

Variations on a theme, the cardiopulmonary changes in sleep-disordered breathing, 'the overlap syndrome'

Abstract

“Given the acute cardiopulmonary stressors consequent to repetitive upper airway collapse, as well as evidence for cardiovascular homeostatic dysregulation in subjects with apnea, there is ample biologic plausibility that OSA imparts increased cardiovascular risk, independent of comorbid disease” (ATS, 2008). When it comes to the ‘Overlap Syndrome’, there is a 3-fold increase of cardiovascular morbidity/death. The heart suffers greatly and the workload caused by the syndrome is tremendous. In this paper we will discuss both diseases involved, and the destruction it causes to the human body.

Keywords: overlap syndrome, COPD, OSA, SDB, CSA, cheyne-stokes, apnea, hypopnea, cor pulmonale, renin-substrate angiotensin, nor epinephrine, angiotensin II, fibrinogen, factor VII, emphysema, hyperinsulinemia, plasminogen activator inhibitors, antithrombin III, spirometry, asthma, hypercapnia, hypoxemia

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Abbreviations: COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; SDB, sleep-disordered breathing; CSA, central sleep apnea; AHI, apnea-hypopnea index; CHF, congestive heart failure; LHF, left-sided heart failure; RHF, right-sided heart failure; CAD, coronary artery disease; CB, chronic bronchitis; FEV1, forced expiratory volume in 1 second; FEV1/FVC ratio, forced expiratory volume in one second/forced vital capacity ratio; LV, left ventricle; LVH, left ventricular hypertrophy; ANP, atrial natriuretic peptide; Factor VIII, von willebrand factor; LVEDV, left ventricular end-diastolic volume; EF, ejection fraction; HF, heart failure; DLCO, diffusing capacity of the lungs for carbon monoxide; V/Q, ventilation/perfusion ratio; CSF, cerebral spinal fluid; HST, home sleep testing; AATD, alpha-1 antitrypsin deficiency; AAT, alpha-1 antitrypsin

Introduction

What is Sleep-Disordered Breathing, and why do we have so many names to refer to it by? Sleep-Disordered Breathing is what we call any ‘sleep abnormality/disease’. It is also referred to as Central Sleep Apnea, Obstructive Sleep Apnea, or the ‘Overlap Syndrome’, which is a combination of COPD and OSA. These conditions can be caused by many different factors, whether from an anatomical standpoint or from a neurological/genetic defect.

Sleep is one of the most important functions of our daily life. It is a time when the cells in our body can begin to heal themselves, and restoration of the damage can begin. When we sleep, our brain and body function differently than when we are awake and active. Knowing these characteristics of sleep is essential before embarking on a journey to understanding the abnormal process of disease on sleep. We need to know what these disease processes, separate and combined, do to our normal physiologic state. Sleep-disordered breathing is one of the main opposing factors to not being able to sleep. When our sleep is impaired due to abnormalities caused by disease, we are unable to have that resting/recovery period. This ‘butterfly effect’ of the disease and its ailments are progressive but it can be treated. The cardiovascular effects due to this overlapping of COPD

and OSA are detrimental to the human body but the research shows that there are treatments to help reduce the mortality and morbidity associated with the disease process and its secondary complications.

Definitions

Central Sleep Apnea is when periods of apnea (>30seconds per apnic period) occur during sleep. The brain does not function properly and the effort to breathe does not resume. The signals in the brain (in the respiratory center) that detect when you’re not breathing are severely damaged or no longer working. Also, periods of abnormal breathing called “Cheyne-Stokes Breathing” happens with CSA. The pathophysiology of this type of breathing pattern is characterized by an increased CO₂, therefore causing hyperventilation. This is followed by periods of low CO₂ due to the rapid breathing. This crescendos into very shallow breathing and then becomes periods of apnea.

Obstructive Sleep Apnea is the most common form of Sleep-Disordered breathing and is characterized by episodes of apnea (>30seconds) or periods of hypopnea (at least 50% reduction in airflow). The severity is shown by the AHI (Apnea-Hypopnea Index). If the person has less than five episodes an hour it is considered normal. A mild severity is shown by >5 but less than 15 episodes an hour. Next, a moderate severity is >15 but less than 30 episodes an hour. Lastly, anything >30 episodes an hour is considered severe. There are predisposing and anatomical factors that also give reason to diagnose someone with OSA. Further analysis of these factors will be discussed later in this paper. Also there is some additional information regarding the blood chemistry in our body and how it affects our breathing.

- i. Central Chemoreceptor’s are a part of the CNS (Central Nervous System), and are located in the Medulla Oblongata. It monitors the different elements that enter the CSF (Cerebral Spinal Fluid). When Carbon Dioxide from the blood goes into the CSF, it creates HCO₃⁻ and H⁺, therefore making the pH drop. Due to the drop in pH, the respiratory centers are stimulated and the breathing frequency is increased.

ii. Peripheral Chemoreceptor's (lies within the Peripheral Nervous System) are located in the aortic arch and carotid bodies. These chemoreceptor's monitor the blood chemistry. An increase in acidity, either by pH or CO₂, or a decrease in the oxygen tension in the blood will activate and stimulate the respiratory center of the brain.

"Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.¹ Exacerbations and co-morbidities contribute to the overall severity in individual patients".² There are many different testing techniques that must be done to diagnose this disease and its severity, as seen later in this paper.

Diagnosis

There are many ways to diagnose or confirm Obstructive Sleep Apnea (OSA). There are cardinal signs and symptoms that are important to know. The most common clinical sign is snoring. This happening is due to the relaxation and loss of sympathetic tone in the oral airway during sleep. This is causing the tongue to fall back and occlude the airway or the tissue in the airway itself is decreasing the diameter. Also keep in mind that not everyone who snores has OSA, there are anatomical features that can cause snoring to. The biggest sign is "Daytime Sleepiness", this shows that they are either not sleeping well due to the apnea/hypopnea or that they are hypo ventilating due to the airway collapse/obstruction. This is also causing headaches due to the carbon dioxide retention caused by the hypoventilation. Due to the increase in work to fight against that airway obstruction, the body increases its intra thoracic pressure, causing it to be more negative. This can cause many cardiac problems such as "acute leftward intra ventricular septal shift", "alterations in transmural cardiac pressures", "impedance of Left Ventricular filling", and "an increase in myocardial oxygen demand", due to the increased venous return to the heart and from the taxing nature of the disease process itself. There is also a major concern with the Nocturnal Oxygen Desaturation, which is can be monitored via Oximetry.³

The most important test is the "Sleep study". This involves the patient spending the night at the Sleep Lab, and monitoring the patient for apnic or hypopnic episodes. There are many types of monitors and wires placed on the patient as they sleep. This data is collected and compiled into the patients results trended through the night. The results are based on Apnea-Hypopnea Index, normal, mild, moderate, or severe. In some of the more severe cases of OSA, it has been noted that a patient has had more than 100 episodes of apnea in an hour and they lasted from 20-40seconds for each one. This is why monitoring and diagnosis of OSA is so important. Of course, further physician assessment and treatment is needed throughout and after testing.³

The diagnosis of COPD is shown by testing and values. Spirometry is a big part of diagnosing whether the patient has a disease that is restrictive or obstructive. When diagnosing COPD, we use this testing to verify the disease process that is currently going on and its severity. "Spirometric criteria (forced expiratory volume in 1 second [FEV1] and the ratio of FEV1 to forced vital capacity [FVC] after bronchodilation) are used to assess the severity of COPD. Approximately 10% of people around the world have moderate COPD (FEV1/FVC 0.70, and 50% FEV1 80% predicted) or more severe COPD. COPD affects approximately 20million people in the

United States".⁴ A test called the DLCO shows us how much of the diffusion process has been impaired due to the destruction caused by COPD. This is also how you can tell the difference when diagnosing someone Asthma. With Asthma, the DLCO will be normal because the gas exchange units (alveoli) are not affected. When it comes to COPD, the test will show it as being decreased. This all depends on how much damage has been done to the lungs (Table 1).

Table 1 Classification of severity of airflow²

Limitation in COPD (Based on Post-Bronchodilator FEV1)	
In Patients with FEV1/ FVC<0.70	
GOLD 1	Mild FEV1 ≥80% predicted
GOLD 2	Moderate 50% ≤ FEV1 <80% predicted
GOLD 3	Severe 30% ≤ FEV1 <50% predicted
GOLD 4	Very Severe FEV1 <30% predicted

Popular diagnostic techniques

Home Sleep Testing (HST) is becoming a very popular option to diagnosing patients with Sleep-Disordered Breathing. It is being realized now as a better way to get more accurate results during testing and insurance companies are reimbursing for it again. "The United States Centers for Medicare and Medicaid Services (CMS) released guidelines on May 21, 2014, stating that results from HST can be used to support a prescription for positive airway pressure therapy. However, the organization does indicate that positive airway pressure therapy prescriptions will be covered by Medicare and Medicaid only if OSA is diagnosed using a type 1, 2, or 3 device, or a type 4 device that measures at least three variables".⁵

As stated by the Advanced Healthcare website, the use of HST should only be for the use of either adolescent patients and/or adults both with no pre-existing co-morbidities present at the time of testing. This is a great step forward for diagnostics in sleep medicine. Sleep-Disordered Breathing is drastically under diagnosed in this country and even worldwide. Sleep medicine is truly under recognized and educations in its specifics are not widely known. Bringing new techniques to light that work and are resourceful can in the end save patients and labs time and money.

OSA and COPD

The combination of Obstructive Sleep Apnea (aka, Sleep-Disordered Breathing) and Chronic Obstructive Pulmonary Disease (COPD) is what we call the 'Overlap Syndrome'. These two distinctive diseases create a synergistic effect that is injurious to our cardiopulmonary systems. This effect caused by the combination of these two diseases is not completely known to us. We know that at a certain point, they cause a larger increase in mortality and morbidity in the patient than if they were separate. There is no current research that shows at what severity each disease would have to be at to cause this effect specifically. More research and studies will need to be performed before those answers are truly realized. In this paper we will delve deeper into understanding the disease process of each disease and what it does to the body as co-existing parts. A symphony of destruction occurs systemically with this progressive disease process, but if caught early and/or treated at any point the progression can be slowed down.

Pathogenesis

Obstructive Sleep Apnea is a multifaceted disease and the body varies in response for every person it affects. These individuals may also have different factors or co-morbidities that will worsen their disease more than others. This disease destroys the body with toxins which in turn cause the worst part. The inflammatory and oxidative stress the body goes through plays a major role in the pathogenesis of COPD and also OSA. It allows free radicals to flow through the body and it creates systemic destruction. See the respiratory care journals for more in depth research on this topic.

There are two types of factors that can affect OSA separate from its own disease process. One is the genetic factor, and the other is the "self-induced" co-morbidities. These can both occur at the same time or can appear separate in their own forms.³

Genetic factors

The genetic factor is still being researched even now, 30 years later. As everyone knows the anatomy of every person is different, some more different than others. The biggest concern is any enlargement of the tissues or tongue that would affect the patency of the patients' airway. A smaller airway is a predisposing factor in and of itself for OSA. A family history or close relatives that have or had OSA will increase your risk of acquiring it. Just being the male gender increases your risk. Understanding these factors, and the many others not listed, could help with diagnosing appropriately and getting early treatment for those who don't actually know they have OSA. This could potentially, if caught early, decrease the severity of their symptoms in the future and help with a better quality of life for them.³

Alpha-1-antitrypsin deficiency is becoming more recognized in the last few years. It is more common than people realize. Some patients may only display Asthma-like symptoms and not even show the severity of COPD and still have it. There are specialty sites that even send free testing kits home to you and they can map your genetic marker to see who will have it down the line. "Alpha-1 antitrypsin deficiency (AATD) is an inherited condition that causes low levels of, or no, alpha-1 antitrypsin (AAT) in the blood. AATD occurs in approximately 1 in 2,500 individuals. This condition is found in all ethnic groups.

However, it occurs most often in whites of European ancestry. Alpha-1 antitrypsin (AAT) is a protein that is made in the liver. The liver releases this protein into the bloodstream. AAT protects the lungs so they can work normally. Without enough AAT, the lungs can be damaged, and this damage may make breathing difficult. Everyone has two copies of the gene for AAT and receives one copy of the gene from each parent. Most people have two normal copies of the alpha-1 antitrypsin gene. Individuals with AATD have one normal copy and one damaged copy, or they have two damaged copies. Most individuals who have one normal gene can produce enough alpha-1 antitrypsin to live healthy lives, especially if they do not smoke. People who have two damaged copies of the gene are not able to produce enough alpha-1 antitrypsin, which leads them to have more severe symptoms".⁶⁻⁹

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Self-induced co-morbidities

The "self-induced" co-morbidities that affect OSA and COPD are great in number.

Obesity

This subject matter is becoming more and more enlightening as the years go by. The rates of obesity are climbing in the United States in adults and children. OSA is not an age specific problem but it is a more anatomical-based condition. Obesity is one of the biggest co-morbidities but is not a predisposing factor. Having a large neck or large amounts of adipose tissue can cause interference with the ability to breath, whether awake or asleep. When severely overweight individuals lay down, and their anatomy falls to the back of the airway causing obstruction with normal quiet breathing. The cardiovascular effects of being obese are astronomical. Not only is there tremendous strain/stress on the body, but the heart has to fight against the secondary issues cause by plaque and vascular remodeling.

When it comes to obesity, it causes a restrictiveness. There is decreased space for the lungs to expand due to the heavy weight of adipose tissue on the diaphragm. This causes, even before the sleep aspect, an inability to ventilate and oxygenate the body to its full potential. Also, the metabolic demand of the body is increased largely, and the body is unable to compensate and catch up. Making the debt on the body unable to be paid.

"Obesity affects the cardiovascular system in multiple ways. Obese individuals have an increased total blood volume to meet the perfusion needs of the increased adipose tissue. Increases are seen in both intracellular and extracellular fluid and are associated with increased stroke volume, although resting heart rate remains unchanged. The increased stroke volume increases resting cardiac output and left ventricular (LV) work. Cardiac and stroke work indices remain normal in normotensive obese individuals. The increase in cardiac output is also accompanied by a decrease in systemic vascular resistance in normotensive obese individuals. Because of increased LV workload, oxygen consumption is also increased; the oxygen consumption increases linearly with the increase in body weight. The incidence of hypertension is more prevalent in the obese. Mild to moderate hypertension is seen in 50%-60% of obese individuals, and 5%-10% of obese individuals have severe hypertension. The exact etiology is unknown but may be related in part to volume overload and resistance for blood transit in the capillaries, particularly vessels in the adipose-filled subcutaneous tissue. In addition, adipocytes themselves have been recognized as a direct source of hormones, such as atrial natriuretic peptide and the renin-substrate angiotensin, which regulate fluid volume. Two other common problems seen in the obese are hyper insulinemia and insulin resistance.

Hyperinsulinemia can stimulate the sympathetic nervous system, causing sodium retention; insulin resistance may be responsible for increased activity of nor epinephrine and angiotensin II. Obese individuals tend to have increased values of fibrinogen, factor VII,

factor VIII (von Will brand factor), and Plasminogen activator inhibitors, as well as decreased levels of antithrombin III and circulating fibrinolytic activity. Polycythemia may also develop as a result of chronic hypoxia. These homeostatic and fibrinolytic changes, when combined with decreased mobility and venous stasis, place obese individuals at increased risk for thromboembolic disease, especially deep vein thrombosis. One recent study reported that obesity is the single most important risk factor for pulmonary embolism. As a result of the continuous pressure overload, increased blood viscosity, obesity-related hypertension, and concentric left ventricular hypertrophy (LVH) develop. In the obese, systolic dysfunction is most evident. Increased LV end-diastolic volume is often accompanied by decreased ejection fraction in the chronically obese, putting them at risk for congestive heart failure and cardiac arrhythmias. The incidence of premature ventricular contractions is higher in individuals with concentric LVH. Because of dilatation of the atria related to increased fluid volume, the prevalence of atrial fibrillation and stroke is also higher in this population.¹⁰

Smoking

Smoking is not only a problem and risk factor but it's also a risk for actually getting the disease itself. The airway trauma caused by the heat of smoking, and the toxins in the cigarettes themselves can cause such severe cardiopulmonary effects that this one co-morbidity can end your life via heart dysfunction/failure. This trauma and inflammation in the body have a tremendous effect on the severity of the symptoms the patient faces. There are many things like over eating and bad habits that we do to ourselves on a daily basis that if we fought to get rid of those things are body would only be fighting the disease and not fighting itself too. (Mower, 2014).

COPD's increased risk

It is well known that if you have one disease or the other in the 'Overlap Syndrome' it causes you an increased risk of obtaining the other. As I have read in other journals it has been stated that having COPD causes you to have an approximate 50% increase in being diagnosed with OSA. Now if you can imagine the airway damage caused by inhaled toxins destroying the anatomy in the back of the throat and airway. Also, the inflammation caused by this can cause the diameter of the airway to decrease. There are many factors that can cause our anatomy to be changed, so it is clear that each disease has a part in the other. How much is unknown.

Cardiovascular consequences

The link of devastating cardiovascular effects is between OSA and Hypertension. The events caused by this cessation of breathing, start a devastating butterfly effect on the body. It creates destruction on the body therefore causing an oxidative stress, inflammation, and free radicals to flood systemically. This oxidative stress and inflammation can overtime cause atherosclerosis, which in turn causes the patient to develop Coronary Artery Disease. The apnic episodes cause the patient to be in a hyper capnic state, which worsens until the renal system compensates. That in and of itself after time can cause renal failure etc... Hypoxemia is caused by the inability to get oxygen into the body and therefore the blood. The signs and symptoms of Hypercapnia and hypoxemia are mainly headaches and daytime sleepiness. This in turn causes a tremendous strain on the heart, and it compensates by increasing the heart rate and blood pressure so that it may get the

oxygen it needs to function. By changing its normal physiology, it is causing damage to the heart itself. The heart requires 70% of the oxygen taken into the body. If disease decreases this intake, it will have to work so much harder to keep that up or it will begin to fail sooner or later. When heart failure occurs, and the heart can't pump the way it needs to, the fluid/ blood begins to back up. "Heart failure is often a long-term (chronic) condition, but it may come on suddenly. It can be caused by many different heart problems. The condition may affect only the right side or only the left side of the heart. More often, both sides of the heart are involved. Heart failure is present when,

- I. Your heart muscles cannot pump (eject) the blood out of the heart very well. This is called systolic heart failure.

- II. Your heart muscles are stiff and do not fill up with blood easily. This is called diastolic heart failure. As the heart's pumping becomes less effective, blood may back up in other areas of the body. Fluid may build up in the lungs, liver, gastrointestinal tract, and the arms and legs. This is called congestive heart failure".¹¹ The level of severity is dependent upon the genetic susceptibility of the patient and the lifestyle that they lead. Statistically, people with OSA will have systemic hypertension by the fourth year; usually from the time the symptoms start.

Treatments

The main treatment for OSA is Continuous Positive Airway Pressure (CPAP). CPAP is a continuous positive pressure given to the patient evenly throughout inspiration and expiration. This stenting of the airways helps to relieve some or most of the obstruction depending on the patients' severity of the OSA and other factors. By doing this, the patient is able to ventilate and therefore oxygenate better due to this constant flow of pressure. This helps to reduce the work of breathing, vital signs, hypoxemia, Hypercapnia, and the list goes on. Smoking cessation is one of the best treatments for the patient. Removing the noxious smoke and material will have the most significant positive effect on their body. If they are a smoker they need to get in a smoking cessation class as soon as possible, with nicotine patches if necessary.³

The diet will be a significant part of the treatment. This will allow, if obese, for them to lose weight and if they are not overweight, the diet and nutrition will help their overall well-being and help the body. Nutrition, electrolytes, water, and the list can go on. A big part of our body functioning is dependent upon diet. Patients should not just see a dietitian in the hospital, but have someone see them periodically to monitor their intake and recreational habits.

Positional treatment is always an option. You can have the patient try to sleep on their side by using pillows and other techniques. Also, oral appliances can be made to help bring the bottom jaw forward hence bringing the base of the tongue forward to helping with the obstruction when the muscles relax. There are quite a few surgeries, but most have less than a 50% chance of even working and most do not. Follow up labs and vital signs are essential for trending the results of that treatments.³ Oxygen therapy is an important part of keeping the patients' body from failing. Nocturnal oxygen Desideration is more severe for COPD patients because they are already on the steep end of the Oxyhemoglobin curve. They are more rapidly affected by a decreasing oxygen level, than someone with a normal oxygenation. The oxygen levels will have to be monitored with Oximetry and periodic ABG's when necessary. The goal for most is to keep the PaO₂ around 60-65mmHg, to stave off the Hypercapnia, and keep them their impending respiratory failure.

Medication is another factor to consider for these patients for their day-to-day living. The most common med is given via an inhaler. Beta-adrenergics are given as a short-acting rescue inhaler for prn use. This med actively dilates the airway so they are able to breathe. Then they are given an anti-cholinergic medication, usually in combination with a steroid as a once or twice daily prescription. This medication helps to keep the airway open, it does not open the airway. This is only used as a maintenance medication and not as a rescue. If used as a rescue inhaler, it can build a toxic blood level of the medication and harm the patient. When it comes to a COPD exacerbation, usually the only time they give systemic corticosteroids is in the hospital. During such time as an exacerbation, an infection is brewing most of the time. This is very common for infections to occur more frequently than in normal individuals. A sputum culture is taken to see if the bacteria has any susceptibility to the many different antibiotics that are placed on the glass slide. This will let the physician know which antibiotic to place them on.

Pulmonary rehabilitation

Pulmonary rehabilitation is a great avenue for patients that are not in an exacerbation or hemo dynamically unstable. This is a way to get them physically active and also, at the same time, assess where they at being able to do normal activities of daily living are very important for us and our patients. The inability to do so caused depression and also if unable to move around, they are more apt to decubitus ulcers. This is only further endangering them with an open site to infection.

The patient should also seek a cardiology consult if heart failure/disease is involved. Testing such as cardiac ultrasound should be done to evaluate a trial/ventricular function and ejection fraction. If cardiomyopathy (heart failure) is involved, drugs such as positive inotropes, diuretics, and diet regulation may be needed. Fluid retention is a serious complication and needs to be monitored and controlled so the patient can avoid exacerbations when possible, and being hospitalized. They are already susceptible for infection, so keeping them out of the hospital will save them from more illness and pain.

Prognosis

The prognosis will always vary with each individual and it will also be dependent on what type or how many co-morbidities they are dealing with. The increase work of the heart caused by the chronic hypoxemia stresses and affects the heart but it also causes defects in neural control of the respiratory centers of the brain. The prognosis will also vary due to severity and how compliant the patient is to the treatments that have been established for them. It's up to the patient and physician to find what works for them. We as providers of health care, especially the Primary Care Physicians, need to be more aware of the signs and symptoms of OSA and COPD (Overlap syndrome). A patient with COPD will have a 50% of developing OSA, so we know that there is a cascading effect with these disease and that should be taken into consideration when discussing a prognosis. Education of our patients is the key to a better prognosis and outcome

of the individual. Patients of every educational level should be able to understand to a point about how these diseases progress and what makes them better. We as educators are responsible for making sure they understand their illness and the treatments that come with it. If they are knowledgeable, compliance of devices and treatments will increase and the prognosis will be better.

Conclusion

The 'Overlap Syndrome' is a very frightening disease combination and can have life-threatening effects on the body. Just these two diseases alone you are 7-10times more likely to have a stroke or a heart attack just based on the effects of these conditions. We are still researching and learning more about the diseases of sleep, and the results of these studies have brought new therapies and ideas to light. This will, in the future, help saving people's lives and give them a better quality of life.³

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None.

Conflict of interest

The author declares no conflict of interest.

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