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Short Communication

Prothrombotic Markers in Patients with Arterial Hypertension and Obstructive Sleep Apnea Syndrome

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Abstract

Introduction: Obstructive sleep apnea syndrome (OSA) may cause more than 500 pauses in breathing, what leads to reduction in oxygen saturation of blood. In some individuals OSA is also associated with higher risk of thrombotic events.

Material and methods: In our study we included forty-five patients with arterial hypertension (duration of AH=9.8±5.7 years), middle-aged (47.6±9.1 years). 25(55.5%) of patients had severe OSA (AHI= 59.2±27). In 12 patients with severe OSA blood samples (D-dimer, viscosity of blood, erythrocyte aggregation) were taken at baseline and after 3-4 nights of effective CPAP therapy (AHI <5). OSA was diagnosed by means of cardio respiratory monitoring.

Results: Patients with severe OSA have higher activity of coagulation system in levels of D-dimer (319.7± 162.6 ng/ml *vs* 200.1±95.8 ng/ml p = 0.04), elevated blood viscosity in areas with slow blood flow (32.9± 6.6 cP. *vs* 29.0±6,5cP. p = 0.04) and erythrocyte aggregation (5.6 ± 0.5 cP. *vs* 5.0 ± 1,0 cP. p = 0.01). No significant changes of blood rheological properties were found in patients on short-term CPAP therapy (3-4 nights).

Conclusions: Patients with severe OSA are demonstrating increased activity of the coagulation system: higher levels of D-dimer, blood viscosity in veins, microcirculation and erythrocyte aggregation. We found no effect of CPAP therapy on these parameters, what may be associated with a small number of subjects and the short duration of CPAP therapy. The study will continue recruiting patients and analyzing the parameters mentioned above after 3 months of effective CPAP therapy.

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Keywords

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- CPAP
- Coagulation
- Hypertension

ABBREVIATIONS

OSA: Obstructive Sleep Apnea; AH: Arterial Hypertension; AHI: Apnea/Hypopnea Index; Cp: Centipoises; PE: Pulmonary Embolism; ODI: Oxygen Desaturation Index; CRM: Cardio Respiratory Monitoring.

INTRODUCTION

Obstructive sleep apnea (OSA) may cause up to 400-500 pauses in breathing during the night, what usually equals to 3-4 hours of reduced blood oxygen saturation (below 55%).

According to *multi-center* cohort *study* SHHS [1] with 6424 patients included, OSA is an independent risk factor for hypertension and other cardiovascular diseases as well as stroke. It also increases the risk of all-cause mortality by more than 1.5 times comparing with healthy volunteers. Individuals with OSA demonstrate a significantly higher risk of venous thrombosis and thromboembolism [2].The severity of OSA has a positive correlation with the severity of hypertension [3], often being the cause of refractory hypertension [4]. The pathophysiological mechanisms of increasing risks of mortality in OSA are still the subject of debate. Activation of blood coagulation as a result of acute and chronic hypoxia is one of the most likelihood causes of vascular events in patients with OSA.

In vivo experiments on animals [5], who were in hypoxic (10.0% O2, 0.01% CO2) and hypercapnic (9-11% O2, 7-8% CO2) for1 up to 24 hours, activation effect on blood clotting was observed in both models. Also a reduction of blood plasma anticoagulant

activity was shown, especially in the group of hypoxic hypoxia. Procoagulant effects of hypoxia may explain the development of vascular complications in patients with OSA. Ciccone at al found out that OSA patients showed increased inflammatory markers levels with correlated to cIMT in OSA patients [6]. Patients with pulmonary embolism (PE) and OSA needed significantly higher doses of warfar in to achieve a therapeutic level of international normalized ratio (INR), than patients with PE without OSA [7]. It demonstrates the hyperactivity of the coagulation system in patients with OSA and confirms the necessity of further researches in this field.

MATERIALS AND METHODS

Our *study included* 45 patients with arterial hypertension (AH) who underwent cardio respiratory monitoring (CRM). According to AHI patients were divided in 2 groups. Group I (20 patients with mild OSA (AHI=5-15) and without OSA) and group II (25 patients with severe OSA (AHI> 30)).

All patients received standard antihypertensive therapy: ACE-I (angiotensin-converting-enzyme inhibitor) or ARB (Angiotensin II Receptor Blockers), CCB (Calcium channel blockers) and diuretics (thiazide antagonist aldosterone).

Office blood pressure was measured by Korotkoff's method. OSA was diagnosed by CRM using several devices: "Grass Technologies" (USA), "SOMTE/Compumedics" (Australia). The overnight study included: analysis of respiratory movements of the chest and abdomen, nasal and oral airflow, body position, leg movements, snoring, pulse oximetry and electrocardiogram.

Following blood viscosity parameters were analyzed in all patients: blood viscosity at high shear rates (128s(-1)), indicating blood viscosity in areas with fast blood flow (in arteries), blood viscosity at low shear rates (0.95s(-1)), indicating blood viscosity in areas with slow blood flow (in veins, microcirculation), hpl - plasma viscosity, the ratio h2 / h1, characterized by steady erythrocyte units (aggregation), hematocrit (Ht) - volume ratio of blood cells and plasma ("Contaves low shear 30" /Pro Rheo/ Germany). Markers of hemostasis system: D-dimer, f. Von Willebrand, complex plasmin-α2-antiplasmin, plasminogen activator inhibitor-1 (Multiscan go/Thermo scientific/ Canada) were performed (Figures 1-3). 25 patients with AH and severe OSA (AHI> 30)underwent 3-4 nights of effective CPAP therapy(Somnobalance-e,Weinmann, Germany)with achievement of AHI <5and evaluation of the above analysis at baseline and in the end of therapy.

RESULTS AND DISCUSSION

We compared parameters of two groups: with severe OSA (AHI> 30) and with mild form of OSA or without OSA (AHI <15) to find the effect of chronic and hypoxia on activation markers of hemostasis.

Table1. Main characteristics of the groups n=45 (M±m) Statistically significant difference - age, BMI (body mass index), AHI and ODI. Table 2 Comparison of coagulation factors (M±m) in both groups (n = 45).

Levels of D-dimer were significantly increased in group with severe OSA. Analysis of fibrinogen, tissue Plasminogen activator

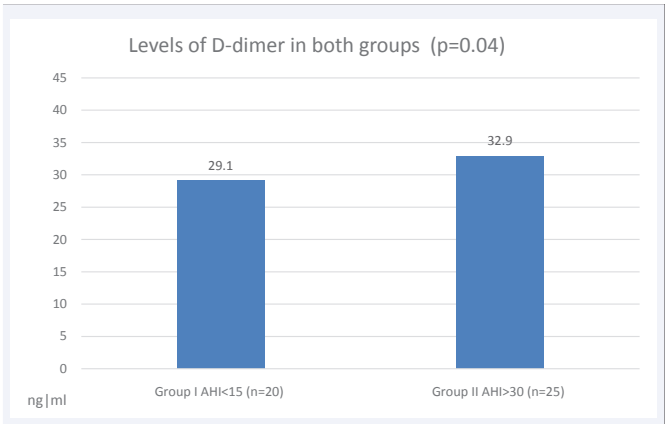

Figure 1 Levels of D-dimer in both groups.

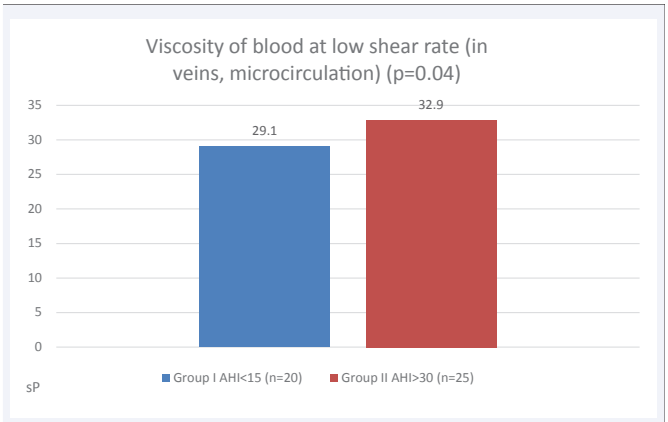

Figure 2 Viscosity of blood at low shear rate (in veins, microcirculation).

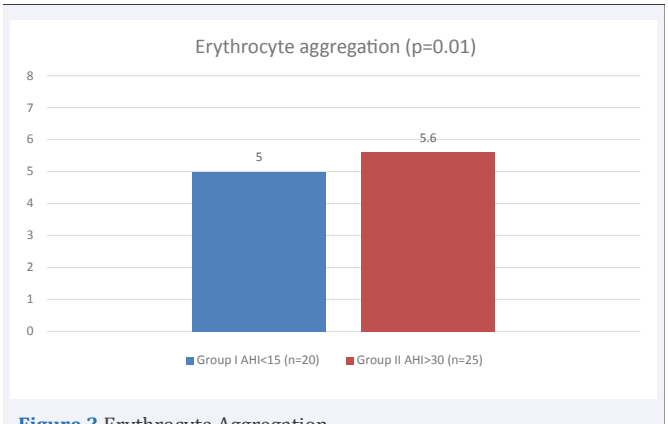

Figure 3 Erythrocyte Aggregation.

inhibitor-1 complex plasmin-α2-antiplasmin levels showed no significant difference between both groups, but there was an upward trend in severe OSA group. Willebrands factor and Plasminogen activator inhibitor levels showed no statistical difference.

We compared the blood viscosity in patients with severe OSA (AHI> 30) and the group with mild or without OSA (AHI <15). We found a significant increase of viscosity in areas with slow blood flow and erythrocyte aggregation in the group with severe OSA, as well as a tendency to increase the viscosity of plasma,

Table 1: Main characteristics of the population n=45 (M±m).

	Group I AHI<15 (n=20)	Group II AHI>30 (n=25)	*p*
Age (years)	39.9±9.9	47.8±10.1	0.02*
BMI (Body mass index)	26.9±3.6	36.3±6.7	0.01*
AHI	10.7±11.7	59.2±27.0	0.01*
ODI	12.1±11.7	56±27.5	0.01*
Mean systolic blood pressure (mmHg)	138.2±9.3	143±13.8	0.15
Mean diastolic blood pressure (mmHg)	82.0±7.5	84.0±10.1	0.55
Mean duration of AH (years)	7.95±3.92	8.48±3.8	0.66

Abbreviations: ODI: Desaturation Index; AHI – Apnea/hypopnea Index; AH: Arterial Hypertension

Table 2: Comparison of coagulation factors (M ± m) in both groups (n = 45).

	Group I AHI<15 (n=20)	Group II AHI>30 (n=25)	units	*p*
Fg	3.1±0.6	3.45±0.3	g/l	0.06
vWF	101.4± 38	152.2±91.6	%	0.1
PAI-1	21.1±10.5	23.7±20.8	U/ml	0.59
D-d	200.1±95.8	319.7±162.6	ng/ml	0.04*
tPa-PAI	16.3±2.2	19.1±3.6	ng/ml	0.07
PAP	153.3±110.9	363.2±379	ng/ml	0.08

Abbreviations: Fg: Fibrinogen; vWF: Von Willebrand Factor; PAI-1: Plasminogen Activator Inhibitor-1; D-d: D: Dimer; tPa-PAI: Tissue Plasminogen Activator/Plasminogen Activator Inhibitor Complex; PAP: Plasmin-α2-Antiplasmin Complex

Table 3: Comparison of the viscosity of whole blood (M ± m) in both groups (n = 45).

	Group I AHI<15 (n=20)	Group II AHI>30 (n=25)	Normal levels	Units	*p*
ŋ1	5.5±0.5	5.8±0.7	4.07-5.30	sP	0.22
ŋ2	29.0±6.5	32.9±6.6	14-23	sP	0.04*
ŋ2/ŋ1	5.0±1.0	5.6±0.5	3.26-4.44	Units	0.01*
ŋpl	1.7±1.0	1.5±0,08	1.45-3,26	sP	0.07
Ht	52.4±5.0	53.9±4.5	40-48%	%	0.44

Abbreviations: ŋ1: Viscosity of blood at high shear rate (in arteries); ŋ2: Viscosity of blood at low shear rate (in veins, microcirculation); ŋ2/ŋ1: Erythrocyte Aggregation; ŋpl: Plasma Viscosity; cP: Centipoise

Table 4: Blood coagulation factors (M±m) on CPAP therapy (n = 25).

	at baseline	after 3-4 nights of CPAP therapy	units	*P*
Fg	3.45±0.3	3.57±0.4	g/l	0.71
vWF	152.02±91.6	150.9±99.8	%	0.97
PAI-1	23.7±20.8	20.8±18.3	U/ml	1
D-d	319.7±162.6	323.3±101.4	ng/ml	0.68
tPa-PAI	19.1±3.6	18.7±4.3	ng/ml	0.66
PAP	363.2±379	333.1±366.5	ng/ml	0.57

Abbreviations: Fg: Fibrinogen; vWF: Von Willebrand Factor; PAI-1: Plasminogen Activator Inhibitor-1; Д–д – D-dimer; tPa-PAI: Tissue Plasminogen Activator/Plasminogen Activator Inhibitor Complex; PAP: plasmin-α2-Antiplasmin Complex

Table 5: Viscosity of whole blood (M ± m) on CPAP therapy (n = 25).

	at baseline	after 3-4 nights of CPAP therapy	Normal levels	units	*p*
ŋ1	5.8±0.7	5.5±0.5	4.07-5.30	sP	0.28
ŋ2	32.9±6.6	30.4±6.2	14-23	sP	0.83
ŋ2/ŋ1	5.6±0.5	5.5±0.7	3.26-4.44	units	0.51
ŋpl	1.5±0.08	1.5±0.06	1.45-3.26	sP	0.51
Ht	53.9±4.5	52.0±3.1	40-48%	%	0.51

Abbreviations: ŋ1: Viscosity of blood at high shear rate (in arteries); ŋ2: Viscosity of blood at low shear rate (in veins, microcirculation); ŋ2/ŋ1: Erythrocyte Aggregation; ŋpl :plasma viscosity; cP: Centipoise

with no significant difference. Levels of hematocrit, erythrocyte aggregation, blood viscosity in the areas with the fast and slow blood flow were analyzed and determined as abnormal (higher than normal) in both groups (Table 3). It may be due to arterial hypertension or hypoxia and obesity in patients with mild form of OSA. Coagulation system markers and whole blood viscosity were analyzed after 3-4 nights of effective CPAP therapy to identify the short-term effects of CPAP therapy in patients with severe OSA (n = 12) (Table 4). No significant difference in levels of coagulation cascade markers after 3-4 nights of CPAP therapy were detected (Table 5). We analyzed the dynamic changes of blood viscosity after 3-4 nights of CPAP therapy. No significant changes were detected. Due to the limited number of participants, multivariate regression model was not performed now.

CONCLUSION

Significant increase of D-dimer levels, blood viscosity in areas with slow blood flow (veins, microcirculation) and erythrocyte aggregation was observed in group of patients with severe OSA, AH and obesity compared with the group of patients with mild OSA or without OSA. Elevated levels of whole blood viscosity parameters were identified in both groups without significant difference, what could be mainly associated with arterial hypertension and not OSA. No significant changes in blood rheology and clotting factors analysis were observed in patients after short-term CPAP therapy. Lack of the difference may be due to the small number of patients included in study and short duration of CPAP-therapy.

These findings confirm the necessity of further research in this field. This study will continue with increasing number of patients in each group and prolongation of effective CPAP therapy up to 3 months. Apart from standard observation estimation of the blood pressure profile in severe OSA group is planned.

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