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Original Article

Left and Right Ventricle Functions in Patients Obstructive Sleep Apnea and Their Relationship with Apelin Levels

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ABSTRACT

Aim of this study is to determine the left and right ventricle functions by echocardiography in patients with newly diagnosed obstructive sleep apnea (OSA) and to investigate whether there is a relationship between the apelin levels and systolic and diastolic functions of the right and left ventricles. Study included 44 patients (30 males, 14 females; mean age 49.8±11.5 years) diagnosed with obstructive sleep apnea according to polysomnographically determined apnea hypopnea index, and 30 control subjects (25 males, 5 females; mean age 43.03±10.89 years) diagnosed with simple snoring. Apelin levels of all the study subjects are measured. Systolic and diastolic functions of both ventricles were evaluated with the help of conventional and tissue Doppler methods. Results: Systolic and diastolic blood pressure levels of the OSA group were significantly higher compared to those of the AHI control group. Lateral inferior and anterior E' were significantly lower whereas E/E' was significantly higher in the OSA group compared to the control group (8.40±3.24 vs. 10.80±3.24; p=0.001, 7.50±2.60 vs 9.00±2.51; p=0.009, 7.90±2.68 vs. 8.90±2.73; p=0.006, 7.57±3.20 vs. 6.44±1.55; p=0.023, respectively). Although the apelin levels were higher in the OSA group compared to the control group, this difference did not reach statistical significance. Age, AHI, and echocardiographic indices were not correlated with the apelin levels. There was no relationship between the severity of OSA and the apelin levels, either. This study showed diastolic functions may be impaired in patinets with newly diagnosed OSA. Apelin levels which has been shown to play an important role in cardiovascular hemodynamics, had no significant correlation with OSA severity. Moreover, there was no significant correlation between the apelin levels and echocardiographically assessed systolic and diastolic functions of both ventricles.

Key words: *Obstructive sleep apnea, apelin, cardiac functions*

Obstruktif uyku apneli hastalarda sol ve sağ ventrikül fonksiyonları ve apelin düzeyleri ile ilişkisi

ÖZET

Bu çalışmada obstrüktif uyku apnesi (OUA) tanısı almış hastalarda ekokardiyografi ile sağ ve sol ventrikül fonksiyonlarının araştırılması ve bu parametrelerin apelin düzeyleri ile ilişkisi araştırılmıştır. Polisomnografi sonucu ile elde edilen apne hipopne indeksleri sonucuna göre yeni OUA tanısı almış 44 hasta (30 E, 14 K yaş ort 49.8±11.5) ile basit horlama tanısı almış 30 kontrol grubu (25 E, 5 K, 43.03±10.89) çalışmaya dahil edildi. Tüm çalışma grubundan apelin düzeyleri ölçüldü. Her iki ventrikülün sistolik ve diyastolik fonksiyonları konvansiyonel yöntemler ve doku Doppler yöntemi ile incelendi. OUA grubunun sistolik ve diyastolik kan basınçları ile AHI değerleri kontrol grubuna göre anlamlı olarak yüksekti. Doku Doppler parametrelerinden lateral, inferior ve anterior E' hızları OUA hastalarında kontrol grubuna göre düşüktü, E/E' düzeyleri ise anlamlı olarak yüksekti (sırası ile 8.40±3.24'e karşın 10.80±3.24 cm/sn; p=0.001, 7.50±2.60'e karşın 9.00±2.51 cm/sn; p=0.009,7.90±2.68'e karşın 8.90±2.73 cm/sn; p=0.006, 7.57±3.20'e karşın 6.44±1.55; p=0.023). Apelin düzeyleri OUA grubunda kontrol grubuna göre yüksek olmasına rağmen istatistiki olarak anlamlı değildi. Apelin düzeyleri ile yaş, AHI, ekokardiyografik verilerin hiçbirisi ile ilişki bulunamadı. OUA hastalığının ciddiyeti ile apelin düzeyleri arasında ilişki yoktu. Yeni tanı almış OUA hastalarında sol ventrikül diyastolik fonksiyonları bozulabilmektedir. Çalışmamızın sonucunda, kardiyovasküler hemodinamide önemli rol oynadığı gösterilen apelin düzeyleri ile OUA arasında ilişki bulunamamıştır. Bununla birlikte ekokardiyografi ile tespit edilen her iki ventrikülün sistolik ve diyastolik fonksiyonlarının apelin düzeyleri ile ilişkisi bulunamamıştır.

Anahtar Kelimeler: *Obstruktif uyku apnesi, apelin, kardiyak fonksiyonlar*

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INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by repetitive obstruction of upper airways coupled with ineffective respiratory effort during sleep. Hypoxia developing as a result of upper airway obstruction, arousals during sleep not only cause fragmented sleep, but also somnolence in patients during the day (1). There is a relationship between OSA and hypertension, heart failure, myocardial ischemia, and various vascular complications; the leading cause of mortality and morbidity in OSA are the cardiovascular diseases (2-4).

Apelin is a relatively novel molecule with an endogenous peptide structure and it is the ligand of angiotensin-like receptor (APJ1). The mechanism of action of the apelin-APJ system is exactly the opposite of that of the angiotensin II- AT1 receptor pathway. This has suggested that apelin may play a key role in the pathophysiology of certain cardiovascular disorders and be a target in their treatment (5). In addition, some studies have shown that apelin, which is a potent angiogenic factor, is upregulated under hypoxic conditions (6). In this study we investigated the levels of apelin, which has been shown to be closely associated with hypoxia and cardiovascular disorders, and its relationship between systolic and diastolic functions of the ventricles. We also explored if a correlation existed between apelin levels and OSA.

MATERIALS AND METHOD

This study included 44 patients (30 males, 14 females ; mean age 49.8±11.5 years) diagnosed with obstructive sleep apnea syndrome (OSA) at our Chest Diseases Department, Sleep Laboratory between 1 April 2011 and 1 October 2011, and 30 control subjects (25 males, 5 females; mean age 43.03±10.89 years) tested with the prediagnosis of OSA but diagnosed with simple snoring rather than OSA. All patients underwent detailed medical history taking and cardiovascular and other systemic physical examination. Patient weight and length, systolic and diastolic blood pressures, and pulse rate were recorded. Blood pressure measurements were simultaneously performed from the brachial artery and ankle. The systolic blood pressure measurements were proportioned and the ankle/brachial index was calculated. The vascular probe of the echocardiography device was used to measure the carotid intima-media thickness. Blood pressure measurements were simultaneously preformed from the brachial artery and the ankle. The systolic blood pressure values from both sites were then proportioned and the ankle-brachial index is calculated.

All procedures were carried out in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave informed written consent. Local ethic committee approved the study.

Polysomnography

Overnight polysomnography was performed in all patients by a computerized system (55 channels; Respironics, USA) and included the following variables: electrooculogram (2 channels), electroencephalogram (4 channels), electromyogram of submental muscles (2 channels), electromyogram of the anterior tibialis muscle of both legs (2 channels); electrocardiogram, and airflow (with a nasal cannula). Chest and abdominal efforts (2 channels) were recorded using inductive plethysmography, arterial oxyhemoglobin saturation (SaO_2 : 1 channel) by pulse oximetry with a finger probe. The recordings were conducted at a paper speed of 10 mm/s, and sleep stage was scored according to the standard criteria of Rechtschaffen and Kales. Arousals were scored according to accepted definitions. The AHI was obtained by dividing the total number of apneas and hypopneas by the total sleep time. Apneas were defined as complete cessation of airflow ≥10 seconds. Hypopneas were defined as a reduction of >50% in one of three respiratory signals, airflow signal or either respiratory or abdominal signals of respiratory inductance plethysmography, with an associated decrease of ≥3% in oxygen saturation or an arousal. According to the recently updated International Classification of Sleep Disorders published by the American Academy of Sleep Medicine, a diagnosis of OSA is to be made if the AHI is ≥15, independent of occurrence of symptoms, or whenever an AHI >5 is associated with any of the following: (1) sleep attacks or excessive daytime sleepiness, unrefreshing sleep, fatigue or (2) insomnia, or (3) witnessed heavy snoring and/or breathing pauses referred by the partner. The Epworth sleepiness scale is a questionnaire that especially evaluates daytime sleepiness. OSA was excluded by a negative history of sleep-related symptoms (snoring, witnessed apneas, and excessive daytime sleepiness) and with an AHI <5 at overnight PSG. Patients with sleep disorders, except OSA, such as upper airway resistance syndrome, periodic leg movement syndrome or narcolepsy, were ex-

cluded (7). AHI levels of 5-15 were considered mild OSA, 15-30 moderate OSA, and > 30 severe OSA.

Echocardiography

Standard electrocardiographic examinations were performed by a Vingmed Vivid System 5 (General Electric, Horten, Norway) device. A 2.5 MHz probe was used for the Doppler measurements and a 2.5-3.5 MHz probe for tissue Doppler measurements. All measurements were averaged from three cardiac cycles. Two-dimensional echocardiographic measurements were performed according to standards outlined by the American Society of Echocardiography (8). Pulsed TDI was performed on the apical 4-chamber view using a 5-mm pulsed Doppler sample volume with as minimum optimal gain as possible to obtain the best signal-to-noise ratio. Care was taken to align the echo image so that the annular motion was parallel to the TDI cursor. Spectral pulsed-wave Doppler signal filters were adjusted until a Nyquist limit of 15– 20 cm/s was reached. The monitor sweep speed was set at 50-100 mm/s to optimize the spectral display of myocardial velocities.

Laboratory tests

All patients underwent routine laboratory tests (FBG, lipid panel, complete blood count) from a venous blood sample obtained after an 8-hour fasting period. After physical examination telecardiogram and respiratory function tests were ordered and other complex lung tests were performed as necessary.

Measurement of Apelin

Patient and control groups included in the study gave venous blood samples into EDTA containing tubes after 8 hours of fasting. The blood samples were centrifuged at 4000 rpm for 10 minutes to separate plasma, and were then stored at -80˚C in the immunology department of our hospital. From the taken blood samples the apelin kits (Apelin-36 Human EIA kit, PHOENIX PHARMACEUTICALS, INC., USA) were studied using the ELISA method.

Statistical Analysis

Analysis of the study data was accomplished using SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA) 13.0 software package. The continuous variables were expressed as mean, standard deviation, minimum, and maximum, while the categorical variables were presented as frequency and percentages. The normality of distribution of the continuous variables was tested using the Shapiro Wilk test. The normally distributed variables were compared between the two groups with the independent sample t test while the non-normally distributed variables were compared between the two groups using the Mann Whitney-U test. The OSA group was trichotomized into mild, moderate, and severe subgroups and the variables were compared across the subgroups using One way ANOVA test or the Kruskal Wallis test. The categorical variables were compared in the groups with the Pearson Chi-square test and Fisher's exact Chi-square test. The correlation between the continuous variables was interpreted using the Pearson's or Spearman's correlation coefficients. In the study, the comparisons having a p value less than 0.05 was considered statistically significant.

RESULTS

Demographic Data

There were no significant differences between the OSA and the control group with respect to age, sex, body mass index, hypertension, diabetes, smoking, hyperlipidemia, and pulse rate (Table 1). Systolic and diastolic blood pressures were significantly higher in the OSA group compared to the control group (140±16 mmHg vs. 132.5±15.3 mmHg; p=0.023; 90±11.8 mmHg vs. 80.0±10.7 mmHg; p=0.026, respectively). Nineteen patients in the OSA group and 8 patients in the control group were using antihypertensives and the groups were not significantly different with respect to antihypertensive use. Polysomnographically measured AHI and arousal indices were significantly higher in the OSA group (28.05±28.82 vs. 1.35±2.94; p<0.0001, 19.65±20.05 vs. 13.20±11.11; p=0.013, respectively). ABI values were significantly higher in the OSA group compared to the control group, while the carotid IMT was similar (1.23±0.16 vs. 1.35±0.15; p=0.038, 0.62±0.14 vs. 0.56±0.10; p=0.138, respectively).

Echocardiographic Data

Among the conventional parameters, interventricular septum and aortic diameter were significantly higher in the OSA group compared to the control group (1.10±0.12 vs. 1.05±0.09; p=0.021, 3.07±0.25 vs. 2.97±0.20, p=0.012, respectively). Other parameters were similar (Table 2). There were no significant differences with respect to the conventional mitral Doppler parameters obtained from the mitral valve (Table 2). As for the tissue Doppler parameters obtained from the 5 anuli, lateral and ante-

***Table 1**. The demographic parameters, laboratory parameters, apelin levels and statistically significant parameters between the groups.*

	OSA (n:44)	Control (n:30)	p value
Age (years)	49.8±11.5	43.03±10.89	0.164
Gender (M)	30	25	0.241
BMI(kg/m^2)	34.0±6.7	30.8±4.6	0.145
Diabetes Mellitus (n)	6	4	0.970
Hypertension (n)	19	8	0.147
Smoking (n)	7	13	0.009
Hyperlipidemia(n)	9	3	0.231
Diastolic blood pressure (mmHg)	90.0±11.8	80.0±10.7	0.026
Systolic blood pressure (mmHg)	140.0±16.0	132.5±15.3	0.023
Heart rate (beat/min)	75.9±9.8	72.7±12.2	0,214
AHI	28.05±28.82	1.35±2.94	<0.0001
AI	19.65±20.05	13.20±11.11	0.013
ABI	1.23±0.16	1.35±0.15	0.038
Carotis IMT	0.62±0.14	0.56±0.10	0.138
Apelin	13.3±6.3	16.6±8.4	0.362

Abbrevations:AHI; apea-hypopnea index, AI; arousal index, ABI; Ankle brachial index, IMT; intima media thickness.

rior E' were significantly lower whereas E/E' was significantly higher in the OSA group compared to the control group (8.40±3.24 vs. 10.80±3.24; p=0.001, 7.90±2.68 vs. 8.90±2.73; p=0.006, 7.57±3.20 vs. 6.44±1.55; p=0.023, respectively). Both groups did not differ significantly with regard to other tissue Doppler parameters (Table 3). IVA and TAPSE values obtained from the right ventricle were not different between the groups, either (Table 2, 3).

The apelin levels were similar in both groups (15.1±14.3 vs. 13.6±18.4; p=0.098). Furthermore, apelin levels were also similar across the hypertensive and non-hypertensive subgroups of the OSA patients (13.3±6.3 vs. 16.6±8.4; p=0.362). There was no significant correlation between the apelin levels and polysomnographic parameters. Moreover, no significant correlation could be found between the apelin levels, right and left ventricle sizes, conventional and tissue Doppler parameters, ejection fractions, and diastolic functions. Similarly, there was no significant correlation between the apelin levels and carotid IMT or ABI. When the OSA group was trichotomized into mild, moderate, and severe subgroups based on the AHI values, 13 patients fell into the mild, 12 into moderate, and 21 into severe OSA subgroup. The subgroups

***Table 2**. Conventional echocardiographic parameters of the groups*

	OSA (n:44)	Control (n:30)	p value
LVEDD (cm)	4.82±0.30	4.70±0.26	0.108
LVESD (cm)	3.00±0.25	2.91±0.17	0.078
IVS (cm)	1.10±0.12	1.05±0.09	0.021
PW (cm)	1.00±0.12	1.00±0.10	0.201
LA diameter (cm)	3.80±0.36	3.70±0.19	0.096
Aortic diameter (cm)	3.07±0.25	2.97±0.20	0.012
RVEDD (cm)	3.23±0.31	3.13±0.26	0.261
RVESD (cm)	1.99±0.32	1.94±0.31	0.186
Aortic velocity (m/sn)	1.30±0.13	1.30±0.08	0.059
Pulmoner velocity (m/sn)	0.80±0.12	0.80±0.09	0.641
Mitral E wave (m/sn)	0.61±0.16	0.76±0.14	0.088
Mitral A wave (m/sn)	0.71±0.17	0.65±0.14	0.155
Mitral E/A	0.77±0.36	1.21±0.36	0.086
EDT (msn)	280.1±58.3	184.5±55.5	0.076
IVRT (msn)	102.9±13.3	100.0±22.3	0.746
ICT (msn)	58.80±13.71	58.8±11.3	0.084
ET (msn)	291.1±30.3	294.1±44.0	0.494

Abbrevations:LVEDD;Left ventricle enddiastolic diameter, LVESD;left ventricle endsystolic diameter, EF; ejection fraction, EDT; mitral E wave deceleration time, IVRT; isovolumic relaxation time, ET; ejection time, ICT; isovolumic contraction time, RVEDD: Right ventricle enddiastolic diameter , RVESD:Right ventricle endsystolic diameter.

Table 3. Tissue Doppler parameters of the groups.

	OSA (n:44)	Control (n:30)	p value
S' septum (cm/sn)	6.86±1.58	6.86±1.20	0.947
E' septum (cm/sn)	6.66±1.85	7.34±2.51	0.072
A' septum (cm/sn)	8.59±1.77	9.05±1.80	0.969
S' lateral (cm/sn)	8.28±2.33	8.68±2.09	0.420
E' lateral (cm/sn)	8.40±3.24	10.80±3.24	0.001
A' lateral m(cm/sn)	10.60±2.70	9.90±2.25	0.163
S' tricuspit (cm/sn)	12.50±3.40	12.80±2.21	0.956
E' tricuspit (cm/sn)	9.60±3.18	11.40±2.30	0.074
A' tricuspit (cm/sn)	13.40±3.71	13.00±3.64	0.690
RV IVA (m/sn2)	2.15±0.65	2.40±0.72	0.131
S' anterior (cm/sn)	7.50±2.66	7.70±2.20	0.917
E' anterior (cm/sn)	7.90±2.68	8.90±2.73	0.006
A' anterior (cm/sn)	9.22±3.84	7.80±2.91	0.047
S' inferior (cm/sn)	8.00±1.67	7.60±1.46	0.939
E' inferior (cm/sn)	7.50±2.60	9.00±2.51	0.009
A' inferior (cm/sn)	10.40±2.22	10.00±2.09	0.729
E/E' lateral	7.57±3.20	6.44±1.55	0.023
E/E' septum	9.69±2.94	9.21±2.80	0.415

Abbrevations IVA; isovolumic acceleration time

were not significantly different with respect to the apelin levels. Any of the subgroups did not demonstrate a significant correlation between the apelin levels and either demographic or echocardiographic parameters.

DISCUSSION

Apelin is a multifunctional peptide with important role in regulation of cardiovascular system, including blood pressure and cardiac functions, and it has been even implicated in the pathophysiology of hypertension (9). The fact that apelin is a potent inotrope and peripheral vasodilator, and has an important function in fluid hemostasis suggested that apelin may be beneficial both in diagnosis and treatment of cardiovascular disorders, particularly heart failure (5). An experimental study demonstrated that apelin is a peripheral vasodilator acting through a nitric oxide-dependent mechanism and it exerts its heart rate modulating effects not through a chronotropic action, but rather secondary to baroreceptor reflex (5). In vivo studies have suggested that apelin's effect on vascular tonus may be dependent on the dynamic interaction between the apelin-APJ system and angiotensin II-ATI (10). The inotropic action of apelin is realized through increasing intracellular calcium amount as well as increasing sensitivity of myofilaments to calcium (10-11).

Apelin is a potent angiogenic factor; apelin gene is known to be upregulated in hypoxic conditions (6). Its close relationship with cardiovascular complications, as well as a higher prevalence of cardiovascular risk factors in OSA patients has led to studies investigating the relationship between OSA and apelin. In a study by Henley et al., no change in apelin levels occurred over a 24-hour period but the levels increased after glucose challenge in a group of patients with OSA (12). They showed that apelin levels were reduced during CPAP therapy. Zirlik et al. found similar apelin levels to the control group in 10 OSA patients and they demonstrated, as Henley et al. did, that apelin levels decreased with CPAP therapy (13). Zeng et al., in a study comparing patients with polysomnographically diagnosed OSA and patients with simple snoring, found higher apelin levels in patients with OSA (14). We, on the other hand, found similar apelin levels in patients with simple snoring and OSA. One additional interesting finding of our study was the lack of a significant correlation between the apelin levels and the conventional and tissue Doppler parameters in the entire study population. We could not detect any significant correlation between the diastolic and systolic functions of the right and left ventricle and the apelin levels. There were also no significant differences between the subgroups created by the OSA severity with respect to apelin levels. The close association between OSA and obesity, hypertension, insulin resistance, and diabetes is well known. Cebeci et al. found a correlation between apelin levels and body mass index in obese adolescents (15). There are some studies investigating the relationship between apelin levels and these patient groups. Habchi et al. found significantly

higher apelin levels in 130 type 1 and 98 type 2 diabetic patients compared to the control group. They also demonstrated that apelin plays an important role in insulin resistance and glucose hemostasis (16). Soriquer et al. similarly found higher apelin levels in morbid obese type 2 diabetic patients. In those 2 studies, however, it was shown that obesity was not the primary determinant for apelin levels (17). We, on the other hand, could not find any significant relationship between the apelin levels and body mass index or waist circumference. Kosmala et al. found lower apelin levels in hypertensive patients. They also detected a correlation between various systolic and diastolic parameters, with the left ventricular wall mass being in the first place in that patient population (9). In our study, the apelin levels still remained similar when the OSA group was divided into subgroups based on the presence of hypertension (hypertensive vs. non-hypertensive groups); moreover, none of the parameters were correlated with the apelin levels.

In conclusion, OSA is a disease with significant cardiovascular morbidity and mortality and it is closely related to various cardiovascular risk factors. In the present study there were no correlation between the levels of apelin, which has been shown to play an important role in cardiovascular hemodynamics, and OSA. Moreover, according to results of our study, apelin levels may not be related to echocardiographically diagnosed systolic and diastolic functions of both ventricles. Future studies with a larger sample size may shed light on this subject.

Conflict of interest

No potential conflict of interest relevant to this article was reported

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