Hemostatic Alterations in Patients With Obstructive Sleep Apnea and the Implications for Cardiovascular Disease*

Roland von Ka¨nel, MD; and Joel E. Dimsdale, MD

**Study objectives:** Patients with obstructive sleep apnea (OSA) are at increased risk for coronary artery and cerebrovascular diseases. Numerous studies suggest that a hypercoagulable state is prospectively related to atherothrombotic events. This review explores whether changes in hemostasis may constitute one biological link between OSA and vascular disease.

**Design:** Ten studies on hemostatic variables in OSA were located by electronic library search and descriptively reviewed. Work on hemostatic function with physiologic conditions similar to those found in OSA (hypoxemia and hyperactivity of the sympathetic nervous system) was considered to discuss potential molecular mechanisms of procoagulant disturbances in OSA.

**Measurements and results:** The reviewed data suggest that, as compared to non-OSA control subjects, patients with OSA have elevated plasma fibrinogen levels, exaggerated platelet activity, and reduced fibrinolytic capacity. Although not consistently shown, severity of OSA (ie, apnea-hypopnea index) and plasma epinephrine were independent predictors of platelet activity, and average minimal oxygen saturation was an independent predictor of fibrinogen. In some studies, treatment with continuous positive airway pressure decreased platelet activity, plasma fibrinogen levels, and activity of clotting factor VII.

**Conclusions:** There is some evidence for a hypercoagulable state in OSA, which might help explain the increased prevalence of vascular diseases in this population. To further confirm such a notion, future studies need to be performed on sufficiently large samples to be able to control for confounders of hemostatic activity. Prospective studies are needed to examine the association between hemostasis molecules and strong vascular end points.


Key words: blood coagulation; cardiovascular disease; catecholamines; cerebrovascular disease; fibrinolysis; hemostasis; hypoxia; obstructive sleep apnea; sympathetic nervous system

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea; PAI-1 = type 1 plasminogen activator inhibitor; RDI = respiratory disturbance index; Sats = arterial oxygen saturation; Satmin = minimum arterial oxygen saturation; SNS = sympathetic nervous system; TAT = thrombin-antithrombin III complex; t-PA = tissue-type plasminogen activator inhibitor; vWF = von Willebrand factor

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There is much evidence that patients with obstructive sleep apnea (OSA) have an increased risk for coronary artery disease1,2 and cerebrovascular disease,3,4 as well as premature death from vascular events.5 The pathophysiologic underpinnings of these associations are unclear.6,7 Candidate mechanisms most often identified may be the clus-
tering of established cardiovascular risk factors in OSA, such as systemic hypertension,8 obesity,9 smoking,10 heightened susceptibility for cardiac arrhythmias,11 and an activated sympathetic nervous system (SNS) due to repetitive nocturnal hypoxemia and arousals from sleep.12 In addition, a few studies have suggested that cellular adhesion processes that are proinflammatory in nature13,14 and impaired endothelial vasodilating function15 might also contribute to this relationship. This is evidenced by increased plasma levels of soluble cellular adhesion molecules and selectins,14,16 as well as by a mismatch between vasoconstricting endothelin-117 and vasodilating nitric oxide18 in the circulation of patients with OSA.

Up-regulated cellular adhesion and dysfunction of the endothelium with concomitant loss of its anticoagulant properties might give raise to firm adhesion of inflammatory cells to the endothelium19 and coagulation disturbances.20 There is a strong interplay between inflammatory and hemostatic processes ultimately resulting in fibrin formation and atherosclerotic plaque growth.21–25 Taken together, there is much reason to assume that the pathophysiological changes in OSA might accelerate atherosclerosis development toward overt vascular disease by altering endothelial, inflammatory, and hemostatic processes.

This review will focus on a promising area of research that has emerged since the mid-1990s suggesting that OSA might confer a hypercoagulable state that, in part, could mediate the adverse impact of OSA on vascular health.36 The rationale for such a hypothesis derives from the finding that, in numerous studies, molecules of the hemostatic system entailing blood coagulation, platelets, fibrinolysis, and endogenous anticoagulants have been prospectively associated with cardiac events27–29 and, to a lesser extent, with cerebrovascular incidents.30

Among hemostatic risk factors, increased plasma levels of fibrinogen31 and of the fibrin degradation product d-dimer32 have been most consistently related to enhanced cardiovascular risk.28 It is assumed that accelerated clotting contributes to atherosclerosis progression by promoting gradual fibrin deposition within atherosclerotic plaques.33 Similarly, accelerated clotting may contribute to acute coronary occlusion by triggering thrombus formation following plaque rupture.34

Studies on hemostasis variables in OSA were located by electronic library search (PubMed), using sleep apnea syndrome, hemostasis, blood coagulation, fibrinolysis, fibrinogen, and platelets as key words. Hemostasis research in OSA has not resulted in a large number of publications. For this reason, we decided not to exclude particular studies based on defined methodologic criteria or required sample sizes. Instead, we discuss study limitations as a guide for building on this foundation and extending the knowledge base. The small number of studies and the broad methodologic differences across studies precluded formal meta-analysis. Thus, we have provided a descriptive review, while providing some “quantification” of our search criteria so the reader would know how we made our inferences.

Since many sleep researchers may not be conversant with hemostasis physiology, we will provide an initial overview on blood coagulation and fibrinolysis pathways. We then will move on to summarize the particular studies on hemostasis in OSA, focusing on methodologic issues pertinent for future research in the field. Moreover, we will selectively discuss hemostatic alterations in physiologic states similar to those accompanying OSA (eg, experimental exposure to hypobaric hypoxia in humans and animals) that may help better understand molecular mechanisms underlying hemostatic alterations in OSA. Although speculative, we feel that such parallel lines of investigation may logically relate to OSA physiology, and that they might attract researchers to generate additional hypotheses advancing the field.

Hemostasis Physiology

Two closely intertwined coagulation pathways have been described (Fig 1).35,36 The intrinsic, or contact activation pathway is initiated by contact of clotting factor XII with negatively charged surfaces. The extrinsic or tissue factor pathway is triggered by the interaction of tissue factor exposed on vascular cells on injury with activated factor VII in plasma. In a progressive cascade that comprises activation of several serine proteases, both pathways converge to form a common pathway leading to activation of factor X in the presence of factor V. In addition, activated platelets provide binding sites for factor V and factor VIII on their surface exhibiting platelet procoagulant activity.37,38 These steps result in thrombin formation, which converts fibrinogen to soluble fibrin and eventually a firm clot. The von Willebrand factor (vWF) is crucial for platelet adhesion to subendothelial structures, platelet aggregation, and protection of factor VIII from proteolysis in circulation.39

Several anticoagulant mechanisms terminate clot formation. For instance, antithrombin III will bind to thrombin thus inhibiting thrombin activity in a thrombin-antithrombin III complex (TAT).35 The fibrinolytic systems proteolytically degrades fibrin into soluble fragments such as d-dimer. Fibrinolysis is triggered by tissue-type plasminogen activator (t-PA) that converts fibrin-bound plasminogen to
fibrin cleaving plasmin; t-PA itself is inhibited by type I plasminogen activating inhibitor (PAI-1).40,41 TAT and d-dimer indicate activation of coagulation and downstream fibrinolysis without overt thrombosis. Many investigators consider elevations in TAT and d-dimer to be procoagulant harbingers of a hypercoagulable state.42,43

Figure 1. The scheme presents coagulation and fibrinolysis pathways. Roman numerals indicate coagulation factors. Prothrombotic markers of a hypercoagulable state are depicted in boxes. The sign “F” indicates inhibition steps of thrombin and of t-PA. DD = fibrin d-dimer. Redrawn with permission from von Kanel et al.29

Studies on Hemostasis Molecules in OSA

Technical Issues

Table 1 lists the 10 studies reviewed that were published between 1995 and 2002.44–53 Three studies had a sample size of approximately 100 subjects,47,50,52 but the bulk of studies included < 25 subjects.44–46,48,51,53 All studies performed full overnight polysomnography and followed methods by Rechtschaffen and Kales54 to score sleep recordings. Blood-drawing techniques are of particular relevance for studies of hemostasis. Authors have favored two approaches, with venous blood being obtained either through an indwelling line44,45,52 or by separate venipunctures.46–51,53 Both techniques may have their advantages and disadvantages. In particular, while an indwelling catheter may more readily result in artifactual activation of hemostasis,51,55 repeated venipuncture may require coagulation activating venipuncture in obese patients with apnea.46 Similarly, repeated serial venipuncture during sleep obviously interferes with sleep itself.45 Elicited arousal from sleep and concomitant pain or fear from blood draws by venipuncture may activate the SNS, possibly affecting hemostasis. It is known that acute-state anxiety (eg, fear of donating blood) and other forms of short-term sympathetic activation may accelerate blood clotting time.29

Standardized use of a particular preservative for blood specimens is crucial to compare hemostasis findings across studies. For instance, particular anticoagulants may have differential effects on platelet activation in vitro.56 Of studies investigating platelet aggregation in OSA, three studies44,47,49 used sodium citrate and one study45 used heparin as the anticoagulant. Likewise, fibrinogen values obtained in clotting assays from plasma anticoagulated with either sodium citrate (usually recommended) or ethylenediaminetetraacetic acid require correction to be comparable.57 Of three studies measuring fibrinogen, one study51 used sodium citrate as the preservative, and two studies46,50 did not mention the particular preservative used.

Sleep Variables and Associations With Hemostasis

It is beyond the scope of this review to argue for the optimal cutoff for the number of apneic and hypopneic events per hour (ie, apnea-hypopnea index [AHI] or respiratory disturbance index [RDI]) that best defines OSA in terms of its clinical significance.58 Accordingly, the studies reviewed here employed different OSA definitions based on an AHI or RDI between > 5/h and ≥ 20/h, respectively (Table 1). There was more consistency in terms of how apnea was defined (ie, airflow cessation ≥ 10 s). To define hypopnea, most authors required airflow cessation of ≥ 50% accompanied by a drop in arterial oxygen saturation (SaO2) between at least 2% and 4% (not shown in Table 1).

Hemostatic measurements from studies categorizing OSA across such a wide range of severity are difficult to compare except in terms of plotting a continuous relationship between AHI, RDI, or minimal SaO2 (SaO2min) and hemostasis variables. Two studies found a positive association between AHI and 9 pm platelet activation,47 and between RDI and fibrinogen (Fig 2, top).50 In one of these studies,50 fibrinogen also showed an inverse association with both SaO2min and average SaO2min (Fig 2, bottom). Multiple linear regression analyses showed independent associations between AHI and platelet activity,47 epinephrine and platelet activity,46 and average
Sao2min and fibrinogen.\textsuperscript{50} These significant associations may suggest that the relationship between OSA physiology and procoagulant changes lies along a continuum of OSA severity. This statement must be made tentatively, as seven studies\textsuperscript{44,45,48,49,51–53} reported on insignificant associations of AHI, RDI, or Sao2min with hemostasis. Nonetheless, we assume that differences between studies that found a significant association between sleep and hemostasis variables and those studies that did not may largely be a matter of sample sizes. The two studies\textsuperscript{24,70} showing significant associations included almost 100 subjects, which also allowed extensive control for confounders of hemostatic activity.

**Hemostatic Findings in Patients With OSA vs Non-OSA Control Subjects**

Platelet activity (five studies) and fibrinogen (three studies) were most often investigated, followed by clotting activity of factor VII (factor VII:C), PAI-1, vWF, and the hypercoagulability markers TAT and d-dimer, which were investigated in one study each. Three platelet studies\textsuperscript{45,47,53} found higher platelet activation in patients with OSA than in control subjects; however, only one study\textsuperscript{53} provided the p value of this difference, and platelet activation was not different between patients with apnea and control subjects in two other studies.\textsuperscript{44,49} While lack of significance in one of these platelet studies\textsuperscript{44} is difficult to interpret because we do not know how OSA was defined, the maintenance of different categories of antihypertensive drugs in both patients and control subjects may have confounded assumed differences in the other study.\textsuperscript{49}

Findings on fibrinogen are consistent, given that two studies\textsuperscript{50,51} showed higher plasma fibrinogen levels in OSA, with the third study\textsuperscript{46} lacking a control group. One study\textsuperscript{44} found twofold elevated PAI-1 activity, suggesting impaired fibrinolysis in patients with OSA as compared to control subjects. Of note, reduced fibrinolytic capacity in OSA seems not to be related to the 4G/5G PAI-1 gene polymorphism that has been previously associated with increased risk for myocardial infarction.\textsuperscript{59} We found no difference in TAT, d-dimer, and vWF between patients with OSA as compared to non-OSA control subjects.\textsuperscript{52}

**Effects of Treatment With Continuous Positive Airway Pressure on Hemostasis**

While four studies\textsuperscript{45,46,48,49} found that continuous positive airway pressure (CPAP) treatment significantly decreased hemostatic activity in patients with OSA, one study,\textsuperscript{53} most likely due to insufficient statistical power, found an insignificant decrease in platelet activation during sleep. Treatment with CPAP significantly decreased overnight platelet aggregability in patients with OSA vs non-OSA control subjects in one study,\textsuperscript{49} while another study\textsuperscript{44} found that CPAP reduced platelet activity and aggregation during sleep (no control group). Treatment with CPAP led to a gradual decrease in factor VII:C assessed up to 18 months, which was not observed at 2 months in OSA control subjects not receiving CPAP.\textsuperscript{48} As compared to pre-CAP, fibrinogen levels in patients with OSA were significantly lower following CPAP treatment, and CPAP also resulted in a significant decrease of fibrinogen from the previous afternoon to the next morning (no control group).\textsuperscript{46}

These studies on CPAP effects on hemostasis raise an important methodologic issue. In essence, there are well-known circadian and seasonal changes across numerous hemostasis molecules,\textsuperscript{60–62} which should be accounted for by an appropriate control situation like a placebo-CAP condition or by including a nonapneic comparison group. Such a design may help prevent spurious assignment of changes in overnight or seasonal hemostatic activity to assumed effects of treatment with CPAP. One study\textsuperscript{49} observed subjects over an 18-month course of CPAP treatment; because there was a steady decrease in factor VII:C at 1, 6, 12, and 18 months, a seasonal effect on decrease in factor VII:C can likely be ruled out. Given the lack of a control group, a seasonal effect might account as well as CPAP for the decrease in platelet aggregability observed over a 6-month period in another study.\textsuperscript{49}

**Health-Related Variables Confounding Hemostatic Activity in Sleep Studies**

As shown in Table 1, the studies were similar in terms of age, body mass index (BMI), and male gender preponderance of participants, reflecting the epidemiology of OSA being most prevalent among middle-aged and elderly men and in the obese.\textsuperscript{63} The established cardiovascular risk factors—hypertension, type II diabetes, smoking, hyperlipidemia, and obesity—may all affect hemostatic activity.\textsuperscript{64–68} A weakness of most apnea/hemostasis studies is lack of control of hemostasis findings for these risk factors (Table 1), which makes it difficult to test for unique effects of OSA on hemostatic function. According to our previous study,\textsuperscript{52} this notion seems of particular importance in terms of comorbid hypertension that is most prevalent in OSA.\textsuperscript{6,69} In fact, in subjects with symptoms suggestive of OSA, we found that in-
Table 1—Studies on a Hypercoagulable State in Patients With OSA

<table>
<thead>
<tr>
<th>Source</th>
<th>Population</th>
<th>OSA Definition</th>
<th>Sleep Variables</th>
<th>Variables Confounding</th>
<th>Hemostatic Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rangemark et al</td>
<td>13 men with OSA, 11 hypertensive, mean age 53 yr, mean BMI 29; 10 male control subjects</td>
<td>AHI and RDI not provided</td>
<td>Mean ± SEM AI 32 ± 5/h; mean ± SEM SaO₂min 75 ± 2%</td>
<td>E: BMI ≥ 150% ideal body weight, smokers, NSAIDs, coagulation disorder; antihypertensive drugs washed out</td>
<td>S: higher PAI-1 activity in OSA vs control subjects</td>
</tr>
<tr>
<td>Bokinsky et al</td>
<td>6 men with OSA, 5 hypertensive, mean age not provided, mean BMI 40; 5 control subjects</td>
<td>AHI and RDI not provided</td>
<td>Mean ± SEM AHI 87 ± 23/h; mean ± SEM SaO₂min 71 ± 4%</td>
<td>I: smokers, any drugs, including antihypertensives</td>
<td>S: decrease in spontaneous platelet activity (P-selectin) and aggregation with CPAP night vs diagnostic night at hours 1 to 6 of sleep; elevated platelet activity in OSA (diagnostic night) vs control subjects (no p value)</td>
</tr>
<tr>
<td>Chin et al</td>
<td>11 patients with OSA, 2 hypertensive, mean age 46 yr, mean BMI 31; no control group</td>
<td>AHI &gt; 20/h</td>
<td>Mean ± SEM AHI 63 ± 6/h; mean ± SEM SaO₂min 60 ± 4%</td>
<td>I: antihypertensive drugs maintained</td>
<td>S: higher fibrinogen at 8:30 AM without CPAP vs with CPAP; decrease in fibrinogen from 3:30 PM to 8:30 AM the following day with CPAP vs without CPAP; association between OSA severity and fibrinogen not reported</td>
</tr>
<tr>
<td>Eisenshr et al</td>
<td>76 subjects with symptoms suggestive of OSA, 21 hypertensive, mean age 43 yr, mean BMI 29; 3 “truc” non-OSA control subjects</td>
<td>AHI &lt; 5/h non-OSA (n = 50), AHI 5-50/h mild-to-moderate OSA (n = 19), AHI &gt; 50/h severe OSA (n = 7)</td>
<td>Mean ± SD AHI non-OSA 2 ± 1, mild-to-moderate OSA 14 ± 8, severe OSA 60 ± 9; mean ± SD SaO₂min, non-OSA 92 ± 3%, mild-to-moderate OSA 90 ± 3%, severe OSA 83 ± 6%</td>
<td>E: caffeine, nicotine and alcohol in previous 24 h I: smokers, NSAIDs; antihypertensive drugs maintained</td>
<td>S: positive and independent associations between 9 PM P-selectin and both AHI and 6 AM plasma epinephrine; positive association between 9 PM ADP-stimulated platelet aggregation and 6 AM epinephrine; 9 PM and 6 AM platelet aggregation highest in severe OSA group (no p value)</td>
</tr>
<tr>
<td>Chin et al</td>
<td>15 men with OSA, mean BP 141/90 mm Hg, mean age 45 yr, mean BMI 31; 8 OSA control subjects not receiving CPAP</td>
<td>AHI &gt; 20/h</td>
<td>Mean ± SEM AHI 62 ± 4/h; mean ± SEM SaO₂min 55 ± 3%</td>
<td>I: any drugs</td>
<td>S: gradual decrease in factor VII:C at 1, 6, 12, and 18 mo with CPAP vs no CPAP (factor VII:C unchanged in control subjects between first and second measurement 50 d apart); NS: associations between factor VII:C and both AHI and SaO₂min</td>
</tr>
</tbody>
</table>
Sanner et al 50 17 men with OSA, 9 hypertensive, mean age 53 yr, mean BMI 33; 15 male control subjects

AHI ≥ 10/h

Mean ± SEM AHI 32 ± 4/h; mean ± SEM SaO₂min 77 ± 4%; usage of CPAP 3.6 ± 0.6 h/night

E: NSAIDs, glucocorticoids, smoking, hemostatic disorder
I: diabetes, any other drug, including antihypertensives

S: decrease in epinephrine-stimulated platelet aggregation after 6 mo of CPAP at midnight and at 6 AM vs pre-CPAP
NS: epinephrine-, ADP-, collagen- and arachidonic acid-stimulated platelet aggregation at 8 PM, at midnight, and at 6 AM; changes in overnight aggregability in CPAP-OSA vs controls.

Wessendorf et al 50 82 men and 31 women with stroke, mean age 58 yr, mean BMI 27

RDI ≥ 20 OSA (n = 27), RDI < 5 non-OSA (n = 54)

Mean RDI 15/h; mean SaO₂min 84%

E: patients with central apneas
I: smokers

S: higher fibrinogen in OSA vs non-OSA; inverse associations between both SaO₂min and average SaO₂min (independent predictor) and fibrinogen; positive association between RDI and fibrinogen.

Nobili et al 51 10 men and 2 women with OSA, 5 hypertensive, mean age 52 yr, mean BMI; 8 age- and sex-matched healthy control subjects

RDI > 5

Mean ± SD RDI 60 ± 16; mean ± SD SaO₂min 63 ± 6%

E: hematologic disorders
I: smokers, any drugs, including antihypertensives

NS: associations between both RDI and SaO₂ and fibrinogen

von Kanel et al 52 87 subjects with symptoms suggestive of OSA; 30 hypertensive, mean age 47 yr, mean BMI 29

RDI ≥ 15 OSA (n = 57), RDI < 15 non-OSA (n = 30)

Mean ± SEM RDI 52 ± 4/h; mean ± SEM SaO₂min 72 ± 2%

E: BMI > 150% of ideal body weight, all drugs, including NSAIDs, anticoagulants; antihypertensive drugs washed out
I: smokers

E: anticoagulants, aspirin, glucocorticoids
I: smokers, diabetes, hypercholesterolemia; antihypertensive drugs maintained

Geiser et al 53 12 OSA patients, 3 hypertensive, mean age 60 yr, mean BMI 29; 6 healthy control subjects

AHI > 10/h OSA, AHI < 10/h non-OSA

Mean ± SEM AHI 20 ± 3/h mild-to-moderate OSA (n = 6), 33 ± 6/h moderate-to-severe OSA (n = 5), 55 ± 6/h severe OSA (n = 1)

E: anticoagulants, aspirin, glucocorticoids
I: smokers, diabetes, hypercholesterolemia; antihypertensive drugs maintained

NS: platelet microparticles, CPAP effect
NS: association between AHI and platelet activation

*NSAIDs = nonsteroidal anti-inflammatory drugs; AI = apnea index; ADP = adenosine diphasphate; E = excluded; FVII:C = clotting activity of coagulation factor VII; I = included; NS = not significant; S = significant.
creases in the two hypercoagulability markers TAT (Fig 3, top) and d-dimer (Fig 3, bottom) related to comorbid hypertension rather than to OSA. Moreover, many of the established cardiovascular risk factors relate to the insulin resistance syndrome, which in itself confers a prothrombotic state, and which has been associated with OSA on its own. For instance, increased PAI-1 is a feature of the insulin resistance syndrome, and PAI-1 was higher in patients with OSA than in control subjects.
however, while this finding held significance when controlling for age, it became only a trend when BMI and BP were also accounted for.44

One would ideally wish that lifestyle variables such as alcohol consumption, caffeine intake, and physical exercise would be controlled for, but this has been reported by only one study.47 Intake of 30 to 40 g of alcohol with dinner results in an ultimate increase in coagulability for up to several hours that is followed by hypocoagulability the next morning.73,74 Likewise, caffeine and physical exercise both may affect hemostasis.75,76 It has been shown that after the end of a marathon race, clotting as well as fibrinolysis were activated up to 24 h.77 When unaccounted for, even subtle hemostatic changes resulting from mild exercise in the hours preceding blood draws for apnea studies might complicate interpretation of findings.

A methodologic strength of some studies is explicit exclusion of subjects who received nonsteroidal anti-inflammatory drugs,44,49,52,53 oral anticoagulants,52,53 or glucocorticoids.49,52,53 These drugs may influence hemostatic activity and, in part, are prescribed because of this particular effect in cardiovascular diseases.78,79 In a study80 of healthy men, enteric-coated aspirin inhibited platelet aggregation up to 4 days in most subjects. Only two studies44,52 performed a wash-out phase of antihypertensive medications, and six studies maintained the antihypertensive drug regimen45–47,49,51,53 or did not specifically report on this issue.48,50 Antihypertensive drugs may contribute to both hypercoagulability and hypocoagulability. For instance, angiotensin-converting enzyme inhibiting drugs may increase the fibrinolytic potential by decreasing PAI-181 and calcium antagonists may exert antiplatelet effects,82 whereas nonselective β-blockade may impair fibrinolysis and enhance platelet activity.83 Thus, studying apnea patients taking antihypertensive drugs might further obscure tracking down an assumed unique relationship between OSA physiology and increased clotting diathesis.

**Studies of Hemostatic Changes in Experimental States Resembling OSA**

Mechanisms causing blood to clot in OSA are elusive. Aside from comorbid cardiovascular risk factors, lifestyle variables, and medication potentially confounding hemostatic activity, increased SNS activity and catecholamine surges with arousal from sleep12 might contribute to increased clotting diathesis in OSA. This is underlined by one study47 that found an association between morning plasma epinephrine levels and evening platelet aggregability. This notion gains much support from previous work84–88 showing that activation of the SNS by physical and mental stress as well as adrenergic infusions may elicit thrombin formation and exaggerated fibrin turnover. These effects appear to be mediated by adrenergic receptors, and their state of sensitivity in particular.84,88 Whether changes in adrenergic receptor functioning observed in OSA89,90 may have any effect on hemostasis remains to be seen.

The finding of an association between RDI, AHI, and SaO2 with fibrinogen90 suggests that severity of intermittent nocturnal hypoxemia may contribute to procoagulant disturbances in OSA. The following section provides some of the information from diverse models of experimentally induced hypoxia of different degree and duration. Hypercoagulability and associated thromboembolic events in mountaineers may be a combined consequence of exposure to altitude hypobaric hypoxia91 and of physical exercise with climbing.92 A 20-min exposure to severe hypobaric hypoxia (mean final SaO2 of 61.5%) in a decompression chamber resulted in platelet activation, shortening of coagulation time, and rise in factor VIII:C in pilots.93 Also, under atmospheric pressure in airplane cabins, healthy men showed increases in activated factor VII and in the hypercoagulability markers prothrombin fragments 1 + 2 and TAT,94 which was prevented by prophylactic treatment with low-molecular-weight heparin.95 Patients with chronic airflow obstruction who were hypoxic (PaO2 < 60 mm Hg) had enhanced baseline platelet activity as compared to patients with normoxemia and control subjects.90 In subjects with a diagnosis of OSA, we have found that short-term hypoxemia achieved by oxygen deprivation inhaled air provokes increases in both TAT and d-dimer (unpublished data).

Hypoxemia in a clinical setting is often accompanied by acidosis explaining some of the variance of increase in factor VIII:C during hypoxemia.93 In a fetal lamb model that allowed control for metabolic and cardiovascular changes associated with hypoxemia, 30-min exposure to severe hypoxemia (decrease of PO2 from 26 to 14 mm Hg), had no influence on blood coagulation factor activities.97 In contrast, and highlighting the importance of the overall time spent under a hypoxic condition, male Wistar rats showed platelet aggregation with thrombus formation at the subendocardial matrix that was accompanied by consumption coagulopathy after a 2-week exposure to hypobaric hypoxia in a mechanical chamber at the equivalent of 5,500 m in altitude.98

In a mouse model, fibrin deposition occurred in the pulmonary vasculature within 6 h after exposure to an oxygen concentration of 6% in an environmental chamber.99 In that model, hypoxia appeared to trigger transcription and cell surface expression of...
tissue factor in vascular smooth-muscle cells and macrophages as well as suppression of fibrinolysis. Environmental hypoxia (PO₂ < 40 torr) decreased t-PA messenger RNA and increased PAI-1 messenger RNA in the lung of mice with enhanced transcription of PAI-1 being followed by an increase in plasma PAI-1 levels as early as 4 h following the hypoxic stimulus. Basic research in cultured cell models suggests that it is not only the dramatic desaturations that might activate coagulation in OSA, but also closely linked reoxygenation phases. For instance, a hypoxic media (PO₂ < 60 mm Hg) increased procoagulant activity of human umbilical venous endothelial cells after 24 h, with a further twofold increase in procoagulant activity after cells had been reoxygenated for 4 h.

Conclusions

The evidence from the articles reviewed here is strongly suggestive of a procoagulant state in OSA that might possibly provide an explanatory link for the high prevalence for vascular diseases in patients with OSA. The evidence for a procoagulant state in OSA seems also strong enough to justify an epidemiologic study to determine if there is a relationship between OSA and venous thrombosis or thromboembolism. A case-control study of the incidence of OSA in patients with venous thromboses and control subjects has not been performed, and it might be informative and of only moderate expense. The major problem with the studies reviewed is lack of adequate control. Although it is difficult to control for the many drugs, diseases, and lifestyle variables in patients with OSA, it may not be impossible. A moderate-sized study with close attention to controls and to technical problems surrounding coagulation studies would be helpful in tracking down unique effects of OSA physiology on the hemostatic system. Definitely more intervention studies, preferably including a CPAP-placebo condition, are needed to reconcile the discussion whether CPAP treatment may favorably regulate the hypercoagulable state in OSA.

Intermittent hypoxemia and related sympathetic activation are core features of OSA physiology. Thus, work from different fields on effects of sympathetic activation and hypoxia on hemostasis offers attractive avenues for the understanding of and future research on the contribution of the hemostatic system to vascular disease in OSA. Such research may want to investigate procoagulant perturbations on both the cellular (eg, expression of messenger RNA of hemostasis factors) and protein level (eg, activities of hemostasis molecules in plasma).

The studies of coagulation in OSA are certainly not definitive; however, we would like to offer some clinical speculations concerning treatment that may be prudent in light of these observations. Because of thrombosis-related complications in hypertension, many high-risk hypertensive patients are already advised to take low-dose aspirin. Patients with OSA very often fall in the category of those with such a high risk for severe cardiovascular events that daily aspirin therapy may have benefits that strongly outweigh the risks. It is likely that such patients might benefit from daily aspirin therapy. While clinical trials in this area are lacking, it would seem sensible to treat the elevated BP associated with OSA before instituting treatment with aspirin or other anticoagulants to diminish the risk of intracerebral hemorrhage. Taken together, while the blood of patients with OSA may clot more rapidly, the question whether such hypercoagulability is of clinical significance can only be resolved if carefully controlled prospective and case-control studies were to show an association between hemostasis molecules and enhanced risk for arterial and/or venous thrombotic events in patients with OSA.

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