Coagulability in obstructive sleep apnea

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BACKGROUND: Obstructive sleep apnea (OSA) is a common disorder that affects both quality of life and cardiovascular health. The causal link between OSA and cardiovascular morbidity/mortality remains elusive. One possible explanation is that repeated episodes of nocturnal hypoxia lead to a hypercoagulable state that predisposes patients to thrombotic events. There is evidence supporting a wide array of hematological changes that affect hemostasis (eg, increased hematocrit, blood viscosity, platelet activation, clotting factors and decreased fibrinolytic activity).
OBJECTIVE: To provide a comprehensive review of the current evidence associating OSA with increased coagulability, and to highlight areas for future research.
METHODS: Keyword searches in Ovid Medline were used to identify relevant articles; all references in the articles were searched for relevant titles. The Web of Science was used to identify articles citing the relevant articles found using the Ovid Medline search. All original peer-reviewed articles, meta-analyses and systematic reviews regarding the pertinent topics between 1990 and present were selected for review.
RESULTS: Hematocrit, blood viscosity, certain clotting factors, tissue factor, platelet activity and whole blood coagulability are increased in patients with OSA, while fibrinolysis is impaired.
CONCLUSION: There is considerable evidence that OSA is associated with a procoagulant state. Several factors are involved in the procoagulant state associated with OSA. There is a need for adequately powered clinical studies involving well-matched control groups to address potential confounding variables, and to accurately delineate the individual factors involved in the procoagulant state associated with OSA and their response to treatment.

Key Words: *Coagulation; Hemostasis; Hypercoagulable; Obstructive sleep apnea*

La coagulabilité en cas d'apnée obstructive du sommeil

HISTORIQUE : L'apnée obstructive du sommeil (AOS) est un trouble courant qui nuit à la fois à la qualité de vie et à la santé cardiovasculaire. Le lien causal entre l'AOS et la morbidité ainsi que la mortalité cardiovasculaires demeure fugace. Parmi les explications possibles, on avance que les épisodes répétés d'hypoxie nocturne entraînent un état d'hypercoagulabilité qui prédispose les patients à des événements thrombotiques. Des données probantes appuient toute une série de modifications hématologiques qui influent sur l'hémostase (p. ex., augmentation des hématocrites, de la viscosité sanguine, de l'activation plaquettaire ainsi quedes facteurs de coagulation et diminution de l'activité fibrinolytique).
OBJECTIF : Faire une analyse complète des données probantes à jour liant l'AOS à une augmentation de la coagulabilité et faire ressortir les domaines exigeant de futures recherches.
MÉTHODOLOGIE : Les auteurs ont utilisé des recherches par mots-clés dans Ovid Medlinepour repérer les articles pertinents. Ils ont fait des recherches sur toutes les références des articles afin de trouver des titres pertinents. Le service *Web of Science* a permis de repérer les articles citant les articles pertinents trouvés au moyen de la fonction de recherche d'Ovid Medline. La totalité des articles originaux révisés par des pairs, des méta-analyses et des analyses systématiques portant sur les sujets pertinents entre 1990 et maintenant ont été sélectionnés en vue de leur analyse.
RÉSULTATS : Les hématocrites, la viscosité sanguine, certains facteurs de coagulation, le facteur tissulaire, l'activité plaquettaire et la coagulabilité du sang total sont plus élevés chez les patients faisant de l'AOS, tandis que la fibrinolyse est compromise.
CONCLUSION : D'innombrables données probantes indiquent que l'AOS s'associe à un état procoagulant. Plusieurs facteurs y contribuent. Des études cliniques aux effectifs suffisants comportant des groupes témoins bien appariés pour tenir compte des variables confusionnelles éventuelles et pour délimiter précisément les facteurs individuels liés à l'état procoagulant associé à l'AOS et pour établir leur réponse au traitement s'imposent.

Obstructive sleep apnea (OSA) is a common sleep disorder affecting approximately 5% of North American adults. Repeated obstruction of the upper airway during sleep results in sleep fragmentation, excessive daytime sleepiness and diminished quality of life (1,2). The gold standard therapy for OSA is continuous positive airway pressure (CPAP), which acts as a pneumatic splint that keeps the airway open during sleep. Untreated OSA increases the risk of all-cause mortality – cardiovascular mortality in particular – and is associated with cardiovascular complications such as hypertension, stroke, arrhythmias, myocardial infarction and heart failure (2-7). The association between stroke and OSA persists even after controlling for common stroke risk factors such as diabetes mellitus, dyslipidemia, smoking and hypertension (8), suggesting that OSA is an independent risk factor for stroke (9). Although the strong association between OSA and cardiovascular disease has been well documented, the pathophysiological mechanism that leads to the increased risk remains controversial.

One possible explanation is increased blood coagulability. Individuals with OSA have a complex array of factors that may result in a state of hypercoagulability. Research suggests that hypoxemia experienced by patients during apneas triggers the release of inflammatory factors that alter the micromilieu of the blood, resulting in increased blood coagulability (10-12). These factors may, in combination, lead to a hypercoagulable state. In the present review, we examine coagulability as a potential mechanism for the increased incidence of cardiovascular morbidity and mortality observed among patients with OSA, and the factors that contribute to this state.

FACTORS CONTRIBUTING TO HYPERCOAGULABLITY

Hematocrit (Table 1)

Hematocrit plays an important role in hemostasis because it affects blood viscosity and platelet aggregation. Individuals who experience hypoxic conditions often have increased hematocrit (eg, those living at higher altitudes compensate for lowered arterial oxygen tension through an increased hematocrit) (13). Several studies have determined that patients with OSA have increased hematocrit levels (14-19), and that the increases in hematocrit correlate positively with OSA severity (14). Only one study (Reinhart et al [20]) found no differences in hematocrit among CPAP-naive patients, CPAP-treated patients and controls. Both short-term (one night, one month and three months), and long-term (one year) CPAP therapy were found to decrease hematocrit levels (16,17,21,22) and, when examining

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TABLE 1
Hematocrit (Hct)

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Chin et al (18), 1996	Intervention study	11 patients with OSA	AHI >20/h	Yes	*One night CPAP decreased Hct levels from 48.5±1.5% to 46.9±1.4% (P<0.005)
Choi et al (14), 2006	Case-control study	202 patients with OSA 62 controls	RDI >5/h	No	Severity of OSA correlated with mean Hct levels (Control: 39.8±4%; mild: 41.2±4%; severe: 43.5±3.6%) [P<0.05])
Hoffstein et al (15), 1994	Case-control study	624 patients suspected OSA: n=352 no OSA n=272 OSA	AHI >10/h	No	Small increase in Hct found in males who spent at least 13 min at SaO_2 <85% versus nonapneics (45±5% versus 44±5% [P<0.05]). Mild increase in Hct found in females who spent at least 8 min at SaO_2 <85% versus nonapneics (41±3% versus 40±3% [P<0.05])
Krieger et al (16), 1990	Uncontrolled intervention study	8 patients with OSA	AHI ≥10/h	Yes	*After one night of CPAP, Hct decreased from 45.6±1.2% to 43.0±1.4% (P<0.0005)
Krieger et al (17), 1992	Uncontrolled intervention study	80 patients with OSA	AHI >30/h	Yes	*One night of CPAP decreased Hct from 44.0±0.5% to 42.4±0.4% (P<0.0001)
Nobili et al (19), 2000	Case-control study	12 patients with OSA, 8 healthy controls	RDI >5/h	No	Increase in Hct from evening to morning in patients with OSA (evening: 42.75±4.7%; morning: 44.6±4.4% [P<0.009])
Reinhart et al (20), 2002	Case-control study	13 patients with OSA, 8 age-matched controls	Not specified	Yes	No difference (ie, P not significant) in Hct between patients (with/without CPAP) and controls (CPAP: 45.3±2.6%; no CPAP: 45.8±3.8%; control: 43.5±2.5%)
Saarelainen et al (21), 1996	Uncontrolled intervention study	11 men with OSA	AHI >20/h	Yes	Decrease in Hct after 3 months of CPAP (46±2% to 43±3% [P<0.0001])
Tazbirek et al (23), 2009	Case-control study	31 male patients with OSA,19 matched controls	AHI ≥15/h or AHI ≥5/h + OSA symptoms	Yes	Difference in Hct between patients and controls (patients: 46.0±4.7% versus controls: 43.4±2.9% [P<0.05]). No difference (ie, P not significant) in Hct between patients treated with 5 nights of CPAP and controls (CPAP patients: 43.8±3.6% versus controls: 43.4±2.9%)
Zhang et al (22), 2003	Nonrandomized, nonequivalency controlled trial	41 patients with OSA, 32 healthy controls	AHI ≥5/h	Yes	Patients had significantly lower Hct levels, after 30 days of CPAP, which was comparable with controls (before: 59.1±4.2%; after: 44.0±4.8%; controls: 44.1±4.9% [P<0.01])

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hypopnea index; CPAP Continuous positive airway pressure; OSA Obstructive sleep apnea; RDI Respiratory disturbance index; ref Reference

CPAP-naive and CPAP-treated patients, significant differences were found in their hematocrit levels (23). Despite statistically significant elevations in hematocrit among untreated patients with OSA, these elevations did not reach the threshold of clinical polycythemia, but resulted in a mean hematocrit of 43.5% in patients with severe OSA (14). Although an elevated hematocrit would predispose patients to clot formation, no studies have been conducted to elucidate whether a raised, but subpolycythemic, hematocrit level affects cardiovascular outcomes in patients with OSA.

Blood viscosity (Table 2)

Untreated patients with OSA have increased blood viscosity, which may contribute to slowing of blood flow, stasis, clot formation and vessel occlusion (19,23-25). Thus, hyperviscosity is a potential mechanism for increased coagulability (25,26).

Dikmenoglu et al (24) reported that the decline in oxygen saturation correlated inversely with morning plasma viscosity in untreated patients with OSA. The cause of the increased viscosity is likely related, at least in part, to raised hematocrit and fibrinogen levels, which can alter blood viscosity independent of cardiovascular risk factors such as hypertension (19,25).

In a study examining the effect of CPAP therapy on various blood rheology parameters (20), plasma viscosity and fibrinogen levels remained elevated in patients with OSA even after six months of CPAP therapy, although compliance was not reported. This finding is controversial because more recently Tazbirek et al (23) found that blood viscosity fell rapidly after initiation of effective CPAP treatment (blood viscosity in untreated patients with OSA was 18.6% higher than in controls, and decreased by 10.5% after only five nights of CPAP treatment). Similarly, the same investigators demonstrated an increase in plasma viscosity among patients with OSA (7.2% versus controls), which decreased by 4.1% after five nights of therapy (23).

Limitations to the studies examining blood viscosity include small sample sizes and poorly matched controls. Nevertheless, the findings warrant further investigation because they suggest that OSA may be an independent contributor to hyperviscosity, and that the effect is reversible with CPAP treatment.

Clotting factors (Table 3)

Factors XIIa and VIIa, and thrombin: The clotting factors XIIa (FXIIa) and VIIa (FVIIa), and thrombin are necessary components of the clotting cascade. Increased levels of FXIIa, FVIIa and thrombin-antithrombin (TAT) have been found in patients with OSA (27). TAT is formed when thrombin is bound by antithrombin III, and is a marker of thrombin turnover, suggesting increased coagulation (28). TAT levels, specifically, have been found to increase significantly when induced by hypoxic conditions (29), and FVIIa levels have been shown to decrease by as much as 30% after long-term CPAP therapy (30). Conversely, Robinson et al (27) found that despite increased levels of these clotting factors in patients with OSA, one month of CPAP therapy (mean [± SD] 5±1.9 h/night) had no effect on post-treatment levels (27). This may be because the decrease in clotting factors is indirectly caused by a decrease in hypertension and sympathetic activation and, thus, requires longer therapy to elicit a significant change (31). Because both FXIIa and FVIIa have been associated with increased mortality from cardiovascular events (30,32,33), the observed increase in these clotting factors in association with OSA is another potential mechanism by which OSA may predispose individuals to an increased risk of cardiovascular events. However, the role of CPAP in negating these effects remains unclear.

Fibrinogen (Tables 4 and 5)

Fibrinogen is an acute phase protein, which increases during infection or inflammation, and is an independent risk factor for cardiovascular disease (34-36). Fibrinogen influences platelet aggregation and hemorheology and, when converted to fibrin, has the ability to form fibrin

TABLE 2
Blood viscosity

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Dikmenoglu et al (24), 2006	Case-control study	11 patients with OSA (AHI >30), 11 healthy controls	AHI ≥5/h	No	Patients with OSA have higher plasma viscosity than controls (morning: 1.74±0.3 mPa·s versus 1.36±0.2 mPa·s [P<0.002]; evening: 1.55±0.2 mPa·s versus 1.27±0.1 mPa·s [P<0.002]) Negative correlation between mean nocturnal SaO_2 and plasma viscosity r=−0.64)
Nobili et al (19), 2000	Case-control study	12 patients with OSA, 8 healthy controls	RDI >5/h	No	Increase in morning whole blood viscosity in patients with OSA (P<0.001) (no mean values reported)
Reinhart et al (20), 2002	Case-control study	13 patients with OSA, 8 age-matched controls	Not specified	Yes	OSA patients on chronic CPAP had a higher plasma viscosity than controls (1.37±0.11 mPa·s versus 1.19±0.11 mPa·s [P<0.05]). One night without CPAP had no effect on PV (ie, P not significant). No difference in WBV between patients with OSA (with/without CPAP) and controls (ie, P not significant)
Steiner et al (25), 2005	Case-control study	63 patients with OSA, 47 controls	AHI >10/h	No	Higher PV in patients with OSA (1.36±0.09 mPa·s) versus controls (1.31±0.08 mPa·s) (P=0.05)
Tazbirek et al (23), 2009	Case-control study	31 male patients with OSA, 19 matched controls	AHI ≥15/h or AHI ≥5/h + OSA symptoms	Yes	WBV 18.6% higher in patients with untreated OSA (5.43±0.95 mPa·s) versus controls (4.58±0.25 mPa·s) (P<0.001). PV 7.2% higher in in patients with untreated OSA (1.48±0.10 mPa·s) versus controls (1.38±0.08 mPa·s) (P<0.001). WBV and PV decreased significantly after 5 days of CPAP (WBV: 4.86±0.64 mPa·s; plasma viscosity: 1.42±0.11 mPa·s [P<0.05])

Data presented as mean ± SD. AHI Apnea/hypopnea index; CPAP Continuous positive airway pressure; OSA Obstructive sleep apnea; PV Plasma viscosity; RDI Respiratory disturbance index; ref Reference; SaO_2 Oxygen saturation; WBV Whole blood viscosity

clots. Thus, fibrinogen is a crucial mediator of coagulation. Several studies have attempted to determine the relationship between fibrinogen and OSA, with inconsistent results. Several authors have found that fibrinogen (18,19,25,26,37,38) and D-dimer levels (29,39) are raised in patients with OSA. Conversely, randomized controlled trials found that fibrinogen levels in patients with OSA were within normal limits (27,40). In a study investigating D-dimer (29), a by-product of fibrin degradation (thus, a proxy measure for fibrin), D-dimer levels increased significantly when patients were exposed to hypoxic conditions. This suggests that the patients were in a hypercoagulable state that was mediated, at least partially, by fibrin. However, a more recent study found baseline D-dimer levels to be lower in patients with OSA versus controls (41). Researchers suggested that because D-dimer is a by-product of fibrin degradation, a decreased level indicates impaired fibrinolysis. Thus, it is unclear what D-dimer levels truly represent in patients with OSA (ie, impaired fibrinolysis or increased fibrin formation). Further investigation is required to clarify this relationship.

Wessendorf et al (38) studied 113 patients undergoing rehabilitation after suffering an ischemic stroke. After overnight polysomnography, it was discovered that 42 had mild OSA and 27 had moderate to severe OSA. Furthermore, the level of fibrinogen in these stroke survivors was positively correlated with the number and duration of apneic events (38). This finding suggests that raised fibrinogen levels may be a pathophysiological link between OSA and stroke. Currently, the evidence describing the effect of CPAP therapy on fibrinogen levels is inconsistent. While some studies have found that fibrinogen levels decrease with CPAP therapy (18,22), others have found no change after five nights, four weeks or six months of treatment (20,23,27,42). The reason for this inconsistency among studies may relate to small sample sizes, varying degrees of sleep apnea severity and associated hypoxemia (hypoxemia is known to increase fibrinogen levels), inconsistent adherance to treatment between studies, variable comorbidities and other methodological issues (43). Overall, however, despite some inconsistency among studies, the majority have demonstrated an increase in fibrinogen levels in patients with OSA.

Impaired fibrinolysis

Impaired fibrinolysis may lead to a hypercoagulable state (44). Plasminogen activator inhibitor-1 (PAI-1) plays an important role in the regulation of fibrinolytic activity because it inhibits the enzyme tissue plasminogen activator, which is vital to the dissolution of blood clots (45). Excess PAI-1 has been shown to increase the risk of myocardial infarction (46-49). Although several studies have found overall levels of PAI-1 to be increased in patients with OSA, their results are relatively inconsistent (37,41,45,50-53). von Kanel et al (50-52) repeatedly found a positive correlation between patients' apnea hypopnea index (AHI) and PAI-1 levels; however, Zamarron et al (45), found a negative correlation, despite an overall increase in PAI-1 in patients with OSA versus controls. Two weeks of CPAP therapy was shown to decrease PAI-1 (52). Overall, the majority of studies have found an increase in PAI-1 in patients with OSA. However, because PAI-1 is only a surrogate measure of fibrinolytic activity, the effects on fibrinolysis and overall coagulability can only be inferred.

C-reactive protein

C-reactive protein (CRP) is an acute phase protein and a marker of inflammation. CRP levels have been reported to be elevated in patients with OSA (54,55). However, the nature of the relationship between OSA and CRP is uncertain because obesity, a common associated condition in patients with OSA, is also reported to be associated with increased CRP levels (54,55). Recently, however, OSA has been linked to increased CRP levels independent of visceral obesity (56), and CRP levels have also been reported to increase with increasing severity of OSA (57). Lui et al (56) reported that CRP was significantly associated with both AHI (P<0.001) and duration of oxygen saturation <90% (P=0.002), after adjusting for weight and body mass index (56). Furthermore, treatment of OSA over a six-month period with CPAP was associated with a significant reduction in CRP levels (58,59).

In a novel study (60), researchers showed that CRP increased PAI-1 levels. Previously, there was no evidence suggesting that CRP contributed to clot formation through this mechanism. To date, there has only been one study that examined the relationship among CRP, PAI-1 and OSA (61). CRP and PAI-1 were found to be raised in patients with OSA and this corresponded with a decrease in tissue plasminogen activator activity, suggesting that CRP, which is generally considered to be an important marker for cardiovascular disease, may also be a marker for increased risk of thrombotic events (61).

TABLE 3
Clotting factors

Factor	Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Thrombin	Robinson et al (27), 2004	Randomized controlled trial	220 patients with OSA: 112 tx/w subtherapeutic CPAP; 108 tx/w CPAP; 46 had TAT measured	AHI >10/h and >4% drop in SaO_2	Yes	TAT levels higher in patients with OSA at baseline than normal control values (Before CPAP: 12.3±25.1 µg/L versus controls: 2.6±1.4 µg/L [P=0.007]). One month of CPAP had no effect on TAT levels (ie, P not significant)
	von Kanel et al (29), 2005	Uncontrolled intervention study	32 patients with OSA given hypoxic challenge and observed???	AHI >15/h	No	Hypoxic challenge increased TAT levels (P<0.001) (no mean values provided)
FVII	Chin et al (30), 1998	Nonrandomized, controlled trial	15 males with OSA, 8 males with OSA served as controls	AHI >20/h	Yes	*Six months of CPAP decreased FVII levels (141±11.7% versus 110.7±6.2% [P<0.01]). No correlation between FVII and AHI or lowest SaO_2
	Robinson et al (27), 2004	Randomized controlled trial	220 patients with OSA: 112 tx/w subtherapeutic CPAP; 108 tx/w CPAP; 44 had FVIIa measured; 46 had FVII measured	AHI >10/h and >4% drop in SaO_2	Yes	FVIIa levels higher than normal control values (before CPAP: 93.7±50.7 mU/mL versus controls: 32.0±14.0 mU/mL [P<0.001]). FVII levels within laboratory reference ranges. One month CPAP had no effect on either FVII or FVIIa levels (ie, P not significant)
FXII	Robinson et al (27), 2004	Randomized controlled trial	220 patients with OSA: 112 tx/w subtherapeutic CPAP;108 tx/w CPAP; 46 had FXII/a measured	AHI >10/h and >4% drop in SaO_2	Yes	FXIIa higher than normal control values (before CPAP: 2.1±1.0 ng/mL versus controls: 1.7±0.3 ng/mL [P<0.001]) FXII baseline levels within laboratory reference ranges One month of CPAP had no effect on FXIIa levels
Fibrinogen	Chin et al (18), 1996	Uncontrolled intervention study	11 patients with OSA	AHI >20/h	Yes	*One night CPAP decreased fibrinogen levels from 8.76±0.47 µmol/L to 8.11±0.32 µmol/L (P<0.02)
	Comondore et al (42), 2009	Randomized crossover trial	13 patients with OSA	AHI ≥15/h	Yes	No significant change in fibrinogen after 4 weeks CPAP (ie, P not significant)
	Nobili et al (19), 2000	Case-control study	12 patients with OSA, 8 healthy controls	RDI >5/h	No	Increase in fibrinogen level from evening to morning in patients with OSA (evening: 10.27±3.52 µmol/L; morning: 10.93±3.77 µmol/L [P<0.007])
	Saletu et al (40), 2006	Case-control study	27 patients with mild OSA, 25 with moderate OSA, 51 with severe OSA, 44 controls	AHI ≥5/h	No	No association between fibrinogen and OSA (ie, P not significant) – could not conclude OSA independently associated with raised fibrinogen
	Steiner et al (25), 2005	Case-control study	63 patients with OSA, 47 controls	AHI >10/h	No	Fibrinogen correlated with nocturnal minimum SaO_2 (r= –0.275) and AHI (r=0.297). OSA associated with higher fibrinogen levels (OSA:10.38±2.44 µmol/L; controls: 9.32±1.82 µmol/L [P=0.015])
	Reinhart et al (20), 2002	Case-control study	13 patients with OSA, 8 age-matched controls	Not specified	Yes	OSA patients on chronic CPAP had higher fibrinogen levels (261±49 mg/dL versus 211±29 mg/dL [P<0.05]). One night without CPAP did not affect fibrinogen levels
	Robinson et al (27), 2004	Randomized controlled trial	220 patients with OSA: 112 tx/w subtherapeutic CPAP; 108 tx/w CPAP; 44 had fibrinogen measured	AHI >10/h and >4% drop in SaO_2	Yes	Fibrinogen baseline levels normal and did not change with either therapeutic or subtherapeutic CPAP (ie, P not significant)
	Wessendorf et al (38), 2000	Case-control study	Participants recruited from group undergoing neurological rehabilitation after ischemic stroke: no OSA (n=44); mild OSA (n=42); moderate-severe OSA (n=27)	RDI ≥5/h	No	Fibrinogen positively correlated with AHI (r=0.27) Fibrinogen negatively correlated with average minimal O_2 saturation (r=−0.41). Difference in fibrinogen levels between patients with OSA and no OSA (10.94 µmol/L [95% CI 9.67 µmol/L to 12.20 µmol/L] versus 9.35 µmol/L [95% CI 8.47 µmol/L to 10.20 µmol/L]; P=0.031)
	Zhang et al (22), 2003	Nonrandomized, nonequivalency controlled trial	41 patients with OSA, 32 healthy controls	AHI ≥5/h	Yes	Patients had significantly lower fibrinogen levels, after 30 days CPAP, which was comparable with controls (before: 8.70±0.0038 µmol/L; after: 8.14±0.004 µmol/L; controls: 8.08±0.0.005 µmol/L [P<0.05])

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hypopnea index; CPAP Continuous positive airway pressure; FVII Factor VII; OSA Obstructive sleep apnea; PAI-1 Plasminogen activator inhibitor type 1; ref Reference; SaO_2 Arterial oxygen saturation; TAT Thrombin antithrombin; tx/w Treated with

Hence, there is reasonably strong evidence to suggest that OSA is associated with increased CRP levels, and limited evidence that elevated CRP levels may induce a state of increased coagulability.

Tissue factor (Table 6)

Tissue factor (TF) is a protein that initiates the extrinsic coagulation pathway and the formation of a fibrin clot (62). TF levels are

TABLE 4
Fibrinolysis

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Ishikawa et al (53), 2008	Uncontrolled comparison study	121 patients with suspected OSA	AHI >15/h	No	PAI-1 increased in patients with OSA that do not experience nocturnal BP dips compared with controls (OSA nondippers: 41.5±18.1 ng/mL versus control nondippers 26.7±12.2 ng/mL [P<0.05])
Rangemark et al (37), 1995	Case-control study	13 patients with OSA, 10 age/sex-matched controls	Not reported	No	PAI-1 levels increased in patients versus controls both at rest (OSA: 18.4±3.62 IU/mL, controls: 8.2±1.66 IU/mL [P<0.029]). No difference in tPA levels at rest and during exercise in patients versus controls (ie, P not significant)
von Kanel et al (52), 2006	Randomized controlled study	44 patients with OSA: 18 given 2 weeks CPAP; 16 given 3 L/min suppl O_2; 10 given placebo CPAP	AHI >15/h	Yes	Pre-tx association between PAI-1 and AHI (P=0.001) and SpO_2 (P=0.035). *2 weeks CPAP decreased PAI-1 (pre: 91.0±44.3 ng/mL; post: 44.6±12.4 ng/mL [P=0.039]). Suppl O_2 and placebo CPAP had no effect on PAI-1 (ie, P not significant)
von Kanel et al (51), 2007	Cross-sectional	135 patients; no Hx sleep disorders	AHI >15/h	No	PAI-1 associated with higher AHI (P=0.034) and time spent at mean O_2 saturation <90% (P=0.020)
von Kanel et al (50), 2007	Case-control study	180 apneics and nonapneics, (20% metabolic syndrome); study group A (n=125) (BP <180/110 mmHg); study group B (n=55) (AHI >15/h)	AHI ≥5/h	No	In study groups A and B, those with metabolic syndrome had higher PAI-1 levels than those without (A: 121.3±33.7 ng/mL versus 33.9±6.6 ng/mL [P<0.001]) (B: 69.0±26.8 versus 68.4±10.6 ng/mL [P=0.013]). PAI-1 correlated positively with AHI (A: r=0.37) (B: r=0.41)
von Kanel et al (41), 2010	Case-control study	38 untreated patients with OSA, 22 non-OSA controls	AHI ≥10/h	No	*PAI-1 increased in OSA versus non-OSA (3.70±0.12 ng/mL versus 3.22±0.18 ng/mL [P<0.05]) (values were logarithmically transformed)
Zamarron et al (45), 2008	Case-control study	96 male patients: 32 patients with OSA; 32 patients with OSA and HTN; 32 unmatched controls	AHI >10/h	No	Patients with OSA had higher levels of PAI-1 than controls (mean 57.0 ng/mL, range 29.0 ng/mL to 122.3 ng/mL [P<0.001]). Patients with OSA and HTN had higher levels of PAI-1 than OSA-only group (mean 105.0 ng/mL, range 54.9 ng/mL to 202.7 ng/mL [P<0.001]). PAI-1 is negatively correlated with AHI (P<0.001)

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hypopnea index; BP Blood pressure; CPAP Continuous positive airway pressure; HTN Hypertension; Hx History; OSA Obstructive sleep apnea; PAI-1 Plasminogen activator inhibitor type 1; ref Reference; SpO_2 Oxygen saturation; suppl Supplemental; tPA Tissue plasminogen activator; tx Treatment

TABLE 5
D-dimer

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Shitrit et al (39), 2005	Prospective group comparison	103 with suspected OSA	AHI >10/h and symptoms of OSA	No	Higher D-dimer (>250 ng/mL) levels correlated with lowest SaO_2% (High D-dimer: 72.1±16.4%; low D-dimer: 81.7±11.6% [P=0.008]) and a longer mean time with an SaO_2 <90% (High D-dimer: 84.1±86.2 min; low D-dimer: 38.5±70.8 min [P=0.032]). D-dimer not associated with sleep architecture or AHI (ie, P not significant)
von Kanel et al (29), 2005	Cross-sectional	32 patients with OSA	RDI >15/h	No	Hypoxic challenge increased D-dimer levels (P=0.037) Those with a FHx of HTN showed even greater response to hypoxia (P=0.035)
von Kanel et al (52), 2006	Randomized controlled trial	44 patients with OSA: 18 tx/w 2 weeks CPAP; 16 tx/w 3 L/min supplemental O_2; 10 tx/w placebo CPAP	AHI >15/h	Yes	No association between D-dimer and AHI or mean nighttime SpO_2 (P not significant). CPAP, supplemental O_2, placebo had no effects D-dimer (ie, P not significant)
von Kanel et al (51), 2007	Cross-sectional	135 patients; no Hx of sleep disorders	AHI >15/h	No	D-dimer not associated with sleep variables (ie, P not significant)
von Kanel et al (41), 2010	Case-control study	38 untreated patients with OSA, 22 non-OSA controls	AHI ≥10/h	No	*Baseline D-dimer levels lower in OSA versus non-OSA patients (5.46±0.09 ng/mL versus 5.93±0.13 ng/mL [P<0.01]) (values were logarithmically transformed)

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hyponea index; CPAP Continuous positive airway pressure; FHx Family history; HTN Hypertension; Hx History; OSA Obstructive sleep apnea; RDI Respiratory disturbance index; ref Reference; SaO_2 Arterial oxygen saturation; SpO_2 Oxygen saturation; tx/w Treated with

increased in patients with OSA (63,64). However, results from several studies suggest that the increase in TF is not correlated with patients' AHI or OSA severity (51,52,63), and studies investigating the effect of CPAP therapy (52,63) have yielded inconsistent results. Following these reports, it was determined that TF is correlated with time awake after sleep onset and general sleep inefficiency rather than apneic events (51). This is contrary to the previous hypothesis that TF is released as a result of the hypoxic conditions experienced during sleep apneas (63). Currently, the relationship between TF and OSA is unclear. Hypoxia has been shown to induce TF production via activation of transcription factor early growth factor-1 (65). However, it is unclear why the hypoxic conditions experienced by individuals with OSA are not correlated with TF despite an overall increase in TF in this patient population. Further investigation is

TABLE 6
Tissue factor (TF)

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
El Solh et al (63), 2008	Nonrandomized nonequivalency controlled trial	35 with OSA, 12 healthy controls	AHI > 5/h	Yes	Patients with OSA have higher levels of TF (OSA: 66.78±41.59 pg/mL; controls: 42.83±14.18 pg/mL [P<0.001]). No correlation between TF and AHI or AI (P not significant). Decrease in TF after 8 weeks CPAP (66.74±41.59 pg/mL to 62.34±38.24 pg/mL [P=0.01])
Hayashi et al (64), 2006	Case-control study	60 males with OSA, 30 male controls	AHI ≥10/h	No	*TF levels higher in patients with OSA (Controls: 49.7±2.3 pg/mL; OSA: 87.7±2.8 pg/mL [P<0.01]). TF increased with OSA severity (controls: 49.7±2.3 pg/mL, mild: 72.0±1.3 pg/mL; moderate: 83.9±3.2 pg/mL; severe: 103.7±5.6 pg/mL [P<0.01]).
von Kanel et al (52), 2006	Randomized controlled trial	44 patients with OSA: 18 tx/w 2 weeks CPAP 16 tx/w 3 L/min suppl O_2 10 tx/w placebo CPAP	AHI >15/h	Yes	No association between TF and AHI or mean nighttime SpO_2 (ie, P not significant) CPAP, supplemental O_2, placebo had no effects on TF (ie, P not significant)
von Kanel et al (51), 2007	Cross-sectional study	135 patients; no Hx sleep disorders	AHI >15/h	No	Total time awake after sleep onset associated with TF levels (P=0.023)

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hypopnea index; AI Apnea index; CPAP Continuous positive airway pressure; OSA Obstructive sleep apnea; ref Reference; SpO_2 Oxygen saturation; ref Reference; suppl Supplemental; tx/w Treated with

TABLE 7
von Willebrand factor (VWF)

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
El Solh et al (63), 2008	Non-randomized, nonequivalency controlled trial	35 with OSA, 12 healthy controls	AHI >5/h	No	*Patients with OSA have higher levels of VWF (OSA: 189.70±69.24 IU/dL; Controls: 124.48±31.43 IU/dL) No association between VWF and AHI or AI (ie, P not significant). Decrease after 8 weeks CPAP therapy (189.7±75.5 IU/dL to 178.03 ± 61.39 IU/dL [P=0.07])
Robinson et al (27), 2004	Randomized controlled trial	220 OSA patients: 112 tx/w subtherapeutic CPAP 108 tx/w CPAP 90 had VWF measured	AHI >10/h and > 4% drop in SaO_2	Yes	VWF within the normal laboratory range (ie, P not significant). One month CPAP had no effect on VWF levels (ie, P not significant)
von Kanel et al (52), 2006	Randomized controlled trial	44 patients with OSA: 18 tx/w 2 weeks CPAP; 16 tx/w 3L/min supplemental O_2; 10 tx/w placebo CPAP	AHI >15/h	Yes	No association between VWF and AHI or mean nighttime SpO_2 (ie, P not significant) Two weeks of CPAP, supplemental O_2 or placebo had no effects on VWF (ie, P not significant)
von Kanel et al (51), 2007	Cross-sectional study	135 patients; no Hx of sleep disorders	AHI >15/h	No	Number of nocturnal arousals associated with VWF (P=0.011)

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hypopnea index; AI Apnea index; CPAP Continuous positive airway pressure; OSA Obstructive sleep apnea; ref Reference; SaO_2 Arterial oxygen saturation; SpO_2 Oxygen saturation; tx/w Treated with

required to clarify this interaction, but currently available data do not support TF as a pathophysiological link between OSA and cardiovascular events.

von Willebrand factor (Table 7)

von Willebrand Factor (VWF) is a circulating, procoagulant molecule that mediates platelet adhesion to injured endothelial cells and prevents factor VIII degradation (66). At this time, there is conflicting evidence regarding the relationship between OSA and VWF – some reports describe no significant difference in VWF levels between controls and patients (27,52), while others have found an increase in VWF in patients with OSA (63). Several reports have demonstrated that VWF levels do not change with CPAP treatment (27,52,63). Thus, similar to TF, VWF may be a marker of sleep fragmentation rather than OSA specifically and, at this time, cannot be characterized as a causal link between OSA and cardiovascular events (51,52).

Platelet activity (Table 8)

Blood platelets are an important component in the maintenance of hemostasis; however, they also contribute to the development of thrombotic clots, which lead to coronary and cerebral ischemia (67). While some authors found no association between platelet activation and OSA (20,37), many others have found platelet activity to be increased in patients with OSA (22,68-73). Platelet aggregation was best correlated with AHI (70), and significantly increased in moderate-to-severe OSA versus non-to-mild OSA (74). The severity of OSA (as measured by the 3% oxygen desaturation index) influenced platelet aggregability to a greater degree than total hypoxic time (72). A study by Hui et al (70) found that platelet aggregation in patients with OSA decreased significantly after both one-night and three-month CPAP therapy, while control subjects experienced no change. Others have found one month of CPAP therapy to be sufficient to produce an effect (22,75). Conversely, a study by Oga et al (72) found 30 days to be inadequate, and only after 90 days of CPAP therapy did they see a statistically significant reduction in platelet aggregability. Overall, the available data suggest a decrease in platelet activation after CPAP treatment in patients with OSA, although the duration of therapy required remains unclear.

Silent brain infarction

Magnetic resonance imaging has been used to determine the prevalence of silent brain infarction (SBI) in patients with OSA. Twenty-

TABLE 8
Platelet activity

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Akinnusi et al (68), 2009	Nonrandomized, nonequivalency controlled trial	12 patients with OSA, 12 healthy controls	AHI ≥5/h	Yes	PMAs and sCD40 increased in patients versus controls (PMA: 41.3±23.7% versus 6.7±4.9% [P=0.001]), (sCD40: 7.6±4.3% versus 1.7±1.1% [P=0.004]). In patients with OSA, PMAs decreased by 42% after 8 weeks of CPAP (41.3±23.7% to 23.9±20.1% [P=0.002]). In patients with OSA, sCD40L after 8 weeks CPAP decreased by 47% (7.6±4.3 ng/mL to 4.0±2.9 ng/mL [P=0.003])
Bokinsky et al (69), 1995	Nonrandomized, nonequivalency controlled trial	6 patients with OSA, 4 healthy controls	Not specified	Yes	Platelet aggregability increased in patients with OSA *Increase in platelet activation after one night both with and without CPAP (no CPAP: 16.6±3.5% versus 36.9±7.5%; CPAP: 11.9±3% versus 39.5±9.1% [P=0.04])
Eisensehr et al (74), 1998	Cross-sectional study	76 referred patients: AHI <5 (n=50) AHI >5 ,<50 (mild-mod) (n=19) AHI >50 (severe) (n=7)	AHI >5/h	No	Increased platelet activity correlated positively with AHI (R=0.296, P<0.009) and time spent in apnea or hypopnea (R=0.245, P<0.033) Increased platelet activation in patients with severe OSA versus controls (7.70±2.4% versus 3.19±2.35% [P<0.015])
Geiser et al (73), 2002	Case-control study	12 patients with OSA 6 healthy controls	AHI ≥10/h	No	*Increased P-sel in OSA versus controls (2.0±0.5% versus 1.1±0.3% [P<0.05])
Hui et al (70), 2004	Case-control study	42 patients with OSA, 23 unmatched controls	AHI ≥10/h	Yes	Decrease in index of platelet activation (IPA+) in patients treated with CPAP for one night and three months (Baseline: 15.1±2.2 U; one night: 12.2±5.2 U [P<0.001]; 3 months: 9.8±4.3 U [P=0.005])
Oga et al (72), 2009	Nonrandomized, nonequivalency controlled trial	58 patients with mod-severe OSA (35 lost to follow-up), 66 nonmild OSA	AHI >5/h	Yes	*Platelet aggregation increased in non-mild OSA versus moderate-severe OSA as represented by the platelet aggregation threshold index (PATI) (nonmild OSA: 1.04±0.07 µM versus severe OSA: 0.78±0.09 µM [P=0.029]) (lower PATI indicates enhanced aggregability) *On CPAP therapy, platelet aggregation increased from day 0 to 30 (0.91±0.14 µM to 0.62±0.16 µM [P= 0.035]) and decreased from day 30 to 90 (0.97±0.15 µM [P=0.011] [values logarithmically transformed])
Rangemark et al (37), 1995	Case-control study	13 patients with OSA, 10 age/sex-matched controls	Not reported	No	No difference (ie, P not significant) between B-thromboglobulin, platelet factor-4, or adrenaline/ADP-induced platelet activation between controls and patients (ie, P not significant)
Reinhart et al (20), 2002	Case-control study	13 patients with OSA, 8 age-matched controls	Not specified	Yes	No difference (ie, P not significant) in platelet activity between patients with OSA and controls
Sanner et al (71), 2000	Nonrandomized, nonequivalency controlled trial	17 males with OSA, 15 controls	AHI ≥10/h	Yes	*Platelet aggregability lowered by 6 months of CPAP therapy (24:00 h: 64.0±6.5% versus 55.3±6.7% [P<0.05]; 06:00 h: 64.1±6.5 versus 45.8±7.6% [P=0.01])
Shimizu et al (75), 2002	Nonrandomized, nonequivalency controlled trial	94 patients with OSA, 31 age-matched controls	AHI >20/h and time <90% SaO_2 >5%	Yes	PAC1 and P-sel increased in OSA versus controls (PAC1: 52.6±22.9% versus 16.7±8.6% and P-sel: 6.8±7.1% versus 0.7±0.5% [P<0.001]) One month CPAP lowered PAC1 and P-sel (Post-PAC1: 44.2±22.4% [P<0.05]; post-P-sel: 5.3±5.5% [P<0.05])
Zhang et al (22), 2009	Nonrandomized, nonequivalency controlled trial	41 patients with OSA, 32 healthy controls	AHI ≥5/h	Yes	Patients had significantly lowered platelet aggregation, after 30 days CPAP, which was comparable with control (Before: 82.3±8.7%; after: 68.4±7.8%; controls: 67.9±7.3% [P<0.01])

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hyponea index; CPAP Continuous positive airway pressure; mild-mod Mild to moderate; mod-severe Moderate to severe; OSA Obstructive sleep apnea; PAC1 Procaspase activating compound monoclonal antibody specific for fibrinogen; PMA Platelet-monocyte aggregates; P-sel P-selectin; ref Reference; SaO_2 Arterial oxygen saturation; sCD40 Soluble CD40; sCD40L sCD40 ligand

five per cent of individuals with moderate-to-severe OSA had magnetic resonance imaging evidence of SBI compared with 7.7% in patients with mild OSA and 6.7% in controls (4). Patients and controls were well matched, and all study participants were free from the major confounding factors (eg, hypertension and smoking). In the moderate-to-severe group, levels of soluble CD40 ligand (sCD40L) and soluble P-selectin – two important markers of platelet activation – were significantly raised in patients with OSA, and fell significantly after three months of CPAP therapy (4). A subsequent study (68) determined that the levels of sCD40L were correlated with the severity of hypoxia experienced and, again, improved with CPAP. These data suggest that OSA is associated with an increased prevalence of SBI, and this is associated with (and possibly mediated by) increased platelet activation (4).

Catecholamines (Table 9)

The exact cause of the increased platelet activation in patients with OSA remains unclear. One possible explanation is catecholamine-induced platelet activation (76). This is evidenced by the fact that patients with OSA exhibit increased sympathetic activation, due to repeated episodes of nocturnal oxyhemoglobin desaturation, which leads to the release of circulating catecholamines (77,78). Patients with OSA have increased levels of urinary noradrenaline, and this increase is associated with the degree of oxygen desaturation experienced during sleep (14,78). Furthermore, most studies have concluded that CPAP therapy decreases both urinary noradrenaline and adrenaline through increased clearance from the circulation (77), which supports the suggestion that OSA is an independent factor mediating catecholamine release (78,79). Only Comondore et al (42) found that

TABLE 9
Catecholamines

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Choi et al (14), 2006	Case-control study	202 with OSA, 62 controls	RDI >5/h	No	Patients with severe OSA have higher mean urinary noradrenaline levels than patients with non/mild OSA (Control: 0.45 ng/h; mild: 0.58 ng/h; severe: 1.04 ng/h [P<0.05])
Comondore, et al (42), 2008	Randomized crossover trial	13 patients with OSA	AHI ≥15/h	Yes	No significant change in urine noradrenaline levels after 4 weeks CPAP
Mills et al (77), 2006	Randomized controlled trial	50 patients with OSA: 17 tx/w CPAP 17 tx/w nocturnal oxygen 16 tx/w placebo CPAP	AHI >15/h	Yes	*14 days CPAP decreased plasma noradrenaline levels (278±29 pg/mL to 229±19 pg/mL [P<0.018]) and increased noradrenaline clearance (3.17±0.28 L/min to 3.89±0.24 L/min [P<0.01]) *CPAP decreased urinary noradrenaline excretion (day: 2.88±0.32 µg/h to 1.80±0.25 µg/h [P<0.001]; night: 1.35±0.22 µg/h to 1.02±0.13 µg/h [P<0.05]) *14 days nocturnal oxygen decreased daytime urine noradrenaline excretion (3.21±0.51 µg/h to 2.53±0.33 µg/h [P<0.01]) Noradrenaline release rate during CPAP treatment (P not significant) Effect of oxygen on plasma noradrenaline, and effect of placebo on plasma noradrenaline or excretion (P not significant)
Minemura et al (79), 1998	Uncontrolled intervention study	26 men with severe OSA	Not reported	Yes	One night CPAP decreased plasma noradrenaline (385±192 pg/mLto 270±146 pg/mL [P<0.02]) Nasal CPAP significantly reduced the daytime and nighttime urinary noradrenaline levels (Day: 156±112 µg/14h to 119±101 µg/14h; night: 143±91 µg/10h to 112±65 µg/10h)
Sukegawa et al (78), 2005	Uncontrolled intervention study	17 patients with OSA	AHI ≥5/h	Yes	One night CPAP decreased urine noradrenaline (81.5±47.8 nmol/mmoL to 47.0±26.8 nmol/mmoL creatinine [P=0.048]) Lowest SpO_2 most important factor for increased 24 h noradrenaline urine levels (P=0.048)

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hyponea index; CPAP Continuous positive airway pressure; OSA Obstuctive sleep apnea; RDI Respiratory distubance index; ref Reference; SpO_2 Oxygen saturation; tx/w Treated with

four months of CPAP therapy had no effect on urinary noradrenaline. In a study of noradrenaline-activated platelets, it was found that acetylsalicylic acid is not entirely effective as an antithrombotic agent (76). The combined effects of acetylsalicylic acid and CPAP therapy may be more effective, although this remains to be studied in this patient population.

Platelet activation and its effects on coagulation may, in part, explain why patients with OSA are at an increased risk for both fatal and nonfatal cardiovascular accidents, and why CPAP therapy effectively reduces the incidence of cardiovascular events (6).

Venous thromboembolism

Relatively few studies have examined the association between coagulation-related clinical events such as venous thromboembolism (VTE) and pulmonary embolism (PE). Existing studies are hampered by small sample size and a lack of adequate control groups (80-84). Recently, Epstein et al (82) reported that patients with PE exhibited a higher prevalence of snoring than those without PE (75% versus 50%; OR 2.91; P=0.001). They also reported that patients with PE had an increased risk of OSA as determined using the Berlin Questionnaire (65% versus 36%; OR 3.25 [P<0.001]) compared with those without PE. However, the latter study was limited by the failure to objectively confirm or refute OSA and snoring using overnight polysomnography. Furthermore, the study did not examine whether there was a difference in laboratory-based coagulability testing between those with high probability for OSA and PE versus those with low probability for OSA and PE (82). A recent retrospective analysis (83) revealed a prevalence of objectively documented OSA of 15.5% among patients with VTE – a higher prevalence than is reported for the general population – but did not adjust for confounding variables. Hence, although it is tantalizing to speculate that patients with OSA are at increased risk of VTE because of a hypercoagulable state, there is relatively little published evidence to support that contention. In particular, there is a need for adequately powered clinical studies involving well-matched control groups that address potential confounding variables to answer this question.

Whole blood coagulability (Table 10)

As demonstrated above, many studies have attempted to determine the relationship between OSA and coagulation. However, only two studies to date have examined whole blood coagulability and OSA – one animal model of OSA (85) and one study involving human subjects (86). Both studies used thromboelastography, which is a global assay of hemostatic function. Thromboelastography is able to measure various aspects of coagulation including time before initial fibrin formation, rapidity of clot formation and maximum clot strength. This provides a more complete picture of coagulation because all blood components are involved.

In anesthetized rats, Othman et al (85) found that a hypercoagulable state was induced by repeated inspiratory occlusions. Guardiola et al (86) determined that untreated patients with OSA were in a state of increased coagulability compared with CPAP-treated patients. However, unlike previous studies that reported significant reductions in plasma fibrinogen levels after only one night of CPAP therapy (37,69), and alluded to a potential decrease in overall coagulability, Guardiola et al (86) did not find a change in whole blood coagulability after a single night of CPAP therapy. This suggests that while hematological factors may change rapidly, chronic therapy may be required to realize any effects on overall hemostasis.

SUMMARY AND FUTURE DIRECTIONS

Table 11 summarizes the major findings from the present comprehensive literature review. The available data suggest that patients with OSA are in a procoagulant state, but the relationships between OSA and individual clotting factors are uncertain. Future research will require the use of randomized controlled trials with sufficient statistical power and careful attention to treatment efficacy and adherence, to determine the relationship between individual procoagulant factors and OSA. Given the high degree of cardiovascular morbidity and mortality associated with OSA, the hypercoagulable state induced by OSA clearly warrants further study. In particular, the potential for

TABLE 10
Whole blood coagulability

Author (ref), year	Design	Participants	OSA criteria	CPAP used?	Findings (statistically significant at P<0.05)
Guardiola et al (86), 2001	Nonrandomized, nonequivalency controlled trial	11 chronically CPAP treated OSA patients 22 CPAP-naive OSA patients (16 given one night CPAP)	AHI >5/h	Yes	*Patients on chronic CPAP have decreased morning and evening whole blood coagulability compared with CPAP-naive patients (chronic AM: 7.08±0.52 min versus naive AM: 4.31±0.34 min; chronic PM: 6.12±0.66 min versus naive PM: 3.33±0.31 min [P<0.05]) One night of CPAP did not alter whole blood coagulability (ie, P not significant)
Othman et al (85), 2010	Animal model	Anesthetized rats	N/A	No	3 h of repeated inspiratory occlusions resulted in more rapid onset of fibrin formation (12.95 min versus 6.17 min [P<0.031])

Data presented as mean ± SD unless indicated by an asterisk, in which case the data are presented as mean ± SEM. AHI Apnea/hyponea index; AM Morning; CPAP Continuous positive airwway pressure; OSA Obstructive sleep apnea; PM Evening; ref Reference

TABLE 11
Summary table describing the major findings from the literature review examining obstructive sleep apnea (OSA) and coagulability

Factors that increase coagulability	Associated with OSA?	Summary findings
Increased hematocrit	Yes	Results on the effect of CPAP inconsistent
Increased viscosity	Yes	Possibly reversible with CPAP
Increased factor XIIa and VIIa, and thrombin levels	Yes	Results on effect of CPAP inconsistent
Increased fibrinogen levels	Yes	Results on effect of CPAP inconsistent
Increased tissue factor levels	Yes	Not associated with AHI or OSA severity, although increased in patients with obstructive sleep apnea. Results on the effect of CPAP inconsistent
Increased von Willebrand factor levels	Unclear	May be related to sleep fragmentation rather than OSA specifically. No change with CPAP therapy
Increased platelet activity	Yes	Decreased with CPAP
Increased catecholamine levels	Yes	Decreased with CPAP
Increased PAI-1 levels	Yes	Decreased with CPAP
Increased whole blood coagulability	Yes	Decreased with CPAP

AHI Apnea/hypopnea index; CPAP Continuous positive airway pressure; PAI-1 Plasminogen activator inhibitor type 1

anticoagulant and antiplatelet medications to reduce mortality in patients with OSA merits exploration, particularly for patients who are unwilling or unable to achieve full control of OSA with currently available treatment options.

REFERENCES

1. Young T, Peppard PE, Gottlieb DJ, . Epidemiology of obstructive sleep apnea: A population health perspective. Am J Respir Crit Care Med 2002;165:1217-39.
2. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin sleep cohort. Sleep 2008;31:1071-8.
3. Wolk R, Kara T, Somers VK. Sleep-disordered breathing and cardiovascular disease. Circulation 2003;108:9-12.
4. Minoguchi K, Yokoe T, Tazaki T, et al. Silent brain infarction and platelet activation in obstructive sleep apnea. Am J Respir Crit Care Med 2007;175:612-7.
5. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med 2006;173:910-6.
6. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. Lancet 2005;365:1046-53.
7. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease. Cross-sectional results of the sleep heart health study. Am J Respir Crit Care Med 2001;163:19-25.
8. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353:2034.
9. Dziewas R, Humpert M, Hopmann B, et al. Increased prevalence of sleep apnea in patients with recurring ischemic stroke compared with first stroke victims. J Neurol 2005;252:1394-8.
10. Schulz R. The vascular micromilieu in obstructive sleep apnoea. Eur Respir J 2005;25:780-2.
11. Ryan S, Taylor CT, McNicholas WT, Ryan S, Taylor CT, McNicholas WT. Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 2005;112:2660-7.
12. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 1997;82:1313-6.
13. Zubieta-Calleja GR, Paulev PE, Zubieta-Calleja L, Zubieta-Castillo G. Altitude adaptation through hematocrit changes. J Physiol Pharmacol 2007;58(Suppl 5):811-8.
14. Choi JB, Loredo JS, Norman D, et al. Does obstructive sleep apnea increase hematocrit? Sleep Breath 2006;10:155-60.
15. Hoffstein V, Herridge M, Mateika S, Redline S, Strohl KP. Hematocrit levels in sleep apnea. Chest 1994;106:787-91.
16. Krieger J, Sforza E, Barthelmebs M, Imbs JL, Kurtz D. Overnight decrease in hematocrit after nasal CPAP treatment in patients with OSA. Chest 1990;97:729-30.
17. Krieger J, Sforza E, Delanoe C, Petiau C. Decrease in haematocrit with continuous positive airway pressure treatment in obstructive sleep apnoea patients. Eur Respir J 1992;5:228-33.
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, De Carli F, Ferrillo F, Nobili F. Morning increase of whole blood viscosity in obstructive sleep apnea syndrome. Clin Hemorheol Microcirc 2000;22:21.
20. 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.
21. Saarelainen S, Hasan J, Siitonen S, Seppala E. Effect of nasal CPAP treatment on plasma volume, aldosterone and 24-h blood pressure in obstructive sleep apnoea. J Sleep Res 1996;5:181-5.

22. Zhang XL, Yin KS, Wang H, Su M, Yang Y. Effect of continuous positive airway pressure treatment on elderly Chinese patients with obstructive sleep apnea in the prethrombotic state. Chin Med J (Engl) 2003;116:1426-8.
23. Tazbirek M, Slowinska L, Skoczynski S, Pierzchala W. Short-term continuous positive airway pressure therapy reverses the pathological influence of obstructive sleep apnea on blood rheology parameters. Clin Hemorheol Microcirc 2009;41:241-9.
24. 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.
25. Steiner S, Jax T, Evers S, Hennersdorf M, Schwalen A, Strauer BE. Altered blood rheology in obstructive sleep apnea as a mediator of cardiovascular risk. Cardiology 2005;104:92-6.
26. Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JC. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. N Engl J Med 1995;332:635-41.
27. 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.
28. Takano K, Yamaguchi T, Uchida K. Markers of a hypercoagulable state following acute ischemic stroke. Stroke 1992;23:194-8.
29. von Kanel R, Loredo JS, Powell FL, Adler KA, Dimsdale JE. Short-term isocapnic hypoxia and coagulation activation in patients with sleep apnea. Clin Hemorheol Microcirc 2005;33:369-77.
30. 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.
31. von Kanel R, Le DT, Nelesen RA, Mills PJ, Ancoli-Israel S, Dimsdale JE. The hypercoagulable state in sleep apnea is related to comorbid hypertension. J Hypertens 2001;19:1445-51.
32. Junker R, Heinrich J, Schulte H, van de Loo J, Assmann G. Coagulation factor VII and the risk of coronary heart disease in healthy men. Arterioscler Thromb Vasc Biol 1997;17:1539-44.
33. Heidi G, Dennis Winston TN, Ã˜yvind H, Edward V, Hans Eirik F. Activated factor 12 (FXIIa) predicts recurrent coronary events after an acute myocardial infarction. Am Heart J 2004;147:260-6.
34. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA 1987;258:1183-6.
35. Ernst E. The role of fibrinogen as a cardiovascular risk factor. Atherosclerosis 1993;100:1-12.
36. Fibrinogen Studies Collaboration. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: An individual participant meta-analysis. JAMA 2005;294:1799-809.
37. Rangemark C, Hedner JA, Carlson JT, Gleerup G, Winther K. Platelet function and fibrinolytic activity in hypertensive and normotensive sleep apnea patients. Sleep 1995;18:188-94.
38. Wessendorf TE, Thilmann AF, Wang Y, Schreiber A, Konietzko N, Teschler H. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. Am J Respir Crit Care Med 2000;162:2039.
39. Shitrit D, Peled N, Shitrit ABG, et al. An association between oxygen desaturation and D-dimer in patients with obstructive sleep apnea syndrome. Thromb Haemost 2005;94:544-7.
40. Saletu M, Nosiska D, Kapfhammer G, et al. Structural and serum surrogate markers of cerebrovascular disease in obstructive sleep apnea (OSA): Association of mild OSA with early atherosclerosis. J Neurol 2006;253:746-52.
41. von Kanel R, Natarajan L, Ancoli-Israel S, Mills PJ, Loredo JS, Dimsdale JE. Day/night rhythm of hemostatic factors in obstructive sleep apnea. Sleep 2010;33:371-7.
42. Comondore VR, Cheema R, Fox J, et al. The impact of CPAP on cardiovascular biomarkers in minimally symptomatic patients with obstructive sleep apnea: A pilot feasibility randomized crossover trial. Lung 2009;187:17-22.
43. von Kanel RDJE. Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease. Chest 2003;124:1956-67.
44. Saigo M, Hsue PY, Waters DD. Role of thrombotic and fibrinolytic factors in acute coronary syndromes. Prog Cardiovasc Dis 2004;46:524-38.
45. Zamarron 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.
46. Eren M, Painter CA, Atkinson JB, Declerck PJ, Vaughan DE. Age-dependent spontaneous coronary arterial thrombosis in transgenic mice that express a stable form of human plasminogen activator inhibitor-1. Circulation 2002;106:491-6.
47. Kohler HP, Grant PJ. Plasminogen-activator inhibitor type 1 and coronary artery disease. N Engl J Med 2000;342:1792-801.
48. Meade TW, Ruddock V, Stirling Y, Chakrabarti R, Miller GJ. Fibrinolytic activity, clotting factors, and long-term incidence of ischaemic heart disease in the Northwick Park Heart Study. Lancet 1993;342:1076-9.
49. Thogersen AM, Jansson J-H, Boman K, et al. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: Evidence for the fibrinolytic system as an independent primary risk factor. Circulation 1998;98:2241-7.
50. von Kanel R, Loredo JS, Ancoli-Israel S, et al. 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.
51. von Kanel R, Loredo JS, Ancoli-Israel S, Mills PJ, Natarajan L, Dimsdale JE. Association between polysomnographic measures of disrupted sleep and prothrombotic factors. Chest 2007;131:733-9.
52. von Kanel R, Loredo JS, Ancoli-Israel S, Dimsdale JE. Association between sleep apnea severity and blood coagulability: Treatment effects of nasal continuous positive airway pressure. Sleep Breath 2006;10:139-46.
53. Ishikawa J, Hoshide S, Eguchi K, et al. Increased low-grade inflammation and plasminogen-activator inhibitor-1 level in nondippers with sleep apnea syndrome. J Hypertens 2008;26:1181-7.
54. Chung S, Yoon IY, Shin YK, et al. Endothelial dysfunction and C-reactive protein in relation with the severity of obstructive sleep apnea syndrome. Sleep 2007;30:997-1001.
55. Kapsimalis F, Varouchakis G, Manousaki A, et al. Association of sleep apnea severity and obesity with insulin resistance, C-reactive protein, and leptin levels in male patients with obstructive sleep apnea. Lung 2008;186:209-17.
56. Lui MM, Lam JC, Mak HK, et al. C-reactive protein is associated with obstructive sleep apnea independent of visceral obesity. Chest 2009;135:950-6. (Erratum 2009;135:1406)
57. Bhushan B, Guleria R, Misra A, et al. Obstructive sleep apnoea correlates with C-reactive protein in obese Asian Indians. Nutr Metabol Cardiovasc Dis 2009;19:184-9.
58. Steiropoulos P, Tsara V, Nena E, et al. Effect of continuous positive airway pressure treatment on serum cardiovascular risk factors in patients with obstructive sleep apnea-hypopnea syndrome. Chest 2007;132:843-51.
59. Ishida K, Kato M, Kato Y, et al. Appropriate use of nasal continuous positive airway pressure decreases elevated C-reactive protein in patients with obstructive sleep apnea. Chest 2009;136:125-9.
60. Devaraj S, Xu DY, Jialal I. C-Reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: Implications for the metabolic syndrome and atherothrombosis. Circulation 2003;107:398-404.
61. Wang Y, Yang H, Dong M, Wang Y, Yang H, Dong M. [Study on the levels of C-reactive protein and fibrinolytic activity in patients with obstructive sleep apnea syndrome.] Lin Chuang Erh Pi Yen Hou Ko Tsa Chih. J Clin Otorhinolaryngol 2004;18:147-8.
62. Banner DW, D'Arcy A, Chene C, et al. The crystal structure of the complex of blood coagulation factor VIIa with soluble tissue factor. Nature 1996;380:41-6.
63. El Solh A, Akinnusi M, Berim I, Peter A, Paasch L, Szarpa K. Hemostatic implications of endothelial cell apoptosis in obstructive sleep apnea. Sleep Breath 2008;12:331-7.
64. Hayashi M, Fujimoto K, Urushibata K, et al. Hypoxia-sensitive molecules may modulate the development of atherosclerosis in sleep apnoea syndrome. Respirology 2006;11:24-31.
65. Yan S-F, Mackman N, Kisiel W, Stern DM, Pinsky DJ. Hypoxia/hypoxemia-induced activation of the procoagulant pathways and the pathogenesis of ischemia-associated thrombosis. Arterioscler Thromb Vasc Biol 1999;19:2029-35.
66. De Meyer SF, Deckmyn H, Vanhoorelbeke K, De Meyer SF, Deckmyn H, Vanhoorelbeke K. von Willebrand factor to the rescue. Blood 2009;113:5049-57.
67. Davi G, Patrono C. Platelet activation and atherothrombosis. N Engl J Med 2007;357:2482-94.

68. Akinnusi ME, Paasch LL, Szarpa KR, Wallace PK, El Solh AA. Impact of nasal continuous positive airway pressure therapy on markers of platelet activation in patients with obstructive sleep apnea. Respiration 2009;77:25-31.
69. 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.
70. Hui DS, Ko FW, Fok JP, et al. The effects of nasal continuous positive airway pressure on platelet activation in obstructive sleep apnea syndrome. Chest 2004;125:1768-75.
71. Sanner BM, Konermann M, Tepel M, Groetz J, Mummenhoff C, Zidek W. Platelet function in patients with obstructive sleep apnoea syndrome. Eur Respir J 2000;16:648-52.
72. Oga T, Chin K, Tabuchi A, et al. Effects of obstructive sleep apnea with intermittent hypoxia on platelet aggregability. J Atherosc Thromb 2009;16:862-9.
73. 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.
74. Eisensehr I, Ehrenberg BL, Noachtar S, et al. Platelet activation, epinephrine, and blood pressure in obstructive sleep apnea syndrome. Neurology 1998;51:188-95.
75. 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.
76. Larsson P, Wallen N, Hjemdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. Circulation 1994;89:1951-7.
77. Mills PJ, Kennedy BP, Loredo JS, Dimsdale JE, Ziegler MG. Effects of nasal continuous positive airway pressure and oxygen supplementation on norepinephrine kinetics and cardiovascular responses in obstructive sleep apnea. J Appl Physiol 2006;100:343-8.
78. Sukegawa M, Noda A, Sugiura T, et al. Assessment of continuous positive airway pressure treatment in obstructive sleep apnea syndrome using 24-hour urinary catecholamines. Clin Cardiol 2005;28:519-22.
79. Minemura H, Akashiba T, Yamamoto H, Akahoshi T, Kosaka N, Horie T. Acute effects of nasal continuous positive airway pressure on 24-hour blood pressure and catecholamines in patients with obstructive sleep apnea. Intern Med 1998;37:1009-13.
80. Ambrosetti M, Lucioni A, Ageno W, Conti S, Neri M. Is venous thromboembolism more frequent in patients with obstructive sleep apnea syndrome? J Thromb Haemost 2004;2:1858-60.
81. Arnulf I, Merino-Andreu M, Perrier A, et al. Obstructive sleep apnea and venous thromboembolism. JAMA 2002;287:2655-6.
82. Epstein MD, Segal LN, Ibrahim SM, et al. Snoring and the risk of obstructive sleep apnea in patients with pulmonary embolism. Sleep 2010;33:1069-74.
83. Bosanquet JP, Bade BC, Zia MF, et al. Patients with venous thromboembolism appear to have higher prevalence of obstructive sleep apnea than the general population. Clin Appl Thromb Hemost Dec 2010 (E-pub ahead of print).
84. Hasegawa R, Shiomi T, Sasanabe R, et al. Sleep apnea syndrome in patients with pulmonary thromboembolism. Psychiatry Clin Neurosci 2000;54:342-3.
85. Othman M, Gordon SP, Iscoe S. Repeated inspiratory occlusions in anesthetized rats acutely increase blood coagulability as assessed by thromboelastography. Respir Physiol Neurobiol 2010;171:61-6.
86. Guardiola JJ, Matheson PJ, Clavijo LC, Wilson MA, Fletcher EC. Hypercoagulability in patients with obstructive sleep apnea. Sleep Med 2001;2:517-23.