Obstructive Sleep Apnea and Venous Thrombosis: Clinical Implications

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ABSTRACT

Obstructive sleep apnea (OSA), although a disease of upper respiratory airway, has profound effects on body systems. The breathing abnormalities have effects on venous return. Pooling of blood in legs during apnea–hypopnea, coupled with hemodynamic changes and pathological cascades, favors thrombosis in legs and subsequent thromboembolism. An OSA has possible implications in vascular endothelial injury, stagnant blood flow, increased coagulability (Virchow’s triad), and Trousseau’s syndrome. An OSA suspicion is high in all patients with venous thrombosis, particularly in those who have recurrent episodes of this disorder.

Keywords: Obstructive sleep apnea, Venous return, Venous thromboembolism.

Indian Journal of Sleep Medicine (2020): 10.5005/jp-journals-10069-0057

INTRODUCTION

Obstructive sleep apnea (OSA) has been recognized as a common and treatable disorder. It is characterized by repetitive pharyngeal collapse in sleep, which leads to cyclical hypoxia and cyclical sympathetic stimulation. These events pave the way for thrombosis. In fact, OSA has been labeled as a prothrombotic state. Thrombosis in the venous systems in patients with OSA is being increasingly recognized.

Venous return from legs is dependent upon the skeletal muscle pump, which is effective while the subject is walking. The changes in venous pressure coupled with normal functioning valves help the blood to go caudally. While standing, the postural muscles in legs alternately contract and relax to keep the body in balance. This muscle activity promotes venous return, maintains central venous pressure, lowers venous and capillary pressure in feet and lower limbs. Respiratory activity also contributes to venous return by the following mechanisms: (a) Increasing the rate and depth of respiration promotes venous return and therefore enhances the cardiac output. (b) Intrapleural pressure becomes more negative during inspiration, which leads to the expansion of lungs, cardiac chambers (right atrium and right ventricle), and superior and inferior vena cava. The resultant fall in the intravascular and intracardiac pressure leads to increased venous return, increased preload and increased stroke volume. During expiration, the opposite occurs.

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea, although a common disorder, often escapes clinical recognition due to poor awareness among society and health professionals. An OSA is characterized by repetitive pharyngeal collapse in sleep, leading to cyclical hypoxemia, cyclical hypertension, release of catecholamines, and stress hormones. An OSA can affect any system since oxygen is the basic nutrient of all cells. It is a chronic condition where nocturnal events occur night after night. The effects of intermittent hypoxia (akin to intermittent respiratory failure) and reoxygenation may provoke a number of pathological cascades that involve sympathetic overactivity, oxidative stress, endothelial dysfunction, increased oxidative vascular injury and systemic inflammation. These nocturnal events are believed to be mechanisms contributing independently to increased cardiometabolic risk.1 Chief metabolic effects include decreased insulin sensitivity and worsening of glucose tolerance. OSA is a risk factor for hypertension, diabetes, ischemic heart disease, stroke, dementia and others.7 There is a high prevalence of sleep-disordered breathing in patients with congestive heart failure (CHF).3 Studies have suggested that 40–50% of patients with CHF and left ventricular systolic dysfunction will have some form of sleep-disordered breathing, either obstructive or central sleep apnea.3 The presence of SDB affects cardiac function and ejection fraction adversely.

EFFECTS OF OBSTRUCTIVE SLEEP APNEA ON VENOUS SYSTEM

Sympathetic activation causes vasoconstriction. The apneas and hypopneas contribute to reduced venous flow and pooling of blood in legs. Both contribute to venous hypertension. The changes in pleural pressure that promote venous return are also absent in apneas and hypopneas.

OBSTRUCTIVE SLEEP APNEA AND VENOUS THROMBOSIS

In a nationwide population-based cohort study, Peng et al.4 stated that patients with OSA exhibit a higher risk of subsequent deep vein thrombosis and pulmonary embolism. The specific underlying

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mechanism explaining the association between OSA and venous thromboembolism remains unclear. However, three mechanisms operate: (1) vascular endothelial injury, (2) stagnant blood flow, and (3) increased coagulability (Virchow’s triad). It should be noted that elevated platelet activity, fibrinogen levels, plasminogen activator inhibitor-1 levels, erythrocyte adhesiveness and aggregation but reduced fibrinolytic capacity contribute to this hypercoagulable state.\(^5\)\(^6\) Studies have indicated that most Asian patients with OSA are not obese.\(^7\) Caucasians are more obese than Asians. Also, Asians exhibit more craniofacial bone restriction.

Alonso-Fernandez et al.\(^8\) reported that after a first episode of pulmonary embolism, OSA is an independent risk factor for pulmonary embolism recurrence or restarting oral anticoagulants for a new thromboembolic event. We reported the first case of Schamberg’s disease in a patient of severe OSA.\(^9\)

**VENOUS THROMBOEMBOLISM**

Venous thromboembolism (VTE) is a frequent, chronic and potential fatal disease. Pulmonary embolism (PE) is a major manifestation of VTE with an annual incidence of one to two cases per 1,000 person-years; it is strongly age dependent. Risk factors such as advanced age, obesity, and physical inactivity are common for both OSA and PE.\(^10\)\(^11\) OSA is an independent risk factor for deep vein thrombosis.\(^12\) Patients with a first episode of PE have a cumulative recurrence rate of approximately 30% at 10 years.\(^13\)

The risk of recurrence depends on the number and severity of risk factors in an individual patient. Significant risk factors for the recurrence of PE include the following: (a) a previous unprovoked episode, (b) high post-anticoagulation plasma D-dimer levels, (c) cancer, (d) continued estrogen use, (e) vena cava filters, (f) male sex, and (g) obesity. The last two are also risk factors for OSA. Intermittent hypoxia plays an important role in the procoagulant state of patients with OSA. Obesity and daytime sleepiness promote venous stasis, which also contributes to hypercoagulable state. Endothelial injury in venous valves results in creating a hypercoagulable microenvironment (Flowchart 1).
Obstructive Sleep Apnea and Pregnancy and Venous Sinus Thrombosis

Pregnant women possessing craniofacial abnormalities in both bony and soft tissues are believed to be predisposed to sleep-disordered breathing (SDB). Weight gain and obesity are important risk factors for the development of SDB in pregnancy. Aggarwal et al. reported that maternal morbidity in terms of preeclampsia and meconium-stained liquor was higher among snorers and SDB population of pregnant women. SDB has been proposed as a risk factor for adverse maternal–fetal outcomes, including pregnancy-induced hypertension and small for gestational age births. Venous sinus thrombosis in puerperium is possibly related to OSA.

Obstructive Sleep Apnea and Retinal Vein Occlusion

Glacet-Bernard et al. found a higher-than-expected prevalence of OSA in a series of patients with retinal vein occlusion (RVO), suggesting that OSA could be an additional risk factor that plays an important role in the pathogenesis of RVO or at least that it is a frequently associated condition that could be a triggering factor. This association may explain why most patients discover visual loss on awakening.

Obstructive Sleep Apnea, Cancer and Venous Thrombosis

Deep vein thrombosis and pulmonary embolism are the most common thrombotic conditions in patients with cancer. Nearly 15% of patients who develop deep venous thrombosis or pulmonary embolism have a diagnosis of cancer. The coexistence of peripheral venous thrombosis/migratory thrombophlebitis with visceral carcinoma, particularly pancreatic cancer, is called Trousseau’s syndrome. Rodriguez et al. have reported increased overnight hypoxia, as a surrogate of OSA severity was associated with increased cancer incidence. This association seems to be limited to men and patients younger than 65 years of age.

Notwithstanding the potential limitations of the methodological approaches employed to date, the existing evidence strongly suggests that intermittent hypoxia and sleep fragmentation could play an important role in increasing cancer incidence and mortality in patients with sleep-disordered breathing, most likely by promoting sympathetic outflow, immunological alterations, or angiogenesis in the host response to tumor that ultimately results in markedly adverse tumor properties.

The most common and accepted mode of therapy of OSA is the usage of continuous positive airway pressure while sleeping. This therapy has been found to be highly rewarding (opens the pharyngeal gate and closes the gates to various systemic disorders).

Conclusion

There is a close relation between OSA and venous thrombosis. In a given clinical setting, it is important to recognize and treat this condition. The treatment of OSA by CPAP results in an overall improvement in all the consequences of OSA.

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