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Original Article

Prothrombotic state in children with obstructive sleep apnea

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ABSTRACT

Objective: Increased blood coagulation might be one important mechanism linking obstructive sleep apnea (OSA) with cardiovascular diseases. We tested the association between several hemostatic parameters and sleep breathing-related variables in a representative pediatric population with a clinical suspicion of OSA.

Methods: Polysomnography was performed in 152 snoring children to diagnose OSA. Anthropometric and clinical data were registered and venous blood samples were collected for the measurement of platelet count, plateletcrit, platelet distribution width (PDW), mean platelet volume (MPV), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen and C-reactive protein.

Results: Children with OSA had significantly higher platelet count, plateletcrit and PDW compared with those without OSA. After controlling for the anthropometric characteristics (age, gender, body mass index (BMI) z-score), platelet count negatively correlated with minimum SaO_2 while the plateletcrit correlated with time with SaO_2 <90% and MPV correlated with apnea–hypopnea index. PT and PT international normalized ratio correlated with mean SaO_2 and aPTT correlated with the oxygen desaturation index.

Conclusion: Our findings suggest that different OSA-related effects may be factors contributing to an enhanced coagulability in pediatric OSA. Measures reflecting apnea severity and disrupted sleep were associated with clotting factor changes independent of covariates affecting hemostatic function.

1. Introduction

Patients with obstructive sleep apnea (OSA) have an increased risk for cardiovascular diseases [1–3] and there is growing evidence suggesting that the deleterious effects of OSA could start early in life. As shown in adults, pediatric OSA has been associated with several cardiovascular consequences [4]. Studies in children with OSA have reported increased blood pressure, changes in heart rate, endothelial dysfunction, autonomic cardiovascular abnormalities and increased inflammatory response as markers of possible cardiovascular damage [5–7].

An elevated blood coagulation might be one important mechanism linking OSA with cardiovascular diseases [8–10]. In this sense, numerous studies in adults have shown a hypercoagulable state in OSA by describing a greater platelet activity, higher levels of clotting factors and impaired fibrinolysis [11–13]. Patients with OSA present a combination of pathophysiological events that may induce a state of increased coagulability. Repeated episodes of nocturnal hypoxia and sympathetic overactivation due to recurrent airway obstructions and disrupted sleep, may promote changes in hemostasis (platelet activation, fibrinogen, clotting factors) resulting in a pro-thrombotic state [10,14,15]. In addition, previous

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research points out that hypercoagulability is a dynamic process that relates to changes in OSA status over time [16].

Currently, little is known about the relationships between hemostasis and OSA in children and also whether OSA severity accelerates the coagulation process [17–19]. We hypothesized that the repetition of apneas and oxygen desaturation events that characterize OSA may modify the normal coagulation rhythm, rendering children with OSA more susceptible to cardiovascular complications.

In this context, we tested the association between several hemostatic parameters and sleep breathing-related variables in a representative pediatric population with a clinical suspicion of OSA.

2. Material and methods

2.1. Subjects and ethics

A case–control study was carried out with 209 snoring children who were evaluated for suspected OSA. Between January 2014 and June 2017, a total of 152 snoring children were referred to the Pediatric Sleep Unit for overnight polysomnography (PSG) and selected for the study. We included children aged from 3 to 14 years. Exclusion criteria included a history of chronic medical disease or genetic condition as well as the use of medications potentially affecting sleep. Up to 51 patients were excluded due to the exclusion criteria and six patients did not have a valid register of PSG. This research was approved by the Ethics Committee of our institution (IB2136/13) and written parental consent was obtained from all of the participants.

2.2. Clinical interview and anthropometric data

Demographic and medical records were obtained and registered. A physical examination was performed before the sleep study and body mass index (BMI) z-scores were determined based on age and gender. A complete PSG was performed (Grael, Compumedics, Abbotsford, Australia) at the multidisciplinary Sleep Unit of our hospital, following the American Academy of Sleep Medicine guidelines [20]. Up to six encephalogram channels were studied, in addition to chin and anterior tibial electromyogram, bilateral electrooculogram, heart rate by electrocardiogram, airflow monitoring by nasal pressure transducer and oronasal thermistor, as well as chest and abdominal wall movement by respiratory inductance plethysmography. Transcutaneous measurement of arterial oxygen saturation (SaO_2) was performed by pulse oximetry. Apnea was defined as a decrease in nasal flow $\geq$90% in at least two respiratory cycles.

Hypopnea was defined as a decrease $\geq$30% followed by an arousal in electroencephalogram or an oxygen desaturation greater than 3%. The apnea–hypopnea index (AHI) was calculated by adding the number of apneas and hypopneas, divided by the hours of sleep. An AHI >1/h was used for the classification of OSA [21].

2.3. Laboratory analysis

In the morning following the sleep study, fasting blood samples were drawn from an antecubital vein into serum, potassium EDTA and citrate tubes for measurements. The platelet count, platelet distribution width (PDW) and the mean platelet volume (MPV) were measured within 60 min of sampling on a blood counter by flow cytometry (Cell-Dyn Sapphire, Abbott Diagnostics, USA). Prothrombin time (PT) and its international normalized ratio (PT-INR), activated partial thromboplastin time (aPTT) and fibrinogen were analyzed by turbidimetry on the ACLTOP 700 platform (Werfen, Spain). Plasma C-reactive protein (CRP) was measured in serum using a commercially available assay (Architect c1600, Abbott Diagnostics, USA).

2.4. Statistical analysis

Descriptive statistics were presented as mean ± standard deviation or median and interquartile range for continuous variables and as number and percentage for categorical variables.

Continuous variables were analyzed using the Student's *t*- or Mann–Whitney's *U*-tests when appropriate and the Chi-squared test was used for categorical variables. Spearman's correlation was used to evaluate the association between variables.

Linear regression analysis was performed when hemostatic measures correlated with both PSG parameters and anthropometric variables to determine whether correlations persisted after controlling for them (age, gender, BMI z-score).

A *p*-value lower than 0.05 was considered to indicate statistical significance. Statistical analysis was performed with the software SPSS v.19 (IBM corporation, Armonk, NY, USA).

3. Results

Anthropometric and sleep characteristics of the participants are summarized in Table 1. There were no significant differences in age, gender, BMI and BMI z-score between the OSA and non-OSA groups.

Results of coagulation parameters are shown in Table 2. In our population, platelet count, plateletcrit and PDW were significantly higher in children with OSA. No significant differences were found in MPV, PT, aPTT and fibrinogen values.

3.1. Relationships between PSG characteristics and coagulation parameters

Bivariate associations are displayed in Table 3. There were significant correlations between PSG variables (AHI, mean SaO_2, minimum SaO_2, the oxygen desaturation index and the arousal index) and platelet count, plateletcrit and fibrinogen values. In addition, platelet count correlated with the amount of time with SaO_2 <90% and with sleep efficiency. MPV data also showed a statistically significant association with AHI. A significant correlation was also obtained between mean SaO_2, minimum SaO_2, time

Table 1
Anthropometrical, clinical and polysomnographic characteristics of subjects.

	No OSA ($N = 65$)	OSA ($N = 87$)	*p*
Age (years)	8.6 ± 3.5	8.3 ± 3.5	0.582
Gender, male *N* (%)	36 (55.4%)	50 (57.5%)	0.869
BMI (kg/m^2)	23.3 ± 8.5	24.7 ± 9.1	0.580
BMI z-score	1.24 ± 1.1	1.52 ± 1.1	0.612
SBP (mmHg)	115 ± 35	110 ± 11	0.606
DBP (mmHg)	59.6 ± 7.2	61.6 ± 7.9	0.314
AHI (per h)	0.4 (0.1–0.6)	3.1 (1.9–8.3)	<0.0001
Mean SaO_2 (%)	96.9 ± 2.2	96.1 ± 2.1	0.086
Minimum SaO_2 (%)	88.6 ± 6.5	85.1 ± 6.4	0.061
Time with SaO_2<90% (%)	0.01 (0–0.4)	0.1 (0–0.6)	0.07
ODI (per h)	0.3 (0–0.4)	1 (0.4–4.8)	<0.0001
Arousal index (per h)	7.8 ± 5.4	13.3 ± 6.7	<0.0001
TST (min)	423 ± 65	428 ± 65	0.972
N1 (%TST)	2.2 ± 1.2	1.9 ± 1.1	0.236
N2 (%TST)	27.2 ± 9.8	29.7 ± 8.1	0.307
N3 (%TST)	50.2 ± 10.8	47.4 ± 9.9	0.368
REM (%TST)	20.7 ± 4.7	21.9 ± 4.9	0.296
Sleep efficiency (%)	89.6 ± 6.1	89.3 ± 5.9	0.741
Sleep latency (min)	18.1 ± 18.3	17.9 ± 16.1	0.851
REM latency (min}	101.7 ± 45.7	139.6 ± 98.7	0.754

Data are presented as *N* (%) for categorical data or as mean ± standard deviation or median (interquartile range) for continuous data. AHI, apnea–hypopnea index; BMI, body mass index; DBP, diastolic blood pressure; N1, sleep stage 1; N2 sleep stage 2; N3, sleep stage 3; ODI, O_2 desaturation index (<3%); OSA, obstructive sleep apnea; REM, rapid eye movement; SBP, systolic blood pressure; TST, total sleep time.

Table 2
Hemostatic parameters.

	No OSA ($N = 65$)	OSA ($N = 87$)	p
Platelet count ($\times 10^3/\mu L$)	302 ± 71	330 ± 86	0.029
Plateletcrit (%)	0.22 ± 0.04	0.24 ± 0.06	0.035
PDW (%)	15.8 ± 0.54	16.04 ± 0.62	0.036
MPV (fL)	7.40 ± 0.95	7.40 ± 0.97	0.926
PT (%)	87.8 ± 7.8	89.5 ± 8.2	0.330
PT-INR	1.09 ± 0.07	1.08 ± 0.07	0.354
aPTT (s)	33.9 ± 3.3	33.1 ± 3.5	0.110
aPTT ratio	1.06 ± 0.10	1.04 ± 0.12	0.133
Fibrinogen (mg/dL)	396 ± 73	423 ± 77	0.060
CRP (mg/dL)	0.08 (0.03–0.22)	0.11 (0.04–0.28)	0.146

Data are presented as mean ± standard deviation or median (interquartile range). aPTT, activated partial thromboplastin time; CRP, C-reactive protein; MPV, mean platelet volume; PDW, platelet distribution width; PT, prothrombin time; PT INR, prothrombin time international normalized ratio.

with SaO_2 <90% and PT, PT-INR results, while the oxygen desaturation index correlated with aPTT and aPTT ratio.

Age was associated with platelet indices, PT, PT-INR and fibrinogen, whereas BMI z-score was associated with plateletcrit, MPV and fibrinogen values.

The results of the linear regression analysis are described in Table 4. Platelet count remained negatively correlated with minimum SaO_2, while plateletcrit correlated with time with SaO_2 <90% and MPV correlated with AHI. Regarding the coagulation pathways, the correlations between mean SaO_2 and both PT and PT-INR remained correlated with mean SaO_2 and aPTT also remained correlated with the oxygen desaturation index.

4. Discussion

In the present cross-sectional study, we analyzed the relationships between polysomnographic parameters and hemostasis-related markers in snoring children.

Higher values of platelet count, plateletcrit and PDW were found in children with OSA compared with children without OSA. Significant associations were also detected between indices reflecting apnea severity and disrupted sleep and measures of hemostatic function. These data suggest that the presence of OSA is associated with a procoagulant state in snoring children independently of obesity.

OSA is known to have adverse effects on the cardiovascular system and multiple studies demonstrate that OSA contributes to or exacerbates cardiovascular diseases [22,23]. Changes in blood coagulation may be an underlying mechanism of the effect of OSA on these diseases [12,15,24]. It has been shown elsewhere that platelet size, measured by MPV, is a marker of platelet activation and closely related with cardiovascular complications [25–29]. Currently, the evidence describing the association between MPV and OSA is limited and inconsistent [30–33]. In a recent study, no correlation was found between MPV and OSA in obese children [17]. In our population, platelet count was significantly higher in children with OSA than in those without OSA, and inversely related to minimal nocturnal oxyhemoglobin saturation. Platelet size was also found to correlate with AHI. Hence, these findings could imply that measures reflecting apnea severity are related to platelet indices and that platelet activation is associated with hypoxia during sleep.

There were no differences between groups in terms of MPV, PT and aPTT levels. Nevertheless, multiple linear regression analyses showed independent associations between AHI and MPV and between plateletcrit and time with $SatO_2$ <90%. Among the blood coagulation tests, higher PT was significantly associated with lower mean nocturnal oxyhemoglobin saturation, while greater values of aPTT correlated with a higher oxygen desaturation index. Given that the definition of OSA is based on cut–off parameters, it is reasonable to suppose that snoring may be considered a part of the spectrum of disease; and the significant associations detected might demonstrate that the relationship between OSA physiology and procoagulant changes lies along a continuum of OSA severity.

Table 3
Bivariate relationships between hemostatic parameters and age, body mass index (BMI) z-score and polysomnographic characteristics.

	PLT	PTC	PDW	MPV	PT	PT-INR	aPTT	aPTT r	Fibrinogen
Age	−0.299**	−0.206*	0.213*	0.287**	−0.240*	0.237*	−0.023	−0.038	0.226*
BMI z score	0.064	0.185*	0.138	0.208*	−0.059	0.062	−0.041	−0.061	0.318**
AHI	0.202*	0.254*	−0.111	0.204*	0.058	−0.058	−0.085	−0.080	0.183*
Mean SaO_2	−0.246*	−0.379**	0.121	0.183	−0.332**	0.333**	0.077	0.085	−0.200*
Minimum SaO_2	−0.223*	−0.355*	0.031	0.137	−0.210*	0.201*	−0.012	−0.018	−0.224*
Time with $SatO_2$<90%	0.300**	0.344**	0.080	0.082	0.259**	−0.251**	−0.153	−0.154	0.096
ODI	0.184*	0.279**	−0.059	0.125	0.119	−0.124	−0.204*	−0.196*	0.312**
Arousal index	0.225*	0.322*	−0.022	0.161	0.023	−0.007	−0.029	−0.020	0.254*
Sleep efficiency	−0.217*	−0.129	0.131	0.089	−0.079	0.084	0.117	0.120	−0.070

aPTT, activated partial thromboplastin time; aPTT r, activated partial thromboplastin time ratio; PLT, plateletcrit; AHI, apnea–hypopnea index; MPV, mean platelet volume; ODI, O_2 desaturation index (<3%); PDW, platelet distribution width; PT, prothrombin time; PTC: plateletcrit; PT-INR, PT international normalized ratio. $^*p < 0.05$.$^{**}p < 0.01$.

Table 4
Multiple lineal regression analysis.

Regression analysis results			
Dependent variable	Independent variable	β-Coefficient	p
Platelet count	Min SaO_2 (%)	−0.373	0.011
PTC	Time with $SatO_2$<90%	0.469	0.001
MPV (fL)	AHI	0.473	0.001
PT (%)	Mean SaO_2 (%)	−0.657	<0.001
PT-INR	Mean SaO_2 (%)	0.639	<0.001
aPTT (s)	O_2 desaturation index	−0.376	0.015
Fibrinogen	Arousal index	0.347	0.022

Each β-coefficient represents a separate regression model, controlling for age, gender and BMI-z score. aPTT, activated partial thromboplastin time; MPV, mean platelet volume; PT, prothrombin time; PTC, plateletcrit; PT-INR: PT international normalized ratio.

PT is a reflection/indicator of the extrinsic coagulation pathway, whereas aPTT is a reflection/indicator of the intrinsic coagulation pathway. Previous literature highlights that intermittent hypoxia experienced by OSA patients can induce endothelial injury and this in turn may initiate the extrinsic coagulation pathway. In addition, clinical studies provide some evidence for a causal association between OSA and blood coagulation [10,16,34]. In this sense, our findings of an association between AHI and MPV and between PT and mean nocturnal oxyhemoglobin saturation suggest that the severity of hypoxemia may induce a procoagulant state in snoring children with OSA.

Among hemostatic factors, fibrinogen has emerged as a possible marker linking OSA with cardiovascular risk [9,35,36]. In the present study, fibrinogen values tended to be higher in children with OSA compared to non-OSA snoring children, although differences did not reach statistical significance. Moreover, fibrinogen levels were related to arousal index. By contrast, a previous investigation in children with OSA did not find any significant association between fibrinogen levels and PSG indices [18]. A possible explanation for this discrepancy is that children with OSA were younger than snoring children without OSA in that approach. An alternative explanation is that fibrinogen is associated with systemic inflammation. However, in this sense, we could not find any significant difference in CRP levels between children with and without OSA. In fact, a major strength of our approach is that age, gender and BMI z-score were similar between groups. Consequently, our results point out that partial sleep loss due to repeated arousals may be a possible additional mechanism by which OSA may influence fibrinogen levels in snoring children.

The mechanisms underlying increased coagulability in OSA appear to be complex, mutually interacting or additive [12]. Hypoxia, sympathetic overactivity and chronic inflammation are the most probable pathways implicated [14,24,37]. Childhood obesity, an important risk factor for OSA, has also been also linked to alterations in hemostasis [38]. We found significant associations between age, BMI z-score and hemostatic parameters. Nevertheless, although the strength of the correlations were weak, multiple regression analysis indicated that pediatric OSA seems to be an independent factor that may induce measurable coagulation disturbances using a combination of routine markers. Taken together, these observations suggest the convergence of the deleterious consequences of obesity and OSA and underline the importance of considering the dysfunction of the coagulation system as an important contributor to cardiovascular complications in the context of OSA.

A potential limitation of this study is the lack of a healthy non-snoring children group. The individuals included in our study are only snoring children, this fact may pose a selection bias. However, this provides added value in terms of diagnostic use, since it aids in the selection of patients with a clinical suspicion of the disease. The addition of a non-snoring control group could strengthen the observed differences.

In summary, our findings lead to the idea that different OSA-related effects may be factors contributing to an enhanced coagulability. Measures reflecting apnea severity and increased sleep fragmentation were associated with clotting factor changes independent of covariates affecting hemostatic function. Further studies are needed to identify snoring children at high risk for developing cardiovascular diseases, to check the treatment effect and validate the long-term significance of these findings.

Author contributions

A.B., D.M.G., A.A. and J.A.P.Z. conceived of and designed the study. A.B., D.M.G., J.P., P.G., C.R. and J.A.P.Z. supervised the data collection and managed the data, including quality control. P.S., N.T., M.P. and A.B. provided statistical advice on study design and analyzed the data, A.B. and A.A. chaired the data oversight committee. A.B. and D.M.G. drafted the manuscript, and all authors contributed substantially to its revision. A.B. and A.A. take responsibility for the paper as a whole.

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Conflicts of interest

All authors declare no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.022.

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