Review

Hypercoagulability in obstructive sleep apnea syndrome

Konstantina Nikolaou[1] MD,
Ioanna Sigala[2],
Paschalis Steiropoulos[1] MD, PhD, FCCP

[1]Master of Science in Sleep Medicine (MSc Programme), Medical School, Democritus University of Thrace, Alexandroupolis, Greece
[2]Medical School, Democritus University of Thrace, Alexandroupolis, Greece

Key words:
- Platelets
- Platelet activation
- Fibrinogen
- Obstructive sleep apnea syndrome
- Hypercoagulability

Correspondence:
Paschalis Steiropoulos, MD, PhD, FCCP
Medical School, Democritus University of Thrace
Dragana 68100, Alexandroupolis, Greece
Tel.: +30 2551030377
E-mail: pstirop@med.duth.gr, steiropoulos@yahoo.com

ABSTRACT
Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of upper airway obstruction, leading to intermittent hypoxia, hypercapnia and increased sympathetic nervous system activity and proposed to induce platelet activation. Additionally, OSAS has been linked to increased cardiovascular mortality and morbidity. Blood coagulation abnormalities have been suggested to play a fundamental role in increased cardiovascular risk in OSAS patients. The aim of the present review was to summarize the current evidence that revealed the pathogenetic alterations in blood coagulation in patients with OSAS.
Pneumon 2016, 29(1):22-26.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of complete or partial collapse of the upper airway during sleep, resulting in apneas or hypopneas, respectively. Repetitive episodes of obstruction, which lead to intermittent hypoxia and increase in carbon dioxide levels, result in frequent arousals from sleep and consecutively to increased activity of the sympathetic nervous system[1]. Increased cardiovascular morbidity and mortality is observed in OSAS[2,3] but it is hard to determine if this is attributed solely to OSAS rather than to other cardiovascular risk factors such as central obesity, insulin resistance, increasing age, alcohol consumption and cigarette smoking. The abovementioned factors have been linked to coagulation abnormalities, (i.e. increased blood viscosity and excessive platelet activation) that occur in OSAS as well. It was suggested that blood coagulation abnormalities and specifically increased blood clotting, caused by changes in rheological properties of blood and plasma, is an important factor linking OSAS and cardiovascular complications. Aim of our review was to summarize the current evidence about the relationship between the pathogenetic alterations in blood coagulation and patients with OSAS.

PLATELET ACTIVATION IN OSAS

During normal sleep, platelet aggregability is decreased[4]. The immediate physiological consequences of OSAS such as nocturnal hypoxia, haemodynamic changes and sleep disruption can lead to increased sympathetic activity shown by increased epinephrine levels in OSAS patients[5]. Subsequently, it is hypothesized that the increased sympathetic activity can induce an increase in platelet activation, especially during sleep[6]. Elevated circulating catecholamines cause concentration-dependent platelet activation in vitro and in vivo[7]. The epinephrine-induced platelet responses are more effectively blocked by yohimbine and rauwolscine than by prazosin, indicating that epinephrine stimulates human blood platelets by an a_2-adrenergic receptor mechanism[8] and induces fibrinogen receptor exposure on the platelet surface and fibrinogen binding[9].

Geiser et al[10] examined in vivo platelet activation and platelet-derived microparticles (PMP) using flow cytometry in 12 patients with untreated OSAS during and after sleep. They confirmed that platelet activation is enhanced during sleep when the pathophysiological changes in patients with OSAS are maximal, also representative data for the status of platelet activation during sleep were extracted, by drawing the blood samples during sleep. They have shown that highest levels of platelet activation 6 hours after sleep onset, which corresponds to the time point they chose for blood sampling (04.00), even with the limitation that an alteration in platelet function cannot be excluded using a continuously placed peripheral intravenous catheter than direct venipunctures.

In the same study[10] platelet activation was furthermore examined studying platelet glycoprotein alterations during in vivo platelet activation. The two independent antibodies used to determine in vivo platelet activation are specific for activated platelets: P-selectin (CD62P) is released on the platelet membrane, whereas CD63 is exposed on the platelet membrane after lysosome degranulation. The fact that similar results were obtained using different activation-dependent antibodies further supports the previous hypothesis that OSAS patients have increased platelet activation during sleep[11]. In order to study the effect of treatment with continuous positive airway pressure (CPAP), the measurements were repeated at the same time points after initiation of effective CPAP therapy. Platelet activation was lower during sleep on CPAP, although this difference did not reach statistical significance.

A study by Bokinsky et al[12] examined patients with suspected OSAS. Blood was drawn for spontaneous platelet aggregation (sAGG) and activation (sACT) measurements at hourly intervals during diagnostic polysomnography (PSG) and, in patients with confirmed OSAS, on a separate night during which CPAP treatment was applied. They found that there is a significant increase in sACT and, to a lesser extent, in sAGG, during sleep of OSAS patients compared to presleep baseline values[12]. Due to the lack of previously published relative studies, it cannot be stated with certainty whether this finding represents a pathological process or circadian variation of platelet function. However, in five additional subjects without OSAS, there was a rise in sACT during sleep to a smaller extent. This finding, in conjunction with the large rise seen in OSAS patients, suggests that the observed changes were pathologic sequelae of sleep apnea, rather than a normal response to sleep.

Sanner et al[13] measured platelet aggregability to epinephrine, collagen, arachidonic acid and adenosine diphosphate in vitro in 17 male patients with polysomnographically confirmed OSAS and compared with that of 15 male controls at 20.00h, 24.00h and 06.00h. The results indicate that in vitro platelet aggregability is altered in patients with OSAS. While it usually decreases overnight, as previously described in healthy males and confirmed in the controls, it increased slightly, although not significantly, in OSAS patients.

A more recent study by Nena et al[14] in a large line of 610 non-diabetic subjects with suspected OSAS, Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW), both indices of platelet activation are higher in patients with severe OSAS and correlated with different parameters of breathing function during sleep.

BLOOD VISCOSITY

Blood viscosity is defined as the inherent resistance of blood to flow and it is determined by plasma viscosity, hematocrit and the mechanical behavior of erythrocytes[15]. Normal adult blood viscosity is 40/100 and reported in units of millipoise. Increased blood viscosity is the only biological parameter linked with all other major cardiovascular risk factors, including elevated blood pressure, elevated LDL cholesterol, low HDL cholesterol, type-II diabetes, metabolic syndrome, obesity, smoking, age, and male gender. Furthermore, high blood viscosity has been shown to be present in OSAS patients[16].

FIBRINOGEN

Fibrinogen affects blood coagulation, blood rheology, as well as platelet aggregation and it has direct effects on the vascular wall and it is a prominent acute-phase reactant. In addition, fibrinogen is closely linked to atherosclerosis and prospective epidemiological trials suggest it as a major independent cardiovascular risk factor[17].

In another study[18] increased levels of fibrinogen and hematocrit in 11 patients with OSAS in the morning were found, suggesting increased blood viscosity. Similarly, more recent data[19] showed that fibrinogen and blood viscosity were increased at the morning in a group of 12 patients with OSAS but not in a group of 8 healthy controls. On accordance[20] elevated plasma fibrinogen levels in stroke patients are accompanied by a higher incidence of OSAS. This data confirmed a positive correlation between the plasma fibrinogen concentration and the number and duration of recorded respiratory events during sleep, and a negative correlation with minimum and average blood oxygen saturation. The authors suggest that high concentrations of fibrinogen may lead to an increased incidence of vascular disease in OSAS.

A study by Zhang et al[21] reported similar results. The biochemical characteristics of a prothrombotic state were evaluated in a group of 16 OSAS patients (mean age 63.4±4 years) before and after 30 days of CPAP therapy and compared the results to those of healthy, age-matched controls. Before CPAP therapy, they confirmed a statistically significant increase in hematocrit, blood viscosity and platelet aggregation in OSAS patients. The 30-day CPAP therapy resulted in a morning reduction of hematocrit, total blood viscosity and platelet aggregation.

TYPE 1 PLASMINOGEN ACTIVATOR INHIBITOR (PAI-1)

Increased levels of type 1 plasminogen activator inhibitor (PAI-1) nominate decreased fibrinolytic activity. In a study of Von Kanel et al[22] higher PAI-1 levels were found in OSAS patients. Furthermore, the severity of OSAS seemed to be independently associated with PAI-1 concentration[22]. Zammaron et al[23] presented similar findings, in a study of male patients with OSAS and arterial hypertension. Additionally, the results of the Cleveland Family Study in 537 patients with OSAS, suggested a dose-depended relationship between PAI-1 levels and AHI, until an AHI ≤15/h[24].

D-DIMERS

D-dimers is a degradation product of fibrin and represent a marker of various thrombotic states. Shitrit et al[25] in a study of 103 patients with OSAS demonstrated an inverse relationship between d-dimer levels and oxygen saturation, although no correlation was found between those levels and AHI. Furthermore, in a study of 64 subjects by Von Kanel et al[26], d-dimer levels were correlated with poor sleep quality.

EFFECT OF CPAP TREATMENT ON HAEMOSTASIS

Factor VII clotting activity (FVIIc) is an independent risk factor for ischaemic heart disease and it strongly predicts fatal episodes[27]. Chin et al[28] studied the effects of CPAP treatment on FVIIc in 15 patients with OSAS before and after 1 and 6 months after CPAP initiation. The levels of FVIIc were found to be significantly decreased in patients with severe OSAS during CPAP treatment, a finding that could indicate an improvement in those patients[28].

Similar were the results of another randomized study by Robinson et al[29] who found raised baseline levels of VII factor in untreated OSAS patients, suggesting a potential mechanism for the increased vascular risk, via activation of the coagulation pathways and clot generation. The levels of VII factor were decreased in the group treated with subtherapeutic CPAP, but not in those treated with therapeutic CPAP.

Another important finding reported was the marked reduction in sACT and sAGG following CPAP the application[12]. Sanner et al[13] proved that the normal diurnal pattern could be restored with long-term therapy of OSAS over 6 months. Furthermore, treatment with CPAP significantly decreased mean platelet aggregability at 24:00h and 06:00h. The extent of the in vitro CPAP-induced decrease in aggregability was small, and the measured variables at baseline were generally within the established normal range.

Reinhart et al[30] described the effect of 6 months of CPAP therapy on morning plasma viscosity in a group of 13 patients with OSAS in comparison to 8 controls. Morning plasma viscosity was found to be higher in patients with OSAS and was correlated with fibrinogen levels. Furthermore, blood viscosity and platelet activity were normalized after CPAP treatment to levels comparable to those of healthy controls, suggesting that short-term CPAP therapy is effective in reducing blood viscosity in OSAS patients.

The findings on fibrinogen levels remain controversial. Chin et al[18] reported a decrease in elevated fibrinogen levels after CPAP treatment in 11 patients with OSAS, however, similar results were not reproduced in the study by Robinson et al[29].

CONCLUSIONS

There is an increasing interest about the pathogenetic mechanisms of OSAS in both cardiovascular morbidity and mortality. However, the independent role of OSAS on increased blood coagulability remains unclear, mainly due to the coexistence of other cardiovascular risk factors[30,31], the lack of correlation between markers such as fibrinogen and severity of sleep disorder breathing in children[32] and the incomplete normalization of coagulation after CPAP treatment[33]. Further research is required to establish the practical value of biomarkers associated with coagulation in OSAS[34,35].

REFERENCES

1. Fietze I, Penzel T, Alonderis A, et al. Management of obstructive sleep apnea in Europe. Sleep Med 2011;12:190-7.
2. Kostapanos MS, Mikhailidis DP, Elisaf MS, Steiropoulos P, Papanas N. Obstructive sleep apnoea syndrome and cardiovascular risk. Arch Med Sci 2012;8:1115-6.
3. Pafili K, Steiropoulos P, Papanas N. The relationship between obstructive sleep apnoea and coronary heart disease. Curr Opin Cardiol 2015;30:439-46.
4. Tofler GH, Brezinski D, Schafer AI, et al. Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden cardiac death. N Engl J Med 1987;316:1514-8.
5. Carlson J, Hedner J, Elam M, et al. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993;102:1763-8.
6. Jennum P, Wildschiodtz G, Christensen NJ, Schwartz T. Blood pressure, catecholamines and pancreatic polypeptide in obstructive sleep apnea with and without nasal continuous positive airway pressure (nCPAP) treatment. Am J Hypertens 1989;2:847-52.
7. Larsson PT, Wallen NH, Hjemdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. Circulation 1994;89:1951-7.
8. Grant JA, Scrutton MC. Novel alpha2-adrenoceptors primarily responsible for inducing platelet aggregation. Nature 1979;277:659-61.
9. Shattil SJ, Budzynski A, Scrutton MC. Epinephrine induces platelet fibrinogen receptor expression, fibrinogen binding, and aggregation in whole blood in the absence of other excitatory agonists. Blood 1989;73:150-8.
10. Geiser T, Buck F, Meyer BJ, et al. In vivo platelet activation is increased during sleep in patients with obstructive sleep apnea syndrome. Respiration 2002;69:229-34.
11. Oga T, Chin K, Tabuchi A, et. al. Effects of obstructive sleep apnea with intermittent hypoxia on platelet aggregability. J Atheroscler Thromb 2009;16:862-9.
12. Bokinsky G, Miller M, Ault K, Husband P, Mitchell J. Spontaneous platelet activation and aggregation during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure: a preliminary investigation. Chest 1995;108:625-30.
13. Sanner BM, Konermann M, Tepel M, et al. Platelet function in patients with obstructive sleep apnoea syndrome. Eur Respir J 2000;16:648-52.
14. Nena E, Papanas N, Steiropoulos P, et al. Mean Platelet Volume and Platelet Distribution Width in non-diabetic subjects with obstructive sleep apnoea syndrome: new indices of severity? Platelets 2012;23:447-54.
15. Dikmenoglu N, Ciftci B, Ileri E, et al. Erythrocyte deformability, plasma viscosity and oxidative status in patients with severe obstructive sleep apnea syndrome. Sleep Med 2006;7:255-61.
16. Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc 2004;79:1036-46.
17. Ernst E. Fibrinogen as a cardiovascular risk factor-interrelationship with infections and inflammation. Eur Heart J 1993;14 (Suppl K):82-7.
18. Chin K, Ohi M, Kita H, et al. Effects of nCPAP therapy on fibrinogen levels in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1996;153:1972-6.
19. Nobili L, Schiavi G, Bozano E, et al. Morning increase of whole blood viscosity in obstructive sleep apnea syndrome. Clin Hemorheol Microcirc 2000;22:21-7.
20. Wessendorf TE, Thilmann AF, Wang YM, et al. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. Am J Respir Crit Care Med 2000;162:2039-42.
21. Zhang X, Yin K, Wang H, Su M, Yang Y. Effect of continuous positive airway pressure treatment on elderly Chinese patients with obstructive sleep apnea in the prothrombotic state. Chin Med J (Engl) 2003;116:1426-8.
22. von Känel R, Loredo JS, Ancoli-Israel S, Mills PJ, Dimsdale JE. Elevated plasminogen activator inhibitor 1 in sleep apnea and its relation to the metabolic syndrome: an investigation in 2 different study samples. Metabolism 2007;56:969-76.
23. Zamarrón C, Ricoy J, Riveiro A, Gude F. Plasminogen activator inhibitor-1 in obstructive sleep apnea patients with and without hypertension. Lung 2008;186:151-6.
24. Mehra R, Xu F, Babineau DC, et al. Sleep-disordered breathing and prothrombotic biomarkers: cross-sectional results of the Cleveland Family Study. Am J Respir Crit Care Med 2010;182:826-33.
25. Shitrit D, Peled N, Shitrit AB, et al. An association between oxygen desaturation and D-dimer in patients with obstructive sleep apnea syndrome. Thromb Haemost 2005;94:544-7.
26. von Känel R, Dimsdale JE, Ancoli-Israel S, et al. Poor sleep is associated with higher plasma proinflammatory cytokine interleukin-6 and procoagulant marker fibrin D-dimer in older

caregivers of people with Alzheimer's disease. J Am Geriatr Soc 2006;54:431-7.
27. Heinrich J, Balleisen L, Schulte H, Assamann G, van de Loo J. Fibrinogen and factor VII In the prediction of coronary risk. Results from the PROCAM study in healthy men. Arterioscler Thromb 1994;14:54-9.
28. Chin K, Kita H, Noguchi T, et al. Improvement of factor VII clotting activity following long-term nCPAP treatment in obstructive sleep apnoea syndrome. QJM 1998; 91:627-33.
29. Robinson GV, Pepperell JC, Segal HC, Davies RJ, Stradling JR. Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials. Thorax 2004;59:777-82.
30. Reinhart WH, Oswald J, Walter R, Kuhn M. Blood viscosity and platelet function in patients with obstructive sleep apnea syndrome treated with nasal continuous positive airway pressure. Clin Hemorheol Microcirc 2002;27:201-7.
31. Steiropoulos P, Papanas N, Nena E, et al. Inflammatory markers in middle-aged obese subjects: does obstructive sleep apnea syndrome play a role? Mediators Inflamm 2010;2010:675320.
32. Kaditis AG, Alexopoulos EI, Kalampouka E, et al. Morning levels of fibrinogen in children with sleep disordered breathing. Eur Respir J 2004;24:790-7.
33. Shimizu M, Kamio K, Haida M, et al. Platelet activation in patients with obstructive sleep apnea syndrome and effects of nasal-continuous positive airway pressure. Tokai J Exp Clin Med 2002;27:107-12.
34. Toraldo D, Peverini F, De Benedetto M, De Nuccio F. Obstructive sleep apnea syndrome: blood viscosity, blood coagulation abnormalities, and early atherosclerosis. Lung 2013;191:1-7.
35 Archontogeorgis K, Nena E, Papanas N, Steiropoulos P. Biomarkers to improve diagnosis and monitoring of obstructive sleep apnea syndrome: current status and future perspectives. Pulm Med 2014;2014:930535.