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Obstructive Sleep Apnoea and Its Association with Left Ventricular Function and Aortic Root Parameters in Newly Diagnosed, Untreated Patients: a Prospective Study

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This prospective study investigated whether untreated obstructive sleep apnoea–hypopnoea syndrome (OSAHS), which is strongly associated with cardiovascular disease, is a risk factor for left ventricular (LV) systolic and diastolic dysfunction and aortic root dilatation. Ninety consecutive patients with breathing and snoring problems, including 64 with newly diagnosed, untreated OSAHS, were classified into four groups based on their apnoea–hypopnoea index (AHI). All participants underwent overnight polysomnographic and complete echocardiographic examinations, and LV systolic, diastolic and aortic measurements were compared. Body mass index was the only demographic characteristic that significantly increased as the severity of OSAHS (AHI) increased and it significantly correlated with AHI. Patients with a higher AHI had a significantly higher aortic root diameter and aortic stiffness index, and significantly lower aortic strain. The LV diastolic parameters were least favourable in patients with more severe OSAHS. The LV ejection fraction did not differ significantly between groups. It was concluded that LV diastolic function and aortic elastic parameters deteriorate with OSAHS.

KEY WORDS: Obstructive sleep apnoea; Aortic stiffness index; Aortic strain; Ventricular function

Introduction

Obstructive sleep apnoea–hypopnoea syndrome (OSAHS) is characterized by apnoea and hypopnoea during sleep, typically preceded by snoring.[1] There is usually a high incidence of cardiovascular disease in patients with OSAHS.[1 – 3] In clinical practice, however, the effects of OSAHS on left ventricular (LV) function and aortic root dilatation can be difficult to determine because many of the risk factors for OSAHS, such as obesity, male sex,

hypertension and age, are identical to those for cardiovascular disease. The effects of OSAHS on LV diastolic[4 – 6] and systolic[7 – 9] function and aortic parameters,[10 – 14] evaluated using conventional Doppler echocardiography, have previously been reported, but some of the data are conflicting.

In this study, LV function and aortic root diameter were investigated in newly diagnosed, untreated patients with OSAHS.

Patients and methods

PATIENTS AND STUDY DESIGN

The initial assessment was conducted in the pneumology sleep unit at Baskent University School of Medicine, Antalya, Turkey, in consecutive patients with breathing problems and snoring, between November 2009 and March 2010. The study was approved by the Ethics Committee and Review Board of Baskent University School of Medicine. Written informed consent for participation in the study was obtained from all patients.

Exclusion criteria were: (i) unstable cardiorespiratory status, defined as the occurrence of respiratory failure, bronchopulmonary infection or congestive heart failure in the previous 2 months; (ii) coronary artery disease, defined as typical angina pectoris, prior myocardial infarction, a positive exercise test result, positive myocardial scintigraphy, or positive coronary angiography findings; (iii) valvulopathy; (iv) permanent atrial fibrillation; and (v) congenital heart disease.

The patients were divided into four groups according to their apnoea–hypopnoea index (AHI), defined as the total number of apnoea or hypopnoea episodes per hour of sleep: group A, AHI ≤ 5 episodes/h; group B, 5 episodes/h < AHI < 15 episodes/h; group C, 15 episodes/h ≤ AHI < 30 episodes/h; group D, AHI ≥ 30 episodes/h. Participants in groups B, C and D were classified as having OSAHS; those in group A constituted the control group.

ECHOCARDIOGRAPHY

Transthoracic echocardiography was performed with a Vivid™ 4 system (GE Vingmed, Horten, Norway) using a 2.5 MHz transducer according to the recommendations of the American Society of Echocardiography.[15] The echocardiograms were reviewed and excluded from analysis if the two-dimensional images were inadequate. Imaging was performed by one experienced echocardiographer (D.C.), who was blinded to the study groups.

Left ventricular end-diastolic and end-systolic diameters were obtained by M-mode measurements during two-dimensional echocardiography according to the recommendations of the American Society of Echocardiography.[16] The LV mass index was calculated according to Devereux *et al.*[17] Systolic function was assessed by measurement of the LV ejection fraction (LVEF).[18]

Left ventricular diastolic function was assessed by both two-dimensional and Doppler echocardiography in accordance with the recommendations of the American Society of Echocardiography.[16] The mitral inflow pattern of the sample volume between the leaflet tips was recorded using the pulsed-wave Doppler technique. The following variables were measured: peak flow velocity in early diastole (E wave), peak velocity at atrial contraction (A wave), isovolumic relaxation time and mitral deceleration time. The E / A wave ratio was calculated. The modified Bernoulli equation for tricuspid regurgitation was used to calculate systolic pulmonary artery pressure.[19] Measurements were made in three cardiac cycles and the mean of three

consecutive analyses was calculated.

Aortic root diameter was measured in systole and diastole, according to the method of Stefanadis *et al.*,[20] using a calliper to measure the distance between the trailing edge of the anterior aortic wall and the leading edge of the posterior aortic wall. Aortic systolic (AoS) diameter was measured at full opening of the aortic valve and aortic diastolic (AoD) diameter was measured at the QRS peak. Three consecutive beats were measured and the mean was calculated. The aortic strain (%Ao), expressed as the percentage change in aortic root diameter, was calculated as %Ao = 100 × (AoS – AoD) / AoD. The aortic stiffness index was calculated as (SBP/DBP) / (AoS – AoD) / AoD, where DBP is diastolic blood pressure and SBP is systolic blood pressure.

All Doppler and echocardiographic recordings were stored on optical disks and were analysed off-line by a single experienced investigator (D.C.) blinded to patient status and treatment.

POLYSOMNOGRAPHY AND SLEEPINESS EVALUATION

All participants underwent attended overnight polysomnography using the E-Series™ 44-channel system (Compumedics, Abbotsford, Australia). The recordings comprised a two-channel electro-encephalogram, electromyogram, electro-cardiogram, electro-oculogram, body position, chest and abdominal excursions, naso-oral airflow assessed with a nasal cannula, and oxyhaemoglobin saturation (finger pulse oximetry). A single, attended polysomnographic study throughout one night was used to assess night-time breathing and snoring disorder and the presence of sleep apnoea.[21] Total cessation of airflow at the nose and mouth for at least 10 s was classified as apnoea (obstructive or central apnoea if respiratory effort was present or absent, respectively). An airflow reduction of > 30% for ≥ 10 s associated with oxygen desaturation of ≥ 4% was classified as hypopnoea.[22] Calculated polysomnographic variables included the AHI and the percentage of total sleep time during which the oxygen saturation of peripheral blood (SpO_2) was < 90%.

Participants were also evaluated according to the Epworth Sleepiness Scale, in which the likelihood of dozing in eight situations was scored (0, no likelihood; 1, slight likelihood; 2, moderate likelihood; 3, high likelihood), giving a maximum score of 24. Sleep studies were performed in the Baskent University Alanya Hospital Chest Disease Sleep Laboratory and were supervised throughout by an experienced technician.

STATISTICAL ANALYSES

Data were expressed as mean ± SD. Student's *t*-test or one-way analysis of variance, as appropriate, were used to compare continuous variables and the χ^2-test was used to compare proportions among groups. Linear regression analysis with Pearson's correlation coefficient was used to assess the strength of associations between variables. Multivariate regression analysis was used to identify determinants of aortic stiffness and strain and to evaluate the interaction between indices of OSAHS and determinants of stiffness. The strength of these associations was expressed as the β coefficient and *P*-value. A *P*-value < 0.05 was considered statistically significant. All analyses were performed with the SPSS® statistical program, version 11 (SPSS Inc., Chicago, IL, USA).

Results

A total of 90 consecutive patients were included in the study and their clinical and

demographic characteristics are summarized in Table 1. There were no significant differences among the four AHI groups with regard to age, sex, SBP, DBP or the prevalences of hypertension, diabetes mellitus, smoking and dyslipidaemia. Patients with severe OSAHS (group D, AHI ≥ 30 episodes/h) had a significantly higher mean body mass index than patients in group A (control group; AHI ≤ 5 episodes/h), group B (5 episodes/h < AHI < 15 episodes/h) and group C (15 episodes/h ≤ AHI < 30 episodes/h) ($P < 0.05$; Table 1).

Table 2 shows the overnight polysomnographic findings for the patients in the four groups. The mean AHI differed significantly among the four groups ($P = 0.0001$). There were also significant differences between the four groups in the Epworth Sleepiness Scale ($P = 0.003$), mean SpO_2 at night ($P = 0.0001$), minimum SpO_2 ($P = 0.0001$) and total sleep time ($P = 0.016$).

Left ventricular systolic measurements did not differ significantly among the four groups, with no differences in LVEF, LV mass index or LV end-diastolic and LV end-systolic diameters (Table 3). The left atrium diameter and interventricular septum and posterior wall diastolic thicknesses were also similar among the four groups. None of the patients had LV systolic dysfunction.

Left ventricular diastolic parameters were unfavourable in groups C and D. Diastolic cardiac function, expressed as the E/A ratio, was inversely and significantly correlated with AHI ($P = 0.003$; Table 3).

Aortic parameters for the four study groups are shown in Table 4. The mean diastolic aortic diameter was significantly higher in patients with severe OSAHS (group D) compared with the other three groups ($P < 0.05$). Aortic root diameter (systolic, $P = 0.010$; diastolic, $P = 0.004$) and the aortic stiffness index were positively and significantly associated with AHI ($P = 0.001$), though there was no significant difference in the stiffness index between groups C and D. Aortic strain was inversely and significantly associated with AHI ($P = 0.003$), though groups C and D did not differ significantly from each other and neither did groups A and B.

Discussion

In this study, the main findings in patients with untreated OSAHS were: (i) no change in LV systolic function; (ii) deterioration in LV diastolic function; and (iii) aortic root dilatation and deterioration of aortic elastic parameters.

Previous studies on LV diastolic function in patients with OSAHS have yielded conflicting results, depending on the methods used and the way the study populations were selected.[4,5,9,21 – 23] Niroumand *et al.*[4] showed that OSAHS did not impair LV diastolic function in a large clinic population and the large sample size increased the credibility of the statistical analysis. Most studies, however, have reported impaired diastolic function, as assessed by conventional echocardiographic parameters, in patients with OSAHS.[5,24,25] Conventional Doppler and two-dimensional parameters were used in the present study to evaluate LV diastolic function in patients with OSAHS and impaired LV diastolic function was found in patients with severe OSAHS.

There are conflicting data on LV systolic function in OSAHS. Alchanatis *et al.*[26] showed that OSAHS patients without cardiovascular disease developed LV systolic and diastolic dysfunction, which was partially or completely reversible with 6 months of continuous positive airway pressure treatment. Shahar *et al.*[27] identified a significant relationship between OSAHS

TABLE 1:
Clinical and demographic characteristics of 90 consecutive participants who had breathing and snoring problems without (group A) or with (groups B – D) obstructive sleep apnoea–hypopnoea syndrome, stratified according to apnoea–hypopnoea index (AHI)

Characteristic	AHI ≤ 5 episodes/h (group A; *n* = 26)	5 episodes/h < AHI < 15 episodes/h (group B; *n* = 20)	15 episodes/h ≤ AHI < 30 episodes/h (group C; *n* = 20)	AHI ≥ 30 episodes/h (group D; *n* = 24)	Statistical significance[a]
Age, years	49.4 ± 12.3	59.3 ± 9.5	60.1 ± 13.5	57.3 ± 16.2	NS
Males/females	13/13	9/11	6/14	6/18	NS
Diabetes mellitus	4 (15.4)	2 (10.0)	5 (25.0)	8 (33.3)	NS
Hypertension	12 (46.2)	4 (20.0)	8 (40.0)	15 (62.5)	NS
Smoking	12 (46.2)	3 (15.0)	10 (50.0)	15 (62.5)	NS
Dyslipidaemia	6 (23.1)	4 (20.0)	5 (25.0)	9 (37.5)	NS
Body mass index, kg/m^2	21.1 ± 2.3	23.5 ± 3.1	26.5 ± 4.2	30.5 ± 6.4[b]	$P = 0.002$
Systolic blood pressure, mmHg	131.4 ± 4.2	127.1 ± 6.3	129.6 ± 3.8	133.6 ± 4.1	NS
Diastolic blood pressure, mmHg	72.1 ± 3.4	74.3 ± 4.3	75.5 ± 5.2	79.4 ± 6.3	NS

Data presented as mean ± SD or *n* (%).
[a]Student's t-test. [b]$P < 0.05$ versus groups A, B and C (Student's *t*-test).
NS, not statistically significant ($P > 0.05$).

TABLE 2:
Overnight polysomnographic findings in 90 consecutive participants who had breathing and snoring problems without (group A) or with (groups B – D) obstructive sleep apnoea–hypopnoea syndrome, stratified according to apnoea–hypopnoea index (AHI)

Characteristic	AHI ≤ 5 episodes/h (group A; *n* = 26)	5 episodes/h < AHI < 15 episodes/h (group B; *n* = 20)	15 episodes/h ≤ AHI < 30 episodes/h (group C; *n* = 20)	AHI ≥ 30 episodes/h (group D; *n* = 24)	Statistical significance[a]
AHI	2.4 ± 1.5	8.4 ± 3.6	25.5 ± 4.2	62.9 ± 23.6	$P = 0.0001$
Epworth Sleepiness Scale (range 0 – 24)	7.5 ± 4.7	7.4 ± 4.3	8.1 ± 4.2	8.8 ± 5.9	$P = 0.003$
SpO_2 night	96.2 ± 1.7	93.4 ± 1.5	90.6 ± 2.6	87.9 ± 3.8	$P = 0.0001$
SpO_2 day	94.8 ± 2.9	95.8 ± 1.3	96.4 ± 2.2	94.7 ± 2.8	NS
Minimum SpO_2	91.6 ± 3.7	89.4 ± 2.4	84.4 ± 6.7	73.5 ± 7.7	$P = 0.0001$
Total sleep time	5.2 ± 2.4	5.7 ± 0.8	6.3 ± 0.6	6.5 ± 0.2[b]	$P = 0.016$

Data presented as mean ± SD.
[a]χ^2-test. [b]$P < 0.05$ versus groups A and B (χ^2-test).
SpO_2, oxygen saturation of peripheral blood; NS, not statistically significant ($P > 0.05$).

TABLE 3:
Left ventricular systolic and diastolic parameters in 90 consecutive participants who had breathing and snoring problems without (group A) or with (groups B – D) obstructive sleep apnoea–hypopnoea syndrome, stratified according to apnoea–hypopnoea index (AHI)

Parameter	AHI ≤ 5 episodes/h (group A; *n* = 26)	5 episodes/h < AHI < 15 episodes/h (group B; *n* = 20)	15 episodes/h ≤ AHI < 30 episodes/h (group C; *n* = 20)	AHI ≥ 30 episodes/h (group D; *n* = 24)	Statistical significance[a]
LVEF, %	68.2 ± 6.1	69.3 ± 4.5	69.8 ± 3.8	69.2 ± 6.2	NS
LV mass index	101.2 ± 4.1	98.4 ± 3.1	96.3 ± 2.2	103.5 ± 2.5	NS
LVED, mm	43.5 ± 4.4	41.9 ± 3.9	41.5 ± 5.9	42.7 ± 4.8	NS
LVES, mm	26.4 ± 3.4	29.1 ± 3.2	29.2 ± 5.8	28.7 ± 3.9	NS
LA diameter, mm	32.1 ± 5.0	31.7 ± 2.8	33.2 ± 4.5	33.2 ± 3.8	NS
IVS (diastolic thickness), mm	1.1 ± 0.2	1.1 ± 0.1	1.2 ± 0.2	1.2 ± 0.2	NS
PW (diastolic thickness), mm	0.9 ± 0.2	1.0 ± 0.1	1.1 ± 0.2	1.0 ± 0.1	NS
Mitral E wave, cm/s	1.2 ± 0.5	1.1 ± 0.1	0.9 ± 1.4	0.8 ± 0.2[b]	$P = 0.002$
Mitral A wave, cm/s	0.7 ± 0.2	0.8 ± 0.2	1.0 ± 0.3	0.9 ± 0.2	NS
Peak E/A ratio	1.7 ± 0.4	1.3 ± 0.3	0.9 ± 0.4	0.8 ± 0.4[b]	$P = 0.003$
IVRT, ms	91.3 ± 13.6	95.6 ± 9.4	102.4 ± 11.3	107 ± 10.3[c]	$P = 0.002$
Mitral deceleration time, ms	205.3 ± 32.1	212.5 ± 41.5	223.6 ± 54.5	245.6 ± 64.1[c]	$P = 0.001$
sPaP, mmHg	18 ± 4.5	22.4 ± 1.6	32.5 ± 4.8	38.5 ± 6.7[c]	$P = 0.002$

Data presented as mean ± SD.
[a]Statistical analysis was performed by linear regression with Pearson coefficients.
[b]$P < 0.05$ versus groups A and B (linear regression with Pearson coefficients).
[c]$P < 0.05$ versus groups A, B and C (linear regression with Pearson coefficients).
LVEF, left ventricular ejection fraction; LV, left ventricular; LVED, left ventricular end-diastolic diameter; LVES, left ventricular end-systolic diameter; LA, left atrium; IVS, interventricular septum; PW, posterior wall; E, early diastolic peak flow velocity; A, late diastolic peak flow velocity; IVRT, isovolumic relaxation time; sPaP, systolic pulmonary artery pressure; NS, not statistically significant ($P > 0.05$).

TABLE 4:
Aortic parameters in 90 consecutive participants who had breathing and snoring problems without (group A) or with (groups B – D) obstructive sleep apnoea–hypopnoea syndrome, stratified according to apnoea–hypopnoea index (AHI)

Aortic parameter	AHI ≤ 5 episodes/h (group A; *n* = 26)	5 episodes/h < AHI < 15 episodes/h (group B; *n* = 20)	15 episodes/h ≤ AHI < 30 episodes/h (group C; *n* = 20)	AHI ≥ 30 episodes/h (group D; *n* = 24)	Statistical significance[a]
Aortic diameter, systolic (AoS), mm	29.4 ± 3.6	30.3 ± 4.7	32.1 ± 3.8	33.7 ± 3.6[b]	*P* = 0.010
Aortic diameter, diastolic (AoD), mm	28.3 ± 3.3	28.7 ± 2.5	29.8 ± 2.8	31.1 ± 1.4[c]	*P* = 0.004
Aortic strain, %	27.3 ± 5.7	26.8 ± 6.8	23.6 ± 5.3	22.5 ± 7.2	*P* = 0.003
Aortic stiffness index	6.6 ± 2.2	6.9 ± 1.5	7.4 ± 3.6	7.3 ± 2.8	*P* = 0.001

Data presented as mean ± SD.
Aortic strain = 100 × (AoS – AoD) / AoD; aortic stiffness index = systolic blood pressure/diastolic blood pressure / (AoS – AoD) / AoD.
[a]Statistical analysis was performed by multivariate regression.
[b]$P < 0.05$ versus groups A and B (multivariate regression).
[c]$P < 0.05$ versus groups A, B and C (multivariate regression).

and self-reported heart failure in a large community study. Kaneko *et al.*[28] reported an improvement in LVEF from 27% to 36% associated with reductions in blood pressure and LV dimensions over a 4-week period in 24 patients with OSAHS and systolic heart failure. However, Fung *et al.*[24] concluded that impaired LV diastolic function is common in OSAHS patients with normal LV systolic function and the present study found that patients differing in AHI showed no significant differences in LV systolic function.

In a prospective study of aortic parameters, Serizawa *et al.*[29] reported that the thoracic aorta was significantly larger in patients with than in those without OSAHS. A study of patients with Marfan syndrome and control subjects also found a link between OSAHS and aortic root dilatation.[14] In contrast, a retrospective cohort study of 76 patients failed to demonstrate any link between OSAHS parameters and aortic root dilatation.[11]

A recent report showed that sleep apnoea can accelerate the rate of increase in abdominal aortic aneurysm size.[30] Stöwhas *et al.*[13] showed in healthy subjects that simulation of obstructive hypopnoea/apnoea and central apnoea induced considerable changes in blood pressure and that obstructive hypopnoea was associated with an increase in proximal aortic diameter.

In the present study, the decrease in SpO_2 associated with obstructive events was significantly correlated with the degree of aortic stiffness, suggesting that the hypoxia associated with the obstructive event played an important role in the change in aortic elastic properties. Increased aortic stiffness might be an important variable in assessing the effects of OSAHS on LV function and mass. Tanriverdi *et al.*[10] showed that aortic elastic parameters, which are strongly associated with cardiovascular disease,

deteriorated with OSAHS and they concluded that increased aortic stiffness might cause the LV systolic and diastolic impairment that occurs in OSAHS. The present study also showed that AHI was positively associated with aortic stiffness and that it was inversely associated with aortic strain.

Sudden death from cardiac causes occurs much more often during the night in patients with OSAHS than in patients without this condition; Gami *et al*.[31] showed an association between day–night patterns of sudden death among patients with OSAHS.

Obstructive sleep apnoea can lead to nocturnal cardiac ischaemia[32] and ventricular arrhythmias.[33] Apnoeic episodes elicit increased sympathetic activity,[34] blood pressure elevations[34] and platelet aggregation.[35] OSAHS is associated with abnormalities in cardiac autonomic and electrophysiological factors, including heart rate variability,[36] duration of the QT interval,[37] baroreflex function and chemoreceptor sensitivity.[38] Serious and potentially fatal arrhythmias occur during sleep in patients with OSAHS,[39] but they can be attenuated by effective treatment.[40 – 43] Thus, the multiple pathophysiological mechanisms that occur during sleep in people with OSAHS may explain their increased risk of nocturnal sudden death from cardiac causes.

The present study had several limitations. First, the study population was relatively small. Secondly, patients with hypertension and obesity, which can affect echocardiographic parameters, were not excluded. Thirdly, tissue Doppler imaging was not used to evaluate LV diastolic dysfunction. Fourthly, the effect of cardiac medication was not evaluated.

In conclusion, the present study demonstrated that patients with untreated OSAHS displayed LV diastolic dysfunction and aortic root dilatation, which were positively associated with the severity of the disease. After this study had been completed, continuous positive airway pressure treatment was initiated in the patients with moderate to severe OSAHS. These patients will be followed for 6 months to observe any changes in LV function and aortic root parameters. Further investigation of the clinical applicability of our observations is warranted, but it is hoped that the present study may encourage physicians to try to diagnose and treat sleep apnoea more urgently than at present.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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