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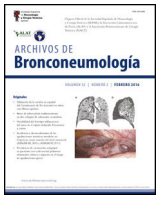

Editorial

Pulmonary Embolism and Obstructive Sleep Apnea: A Two-way Relationship☆

Tromboembolia de pulmón y apnea obstructiva del sueño: una relación bidireccional

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The object of reasoning is to find out, from the consideration of what we already know, something else which we do not know.

The Fixation of Belief. Charles S. Peirce (1877)

Despite advances in prevention and treatment, pulmonary embolism (PE), the most severe presentation of venous thromboembolism (VTE), remains the third cause of cardiovascular death, after acute myocardial infarction and stroke. This situation justifies efforts to identify additional risk factors and their impact on the short-term prognosis of PE.[1]

A growing body of evidence identifies obstructive sleep apnea–hypopnea syndrome (OSA) as a systemic disease involved in the pathogenesis of various diseases, such as cancer and dementia, although its role as a risk factor for cardiovascular disease is the most widely known. However, its association with PE has been studied in less depth, even though (1) both diseases have a major impact in terms of epidemiology and healthcare costs; (2) there is a plausible pathophysiological explanation for this association, and (3) this relationship could be bidirectional, offering potential therapeutic implications.

From Obstructive Sleep Apnea to Pulmonary Embolism

Several prospective population studies have shown that patients with OSA have a higher incidence of DVT or PE than the general population.[2] Some epidemiological studies in patients with acute PE show that the prevalence of OSA is increasing,[3] even after results are adjusted for confounding variables such as age or obesity. These data suggest that OSA may be a risk factor for the development of PE. Moreover, the risk of VTE is directly proportional to the severity of OSA determined by the apnea–hypopnea index during sleep.[4,5]

For the association to be biologically plausible, OSA should act on the main etiopathogenic mechanisms known in VTD, i.e., the Virchow triad of hypercoagulability, endothelial dysfunction, and venous stasis. Some studies show that OSA does act on these 3 pathophysiological pathways.[1] There is evidence that OSA can induce a hypercoagulable state[6] with alterations in various coagulation factors, such as plasminogen activator inhibitor-1 (PAI-1), fibrinogen, factors XIIa and VIIa, and thrombin. The association with endothelial dysfunction is more conclusive and is mediated by intermittent hypoxemia and fragmented sleep.[7] Furthermore, a meta-analysis that included 8 clinical trials with 245 patients with OSA showed that endothelial dysfunction improves with the use of continuous positive airway pressure (CPAP).[8] Finally, OSA can act on obesity-mediated venous stasis, present in about 60% of patients with OSA,[9] which, in turn, is a risk factor for both OSA and VTE.

From Pulmonary Embolism to Obstructive Sleep Apnea

Not only does OSA appear to increase the risk of PE, but PE could also increase, at least in the acute phase, the prevalence and severity of OSA, especially in patients with right ventricular dysfunction. This association might be explained by an increased blood flow in the pharyngeal area, especially in the supine position, which would facilitate upper airway collapse.[1] This phenomenon has already been evaluated in other cardiovascular diseases such as heart failure, hypertension and renal failure, and has even been observed in healthy subjects undergoing a redistribution of blood flow that produces parapharyngeal edema in the supine position, which is associated with an increase in the number of respiratory events during sleep.[10] The confirmation of this hypothesis could have clinical implications when deciding on the ideal time for the diagnosis and treatment of OSA in these patients.

Some studies indicate that the presence of concomitant OSA could worsen the prognosis of acute PE,[11] possibly due to nocturnal desaturations, endothelial dysfunction, and increased afterload. Others suggest it could induce a state of hypercoagulability that requires therapeutic modifications with higher doses of coumarin derivatives or prolongation of the time required for anticoagulation.[12–14]

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Future Challenges

In spite of the above, understanding of the epidemiological and physiopathological relationships between OSA and PE is limited. The current challenge is how to correctly answer the many outstanding questions: Is there a causal relationship between OSA and VTE? What is the role of certain biomarkers and clotting factors in this relationship? Does OSA worsen PE prognosis in the short or long term? Does the severity of OSA in patients with PE change depending on the time of diagnosis? What is the impact of CPAP on the primary and secondary prevention of VTE in patients with OSA?

All these issues are opportunities for learning, and answering questions that have such enormous clinical impact will require close collaboration between PE and OSA working groups. Aware of this important scientific challenge, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) has agreed to support this line of investigation by funding ongoing studies, namely, POPE (Prognostic value of OSA in patients with acute symptomatic PE) and ESAET (Evaluation of OSA in acute and stable PE). These are prospective, multicenter studies, that aim to assess the impact of OSA on the prognosis of PE,[15] and the impact of right ventricular dysfunction on sleep-disordered breathing in the acute phase of PE.

These ongoing projects will lead to important advances in the understanding of this complex 2-way relationship, and will clarify many questions that still need answers.

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