JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Association Between Hypercoagulability and Severe Obstructive Sleep Apnea

Seung-No Hong, MD; Hee-Chul Yun, MD; Joon Hyuk Yoo, MD; Seung Hoon Lee, MD, PhD

IMPORTANCE Obstructive sleep apnea (OSA) is related to the increased risk of cardiovascular disease. Although the pathogenesis of this association remains unclear, an alteration in coagulability is suspected as a link.

OBJECTIVE To investigate the association between the severity of OSA and blood coagulability.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study conducted at a tertiary care university hospital evaluated 146 patients with OSA from January 1, 2009, to July 31, 2015. The participants were divided into 4 groups according to the severity of OSA: control, mild, moderate, and severe.

MAIN OUTCOMES AND MEASURES Association between the severity of OSA and coagulation test results, including platelet count, bleeding time, prothrombin time (PT) in seconds and as international normalized ratio (INR), and activated partial thromboplastin time.

RESULTS Of the 146 patients, 135 (92.5%) were men; mean (SD) age was 34.8 (11.1) years. The control group included 41 (28.1%) patients; mild OSA, 32 (21.9%); moderate OSA, 30 (20.5%); and severe OSA, 43 (29.5%). Significant correlations were found between the apnea-hypopnea index and the PT seconds (Spearman *r* coefficient, −0.30; 95% CI, −0.44 to −0.14) and PT INR (Spearman *r* coefficient, −0.30; 95% CI, −0.44 to −0.14). There were significant differences between the OSA severity groups for PT seconds for the control group (mean, 11.26 [0.78] seconds) vs the moderate OSA group (10.74 [0.62] seconds; mean difference [MD], 0.52; 95% CI, 0.27 to 1.01) and the severe OSA group (10.67 [0.77] seconds; MD, 0.59; 95% CI, 0.14 to 1.03). Significant differences were also noted in PT INR between the control group (1.00 [0.07]) vs the moderate OSA group (0.95 [0.05]; MD, 0.04; 95% CI, 0.01 to 0.07) and the severe OSA group (0.94 [0.07]; MD, 0.05; 95% CI, 0.02 to 0.08). However, there was no significant difference between the control and mild OSA groups in PT seconds.

CONCLUSIONS AND RELEVANCE These results suggest that patients with moderate to severe OSA have elevated blood coagulability markers compared with healthy individuals, which may contribute to the occurrence of cardiovascular complications.

JAMA Otolaryngol Head Neck Surg. doi:10.1001/jamaoto.2017.1367
Published online August 17, 2017.

Author Affiliations: Department of Otorhinolaryngology–Head and Neck Surgery, Korea University College of Medicine, Korea University Ansan Hospital, Ansan-si, Republic of Korea.

Corresponding Author: Seung Hoon Lee, MD, PhD, Department of Otorhinolaryngology–Head and Neck Surgery, Korea University College of Medicine, Korea University Ansan Hospital, 123, Jeokgeum-ro, Danwon-gu, Ansan-si, Gyeonggi-do 15355, Republic of Korea (shleeent@korea.ac.kr).

Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing, affecting 9% to 15% of middle-aged adults.[1] Obstructive sleep apnea is clinically important because it has a potential risk of causing a wide range of comorbidities. Among those possible associated comorbidities, cardiovascular diseases, including myocardial infarction, ischemic heart disease, and stroke, can result in high levels of morbidity and mortality, which require clinical intervention.[2-5] Nevertheless, it is unclear how OSA can cause these diseases, and numerous studies have attempted to determine the underlying pathogenic mechanism of this undesirable association.

In patients with persistent sleep apnea, several regulatory mechanisms are disrupted owing to the burden placed on their systems that is triggered by airway obstruction, including hypoxemia, hypercapnia, strenuous inspiratory effort, and arousal from sleep.[6,7] These conditions can impose consecutive stress on the hemodynamic and/or autonomic nervous systems by affecting the peripheral and central chemoreceptors leading to cardiovascular disease.[4,8] Another possible explanation is increased blood coagulability. Hemostatic alterations that increase the risk of thrombi formation can also be influenced by chronic inflammation, which is a major pathophysiologic effect of OSA.[9,10] Therefore, hypercoagulability may be a reasonable link between OSA and cardiovascular complications by contributing to both inflammation and thrombosis. However, limited data are available regarding the effects of OSA on coagulation, and whether OSA predisposes individuals to intravascular thromboembolic disease remains unproven. Moreover, there is scarce evidence regarding the correlation between the severity of OSA and various clinical blood coagulation tests that may provide an explanation for the elevated prevalence of cardiovascular disease in patients with OSA. To address this knowledge gap, we investigated the association between the severity of OSA and blood coagulability.

Key Points

Question What is the association between the severity of obstructive sleep apnea and blood coagulability, which is a cardiovascular risk marker?

Findings In this cohort study of 146 patients, severity of obstructive sleep apnea was significantly correlated with prothrombin time, but not with activated partial thromboplastin time or platelet count. Patients with moderate to severe obstructive sleep apnea had elevated blood coagulability markers compared with control patients.

Meaning Blood coagulation markers increase to a more procoagulant state in patients with obstructive sleep apnea, especially those in whom levels were moderate to severe.

Methods

Patients

From January 1, 2009, to July 31, 2015, we retrospectively analyzed 183 consecutive individuals who had visited a tertiary care hospital for treatment of snoring or sleep apnea. The patients underwent full-night polysomnography and coagulation function tests. Patients with coagulation diseases, liver disease, diabetes, hypertension, and a history of anticoagulant medication use or surgery for sleep disorders were excluded. A total of 146 patients were enrolled and categorized according to the apnea-hypopnea index (AHI) into the following groups of OSA episodes per hour: control (0-5.0), mild (5.0-14.9), moderate (15.0-29.9), and severe (≥30.0).[11]

We examined the association between the severity of OSA and the coagulation test results, including platelet (PLT) count; bleeding time (BT); prothrombin time (PT), measured in seconds and as international normalized ratio (INR); and activated partial thromboplastin time (aPTT). This study was approved by the ethics committee of the Korea University College of Medicine. The patients provided written informed consent; no financial compensation was provided.

Full-Night Polysomnography

Full-night polysomnography (Alice 4; Respironics) was performed to evaluate sleep structure and respiratory variables (apnea index, AHI, oxygen desaturation index, and minimum arterial oxygen saturation). Electroencephalography electrodes were applied at C3/A2, O1/A2, and O2/A1, and 2 electrooculography electrodes were applied at the sides of both eyes to record horizontal and vertical eye movements. Submental electromyography electrodes were applied at the submentalis muscle, and leg movements during sleep were recorded via electromyography electrodes from both anterior tibialis muscles. Strain gauges were used for recording the chest and abdominal respiratory movements. Airflow was estimated using nasal pressure cannulas and oronasal thermistor. Arterial oxygen saturation was measured using pulse oximeters placed on the index fingers. The polysomnography data were manually scored by a sleep technician and reviewed by one of us, a certified physician (S.H.L.) in accordance with the criteria of the *American Academy of Sleep Medicine*.[11] Apnea was defined as a decrease in airflow by 90% or more that lasts for at least 10 seconds and hypopnea was defined as a decrease in airflow by 30% or more associated with a reduction in oxygen saturation of 4% or more for at least 10 seconds. The apnea index was defined as the number of apnea episodes per hour of sleep, and AHI was defined as the number of apnea and hypopnea episodes per hour. Oxygen desaturation index was defined as the number of desaturations of 4% or more per hour of sleep.

Blood Coagulation Tests

After a fasting period of 12 hours, blood samples were drawn (21-gauge sterile syringe) from an antecubital vein into citrate tubes, with patients placed in a seated position at the same time of day (9:00-10:00 AM). Samples were then centrifuged at 3000*g* for 10 minutes; the platelet-poor plasma component was separated and stored at −80°C until further analysis. After storage, the frozen samples were thawed and measured (ACL TOP analyzer; Instrumentation Laboratory, Werfen Group, Barcelona, Spain). The blood coagulation analysis was performed in the hospital laboratory using standard methods. The following blood coagulation factors were measured: PLT count, BT, aPTT, and PT in seconds and as INR.

Table 1. Demographic and Polysomnography Characteristics of 146 Patients

Characteristic	Mean (SD)			
	Control	Mild OSA	Moderate OSA	Severe OSA
Demographic variables				
Patients	41 (28.1)	32 (21.9)	30 (20.5)	43 (29.5)
Age, y	28.9 (10.5)	35.9 (10.4)	37.7 (10.8)	37.7 (10.6)
Sex, No. (%)				
Men	31 (75.6)	32 (100)	30 (100)	42 (97.7)
Women	10 (24.4)	0	0	1 (2.3)
BMI	24.15 (2.80)	25.53 (2.62)	25.63 (2.65)	28.3 (3.63)
Sleep variables				
TST, min	376.21 (90.41)	385.27 (85.12)	404.94 (44.59)	383.6 (65.65)
SE, %	85.65 (12.35)	86.7 (8.10)	89.23 (5.87)	85.3 (11.49)
Sleep stage, %				
1	17.96 (10.35)	25.82 (9.85)	29.11 (10.32)	50.6 (17.99)
2	60.57 (7.62)	55.14 (7.93)	51.89 (8.29)	32.8 (16.21)
3	4.949 (6.06)	1.30 (2.58)	1.16 (3.03)	1.11 (2.81)
REM	16.52 (5.82)	17.73 (6.20)	17.84 (4.75)	14.6 (4.25)
Arousal index, episodes/h	18.97 (9.69)	27.58 (9.67)	32.35 (9.37)	64.11 (23.30)
Respiratory variables				
AHI, episodes/h	1.77 (1.14)	9.41 (2.57)	21.93 (4.87)	61.31 (24.97)
AI, episodes/h	0.83 (1.14)	5.05 (2.90)	15.09 (6.57)	50.87 (28.70)
RDI, episodes/h	12.00 (8.26)	24.67 (8.06)	33.05 (7.61)	67.43 (22.20)
Min Sao_2, %	90.66 (4.25)	85.81 (7.59)	81.10 (6.57)	70.33 (16.67)
Snoring, %	21.33 (17.60)	33.48 (18.88)	38.75 (18.12)	26.17 (14.86)

Abbreviations: AHI, apnea-hypopnea index; AI, apnea index; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Min Sao_2, minimum saturation of arterial blood; OSA, obstructive sleep apnea; RDI, respiratory disturbance index; REM, rapid eye movement; SE, sleep efficiency; TST, total sleep time.

Statistical Analysis

The sample size was estimated by G*Power, version 3.1.9 (Franz Faul, Kiel University) with power = 0.80, α = .05, and effect size = 0.285 (estimated from results of a previous study) for a 2-tailed correlation analysis (target sample size, 94).[12] SPSS, version 20 (IBM Corp) was used to analyze the data. The continuous variables are described as means (SDs). The variables were investigated using analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests) to determine normality. Differences between groups were identified by analysis of variance or Kruskal-Wallis test (in the case of nonnormality) followed by post hoc comparisons (Tukey honest significant difference test and Bonferroni-adjusted Mann-Whitney test). The adjusted α level was set at 0.0083. The Pearson or Spearman correlation test (in case of nonnormality) was used to assess the correlation between variables (coefficient, *r*). In all cases, 95% CIs were determined to estimate the effect size and mean differences.

Results

Demographic and Polysomnography Data

A total of 146 patients (135 [92.5%] men and 11 [7.5%] women; mean [SD] age, 34.8 [11.1] years) were evaluated. Mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) was 26.0 (3.4). The participants were categorized according to the severity of OSA: there were 41 (28.1%) control patients, 32 (21.9%) with mild OSA, 30 (20.5%) with moderate OSA, and 43 (29.5%) with severe OSA. Other sleep and respiratory variables are reported in **Table 1**.

Correlation Between AHI Score and Coagulation Test

There was a significant correlation between AHI and the coagulation test results, including PT seconds (Spearman *r*, −0.30; 95% CI, −0.44 to −0.14), and PT INR (Spearman *r*, −0.30; 95% CI, −0.44 to −0.14). Because PT seconds and PT INR both indicate the function of extrinsic and common coagulation pathways, the strength of the association with AHI was similar. However, a significant correlation was not found between AHI and BT (Spearman *r*, −0.07; 95% CI, −0.23 to 0.09), PLT count (Spearman *r*, 0.17; 95% CI, 0.01 to 0.32), or aPTT (Pearson *r*, 0.08; 95% CI, −0.08 to 0.24) (**Figure 1**).

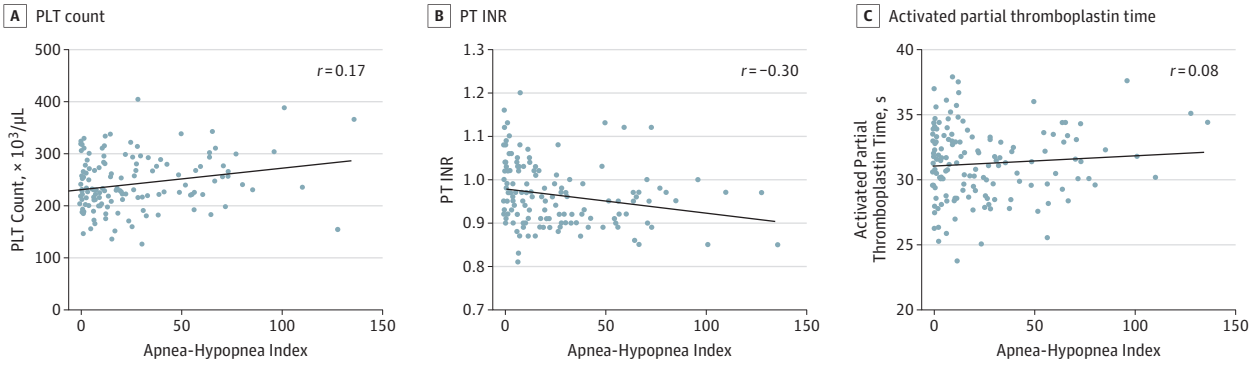
Coagulation Test Results According to AHI Grade

The post hoc analysis revealed that the duration of PT seconds of the control group was significantly longer than that of the moderate OSA group (mean difference [MD], 0.52; 95% CI, 0.27 to 1.01) and the severe OSA group (MD, 0.59; 95% CI, 0.14 to 1.03). With regard to the PT INR, the ratio in the control group was greater than that of the moderate OSA group (median difference, 0.04; 95% CI, 0.01 to 0.07) and the severe OSA group (median difference, 0.05; 95% CI, 0.02 to 0.08) (**Figure 2**). The magnitude of MDs between the control group and moderate or severe OSA groups was comparable. However, there was no significant difference between the control group and the mild OSA group for PT seconds (MD, 0.34; 95% CI, −0.14 to 0.82) and PT INR (median difference, 0.03; 95% CI, −0.01 to 0.07). Other results of coagulation tests are reported in **Table 2**.

Other Polysomnography Variables and Coagulation Function

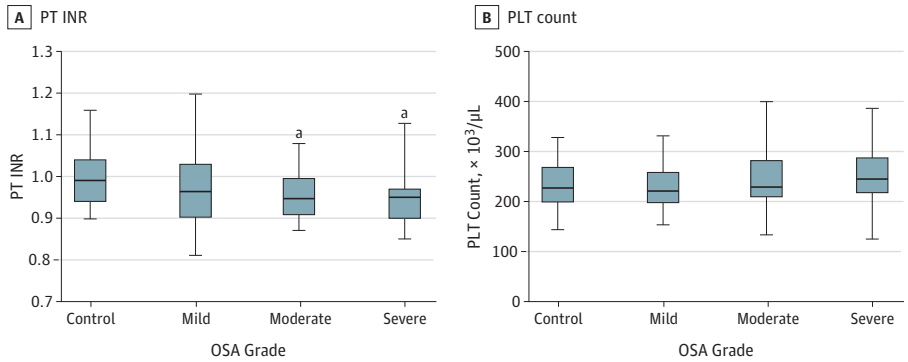
The oxygen desaturation index level showed a significant association between the PT seconds (Spearman *r*, −0.29;

Figure 1. Correlation Between the Apnea-Hypopnea Index Grades and Coagulation Test Results



A, Platelet (PLT) count. B, Prothrombin time as international normalized ratio (PT INR). C, Activated partial thromboplastin time. Apnea-Hypopnea Index is defined as the number of apnea and hypopnea episodes per hour. To convert PLTs to ×10^9/L, multiply by 1.

Figure 2. Results From the Coagulation Tests According to the Apnea-Hypopnea Index (AHI) Grade



A, The control group had significantly higher values of prothrombin time as international normalized ratio (PT INR) compared with those of the moderate and severe obstructive sleep apnea (OSA) groups. B, There was no significant difference in the platelet (PLT) count between the AHI groups. To convert PLTs to ×10^9/L, multiply by 1. Data shown as medians; error bars indicate 95% CIs.

[a] Compared with control, $P \leq .008$ for the test (adjusted with a Bonferroni correction).

Table 2. Results of Coagulation Tests According to the Apnea-Hypopnea Index Grade

Coagulation Test	Control	Mild OSA	Moderate OSA	Severe OSA
PLT count, ×10^3/µL	228 (146-329)	222 (155-333)	230 (135-401)	247 (126-387)
MPV, fL	8.2 (6.8-10.4)	8.0 (7.1-9.4)	8.4 (7.1-11.1)	8.1 (6.9-10.6)
BT, s	122 (84-231)	131 (97-214)	117 (84-183)	120 (70-295)
PT seconds				
Median (range)	11.2 (10.1-13.1)	10.8 (9.1-13.6)	10.7 (9.9-12.2)	10.6 (9.6-12.8)
Mean (SD)	11.26 (0.78)	10.92 (0.95)	10.74 (0.62)	10.67 (0.77)
PT INR				
Median (range)	1.00 (0.90-1.16)	0.96 (0.81-1.20)	0.95 (0.87-1.08)	0.94 (0.85-1.13)
Mean (SD)	1.00 (0.07)	0.97 (0.08)	0.95 (0.05)	0.94 (0.07)
aPTT, s				
Median (range)	31.6 (25.3-37.0)	32.3 (23.8-37.9)	30.2 (25.1-34.5)	31.5 (25.6-37.6)
Mean (SD)	31.26 (2.64)	31.93 (3.38)	30.26 (2.11)	31.45 (2.45)

Abbreviations: aPTT, activated partial thromboplastin time; BT, bleeding time; INR, international normalized ratio; MPV, mean platelet volume; OSA, obstructive sleep apnea; PLT, platelet; PT, prothrombin time.

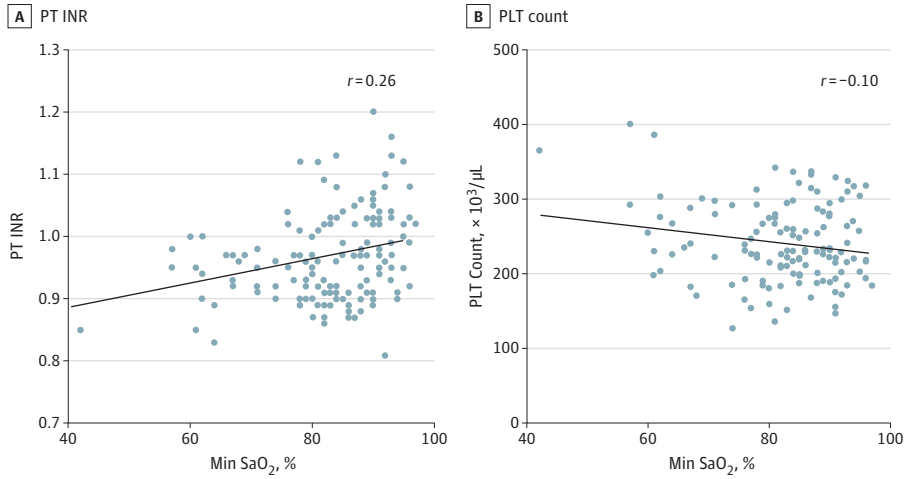
SI conversion factor: To convert platelets to ×10^9/L, multiply by 1.

95% CI, −0.43 to −0.13), and INR (Spearman *r*, −0.29; 95% CI, −0.43 to −0.13). Minimum oxygen saturation also showed a statistically significant correlation with PT seconds (Spearman *r*, 0.26; 95% CI, 0.09 to 0.41) and PT INR (Spearman *r*, 0.26; 95% CI, 0.10 to 0.41), but not with the PLT count (Spearman *r*, −0.10; 95% CI, −0.24 to 0.09) (**Figure 3**). Bleeding time and aPTT did not show any statistically significant correlation with either the oxygen desaturation index and minimum oxygen saturation.

Discussion

Our results suggest that blood coagulation test results increase to a more procoagulant state in patients with OSA, especially in the moderate to severe OSA groups, as estimated by AHI. Among the coagulation variables, PT seconds and PT INR were significantly correlated with the severity of OSA, while aPTT, BT, and PLT count showed no association.

Figure 3. Correlation Between the Minimum Arterial Blood Saturation (Min Sao_2) and the Coagulation Test Results



A, Prothrombin time as international normalized ratio (PT INR). B, Platelet (PLT) count. To convert PLTs to $\times 10^9$/L, multiply by 1.

Because cardiovascular disease is one of the most crucial complications of OSA, many studies have attempted to explain the correlation between the diseases. It remains uncertain whether OSA acts as an independent risk factor for cardiovascular disease. However, several studies reported an increased risk of cardiovascular disease in patients with OSA, even after adjusting for the well-known risk factors of cardiovascular disease, such as hypertension, hyperlipidemia, diabetes, and smoking.[13,14]

There are several proposed underlying mechanisms for the occurrence of cardiovascular disease in OSA. For example, acute hemodynamic changes during episodes of apnea, decreased cerebral blood flow, paradoxical embolization, atherosclerosis, hypoxia-related cerebral ischemia, and hypercoagulability are the suggested mechanisms.[13,15,16] Although it is yet less studied, increased coagulability has emerged as a possible mediator of cardiovascular pathophysiology in OSA, and evidence is accumulating. Previous epidemiologic studies have shown that a disrupted coagulation system is a significant risk factor for cardiovascular disease.[17,18] Investigation has shown that the level of fibrinogen—the end product of the coagulation pathway—was positively correlated with the respiratory disturbance index in patients with OSA who had a history of stroke.[19] Saygin et al[20] reported that the PLT count was associated with the severity of OSA in patients with cardiovascular disease, but no correlation was found in patients without cardiovascular disease.

Our study also displayed some association between the blood coagulation factors and OSA; this finding is in accord with other published data. Furthermore, after dividing the patients with OSA into groups based on AHI severity, there was a significant difference in the coagulability of the moderate to severe OSA groups, compared with that of the control group, whereas the mild OSA group did not show any significant difference. This finding may indicate the underlying pathophysiologic mechanism of inducing cardiovascular complications. Several previous reports demonstrated that the majority of the cardiovascular complications were connected with severe OSA rather than with mild OSA. In an 18-year mortality follow-up study, Young et al[21] reported that the adjusted hazard ratio for cardiovascular mortality association for patients with severe OSA (AHI≥30) was 5.2 (95% CI, 1.6-9.0), but the findings in those with mild OSA were negligible. It was determined that there was no significant change in cardiovascular mortality of patients with mild to moderate OSA, whereas those with severe OSA showed significant differences in outcome following continuous positive airway pressure (CPAP) treatment. As such, greater attention should be paid to patients with severe OSA, since it is an independent predictor for risk for cardiovascular mortality.[3,4,22] In a prospective observational study of 166 patients with a history of ischemic stroke, the group of patients with an AHI of 20 or greater and poor tolerance of CPAP showed higher rates of mortality after 5 years of follow-up than did those with an AHI of less than 20 or patients who tolerated CPAP.[23] Therefore, in terms of its influence on the concordant, severe cases, this finding may reflect the effects of increased blood coagulability markers as an important candidate mediator on inducing cardiovascular complications in patients with OSA.

The hypercoagulable state usually occurs with genetic conditions, such as coagulation factor mutation, deficiencies of natural proteins that prevent clotting, and an abnormal fibrinolytic system. In addition, hypercoagulability can be acquired following surgery, trauma, cancer, pregnancy, or medication use.[24,25] Unfortunately, the mechanism of how OSA elicits the hypercoagulable state remains vague. In accounting for the induction of the hypercoagulable state, Eisensehr et al[26] implicated the interplay between coagulation and the sympathetic nervous system. They demonstrated that the activation of hemostasis was induced by the morning epinephrine surges in patients with severe OSA. Evidence has also suggested that OSA was an independent risk factor of excessive platelet activation and arterial thrombosis.[27] Furthermore, repeated episodes of nocturnal hypoxia lead to a

hypercoagulable state that predisposes patients to thrombotic events.[28] Most studies are underpinned by the concept that the procoagulant state is induced by OSA; however, the lack of adequate control remains the major drawback in explaining the correlation between OSA and coagulation.

In our study, PT was shortened, but aPTT did not show any difference in patients with moderate to severe OSA compared with the control group. Because the PT, aPTT, and BT levels indicate the actual time of coagulation in certain circumstances, the difference in PT level is clinically significant even though data are within the reference range. In addition, PT is an important factor, as it reflects the function of the extrinsic and common coagulation pathways.[29,30] Robinson et al[31] reported increased levels of extrinsic coagulation factor VII in patients with OSA compared with the controls, whereas levels of factor VIII, an intrinsic factor, did not show any difference. It was also demonstrated that the increase in the levels of factor VII was reversed after nasal CPAP treatment in patients with OSA.[32] An acquired PT abnormality while aPTT is normal often indicates liver damage, deficiencies in clotting factors and vitamin K, or the use of medication.[30] However, these conditions promote the elongation of PT rather than its contracture.

It is known that chronic inflammatory responses are often associated with the activation of coagulation.[33,34] One of the primary proposed mechanisms of hypercoagulability in inflammatory conditions is tissue factor–mediated thrombin production, which is induced by proinflammatory cytokines.[13,19,35] Because tissue factor also initiates the extrinsic coagulation pathway, inflammatory response can be an etiologic factor for PT shortening that occurs when the extrinsic coagulation pathway is activated. Studies demonstrated that the endothelial dysfunction caused by the intermittent hypoxia of OSA may initiate the extrinsic pathway.[36,37] Systemic inflammatory processes have been shown as the key contributors to the pathogenesis of OSA.[10,38] Therefore, in our study, shortening of the PT in patients with OSA may be due to the underlying chronic inflammatory processes of OSA.

Limitations

Because this was a retrospective study, the causal association between OSA and coagulation is difficult to establish. This fact may limit the interpretation of our results. However, several studies have demonstrated that a change in coagulability was evident, and a prospective study showed that thrombus formation was reduced following CPAP; this finding may suggest that there is a causal association between OSA and blood coagulation.[39,40] Another limitation of this study is potential confounding of the association between AHI and coagulation measures by age, body mass index, smoking status, and/or other potential confounding variables. Further intervention studies, including additional investigation into possible confounding factors that requires a larger sample size, are needed to clearly elucidate and explain the contribution of coagulation to the incidence of cardiovascular diseases in OSA.

Conclusions

This study has shown that there is a correlation between OSA and the coagulation system. The AHI level was correlated with the PT level, which represented extrinsic coagulation pathway function, whereas there was no observed correlation with BT or aPTT level. Patients with severe OSA may have elevated coagulability levels, particularly in the length of PT, compared with those without OSA.

ARTICLE INFORMATION

Accepted for Publication: June 3, 2017.

Published Online: August 17, 2017. doi:10.1001/jamaoto.2017.1367

Author Contributions: Dr Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hong, Yoo, Lee.
Acquisition, analysis, or interpretation of data: Hong, Yun, Lee.
Drafting of the manuscript: Hong, Lee.
Critical revision of the manuscript for important intellectual content: Yun, Yoo, Lee.
Statistical analysis: All authors.
Administrative, technical, or material support: Hong.
Study supervision: Yoo, Lee.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Ferini-Strambi L, Fantini ML, Castronovo C. Epidemiology of obstructive sleep apnea syndrome. *Minerva Med*. 2004;95(3):187-202.

2. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *JAMA*. 2003;290(14):1906-1914.

3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. 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(9464):1046-1053.

4. Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. *Chest*. 2008;133(3):793-804.

5. Dart RA, Gregoire JR, Gutterman DD, Woolf SH. The association of hypertension and secondary cardiovascular disease with sleep-disordered breathing. *Chest*. 2003;123(1):244-260.

6. Somers VK. Sleep—a new cardiovascular frontier. *N Engl J Med*. 2005;353(19):2070-2073.

7. Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea: pathophysiology and diagnosis. *Chest*. 2007;132(1):325-337.

8. von Känel R, Dimsdale JE. Hemostatic alterations in patients with obstructive sleep apnea and the implications for cardiovascular disease. *Chest*. 2003;124(5):1956-1967.

9. Toraldo DM, Peverini F, De Benedetto M, De Nuccio F. Obstructive sleep apnea syndrome: blood viscosity, blood coagulation abnormalities, and early atherosclerosis. *Lung*. 2013;191(1):1-7.

10. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? *Thorax*. 2009;64(7):631-636.

11. Iber C. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications*. Westchester, IL: American Academy of Sleep Medicine; 2007.

12. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods*. 2009;41(4):1149-1160.

13. 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(19):2034-2041.

14. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. *Am J Respir Crit Care Med*. 2002;166(2):159-165.

15. Kraiczi H, Caidahl K, Samuelsson A, Peker Y, Hedner J. Impairment of vascular endothelial

function and left ventricular filling: association with the severity of apnea-induced hypoxemia during sleep. *Chest*. 2001;119(4):1085-1091.

16. Baltzan M, Suissa S. Mortality in sleep apnea patients: a multivariate analysis of risk factors—a response to Lavie and collaborators. *Sleep*. 1997;20(5):377-380.

17. Wilhelmsen L, Svärdsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med*. 1984;311(8):501-505.

18. Folsom AR, Wu KK, Davis CE, Conlan MG, Sorlie PD, Szklo M. Population correlates of plasma fibrinogen and factor VII, putative cardiovascular risk factors. *Atherosclerosis*. 1991;91(3):191-205.

19. Wessendorf TE, Thilmann AF, Wang YM, Schreiber A, Konietzko N, Teschler H. Fibrinogen levels and obstructive sleep apnea in ischemic stroke. *Am J Respir Crit Care Med*. 2000;162(6):2039-2042.

20. Saygin M, Ozturk O, Ozguner MF, Akkaya A, Varol E. Hematological parameters as predictors of cardiovascular disease in obstructive sleep apnea syndrome patients. *Angiology*. 2016;67(5):461-470.

21. 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(8):1071-1078.

22. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. *Sleep Breath*. 2017;21(1):181-189.

23. Martínez-García MA, Soler-Cataluña JJ, Ejarque-Martínez L, et al. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. *Am J Respir Crit Care Med*. 2009;180(1):36-41.

24. Schafer AI. Hypercoagulable states: molecular genetics to clinical practice. *Lancet*. 1994;344(8939-8940):1739-1742.

25. Rosenberg RD, Aird WC. Vascular-bed–specific hemostasis and hypercoagulable states. *N Engl J Med*. 1999;340(20):1555-1564.

26. Eisensehr I, Ehrenberg BL, Noachtar S, et al. Platelet activation, epinephrine, and blood pressure in obstructive sleep apnea syndrome. *Neurology*. 1998;51(1):188-195.

27. Liak C, Fitzpatrick M. Coagulability in obstructive sleep apnea. *Can Respir J*. 2011;18(6):338-348.

28. Lavie L. Obstructive sleep apnoea syndrome—an oxidative stress disorder. *Sleep Med Rev*. 2003;7(1):35-51.

29. Mann KG. Thrombin formation. *Chest*. 2003;124(3)(suppl):4S-10S.

30. Dahlbäck B. Blood coagulation. *Lancet*. 2000;355(9215):1627-1632.

31. 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(9):777-782.

32. 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(9):627-633.

33. Levi M, Opal SM. Coagulation abnormalities in critically ill patients. *Crit Care*. 2006;10(4):222.

34. D'Angelo G. Inflammation and coagulation: a "continuum" between coagulation activation and prothrombotic state. *J Blood Disord*. 2015;2(1):1023.

35. Levi M, ten Cate H, Bauer KA, et al. Inhibition of endotoxin-induced activation of coagulation and fibrinolysis by pentoxifylline or by a monoclonal anti-tissue factor antibody in chimpanzees. *J Clin Invest*. 1994;93(1):114-120.

36. Zhan X, Li L, Wang N, et al. Can upper airway surgery for OSA protect against cardiovascular sequelae via effects on coagulation? *Acta Otolaryngol*. 2016;136(3):293-297.

37. Lurie A. Endothelial dysfunction in adults with obstructive sleep apnea. *Adv Cardiol*. 2011;46:139-170.

38. Ifergane G, Ovanyan A, Toledano R, et al. Obstructive sleep apnea in acute stroke: a role for systemic inflammation. *Stroke*. 2016;47(5):1207-1212.

39. von Känel 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(3):139-146.

40. 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(6, pt 1):1972-1976.