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Case Report

# Thromboembolism and Ischemic Stroke in Patient with Obstructive Sleep Apnea and Hyperhomocysteinemia: Case Report and Literature Review

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## Abstract

**Introduction:** Pulmonary thromboembolism (PTE) has a significant disease burden worldwide. Many risk factors for PTE have been reported: surgery, trauma, cancer, obesity, estrogen therapy and genetic blood conditions, such as thrombophilia conditions, one of which is hyperhomocysteinemia, although its remains controversial. Obstructive sleep apnea (OSA) is also being recognized as an independent risk factor for several clinical comorbidities, including systemic hypertension, cardiovascular disease, stroke and abnormal glucose metabolism and PTE. Intermittent hypoxia causes oxidative stress and inflammatory responses that in turn alter endothelial function and increase intravascular coagulation, possible pathogenetic mechanisms of these conditions.

Ischemic stroke (IS) is induced by cell death in the brain due to poor blood supply and is a leading cause of disability and death worldwide. Complex pathological mechanisms are involved in brain injury after cerebral ischemia. Inflammatory processes are central in the pathophysiology of ischemic injury after stroke. Elevated plasma homocysteine is a robust and modifiable risk factor of ischemic stroke.

OSA is a common comorbidity in stroke patients: in particular, the severity of OSA, is significant in the development of stroke. In light of these findings, the combination of hyperhomocysteinemia and OSA could increase the risks for embolism and stroke in such patients. Our case report of a patient with PTE and stroke, demonstrates a potential synergy between the 2 conditions.

**Case Report:** G.C, a 69-year-old male was hospitalized with a diagnosis of PTE and stroke. The search for triggers was negative, except for a high level of homocysteine. At the clinical follow-up 2 months after discharge, the patient underwent nocturnal cardiorespiratory monitoring, from which a profile of severe OSA emerged. Subsequently he was treated with continuous positive airway pressure (CPAP) therapy.

**Conclusion:** This clinical case underscores the importance of identifying comorbidities and all risk factors in the optimal management of PTE and cerebrovascular disease. The pathogenetic mechanisms of OSA, through oxidative stress due to apneic/hypoxemic episodes and hyperhomocysteine could have a synergistic effect on endothelial damage and thus increase the risk for embolism and stroke.

***Keywords:*** *Thromboembolism; Obstructive Sleep Apnea; Ischemic Stroke; Hyperhomocysteinemia*

## Introduction

Venous thromboembolism (VTE) is a chronic disease, of which pulmonary embolism (PE) is the major expression and the third most frequent cardiovascular disease. PE remains a major global health issue [1]. PE is the most common cause of vascular death after myocardial infarction and stroke, and is the leading preventable cause of death in hospital patients [1].

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing that is characterized by the repetitive partial or total collapse of the upper airway during sleep, affecting nocturnal sleep quality and eliciting daytime fatigue and sleepiness [2]. In severe cases, patients suffer from hypoxia, arousal and sleep fragmentation.

Recurrent episodes of complete or partial airway obstruction are associated with intermittent arterial oxygen desaturation [2,3]. Increasingly, obstructive sleep apnea is being recognized as an independent risk factor for several clinical condition, including systemic hypertension, cardiovascular disease, stroke, and abnormal glucose metabolism [4-6]. OSA is a common finding in stroke patients and ischemic stroke (IS) patients and is an independent risk factor for all stroke patients [7-9].

More and more cross-sectional and longitudinal studies have linked OSA to VTE and have postulated various putative pathways to explain how OSA increases the risk of PE [10]. A global interpretation of the studies posits that OSA is highly prevalent in VTE patients. This association represents a major public health burden, given the high prevalence and the mortality rates of both disorders [11-13].

Hypercoagulability has emerged as a potential pathophysiological mediator of cardiovascular morbidity in OSA. Data suggest that the chronic intermittent hypoxia that is experienced by patients during sleep-disordered breathing is responsible for sympathetic hyperactivity, endothelial dysfunction, elevation of inflammatory and oxidative stress markers and subsequent alterations to the coagulation system (Figure 1) [1,14]. Although it remains unproven, treatment with continuous positive airway pressure (CPAP) in OSA patients could improve coagulant activity, platelet function and the fibrinolytic system. However, there remains a lack of randomized controlled trials that have evaluated the value of CPAP and extended oral anticoagulation in reducing the incidence, recurrence and mortality of PE in patients with OSA.

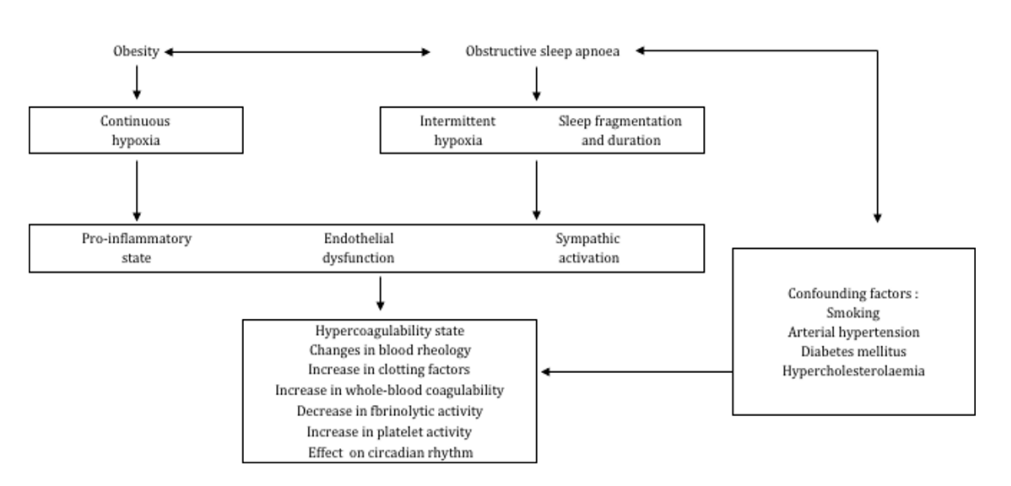


***Figure 1:*** *Possible pathophysiological links between OSA and hypercoagulability.*

Ischemic stroke (IS) is one of the most frequent causes of injury to the central nervous system, in which several pathological mechanisms are involved. For example certain inflammatory processes are mediated by microglial cells, which are rapidly and time-dependently activated after ischemia and are considered the major cellular contributors to post injury inflammation [15]. Patients who suffer from IS have high levels of homocysteine (Hcy) [16,17]. Hcy is an intermediate sulfhydryl containing amino acid that is derived from methionine. Hyperhomocysteinemia manifests as typical clinical cardiovascular symptoms and neurological disorders [18-24], but the correlation between Hcy and independent risk factors for VTE is debated [25-28]. Hcy results from genetic or nutritional disturbances. Hyperhomocysteinemia is commonly caused by genetic alterations in enzymes that metabolize homocysteine, dietary deficiencies in folic acid, vitamin B12 or vitamin B6, chronic renal insufficiency, lifestyle factors (smoking, chronic alcohol, high coffee intake), end-stage diabetes, hypothyroidism, systemic lupus erythematosus, hyperproliferative disorders and medications (methotrexate, sulfonamides, or antacids) [26]. Vitamin B12 and folic acid supplementation lowers homocysteine concentrations regardless of the cause.

Hcy affects haemostasis and shifts its balance in favour of thrombosis. *In vitro* and *in vivo* studies have suggested that Hcy impairs fibrinolysis by altering the plasma levels of fibrinolytic factors or the structure of fibrinogen (Table 1) [29,30].

| | |
|---|---|
| Vascular endothelium | • Impaired endothelium-dependent vasodilatation<br>• Prothrombotic and proinflammatory phenotype of endothelium |
| Platelets | • Increased thromboxane synthesis<br>• Increased platelet reactivity |
| Fibrinolysis | • Decreased binding of tissue plasminogen<br>• Decreased plasmin generation<br>• Increased level of thrombin activatable fibrinolysis inhibitor |
| Coagulation factors and natural inhibitors of coagulation | • Increased synthesis of tissue factor<br>• Increased activity of factor VII<br>• Decreased inactivation of factor Va<br>• Increased activation of factor V<br>• Decreased activity of antithrombin<br>• Increased thrombin generation<br>• Fibrinogen modification<br>• Inhibition of thrombomodulin activity<br>• Inhibition of protein C activation |

***Table 1:*** *Effects of Hyc on endothelium and hemostasis.*

The function of homocysteine in venous thrombosis has been studied less extensively compared with in arterial diseases and remains controversial. Futher, the results of epidemiological studies are unclear - most have found an association between hyperhomocysteinemia and venous thromboembolism albeit a week one - much less robust in prospective than in retrospective studies.

However, some data have confirmed hyperhomocysteinemia as a risk factor for recurrent VTE [31]. We present a nonalcoholic male smoker, who was diagnosed with IS, PE, Hcy and OSA. Thus the patient was treated with vitamin B12 and folic acid and an adequate dose of heparin infusion, followed by oral anticoagulant with CPAP therapy.

## Case Report

G.C. was a 69-year-old male (tobacco smoker at 30 pack/yrs, no alcohol use, body mass index: 30 $Kg/m^2$) whose medical history was significant for coronary artery disease, myocardial infarction, hypertension, chronic obstructive pulmonary disease (COPD) and transient ischemic attack 2 years ago.

His current medication included Breo Ellipta 100/25 mcg inhaled daily, hydrochlorothiazide 25 mg oral daily, nebivolol 5 mg oral daily, cardioaspirin 100 mg oral daily and isosorbide mononitrate 60 mg oral daily.

He was hospitalized, presenting to the emergency department with acute onset shortness of breath, progressive dyspnea and thoracalgia. He denied having any fever, chills, sputum production, abdominal pain or palpitations.

On evaluation the patient had intense dyspnea, was agitated, had no cyanosis. His pulse pressure was normal, rapid and regular and his blood pressure was 190/120 mmHg, His HR was 130/min, RR was 32 a/min, and $SpO_2$ was 88% in room air, without fever. Auscultation revealed normal heart sounds and rare rhonchi and mild bilateral crepitations: the ECG showed only non specific ST e T abnormalities. The remainder of his clinical examination was unremarkable. Routine laboratory analyses were normal except for elevated B natriuretic peptide (BNP 4941 pg/mL normal value < 125) and D dimer (5.8 mg/L normal value < 0.50). Bilateral edema slopes were present.

A bedside ultrasonography was performed and we found 3+ B line bilateral: the chest x-ray detected fluid in the alveolar waits a “bat wing” pattern, patchy bilateral shadowing and increased cardiac size (Figure 2).

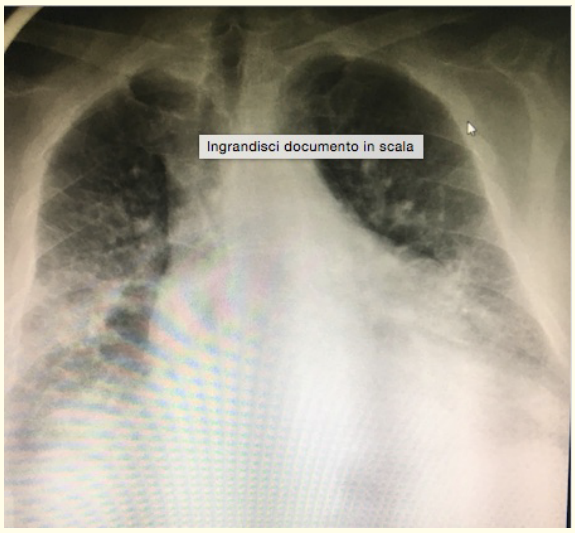


***Figure 2:*** *Images of the chest x-ray.*

An echocardiography showed mild dilatation of the right ventricle with estimated systolic pulmonary artery pressure (PAP) at 40 mmHg: the left ventricular function was impaired and the ejection fraction was 45%.

The patient had hypoxemia with modest hypercapnia ($PaO_2$ 54.2 mmHg, $PaCO_2$ 50 mmHg pH 7.44, $SatO_2$ 88%) and underwent radiography of the chest in 2 projections, showing initial signs of congestions (Figure 2); based on the increase in D dimer indices and the symptoms that presented the patient underwent computed tomographic angiography (CTA) which showed multiple bilateral thrombus-embolic filling defects, predominantly in the right lung and especially in the right pulmonary artery and in both basal pyramids for the lower lobes (Figure 3).

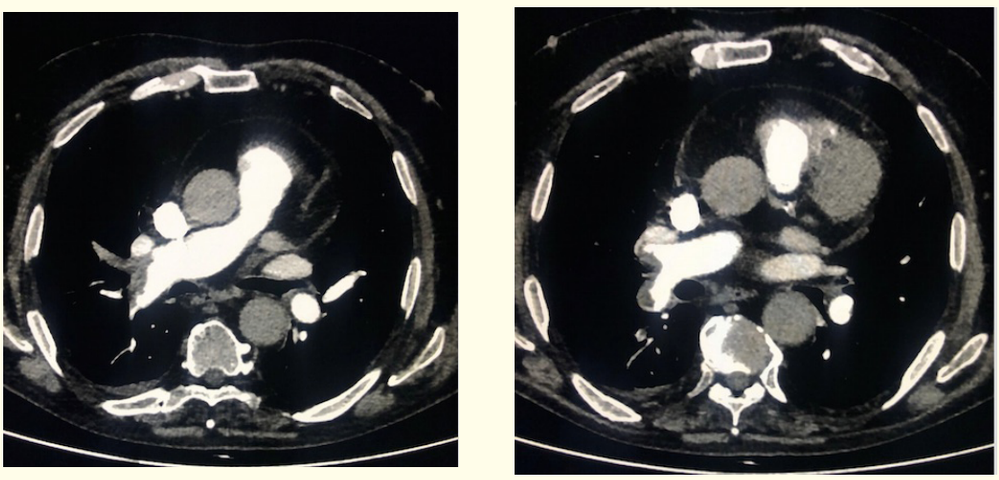

***Figure 3:*** *Images of computed tomographic angiography.*

These examination findings were consistent with VTE.

The medical history of the patient cited no risk factors such as high blood pressure, recent injury or trauma to a vein, burns or fractures of the hips or thigh bone and chronic inactivity or immobility.

Due to worsening gas exchange during oxygen therapy ($FiO_2$ 28%, $PaO_2$ 69 mmHg, $PCO_2$ 62 mmHg, pH 7.34, $SatO_2$ 94%, $HCO_3$ 34.4 mmoli/L) the patient was treated with non-invasive ventilation (BiPAP) for 3 days with benefit.

The patient then administered fondaparinux 7.5 mg; on the third day of hospitalization, he experienced an episode of confusion and speech difficulties, without other neurological signs or symptoms. He underwent an CT scan which identified a developing ischemic area in the cortical and subcortical right frontal lobes; malacic areas were present in the right semioval center (Figure 4).

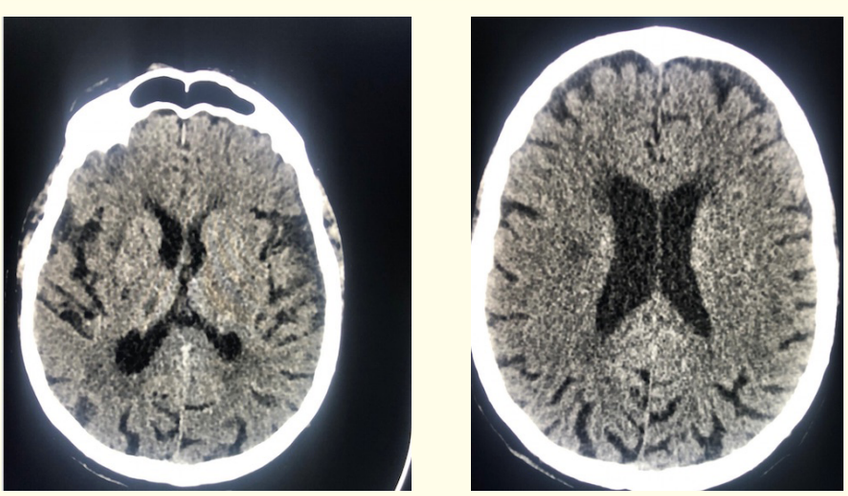

***Figure 4:*** *Images of computed tomography of brain.*

The levels of antiphospholipid-dependent antibodies, beta2 glycoprotein, anticardiolipin antibodies and lupus anticoagulant were normal. Hereditary thrombotic risk factors were also determined: mutations in factor V, and factor II, antithrombin, protein C, protein S and other laboratory tests were all normal.

Doppler ultrasonography of the legs, echocardiography and neoplastic markers were negative.

Homocysteine levels were elevated (43.3 mcmol/L with normal value < 15).

The patient was treated with oxygen therapy, non-invasive ventilation for several days and fondaparinux 7.5 mg and then with dapigatran 150 mg bid, acetylsalicylic acid, vitamin B12 and folic acid.

An arterial blood gas analysis without oxygen, performed at discharge in room air, showed $PaO_2$ 83 mmHg, $PaCO_2$ 41 mmHg, pH 7.46 and $HCO_3$- 29 mmoli/L.

At discharge, the patient underwent a nocturnal cardiorespiratory monitoring in room air.

Apneas, hypopneas, and apnea-hypopnea index (AHI) were defined according to current criteria [32]. Other parameters that were analyzed were: respiratory disturbance index (RDI), events and number of events of obstructive apneas (OA) and central apnea (CA), number and events of hypopnea (H), mixed (M), oxygen desaturation index (ODI) and average of arterial saturation ($SpO_2$ average%) with time of desaturation (T < 90%).

The examination revealed severe OSA (AHI 61/h), several prolonged episodes of obstructive sleep apnea: 460 apnea and hypopnea (A+H) events, 115 obstructive apnea events and 193 hypopnea with a mean duration of 17 sec and an average of arterial saturation of 90%, T < 90% of 42% (Table 2 and figure 5).

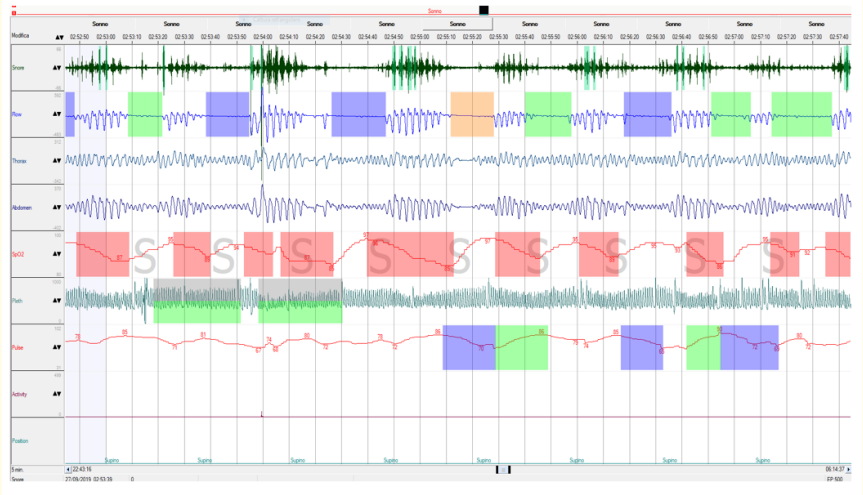

***Figure 5:*** *Image of nocturnal cardio-respiratory monitoring.*

| | Diagnostic |
|---|---|
| AHI (Events/h) | 61.1 |
| OA Events/h- N° events | 24.5 - 115 |
| CA Events/h-N° events | 11.7 - 55 |
| H Events/h - N° events | 41.1 - 193 |
| Apnea (median duration) (sec) | 14 |
| Hypopnea (median duration) (sec) | 17 |
| $SpO_2$ average (%) | 91 |
| T < 90% | 42 |
| ODI Events/h | 65.3 |

***Table 2:*** *Diagnostic nocturnal cardio-respiratory monitoring.*

Then, with the patient received continuous positive airway pressure (CPAP) therapy which had benefit and corrected his polygraphic indexes.

## Discussion

The concomitance of OSA and VT) is high: an increasing number of cross-sectional and longitudinal studies have linked OSA to VTE, and have proposed varoius pathways to explain how OSA increases the risk of PE.

Several observational studies, randomized controlled trials (RCTs) and meta-analyses have examined the risk of IS and cardiovascular events in patients with OSA and CPAP treatment in these patients. Observational studies have shown a greater risk of ischemic stroke in patients with untreated OSA.

It has recently recognized that arterial and venous thromboses are common in patients with homocystinuria [33,34]. Many studies primarily retrospective have shown that mildly hyperhomocysteinemia is also associated with thromboembolism, thrombotic stroke, and peripheral vascular disease [32-35]: thus, this condition has garnered significant interest because homocysteine is potentially reversible cause of thrombophilia.

The classification of hyperhomocysteinemia is as follows: (1) moderate risk, 15 to 30 μmol/L; (2) intermediate risk, 30 to 100 μmol/L; and (3) severe risk, > 100 μmol/L [33].

Hyperhomocysteinemia is attributed to genetic and acquired factors (unhealthy lifestyle with a diet that is poor in folate and vitamin B, elderly age, renal impairment, thyroid diseases and malignancies).

We have presented a case with thromboembolism and ischemic stroke. The coexistence of OSA and high levels of homocysteinemia could have a synergic effect in increasing the risk of VTE and IS. The repeated episodes of hypoxia and normoxia, in OSA are reminiscent of ischemia reperfusion events, and these conditions are believed to upregulate reactive oxygen species (ROS) and oxidative stress and cause ischemia-reperfusion injury to the vascular wall, increasing the risk for atherosclerosis and consequently VTE [36].

It is necessary to evaluate all risk factors in patients with VTE and stroke events, including diagnostic testing for OSA. Our work also emphasizes the importance of measuring homocysteine levels in all patients who present with pulmonary embolism and IS.

## Conclusion

This clinical case underscores the importance of identifying comorbidities in the optimal management of VTE and cerebrovascular stroke. The pathogenetic mechanisms of OSA and hyperhomocysteinemia could have a synergistic effect on endothelial damage and thus increase the risk of VTE and IS.

Finally, a routinely practical approach to the evaluation of sleep disorder in patients with cerebrovascular disease and pulmonary thromboembolism is needed.

An earlier diagnosis of OSA and all other risk factors, including hyperhomocysteinemia are prerequisites for timely treatment and, potentially, improvedthe long-term clinical outcomes of these progressive and ultimately fatal diseases.

## Conflict of Interests

All authors declare that they have no competing interests.

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