Association between mean platelet volume and severity of disease in patients with obstructive sleep apnea syndrome without risk factors for cardiovascular disease

Kalp-damar hastalığı için risk faktörleri bulunmayan tıkayıcı uyku apnesi sendromlu hastalarda ortalama trombosit hacmi ile hastalığın ciddiyeti arasındaki ilişki

Mustafa Serkan Karakaş, M.D., Refik Emre Altekin, M.D.,[#] Ahmet Oğuz Baktır, M.D.,[*] Murathan Küçük, M.D.,[#] Aykut Çilli, M.D.,[†] Selim Yalçınkaya, M.D.[#]

Department of Cardiology, Nigde State Hospital, Niğde; Departments of [#]Cardiology, [†]Chest Diseases, Akdeniz University Faculty of Medicine, Antalya;
[*]Department of Cardiology, Kayseri Training and Research Hospital, Kayseri

ABSTRACT

Objectives: Obstructive sleep apnea syndrome (OSAS) is associated with increased cardiovascular morbidity and mortality. Platelet activation and aggregation are central processes in the pathophysiology of atherothrombosis. Mean platelet volume (MPV), a determinant of platelet activation, is a newly-emerging risk factor for atherothrombosis. Therefore, we have investigated the possible association between OSAS and MPV.

Study design: We selected 30 mild, 32 moderate, and 31 severe OSAS patients and 31 healthy control subjects matched for age, sex, and body mass index. MPV was measured using an automated blood cell counter.

Results: The MPV levels were significantly higher in the severe OSA group than in the control group (8.6±1.1 *vs.* 7.8±0.7 fl, p=0.03). There were no significant differences in respect to MPV between controls and patients with mild and moderate OSA (7.8±0.7 *vs.* 8.3±1.2 fl, p=0.2; 7.8±0.7 *vs.* 8.4±1.3 fl, p=0.08) and between patients with mild, moderate, and severe OSA (8.3±1.2 *vs.* 8.4±1.3 *vs.* 8.6±1.1 fl, p=0.9). Significant correlations were seen between MPV and apnea-hypopnea index (r=0.347, p≤0.001), minimal oxygen saturation (r=-0.224, p=0.03), and the percentage of recording time spent at a oxygen saturation less than 90% (r=0.240, p=0.02).

Conclusion: Our results suggest that OSAS patients tend to have relatively increased platelet activation andatherothrombotic risk.

ÖZET

Amaç: Tıkayıcı uyku apnesi sendromu (TUAS) kalp-damar hastalığı morbidite ve mortalitesinde artışa neden olmaktadır. Aterotromboz patofizyolojisinde trombosit aktivasyonu ve agregasyonu önemli rol oynamaktadır. Trombosit aktivasyonunun göstergesi olan ortalama trombosit hacmi (OTH) aterotromboz için yeni tanımlanan risk faktörlerinden birisidir. Bu çalışmada TUAS ile OTH arasındaki olası ilişkiyi araştırdık.

Çalışma planı: Çalışmaya yaş, cinsiyet ve beden kütle indeksleri açısından benzer olan 30 hafif, 32 orta dereceli ve 31 ciddi dereceli TUAS'lı hasta ile 31 olgulu sağlıklı kontrol grubu alındı. OTH değerleri ölçüldü.

Bulgular: Ciddi TUAS grubunda OTH düzeyi kontrol grubuna göre anlamlı olarak yüksek bulundu (8.6±1.1 ve 7.8±0.7 fl, p=0.03). Hafif ve orta dereceli TUAS'lı hastalar ile kontrol grubu arasında (7.8±0.7 ve 8.3±1.2 fl, p=0.2; 7.8±0.7 ve 8.4±1.3 fl, p=0.08) ve hafif, orta ve ciddi dereceli OSAS'lı hastaların kendi arasında (8.3±1.2 ve 8.4±1.3 ve 8.6±1.1 fl, p=0.9) OTH düzeyleri yönünden anlamlı farklılık saptanmadı. Apne hipopne indeksi (r=0.347, p≤0.001), en düşük oksijen satürasyonu (r=-0.224, p=0.03) ve oksijen satürasyonunun %90'ın altında olduğu zaman dilimi ile OTH arasında korelasyon görüldü (r=0.240, p=0.02).

Sonuç: Çalışmamızda elde ettiğimiz sonuçlar TUAS'lı hastalarda trombosit aktivasyonunun ve aterotrombotiz riskinin arttığını göstermektedir.

Received: June 13, 2012 *Accepted:* August 25, 2012

Correspondence: Dr. Mustafa Serkan Karakaş. Niğde Devlet Hastanesi Kardiyoloji Kliniği, 51100 Niğde.
Tel: +90 388 - 232 22 20 e-mail: mserkan19@hotmail.com

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive apnea or hypopnea due to narrowing of the upper airways during sleep. It is a common disorder of middle-aged adults, affecting 4% of men and 2% of women.[1] OSAS is an independent risk factor for cardiac mortality and morbidity. In patients without underlying cardiovascular disease, hypertension, coronary artery disease, stroke, and heart failure are shown to be associated with OSAS.[2,3] Recent studies have indicated that OSAS is associated with multiple causal factors of endothelial damage and atherosclerosis due to systemic inflammation, oxidative stress, and increased levels of soluble adhesion molecules and coagulation factors. Furthermore, all of these causal factors have been reported to significantly decrease after treatment of OSAS with continuous positive airway pressure.[4,5]

Increased platelet activation plays an important role in the development of cardiovascular complications.[6] Several studies have reported increased platelet activation and aggregation in patients with OSAS.[7-10] Increased platelet activity is associated with increased platelet volume. Large platelets that contain denser granules are metabolically and enzymatically more active than small platelets and have higher thrombotic potential.[10-13] Mean platelet volume (MPV) is an indicator of platelet activation and has an important role in the pathophysiology of cardiovascular diseases[6,14] such as hypertension, diabetes mellitus, hypercholesterolemia, and acute myocardial infarction.[15]

This study investigated the MPV levels in OSAS patients without hypertension, smoking history, diabetes, hyperlipidemia, and any cardiovascular disease, and assessed whether there was any correlation between MPV and severity of disease.

PATIENTS AND METHODS

Patients

Patients between ages 30 and 60 diagnosed with OSAS who were examined in the Department of Chest Diseases outpatient clinic between March 2009 and October 2010 were included in this study. Polysomnographies at the sleep laboratory were conducted prior to inclusion in this study. Patients were examined in three groups according to the severity of their OSAS determined by the apnea-hypopnea index (AHI): 30 in the mild OSAS group (AHI=5-15), 32 in the moderate group (AHI=16-30), and 31 in the severe group (AHI >30). As a control, 31 asymptomatic, healthy individuals between ages 30 and 60 who were seen in the Department of Cardiology outpatient clinic were chosen. This group included patients suitable for the study from the perspective of cardiac anatomy and functions, those with no night snoring or day-time sleepiness, who scored less than 10 in the Epworth sleepiness scale, and had low risk of OSAS in the Berlin survey form evaluation.[16-18] The study was approved by the local Ethics Committee. Informed consents were taken from every individual included in the study. All patients underwent a detailed examination of the cardiovascular system.

Abbreviations:

AHI *Apnea-hypopnea index*
MPV *Mean platelet volume*
OSAS *Obstructive sleep apnea syndrome*

Criteria for exclusion

Exclusion criteria were as follows: (1) impaired cardiopulmonary function, defined as the occurrence of respiratory failure, pulmonary infection or congestive heart failure; (2) coronary artery disease, defined as having a typical angina pectoris, history of a prior myocardial infarction, or the presence of a positive stress test or positive coronary angiographic findings; (3) valvular disease, atrial fibrillation or congenital heart disease; (4) hypertension (hypertension was considered to be present if the systolic pressure was >140 mmHg and/or diastolic pressure was >90 mmHg after averaging three separate blood pressure measurements taken at 10 min intervals, as well as in patients receiving antihypertensive treatment),[19] diabetes mellitus (diabetes mellitus was defined as a fasting blood glucose level >126 mg/dl or current use of a diet or medication to lower blood glucose and/or HbA1c >6.5%), dyslipidemia (LDL cholesterol >160 mg/dl, total cholesterol >240 mg/dl, triglyceride >250 mg/dl), or using antihypertensives, antidiabetics, or lipid-lowering treatment; (5) chronic alcoholism and smoking; (6) malignancy, hyperthyroidism, and hypothyroidism; (7) history of prolonged use of non-steroid anti-inflammatory drugs or anticoagulants; and (8) renal and liver insufficiency.

Polysomnography

Polysomnography was performed with 16 channel Embla (Medcare Inc, Iceland) with continuous sleep technician monitoring. The system consists of 4 channels of EEG, 2 channels of EOG, submental EMG, oronasal air flow, thoracic and abdominal movements,

pulse oximeter oxygen saturation, tibial EMG, body position detector, electrocardiogram and tracheal sound. Apnea was defined as the complete stopping of airflow lasting more than 10 seconds. Hypopnea was defined as a 30% or more reduction in respiratory airflow lasting more than 10 seconds accompanied by a decrease of ≥4% oxygen saturation. The average number of episodes of apnea and hypopnea per hour of sleep were measured as AHI. According to the severity, patients were classified as mild OSAS (AHI=5-15), moderate OSAS (AHI=16-30), and severe OSAS (AHI >30). Sleep stages were scored following standard criteria with 30-second epochs and were reviewed and verified by a certified sleep physician.[20]

Biochemical measurements

Biochemical parameters were obtained from venous blood samples drawn after a 12 hour fasting period. MPV was measured in a blood sample collected in dipotassium EDTA tubes. An automatic blood counter was used for whole blood counts. MPV was measured within 30 minutes after sampling to prevent EDTA-induced platelet swelling.

Statistical analysis

All data was analyzed with "MedCalc 11.0.4" and "SPSS 15.0 for Windows" software. Numerical variables were defined as mean ± standart deviation; categorical variables were defined as percentiles. In a comparision of three or more groups, if the variables fit the normal distribution, one-way analysis of variance (ANOVA) was used; if not, the Kruskal-Wallis test was used. In comparision of the categorical variables, the multiple comparision chi-square test was used. In post-hoc analysis, Tukey's test was used after one-way ANOVA, and the Mann-Whitney U-test was used after Kruskal-Wallis. The Kolmogorov-Smirnov test was used for normality of the distribution. Spearman correlation analysis was performed for determination of correlation. All hypotheses were established as two-way, and alpha critical value was accepted as 0.05.

Table 1. Baseline characteristics in control group and OSAS subgroups

	Control group (n=31) Mean±SD	Mild OSAS (n=30) Mean±SD	Moderate OSAS (n=32) Mean±SD	Severe OSAS (n=31) Mean±SD	*p*
Age (years)	46.7±8.4	46.1±8.2	48.3±7.6	47.3±7.7	NS
BMI (kg/m^2)	28.9±2.9	28.4±3.1	28.7±2.7	29.2±2.9	NS
SBP (mmHg)	119.8±8.8	119.1±6.7	121.7±6.7	121.6±8.9	NS
DBP (mmHg)	73.7±6.0	73.8±5	74.7±5	75.8±5	NS
Fasting blood glucose (mg/dl)	89.4±8.2	89.8±8.6	91.7±10.5	92.5±9.4	NS
HbA1c (%)	5.5±0.4	5.6±0.2	5.6±0.4	5.6±0.4	NS
Total cholesterol (mg/dl)	191.3±23.8	188.7±33.1	190.5±43.1	195.6±26.4	NS
LDL-cholesterol (mg/dl)	117.5±23.5	113±33.9	119.7±35.9	119.8±30.6	NS
HDL-cholesterol (mg/dl)	46.8±10.8	44.9±13.6	44.2±10	45.2±10.4	NS
Triglyceride (mg/dl)	146±67.9	144.6±57.9	148.4±81.7	149.5±50.8	NS
Hemoglobin (g/dl)	14.5±1.1	14.2±1.1	14.1±0.9	13.3±1.3	NS
Platelet count (x10^9/L)	258.9±54.7	246.2±77.2	245.9±89.8	217.0±59.9	NS
MPV (fl)	7.8±0.9	8.3±1.2	8.4±1.3	8.6±1.1*	**0.02**
AHI		10.3±3	21.5±3.5	59.4±15.9	**<0.0001**
SaO_2 min		87.3±3.6	83.2±4.8	71.4±10	**<0.0001**
SaO_2 <90% (TST%)		0.22±0.34	3.9±8.2	20.5±17.3	**<0.0001**

OSAS: Obstructive sleep apnea syndrome; Mean±SD: Mean ± Standart deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; MPV: Mean platelet volume; AHI: Apnea-hypopnea index; SaO_2 min: Minimal oxygen saturation; TST: Total sleep time; SaO_2 <90% (TST%): Percentage of recording time spent at a SaO_2<90%.
*p=0.02 patients with severe OSAS *vs.* control group.

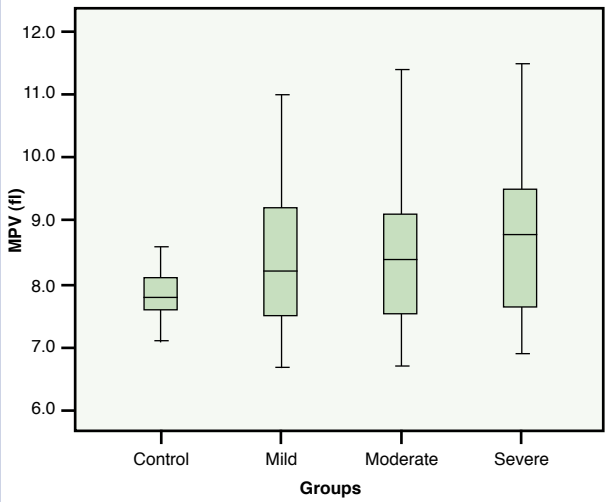

Figure 1. Comparison of obstructive sleep apnea syndrome patients and control values for mean platelet volume.

RESULTS

There were no differences among groups in age, sex, BMI, systolic and diastolic blood pressures, or in laboratory parameters: fasting blood glucose, HbA1c, seurm lipid parameters, hemoglobin, hematocrite, and platelet count (Table 1).

The mean AHI was 10.3±3 in the mild OSAS group, 21.5±3.5 in the moderate OSAS group, and 59.4±15.9 in the severe OSAS group. The difference in AHI, SaO_2 min, and SaO_2 <90% (TST%) between groups was statistically significant (Table 1).

The MPV values were markedly higher in patients with severe OSAS than in the control group (8.6±1.1 *vs.* 7.8±0.7 fl, p=0.03) (Fig. 1). There were no significant differences between controls and patients with mild and moderate OSAS (7.8±0.7 *vs.* 8.3±1.2 fl, p=0.2; 7.8±0.7 *vs.* 8.4±1.3 fl, p=0.08) and between patients with mild, moderate, and severe OSAS (8.3±1.2 *vs.* 8.4±1.3 *vs.* 8.6±1.1 fl, p=0.9) (Fig. 1). Additionally, correlation of MPV with parameters of sleep was noted. MPV correlated with AHI (r=0.347, p=<0.001) (Fig. 2), SaO_2 min (r=-0.224, p=0.03), and TST% (r=0.240, p=0.02).

DISCUSSION

In this study, we have demonstrated significant association between MPV and severity of disease in patients with OSAS.

Obstructive sleep apnea syndrome is a systemic disorder that leads to cardiovascular complications. Recent studies show that OSAS is not a simple respiratory abnormality during sleep; the systemic inflammatory response generated by OSAS can be associated with cardiovascular diseases and increased

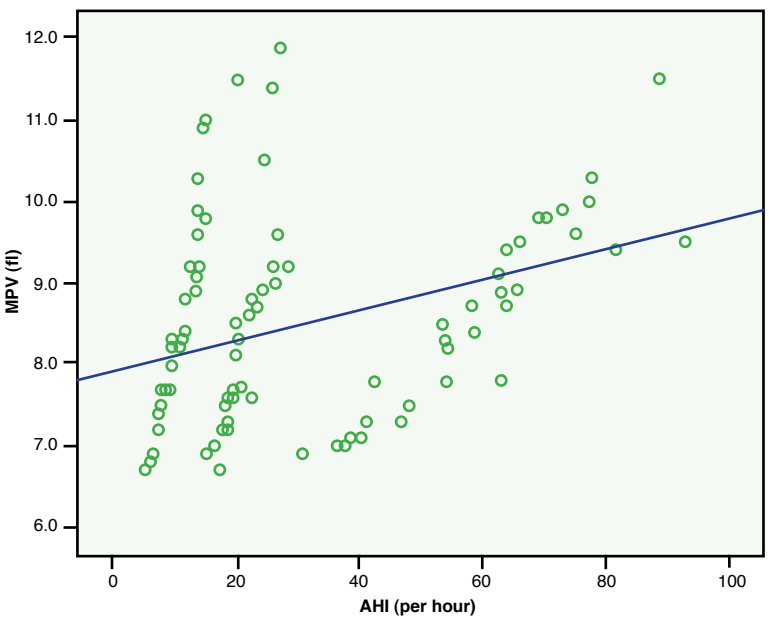

Figure 2. Correlation between mean platelet volume (MPV) and apnea-hypopnea index (AHI) in patients with obstructive sleep apnea syndrome.

atherothrombotic processes.[21,22]

Mean platelet volume is arousing increasing interest as a new, independent cardiovascular risk factor.[15,23] Increased levels of MPV have been shown in hypertension, hypercholesterolemia, diabetes mellitus, obesity, metabolic syndrome, acute myocardial infarction, and acute ischemic stroke.[15] In the study by Varol et al.,[10] levels of MPV were significantly greater in patients with severe OSAS versus patients in the control group and patients with mild to moderate OSAS; however, this study did not exclude hypertension, hypercholesterolemia, and smoking, which could lead elevated MPV. Nena et al.[24] reported that MPV levels in severe OSAS patients were significantly higher than in control and mild to moderate OSAS. The study did not exclude cardiac or lung disease, chronic renal or hepatic disease, hypertension, hypercholesterolemia, or smoking. Our study excluded conditions increasing MPV, such as cardiovascular disease, hypertension, hypercholesterolemia, and smoking; like Nena et al., the new, more sensitive diagnostic criteria incorporating HbA1c was used to exclude diabetes.[24-26] Our results indicate that patients with severe OSAS have significantly higher MPV values versus control and mild to moderate OSAS, similar to the studies by Varol et al. and Nena et al.[10,24]

Enhanced coagulability, possibly mediated by increased sympathetic neural activation, may explain the meaningful relationship between OSAS and cardiovascular disease. The circadian distribution of cardiovascular and vascular events strongly suggests an interaction between sleep, arousal, and acute thrombosis. Myocardial infarction and sudden death exhibit a peak occurrence between 6 a.m. and 11 a.m. Platelets play a key role in ischemic cardiovascular disease and increases in platelet aggregability and activation have been demonstrated in patients with OSAS.[27] Minoguchi et al.[9] found that platelet activation was significantly higher in patients with moderate to severe OSAS than in patients with mild OSAS or control subjects. Oga et al.[28] demonstrated that ADP-induced platelet aggregability was significantly increased in patients with moderate to severe OSAS compared to patients with mild to no OSAS. In this study, increased MPV values are seen only in patients with severe OSAS, which agrees with the studies cited above.

The exact mechanism of platelet activation in patients with OSAS is not clear. Three main pathways may be implicated. First, augmented sympathetic activity increases concentrations of epinephrine and norepinephrine as a result of hypoxemia and repetitive arousals from sleep.[29,30] Platelet activation by catecholamines is dose-dependent.[31,32] Second, acute and chronic intermittent hypoxia can cause platelet activation directly.[33,34] Third, chronic inflammation is symptomatic of OSAS and leads to increased secretion of interleukin-6 (IL-6) and other pro-inflammatory cytokines. Interleukin-3 and IL-6 influence megakaryocyte ploidy and can lead to the production of more reactive and larger platelets. Therefore, elevated IL-6 levels in patients with OSAS can cause an increase in MPV values by stimulating the megakaryocyte ploidy.[5,35,36] According to Oga et al.,[28] in OSAS patients, CPAP therapy may confer some cardioprotective effects through the reduction of platelet activation. They found that ADP-induced platelet aggregability was significantly increased in patients with moderate to severe OSAS compared to patients with mild to no OSAS, and that CPAP treatment improved platelet aggregability at 90 days. Varol et al.[23] found that six months of CPAP therapy caused significant reductions in MPV values in patients with severe OSAS.

Platelet volume is mainly determined in the bone marrow, and large platelets are caused by a reduced fragmentation of megakaryocytes. MPV has been shown to inversely correlate with the total platelet count, which could suggest the consumption of small platelets and a compensatory production of larger reticulated platelets.[10,15] In our study, there was an inverse relationship between platelet count and MPV. Platelet count tended to decrease from the control group to the severe OSAS group, similar to the findings of Varol et al.[10] However, it could not reach statistical significance.

Our study has some limitations including a small sample size and the use of Epworth's method and the Berlin scale rather than AHI in the selection of control individuals. However, in daily clinical practice, those methods are used for the selection of appropriate patients for the polysomnography test. In addition, previous reports have demonstrated the correlation of the Epworth Sleepiness Scale with the AHI.[37] Hypertensive patients were excluded from our study; there-

fore, we were unable to assess the effects of possible increased blood pressure during sleeping which could be induced by apnea and hypopnea episodes.

Conclusion

We found that serum MPV values of patients with severe OSAS were significantly higher than those of the control group, and that MPV correlated with AHI. Our results suggest that patients with severe OSAS, without other cardiovascular risk factors, tend to have an increased platelet activation. Increased platelet activity could contribute to an increased atherothrombotic risk in patients with OSAS. Early diagnosis and CPAP therapy may confer some cardioprotective effects through the reduction of platelet activation.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
2. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003;41:1429-37.
3. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G. Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 2005;172:613-8.
4. Ryan S, Taylor CT, McNicholas WT. Systemic inflammation: a key factor in the pathogenesis of cardiovascular complications in obstructive sleep apnoea syndrome? Thorax 2009;64:631-6.
5. Yokoe T, Minoguchi K, Matsuo H, Oda N, Minoguchi H, Yoshino G, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 2003;107:1129-34.
6. Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: is there a practical index of platelet activity? Clin Appl Thromb Hemost 2003;9:177-90.
7. Geiser T, Buck F, Meyer BJ, Bassetti C, Haeberli A, Gugger M. In vivo platelet activation is increased during sleep in patients with obstructive sleep apnea syndrome. Respiration 2002;69:229-34.
8. Hui DS, Ko FW, Fok JP, Chan MC, Li TS, Tomlinson B, Cheng G. The effects of nasal continuous positive airway pressure on platelet activation in obstructive sleep apnea syndrome. Chest 2004;125:1768-75.
9. Minoguchi K, Yokoe T, Tazaki T, Minoguchi H, Oda N, Tanaka A, et al. Silent brain infarction and platelet activation in obstructive sleep apnea. Am J Respir Crit Care Med 2007;175:612-7.
10. Varol E, Ozturk O, Gonca T, Has M, Ozaydin M, Erdogan D, et al. Mean platelet volume is increased in patients with severe obstructive sleep apnea. Scand J Clin Lab Invest 2010;70:497-502.
11. Martin JF. Platelet heterogeneity in vascular disease. In: Martin JF, Trowbridge EA, editors. Platelet heterogeneity: biology and pathology. London: Springer-Verlag; 1990. p. 205-26.
12. Martin JF, Trowbridge EA, Salmon G, Plumb J. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res 1983;32:443-60.
13. Jakubowski JA, Thompson CB, Vaillancourt R, Valeri CR, Deykin D. Arachidonic acid metabolism by platelets of differing size. Br J Haematol 1983;53:503-11.
14. Park Y, Schoene N, Harris W. Mean platelet volume as an indicator of platelet activation: methodological issues. Platelets 2002;13:301-6.
15. Vizioli L, Muscari S, Muscari A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. Int J Clin Pract 2009;63:1509-15.
16. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999;131:485-91.
17. Manni R, Politini L, Ratti MT, Tartara A. Sleepiness in obstructive sleep apnea syndrome and simple snoring evaluated by the Epworth Sleepiness Scale. J Sleep Res 1999;8:319-20.
18. Grover M, Mookadam M, Armas D, Bozarth C, Castleberry T, Gannon M, et al. Identifying patients at risk for obstructive sleep apnea in a primary care practice. J Am Board Fam Med 2011;24:152-60.
19. Cifkova R, Erdine S, Fagard R, Farsang C, Heagerty AM, Kiowski W, et al. Practice guidelines for primary care physicians: 2003 ESH/ESC hypertension guidelines. J Hypertens 2003;21:1779-86.
20. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specification. 1st ed. Westchester, IL: American Academy of Sleep Medicine; 2007.
21. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/american College Of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council On Cardiovascular Nursing. In collaboration with the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118:1080-111.
22. Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. Prog Cardiovasc Dis 2009;51:434-51.

23. Varol E, Ozturk O, Yucel H, Gonca T, Has M, Dogan A, Akkaya A. The effects of continuous positive airway pressure therapy on mean platelet volume in patients with obstructive sleep apnea. Platelets 2011;22:552-6.
24. Nena E, Papanas N, Steiropoulos P, Zikidou P, Zarogoulidis P, Pita E, et al. Mean Platelet Volume and Platelet Distribution Width in non-diabetic subjects with obstructive sleep apnoea syndrome: new indices of severity? Platelets 2012;23:447-54.
25. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2011; 34: S62–S69.
26. Katsiki N, Papanas N, Mikhailidis DP, Fonseca VA. Glycated hemoglobin A1c (HbA1c) and diabetes: a new era? Curr Med Res Opin 2011;27:7-11.
27. Olson LJ, Olson EJ, Somers VK. Obstructive sleep apnea and platelet activation: another potential link between sleep-disordered breathing and cardiovascular disease. Chest 2004;126:339-41.
28. Oga T, Chin K, Tabuchi A, Kawato M, Morimoto T, Takahashi K, et al. Effects of obstructive sleep apnea with intermittent hypoxia on platelet aggregability. J Atheroscler Thromb 2009;16:862-9.
29. Ziegler MG, Nelesen R, Mills P, Ancoli-Israel S, Kennedy B, Dimsdale JE. Sleep apnea, norepinephrine-release rate, and daytime hypertension. Sleep 1997;20:224-31.
30. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995;96:1897-904.
31. Larsson PT, Wallén NH, Hjemdahl P. Norepinephrine-induced human platelet activation in vivo is only partly counteracted by aspirin. Circulation 1994;89:1951-7.
32. von Känel R, Dimsdale JE. Effects of sympathetic activation by adrenergic infusions on hemostasis in vivo. Eur J Haematol 2000;65:357-69.
33. von Känel R, Loredo JS, Powell FL, Adler KA, Dimsdale JE. Short-term isocapnic hypoxia and coagulation activation in patients with sleep apnea. Clin Hemorheol Microcirc 2005;33:369-77.
34. Rahangdale S, Yeh SY, Novack V, Stevenson K, Barnard MR, Furman MI, et al. The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea. J Clin Sleep Med 2011;7:172-8.
35. Debili N, Massé JM, Katz A, Guichard J, Breton-Gorius J, Vainchenker W. Effects of the recombinant hematopoietic growth factors interleukin-3, interleukin-6, stem cell factor, and leukemia inhibitory factor on the megakaryocytic differentiation of CD34+ cells. Blood 1993;82:84-95.
36. Tauman R, O'Brien LM, Gozal D. Hypoxemia and obesity modulate plasma C-reactive protein and interleukin-6 levels in sleep-disordered breathing. Sleep Breath 2007;11:77-84.
37. Feng J, He QY, Zhang XL, Chen BY; Sleep Breath Disorder Group, Society of Respiratory Medicine. Epworth Sleepiness Scale may be an indicator for blood pressure profile and prevalence of coronary artery disease and cerebrovascular disease in patients with obstructive sleep apnea. Sleep Breath 2012;16:31-40.

Key words: Cardiovascular diseases; platelet activation; platelet count; sleep apnea, obstructive/complications/diagnosis.

Anahtar sözcükler: Kardiyovasküler hastalıklar; trombosit aktivasyonu; trombosit sayısı; uyku apne, tıkayıcı/komplikasyonlar/tanı.