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REVIEW ARTICLE

Obstructive Sleep Apnea and Smoking as a Risk Factor for Venous Thromboembolism Events: Review of the Literature on the Common Pathophysiological Mechanisms

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Abstract Venous thromboembolism events (VTE) are a common and preventable cause of postoperative complications. Interestingly, smoking and obstructive sleep apnea syndrome (OSA) affecting a large part of our population (and especially obese patients) are two underestimated predisposing factors of VTE. Many coagulation disorders favoring thromboembolism have been identified in the case of OSA and smoking and are reviewed in this article. They can be divided into two entities: endothelial dysfunction and hemostasis disorders. Interestingly OSA and smoking share common pathways to the prothrombotic state. The interactions with others comorbidities will also be discussed. This article provides pathophysiological mechanisms of the increased risk of thromboembolism in OSA patients and smokers, which should help manage these patients more adequately during the perioperative period.

Keywords Obstructive sleep apnea · Tobacco smoking · Thromboembolism · Vascular endothelium · Thrombophilia · Perioperative management

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Introduction

Venous thromboembolism events (VTE) are a common and a preventable cause of death in surgical patients and non-surgical patients [1–3]. There are many risk factors for VTE [1–3]. Some are well known (e.g., cigarette smoking) while others are less familiar (e.g., obstructive sleep apnea syndrome) and appear to play an underestimated role. The purpose of this article is to inform the practitioner about the pathophysiological mechanisms of these two predisposing factors leading to VTE and consequently to improve the perioperative management of patients suffering these problems.

Obstructive sleep apnea (OSA) is a complex pathophysiological entity. In a general population, the prevalence of this syndrome is among 3 to 7 % and can greatly exceed 10 % in obese patients [4, 5]. For a long time, this syndrome referred only to notions of nocturnal ventilatory interruption. Since the early 1980s, researchers have found that OSA is a risk factor for many comorbidities (arterial hypertension, obesity, myocardial ischemia, arrhythmia, and stroke).

OSA is a pathophysiological entity in itself [6]. Patients with this syndrome have nocturnal apnea or hypopnea related to the repetitive obstruction of the upper airway. These reductions/interruptions of airway flow lead to hypoxemia and hypercapnia which generate cortical activation causing microarousals. These arousals thus are responsible for an increased tone in the upper-

airway muscles, allowing ventilatory recovery. The severity of OSA is mainly estimated by the apnea hypopnea index (AHI, which gives the hourly average number of apneas and hypopneas) and the oxygen desaturation index (ODI, which gives an hourly average number of arterial oxygen desaturations). The work of Bosanquet et al. also shows that a patient with OSA are at an increased risk of developing venous thromboembolic events outside of a surgical setting [7] or during the perioperative period [1, 8, 9].

Of the population, 30 % are smokers; and smoking is a major cause of cardiovascular morbidity [10]. Passive smoking is also involved. When evaluating the risk of myocardial ischemia, active smokers have an increased risk of 80 % and passive smokers of 30 % compared to a non-smoking population [10, 11]. A recent meta-analysis concludes that cigarette smoking is associated with an increased risk for venous thromboembolic events [12].

Two major pathophysiological axes associated with both OSA and smoking may explain this increased thrombotic risk: (1) endothelial dysfunction leading to atherosclerosis and (2) hemostasis disorders leading to thrombosis. Besides these two primary mechanisms, smoking and OSA also induce rheological (such as a higher hematocrit or blood viscosity) or systemic changes (such as hypertension or hyperactivation of the sympathetic nervous system), which favor the genesis of thrombotic events. This article reviews the pathophysiological changes leading to thrombotic events in both OSA and cigarette smoking patients (Fig. 1) and their interactions with other comorbidities, such as hypertension or obesity (Fig. 2). Figure 1 illustrates that smoking and OSA must be considered as systemic disease and that the interactions leading to VTE are various and complex. Thereafter, potential interactions between OSA and smoking in term of risk of VTE will be described. Finally, perioperative management for prevention of VTE in these patients will be addressed.

Search Strategies and Selection Criteria

For this review, relevant peer-reviewed original or review papers published on one of these topics (obstructive sleep apnea or tobacco cessation) were included. At this time, this paper is the first to describe common pathways for these two pathological features. Researches were made on Medline® and PubMed® using the following terms (and combinations of these): Obstructive Sleep Apnea, Tobacco Smoking, Tobacco Cessation, Thromboembolism, Vascular Endothelium, Thrombophilia, Perioperative.

Endothelial Dysfunction and Atherosclerosis

The vascular endothelium is polyvalent [13]. For many years, the endothelium was considered a simple barrier between the endovascular compartment and the rest of the vascular wall. We now know that the endothelium is also the source as well as the target of many growth factors and vasoactive mediators [13, 14].

Several authors have demonstrated endothelial dysfunction among OSA patients [15], increasing with age [16], correctable under continuous positive airway pressure (CPAP) [17], and independent of patient weight [18]. Endothelial dysfunction and atherosclerosis are also commonly observed among smokers [10, 19].

The endothelial dysfunction leading to atherosclerosis is multifactorial. The major pathophysiological pathways common to both obstructive sleep apnea and smoking (active and passive) are detailed subsequently and summarized in Table 1.

Vasomotor Dysfunction

The arterial diameter is subjected to the influence of vasodilators (such as nitric oxide) and vasoconstrictor agents (such as reactive oxygen species [ROS] and endothelin-1). An excessive vasoconstriction is both a risk factor for the development of thrombi and a cause of hypertension. The latter, in turn, is

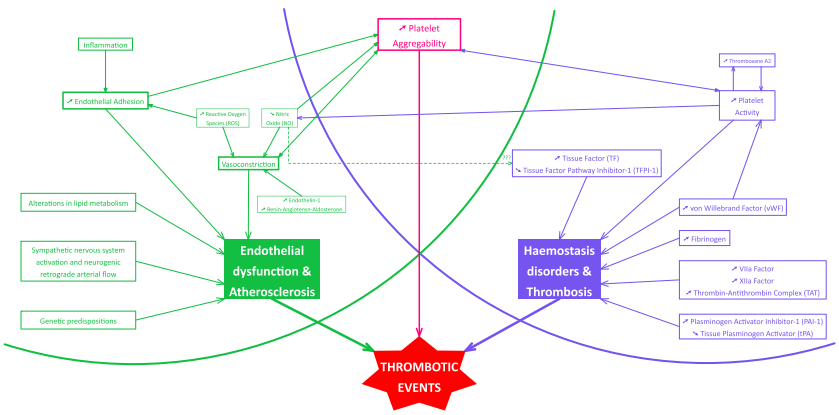

Fig. 1 Pathophysiological changes leading to thrombotic events in both obstructive sleep apnea (OSA) and cigarette smoking patients

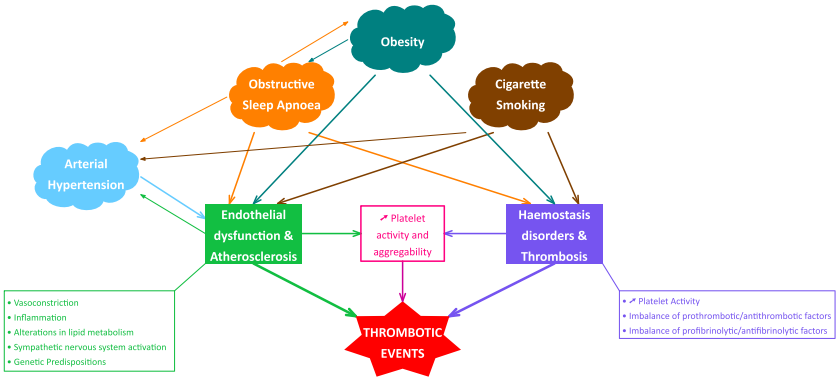

Fig. 2 Interactions between obstructive sleep apnea (OSA) and cigarette smoking with other comorbidities, such as hypertension or obesity

responsible for the damage to the endothelial wall and thus also promotes a prothrombotic state.

Table 1 Synthesis of the effects leading to endothelial dysfunction and atherosclerosis

	OSA	Smoking
1. Vasomotor dysfunction		
Endothelin-1	+	+
Nitric oxide (NO)	–	–
Reactive oxygen species (ROS)	+	+
Renin-angiotensin-aldosterone system	+	
2. Cell adhesion to the luminal wall		
Leukocyte adhesion molecules	+	+
E-selectin	+	+
Intercellular adhesion molecule-1 (ICAM-1)	+	+
L-Selectin	+	+
Vascular cell adhesion molecule-1 (VCAM-1)	+	+
Monocyte adhesion to the endothelial wall	+	+
Neutrophil apoptosis	–	+
3. Circulating levels of inflammatory molecules		
C-reactive protein (CRP)	+	+
Cyclooxygenase-2 (COX-2)	+	
High-mobility group box 1 (HMGB1) proteins	+	
Interleukin-6 (IL-6)	+	+
Tumor necrosis factor alpha (TNF-α)	+	+
4. Lipid metabolism and excess weight		
Lipid compounds responsible for atherosclerosis		+
Beneficial lipid compounds		–
Adiponectin	–	
Orexins	–	
5. Sympathetic nervous system activation	+	+
6. Genetic predisposition		
CYP1A1A MSP		+
Endothelial NO synthase intron 4		+
TNF-α-(308A)	+	

"+" augmented effects or levels, "–" altered effects or levels, *OSA* obstructive sleep apnea

Impaired Balance Between Nitric Oxide Bioavailability and Increased Reactive Oxygen Species Generation

Nitric oxide (NO) produced by the endothelium induces arterial vasodilation and serves as a mechanism of against-regulation in acute hypoxia [20]. Oxidative stress and secondarily produced ROS are in equilibrium with NO and are atherogenic [21]. Overproduction of ROS results in vasoconstriction, increased platelet aggregation, and vascular proliferation [22]. ROS also increase the production of endothelial adhesion molecules [13, 23].

Smoking and OSA undoubtedly induce a state of vasoconstriction. Indeed, on one hand, there is a decrease in the bioavailability of NO observed in OSA (reversible with CPAP) [24] and in the presence of smoking [25]. On the other hand, circulating levels of ROS are increased in apneic patients (also reversible under CPAP) [26] and during smoking [27]. Increased release of ROS among smokers can have three distinct origins: (1) direct inhalation of oxidizing molecules contained in cigarettes, (2) systemic production of ROS due to oxidative stress, and (3) activation of macrophages or neutrophils [28].

Other Factors

Endothelin-1 has a vasoconstrictor activity. Its plasma concentration is increased in OSA and is corrected after the initiation of treatment with CPAP [29]. This molecule is also increased when smoking [30].

Activation of the renin-angiotensin-aldosterone system produces arterial vasoconstriction and is responsible for arterial hypertension. Moller et al. showed an increase in the production of renin and angiotensin (reversible by CPAP) in OSA patients [31]. So far, no such association with smoking has been demonstrated.

Inflammation

Inflammation is one of the mechanisms involved in the development of atherosclerosis [21]. The interaction between inflammation and atherosclerosis may be schematically divided

into two categories: changes in cell adhesion to the luminal wall and increase in circulating levels of inflammatory mediators.

Changes in Cell Adhesion to the Luminal Wall

The adhesion of leukocytes and monocytes to the endothelium is an early event in atherosclerosis. Leukocyte adhesion involves different adhesion molecules. Most studied are the following: intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, and L-selectin. Their expressions are increased in cases of OSA [32, 33] and exposure to tobacco smoke [34]. CPAP treatment corrects overexpression in the apneic patient.

Similarly, smoking [35] and OSA [36] also induce an increase in monocyte adhesion to the endothelial wall.

Smoking increases the rate of neutrophil apoptosis [37], whereas neutrophil apoptosis in OSA patient is delayed compared to healthy subjects [38]. This delay in apoptosis causes a prolonged interaction between neutrophils and the endothelial wall. It leads to an overproduction of free radicals and an increased release of proteolytic enzymes also responsible for endothelial damages [38].

Increase in Circulating Levels of Inflammatory Molecules

Among other things, circulating inflammatory mediators are involved in the atherosclerotic development by expanding the recruitment of leukocytes. C-reactive protein (CRP), interleukin-6 (Il-6), and tumor necrosis factor alpha (TNF-α) levels are elevated in apneic patients [39, 40] as in smokers [10]. OSA patients also exhibit elevated levels of cyclooxygenase-2 and high-mobility group box 1 (HMGB1) proteins [24].

Lipid Metabolism and Excess Weight

Alterations in lipid metabolism are involved in endothelial dysfunction and atherosclerosis.

Smoking causes an elevation of lipid compounds responsible for atherosclerosis (cholesterol, triglycerides, very low-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) and lowers beneficial lipid compounds (high-density lipoprotein cholesterol and apolipoprotein A1) [41, 42]. These changes increase dose dependently as a function of the amount of nicotine smoked. The link between smoking and these changes is still, however, subject to debate [10].

Whereas overweight is a risk factor for OSA, OSA is also a risk factor for gaining weight [29, 43]. This last relation is mediated by an abnormal metabolism of orexins (primarily leptin and adiponectin) [44]. This abnormality results in endothelial dysfunction, especially via the activation of angiogenesis, the proliferation of vascular smooth-muscle cells, and the stimulation of ROS production [45–48]. Plasma levels of adiponectin, an anti-inflammatory cytokine which prevents atherosclerosis and produces cardiovascular protection in general [49], are reduced in the case of OSA [50].

Sympathetic Nervous System Activation

Increased sympathetic nervous system (SNS) activation leads to cardiovascular complications and causes a hypercoagulable state [51]. Both OSA [52] and smoking [53] produce a hyperactivation of the SNS. Millar et al. recently described a novel mechanism of endothelial dysfunction related to SNS in OSA patients: the neurogenic retrograde arterial flow [54]. This retrograde flow originates from a hyperactivation of the SNS located in skeletal muscle, which leads to a significant local vasoconstriction and causes retrograde arterial flow. Although this data has yet to be verified, the authors believe that this retrograde flow is in itself a cause of endothelial injury.

Genetic Predisposition

In all areas, there is a growing interest in research on genetic influence. Although the importance of genetic factors has yet to be clarified, some predispositions seem to favor the development of atherosclerosis in apneic patient and smokers.

The allele TNF-α-(308A) has a higher prevalence in a population of OSA patients [55]. This allele is responsible for the overexpression of TNF-α. Lin et al. demonstrated that OSA patients have a particular gene polymorphism of the angiotensin-converting enzyme, which leads to overexpression of angiotensin [56]. TNF-α and angiotensin are involved in endothelial dysfunction.

At least two genetic polymorphisms (CYP1A1A MSP polymorphism and endothelial NO synthase intron 4 polymorphism) have been cited to explain the individual variability in cardiovascular events among smokers [10, 57–59].

Hemostasis Disorders

In addition to endothelial dysfunction, OSA patients and smokers also have hemostasis disorders. These disorders are characterized by platelet dysfunction and imbalance of profibrinolytic/antifibrinolytic and prothrombotic/antithrombotic factors. They lead to thrombosis. Various factors responsible for these disorders are detailed below and summarized in Table 2.

Platelet Activity and Aggregation

Platelet activity is increased in OSA patients, proportional to the severity of the disease, and reversible by CPAP [60]. This increased activity results in a hyperaggregability state.

Table 2 Synthesis of the effects leading to hemostasis disorders

	OSA	Smoking
1. Platelet activity and aggregation		
Platelet activity	+	+
Thromboxane A_2		+
2. Imbalance of prothrombotic/antithrombotic factors		
D-Dimer	+	
Factor VIIa	+	
Factor XIIa	+	
Fibrinogen (factor I)	+	
Tissue factor (TF)	+	+
TF pathway inhibitor-1 (TFPI-1)	−	−
Thrombin-antithrombin complex (TAT)	+	
von Willebrand Factor (vWF)	+	+
3. Imbalance of profibrinolytic/antifibrinolytic factors		
Plasminogen activator inhibitor-1 (PAI-1)	+	+
Tissue plasminogen activator (tPA)		−

"+" augmented effects or levels, "−" altered effects or levels, *OSA* obstructive sleep apnea

Smokers also exhibit an increased stimulation of platelet and spontaneous aggregation [61]. Cigarette smoking decreases NO production, which inhibits platelet aggregation, by both endothelial cells and platelets resulting in an increased platelet activation and endothelial adhesion, but also results in overproduction of thromboxane A_2 (which in turn activates other platelets) [62, 63].

Imbalance of Prothrombotic/Antithrombotic Factors

Tissue Factor

Tissue factor (TF) is the protein that initiates the extrinsic pathway of coagulation. The link between TF and OSA or smoking is still unclear. TF expression seems to be increased in both smokers [64] and apneic patients [65]. TF pathway inhibitor-1 (TFPI-1), however, appears to be decreased under these conditions. Nevertheless, it is uncertain whether this effect is direct or originates from changes in the bioavailability of NO [66].

Fibrinogen (Factor I)

Fibrinogen participates in platelet aggregation by linking glycoprotein IIb/IIA (GPIIb/IIIA) receptors between activated platelets. Blood fibrinogen levels are elevated both in smokers [67] and OSA patients [68, 69]. In OSA, the fibrinogen level is more correlated with the magnitude of nocturnal arterial oxygen desaturation than with the number of apneas presented by the patient [68]. The level of D-dimer (a fibrin degradation product) is also increased in apneic patients [70]. The introduction of a CPAP treatment corrects plasma fibrinogen in OSA patients [69].

von Willebrand Factor

The von Willebrand factor (vWF) allows platelet adhesion and aggregation but also prevents degradation of factor VIII. It is, therefore, a procoagulant factor. The von Willebrand factor is elevated in both OSA patients [71] and smokers [63].

Other Factors

Apneic patients have an increased level of factor XIIa, VIIa, and thrombin-antithrombin complex (TAT) [72]. The rate of TAT is significantly correlated with the nocturnal oxygen desaturation index [73]. There is no data regarding these factors in patients exposed to nicotine.

Imbalance of Profibrinolytic/Antifibrinolytic Factors

Fibrinolysis is defined by the lysis of fibrin by plasmin. Tissue plasminogen activator (tPA) cleaves plasminogen into plasmin. After this activation, plasmin lyses fibrin into D-dimer. Plasminogen activator inhibitor-1 (PAI-1) inhibits tPA and, therefore, prevents fibrinolysis.

Apneic patients have an increased activity of PAI-1 [74]. This increase is clearly correlated with the degree of nocturnal desaturation and body mass index [74]. CPAP corrects these alterations [75].

Smokers have both an increased PAI-1 activity [76] and a decreased activity of t-PA [77]. The increase in PAI-1 is correlated with the number of smoked cigarettes [76].

Clinical Expression of Perioperative Thrombotic Risk Among OSA and Cigarette Smoking Patients

In a recent systematic review Lippi et al. have highlighted OSA as an independent risk factor for VTE (either vein thrombosis or pulmonary embolism) [78]. Peng et al. confirmed these data in a cohort study involving 38,621 patients [79]. Considering only surgical patients, the association seems less strong. In a case-control study involving 258,455 patients who were admitted for revision of total hip or total knee arthroplasty, OSA was associated with an increased risk of pulmonary embolism (PE) (OR, 2.1; $P = 0.001$) [80]. In a retrospective observational study focussed on fatal PE after bariatric surgery, Sapala et al. demonstrated that 33 % of these patients had a combination of risk factors including venous stasis, morbid obesity, truncal obesity, and OSA [81]. In a retrospective cross-sectional analysis of severe maternal-infant morbidity/mortality including 55,781,965 pregnant women, Louis et al. found that OSA was associated, among

others, with a high risk of PE (OR, 4,5; 95 % CI, 2.3–8.9) [82]. However, in a case-control study evaluating in-hospital symptomatic PE after major orthopedic surgery including 7282 patients, Mraovic et al. did not find a significant correlation between OSA and PE (OR, 1.23; 95 % CI, 0.57–2.67) [83]. Finally, in a retrospective analysis of 2,610,441 orthopedic patients and 3,441,262 general surgical patients, Memtsoudis et al. reported that PE was more frequent in orthopedic OSA patients (0.51 vs. 0.42 %, $P=0.0038$) but not in general surgical patients (0.45 vs. 0.49 %, $P=0.22$) [84].

Smoking was also reported as an independent risk factor for VTE [85]. However, the relationship between cigarette smoking and risk of VTE is a source of debate. In a recent meta-analysis, Zhang et al. found that current smoking (RR, 1.24; 95 % CI, 1.14–1.35) and former smoking (RR 1.05; 95 % CI, 1.01–1.10), in a dose-response relationship, were associated with an increased risk of VTE [86]. However, in a retrospective cohort analysis including 393,794 surgical patients, Hawn et al. reported that smoking was associated with a higher rate of thromboembolic events but not statistically significant [87].

Possible Interactions Between OSA and Smoking in Term of Risk for Venous Thromboembolism

The abovementioned descriptions show that smoking and OSA share several mechanisms predisposing to VTE. The literature was explored to determine whether there is an additive risk of VTE when OSA and smoking are combined.

First of all, is there a relationship between cigarette smoking and OSA? This question has been debated for many years. Theoretically, smoking may increase the severity of OSA through alterations of the upper airway and modifications of sleep architecture. There are more and more evidence supporting this assertion [88]. Three studies involving 301, 811, and 964 patients respectively have shown than cigarette smoking was a predisposing and/or aggravating factor for OSA [89–91]. However, such a relationship was not found in the Sleep Heart Health Study involving more than 6000 patients [92]. Therefore, further evidences are needed to confirm this relationship.

The other question is whether cigarette smoking and OSA have additive effects as risk factors for VTE. To date, there are no published data to answer this question.

Possible Specific Interventions Concerning Prevention of VTE in the Perioperative Period in the OSA and/or Smoking Patients

Perioperative period remains an important risk factor for VTE [93]. Individual risk for a patient depends on his/her health status but also on the kind of surgery undergone. Each of them has specific prevention strategies. American College of Chest Physicians publishes regularly updated guidelines for the prevention of perioperative VTE [1, 9, 94]. Recommendations include graduated elastic stockings and low molecular weight heparins as anticoagulant agent, even if new drugs are emerging [93]. OSA and cigarette smoking may require more specific attention and preventions.

Based on the abovementioned laboratory findings, CPAP reduces (in a few days) the OSA-induced changes responsible for the increased risk of VTE. Almost all the consequences of OSA on coagulation are corrected by CPAP. Therefore, the apneic patient effectively treated with CPAP should not have an increased risk of thrombosis as compared with the non-apneic patient. However, there is currently no evidence that the rapid correction of abnormal laboratory tests by CPAP results in fast clinical benefit with regard to the risk of VTE. Also, the clinician must be careful to ensure that the OSA patient is adherent to CPAP therapy [95, 96]. In contrast, it appears obvious that the apneic patient untreated (or inadequately treated) is exposed to a greater risk of VTE. Accordingly, the clinician will have to adapt the mechanical and pharmacological means of prevention related to others risks factor (obesity, immobility, etc.) and the kind of surgery [1, 9, 94]. For comparison, OSA patients with pulmonary embolism require higher doses of warfarin [97]. OSA-related hypercoagulation may explain this need [97].

Smoking cessation reduces many postoperative complications such as post-operative infections or myocardial ischemias [98, 99]. In the meta-analysis of Cheng et al., former smokers had an overall combined relative risk of 1.10 (95 % CI, 1.03–1.17), in comparison with 1.17 (95 % CI, 1.09–1.25) for ever smokers and 1.23 (95 % CI, 1.14–1.33) for current smokers. However, Zhang et al. found that current smoking (RR, 1.24; 95 % CI, 1.14–1.35) but also former smoking (RR 1.05; 95 % CI, 1.01–1.10), in a dose-response relationship, were associated with an increased risk of VTE [86]. Therefore, it appears logical to further propose smoking cessation prior to surgery. Meanwhile, the optimal period of smoking cessation prior to surgery is still debated [100, 101].

One last question must be discussed: does smoking cessation improve OSA? Little has been reported demonstrating an improvement in the severity of OSA after smoking cessation [88]. Wetter et al. found that former smokers were at the same prevalence than non-smokers [90]. Nevertheless, in the acute smoking cessation, nicotine withdrawal may mimic OSA symptoms [88, 102]. To date, only little effects of pharmacological aids for smoking cessation on OSA are known [88].

Conclusion

Conventionally, the perioperative management of OSA patients takes into account the prevention of nocturnal apnea. This article suggests that we must not limit OSA only to pathology of the upper airway. Rather, OSA is a real systemic entity that deserves appropriate care. Smoking affects nearly 30 % of our population. Thrombotic risk is increased in both OSA patients and smokers. Although the exact relationship between OSA and smoking in thrombotic events is not completely understood, it is clear that smoking and OSA share many pathophysiological mechanisms.

From a pathophysiological point of view, two main axes emerge: endothelial dysfunction leading to atherosclerosis and hemostasis disorders leading to thrombosis.

Most of the factors involved in the OSA are dependent on the importance of nocturnal desaturation incurred by the patient and are correctable with CPAP. Unfortunately, accurate recommendations concerning the optimal delay between the power PAPCn and a reduction of thrombosis risk have yet to be established. The number of cigarettes smoked is the main factor responsible in smokers.

For the practitioner dealing with an apneic patient and/or a smoker, it is important to take into account the risk of thromboembolism in these patients. This one must be added to other risk factors such as obesity. Besides the traditional means of prevention (graduated elastic stockings and low molecular weight heparins), these patients require specific prevention, namely a CPAP therapy and/or an aid for smoking cessation. Smoking and OSA are not only upper airway diseases, they are systemic diseases and should be treated like that.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Ethical Approval For this type of study, formal consent is not required.

Informed Consent Does not apply.

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