and filling problems for the heart, there is also a risk for myocardial hypertrophy which can cause irreversible hypertension. The hypertrophy is caused by the constant strain on the heart muscle- just as constant strain on any muscle leads to muscle growth. If the strain is primarily right sided, then the hypertrophy will affect the right side of the heart. If the strain is primarily left sided then it will affect the left side of the heart. If the strain is on both sides then the entire heart can be effected. Hypertension caused by OSA can last beyond the actual apnea episodes, and even in the absence of myocardial hypertrophy, this hypertension can last for many hours after awakening (Peppard, et.al. 2000, Peker, et.al. 2002). However, treatment for OSA can often reverse systemic and pulmonary hypertension if myocardial hypertrophy has not yet set in. This is one on the many reasons why it's important to properly treat OSA at the earliest opportunity (Adegunsoye, Ramachandran, 2012, Jean-louis et.al. 2010).

In addition to myocardial hypertrophy, there is concern that untreated OSA may cause ion channel remodeling in the heart. This condition can lead to sudden cardiac death (Chahal, Somers, 2016). Gene expression effecting potassium ion channels was studied by examining mRNA associated with potassium ion channels. It was discovered that there was significant altering of several potassium pump genes which may result in an extended repolarization period. Potassium pumps are needed to pump positively charged potassium ions across the myocardial cell membranes so that a new muscle contraction can begin. If they don't pump ions efficiently, then this period of repolarization will take longer. One potential problem with this is that there is a danger of ventricular extrasystole (premature ventricular contraction). This kind of arrhythmia can cause sudden cardiac death. The mechanism for how exactly the OSA causes the altered gene expression has not been fully elucidated, but it seems to be multifactorial, including stressors such has hypoxia, sympathetic stimulation, and increased intrathoracic pressure. Individuals who undergo treatment for OSA can reverse the pathologic alterations to the potassium ion channels and regain proper gene expression for potassium pumps that work correctly (Chahal, Somers, 2016, Bradley, Floras, 2003).

The risk of sudden cardiac death in patients with untreated OSA is not limited to extrasystole due to ion channel malfunction. In fact, there are quite a few additional mechanisms by which sudden cardiac death may occur. For example, during REM sleep, there is a general increase in sympathetic stimulation. (This is in contrast to other stages of sleep where the sympathetic nervous system is depressed.) The transition from non-REM to REM thus creates a situation which increases oxygen demand. Experiencing an apnea, with the simultaneously occurring hypoxia, is thus of greater consequence at this point in the sleep cycle. This ensuing trauma to the heart can cause arrhythmias (Chahal, Somers, 2016).

Sudden cardiac death is of even greater concern in the morning hours because that is typically when the longest REM period takes place and because the apneas at this point tend to last for longer periods of time. In addition to the risk of arrhythmias being increased during this longer REM period, there is great risk of myocardial infarction or stroke at this point as well (Mooe, et.al. 2001). In general, blood pressure rises at different points in the sleep cycle. Individuals with

untreated OSA often experience an even greater increase in blood pressure- probably due mainly to the overstimulation of the sympathetic nervous system. The risk for MI or stroke is always increased with an increase in blood pressure, and as such, these individuals will be in the most danger during REM sleep. The longer REM and the prolonged apneas associated with it have claimed many lives (Michael Katzoff MD, personal communication May 2017).

Stimulation of the sympathetic nervous system can also result in tachycardia which further puts a large demand for oxygen on the heart at a time when the heart cannot get oxygen due the apnea. This situation can be even more life-threatening in patients with coronary artery disease (CAD) (Milleron, et.al. 2004). Additionally, a myocardial infarction or stroke is often caused by a plaque rupture which is made more likely by the increase in blood pressure and also because of the intrathoracic pressure caused by the obstructed airway (Chahal, Somers, 2016). In fact, 43-91% of patients who experience a stroke also have sleep apnea (Leung, Bradley, 2001, Shamsuzzaman, et.al. 2003). It is noteworthy that the rise in intrathoracic pressure has also been known to cause the rupture of an aortic aneurism which is typically fatal (Chahal, Somers, 2016).

In patients with pre-existing coronary artery disease (CAD) there is at least a 60-70% increase in sudden cardiac death or myocardial infarction when the individual also has untreated OSA. In addition to heart related problems there is an increase in cerebral vascular complications such as stroke. The cerebral vascular complications may result from the increase in the prothrombotic effect connected with untreated OSA as well as from other factors effecting hemodynamics (Mooe, et.al. 2001, Peker, et.al. 2002). Fortunately, proper treatment for OSA has been shown to decrease the number of new cardiac issues or at least to dramatically slow the rate of coronary artery disease progression (Milleron, et.al. 2004, Peker, et.al. 2002, Jean-louis et.al. 2010). It is likely that treatment would be similarly beneficial to cerebral vascular health (Gottlieb, et.al. 2010).

In general, the sympathetic system stimulation, which often lingers throughout the day in untreated OSA individuals, is known to increase platelet aggregation. This aggregation is detrimental to patients with CAD (Milleron, et.al. 2004). Additionally, prolonged platelet aggregation as well as increased levels of fibrinogen, and general inflammation in individuals with untreated OSA, may be a risk factor in developing a deep vein thrombosis on top of the risk these factors pose to CAD (Milleron, et.al. 2004, Bayram, et.al. 2009).

It is noteworthy that many patients with nocturnal angina experience relief when undergoing proper treatment for OSA. This suggests that the cause of pain, which is normally due to a lack of oxygen, is caused by the OSA and is effectively treated with standard CPAP therapy (Peker, et.al. 2002).

Another area of recent study is the possible connection between untreated OSA and dementia. One study found that the correlation between sleep apnea and dementia may be affected by factors such as age, gender, and duration of the condition. The mechanism for the connection between untreated OSA and dementia are not yet conclusive, but the connection between hypoxia, which is a side effect of untreated OSA, and neurological malfunction has been documented a number of times. For instance, rats which were exposed to hypoxic conditions experienced a greater incidence of apoptosis in their hippocampus, and advanced brain imaging showed reduced grey matter in parts of the brain responsible for executive functions and memory. Damage to these areas in humans may be a factor in the cause of dementia (Svatikova, et.al. 2003, Ju, et.al. 2013).

Another disturbing finding is that rodents placed in hypoxic conditions developed large amounts of cerebral amyloid plaque. Similar results have been found in humans with levels of serum amyloid A being two and a half times higher in patients with untreated OSA (Svatikova, et.al. 2003, Ju, et.al. 2013). Cerebral amyloid plaque is one of the hallmark findings in individuals with Alzheimer's disease. It was also found that there was significant phosphorylation of the tau proteins. Tau proteins are abundant in neural tissue and function in support of microtubules. When they are over-phosphorylated, they can malfunction and cause the structure of the cells in which they are found to become pathologically altered. Additionally, microtubules function as a sort of road or transport pathway for various particles within the cell. The intracellular functions which rely on these transport pathways may stop working properly if the tau proteins become over phosphorylated. Quite tellingly, another common finding in Alzheimer's disease is tau protein phosphorylation. In lab mice, cerebral amyloid plaque buildup and tau phosphorylation has been connected to decreased memory function (Daulatzai, 2015). It is also possible that the general damage to the vasculature throughout the body due to hypoxia can be a factor in dementia because the vasculature in the brain is negatively affected (Chang, et.al. 2013).

It has been shown that treatment of OSA in the early stages of Alzheimer's disease can aid in dramatically slowing its progression. One study demonstrated that with treatment of OSA with CPAP machine, memory and mental processing speed improved in any stage of dementia. Treatment also helped reduce or eliminate neuroinflammation. Additionally, the cardiovascular improvements experienced with CPAP treatment have had positive impact on patients with neurological illnesses. Conversely, some research indicates that the onset of mental decline may begin as much as one decade earlier in individuals with untreated OSA (Emamian, et.al. 2016).

Another connection between sleep apnea and brain function loss in humans is the presence of a common gene known as APOE4 (apolipoprotein epsilon 4) which has been shown to play a role in obstructive sleep apnea as well as being connected

to the development of dementia. The association could be a shared genetic fate, but it could also suggest that the gene is tied mainly to the development of OSA which, if left untreated, could lead to the damage which can cause dementia. Further studies would be necessary to determine the exact nature of the correlation. The long-term effects of sleep deprivation caused by sleep apnea should be considered when determining the long-term effects of untreated OSA on brain function (Chang, et.al. 2013).

A recent study has implicated untreated OSA as one possible cause of Parkinson's disease. The mechanisms seem most likely to include the general oxidative stress caused by hypoxia and reperfusion and the general inflammation characteristic of the body's response to untreated sleep apnea. There is even evidence to support the possibility that the blood brain barrier may be interrupted as a result of cerebral vascular damage which may allow molecules harmful to brain tissue to cross the barrier and reach cells involved in Parkinson's disease and other neurological pathologies (Sheu, et.al. 2015).

Conclusion

Extensive research reveals that untreated obstructive sleep apnea is extremely traumatic and damaging to the body. It has been clearly linked to physical diseases in the heart, brain, endocrine system, and vasculature, and it has been implicated as a cause for psychological and emotion distress, as well as secondary hazards. Mortality rates are consistently higher and earlier in individuals with untreated OSA and as such, individuals presenting to their health care providers with significant health issues associated with OSA should be tested for it. It is extremely important for health care providers to realize the severity of OSA and to understand that it can be present even in patients who experience few of the symptoms commonly indicative of OSA. Even patients with a relatively low AHI of about 4 or 5 are at risk because the trauma to the body is consistent and repeated every time the person sleeps, and this trauma has a tendency to have a cumulative effect on the body. Early diagnosis is key because the negative effects of OSA can be eliminated with early treatment. Treatment should be adamantly encouraged even in individuals in whom permanent damage has already occurred because treatment can reverse some of the damage and certainly help stabilize the patient and prevent the progression of further health issues. Unfortunately, the symptoms of sleep apnea are not always connected immediately to the condition and are often written off as symptoms of other medical or phycological issues. It is therefore prudent of heath care practitioners to be mindful of sleep apnea and diagnose it as early as possible.

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