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Research Article

Cardiovascular Disorders and Obstructive Sleep Apnea

AFRITA AMALIA LAITUPA[1], R P SOEHARSOHADI TJONDRONEGORO[2*]
[1]Faculty of Medicine, University of Muhammadiyah Surabaya, Surabaya, Indonesia
[2]Departemen of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Teaching Hospital, Surabaya, Indonesia
*Corresponding Author
Email ID: djeki23@yahoo.com
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ABSTRACT
Obstructive sleep apnea (OSA) is associated with an increased risk of hypertension, coronary heart disease, heart failure and arrhythmias. The prevalence and severity of OSA in cardiovascular disease are increase with age. Mechanism of OSA in cardiovascular disorders associated with oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, sleep fragmentation and metabolic dysregulation. Although polysomnography is a gold standard diagnostic tool of OSA but it is still expensive, does require questionnaires as a tool for OSA detection. The treatments consist of continuous positive airway pressure (CPAP), oral appliances, surgical and behavioral modification.

Keywords: cardiovascular disorders, CPAP, sympathetic nerve activity.

INTRODUCTION

Sleep is a complex physiological process that occurs in almost one third of human life and affects various physiological regulations of the body. Sleep is an active process with a separate program that has different degrees of sleep and is associated with autonomic nerve function. There are several stages of sleep, namely stage 1 - 4 which is referred to as non-rapid eye movement sleep (NREM) and stage 5, which is called rapid eye movement (REM). The sleep process itself has a circadian rhythm and naturally takes place in the dark phase with an average duration of 7-8 hours a day [1].

Obstructive sleep apnea (OSA) is a common respiratory disorder that occurs during sleep, caused by repeated collapse of the upper airway during sleep, which causes intermittent airway obstruction and the absence of air flow despite attempts to resist diaphragmatic breathing against the blocked pharynx, resulting in a cycle of recurrent hypoxemia, arousal, and sleep fragmentation [2].

OSA severity is classified according to apnea-hypopnea index (AHI), which is seen from the number of episodes of apnea and hypopnea per hour of sleep. This is further classified into mild (AHI 5-15), moderate (AHI 16-30) and severe (AHI> 30). The severity of symptoms can be affected by sleep posture. Based on the influence of the sleep posture, OSA can be categorized as nonpositional OSA (supine AHI <2 times lateral AHI) and positional OSA (supine AHI ≥ 2 times lateral AHI) [3]. The OSA definition includes the AHI criteria (usually ≥5 times / hour) plus symptoms of excessive daytime sleepiness, or twice or more choking or gasping during sleep, repeated waking, non-refreshing sleep, daytime fatigue, or concentration and / or memory [4].

Cardiovascular disease is the most important cause of morbidity and mortality in both developed and developing countries with a tendency to increase throughout the world. More than 17 million people dies each year from cardiovascular disease associated with sleep disorders, which increases the mortality rate due to cardiovascular disorders. So that adequate therapy is needed to control and treat cardiovascular diseases related to OSA [5]. The following will discuss the relationship between OSA-related cardiovascular disorders and their management.

EPIDEMIOLOGY

OSA is estimated to occur in about 9-15% of the adult population. Although a large study reported a large prevalence in women, the majority of studies showed men had a higher risk of developing OSA. The prevalence and severity of OSA increases with age. On the other hand with the increasing age of cardiovascular disease, the coexistence of OSA with cardiovascular disease is a common thing [6]. The study of the Sleep Heart Health Study with 6132 subjects, middle age, who underwent a complete polysomnographic examination at home found that the highest category of AHI had a relative risk of 1.37 to get hypertension compared to the lowest category.

Prospective results were shown in the Wisconsin Sleep Cohort Study which showed the incidence of hypertension in 709 subjects after being observed for 4 to 8 years. The study also reported an increase in relative risk of 2.89 times in subjects with AHI> 15 and this increased risk also occurred at different levels at various levels of AHI [1].

Peker et al. Reported an increased incidence of coronary heart disease in middle-aged patients who were previously reported to be healthy after experiencing OSA in a 7-year observation period. They also got the result that if OSA was not treated properly, the independent risk of developing coronary heart disease increased 5 times, even as a whole it increased 11 times for the occurrence of cardiovascular disease [7]. The Sleep Heart Health Study study shows that subjects with AHI> 11 have a relative risk of 2.2 for congestive heart failure [8]. The research conducted by Mehra et al., Which found that subjects with severe OSA had a relative risk 5 times to develop atrial fibrillation (AF) [9].

EPIDEMIOLOGY

The mechanism of cardiovascular disorders in OSA is very complex and cannot be fully explained. Several factors that can link OSA with cardiovascular disease are oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, sleep fragmentation and metabolic dysregulation. This mechanism is closely interrelated and manifests simultaneously in patients with OSA.

Oxidative stress

In OSA there is an increase in oxidative stress and has a role in the occurrence of cardiovascular disorders. Oxidative stress arises from an imbalance in the redox status between the production and elimination of reactive oxygen species (ROS) [6]. Repeated hypoxic episodes cause intracellular structures to adapt to lower oxygen levels so that in normal oxygen concentrations it causes induction of ROS which has the ability to oxidize lipids, proteins and amino acids which form the basis of pathogenesis in chronic and age-related diseases such as cancer, heart disease, diabetes, inflammation chronic and neuro-degenerative disorders [9]. On the other hand ROS originating from neutrophils and monocytes in OSA patients has a relationship with classic inflammatory mediators (such as bradykinin) which also shows that systemic inflammation is one of the contributing factors in the production of ROS. ROS also contributes to endothelial dysfunction by increasing adhesion molecules and reducing the synthesis of nitric oxide (NO), resulting in NO interference and ultimately leading to a reduction in NO levels. If not repaired it will cause endothelial damage / dysfunction and may lead to atherosclerosis [6].

Sympathetic Activation

Under sleep conditions, there is a cardiovascular "calm" condition, both hemodynamic and autonomic, with an increase in parasympathetic (vagus) tone and a decrease in sympathetic nerve activity (SNA). The apnea cycle - OSA hyperapnea interferes with this balance and disturbances occur, especially chronic intermittent hypoxia and an increase in SNA which causes an increased regulation of the renin-angiotensin system and decreases the regulation of NO synthesis. When OSA occurs, it will end with sudden arousal seen in phase III (hyperpnea) associated with an increase in SNA [3].

The intermittent hypoxia cycle provides a reciprocal link between upper airway obstruction during sleep and sympathetic activation while awake. Intermittent hypoxia cycles can cause sympathetic excitation through two mechanisms: first, the addition of peripheral chemoreflex sensitivity (adjustment of hypoxia) and, second, a direct effect on the area of central sympathetic regulation. An increase in sympathetic activity and intermittent hypoxia associated with episodes of apnea has been suggested as a possible mechanism for a relationship between OSA, systemic inflammation and cardiovascular disease [10].

Inflammation

Increased levels of plasma C-reactive protein (CRP), superoxide leukocytes, and soluble adhesion molecules are indicators of chronic systemic underlying inflammatory responses in OSA patients. Excessive levels of CRP result in direct or indirect reduction (by monocyte activation) against NO synthesis. Many studies link ROS with induction from the cascade of inflammatory pathways that lead to excessive production of adhesion molecules and proinflammatory cytokines [11]. OSA increases various levels of adhesion molecules, such as intercellular adhesion molecules and vascular adhesion molecules, in endothelial cells and in neutrophils, thereby encouraging endothelial cell attachment and oxidative stress. Hypoxia and sleep deprivation also modulate the expression of inflammatory mediators, such as interleukin and tumor necrosis factor alpha (TNF-α) [12,6]. TNF-α also induces the expression of NADPH oxidase, which is a source of ROS production, and this becomes a vicious circle between oxidative stress-inflammation and vice versa [11].

Hypercoagulability

Hypercoagulability resulting from increased coagulation or inhibition of fibrinolysis is associated with an increased risk of cardiovascular disease. The underlying mechanism that causes a decrease in fibrinolysis in OSA patients is not known in detail, but it is suspected that there is involvement of hypoxic tissue induced by oxidative stress, in addition to an increase in SNA [11].

Various studies support the relationship between hypercoagulability, OSA, and cardiovascular disease. First, patients with OSA have higher plasma than some procoagulant factors such as fibrinogen, activation of clotting factors FVII (FVIIa), FXIIa, and thrombin / antithrombin III complex, platelet activity, and fibrinolysis plasminogen activator inhibitor inhibitor enzyme (PAI-1). Second, an increase in D-dimer levels in untreated OSA correlates with the severity of nocturnal hypoxemia, which is a characteristic of OSA. Third, data on sleep fragmentation and sleep efficiency have been associated with increased levels of von Willebrand factors and tissue solubility factors, two markers of prothrombotic conditions [10].

Endothelial Dysfunction

Vascular endothelium has a role in controlling vasomotor tone and as the main regulator of vascular hemostasis. The endothelium continuously maintains a balance between vasoconstriction and vasodilation; if it is not balanced there will be endothelial dysfunction which causes damage to the arterial wall. Endothelial dysfunction occurs in response to cardiovascular risk factors and can cause or accelerate the development of atherosclerosis [13]. Several studies have shown that inflammation and vascular endothelial dysfunction have a role in the development of cardiovascular disease in patients with OSA. In addition, increased SNA and oxidative stress also play a role in the development of endothelial dysfunction. Increased oxidative stress reduces NO availability and increases the expression of ROS, which activates inflammatory pathways that facilitate the recruitment and accumulation of blood cells in blood vessels in the endothelial layer [9].

Metabolic Dysregulation

There is a close relationship between insulin resistance and OSA and with atherosclerosis which shows that metabolic disorders are significantly associated between OSA and cardiovascular disease. The severity of sleep apnea seems to correlate with the level of insulin resistance. In severe OSA there is a 5 times higher risk for diabetes mellitus. One study showed high insulin levels in non-obese OSA patients and worsened with increasing AHI and oxygen desaturation rates. Thus, obesity is not the only determinant of insulin resistance, as previously believed [14]. Leptin is a hormone that affects satiety, controlling body weight and fat distribution which is also considered an independent risk factor for heart failure. Although leptin also increases in obese people, leptin increases the addition of platelet release from body fat distribution. So that correcting OSA will reduce leptin levels [6]. There is a close relationship between insulin resistance and OSA and with atherosclerosis which shows that metabolic disorders are significantly associated between OSA and cardiovascular disease. The severity of sleep apnea seems to correlate with the level of insulin resistance. In severe OSA there is a 5 times higher risk for diabetes mellitus. One study showed high insulin levels in non-obese OSA patients and worsened with increasing AHI and oxygen desaturation rates. Thus, obesity is not the only determinant of insulin resistance, as previously believed [14]. Leptin is a hormone that affects satiety, controlling body weight and fat distribution which is also considered an independent risk factor for heart failure. Although leptin also increases in obese people, leptin increases the addition of platelet release from body fat distribution. So that correcting OSA will reduce leptin levels [6].

Sleep Fragmentation

Some studies that observes the frequency of sleep disorders show that sleep fragmentation has a much more important role in cardiovascular changes in OSA and sleep position alone can significantly alter sleep fragmentation. Leiter et al. Showed that one night's sleep deprivation reduced the upper airway dilator muscle activity during hypercapneic rebreathing, causing upper airway to easily collapse. Sleep deprivation is associated with reduced ventilatory response to hypercapnia and hypoxia, a response that can potentially worsen airway obstruction in breathing. Sympathetic nervous system activation can be an important factor for subsequent cardiovascular risk [11].

OSA AND CARDIOVASCULAR DISEASE

Cardiovascular disorders are serious complications in OSA including hypertension, coronary heart disease, heart failure and arrhythmias. Various studies have shown that acute hemodynamics in physiological parameters and side effects on left ventricular pressure and dimensions associated with changes in

intrathoracic pressure are associated with OSA [6].

Hypertension

The relationship between OSA and hypertension has been extensively investigated and shows that there is a relationship between OSA severity and blood pressure elevation levels. The pathophysiological mechanism of OSA contributing to increased blood pressure is multifactorial. Hypoxemia caused by OSA causes systemic inflammation and oxidative stress, which results in an increase in endothelin-1 and a decrease in NO production in endothelial cells, an increase in peripheral arterial resistance and an increase in blood pressure [6].

On the other hand, periodic hypoxemia, frequent arousal and lack of sleep causes activation of the sympathetic nerves which causes an increase in cardiac output and narrowing of peripheral vessels, and thus causes an increase in blood pressure. A study reports that patients with OSA have a higher prevalence of diastolic hypertension and the underlying mechanism due to tachycardia and shortening of cardiac diastole. Another study reported that when compared to subjects without OSA, there was an increase in renin induction in subjects with OSA caused by efferent activation of renal sympathetic nerves and this effect caused an increase in plasma angiotensin-II and aldosterone, resulting in blood pressure elevation by vasoconstriction and retention liquid sodium. Research shows that patients with OSA and primary hyperaldosteronism are more likely to develop drug-resistant hypertension. Sleep deprivation in OSA is associated with endothelial dysfunction and arterial stiffness, both of which initiate and accelerate the occurrence of hypertension [15,16].

Coronary Heart Disease

Many epidemiological studies link OSA with coronary heart disease. some studies report a high prevalence in OSA with coronary heart disease. Circulatory physiology is strongly influenced by changes in sleep patterns, OSA associated with hypoxia, hypercapnia, soaring blood pressure due to increased SNA, and acute imbalance of vasoactive hormones [6]. Imbalance of myocardial work and coronary blood flow and increased resistance of coronary arteries, can cause myocardial ischemia. Increased transmural pressure (afterload) resulting from excessive intrathoracic pressure during apnea, and increased sympathetic activity, heart rate, systemic blood pressure, and cardiac output will increase myocardial oxygen demand [3]. Meanwhile hypoxia due to intermittent apnea, and reduced coronary flow due to atherosclerosis, can reduce oxygen supply, causing coronary ischemia. This proinflammatory condition is characterized by an increase in CRP and prothrombosis characterized by an increase in plasminogen activator inhibitor-1 and fibrinogen. These changes not only can provoke acute coronary syndromes but also lead to chronic consequences such as heart failure [6].

Heart Failure

There is a lot of evidence that shows the tight relationship between OSA and heart failure. One mechanism from OSA that leads to heart failure is OSA will increase transmural pressure in the left ventricle due to the creation of intrathoracic (Pit) negative pressure and increased systemic blood pressure [17]. Blood pressure alone increases due to hypoxia, microarousal conditions and increased SNA. Apnea also has the effect of inhibiting sympathetic activity of pulmonary stretch receptors, thus increasing SNA [18]. The combination of increased left ventricle and heart rhythm due to increased SNA, will increase the need for 02, even when supply 02 to the heart muscle decreases. This situation causes acute cardiac ischemia and arrhythmias, and chronic causes of left ventricular hypertrophy and heart failure [19,1].

Arrhythmia

Heart rhythm disorders have been described in patients with OSA, the most common type being unsustained ventricular tachycardia, sinus arrest, and second degree AV block. Bradyarrhythmias can arise from vagal heart activation caused by apnea-related hypoxemia even though the heart is normal. A decrease in nocturnal oxygen saturation has been identified as a predictor of the incidence of atrial fibrillation. In non-treated OSA there is a higher degree of recurrence for atrial fibrillation after cardioversion when compared with OSA treated. And in these patients also have a higher risk of ablation failure [9].

DIAGNOSIS

The most common symptoms that arise from OSA include loud snoring, excessive daytime sleepiness, restless sleep, choking during sleep, or signs of apnea. Other symptoms include mood disorders, irritability, disruption of social interactions, morning headaches, dry mouth, nocturia, or decreased libido. On examination, high BMI, large neck circumference, upper airway narrowing by the lateral pharyngeal wall, and tonsillar enlargement are signs that can help predict OSA. Men with neck circumferences greater than 42 cm and women with neck circumferences larger than 37 cm have a higher incidence of OSA [8].

Gold standard to ascertain the diagnosis and estimate of OSA severity using polysomnographic examination. The American Academy of Sleep Medicine (AASM) recommends a complete polysomnographic examination in a laboratory with the supervision of a trained technician. This examination is performed at least 6 hours at night and simultaneously records various physiological signals during the patient's sleep [1].

Polysomnography as the gold standard OSA diagnostic tool is still expensive and still limited in number so it requires other tools that are effective and efficient in identifying OSA. Several forms of questionnaires as OSA detection tools we Berlin questionnaires, STOP questionnaire, Stanford Sleepiness Scale (SSS) and Epworth Sleepiness Scale (ESS). The SSS questionnaire is rarely used in daily practice. The results of this questionnaire indicate the occurrence of fragmented sleep. While the ESS questionnaire is used to measure the likelihood of someone sleeping in various situations. ESS scores can significantly distinguish primary snoring conditions with OSA [1]. The STOP questionnaire is an optimal test tool in predicting severe OSA consisting of 4 questions related to Snoring, Tired, Observed apnea and high blood Pressure [20]. The Berlin questionnaire is a simple and inexpensive tool that emphasizes risk factors. This questionnaire has a fairly good sensitivity, specificity and positive predictive value so that it can be used in primary services [1,5].

THERAPY

The patient's treatment decision must be based on a combination of symptoms and signs of OSA, as well as the severity of the disease determined by polysomnography. Based on AASM, first-line standards use continuous positive airway pressure (CPAP). Other methods used for OSA therapy include oral appliances, surgery and behavior therapy [1].

CPAP is an effective therapy in OSA patients by providing ventilation by making positive pressure on the airways so that air enters the lungs. The purpose of this therapy is to improve clinical symptoms and normalize physiological variables in polysomnography. A study shows that the tendency for neutrophils to produce more ROS in OSA can be reversible again when receiving CPAP therapy [8]. Effective CPAP therapy (> 4 hours every night) in OSA patients reduces sympathetic nerve activity, reduces inflammation, improves endothelial dysfunction and improves endothelial repair [1]. The use of CPAP in OSA patients reduces the number of new coronary events, eliminates arrhythmias, prevents AF so as to reduce mortality [14]. Kanagala et al. Showed that patients with OSA and AF could return to sinus rhythm after cardioversion if treated with CPAP [8].

Oral appliance is made to increase the volume of the upper airway. This tool is indicated for patients with moderate to severe OSA who are intolerant of CPAP or refuse CPAP therapy, and for patients who cannot be surgically removed [21].

Behavioral therapy is carried out, among others, by avoiding things that can worsen the disease. In mild OSA patients, apnea occurs when sleeping in the supine position so sleeping in one position helps the patient to breathe. OSA overweight patients must lose weight to achieve an ideal BMI of 25kg / m2 or less [1,21].

Surgery is performed if non-invasive CPAP medical therapy, or oral appliance fails or is refused by the patient. The Powell-Riley surgical protocol is a 2-phase approach to surgical treatment in OSA. Stage 1 is in the form of nose surgery, oropharynx, and hypopharyngeal obstruction during sleep and should be done before stage 2. Stage 1 surgery can help increase tolerance for CPAP. Stage 2 surgery includes bimaxillary advancement skeletal reconstruction called maxilla-mandibular osteotomy. Patient selection must be careful to minimize the failure rate, and the procedure must be carried out only after considering non-surgical treatment options [8].

SUMMARY

OSA is associated with an increased risk of hypertension, coronary heart disease, heart failure and arrhythmias, thus increasing the mortality rate from cardiovascular disorders. Several factors that can link OSA with cardiovascular disease are oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, sleep fragmentation and metabolic dysregulation. Polysomnography as the gold standard OSA diagnostic tool is still expensive and still limited in number so it requires other tools that are effective and efficient in identifying OSA. Therapy of OSA patients by using Continuous Positive Airway Pressure (CPAP) has proven effective in reducing cardiovascular events. Other methods that can be used for OSA therapy include oral appliances, surgery and behavioral therapy.

CONFLICT OF INTEREST

None

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