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Association between sleep apnea severity and blood coagulability: treatment effects of nasal continuous positive airway pressure

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Abstract A prothrombotic state may contribute to the elevated cardiovascular risk in patients with obstructive sleep apnea (OSA). We investigated the relationship between apnea severity and hemostasis factors and effect of continuous positive airway pressure (CPAP) treatment on hemostatic activity. We performed full overnight polysomnography in 44 OSA patients (mean age 47±10 years), yielding apnea–hypopnea index (AHI) and mean nighttime oxyhemoglobin saturation (SpO_2) as indices of apnea severity. For treatment, subjects were double-blind randomized to 2 weeks of either therapeutic CPAP (n=18), 3 l/min supplemental nocturnal oxygen (n=16) or placebo–CPAP (<1 cm H_2O) (n=10). Levels of von Willebrand factor antigen (VWF:Ag), soluble tissue factor (sTF), D-dimer, and plasminogen activator inhibitor (PAI)-1 antigen were measured in plasma pre- and posttreatment. Before treatment, PAI-1 was significantly correlated with AHI (r=0.47, p=0.001) and mean nighttime SpO_2 (r=−0.32, p=0.035), but these OSA measures were not significantly related with VWF:Ag, sTF, and D-dimer. AHI was a significant predictor of PAI-1 (R^2=0.219, standardized β=0.47, p=0.001), independent of mean nighttime SpO2, body mass index (BMI), and age. A weak time-by-treatment interaction for PAI-1 was observed (p=0.041), even after adjusting for age, BMI, pre-treatment AHI, and mean SpO_2 (p=0.046). Post hoc analyses suggested that only CPAP treatment was associated with a decrease in PAI-1 (p=0.039); there were no changes in VWF:Ag, sTF, and D-dimer associated with treatment with placebo–CPAP or with nocturnal oxygen. Apnea severity may be associated with impairment in the fibrinolytic capacity. To the extent that our sample size was limited, the observation that CPAP treatment led to a decrease in PAI-1 in OSA must be regarded as tentative.

Keywords Cardiovascular disease · Fibrinolysis · Hemostasis · Obstructive sleep apnea · Treatment

Introduction

Patients with obstructive sleep apnea (OSA) suffer from increased cardiovascular morbidity and mortality [1–7]. A prothrombotic state, resulting from either elevated procoagulant molecules or impaired fibrinolytic activity, has been prospectively associated with an increased risk of coronary artery disease (CAD) [8, 9]. Accordingly, a prothrombotic state could contribute to the increased prevalence of atherothrombotic diseases in apneics by promoting fibrin deposits within coronary arteries and thereby atherosclerosis progression [10–12]. Studies have shown that compared to non-apneic controls, apneics had higher plasma levels of the procoagulant molecule fibrinogen [13–15], activated clotting factor FVII ($FVII_a$), $FXII_a$, and thrombin/antithrombin III complexes [16]. Platelet

activity [17, 18] and fibrinolysis inhibiting plasminogen activator inhibitor (PAI)-1 [19] have also been reported as increased in apneics.

Previous studies suggest that continuous positive airway pressure (CPAP) might diminish exaggerated coagulant activity in apneics, but it is unknown whether CPAP also affects fibrinolysis. CPAP treatment has been shown to lead to a significant decrease in fibrinogen [20], factor VII clotting activity (FVII:C) [21], and platelet activity [18, 21, 22]. However, control subjects in these studies were untreated apneics. Therefore, it is not possible to reconcile the argument that changes in hemostatic function can be attributed to CPAP alone rather than reflecting a nonspecific placebo or time effect.

We studied plasma levels of von Willebrand factor antigen (VWF:Ag), soluble tissue factor (sTF), D-dimer, and PAI-1 antigen in 44 patients with OSA in relation to two measures of apnea severity, namely, the apnea–hypopnea index (AHI) and the mean nighttime oxyhemoglobin saturation (SpO_2). An increased plasma concentration in each of these hemostasis measures would indicate thrombogenicity. Soluble tissue factor forms a catalytic complex with $FVII_a$ and initiates coagulation by activating FIX and FX, ultimately resulting in thrombin formation; accordingly, sTF is found to be elevated in a number of disease states associated with increased activation of the coagulation system [23]. VWF exerts procoagulant function by mediating platelet adhesion to endothelial lesions and by protecting plasma FVIII from degradation [24]. The fibrin degradation product D-dimer is a widely used marker of a hypercoagulable state. D-dimer is typically increased in venous thromboembolic events reflecting activation of the entire coagulation and fibrinolysis cascades [25]. PAI-1 binds to and subsequently inactivates circulating tissue-type plasminogen activator (t-PA), whose job is lysis of a fibrin clot; high levels of PAI-1, thus, are compatible with a reduction in fibrinolytic activity [26].

We further studied whether these hemostasis molecules would be responsive to a 2-week treatment with traditional nasal CPAP, placebo–CPAP, or nocturnal supplemental oxygen. We chose one arm to receive supplemental oxygen because desaturation may be a major factor in the derangements in coagulation noted in OSA [11]. By using a supplemental oxygen arm, we attempted to isolate the two major components of sleep apnea and their effects on coagulation: (1) the mechanical aspect of the apnea itself with its associated swings in intrathoracic pressure, and (2) the resultant hypoxemia. Whether nocturnal supplemental oxygen affects hemostatic function in OSA is unknown but of clinical importance. Some OSA patients cannot tolerate CPAP and are not candidates for a surgical procedure. In these patients, supplemental oxygen therapy can be an alternative in an attempt to reverse transient desaturations during sleep and associated cardiovascular threat [27, 28], perhaps by mitigating hypercoagulability [11].

Our first hypothesis was that AHI and SpO_2 both would be positively associated with plasma levels of VWF:Ag, sTF, D-dimer, and PAI-1 antigen. Our second hypothesis was that, compared to placebo-CPAP, nocturnal oxygen and therapeutic CPAP would result in a decrease in plasma levels of hemostasis molecules from pre- to posttreatment.

Materials and methods

Study participants

The University of California San Diego (UCSD) Institutional Review Board approved the study protocol, and all participants provided written informed consent. In the study interval between 2000 and 2004, 413 subjects were screened and 337 were ineligible. Many patients who sought to be in the study did not meet eligibility

Table 1 Baseline characteristics of 44 sleep apnea patients as per treatment arm

	Therapeutic CPAP (*n*=18)	Nocturnal oxygen (*n*=16)	Placebo-CPAP (*n*=10)	*P*
Men/women	15/3	11/5	9/1	.372
Ethnicity (white, black, Hispanic, Asian, other)	10, 2, 3, 2, 1	12, 2, 0, 2, 0	6, 1, 1, 0, 2	.429
Age (years)	47.1±2.76	46.1±2.25	48.4±3.42	.868
Current smoker (yes/no)[a]	13/4	13/3	7/3	.803
Apnea–hypopnea index	66.6±6.87	61.0±8.82	59.1±9.99	.616
Mean nighttime SpO_2 (%)	92.7±1.00	92.6±1.28	93.4±0.93	.878
Body mass index (kg/m^2)	31.3±1.37	30.4±1.10	30.8±1.89	.874
Systolic blood pressure (mmHg)	135.1±3.71	130.6±3.10	128.9±5.33	.512
Diastolic blood pressure (mmHg)	79.3±2.09	77.9±2.22	80.0±3.24	.833
Hypertension (yes/no)	8/10	3/13	2/8	.197
Hematocrit (%)	42.3±0.76	42.3±0.88	42.9±0.91	.896

Values are means±SEM. Statistical analyses used Pearson chi-square test or univariate analysis of variance
CPAP Continuous positive airway pressure
[a]Smoking status was missing in one subject who received therapeutic CPAP

requirements in terms of factors such as age, weight, and medical comorbidity. Screening criteria included clinical suspicion of OSA as per loud snoring or excessive daytime sleepiness, age 30 to 65 years, and weight between 1.0 and 2.0 times ideal body weight as determined from Metropolitan Life tables [29]. Exclusion criteria included congestive heart failure, symptomatic obstructive pulmonary, coronary, and cerebrovascular disease, history of life-threatening arrhythmias, cardiomyopathy, history of narcolepsy, current alcohol or drug abuse, psychosis, previous surgery for treatment of OSA, or regular use of medications. Of the 76 eligible individuals, 66 agreed to participate in the present study. Due to factors such as freezer malfunction and blocked IV lines, we report data on 44 subjects who had a complete data set in terms of health characteristics, pretreatment sleep variables, and at least one of the four hemostasis measure pre- and posttreatment.

Table 1 shows the sample characteristics. Ethnicity was defined by subjects' self-identification. Because research suggests procoagulant changes even in the presence of relatively small smoking exposure [30], subjects who currently smoked ≥1 cigarette per day were termed smokers and all others were termed nonsmokers. Body mass index (BMI) was computed as the ratio of body weight in kilograms divided by the square of height in meters (kg/m^2). The average systolic and diastolic blood pressure was computed based on three, seated resting measurements. Blood to determine hematocrit was obtained after an overnight fast.

Experimental design

Participants were recruited from diverse sources including public advertisements and referrals from sleep clinics and local medical practitioners. Potentially eligible candidates underwent an unattended overnight home screening sleep study using the Stardust (Respironics, Marietta, GA) home sleep recording system to identify probable cases of OSA. Subjects with >15 apneas plus hypopneas per hour of sleep (AHI) and <15 periodic limb movements per hour of sleep were admitted for three nights to the UCSD General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology (GCRC LSC), with the first night's full polysomnography (PSG) confirming the diagnosis of sleep disordered breathing.

The study involved a parallel group comparison of 2 weeks' treatment with either therapeutic nasal CPAP (n=18), placebo-CPAP (n=10), or oxygen (n=16). Patients were randomized by random number allocation to one of three treatment groups in a double-blind fashion. In essence, investigators and coordinators, recruiters, and those who analyzed the data were blinded to the patients' treatment. Only the polysomnography technician, by necessity, was unblinded to the randomization. CPAP equipment for the three treatment arms was identical in appearance and consisted of a CPAP generator (Aria LX CPAP System, Respironics, Murrysville, PA), CPAP mask (Profile Light, Respironics, Murrysville, PA), and tubing, heated humidifier (Fisher and Pykel HC199, Aukland, New Zealand), and oxygen concentrator (Alliance, Healthdyne Technologies Model 505, Marietta, GA). The concentrator could be switched to produce room air. The supplemental gas (room air or oxygen) was introduced into the CPAP system at the level of the humidifier.

To maintain the blind, subjects randomized to therapeutic CPAP received active CPAP plus an oxygen concentrator providing room air. Subjects randomized to placebo–CPAP received subtherapeutic CPAP (<1 cm H_2O at the mask) plus an oxygen concentrator providing room air. Those assigned to nocturnal oxygen received placebo–CPAP plus an oxygen concentrator delivering oxygen. In this study, our goal was to use the minimal amount of oxygen (fixed oxygen flow rate of 3 l/min) in the supplemental oxygen arm previously shown to improve mean SpO_2 during sleep in patients with OSA [31].

A modified version of a previously described placebo–CPAP system was used [32]. In brief, the placebo-–CPAP consisted of a CPAP mask with ten 1/4-in. drill holes for adequate room air exchange with pressure set at a constant 3 cm H_2O. A pressure reducer was placed in the tubing between the CPAP unit and the modified mask. With this system, the pressure at the mask was 0.5 cm H_2O at end-expiration and 0 cm H_2O during inspiration, and the patients felt a gentle breeze at the nose.

All patients had the same standard PSG hook-up on all three nights. Titrations took place on the second night of admission. In the therapeutic CPAP group, conventional manual overnight CPAP titration was performed in increasing steps of 1–2 cm H_2O until unequivocal obstructive apneas or hypopneas were controlled in the second or third rapid eye movement sleep period, or when a pressure of 20 cm H_2O had been reached. All subjects randomized to CPAP had an effective titration as defined by an AHI<10. Subjects randomized to placebo–CPAP or supplemental oxygen underwent a mock titration. On the third night of admission, subjects slept with their assigned treatment. The next morning, they were instructed and discharged with their assigned home treatment. Research staff conducted frequent phone calls with patients to answer questions about the equipment and to encourage compliance with the therapy. All CPAP units had a hidden compliance clock allowing measurement of the nightly time the unit was switched on at pressure. After 2 weeks of home treatment, subjects were readmitted to the GCRC LSC for another full overnight PSG with their assigned treatment.

Sleep recordings

Sleep was recorded using the Grass Heritage (model PSG36-2, West Warwick, RI) sleep recording system using a standard montage previously described [33]. All records were scored according to Rechtshaffen and Kales criteria [34], and AHI and mean nighttime SpO_2 were computed. SpO_2 was monitored using a pulse oximeter (Biox 3740, Ohmeda, Louisville, CO) and analyzed by software from Profox (Escondido, CA). An apnea was defined as a decrement in airflow ≥90% from baseline for ≥10 s. A hypopnea was defined as a decrement in airflow ≥50% but <90% from baseline for ≥10 s and did not require an associated arousal or decrease in SpO_2.

Hemostasis assays

On the morning before randomization to treatment, all patients received a light standardized breakfast. At 9:00 a.m., blood was drawn through an indwelling 22-gauge venous forearm catheter into 10 cm^3 plastic tubes containing 3.8% sodium citrate (ratio 9:1). Blood was spun twice for 15 min at 2,000×*g* at room temperature. Obtained plasma was frozen in polypropylene tubes at −80°C until analyzed.

Plasma levels of VWF:Ag, fibrin D-dimer, and PAI-1 antigen (all from Asserachrom, Diagnostica Stago, Asnières, France), and of sTF antigen (Imubind Tissue Factor, American Diagnostica, Stamford, CT) were determined by enzyme-linked immunosorbent assays as per the manufacturers' instructions. The lower detection limits of these assays are 2% of vWF, 5 ng/ml of D-dimer, 1.0 ng/ml of PAI 1, and 10 pg/ml of sTF.

The same blood processing technique was applied for measuring morning plasma levels of hemostasis molecules posttreatment.

Statistical analyses

SPSS Graduate Pack 13.0 for Windows (SPSS, Chicago, IL) was used to analyze the data. The significance level was set at $p<0.05$, and all testing was two-tailed. Sleep and hemostasis measures were not normally distributed and thus logarithmically transformed before parametric testing. We provide means±SEM of original sleep and hemostasis data in the text and tables and log-transformed data in figures.

To test the first hypothesis of an association between apnea and hemostasis measures, we used Pearson's correlation analysis to estimate the univariate relationships between gender, ethnicity, age, smoking status, BMI, blood pressure, hypertension status, hematocrit, and AHI and SpO_2, as well as with hemostasis measures. All variables associated with VWF:Ag, sTF, D dimer, and PAI-1 antigen at $p<0.10$ were then entered in a linear regression equation to test for an independent relationship between respective variables and each hemostasis measure.

To test the second hypothesis of a treatment effect on hemostasis, we used repeated measure analyses of variance to estimate effects of treatment (therapeutic CPAP, placebo–CPAP, oxygen), time (pre- and posttreatment), and time-by-treatment interaction on hemostasis and sleep variables (AHI, mean nighttime SpO_2). In case of a significant main (i.e., time or treatment) or time-by-treatment interaction effect, we performed post hoc analyses using Fisher's least significant difference. Analyses were repeated with repeated measures analysis of covariance and controlling only for variables that were associated with hemostasis variables in univariate analyses at $p<0.10$ to prevent overfitting of models.

Results

Subjects' characteristics

Table 1 demonstrates that there were no significant differences in baseline characteristics between treatment groups.

Association between subject characteristics, sleep apnea measures, and hemostasis

There was a significant correlation between PAI-1 and AHI ($r=0.47$, $p=0.001$, $n=44$; Fig. 1a) and between PAI-1 and mean SpO_2 ($r=-0.32$, $p=0.035$, $n=44$; Fig. 1b). PAI-1 also correlated with BMI ($r=.47$, $p=.001$; $n=44$) and with age ($r=-.29$, $p<0.07$). Stepwise linear regression revealed AHI as the only significant predictor of PAI-1, explaining 22% of the variance ($R^2=0.219$, $p=0.001$; standardized $\beta=0.47$, $p=0.001$), whereas mean SpO_2, BMI, and age were not retained in the final model.

In contrast, there were no significant associations between sleep measures and VWF:Ag, sTF, or D-dimer, but there were further health variables correlating with these hemostasis measures at the $p<0.10$ significance level: age correlated with D-dimer ($r=.28$, $p<0.08$), and BMI correlated with sTF ($r=-.27$, $p<0.09$). Age and BMI were, therefore, considered as covariates in the analyses of covariance investigating treatment effects.

Gender, ethnicity, smoking status, blood pressure, hypertension status, and hematocrit showed no relationship in bivariate correlation analysis with any of the hemostasis factors at $p<0.10$. These variables were therefore not considered as covariates in regression equations and subsequent analyses of variance.

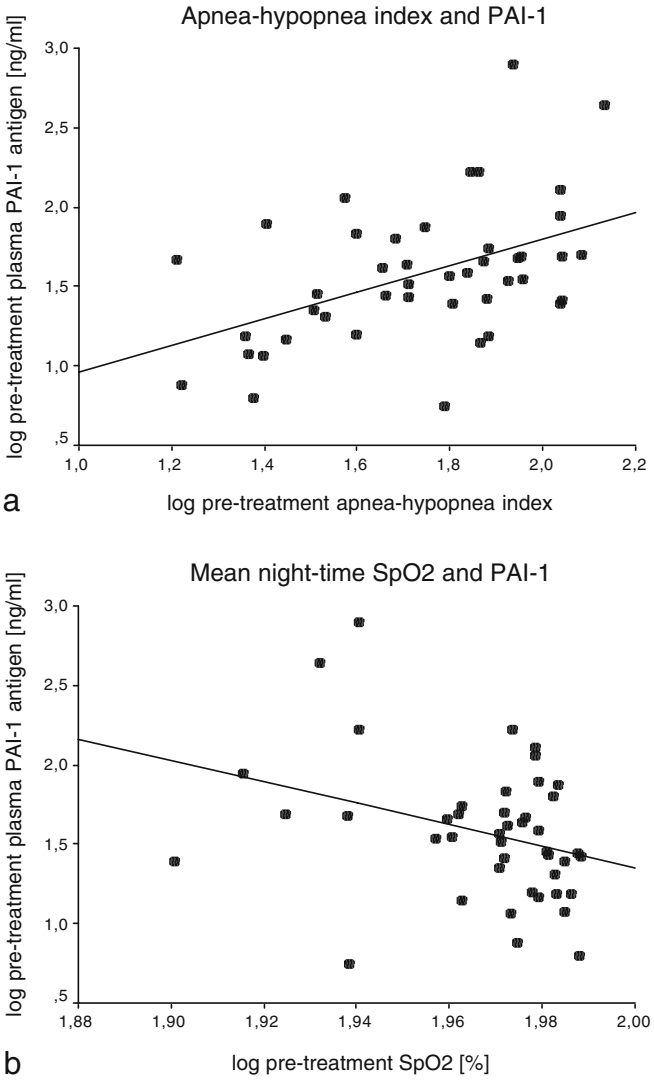

Fig. 1 The scatter plots show the bivariate significant relationships ($p<0.050$) between apnea–hypopnea index (AHI) and plasminogen activator inhibitor (PAI)-1 antigen (**a**) and between mean nighttime oxyhemoglobin saturation (SpO_2) and PAI-1 (**b**). Data are given as log-transformed values on which statistics were computed

Treatment effects on sleep apnea

Table 2 shows that average CPAP use during the 2-week treatment was not significantly different between treatment groups. There was a significant time-by-treatment interaction for AHI ($p<0.001$) and SpO_2 ($p=0.007$). Post hoc analyses revealed that therapeutic CPAP treatment led to a significant decrease in AHI and to a significant increase in mean SpO_2. Similarly, nocturnal oxygen decreased AHI and increased SpO_2. Placebo–CPAP had no significant effect on sleep measures.

Treatment effects on hemostasis

There was a marginally significant time-by-treatment interaction for PAI-1 antigen ($p=0.041$), even after adjusting for BMI, age, AHI, and mean SpO_2 ($p=0.046$). Post hoc analyses suggested that PAI-1 decreased with therapeutic CPAP treatment, but not with either placebo–CPAP or nocturnal oxygen treatment. Treatment did not significantly affect VWF:Ag, D-dimer, and sTF levels, even when accounting for the average duration of CPAP treatment and for univariate correlates (i.e., age, BMI) of coagulation measures.

Discussion

We found that AHI and mean nocturnal SpO_2 correlated with PAI-1 in univariate analyses. AHI was a predictor of PAI-1, independent of mean nocturnal SpO_2, BMI, and age, explaining a substantial 22% of the variance in plasma PAI-1 concentration. This finding suggests that the more severe OSA, the greater the increase in antifibrinolytic activity, as inferred from plasma PAI-1 levels. Our finding is in agreement with and extends the study by Rangemark et al. [19], who found higher PAI-1 activity and lower t-PA activity in apneics than in non-apneics. We extend these observations by examining the relationship across a range of apnea severity.

We also found that 2 weeks of therapeutic CPAP treatment, but not treatment with subtherapeutic CPAP or with nocturnal oxygen, were possibly effective in reducing plasma concentration of the antifibrinolytic enzyme PAI-1. Because we did not investigate other components of the fibrinolysis system, particularly t-PA, the fall in PAI-1 antigen reflects only a proxy measure of a correction in fibrinolytic activity with CPAP treatment. In addition, the sample size was limited; hence, replication of treatment effects on PAI-1 is sorely needed. If findings hold up, they would imply that CPAP might reduce the prothrombotic state in apneics.

PAI-1 plays an important role in the development of atherosclerotic diseases mainly through inhibition of t-PA [26, 35–38]. Treatment with either CPAP or upper airway surgery reduces the prospective risk of an acute coronary syndrome or the need for coronary revascularization in sleep apnea patients with preexistent CAD [39]. Our finding suggests that some of the clinical benefits of CPAP in reducing hard cardiovascular endpoints could relate to its observed potential to decrease the plasma PAI-1 concentration. The physiological mechanisms contributing to the reduction in PAI-1 with CPAP treatment remain elusive.

Of the many procoagulant molecules, we selected VWF:Ag, sTF, and D-dimer, because they measure diverse functions in the hemostatic system and because either their association with OSA or their responsiveness to CPAP

Table 2 Treatment effects across the three treatment arms

		Therapeutic CPAP (n=18)	Nocturnal oxygen (n=16)	Placebo-CPAP (n=10)	Time-by-treatment interaction (P)
CPAP use [h]		6.63±0.30	6.73±0.35	6.28±0.38	.658
AHI	Pre	66.6±6.87	59.5±9.28	59.1±9.99	<.001
	Post	3.57±0.85	50.0±10.2	52.1±9.51	
Post hoc		*P<.001*	*P=.003*	*P=.299*	
Mean SpO_2 (%)	Pre	92.7±1.00	92.7±1.36	93.4±0.93	.007
	Post	96.1±0.65	96.3±0.80	91.5±1.02	
Post hoc		*P=.012*	*P<.001*	*P=.265*	
VWF: Ag (%)	Pre	102.5±13.0	138.5±17.8	136.5±22.9	.948
	Post	111.7±14.4	140.9±16.3	135.5±19.8	
sTF:Ag (pg/ml)	Pre	182.9±20.2	158.1±16.8	169.8±28.7	.232
	Post	183.2±20.8	181.3±18.0	176.1±25.1	
D-dimer (ng/ml)	Pre	296.1±30.0	314.6±40.2	340.1±99.8	.491
	Post	324.1±32.7	275.8±33.9	308.3±80.9	
PAI-1:Ag (ng/ml)	Pre	91.0±44.3	55.3±25.7	66.8±19.8	.041
	Post	44.6±12.4	63.9±21.3	68.0±32.0	
Post hoc[a]		*P=.039*	*P=.249*	*P=.154*	

Values are means±SEM. Last column shows P values for overall repeated measures ANOVA for time-by-treatment interactions. P values in rows refer to post hoc comparisons between pre- and posttreatment values (Fisher's least significant difference)

AHI apnea–hypopnea index, *PAI-1* plasminogen activator inhibitor-1, *SpO_2* oxyhemoglobin saturation, *sTF* soluble tissue factor, *vWF* von Willebrand factor

[a]Using nonparametric post hoc analyses (Wilcoxon signed ranks test) revealed similar significances with P=.013 for therapeutic CPAP, P=.352 for nocturnal oxygen, and P=.139 for placebo-CPAP, suggesting that the significant effect of CPAP treatment, as yielded by parametric post hoc analysis, was not driven by outliers

treatment has not been investigated. In contrast to previous studies [18, 20–22, 40], we did not observe that our procoagulant measures were sensitive to CPAP treatment. However, these earlier studies could not exclude a nonspecific treatment or time effect because they did not include a placebo–CPAP condition. Moreover, the only previous placebo-controlled study found that, although sleep apnea patients had higher procoagulant molecules than non-apnea patients before treatment, it was placebo–CPAP (i.e., subtherapeutic CPAP at <1 cm H_2O pressure) that significantly decreased plasma levels of $FVII_a$ and $FXII_a$ [16]. Together, that study and the present one highlight the utility of including a placebo-CPAP condition when investigating CPAP effects on hemostasis in OSA.

With reference to our analyses of treatment effects on hemostasis, we acknowledge that all of our observations were based on a relatively small sample size and that it is possible that a 2-week treatment phase was too short to realize significant changes in VWF:Ag, sTF, and D-dimer. Thus, our findings must be regarded as provisional, pending further replication in larger samples. However, the literature on the effects of CPAP on hemostasis in OSA is quite scarce [11]. In fact, all of the six earlier studies investigating the effect of CPAP treatment on hemostasis measures had similarly limited sample sizes [16, 18, 20–22, 40]; only one of these studies included a placebo-CPAP condition [16] and none investigated the effect of nocturnal oxygen on hemostasis.

To summarize, apnea severity was associated with impaired fibrinolysis, as judged by PAI-1 levels. In addition, in a placebo–CPAP controlled treatment trial of OSA patients, therapeutic CPAP appeared to decrease the plasma PAI-1 levels. It remains to be established whether the correction of PAI-1 levels or the fibrinolytic activity in general by CPAP treatment improves cardiovascular health in OSA patients.

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