Araştırma Makalesi / Research Article

Düzce Tıp Fakültesi Dergisi / Duzce Medical Journal
2017;19(3):55-58

Relationship of Aortic Stiffness with Severity of Obstructive Sleep Apnea Syndrome

Obstrüktif Uyku Apne Sendromunda Aort Elastikiyetinin Hastalığın Ağırlık Derecesi ile İlişkisi

Emine Nilgün ORDU*, Gülgün ÇETİNTAŞ-AFŞAR, Tülin KUYUCU

Sureyyapasa Chest Diseases and Thoracic Surgery Education and Research Hospital Department of Pulmonary Medicine, Istanbul

ABSTRACT

Aim: Obstructive sleep apnea syndrome (OSAS) is described as repetitive episodes of upper airway obstruction at sleep with frequent decreases of blood oxygen saturation. OSAS is considered as an independent risk factor for cardiovascular disease. Objective of this study is to investigate the relationship between aortic stiffness parameters and severity of OSAS.

Material and Methods: Sixty-five patients diagnosed as OSAS with polysomnography were divided into 2 groups as mild-moderate and severe OSAS according to apnea hypopnea index. Hypertension, coronary artery disease, hyperlipidemia and diabetes mellitus were evaluated as comorbid diseases. Two groups were compared in terms of aortic strain and aortic distensibility in this cross sectional study.

Results: Median apnea hypopnea index was 15.2 in Mild-Moderate OSAS (n=28), and 56.5 in Severe OSAS group (n=37). Oxygen desaturation index ($p<0.001$), body mass index ($p=0.002$) and any comorbid disease presence ($p=0.003$) was significantly higher in severe OSAS group. In all patients, 49 had comorbid disease; and there was no significant relation between aortic strain, aortic distensibility and comorbid disease presence. There was no statistical difference between mild-moderate OSAS and severe OSAS in terms of aortic strain ($p=0.134$) and aortic distensibility ($p=0.085$).

Conclusion: Aortic stiffness does not change between mild-moderate and severe OSAS groups in this study. Because multiple factors may affect the measured values, more studies are needed for evaluation of elastic properties of arteries.

Keywords: Obstructive sleep apnea syndrome; aortic stiffness; aortic strain; aortic distensibility.

ÖZ

Amaç: Obstrüktif uyku apne sendromu (OUAS), uykuda oksijen desatürasyonlarının sıklıkla eşlik ettiği tekrarlayan üst solunum yolu obstrüksiyonu olarak tanımlanır. OUAS'ın kardiyovasküler hastalıklar açısından bağımsız bir risk faktörü olduğu kabul edilmektedir. Bu çalışmada aort elastikiyetini gösteren parametrelerin OUAS'ın ağırlık derecesi ile olan ilişkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Uyku kliniğinde polisomnografi ile OUAS tanısı alan 65 hasta apne hipopne indekslerine göre hafif-orta ve ağır OUAS olmak üzere iki gruba ayrıldı. Hipertansiyon, koroner arter hastalığı, hiperlipidemi ve diyabetes mellitus komorbid hastalıklar olarak değerlendirildi. Bu kesitsel çalışmada iki grubun aortik strain ve aortik distensibilite açısından karşılaştırmaları yapıldı.

Bulgular: Ortanca apne hipopne indeksi, hafif-orta OUAS'ta 15,2 (n=28) iken ağır OUAS'ta 56,5 (n=37) bulundu. Oksijen desatürasyon indeksi ($p<0,001$), beden kitle indeksi ($p=0,002$) ve komorbid hastalık varlığı ($p=0,003$) ağır OUAS'ta istatistiksel olarak yüksek bulundu. Tüm hastaların 49'unda ek hastalık mevcuttu ve ek hastalık varlığıyla aortik strain ve aortik distensibilite arasında anlamlı bir ilişki yoktu. Hafif-orta OUAS ile ağır OUAS grupları arasında aortik strain ($p=0,134$) ve aortik distensibilite ($p=0,085$) açısından istatistiksel anlamlı bir farklılık saptanmadı.

Sonuç: Bu çalışmada aort elastikiyetinin hafif-orta ve ağır OUAS gruplarında farklılık göstermediği saptandı. Bu sonuç, ölçülen değerlerin birden fazla faktörden etkilenmesine bağlı olabileceği için arterlerin elastik özelliklerinin değerlendirilmesine yönelik daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Obstrüktif uyku apne sendromu; aort elastikiyeti; aortik strain; aortik distensibilite.

Sorumlu Yazar / Corresponding Author: Emine Nilgün ORDU, eminenilgunordu@gmail.com

Geliş Tarihi / Received: 09.01.2016 Kabul Tarihi / Accepted: 11.07.2018

This study had been presented as a poster at 17th Annual Congress of Turkish Thoracic Society (April 02-06, 2014, Antalya).

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is described as repetitive episodes of upper airway obstruction at sleep with frequent decreases of blood oxygen saturation (1). Upper airway collapse causes sleep fragmentation, hypoxemia, hypercapnia, increased intrathoracic pressure and sympathetic activity (2). There is an increasing incidence of defined OSAS cases and studies on its effects and treatment are proceeding. While there is not sufficient data in our country, the prevalence of OSAS is estimated as 1-5% in western countries (3). Studies show that OSAS is an independent risk factor for many pathological conditions such as systemic hypertension, cardiovascular disease, stroke and abnormal glucose metabolism (4). Hypoxia, hypercapnia and apneic periods cause release of vasoactive substances and damage of endothelium. Despite endothelial dysfunction and coronary artery disease are seen with hypertension, hyperlipidemia, diabetes mellitus, cigarette smoking etc.; OSAS is thought to be a risk factor for its own (5). Repetitive periods of hypoxia and reperfusion accelerate release of reactive free oxygen radicals and atherosclerosis formation (6). Aortic stiffness is also a risk factor for cardiovascular disease and shown to be increased in OSAS patients (7,8).

Atherosclerosis and the corrosion of collagen and elastin in arterial wall results in decreased compliance especially in central arteries and progression of arterial stiffness. There are many noninvasive and invasive methods used for measurement of arterial stiffness. Pulse wave velocity (PWV) occurred with systole depends on arterial elasticity and vessel diameter. Its noninvasive measurement is accepted as a practical way of evaluating arterial stiffness (9). Aortic PWV is calculated by measuring the pulse's passing time through two particular points. But measuring PWV over skin needs to be corrected according to age, and can be false in situations such as obesity, big breast size, spinal and thoracic deformities. Alternatively, 'aortic strain (AS)' and 'aortic distensibility (AD)' are recommended. These two parameters are aortic stiffness indexes calculated with measurement of blood pressure and echocardiographic aort diameter (10).

It is shown that arterial stiffness is an independent risk indicator for mortality in patients with coronary artery disease and hypertension (11). Stefanadis et al. (7) followed 54 patients with ischemic heart disease for 3 years and stated that aortic stiffness is a strong risk factor for acute coronary events. Diabetes, metabolic syndrome and cigarette smoking also increase arterial stiffness (10,12,13). Aortic stiffness has predictive value for mortality in end stage renal failure patients (14). Roman and colleagues studied on 181 patients with systemic lupus erythematosus and rheumatoid arthritis; and found relation between chronic inflammation and arterial stiffness independent of atherosclerosis (15). Obesity is also related with aortic stiffness (16).

Considering OSAS is risk factor for cardiovascular disease and systemic inflammation, we can expect increased arterial stiffness in OSAS patients. Tavil and colleagues showed that aortic stiffness increases in OSAS patients independent of cardiovascular morbidities (8). A literature review showed arterial stiffness is related with OSAS, but there is not enough data about the effect of disease severity (17). It is aimed to search the relation with OSAS severity and aortic stiffness for the risk of cardiovascular disease in newly diagnosed patients.

MATERIALS and METHODS

We included 65 adults who underwent polysomnography and diagnosed as OSAS in sleep clinic of Süreyyapaşa Chest Diseases and Thoracic Surgery Education and Research Hospital between May-October 2012. Local ethics committee approval was taken from Kartal Dr. Lütfi Kırdar Education and Research Hospital (Dated 12.06.2012 and numbered 1009/43/3). All participants gave informed consent before study. Comorbid disease and smoking history was taken. Patients with heart failure, acute myocardial infarction story, unstable angina pectoris, heart valve dysfunction, arrhythmias, congenital heart disease, cardiomyopathy, stroke, chronic obstructive lung disease, chronic respiratory failure, cancer, chronic liver and renal disease, and active infection were excluded. Hypertension, diabetes mellitus, coronary artery disease and hyperlipidemia and their treatment story were listed and patients were divided into groups whether they have comorbid disease or not.

Body mass index, Arterial blood pressure and Biochemical measurements

Body mass index (BMI) is calculated via the formula: body weight (kg)/height (m^2). Patients are divided into groups as obese (BMI≥30) and nonobese (BMI<30) accordingly. Blood pressures are measured with mercury sphygmomanometer. Fasting glucose level, serum cholesterol, triglycerides, LDL cholesterol, HDL cholesterol and C-reactive protein levels were measured to investigate hyperlipidemia, diabetes mellitus and possible inflammatory processes.

Polysomnography

At sleep clinic, patients underwent one night polysomnography (Grass Telefactor Comet, USA) at least for six hours. Electrodes were placed for electroencephalographic, bitemporal electrooculographic, submental electromyographic and electrocardiographic examination. Thoracic and abdominal movements were recorded with pressure transducer. Oxygen saturation was measured with pulse oxymeter. All values and video display were recorded by a certified sleep technician. Sleep and respiration scores were determined according to American Society of Sleep Medicine (ASSM) 2012 guideline. Apnea was defined as a drop of ≥90% nasal airflow for at least 10 seconds; and hypopnea was defined as a 50% or greater reduction in flow lasting at least 10 seconds associated with either a 3% or greater oxyhemoglobin desaturation or an arousal. The apnea-hypopnea index (AHI), representing the total number of apneas and hypopneas per an hour of sleep was calculated and OSAS was defined as mild if AHI was 5-14, moderate if 15-29, and severe if AHI was more than 30. Patients were also divided into two groups as mild-moderate and severe OSAS.

Aortic Stiffness Measurement

All patients underwent transthoracic echocardiography (Esaote MyLAB40) in the left lateral lying position AS and AD was measured using M-mode echocardiography by calculating the systolic and diastolic diameter of the ascending aorta, approximately 3 cm above the aortic valve in the parasternal long axis view. The systolic diameter of the aorta was measured at the point of highest forward motion of the aorta, whereas the diastolic diameter was measured at the area equivalent to the peak of the QRS complex on electrocardiography. Measurements were repeated at three cardiac beats and the mean value was obtained. AS and AD were accepted as aortic stiffness parameters and were calculated with using the following formulas:

AS (%) = (systolic – diastolic diameter) x 100 / diastolic diameter

Pulse pressure (mm/Hg) = systolic – diastolic blood pressure

AD ($10^{-6}\times cm^2\times dyn^{-1}$) = (2 x AS) / pulse pressure

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 15.0 program was used for analysis of the data. Descriptive statistics were expressed as mean±standard deviation. Student t test was used for comparison of quantitative data with normal distribution, and Mann-Whitney U test was used for not distributed normal. Spearman correlation analysis was used to see correlation between quantitative data. Categorical data were analyzed with chi-square or Fisher's exact test. $p<0.05$ was considered as the level of statistical significance.

RESULTS

Among 65 patients 10 were woman (15.38%), and 55 were men (84.61%). Patients were divided into two groups as mild-moderate OSAS (28 patients whose AHI was between 5 and 29) and severe OSAS (37 patients whose AHI was ≥30). There were

no significant difference between two groups in terms of gender (p=0.306). Median AHI was 15.2 in mild-moderate OSAS, while 56.5 in severe OSAS group. Patients who has hypertension, diabetes, coronary artery disease and hyperlipidemia were evaluated as patients with comorbid disease. The treatments of comorbidities were continued.

Two groups were compared for age, BMI, oxygen desaturation index (ODI), systolic diameter of aorta, diastolic diameter of aorta, pulse pressure and presence of comorbidities (Table 1). Among these parameters, BMI, ODI and comorbid disease presence was significantly higher in severe OSAS group.

Smoking ratio was recorded as packet/years. When two groups were compared, it was found that smoking ratio was higher in severe OSAS group but this was not statistically significant (Table 2). However when sample sizes doubled with the same ratios, severe OSAS group was significantly more heavily smoking. (p=0.012).

Among all patients, 49 patient had comorbid disease and 16 patient had no disease except OSAS. AS and AD were not statistically different between these two groups. Mean AS was 7.72±3.58 in patients with comorbid disease and 7.49±3.84 in patients with solely OSAS (p=0.827). Mean AD was 3.18±1.65 in patients with comorbid disease and 5.42±9.09 in only OSAS patients (p=0.343).

AS and AD were higher in mild-moderate OSAS than in severe OSAS but there was no statistical significance (Table 3).

We investigated correlation of AS and AD with AHI and ODI in all patients with spearman correlation analysis. There was no statistically significant relation between aortic stiffness and AHI and ODI (Table 4).

Table 1. Comparison of OSAS groups by means of age, BMI, ODI, aortic measurements and additional disease presence

	Mild-Moderate OSAS (n=28)	Severe OSAS (n=37)	p
Age*	46.21±8.42	51.40±12.06	0.056
BMI* (kg/m^2)	29.78±4.06	34.06±6.24	**0.002**
ODI#	17.65 (6.8-33.3)	55.60 (29.0-115.2)	**<0.001**
SAD* (mm)	3.29±0.50	3.36±0.34	0.511
DAD* (mm)	3.05±0.54	3.15±0.38	0.383
PP* (mm/Hg)	48.75±12.59	51.75±12.31	0.338
Comorbid disease	%57.1 (n=16)	%89.2 (n=33)	**0.003**

OSAS: Obstructive sleep apnea syndrome, BMI: Body mass index, ODI: Oxygen desaturation index, SAD: Systolic aortic diameter, DAD: Diastolic aortic diameter, PP: Pulse pressure, *Mean±Standard Deviation, #Median (Minimum-Maximum)

Table 2. Comparison of smoking between OSAS groups

Smoking ratios	Mild-Moderate OSAS (n=28)	Severe OSAS (n=37)	p
Nonsmoker	14 (51.9%)	12 (32.4%)	0.146*
0-9 p/y	4 (14.8%)	2 (5.4%)	
10-19 p/y	2 (7.4%)	5 (13.5%)	
>20 p/y	7 (25.9%)	18 (48.6%)	

OSAS: Obstructive sleep apnea syndrome, p/y: pack/years, *Fisher's exact test

Table 3. Comparison of AS and AD in OSAS groups

	Mild-Moderate OSAS (n=28)	Severe OSAS (n=37)	p
AS# (%)	8.45 (2.5-16.0)	6.45 (2.6-17.8)	0.134
AD# ($10^{-6}\times cm^2\times dyn^{-1}$)	3.75 (1.0-38.5)	2.50 (0.3-7.4)	0.085

OSAS: Obstructive sleep apnea syndrome, AS: aortic strain, AD: aortic distensibility, #Median (Minimum-Maximum)

Table 4. Correlation of aortic stiffness indexes with ODI and AHI

	ODI		AHI	
	r	p	r	p
AS (%)	-0.190	0.130	-0.171	0.173
AD ($10^{-6}\times cm^2\times dyn^{-1}$)	-0.206	0.100	-0.194	0.122

ODI: Oxygen Desaturation Index, AHI: Apnea Hypopnea Index, AS: aortic strain, AD: aortic distensibility

DISCUSSION

Literature reveals that OSAS is seen 2-3 times more in men than in women (4). In this study male/female ratio was 5.5. Apnea is a cardinal symptom of OSAS and is witnessed more often by women (18), also our communities' socioeconomic status and smoking patterns may give rise to this noticeable difference.

Boussoffara and colleagues (19) compared nonsmoker and smoker OSAS patients and found AHI higher in smoker group; also severe OSAS risk was 3.7 times higher compared with nonsmoker group. In this study smoking ratio was 67.6% in severe OSAS, while 48.1% in mild-moderate OSAS group. Calculated as pack/years, severe OSAS patients were smoking more heavily. Although it is clear that OSAS increases arterial stiffness and it is expected that disease severity will influence the degree of stiffness; we found no statistically significant difference between mild-moderate OSAS and severe OSAS. There was also no correlation between AS and AD with apnea ODI in newly diagnosed patients.

BMI and cigarette smoking which also decrease arterial elasticity were significantly higher in severe OSAS group, but AS and AD were not different. Patients were untreated and newly diagnosed for OSAS, but the duration of their comorbid diseases (hypertension, coronary artery disease, diabetes mellitus and hyperlipidemia), their medications and adjustment to those drugs may influence the results. Also suggested that arterial stiffness is related with genetic factors (20), the individual differences may also play role.

Mean BMI was 31.92 ±5.15 in whole study group and 34 patients' BMI was higher than 30. Our patients were mostly obese, being concordant with literature (21). Among the total 65 patients, 50 had comorbid diseases. OSAS is a risk factor for hypertension, cardiovascular diseases and metabolic syndrome (22). Obesity is also known to be a risk factor for hypertension, cardiovascular disease, type 2 diabetes, hyperlipidemia, cancer, osteoarthritis, gastrointestinal system diseases and also OSAS (23). So in practice, we evaluated hypertension, diabetes mellitus, coronary artery disease and hyperlipidemia together as comorbid diseases because they are common complications of both OSAS and obesity.

Besides being closely related with obesity and metabolic syndrome, studies reveal that OSAS is an independent risk factor for increased arterial stiffness (17). Similarly with ischemia/reperfusion damage, repetitive episodes of nocturnal hypoxemia/reperfusion periods trigger inflammation due to release of reactive oxygen radicals and cause endothelial damage; the nitric oxide (NO) level in circulation also decreases. Chronic sleep deprivation, sleep fragmentation and genetic factors contribute to endothelial damage (24). Cardiovascular disease risk is increased proportionally with OSAS severity (25). Studies investigating the relationship of arterial stiffness with OSAS severity are limited in number, present data are generally directing an increase in arterial stiffness with disease severity (26). Chung et al. (27) evaluated brachial artery (flow mediated dilation) and carotid artery (carotid pulse wave velocity) in mild-moderate OSAS patients, severe OSAS patients and healthy subjects. Arterial stiffness was found to be increased in severe OSAS group with regard to mild-moderate OSAS and healthy subjects, and was related with age and ODI.

A study that has similar results with ours also evaluated OSAS patients with comorbidities (obesity, hypertension, diabetes and

coronary heart disease) Protogerou et al. (28) used respiratory disturbance index (RDI) instead of AHI to determine severity of OSAS; and there was no statistical difference for comorbidities between groups. Peripheral arterial stiffness (carotid PWV) was increased in severe and very severe OSAS but no relation was found between augmentation index which is used as an aortic stiffness parameter and pulse pressure with severity of OSAS.

Hypoxia may increase sympathetic activity resulting in peripheral vasoconstruction and the effect of OSAS may be detected different in central with regard to peripheral arteries because pulse wave reflections occurs earlier in peripheral arteries (28, 29). Another point is that arterial stiffness measurement may show diurnal differences like blood pressure changes: Philips et al. (30) showed a correlation between arterial stiffness and severity of OSAS. But there were nocturnal changes in arterial stiffness, also morning and evening measurements were different independent of OSAS severity. We did echocardiographic measurements in different hours of the day and this may be a possible factor affecting our patients' blood pressure and arterial stiffness parameters.

CONCLUSION

In conclusion; AS and AD as arterial stiffness parameters were mildly decreased in severe OSAS but we found no statistically significant relation between arterial stiffness and severity of OSAS. Because many factors affect arterial stiffness, more studies will be needed with higher populations and alternative measurement methods.

ACKNOWLEDGEMENTS

We thank to Dr. Can Yücel Karabay from Cardiology Department and Dr. Özlem Oruç from Sleep Clinic in Süreyyapaşa Chest Diseases and Thoracic Surgery Education and Research Hospital for valuable contributions to this study.

REFERENCES

1. Patil SP, Schneider H, Schwartz AR, Smith PL. Adult obstructive sleep apnea: pathophysiology and diagnosis. Chest. 2007;132(1):325-37.
2. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clinical Sleep Med. 2009;5(3):263-76.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea. Am J Respir Crit Care Med. 2002;165(9):1217-39.
4. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):136-43.
5. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290(14):1906-14.
6. Gozal D, Kheirandish-Gozal L. Cardiovascular morbidity in obstructive sleep apnea: oxidative stress, inflammation, and much more. Am J Respir Crit Care Med. 2008;177(4):369-75.
7. Stefanadis C, Dernellis J, Tsiamis E, Stratos C, Diamantopoulos L, Michaelides A, et.al. Aortic stiffness as a risk factor for recurrent acute coronary events in patients with ischaemic heart disease. Eur Heart J. 2000;21(5):390-6.
8. Tavil Y, Kanbay A, Şen N, Ulukavak Ciftci T, Abaci A, Yalcin MR, et al. The relationship between aortic stiffness and cardiac function in patients with obstructive sleep apnea, independently from systemic hypertension. J Am Society Echocardiogr. 2007;20(4):366-72.
9. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D et al. Expert consensus documant on arterial stiffness: methodological issues and clinical applications. European Heart Journal. 2006;27(21):2588-605.
10. Eren M, Gorgulu S, Dagdeviren B, Bolca O, Öz D, Cinsoy S, et al. Aortic stiffness and its relation with the left ventricular diastolic function in patients with hypertension and diabetes mellitus. Arch Turk Soc Cardiol. 2001;29(11):678-86.
11. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension. 2001;37(5):1236-41.
12. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Circulation. 1995;91(5):1432-43.
13. Liang YL, Shiel LM, Teede H, Kotsopoulos D, McNeil J, Cameron JD, et al. Effects of blood pressure, smoking, and their interaction on carotid artery structure and function. Hypertension. 2001;37(1):6-11.
14. Blacher J, GuerinAP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation. 1999;99(18):2434-9.
15. Roman MJ, Devereux RB, Schwartz JE, Lockshin MD, Paget SA, Davis A, et al. Arterial stiffness in chronic inflammatory diseases. Hypertension. 2005;46(1):194-9.
16. Wildman RP, Mackey RH, Bostom A, Thompson T, Sutton-Tyrrell K. Measures of obesity are associated with vascular stiffness in young and older adults. Hypertension. 2003;42(4):468-73.
17. Doonan RJ, Scheffer P, Lalli M, Kimoff RJ, Petridou ET, Daskalopoulos ME, et al. Increased arterial stiffness in obstructive sleep apnea: a systematic review. Hypertens Res. 2011;34(1):23-32.
18. Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. Sleep. 2005;28(3):309-14.
19. Boussoffara L, Boudawara N, Sakka M, Knani J. Smoking habits and severity of obstructive sleep apnea hypopnea syndrome. Rev Mal Respir. 2013;30(1):38-43.
20. Cattan V, Kakou A, Louis H, Lacolley P. Pathophysiology, genetic, and therapy of arterial stiffness. Biomed Mater Eng. 2006;16(4 Suppl):155-61.
21. Patel NP, Schwab RJ. Neural Modulation of Upper Airway Patency, Sleep Apnea Syndromes. In: Fishman AP, Elias JA, Fishman JA, Grippi MA, Senior RM, Pack AI, editors. Fishman's Pulmonary Disease and Disorders. 4th ed. New York, NY, USA: McGraw Hill; 2008. p.1701-5.
22. Ciftci TU, editor. Diagnosis and treatment guide for obstructive sleep apnea. Istanbul: Turkish Thoracic Society; 2012.
23. Malnick SD, Knobler H. The medical complications of obesity. QJM. 2006;99(9):565-79.
24. Atkeson A, Jelic S. Mechanisms of endothelial dysfunction in obstructive sleep apnea. Vasc Health Risk Manag. 2008;4(6):1327-35.
25. Querejeta Roca G, Redline S, Punjabi N, Claggett B, Ballantyne CM, Solomon SD, et al. Sleep apnea is associated with subclinical myocardial injury in the community: The ARIC-SHHS study. Am J Respir Crit Care Med. 2013;188(12):1460-5.
26. 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(5):613-8.
27. Chung S, Yoon IY, Lee CH, Kim JW. The association of nocturnal hypoxemia with arterial stiffness and endothelial dysfunction in male patients with obstructive sleep apnea syndrome. Respiration. 2010;79(5):363-9.
28. Protogerou AD, LaabanJP, Czernichow S, Kostopoulos C, Lekakis J, Safar ME, et al. Structural and functional arterial properties in patients with obstructive sleep apnoea syndrome and cardiovascular comorbidities. J Hum Hypertens. 2008;22(6):415-22.
29. Remsburg S, Launois SH, Weiss JW. Patients with obstructive sleep apnea have an abnormal peripheral vascular response to hypoxia. J Appl Physiol. 1999;87(3):1148-53.
30. Phillips C, Hedner J, Berend N, Grunstein R. Diurnal and obstructivesleep apnea influences on arterial stiffness and central blood pressure in men. Sleep. 2005;28(5):604-9.