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Platelet Function and Fibrinolytic Activity in Hypertensive and Normotensive Sleep Apnea Patients

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Summary: Platelet function and fibrinolytic activity was studied during rest and after ergometric exercise in 13 hypertensive or normotensive patients with obstructive sleep apnea (OSA) and in 10 sex- and weight-matched controls. All patients had undergone a complete polysomnography for the diagnosis of OSA. The controls did not undergo any sleep investigation but had no history of snoring or witnessed apneas during sleep. On antihypertensive drug wash-out, two of the patients were normotensive, whereas 11 had mild to moderate hypertension. Platelet aggregation measured by adenosine 5'-diphosphate- or adrenaline-induced aggregation, platelet factor-4 or β-thromboglobulin did not differ between patients and controls. During exercise β-thromboglobulin decreased significantly in both OSA patients and controls. Plasma tissue plasminogen activator activity was similar in OSA patients and controls and increased significantly in both groups after exercise. Plasminogen activator inhibitor type 1 (PAI-1) was 18.4 ± 3.6 IU/ml in OSA patients compared with 8.2 ± 1.7 IU/ml in controls ($p < 0.029$) during rest, indicating decreased fibrinolytic activity. The difference between groups remained after exercise ($p < 0.017$). Blood pressure elevation was more common and body mass index (BMI) was higher in patients with OSA, but there was no direct relation between blood pressure level or BMI and PAI-1. Nevertheless, differences between groups were smaller when blood pressure and obesity were accounted for. It is concluded that patients with OSA may exhibit decreased fibrinolytic activity. Low fibrinolytic activity may represent a confounding pathophysiological mechanism behind the high incidence of myocardial infarction and stroke in patients with OSA. **Key Words:** Platelets—Fibrinolysis—Hypertension—Stroke—Sleep apnea.

Obstructive sleep apnea (OSA) has been associated with an increased mortality rate (1,2), which appears to be due to a high prevalence of cardiovascular disease (2). A recent report has demonstrated an increased incidence of myocardial infarction in patients with OSA (3). In addition, snoring and possibly OSA appear to be risk factors for development of ischemic brain infarction (4).

The immediate physiological sequelae of OSA involve intermittent nocturnal hypoxia, hemodynamic changes and sleep disruption. Disordered ventilation during sleep has been shown to result in increased sympathetic activity (5–8) and changes in volume and electrolyte metabolism (9,10) not only during sleep and apneic events, but also during the awake resting state. Although the exact pathophysiological mechanisms behind the increased cardiovascular risk in OSA are yet largely unknown, several confounding risk factors have been identified. Obesity is common and over 70% of OSA patients have a body weight exceeding 115% of the ideal (11). Systemic hypertension has been reported in approximately 50% of OSA patients (12–14), whereas other well-recognized cardiovascular risk factors such as plasma insulin or glucose disposal rate or serum lipids have not been systematically studied in OSA.

Bokinsky et al. (15) recently reported increased platelet activation and aggregation during sleep in OSA. This effect may be influenced by apnea-induced hypoxemia, as platelet function seems to be affected by hypoxia (16,17). A reduced platelet survival time was increased by supplemental O_2 in 10 hypoxemic COPD patients (17). Krieger and coworkers (18) found a reduced urinary ratio of a prostacyclin metabolite, 6-keto-PGF_1-alpha, to a thromboxane A_2 metabolite, thromboxane TxB_2, a finding compatible with increased platelet aggregability in OSA. Others, however, have

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found an increased ratio (19). No previous studies have dealt with fibrinolytic activity in OSA, although elevated plasma levels of an inhibitor of fibrinolysis, plasminogen activator inhibitor (PAI-1), have been demonstrated in patients with obesity (20) or hypertension (21). As these conditions are common in patients with OSA, altered platelet function and/or fibrinolytic activity may have implications for cardiovascular complications in this sleep and breathing disorder.

The present study was undertaken to investigate platelet function and fibrinolytic activity during rest and exercise in patients with OSA.

METHODS

Study population

Thirteen male patients with a mean age of 53 years (range 39–66 years) were included in the study. All patients had previously diagnosed OSA and were consecutively selected from patients in the sleep laboratory receiving prescriptions for nasal continuous positive airway pressure (nCPAP). Ten male controls, 51 years of age (range 46–57 years), without any history of snoring or witnessed apnea were selected from the Göteborg City Police Corps, using a best possible age- and body weight-matching procedure. Four of the OSA patients had previously been treated for hypertension and had received antihypertensive medication (see below). These patients were subjected to antihypertensive drug wash-out for 3 weeks. On inclusion into the study, 11 of the OSA patients were hypertensive, that is, they had a resting supine diastolic blood pressure (DBP) $\geq$90 mm Hg. Further characteristics of the OSA and control groups are shown in Table 1. Exclusion criteria from study participation were morbid obesity [body mass index (BMI) > 150% ideal], smoking or tobacco use, intake of NSAIDs within 14 days prior to study day, as well as a history of gastric or duodenal ulcer disease, inflammatory bowel disease, coagulation or platelet disorder and inability to perform an exercise test.

Study protocol

The study was approved by the Ethics Review Committee of the University of Göteborg. Oral consent was obtained from each patient after written information.

Subjects arrived in the laboratory between 8:00 a.m. and 10:00 a.m. after an overnight fast (water intake permitted). All subjects were studied in a randomized fashion, whereby an OSA patient was always followed by a control. A careful history and a physical examination were performed at baseline and anthropomorphic measurements were obtained. Blood pressure was recorded after a minimum of 15 minutes of supine rest. Blood samples were collected in the sitting position immediately before exercise testing and in the supine position immediately after exercise.

Sleep studies

All OSA patients had undergone an overnight diagnostic investigation in the sleep laboratory. The investigation was initiated at 11:00 p.m. and terminated at 6:00 a.m. The study included electroencephalography, extraocular muscle and submental electromyography. Respiratory movements were recorded by impedance electrodes as well as via a static charge-sensitive bed (PVDS motion sensor, Dourek Ltd, Raisio, Finland). Nasal and oral airflow were monitored via thermistors mounted over the nose and mouth. Arterial oxygen saturation (SaO_2) was measured continuously via a finger probe (Biox 3700, Ohmeda, U.S.A.). All recordings were stored on a tape recorder and analyzed by a computerized sleep stager (Oxford Medilog System, Oxford, U.K.) according to standard criteria (22). An apnea was defined as a cessation of airflow lasting $\geq$10 seconds, accompanied with chest wall motion and a drop in SaO_2 $\geq$4% below the immediately preceding baseline. Apnea index (AI) was defined as the number of apneas per hour of sleep. The lowest oxygen saturation (SaO_2min) reached in the overnight recording was determined.

Blood pressure recordings

A careful history of previously known or present hypertension was obtained from each patient. Hypertension was defined as a DBP $\geq$90 mm Hg in three independent measurements after at least 5 minutes of supine rest. At the time of study inclusion, 11/13 OSA patients and 6/10 controls had mild to moderate hypertension according to World Health Organization criteria (23) (Table 1).

Resting blood pressure was measured with an automatic blood pressure recorder (Omega 1400, Invivo Res. Lab. Inc., Broken Arrow, OK, U.S.A.), using an appropriately sized arm cuff on the right arm after a minimum of 15 minutes of supine rest and prior to blood sampling. Blood pressure during exercise (see below) was recorded with a standard sphygmomanometer. Systolic (SBP) and diastolic (DBP) blood pressure were determined with the diastolic pressure defined by the Korotkoff phase V.

Exercise testing

Exercise testing was performed on a standard bicycle ergometer. Standard electrocardiogram (ECG) chest and

TABLE 1. *Physical characteristics and sleep study data in patients with obstructive sleep apnea and controls*

Patient	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)	Blood pressure (mm Hg)	Hypertension (Y/N)[a]	AI (n/hour)	SaO_2min (%)
Controls								
RJ	55	1.84	93	27.5	138/79	N		
SL	55	1.85	75	21.9	138/84	N		
JW	55	1.85	85	24.8	149/98	Y		
JTA	49	1.92	98	26.6	170/94	Y		
TF	49	1.85	95	27.8	150/93	Y		
BÅ	54	1.85	95	27.8	150/93	Y		
DP	48	1.82	87	26.3	127/71	N		
LL	57	1.90	105	29.1	165/102	Y		
LP	46	1.89	105	29.4	141/83	N		
KW	46	1.83	90	26.9	148/98	Y		
Mean	51.4	1.86	92.0	26.6	148/90			
SEM	1.33	0.01	2.94	0.68	4.1/3.2			
Patients								
LÅS	48	1.86	95	27.5	178/105	Y	60	70
NF	47	1.76	94	30.3	156/102	Y	16	82
HW	62	1.73	75	25.1	193/107	Y	25	82
KS	58	1.82	84	25.4	172/100	Y	55	70
HH	55	1.90	100	27.7	130/78	N	14	76
MZ	45	1.70	95	32.9	160/103	Y	13	70
RH	53	1.86	100	28.9	143/99	Y	20	80
JS	39	1.78	86	27.1	166/99	Y	45	80
KE	58	1.70	75	26.0	148/92	Y	42	77
EG	54	1.69	85	29.8	170/101	Y	58	55
ID	66	1.78	104	32.8	125/80	N	27	79
SN	60	1.83	90	26.9	155/97	Y	24	84
PW	48	1.76	93	30.0	155/97	Y	20	72
Mean	53.3	1.78	90.5	28.6	157/97		32	75
SEM	2.12	0.02	2.53	0.76	5.3/2.5		4.8	2.2

[a] Y = yes; N = no.

limb leads were used. Blood pressure and ECG were obtained in the sitting resting state, as well as after each increment in work load, each minute at the highest work load and after 5 minutes of rest in the supine position. The initial work load (70 W) was increased by 10 W each minute until 70% of the calculated maximal heart rate was reached. Maximal heart rate was calculated according to the formula $220 - 0.78 \times$ age (24). The exercise was terminated after 4 minutes at final work load, and blood samples were obtained in the supine position immediately after exercise.

Blood and urine sampling

Baseline inclusion blood samples were obtained from an indwelling intravenous cannula during sitting rest (sample set 1), and a second set of blood samples was obtained in the supine position immediately after termination of exercise (sample set 2). A total of 40 ml blood was withdrawn for each sample set. Urine was collected during 24 hours prior to the investigation and divided into one daytime (7:00 a.m.–10:00 p.m.) and one nighttime (10:00 p.m.–7:00 a.m.) portion. Samples were frozen and kept at −20°C until assay. One sample in the control and two in the OSA group for aggregability testing were lost, as were one urinary and one exercise sample for tissue plasminogen activator (t-PA)/PAI-1 analysis in the OSA group.

Citrated platelet-rich and platelet-poor plasma were prepared as described elsewhere (25). Platelet aggregation was studied turbidimetrically (26). Aggregation was induced with adenosine 5'-diphosphate (ADP) 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 μM or with adrenaline 0.25, 0.5, 1.0, 2.5, 5.0, 10, 50 and 100 μM. The threshold value for aggregation was defined as the lowest concentration causing irreversible aggregation with at least an 80% difference in light transmission between platelet-rich and platelet-poor plasma. Thus, a lowering of the threshold value would indicate enhanced platelet aggregation. Blood samples for β-thromboglobulin (β-TG) and platelet factor-4 (PF-4) assays were immediately transferred to cooled plastic tubes containing 100 μl ethylenediaminetetraacetic acid (EDTA) 0.134 M and 100 μl theophylline 15 mM and placed in ice water for 20 minutes, then centrifuged at 3,000 *g* at 4°C. β-TG and PF-4 were measured by radioimmunoassay (27,28).

The urinary metabolites of thromboxane A_2 (2,3-dinor-thromboxane B_2/Tx-M; marker for platelet activation) and prostacyclin (2,3-dinor-6-keto-prosta-

TABLE 2. *Platelet function in controls and in patients with obstructive sleep apnea. Shown are means ± SEM. The number of controls or patients in each group is shown within parentheses. (Statistics by Fisher's permutation test)*

	Controls	OSA patients	p
ADP aggregability			
Rest	3.6 ± 0.73 (9)	5.6 ± 1.25 (12)	ns
Exercise	4.9 ± 1.42 (9)	6.1 ± 1.49 (12)	ns
Adrenaline aggregability			
Rest	24.5 ± 14.3 (9)	39.2 ± 13.5 (12)	ns
Exercise	19.9 ± 11.3 (9)	38.5 ± 13.7 (12)	ns
Platelet factor −4			
Rest	14.0 ± 2.9 (10)	16.6 ± 4.8 (13)	ns
Exercise	11.1 ± 2.4 (10)	18.5 ± 4.4 (12)	ns
β-Thromboglobulin			
Rest	40.9 ± 10.6 (10)	32.4 ± 6.6 (13)	ns
Exercise	20.3 ± 2.8 (10)	23.8 ± 3.0 (12)	ns

glandin F_{1a}/PGI-M; marker for platelet vessel wall interaction) were analyzed in a subgroup of five OSA patients and five controls by a stable isotope dilution assay using gas chromatography/negative ion-chemical ionization mass spectrometry as previously described (29).

Tissue plasminogen activator (t-PA) activity and activity of the fast-acting inhibitor against t-PA, PAI-1, were measured using reagents from BioPool (Umeå, Sweden) (30,31).

Statistics

All values are expressed as means ± SEM if not otherwise stated. Statistical comparison between groups was performed using Fisher's permutation test, as well as by Mantel's test (32), after stepwise correction for age, BMI, SBP and DBP. Simple regression was calculated by the method of least squares. A p-value <0.05 was considered significant. All calculations were performed on a Macintosh SE computer using standard software (Statview 512+).

RESULTS

Both BMI (approximately 2 kg/m²) and blood pressure (approximately 9/7 mm Hg) tended to be higher in the OSA group (Table 1), although the differences were not significant. Moreover, resting SBP and DBP were unrelated to disease severity expressed as AI or to overnight SaO_2min in patients.

ADP- and adrenaline-induced platelet aggregability, as well as PF-4 and β-TG concentrations, were similar in OSA patients and controls during rest and exercise (Table 2). PF-4 did not change in either group during exercise, whereas the β-TG concentration decreased to a similar degree in both OSA patients and controls.

TABLE 3. *Urinary excretion (10:00 p.m. to 7:00 a.m.) of PGI-M and Tx-M, and the urinary ratio of PGI-M/Tx_M in subgroups of controls and patients with OSA. Data are expressed as means ± SEM. The number of patients in each group is shown within parentheses. (Statistics by Fisher's permutation test)*

	Controls	OSA patients	p
PGI_M (pg/mg creatinine)	142 ± 13.8 (5)	144 ± 23.0 (4)	ns
Tx_M (pg/mg creatinine)	139 ± 32.2 (5)	121 ± 31.5 (5)	ns
PGI-M/Tx-M	1.24 ± 0.28 (5)	1.43 ± 0.44 (4)	ns

Overnight urinary excretion of PGI-M or Tx-M did not differ between the subgroups of OSA patients and controls (Table 3). The ratio of PGI-M to Tx-M was similar, 1.43 ± 0.44 and 1.24 ± 0.28, respectively, in the two groups. Urinary excretion of PGI-M or Tx-M were unrelated to disease severity expressed as AI or minimum overnight SaO_2min in the five patients with OSA.

There was an approximately four-fold increase in t-PA activity after exercise in both groups, and neither resting nor exercise levels differed between groups (Table 4). In contrast, the resting PAI-1 concentration in OSA patients was more than twice that of the controls ($p < 0.03$, Table 3, Fig. 1); and this difference between groups remained after exercise ($p < 0.02$, Table 3). There was a significant relationship between t-PA and PAI-1 both in the control group ($r = 0.79$, $p < 0.008$) and in the whole study population ($r = 0.44$, $p < 0.004$), but not within the OSA patient group. Both PAI-1 and t-PA were unrelated to SBP or DBP in the patient and control groups. PAI-1 values remained significantly higher in the OSA group also after correction for age, BMI or DBP (Table 5). Finally, although there was a trend toward higher PAI-1 values in more severe disease (expressed as minimum overnight SaO_2min), this relation failed to reach significance ($r = 0.49$, $p < 0.09$).

TABLE 4. *Fibrinolytic activity in controls and in patients with OSA. Data are expressed as means ± SEM. The number of patients in each group is shown within parentheses. (Statistics by Fisher's permutation test)*

	Controls	OSA patients	p
Tissue plasminogen activator (t-PA) IU 7 ml			
Rest	0.19 ± 0.04 (10)	0.16 ± 0.04 (13)	ns
Exercise	0.99 ± 0.19 (10)	0.82 ± 0.04 (12)	ns
Plasminogen activation inhibitor (PAI) IU/ml			
Rest	8.2 ± 1.66 (10)	18.4 ± 3.62 (13)	<0.029
Exercise	7.1 ± 1.90 (10)	18.8 ± 3.80 (12)	<0.017

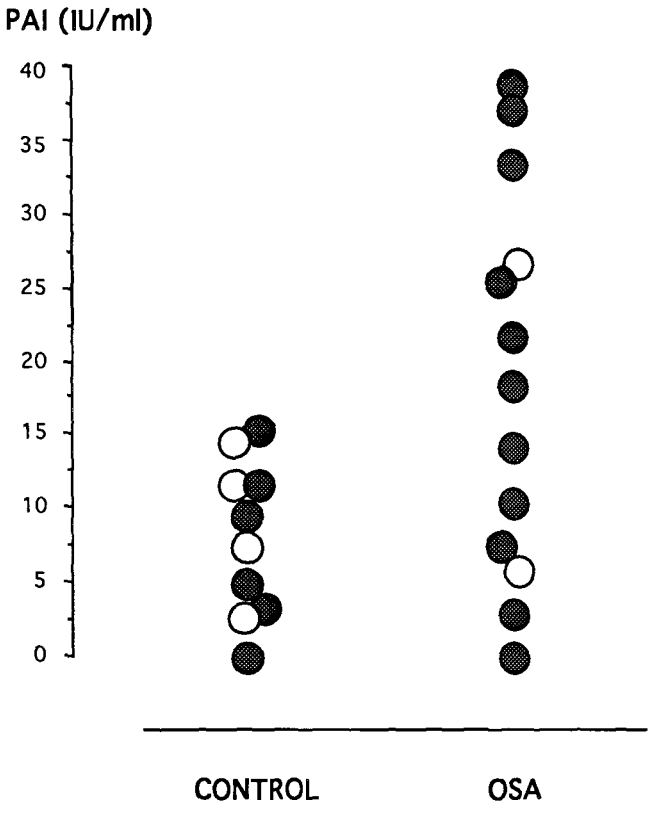

FIG. 1. Resting concentration of plasminogen activation inhibitor (PAI-1, U/ml) in healthy controls and in patients with obstructive sleep apnea (OSA). Each dot indicates the value in one patient or control. Shaded symbols represent subjects with hypertension (see Methods for criteria) and open symbols indicate normotensives. Mean ± SEM are shown adjacent to individual values. Statistics by Fisher's permutation test.

TABLE 5. *Statistical comparison between groups regarding PAI-1 during rest and exercise in OSA patients and controls. (Statistics by Fisher's permutation test)*

Variable corrected for	Two-tailed p-value	Comment
PAI_1 during rest		
Age	0.013	OSA > control
BMI	0.052	—
SBP	0.074	—
DBP	0.087	—
PAI_1 during exercise		
Age	0.009	OSA > control
BMI	0.015	OSA > control
SBP	0.056	—
DBP	0.042	OSA > control

Abbreviations used: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

DISCUSSION

The present study reports on platelet function and fibrinolytic activity in patients with OSA. Patients had normal platelet function, whereas plasma PAI-1 concentration was increased, a finding which at least in part may be explained by coinciding hypertension.

The elevated mortality rate associated with OSA has been attributed to cardiovascular mortality (2). Between 30% and 70% of patients with OSA are hypertensive (12–14). OSA is also overrepresented in cross-sectional materials of patients surviving myocardial infarction (3). Epidemiological studies based on snoring habits have linked habitual snoring with hypertension (33), myocardial infarction (34) and ischemic brain infarction (4,34). Although sleep apneics are commonly obese, OSA has been identified as an independent and additive risk factor for development of systemic hypertension (14). However, the pathophysiological mechanism behind increased cardiovascular morbidity in OSA remains unexplained.

Sleep-related apneic events are associated with repetitive often severe hypoxemia, frequent arousal from sleep and profound hemodynamic changes. Blood pressure elevation is commonly sustained after morning awakening (35). Increased sympathetic activity has been demonstrated both during sleep and awake (5–8). In addition, the pseudohypervolemia associated with apneic events (9) results in changes in volume-regulating hormonal systems such as the atrial natriuretic peptide (36) and the renin-angiotensin-aldosterone systems (9,10).

Hypertension alone may explain at least part of the increased cardiovascular morbidity in OSA. However, the high incidence of stroke (4) and myocardial infarction (5) suggests that other risk factors such as a modified platelet aggregability or fibrinolytic function may be of pathophysiological importance. Increased platelet activation and aggregation during sleep, and reduced hyperaggregability after nCPAP, have recently been reported in OSA (15). The reason for this OSA-related change is unknown but may relate to several different physiological sequelae of the sleep-related breathing disorder. In a study of healthy nonsmoking subjects, short-term steady-state hypoxia reduced plasma β-thromboglobulin but was not found to influence platelet aggregation rate (16). However, platelet survival time was reduced in hypoxemic COPD patients and supplemental O_2 increased survival time (17). Prostacyclin formation was reduced after reoxygenation of anoxic umbilical vein endothelial cells, resulting in an increase in stimulated platelet adherence (37). These data indicate that repeated hypoxia may explain the abnormal release of prostanoids recently demonstrated by Krieger and coworkers in sleep apnea patients (18). The urinary ratio of a prostacyclin metabolite, 6-keto-PGF_1-alpha, to a thromboxane A_2 metabolite, thromboxane TxB_2, was reduced, which would be compatible with an increased tendency for platelets to aggregate. This finding could not be con-

firmed in the present study or in a recent study by Kimura et al. (19), and we could not demonstrate an elevated platelet aggregability. The reason for these discrepancies may relate to the small patient groups studied or to differences in disease severity. Moreover, platelet aggregation in plasma was not measured during the period of sleep and repeated apnea, but rather 2 hours or more after awakening in the present study.

Elevated plasma levels of fibrinolysis inhibitors such as PAI-1 have been demonstrated in patients with obesity (20) and hypertension (21). As both these conditions are common in patients with OSA, controls were selected by a careful matching procedure. Nevertheless, the OSA group was found have a higher BMI, and blood pressure elevation was far more common among OSA patients. Although neither BMI nor blood pressure was directly related to resting plasma PAI-1 levels, three of the seven highest concentration values were seen in patients with documented hypertension. This suggests that hypertension was a powerful confounder for elevated PAI-1 in OSA patients. However, PAI-1 was significantly higher after exercise also after correction for age, BMI or DBP, indicating that OSA alone results in reduced fibrinolytic activity. Moreover, all these factors—blood pressure elevation, high BMI, and OSA—may act in concert to induce an increased cardiovascular risk in the typical OSA patient.

It is unknown whether factors such as elevated sympathetic activity or modified volume regulation in OSA may have influenced the higher PAI-1 levels measured. However, it is likely that these physiological adaptations to OSA, as previously demonstrated (6,9) were present in all patients, whereas plasma PAI-1 was elevated only in a subgroup of sleep apneics in the present study.

It is concluded that patients with OSA have increased plasma PAI-1 concentrations. At least part of this elevation may be explained by coinciding hypertension. Nevertheless, a decrease in fibrinolytic activity may represent a pathophysiological mechanism behind the increased cardiovascular morbidity occurring in OSA, in particular stroke and myocardial infarction.

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