Which Is the Ideal Marker for Early Atherosclerosis in Obstructive Sleep Apnea (OSA) – Carotid Intima-Media Thickness or Mean Platelet Volume?

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Background:
Obstructive sleep apnea (OSA) is known to be closely associated with cardiovascular disease. Carotid intima-media thickness (IMT) is widely used for assessment of atherosclerosis. Mean platelet volume (MPV) is a new marker associated with atherothrombosis. In this study, we aimed to detect early atherosclerosis by measuring carotid intima-media thickness and to investigate the relationship between MPV and IMT and OSA severity.

Material/Methods:
The study population consisted of 158 patients who underwent polysomnography and did not have any overt cardiac disease or risk factors. Carotid IMT was measured by ultrasonography. Blood samples were taken for MPV determination. Subjects were divided into 4 groups according to OSA severity: control, mild, moderate, and severe OSA.

Results:
The patients with OSA (mild, moderate, severe) had an increased carotid IMT (0.59±0.2, 0.60±0.1, 0.64±0.1, respectively) compared to controls (0.50±0.1, p<0.05). There were no differences found between groups regarding mean platelet volume. Carotid IMT was found to be positively correlated with age, systolic blood pressure, apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and time duration with oxygen saturation <90% (T90), and negatively correlated with minimum SpO2 and mean SpO2. MPV was not correlated with OSA severity or other parameters. Carotid IMT was found to be effective in predicting the presence of OSA [AUC=0.769 (0.683, 0.855), p<0.001] but MPV was not found to be effective [AUC=0.496 (0.337, 0.614), p=0.946].

Conclusions:
OSA patients appear to have increased carotid IMT suggestive of an atherosclerotic process. Carotid IMT could be a more useful indicator than MPV in these patients. Long-term prospective studies are needed to confirm these results.

MeSH Keywords: Atherosclerosis • Carotid Intima-Media Thickness • Mean Platelet Volume • Sleep Apnea, Obstructive

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Background

Obstructive sleep apnea (OSA) is a clinical disorder characterized by recurrent episodes of upper airway collapse during sleep. It is well known that OSA patients have an increased risk of cardiovascular disease (CVD) and death [1–4]. Many factors play a role in pathogenesis of atherosclerosis, such as systemic inflammation, oxidative stress, increased vascular endothelial growth factor, adhesion molecules, and coagulant factors [5]. Recent studies have shown that OSA patients without CVD risk factors have increased endothelial dysfunction and atherosclerosis [6,7].

Carotid intima-media thickness (IMT) is used as a marker for the detection of early endothelial defect and subclinical atherosclerosis [8]. Recent studies suggest the presence of OSA is independently associated with increased carotid IMT [9,10]. However, many patients with OSA have other concomitant disease or risk factors, such as diabetes, cardiovascular disease, hypertension, hyperlipidemia, obesity, and smoking. Therefore, it is difficult to determine a direct association between atherosclerosis and OSA.

On the other hand, several studies have reported that patients with OSA have increased platelet activation and aggregation [11–13]. Mean platelet volume (MPV) is an indicator of platelet size and activation. Some clinical studies have reported that MPV could be regarded as a new predictor for atherosclerosis [14–16].

A few studies have reported an association between MPV and sleep apnea [17–19]. However, there is a lack of research directly examining the relevance between MPV and carotid intima-media thickness in sleep apnea. Regarding the association between OSA and cardiovascular disease, we aimed to detect early finding of atherosclerosis by measuring carotid intima-media thickness and to examine the association between MPV and IMT and OSA severity.

Material and Methods

Study population

The subjects were selected consecutively from the Sleep Disorders Clinic of our institution between October 2014 and March 2016. The patients underwent physical examination, chest X-ray, respiratory function test, and routine blood analysis before polysomnography (PSG). All subjects with suspected OSA underwent PSG. Study subjects were categorized into 4 groups according to apnea-hypopnea index (AHI): control (AHI <5), mild (AHI ≥5 and <15), moderate (AHI ≥15 and <30), and severe (AHI ≥30) OSA [20].

Individuals who have symptoms of snoring, daytime sleepiness, and/or witnessed apnea were included in the study. Exclusion criteria were: presence of any known history of CVD, peripheral vascular disease, cerebrovascular accident, heart failure, hypertension, current history of smoking, hyperlipidemia, and diabetes mellitus. Those with blood pressure higher than 140/90 mmHg or having a previous hypertension diagnosis and taking antihypertensive medications were considered as hypertensive patients. Diabetes mellitus was defined as having fasting blood glucose >126 mg/dl or current use of antidiabetic drugs or insulin. Hyperlipidemia was defined as having a previous diagnosis of hyperlipidemia, lipid-lowering medication use, a serum LDL cholesterol >160 mg/dl, or serum total cholesterol >240 mg/dl [21]. We excluded patients who met the exclusion criteria detailed above and those who had chronic pulmonary, renal, liver diseases, malignant diseases, or chronic inflammatory diseases. According to above criteria, we excluded 224 patients for the following reasons: prevalent diabetes mellitus (n=30), hypertension (n=72), diabetes mellitus and hypertension (n=33), ischemic heart disease (n=20), chronic lung disease (n=11), hyperlipidemia (n=15), chronic renal failure (n=4), and being a smoker (n=39). Finally, 158 patients were included in the analysis.

Written informed consent was obtained from all subjects. This study was approved by the local ethics committee.

Polysomnography (PSG)

Standard overnight polysomnography was performed with a 62-channel Embla N7000 device (Medcare Flage, Iceland). The physiological signals monitored included EEG, EOG, chin EMG, ECG, bilateral anterior tibial muscle EMG, nasal airflow, respiratory effort (thorax and abdomen movements), oxygen saturation, tracheal microphone, and body position. The polysomnographic records were scored using American Academy of Sleep Medicine manual scoring criteria [22]. The average number of episodes of apnea and hypopnea per hour of sleep were taken as the apnea-hypopnea index (AHI). Oxygen desaturation index (ODI) was taken as the number of decreases in desaturation >4% per hour of sleep. Patients were categorized in terms of OSA severity as follows: an AHI ≤5 events/h was considered normal (control groups), ≥5 and <15 were considered mild OSA, ≥15 and <30 were considered moderate OSA, and ≥30 was considered severe OSA [20].

Laboratory analysis

Blood samples were drawn from the antecubital vein into tubes containing dipotassium EDTA after a fasting period of 12 h. To measure hematologic parameters, platelet counts, and MPV, samples were analyzed within 30 min after the collection using an automated hematology analyzer (Beckman Coulter, USA).

Mean platelet volume (MPV) is an indicator of platelet size and activation. Some clinical studies have reported that MPV could be regarded as a new predictor for atherosclerosis [14–16]. Mean platelet volume (MPV) is an indicator of platelet size and activation. Some clinical studies have reported that MPV could be regarded as a new predictor for atherosclerosis [14–16].
Coulter LH780, USA; coefficient of variation \( \leq 2.2\% \). The expected values for MPV in our laboratory range from 7 to 11 fl. Biochemical parameters were measured using an autoanalyzer (Beckman Coulter AU680, Japan).

**Assessment of carotid intima-media thickness**

Carotid Doppler ultrasonography was performed by a single qualified radiologist who was blinded to the subject's status. Both carotid arteries were examined in supine position with the head slightly extended and rotated to the opposite side, using high-resolution sonography equipped with a linear transducer at 7.5 MHz in B mode (Toshiba Aplio MX, Tokyo, Japan). Carotid intima-media thickness (IMT) was defined as the distance between the 2 echogenic lines representing the lumen-intima interface and the media-adventitia interface. IMT was measured in the far wall of the distal common carotid artery (CCA) in a plaque-free region within 1 cm proximal to the carotid bifurcation [23]. Three measurements were made in the thickest part of the intima-media. The mean values of IMT on both sides were calculated. The mean carotid IMT was defined as the average of right and left CCAs. We defined carotid atherosclerosis as carotid IMT greater than 0.8 mm or the presence of plaque [24–26]. Plaque was defined as the presence of focal lesion resulting in \( \geq 50\% \) of the surrounding IMT or a thickness greater than 1.5 mm [23].

**Statistical analysis**

The statistical analysis was performed with SPSS v. 20.0 (SPSS Inc., Chicago, IL, USA) for Windows. Continuous variables from the study groups are reported as mean ± standard deviation. Categorical variables are expressed as numbers (percentage). Normality analysis was performed using the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) was applied to analyze demographic and laboratory findings, sleep parameters, and carotid measurements between the AHI groups. Bland-Altman analysis were applied to determine intraobserver variation in IMT measurements. Multivariate regression analysis was performed to identify independent determinants of carotid thickness. Age, sex, total cholesterol, HDL and LDL cholesterol, triglyceride, systolic and diastolic blood pressures, and BMI were included as independent variables.

Initially, our primary end-point was the comparison of carotid IMT and MPV between OSA patients and controls. After this step, we also performed receiver-operating characteristic (ROC) curve analyses to detect the discrimination ability of both IMT and MPV in the prediction of OSA. A p-value of <0.05 was considered statistically significant.

**Results**

The mean age of the 158 subjects was 44.5±10.2 years and 117 (74.1%) were male. They were divided into 4 groups according to apnea-hypopnea index (AHI): 46 subjects were in the control group, 40 patients were in the mild OSA group, 32 patients were in the moderate OSA group, and 40 patients were in the severe OSA group. The mean AHI values were 2.4±1.4, 9.5±2.9, 20.8± 3.9, and 60.3±20.8 for the control, mild, moderate, and severe groups, respectively. The baseline characteristics, laboratory findings, and sleep parameters of the patient and control groups are presented in Table 1.

There were no differences among groups according to age, sex, body mass index (BMI), or blood pressure. Laboratory parameters of the groups were also compared and no differences were found between the groups in terms of fasting blood glucose, serum lipid parameters, white blood cells, red blood cells, red cell distribution width (RDW), hemoglobin, hematocrit, platelet counts, or CRP values. There were also no differences between groups with respect to mean platelet volume (MPV) (p>0.05).

As expected, AHI and oxygen desaturation index (ODI) were found to be significantly different between groups (p<0.001). Time duration with oxygen saturation <90% (T90) in patients with severe OSA was longer than in other groups (p<0.001). Minimum oxygen saturation at sleep (Min SpO\(_2\)) in the control group was significantly higher than in OSA groups (p<0.001) (Table 1). There were no differences between groups in terms of Epworth sleepiness scale and mean oxygen saturation at sleep (Mean SpO\(_2\)).

In the comparison of carotid artery measurements (mean carotid IMT, left carotid IMT, and right carotid IMT), statistically significant differences were found between groups (p<0.001, p=0.001, and p<0.006, respectively). Mean carotid IMT in patients with mild, moderate, and severe OSA was higher (0.59±0.2, 0.60±0.1, 0.64±0.1, respectively) than in the control group (0.50±0.1, p<0.042, and p=0.010, p<0.001, respectively). Similarly, left carotid IMT in patients with severe and moderate OSA was higher than in the control group (p<0.001 and p=0.027, respectively). Right carotid IMT in patients with severe and moderate OSA was also higher than in the control group (p<0.001, p=0.033) (Table 1). Only 9 OSA patients (3 in each OSA group) were observed to have subclinical atherosclerosis; however, none of the control subjects were found to have atherosclerosis.

Intraobserver variability for IMT measurements is demonstrated by Bland-Altman plots (Figure 1A–1D). This analysis revealed low intraobserver variation. Repeat measurements show that they are in good agreement with each other: mean
In the correlation analysis, carotid IMT was found to be positively correlated with age (r=0.594, p<0.001), systolic blood pressure (r=0.254, p=0.005), AHI, ODI, and T90 (r from 0.332 to 0.379, p<0.001), and negatively correlated with MinSpO2 and Mean SpO2 (r=0.322, r=0.401, respectively, p<0.001) (Table 2). No statistically significant correlation was found between IMT and lipid parameters, levels of CRP, hemoglobin, or platelet count. Carotid IMT had a weak correlation with red cell distribution width (RDW) (r=0.230, p=0.011) and MPV (r=0.182, p=0.047). No statistically significant correlation was found between MPV and AHI and other polysomnographic clinical parameters (p>0.05).

Multivariate regression analysis was performed to determine the independent predictors of IMT. AHI/or ODI (95% CI, 0.001 to 0.14) (Figure 1A), mean –0.01, 95%CI, 0.14 to –0.15 (Figure 1B), 95%CI, 0.12 to –0.13 (Figure 1C), and 95%CI, 0.13 to –0.15 (Figure 1D).

Table 1. Comparison of baseline characteristics, laboratory findings, sleep parameters and carotid measurements of the groups.

|                               | Control (AHI <5) n=46 | Mild OSA (AHI: 5–15) n=40 | Moderate OSA (AHI: 15–30) n=32 | Severe OSA (AHI >30) n=40 | p value |
|-------------------------------|-----------------------|---------------------------|-----------------------------|---------------------------|---------|
| **Baseline characteristics**  |                       |                           |                             |                           |         |
| Age                           | 41.7±9.0              | 44.8±10.0                 | 45.9±8.3                    | 46.6±10.3                 | 0.108   |
| Gender (% male)               | 31 (67.4)             | 30 (75.0)                 | 24 (75.0)                   | 32 (80.0)                 | 0.608   |
| BMI                           | 29.6±5.4              | 29.6±5.5                  | 29.6±4.8                    | 32.9±3.6                  | 0.061   |
| Systolic BP (mmHg)            | 118.8±7.2             | 118.2±7.6                 | 120.1±8.2                   | 123.6±8.0                 | 0.075   |
| Diastolic BP (mmHg)           | 76.0±5.8              | 73.8±5.4                  | 75.3±7.2                    | 77.2±5.7                  | 0.183   |
| **Laboratory findings**       |                       |                           |                             |                           |         |
| Glucose (mg/dl)               | 98.3±8.5              | 103.4±15.1                | 101.1±11.7                  | 100.0±8.9                 | 0.452   |
| Cholesterol (mg/dl)           | 189.3±22.1            | 197.5±17.0                | 195±21.2                    | 192.2±23.1                | 0.861   |
| Triglyceride (mg/dl)          | 162.3±69.4            | 155.8±64.5                | 171.8±52.1                  | 154.6±54.6                | 0.258   |
| HDL-C (mg/dl)                 | 103.2±29.3            | 118.7±21.4                | 111.8±25.0                  | 117.9±20.4                | 0.117   |
| CRP (mg/L)                    | 50.6±18.5             | 48.8±16.2                 | 45.2±11.6                   | 44.1±15.6                 | 0.564   |
| Hemoglobin (mg/dl)            | 13.9±2.1              | 14.5±2.3                  | 14.4±1.3                    | 14.4±1.6                  | 0.470   |
| Platelet count (×10^9/L)      | 253.6±49.0            | 251.5±72.1                | 259.3±61.3                  | 286.4±79.2                | 0.066   |
| RDW (%)                       | 13.7±1.2              | 13.5±1.1                  | 13.4±0.9                    | 13.8±1.6                  | 0.415   |
| MPV (fl)                      | 8.5±0.9               | 8.6±1.1                   | 8.7±0.8                     | 8.4±0.8                   | 0.612   |
| **Sleep parameters**          |                       |                           |                             |                           |         |
| Epworth                       | 7.9±5.2               | 7.7±4.9                   | 7.6±4.8                     | 9.5±5.9                   | 0.375   |
| AHI (events/h)                | 2.4±1.4               | 9.5±2.9                   | 20.8±4.3                    | 60.3±20.8                 | <0.001  |
| ODI                           | 2.8±2.2               | 10.3±9.9                  | 19.4±4.7                    | 51.2±20.4                 | <0.001  |
| T90                           | 1.7±8.5               | 3.0±7.1                   | 14.9±33.0                   | 65.5±69.6                 | <0.001  |
| Mean SpO2                     | 94.4±8.8              | 95.1±13.3                 | 94.5±2.0                    | 92.6±2.5                  | 0.151   |
| Min. SpO2                     | 90.3±2.8              | 86.7±3.5                  | 83.7±4.7                    | 75.4±10.1                 | <0.001  |
| **Carotid thickness**         |                       |                           |                             |                           |         |
| Right carotid IMT (mm)        | 0.49±0.1              | 0.57±0.2                  | 0.58±0.1                    | 0.63±0.1                  | <0.001  |
| Left carotid IMT (mm)         | 0.51±0.1              | 0.60±0.2                  | 0.62±0.1                    | 0.66±0.1                  | 0.001   |
| Mean carotid IMT (mm)         | 0.50±0.1              | 0.59±0.2                  | 0.60±0.1                    | 0.64±0.1                  | <0.001  |

BMI – body mass index, AHI – apnea-hypopnea index, IMT – intima media thickness, MPV – mean platelet volume, RDW – red cell distribution width, CRP – C-reactive protein. * Patients with severe OSA vs. other groups (p<0.001); † patients with severe OSA vs. control group (p<0.001); ‡ patients with moderate OSA vs. control group (p=0.033); ‡‡ patients with mild OSA vs. control group (p=0.027); ‡‡‡ patients with mild OSA vs. control group (p=0.042); ‡‡‡‡ patients with moderate OSA vs. control group (p=0.010).

Table 1. Comparison of baseline characteristics, laboratory findings, sleep parameters and carotid measurements of the groups.
to 0.002, \( p=0.001 \), age (95% CI, 0.005 to 0.009, \( p<0.001 \)), and HDL cholesterol (95%CI, –0.003 to 0.000, \( p=0.036 \)) were found to be independent predictors of IMT.

ROC analysis showed that using a cut-off level of 0.56, carotid IMT predicted the presence of OSA with a sensitivity of 64% and specificity of 82% (AUC, 0.796; 95% CI, 0.683 to 0.855; \( p<0.001 \)) (Figure 2). The AUC of MPV shown no significant correlation with OSA (AUC, 0.496; 95% CI, 0.377 to 0.614, \( p=0.946 \)).

**Discussion**

The existence of endothelial dysfunction and cardiovascular risk in patients with OSA has been supported by many studies [1–6,27]. During the last decade, IMT has been a frequently investigated parameter for the determination of subclinical atherosclerosis in OSA patients. Recently, MPV also began to be used for the same purpose as a new parameter. In this study, we evaluated the carotid IMT and MPV in patients with OSA and tried to determine the associations among each other and OSA severity.

Carotid intima-media thickness is frequently used in clinical trials but no international consensus exists on its value for early atherosclerosis. Generally, normal values for carotid IMT are thought to be around 0.5 mm in young adults [28]. Age, sex, ethnicity, and presence of risk factors may affect the values, and these factors should be considered. The mean age of our study population was 44.5±10.2 years and mean carotid IMT

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**Figure 1.** (A–D) Bland-Altman plots illustrating intraobserver agreement for IMT measurements.
was 0.59±0.12 mm. According to some clinical trials, intima-media thickness over 0.8 mm is considered as carotid atherosclerosis [24–26]. In the present study, only 9 OSA patients had subclinical atherosclerosis. This result may be explained by the fact that participants were relatively young and many of the severe OSA patients with atherosclerosis were excluded because of comorbid disease or atherosclerotic risk factors.

One of the main results of the present study is that carotid arterial stiffness among OSA patients was found to be increased compared to controls, consistent with the findings of previous studies. In case-control studies, a direct association between increased carotid IMT and OSA has been shown [29–33]. Unlike these previous studies, in our study we classified the subjects into 4 groups and found that the values of carotid IMT in each OSA group (mild, moderate, and severe) were higher than in controls and subjects with mild-moderate OSA. However, the authors did not exclude patients with cardiovascular risk factors such as hypertension, hyperlipidemia, and active smoking, which could lead to elevated MPV. In another study, elevated MPV was shown to be unrelated to OSA severity [38].

We also found a positive correlation between carotid IMT and apnea-hypopnea index (AHI). Intima-media thickness was found to be positively correlated with oxygen desaturation index (ODI) and time duration with oxygen saturation <90% (T90), and negatively correlated with min SpO₂ and mean SpO₂. All these results lead us to conclude that hypoxemia has a strong effect on carotid IMT. Chronic repetitive nocturnal hypoxia, oxidative stress, and sympathetic nervous system hyperactivity are thought to be responsible for the endothelial damage [34,35]. Many studies have shown that hypoxemia is the most important risk factor for this process [33,36]. Reports in the literature show that carotid IMT is evidence of early alterations in vascular morphology [37].

In this study we also found that age, AHI/or ODI, and HDL are independent determinants of IMT. In the regression analysis, effects of AHI and ODI were found to be identical; therefore, either of them can be used as an independent predictor of IMT. Defining independent predictors of ODI, which is a marker of nocturnal hypoxia, supports the view that hypoxia might be responsible for atherogenesis. Gunnarson et al. [10] reported that baseline AHI is an independent predictor of increased carotid IMT and plaque in long-term follow-up.

The second main topic of our study was to investigate the usefulness of mean platelet volume (MPV) in OSA. The association between OSA and MPV has been previously investigated in a limited number of studies [17–19,38] and conflicting results were found. Nena et al. [17] and Varol et al. [18] reported that MPV was higher in patients with severe OSA compared to controls and subjects with mild-moderate OSA. However, the authors did not exclude patients with cardiovascular risk factors such as hypertension, hyperlipidemia, and active smoking, which could lead to elevated MPV. In another study, enrolling 200 OSA patients without any overt cardiac disease or diabetes, MPV was shown to be unrelated to OSA severity [38].

### Table 2. Correlation of IMT with other parameters.

| Parameters       | IMT measurements | p    |
|------------------|------------------|------|
| Age              | 0.594            | <0.001 |
| BMI              | 0.089            | 0.335 |
| Systolic BP (mmHg) | 0.254            | 0.005 |
| Diastolic BP (mmHg) | 0.035            |      |
| AHI              | 0.393            | <0.001 |
| ODI              | 0.385            | <0.001 |
| T90              | 0.133            | <0.001 |
| Min SpO₂         | −0.401           | <0.001 |
| Mean SpO₂        | −0.322           | <0.001 |
| Epworth scale    | 0.016            | 0.866 |
| Cholesterol (mg/dl) | 0.127            | 0.249 |
| Triglyceride (mg/dl) | 0.181            | 0.100 |
| LDLC (mg/dl)     | 0.108            | 0.240 |
| HDLC (mg/dl)     | −0.143           | 0.120 |
| CRP (mg/L)       | −0.061           | 0.526 |
| Hemoglobin (mg/dl) | −0.030           | 0.747 |
| Platelet count (×10⁹/L) | 0.016          | 0.888 |
| RDW (%)          | 0.230            | 0.011 |
| MPV (fl)         | 0.182            | 0.047 |

Figure 2. ROC curve analysis for carotid IMT and mean platelet volume (MPV) in prediction of OSA. AUC – area under curve.
In the present study, we could not find any significant differences in terms of MPV levels between OSA patients and the control group. We also found no significant associations between MPV and apnea-hypopnea index and other polysomnographic parameters.

There is no research directly examining the relation between MPV and carotid intima-media thickness in sleep apnea. MPV was shown to be associated with carotid atherosclerosis in males [39]; however, no similar relationship between these 2 markers was found in females. In another study, the relation between MPV and subclinical atherosclerosis was investigated in type 2 diabetes mellitus patients [26], revealing that MPV was not associated with subclinical atherosclerosis.

We found only a weak correlation between carotid IMT and MPV values, suggesting that the MPV level may increase in the more advanced stages of atherosclerosis. In the present study, the lack of association between OSA severity and MPV suggests that use of platelet markers could be less useful in OSA patients. Due to the conflicting results on this issue, further studies are needed.

This study has some limitations. This is a single-center study with a relatively small sample size and we have no information regarding long-term outcomes of the patient groups. The strength of our study is that the confounding effects of cardiovascular disease or risk factors on carotid atherosclerosis and MPV were eliminated by excluding patients with these characteristics.

Conclusions

Our findings suggest that OSA patients have increased carotid stiffness and that carotid IMT is a more reliable marker for predicting OSA severity than is MPV. Further research is needed to confirm these results.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication.

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