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OBSTRUCTIVE SLEEP APNEA, INFLAMMATION, AND CARDIOPULMONARY DISEASE

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1. ABSTRACT

Obstructive sleep apnea (OSA) occurs commonly in the U.S. population and is seen in both obese as well as non-obese individuals. OSA is a disease characterized by periodic upper airway collapse during sleep, which then results in either apnea, hypopnea, or both. The disorder leads to a variety of medical complications. Neuropsychiatric complications include daytime somnolence, cognitive dysfunction, and depression. Increased incidence of motor vehicle accidents has been documented in these patients and probably reflects disordered reflex mechanisms or excessive somnolence. More importantly, vascular disorders such as hypertension, stroke, congestive cardiac failure, arrhythmias, and atherosclerosis occur frequently in these patients. The lungs may be affected by pulmonary hypertension and worsening of asthma. Recent data from several laboratories demonstrate that obstructive sleep apnea is characterized by an inflammatory response. Cytokines are elaborated during the hypoxemic episodes leading to inflammatory responses as marked clinically by elevated C-reactive protein (CRP). As elevated CRP levels are considered markers of the acute phase response and characterize progression of vascular injury in coronary artery disease, it is likely that obstructive sleep apnea could lead to worsening of vasculopathy. Moreover, as inflammatory mechanisms regulate bronchial asthma, it is also likely that cytokines and superoxide radicals generated during hypoxemic episodes could exacerbate reactive airway disease. Patients with **C**ough, **O**bstructive sleep apnea, **R**hinosinusitis, and **E**sophageal reflux clustered together can be categorized by the acronym "CORE" syndrome. The purpose of this manuscript is to review the inflammatory responses that occur in patients with obstructive sleep apnea and relate them to the occurrence of cardiopulmonary disease.

2. INTRODUCTION

Obstructive sleep apnea (OSA) is a common disorder that is part of a complex syndrome of sleep-disordered breathing. By definition, OSA is characterized by periodic or complete upper airway obstruction during sleep resulting in intermittent cessation of breathing that may be either complete (apnea) or partial (hypopnea) in spite of ongoing effort (1). Sleep-disordered breathing may occur in as many as 24% of middle aged men and 9% of middle aged women, based on the occurrence of an apnea-hypopnea index of >5/hour (1). It is estimated that up to 4% of men and 2% of women may demonstrate the full blown OSA syndrome that also includes daytime hypersomnolence associated with apnea. The incidence in children is 1-3% (2). Up to 40 million patients with OSA may exist in the U.S. alone. Despite the severe morbidity and mortality associated with OSA, it remains undiagnosed in the majority of men and women afflicted with the syndrome (3). OSA can be complicated by a plethora of cardiac and pulmonary disorders, some arising out of activation of the inflammatory response. Cardiac complications associated with OSA include hypertension, congestive cardiac failure, diastolic dysfunction, coronary and/or cerebrovascular atherosclerosis, and cardiac arrhythmia (2,4). OSA can be complicated acutely by

Table 1. Conditions Associated with Increased Risk for OSA

General risk factors
- Obesity (BMI> 30 kg/m^2)
- Male sex
- Positive family history
- Postmenopausal state

Genetic/Congenital factors
- Down's syndrome
- Pierre-Robin syndrome
- Marfan's syndrome

Nasopharyngeal Abnormality
- Nasal congestion/rhinitis
- Nasal polyposis
- Adenoidal or tonsillar enlargement
- Deviated nasal septum

Medical conditions
- Acromegaly
- Hypothyroidism

Structural upper airway disorders
- Large neck (circumference >40 cm)
- Temperomandibular joint abnormalities
- Micrognathia
- Retrognathia
- Macroglossia
- Palatal abnormalities
- Craniosynostosis
- Tonsillar hypertrophy

Table 2. Definitions

Apnea Cessation of airflow for 10 seconds or more
Hypopnea At least 30% reduction in airflow for 10 seconds that is associated with at least 4% decline in oxygen saturation
Apnea-Hypopnea Index Total number of apneic and hypopneic events/hour (AHI)
Obstructive Apnea Respiratory effort continues in spite of airflow cessation
Central apnea Respiratory effort ceases in conjunction with the apnea
Mild OSA Apnea/hyponea episodes: 5-20/hour; Hgb desaturation: <10%
Moderate OSA Apnea/hyponea episodes: 20-40/hour;Hgb desaturation: 10-15%
Severe OSA Apnea/hyponea episodes: >40/hour;Hgb desaturation: >15%

strokes, myocardial infarction and unstable coronary syndromes and/or angina pectoris, and ischemic ventricular dysfunction (4-9). Left ventricular hypertrophy and diastolic dysfunction have also been described in OSA (10,11). Pulmonary complications include worsening of asthma or chronic obstructive pulmonary disease (1) and pulmonary hypertension (1,6). These are summarized and the inflammatory basis of the disorder described in the sections that follow.

3. OBSTRUCTIVE SLEEP APNEA: CLINICAL ASPECTS

The major risk factors for OSA are listed in table 1. Well recognized factors include obesity, male sex, and a positive family history for the disease. A body mass index (BMI) of greater than 30 represents a significant risk factor for OSA. The postmenopausal state appears to confer a greater risk for the disease as well. Allergic and structural airway disease such as allergic rhinitis, tonsillar enlargement as well as micrognathia may be contributory factors in some patients. In others, several endocrinopathies may play a role. Specifically, hypothyroidism needs to be evaluated for and treated in any patient with OSA.

The definitions of various components of the OSA syndrome are shown in table 2. Central sleep apnea (CSA) is characterized by intermittent apnea and/or hypopnea secondary to cessation of respiratory effort whereas obstructive sleep apnea is characterized by intermittent apnea and/or hypopnea secondary to upper airway collapse during inspiration in spite of continued respiratory effort. In some situations, both forms may coexist in a given patient. Severity of OSA is determined by the numbers of apneas and/or hypopneas occuring per hour. OSA can be classified as mild, moderate, or severe (table 2). Table 3 lists the findings on examination of patients with OSA.

4. CARDIAC DISEASE IN OBSTRUCTIVE SLEEP APNEA

As the awareness of obstructive sleep apnea (OSA) increases, so does the realization of many of its cardiovascular consequences (table 4). While OSA is commonly thought of as a consequence of obesity, a normal BMI is common especially in the elderly and in those from Southeast Asia (3). Mild OSA may be seen in as many as 1 in 5 adults, and 1 in 15 adults may have moderate OSA (12). The Wisconsin Sleep Cohort Study also showed that 25% of middle-aged men and 10% of middle-aged women had sleep disordered breathing (4). With such a high prevalence in the general population, OSA and its cardiovascular consequences need to be recognized and treated. The association between OSA and cardiovascular disease was first appreciated by observational studies that linked snoring with increased cardiac events (4). More recent studies have begun to show links between OSA and hypertension, acute coronary syndrome, markers of vascular inflammation, EKG abnormalities, and congestive heart failure.

4.1. The Cardiovascular System During Normal Sleep

Non-rapid eye movement sleep (NREM) constitutes about 85% of total sleep time and can be seen as a period of cardiovascular relaxation, during which time the myocardial workload is reduced (13). As the body progresses from wakefulness through the stages of NREM, there are marked changes in the regulation of the cardiovascular system. Progression into NREM sleep results in increased parasympathetic nervous tone. As vagal

Table 3. Clinical Findings in Obstructive Sleep Apnea

Symptoms
▪ Non-restorative sleep
▪ Snoring
▪ Daytime somnolence
▪ Neurocognitive dysfunction
▪ Fatigue
▪ Early morning headaches
Phenotypic Findings
▪ Increased body mass index (BMI) >28Kg/m^2
▪ (>30% of patients may not be obese)
▪ Increased neck circumference >40 cm
▪ Short, thick neck
▪ Other abnormalities
• Crowded oropharynx
• Allergic rhinitis or nasal polyps
• Enlarged tongue and/or tonsil
• Redundant pharyngeal tissue
• Mandibular hypoplasia/retrognathia
• Craniosynostosis
Clinical Manifestations
▪ Hypertension
▪ Asthma/cough
▪ Congestive heart failure
▪ Peripheral edema
▪ Cor pulmonale/pulmonary hypertension
▪ Thyroid enlargement
Others
▪ Seizures
▪ Nocturia
▪ Arrhythmia/palpitation
▪ GERD and associated findings

Table 4. Cardiopulmonary Consequences of Sleep Apnea

Cardiac
▪ Hypertension
▪ Congestive heart failure
▪ Diastolic dysfunction
▪ Atherosclerosis
▪ Cerebrovascular accidents
▪ Pulmonary hypertension
▪ Cardiac arrhythmia
Pulmonary
▪ Worsening of asthma
▪ Worsening of COPD
▪ Pulmonary hypertension
▪ GERD-associated aerodigestive disease
▪ LPR
▪ Rhinosinusitis?
▪ Asthma
▪ Otitis media?
▪ Recurrent pneumonia

tone increases, sympathetic nervous activity (SNA), heart rate (HR), blood pressure (BP), stroke volume, cardiac output, and systemic vascular resistance all decrease (13,14). Cardiac output usually decreases 5-10%, more from a decrease in heart rate (HR) than stroke volume. And nocturnal BP usually averages levels about 15% lower than daytime levels, even in essential hypertension (14,15). This normal physiologic response, therefore results in a period of decreased myocardial work and cardiovascular "rest". Conversely, REM sleep produces SNA, HR, BP, and cardiac output levels very similar to wakefulness (14). Yet REM compromises only about 15% of total sleep time.

Sleep arousals usually display increased ventilation that exceeds that expected for the $PaCO_2$ at the time of arousal. There are also noted abrupt elevations in HR and BP due to suddenly increased SNA. However, there is no parasympathetic withdrawal at this point. Arousal therefore, seems to represent a separate heightened state of cardiovascular and respiratory activity (14).

4.2. The Cardiovascular System During OSA

OSA results in multiple arousals during the course of a period of sleep. These arousals produce dramatic surges in HR and BP, usually 5-7 seconds after apnea termination. Along with frequent arousals, exaggerated negative intrathoracic pressure and hypoxia also seem to contribute to the cardiovascular consequences of OSA (14). The physiologic effects usually caused by OSA include increased HR, BP, BP variability, and vascular resistance. There is also a decrease in stroke volume, cardiac output, and HR variability.

Vagal afferent activity from pulmonary stretch receptors in the lung, usually inhibit sympathetic activity during normal breathing. However, in OSA there is disinhibition of this reflex. Therefore, the progression of apneic/hypoxic episodes leads to heightened sympathetic activity and causes vasoconstriction. This results in increased peripheral vascular resistance and BP, with a loss of the normal nocturnal BP drop (13,14,16). As noted, this response usually does not occur until several seconds into the apnea episode. Initially there is a noted decrease in SNA due to the negative intrathoracic pressure activating the aortic baroreceptors that have become increasingly sensitive during NREM sleep. As apnea progresses though, the carotid chemoreceptors sense increasing CO_2 retention and increase SNA. As a result, the HR and BP surge is seen early in arousal (5-7 seconds after apnea termination). The degrees of blood pressure surges post-apnea have been directly related to the magnitude of hypoxia during the apneic episode (14).

The pronounced negative intrathoracic pressure (as low as –80 cm H_20) produced by inspiratory efforts against an occluded pharynx increase left ventricular (LV) transmural pressure (16). This, in turn results in increased afterload. These intrathoracic pressure changes also result in increased venous return to the right ventricle (RV), causing RV distention and a leftward shift in the interventricular septum. As a result LV diastolic filling is impeded, and can be further hampered by decreased LV relaxation also caused by the negative intrathoracic pressure. This combination of increased LV afterload and decreased preload leads to a reduction in stroke volume and cardiac output (13,14,16).

These effects produce chronic physiologic cardiovascular changes as well. It has been found that OSA

also results in increased SNA and BP variability, as well as decreased HR variability and baroreceptor sensitivity in sleep and wakefulness (13,14). The exact mechanism behind these chronic changes are not yet known, however their risks are. It has been found that individuals with decreased HR variability have an increased risk for future development of hypertension (HTN). Increase BP variability has also been linked to an increased risk of target organ damage (16).

4.3. Inflammation, Coagulation, and Endothelial Dysfunction: Relevance to Atherosclerosis

Recent studies have shown OSA to be an independent risk for coronary artery disease (CAD). In a prospective 7-year follow-up study, Peker *et. al.* found that 37% of patients with OSA initially reported cardiovascular disease versus only 7% in those without OSA. In follow-up, they also found that new cardiovascular disease was found in 57% of patients with inadequately treated OSA versus only 7% in adequately treated OSA (17). OSA may also be an important prognostic indicator in patients with established CAD. A five-year follow-up of 62 patients with known CAD showed a 38% mortality in those with OSA versus a 9% mortality in those without OSA (14,16). The mechanisms for these observations are multifold.

4.3.1. Activation of the acute phase response

Hypoxia induced by OSA may lead to increased levels of inflammatory markers. Individuals with OSA seem to have elevated levels of interleukin (IL)- 6, tumor necrosis factor (TNF)-alpha, and C-reactive protein (CRP), as summarized later (18). This indicates activation of the acute phase response in patients with OSA. Shamsuzzaman *et. al*. compared 22 patients with moderate to severe sleep apnea who were free of other diseases, with 20 OSA free control subjects matched for age, BMI, smoking, and lipid levels (18). Plasma CRP was significantly higher in the patients with OSA. Mean CRP in the OSA group was 0.81 +/- 0.15 versus 0.28 +/- 0.12 mg/dL ($p<0.008$) in the control group. They also found that the severity of OSA was directly proportional to CRP levels. OSA also appears to have hematologic effects as well. Generally, platelet aggregability is enhanced by catecholamines. After arising in the morning, there is normally a surge in catecholamines and as a result a peak in platelet aggregability. This corresponds to the peak in cardiovascular and cerebrovascular events seen in the early morning hours in the general population. It is thought that OSA, through its many arousals, further increases catecholamine levels through the night and hence platelet aggregability (16).

4.3.2. Role of homocysteine

Homocysteine is considered an important risk factor for premature atherosclerosis. Lavie *et. al.* investigated homocysteine levels in OSA patients with ischemic heart disease, HTN, or no cardiovascular disease and compared them with healthy control subjects, or those with ischemic heart disease alone. They found that OSA patients with ischemic heart disease had significantly higher homocysteine levels after adjustment for age, BMI, diabetes mellitus (DM), and creatinine. Those with OSA and ischemic heart disease had levels of 14.6 +/- 6.77 micromol/L compared to 11.80 +/- 5.28 micromol/L for HTN/OSA, 11.92 +/- 5.7 micromol/L for ischemic heart disease alone, and 9.85 +/- 2.99 micromol/L for OSA alone (19).

4.3.3. Other factors

The hypoxia, hypercapnia, and hemodynamic surges seen with OSA may cause direct vascular injury, as well as serve as a potent stimuli for release of vasoactive substances and oxygen free radicals. The low oxygen tension in sleep apnea may cause adhesion of PMN's to the vascular endothelium and release of oxygen free radicals (14,16). The physiologic effects of OSA also show how OSA patients could be predisposed to myocardial ischemia from the increased workload demands put on the myocardium. These demands are, in most cases, higher than those found in wakefulness and may be driven by sympathetic activity in wakefulness being about two times that of normal. Animal studies have shown that obstructive apneas can lead to myocardial ischemia even without hypoxia, suggesting the main cause may be an increase in O_2 demand rather than a decrease in O_2 supply (14,16).

The combined effect of these various factors could lead to accelerated atherosclerosis. This could partly explain the increased prevalence of strokes and myocardial ischemic events in patients with OSA.

4.4. Hypertension and OSA

Hypertension affects about 20% of the adult population. However, a secondary cause is identified in only about 5-10% of hypertensive individuals (14). The recently published JNC-VII has listed OSA as an identifiable cause of HTN. As identified, OSA could be an important and treatable secondary cause of HTN. A recent sleep clinic study reported that with each extra apneic episode per hour, the odds of having HTN increased by 1%. The Wisconsin Sleep Cohort study also established the risk of developing HTN and OSA. The investigators measured the incidence of HTN over a four to eight year follow-up in 709 individuals. Not only did they find that 25% of middle-aged men and 10% of middle-aged women had sleep disordered breathing, they also found that these individuals had an increased risk of developing HTN as the severity of the apnea-hypopnea index increased (4,6). Three other large clinical trials also showed a 1.5 to 3-fold increase in the risk of developing HTN in individuals with OSA (1). In yet another investigation, the Sleep Heart Health Study used in-home polysomnography in 6,132 patients. The investigators also found a clear independent association between OSA and the prevalence of HTN. They found that the prevalence of HTN increased as the apnea-hypopnea index increased (4,14).

The possible pathophysiologic mechanisms for OSA resulting in HTN have been investigated in animal studies. Using dog and rat models, investigators have found that exposure of the animals to obstructive apneas resulted in chronic BP elevations in both sleep and wakefulness. Reversal of the obstructive apneas also resulted in a fall in BP back to baseline in a few weeks time. In one study, the

dogs were exposed to acoustic stimuli resulting in arousals. These subjects showed no chronic increase of BP's. These results seem to show that stimuli specific to OSA must cause BP changes (14). The specific stimuli have not been identified, however it is though that the elevated SNA seen in OSA appears to be sustained in wakefulness. Producing a chronic alteration in chemoreceptor and baroreceptor activity leading to heightened sympathetic vasoconstrictor tone (14,15).

In patients who are at risk for OSA and have HTN or have HTN refractory to medical treatment, evaluation for OSA should be considered. It has been reported that in patients with HTN that was not controlled with maximal medical therapy, 87% had OSA (14).

4.5. Arrhythmias and Electrocardiogram Changes in OSA

Arrhythmias are common in OSA with various studies finding rates of 58-75 %. The risk of developing arrhythmias seems to be related to the severity of OSA (4,15). The most common arrhythmia being bradycardia and AV block during the apnea phase followed by tachycardia on termination of the apneic episode. Other possible arrhythmias include sinus arrest, atrial tachycardia, atrial flutter, atrial fibrillation, premature ventricular contractions (PVC's), and nonsustained ventricular tachycardia (1,16). The bradyarrhythmias occur even in the absence of disease of the conduction system, and usually are reversed by effective treatment for OSA. This provides an important clinical implication when considering patients for pacemakers for bradyarrhythmias. The clinician should consider OSA as a cause in the patient at risk for OSA (16). Conversely, atrial overdrive pacing has also been shown to reduce the number of OSA episodes in a recent 15 patient study by Garrigue et. al. (20). Nocturnal ST segment changes on EKG's changes consistent with ischemia have also been identified. Nocturnal ST-segment depression is more frequent in those with severe OSA (16).

4.6. Congestive Heart Failure and OSA

Congestive heart failure (CHF) affects about 4.7 million people in the U.S. and there are 400,000 to 700,000 new cases a year. This translates into an annual cost estimated at $20 to 40 billion (21,22). Any treatment of this disease process that is reaching epidemic proportions would be of great help. There seems to be direct association between OSA and CHF. The Sleep Heart Health Study found the presence of OSA was associated with a 2.38 relative odds for CHF that was independent of other known risk factors. In fact, this risk exceeded that for HTN and CAD (6,14). Two other larger studies with CHF and systolic dysfunction evaluating patients for OSA found that 11% of 81 patients and 37% of 450 patients had OSA. This exceeds the 5-10% prevalence in otherwise healthy adults (14). In addition to the association of OSA with CHF from systolic dysfunction there is also compelling evidence of an association of OSA with CHF from diastolic dysfunction. There has been one small study investigating the prevalence of sleep-disordered breathing in diastolic dysfunction. The investigators found 55% of the 20 patients studied had sleep-disordered breathing with about 2/3 of those having OSA (14,21).

OSA imposed on already present CHF may cause further deterioration in clinical status and cardiovascular function. This is likely due to the increased sympathetic activity as well as increase myocardial demand seen in OSA patients. A recent study by Kaneko *et. al.* looked at 24 patients with a depressed left ventricular ejection fraction and OSA who were receiving optimal medical treatment for CHF. They found that one month of continuous positive airway pressure (CPAP) resulted in a 9% absolute increase and a 35% relative increase in left ventricular ejection fraction. This effect was similar in those receiving and those not receiving beta blockers (22).

5. PULMONARY DISEASE IN OBSTRUCTIVE SLEEP APNEA

5.1. Asthma and OSA

Both snoring and apnea are common phenomena ocurring in patients with asthma and allergic rhinitis (23). Since both OSA and atopy are common disroders, coexistence of these conditions in a given patient is not unusual. As reviewed by Bonekat and Hardin, OSA may coexist with asthma (24). In some instances, upper airway resistance syndrome and OSA may be mistaken for nocturnal asthma (25). Sleep deprivation, upper airway edema and systemic inflammation associated with OSA could complicate the course of asthma (24). On the other hand, in a given asthmatic patient, various upper airway factors (table 1) including rhinitis, nasal polyps, and structural disorders can contribute to the development of sleep apnea. In others, the underlying obesity can contribute to the development of both asthma and sleep apnea (26,27). OSA and obesity-associated gastroesophageal reflux (GERD) can also contribute to bronchial asthma and airway inflammation (28). The role of CRP and inflammatory factors such as cytokines and systemic inflammatory responses is reviewed below (27). Moreover, studies have shown that treatment of OSA with CPAP leads to improvements in peak flow rates in patients with asthma (24). In summary, the ocurrence of rhinitis, nasal polyposis, obesity, and GERD in patients with OSA can contribute to increasing incidence of asthma in this population. These influences are summarized in figure 1. The acronym "CORE" could be used to describe these interactive disease states that culminate in the complex of OSA and asthma: **C**ough/asthma, **O**besity-**O**bstructive sleep apnea, **R**hinosinusitis and **E**sophageal reflux. The caveat is that in asthmatic patients, refractory to therapy, sleep apnea and other CORE components need to be considered in the differential diagnosis. In addition, pulmonary hypertension can often complicate poorly treated OSA due to the associated hypoxemia.

6. ACTIVATION OF THE INFLAMMATORY CASCADE IN OBSTRUCTIVE SLEEP APNEA

Chronic disorders such as asthma (29-31) and atherosclerosis (32) are now considered inflammatory disorders. Mediators and cytokines generated in the process of the immune response to injury result in cellular infiltration and inflammation of the airway in asthma or the vessel wall in atherosclerosis. Recent studies have demonstrated that OSA is associated with an inflammatory response.

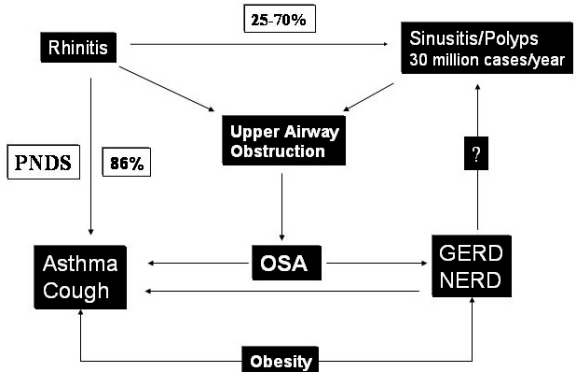

Figure 1. Demonstrating the associations between upper airway disease (rhinitis, sinusitis, nasal polyps), esophageal reflux (GERD), asthma, and obstructive sleep apnea (OSA). PNDS refers to post-nasal drip syndrome. These interactions contribute to the "CORE" syndrome, an acronym describing a syndrome characterized by **C**ough (or asthma), **O**bstructive sleep apnea, **R**hinosinusitis, and **E**sophageal reflux.

Dyugovskaya and coworkers studied the phenotype and activation of gamma delta T-cells in patients with OSA compared to control individuals without OSA (33). Gamma delta T-cells in patients with OSA demonstrated greater expression of the inhibitory natural killer cell B1 receptors and L selectin. The gamma delta T cells in patients with OSA also expressed the cytokines IL-8 and TNF-alpha, while the content of IL-10 was decreased. Cytotoxicity of the gamma delta T cells to endothelium was prevented by pretreatment with antoibody to TNF-alpha. Yokoe *et. al.*, demonstrated elevated levels of C reactive protein (CRP) and IL-6 in patients with OSA (12). These levels were higher than in control obese individuals without OSA. The levels of these proteins were decreased by treatment with CPAP.

The primary factors influencing CRP levels were severity of OSA and BMI, while those influencing IL-6 levels were BMI and nocturnal hypoxemia. Spontaneous production of IL-6 was also elevated in patients with OSA. Shamsuzzaman and coworkers also demonstrated elevated levels of CRP in patients with OSA over controls matched to BMI and age (18). In multivariate analyses, CRP levels were independently associated with severity of OSA. Teramato *et. al.*, also showed that patients with OSA had higher levels of IL-6, TNF-alpha and CRP (34). Levels of IL-6 and TNF-alpha were significantly associated with CRP levels. They suggested this may be one mechanism for progression of coronary atherosclerosis in patients with OSA. In a more recent study, patients with sleep apnea were shown to demonstrate higher levels of intercellular adhesion molecule-1 (ICAM-1), IL-8 and monocyte chemoattractant protein-1 (MCP-1) in their blood (35). Nasal CPAP again reduced levels of these proatherogenic chemokines.

In an interesting study, Carpagnano and colleagues measured levels of IL-6 and 8-isoprostane (as a marker for oxidative stress) in the exhaled breath condensate of obese patients with OSA, obese patients without OSA and non-obese controls (36). Obese patients tended to have higher levels of IL-6 than non-obese individuals. But most striking was the finding that levels of IL-6 and 8-isoprostane in breath condensate of patients with OSA were higher than obese patients without OSA and nonobese controls. A positive correlation was found between these two markers and neck circumference as well as with the apnea/hyponea index. In agreement with these findings, Royblat and coworkers also demonstrated higher levels of IL-6 in patients with OSA and the highest levels were found in patients with obesity-hypoventillation syndrome with daytime oxygen desaturation (37). Another study concurred with these findings and also showed that both plasma levels and monocyte production of IL-6 and TNF-alpha in response to lipopolysaccharide (LPS) were elevated in patients with OSA (38). Entzian *et. al.* have studied the cicardian variations in IL-6, interferon (INF) gamma and TNF-alpha levels in patients with OSA (39). These investigators found that TNF-alpha rhythms were disturbed in patients with OSA, and specifically, while the nocturnal peak of this cytokine disappeared, a new daytime peak appeared. These rhythms were not normalized by treatment with nasal CPAP.

In a recent study, Alberti *et. al.* showed that while IL-6 and TNF-alpha levels increased in patients with OSA, IL-10 levels actually decreased, compared to control individuals (40). This suggested to these investigators that a type-1 T helper cell response (Th1) was occurring. As would be expected with hypoxemic diseases, levels of growth factors and hematopoietins are also altered in patients with OSA.

Imagawa *et. al.* measured levels of vascular endothelial growth factor (VEGF) in patients with severe OSA and found substantial increases in VEGF levels in patients with sleep apnea (41). Erythropoietin levels were shown to increase slightly in this study. Interestingly, while polycythemia occurs in patients with OSA, two published studies were unable to find elevated levels of erythropoietin (42,43). Since it is well known that cytokines such as IL-6 and TNF-alpha promote atherogenesis, several connections appear to exist between cytokines, obesity, sleepiness, and sleep apnea (44).

6.1. Role of the Inflammatory Response In Cardiopulmonary Disease

Inflammation occurring in OSA can exacerbate both cardiac (atherosclerosis) and pulmonary (asthma) disease processes. In the earliest stages of atherosclerosis, normal resting endothelial cells undergo activation by various factors, including low density lipoproteins, nicotine abuse, infection (*Chlamydia pneumoniae*), hypertension, homocysteine, and diabetes mellitus (32). The dysfunctional and/or activated endothelium expresses genes for various molecules involved in the immune response, which include adhesion molecules (CAMs), cytokines and chemokines (like IL-8 and MCP-1) that regulate cellular trafficking and the processes involved in mononuclear recruitment to the vascular wall. Other cytokines such as the monokines, IL-1 beta, TNF-alpha, and IL-6 activate the

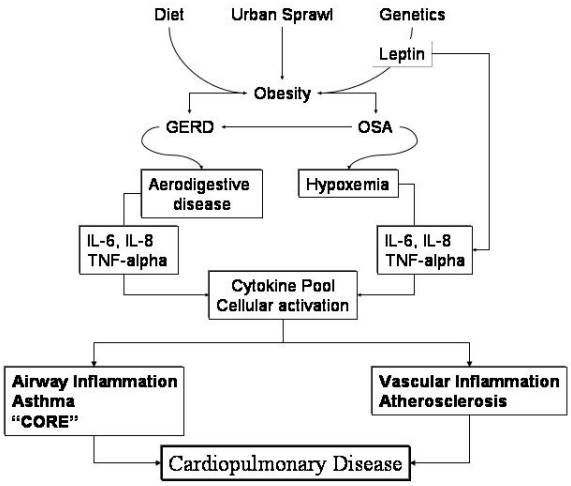

Figure 2. Obesity, esophageal reflux (GERD), and obstructive sleep apnea (OSA) can activate inflammatory mechanisms (IL-6, IL-8, and TNF-alpha) that can lead to airway and vascular inflammation, culminating in either asthma or atherosclerotic cardiovascular disease.

acute phase response characterized by hepatic synthesis of complement proteins, CRP, and fibrinogen (32). These cytokines also activate endothelium and make the endothelial surface more adhesive (by inducing CAMs) and procoagulant.

CRP may play a major role in atherosclerosis besides being a marker for progression of CAD (45). CRP is a member of the pentraxin protein family (proteins that possess five identical subunits) and it's levels increase dramatically during acute inflammatory responses. Besides being a marker for inflammation, CRP also augments the immune response to certain antigens, activates complement, and increases the production of tissue factors by monocytes. CRP acts as an opsonin and plays a key role in host defense. CRP also appears to bind low-density lipoprotein in vitro, suggesting a more direct interaction with the atherogenic lipids. In the case of OSA, IL-6- and TNF-alpha-mediated CRP synthesis could thereby contribute directly to atherogenesis. Atherosclerosis may be accentuated by hypoxemia, hypertension, dyslipidemia, and insulin resistance that often complicate obese patients with OSA. Hypertension and atherosclerosis lead to ventricular remodeling and dysfunction.

Bronchial asthma is an inflammatory airway disease characterized by epithelial exfoliation, mast cell activation, and T-cell and eosinophilic infiltration (29). Cytokines elaborated during hypoxemia induced by OSA such as TNF-alpha, IL-8, and MCP-1 may be involved in asthma pathogenesis, allowing recruitment of inflammatory cells or by endothelial activation. Recruited cells such as monocytes and T-cells or resident cells such as fibroblasts, endothelium, and mast cells undergo further activation, leading to cytokine generation and further inflammation (29). These can lead to worsening of asthma (46). The interactions between obesity, genetics, urban sprawl which has been linked to obesity (47), and inflammatory cytokines leading to asthma or heart disease are shown in figure 2.

7. IMPLICATIONS FOR THERAPY

The complex interactions between obesity and obstructive sleep apnea leading to elaboration of cytokines and culminating in allergic respiratory disease (rhinosinusitis and asthma) and coronary artery disease are important to understand. Early treatment of OSA will lead to amelioration of pulmonary and vascular inflammatory responses, cellular recruitment, superoxide and cytokine generation, and associated cardiopulmonary sequelae. Additional factors such as hypertension, homocysteine elevation, gastroesophageal reflux disease, obesity itself, and insulin resistance as part of the metabolic syndrome need to be addressed as well. Dietary therapy, weight loss, therapy for dyslipidemia, management of hypertension and diabetes are essential. The role of GERD induced by OSA in asthma pathogenesis should not be underestimated and anti-reflux measures and therapies need to be instituted. In conjunction with this, treatment of sleep apnea using CPAP techniques should be instituted.

8. CONCLUSIONS

Patients with OSA represent a complex interplay of risk factors and disease components that can contribute to chronic cardiopulmonary disease. Activation of inflammatory pathways by hypoxemia, superoxide generation, and progressive vascular and airway injury often results. Patient morbidity and mortality can be accentuated by these interactive mechanisms. It is essential for the clinician to suspect this syndrome and evaluate these patients in a multidisiplenary fashion. Polysomnography, 24 hour pH studies, computerized tomography of the sinuses, pulmonary function testing, and coronary perfusion studies may all be required in these complex patients. Anti-reflux therapy, use of CPAP devices, weight reduction, and aggressive anti-inflammatory therapy of airway inflammatory disease can greatly improve quality of life and promote well being in these patients.

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