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Pulmonary Thromboembolism Superimposed on Obstructive Sleep Apnea ： A Case Report

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Abstract

Non-invasive ventilation with continuous positive airway pressure is gaining popularity as a technique for achieving effective treatment in obstructive sleep apnea. However, we observed a patient at our institution complaining of dyspnea on exertion who was diagnosed with pulmonary embolism even after implementation of continuous positive airway pressure for 5 years. This is a worrying problem because obstructive sleep apnea is known to be a risk for cardiovascular complications, and treatment by the mainstay therapy with continuous positive airway pressure didn't seem to eliminate the fatal complication of pulmonary embolism. The association of pathophysiology between obstructive sleep apnea and pulmonary embolism is uncertain; nevertheless, close monitoring is vital to exclude a pathological and fatal event such as pulmonary embolism even after implementation of continuous positive airway pressure. (J Intern Med Taiwan 2007; 18: 350- 355)

Key Words ： **Pulmonary thromboembolism, Obstructive sleep apnea, Continuous positive airway pressure**

Introduction

Obstructive sleep apnea (OSA) is a common disorder[1], characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep that disrupts normal ventilation and sleep architecture and is typically associated with snoring and daytime sleepiness[2]. This leads to sleep fragmentation, and possibly cardiovascular sequelae (including pulmonary and systemic hypertension, cerebrovascular events, and myocardial infarction) [3]. Of course, pulmonary embolism (PE) is a potentially

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fatal sequelae. Non-invasive mechanical ventilation with positive airway pressure is considered a safe procedure and a mainstay therapy for OSA, aimed at maintaining a patent airway during sleep and eliminating apneas, improving symptoms and possibly reducing cardiovascular sequela [4]. The association of PE with OSA has been reported extensively, but to our knowledge, there has been no documentation of occurrence of PE after implementation of continuous positive airway pressure (CPAP) for OSA. We report this case to facilitate recognition and treatment of this possible sequela of OSA, even after implementation of the mainstay therapy by CPAP.

Case Report

A 60-year-old man with a body mass index (BMI) of 24.2 $kg.m^{-2}$, presented with progressive dyspnea on exertion. He had been diagnosed with obstructive sleep apnea and implemented nocturnal CPAP therapy for 5 years. He remained free of symptom until 1 month ago, when he developed increasing dyspnea on exertion. He even searched for help in a regional hospital, where echocardiography demonstrated mild pulmonary hypertension with a maximum pressure gradient of 25 mmHg across the tricuspid valve about 1 week ago. He presented to our hospital when he could only walk 10 meters on level ground.

At the time of admission, he was acutely ill-looking. He was afebrile with a body temperature of 36.2 ℃. His pulse rate was 127/min, respiration rate 31/min and blood pressure of 162/94 mmHg. Physical examination revealed a jugular venous pressure of 10 cm of water. There was a right ventricular heave and an accentuated P_2. Laboratory studies showed an oxygen saturation of 92 % on room air. Echocardiography demonstrated severe pulmonary hypertension, concentric left ventricular hypertrophy with preserved left ventricular systolic function and a pressure gradient of 55 mmHg across the tricuspid valve without structural abnormality (Fig. 1).

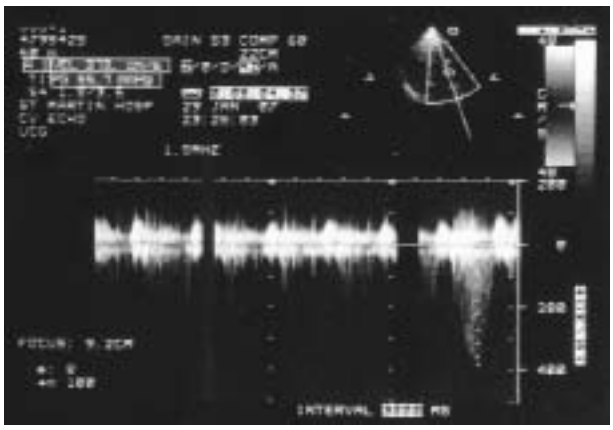

Fig.1.Echocardiography demonstrated a pressure gradient of 55 mmHg between the right atrium and ventricle and it indicated severe pulmonary hypertension of at least 60 mmHg.

The combination of a stable OSA after implementation of CPAP therapy and marked pulmonary hypertension prompted us to investigate for alternative etiologies of his symptoms. The patient denied use of tobacco, anorexigens, intravenous drugs, immobilization or history of traveling and EKG, serologic evaluation for vasculitis, collagen vascular disease, and HIV were unremarkable. Disorders of hemostasis were also excluded with prothrombin time 11.7 s, activated partial thromboplastin time 30.7 s, international normalized ratio 1.02 and platelet count $341000/mm^3$.

On hospital day 2, the patient developed progressive hypoxia. Despite an increase of his F_iO_2 to nearly 0.5, his oxygen saturation remained $<90\%$. A D-dimer of 3883.40 ng/dl was the only unusual laboratory data. Our suspicion of acute pulmonary embolism (PE) was confirmed by chest CT scan, which demonstrated filling defects in bilateral lower lung pulmonary arteries (Fig. 2) and lung perfusion scan, which demonstrated high probability of pulmonary embolism. A source of clot was not identified in the lower extremities by computed tomography.

The patient was started on a continuous intravenous heparin infusion, regularly adjusted to achieve a therapeutic activated partial thromboplastin time (aPTT) of 45-70. Rescue therapy with an-

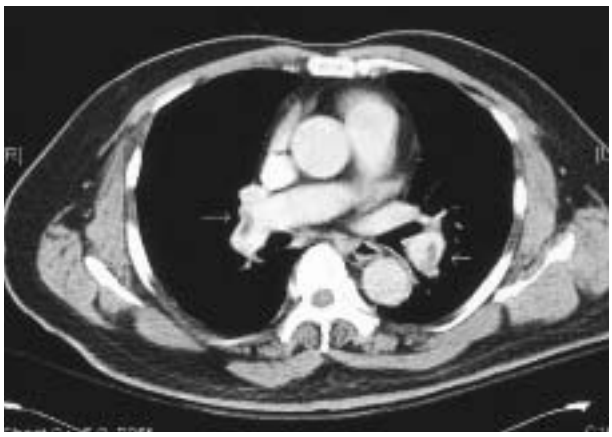

Fig.2.A chest CT scan showing filling defects in bilateral lower lung pulmonary arteries (arrow).

ticoagulants resulted in a rapid increase in P_aO_2 from 67 to 149 mmHg in F_iO_2 50% during 24 hours. The addition of warfarin acutely facilitated reduction of the F_iO_2 and eventual discontinuation of intravascular anticoagulants. The prothrombin time international normalized ratio on discharge was 2.45. The patient continued taking 5 mg warfarin orally every day as an out patient. Four weeks later, he was able to walk 500 meters on level ground.

Discussion

There is an increasing perception that OSA, via various mechanisms, increases cardiovascular morbidity and mortality. There is also increasing information to indicate that OSA is linked to metabolic, vascular, hematologic, and genetic markers associated with increased cardiovascular disease risk. However, many risk factors for OSA, such as obesity and male gender, are the same as for cardiovascular disease[5] and ascertaining the association of PE with OSA is difficult, particularly as cases of PE are often unidentified because of minimal or absent symptoms [6]. Although we also knew the strong association between OSA and PE, the 2 events could potentially occur coincidentally. Patients with OSA may be at increased risk for weight gain, and obesity is a major risk factor for cardiovascular disease. Resistance to the appetite suppressant effects of leptin may be involved because OSA patients have higher leptin levels than similarly obese controls [7]. Similarly, obesity is associated with increased reactive oxygen species (ROS) levels and an increase in ROS can up-regulate vascular adhesion molecules, cause platelet aggregation, and scavenge the potent vasodilator nitrogen oxide. OSA represents a likely mechanism linking obesity and elevated ROS, but it is unclear whether these increased levels are related to vascular disease and hypercoagulability. Even patients with pulmonary embolism or deep vein thrombosis have a higher incidence of OSA [8]. Moreover, several potential mechanisms, e.g. superoxide release from neutrophils [9] or increased levels of catecholamines [10], could explain the association between OSA and a hypercoagulable state. But available studies are limited by small sample size, lack of uniform definition, and failure to consistently control for potential confounders. Thus, a number of mechanisms could potentially explain the relationship between hypercoagulability/thrombosis and OSA, but relevant ones have not been defined and definitive data from large well-controlled studies is lacking.

In 1981, Sullivan et al.[11] first described the use of nasal CPAP as a treatment of OSA. Prior studies persuasively demonstrated improvements in cognitive performance, sleepiness, and quality of life among OSA individuals treated with CPAP [12,13]. We also knew that platelet aggregation as well levels of plasminogen activator inhibitor-1 and fibrinogen are increased in OSA patients, and decrease after CPAP treatment [14]. Furthermore, increased leptin levels associated with OSA decline after treatment with CPAP [15] and treatment with nasal CPAP decreases ROS levels [16]. However, evidence that the restoration of the dipping pattern with CPAP would affect cardiovascular morbidity and mortality is lacking. For instance, results of studies on the effect of CPAP on nocturnal and daytime hypertension are conflicting; some studies demonstrate a reduction in blood pressure with therapy whereas others do not [17,18]. Thus, report-

ing cases of identified PE after CPAP is therefore important to study the benefits of CPAP in OSA. In our patient, the close relationship of PE to OSA, with a normal BMI and no other identified risk factors of trauma, prolonged inactivity, diabetes, inducible drug history or major surgery suggests OSA as the provoking factor. Of course, male gender was an another possible factor. To our knowledge, procoagulant and anticoagulant mechanisms are balanced under physiological conditions. The associations between defects in the homeostatic system and hypercoagulability is well established. Patients with activated protein C resistance (APCR) accompanied by another genetic defects, protein S deficiency, demonstrate the increased risk of severe thromboembolic episodes. APCR is by far the most frequent coagulation disorder predisposing to venous thromboembolism [19]. Others, antithrombin (ATIII) is a potent inhibitor of the coagulation cascade. Congenital deficiency leads to increased risk of venous and arterial thrombosis, acquired type is most commonly seen in situations in which activation of the coagulation system is inappropriate [20]. It is a pity that serum ATIII, protein C and protein S were not checked in this case. Therefore, these rare disorders could not be excluded completely by history and underlying diseases. Nevertheless, our patient with OSA was stabilized by CPAP but still complicated by the potentially fatal PE. The role and responsible mechanisms of OSA as a risk factor "independent" of associated co-morbidities, and whether treatment of OSA will mitigate the risk are unknown and remain to be determined.

In the case reported, the diagnosis of PE is strongly suggested by the onset of dyspnea, oxygen desaturation, pulmonary hypertension and the presence of filling defects in bilateral pulmonary vessels on computed tomography. However, acute aspiration of gastric contents, chronic obstructive pulmonary disease, acute myocardial infarction, and circulatory collapse are other possible causes of respiratory distress in OSA treated by CPAP. Distinguishing pulmonary embolism from other causes of mortality is often difficult as symptoms are similar. Chest CT has virtually replaced lung scanning for diagnosing PE at most hospitals[21], resulting in more rapid and accurate diagnosis. Rapid diagnosis of PE is crucial to initiate potentially life-saving therapy. Chest CT is not only useful to diagnose PE and assess clot burden but helps to identify patients with right ventricular enlargement who are at risk of early death [22].

The patient described in this report may have been at risk for venous stasis because of OSA. However, dyspnea on exertion is also a prominent symptom in fatal cases of pulmonary embolism associated with well-controlled OSA in CPAP treatment. Institution of physiotherapy or low-dose heparin therapy may prevent clot formation. Evaluation of patients for observation of pulmonary hypertension on echocardiography may aid in diagnosis and indicate advisability of further testing. Identification of a thrombus should result in initial anticoagulation with intravenous or subcutaneous heparin, and oral warfarin after a therapeutic aPTT value is achieved. As the presentation of pulmonary embolism can be variable, we recommend consideration of helical computed tomography angiography or ventilation/perfusion scanning of the lungs in patients with suspicious symptoms, particularly in high risk patients with OSA, even after implementation of CPAP. These measures would allow for earlier treatment if pulmonary thromboembolism is present, and hopefully decrease mortality from this condition.

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阻塞性睡眠呼吸終止症候群患者併發肺栓塞：一病例報告

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摘　要

非侵入性陽壓呼吸輔助器是阻塞性睡眠呼吸終止症候群常用的有效治療方式。但是，一位阻塞性睡眠呼吸終止症候群患者在持續穩定使用陽壓呼吸輔助器五年後，出現活動喘息的症狀並診斷爲肺栓塞。阻塞性睡眠呼吸終止症候群確實會導致心血管疾病併發症的風險增加，令人擔憂的是在標準治療方法，陽壓呼吸輔助器的使用之下，卻無法排除肺栓塞這種致命的併發症。顯然阻塞性睡眠呼吸終止症候群和肺栓塞之間的病生理學關聯性還有待確認；無論如何，阻塞性睡眠呼吸終止症候群患者再使用陽壓呼吸輔助器後，仍需嚴密注意這種致命併發症發生的可能性。