ORIGINAL ARTICLE

Relation of elastic properties of pulmonary artery with left ventricular abnormalities and aortic stiffness in patients with moderate to severe obstructive sleep apnea: A cross-sectional echocardiographic study

Orta/ciddi obstrüktif uyku apne sendromu olan hastalarda pulmoner arterin elastik özelliklerinin sol ventrikül anormallikleri ve aort sertliği ile ilişkisi: Kesitsel bir ekokardiyografi çalışması

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ABSTRACT

Objective: In this study, the associations between pulmonary artery stiffness (PAS) and aortic stiffness, left ventricular diastolic parameters, and left ventricular mass (LVM) index in moderate to severe obstructive sleep apnea syndrome (OSAS) patients without coexisting disorders were investigated.

Methods: A total of 66 non-diabetic, non-hypertensive, and non-smoking volunteers were enrolled. Participants were categorized by apnea-hypopnea index (AHI; event/hour). The control group was defined as no OSAS: AHI<5 (n=35), and OSAS group had moderate to severe OSAS: AHI>15 (n=31). Echocardiographic and biochemical tests, including measurement of C-reactive protein (CRP), were performed. PAS (kHz/s) was calculated by dividing the maximal frequency shift of the pulmonary flow by the acceleration time.

Results: PAS (kHz/s), obtained by echocardiography, was statistically significantly higher in the OSAS group than the control group (28±5 vs 18±4, p<0.001), and was positively correlated with AHI, CRP, aortic stiffness index, E/E', and LVM index (p=0.034, p=0.039, p<0.001, p=0.040, and p<0.001, respectively), and negatively correlated with aortic strain (AS), aortic distensibility (AD), E/A, E'/A', and E' (p<0.001). Regression analyses indicated that CRP and PAS are independent predictors of aortic stiffness (p<0.05). E/A and LVM index were independent predictors of PAS (p=0.002 and p=0.001, respectively).

Conclusion: Increased PAS is associated with aortic stiffness, left ventricular diastolic function, and increased LVM index. PAS may be a more effective indicator of aortic stiffness in OSAS patients than CRP.

ÖZET

Amaç: Bu çalışmada, eşlik eden hastalıkları bulunmayan orta ve ciddi derece obstrüktif uyku apne sendromuna (OUAS) sahip hastalarda pulmoner arter sertliğinin (PAS) aort sertliği, sol ventrikül diyastolik fonksiyon bozukluğu parametreleri ve sol ventrikül kitle indeksi ile ilişkisi araştırıldı.

Yöntemler: Hipertansiyon ve diyabeti bulunmayan ve sigara kullanmayan 66 gönüllü çalışmaya alındı. Katılımcılar apne hipopne indeksine göre sınıflandırıldılar (AHI, olay/saat). Kontrol grubu sağlıklı bireylerden oluştu AHI <5 normal (n=35), OUAS grubu orta veya ciddi OUAS'lı hastaları kapsadı AHI >15 orta/ciddi (n=31). Ekokardiyografi ve C-reaktif proteinin (CRP) dahil olduğu biyokimyasal testler değerlendirildi. PAS (kHz/s) = pulmoner akım maksimal sapma sıklığı/akselerasyon zamanı, formülüyle hesaplandı.

Bulgular: Ekokardiyografiyle elde edilen PAS (kHz/s) OUAS grubunda istatistiksel olarak anlamlı derecede daha yüksekti (18±4 ve 28±5, p<0.001) ve AHI, CRP, aort sertlik indeksi, E/E' oranı ve sol ventrikül kitle indeksi ile pozitif (sırasıyla, p=0.034, p=0.039, p<0.001, p=0.040 ve p<0.001) ve aort straini, aort-gerilebilirliği, E/A oranı, E'/A' oranı ve E' ile negatif korelasyona sahipti (p<0.001). Regresyon analizi CRP ve PAS'nin aort sertliği için bağımsız öngördürücüler olduğunu gösterdi (p<0.05). E/A oranı ve sol ventrikül kitle indeksi PAS için bağımsız öngördürücülerdi (sırasıyla; p=0.002 ve p=0.001).

Sonuç: Artmış PAS aort sertliği, sol ventrikül diyastolik fonksiyon bozukluğu ve artmış sol ventrikül kitle indeksiyle ilişkiliydi. OUAS'li hastalarda PAS aort sertliği için CRP'den daha iyi bir belirteç olabilir.

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Obstructive sleep apnea syndrome (OSAS) is a common health problem characterized by increased upper-airway resistance, recurrent apneic or hypoxic attacks, and snore or arousals during sleep, affecting approximately 1 in 5 adults.[1,2] OSAS has unfavorable effects on the cardiovascular system, including increased sympathetic nerve activation, oxidative stress, and inflammation. Previous studies have demonstrated that OSAS patients are at risk for several cardiovascular disorders, including left ventricular diastolic dysfunction, atherosclerosis, acute coronary syndromes, and sudden cardiac death.[1,3–6]

Aortic stiffness and left ventricular diastolic parameters are both abnormal in adult patients with OSAS.[6,7] However, various comorbidities accompany OSAS, and these affect left ventricular diastolic functions and aortic stiffness parameters, the association of which with OSAS remains controversial. In addition, conflicting data persists regarding left ventricular hypertrophy and left ventricular mass (LVM) in OSAS patients.[8–11] While left ventricular diastolic functions and left ventricular hypertrophy are included in routine echocardiographic assessment, aortic stiffness is not generally evaluated. A simple parameter indicating aortic stiffness and left ventricular diastolic dysfunction would aid clinicians in the assessment of cardiovascular risk in OSAS patients. Pulmonary artery stiffness (PAS), a relatively new echocardiographic parameter, reflects impairment of the pulmonary vascular bed.[12] Though its association with right heart functions has been demonstrated, data has yet to be presented regarding its association with left ventricular functions and aortic stiffness.[13–15]

Adults selected by strict criteria, with newly diagnosed moderate to severe OSAS and without coexisting disorders were included. The aims of the present study were first to determine aortic stiffness, left ventricular diastolic dysfunction, and LVM, irrespective of the effects of comorbidities, and second, to establish the the relationship between those factors and PAS derived from echocardiographic calculation.

METHODS

Subjects

Participants were adults who presented with complaints of snoring and/or unexplained daytime sleepiness. All underwent overnight polysomnography. A total of 206 adults were consecutively screened between March and June 2015. A total of 160 were diagnosed with OSAS, while polysomnographic data of 46 patients were within normal range. A total of 129 OSAS patients were excluded from the study; 20 had mild OSAS (as defined in polysomnography section), 7 had apparent coronary artery disease, 2 had chronic obstructive pulmonary disease, 3 had heart failure, 1 had moderate aortic valve stenosis, 12 were smokers, and 84 had hypertension and/or diabetes mellitus and/or hyperlipidemia— while patients with mild hypertriglyceridemia were included, patients with moderate and severe hypertriglyceridemia were excluded. Similarly, of the 46 patients without OSAS, 5 had hypertension and/or diabetes mellitus and/or hyperlipidemia, 2 had apparent coronary artery disease, 1 had moderate mitral regurgitation, and 3 were smokers. Finally, 31 OSAS patients without coexisting disorders were included in the OSAS group, and 35 participants without OSAS were included in the control group.

Abbreviations:

AD	*Aortic distensibility*
AHI	*Apnea-hypopnea index*
AS	*Aortic strain*
ASI	*Aortic stiffness index*
CRP	*C-reactive protein*
DT	*Deceleration time of peak early velocity*
IVRT	*Isovolumic relaxation time*
LAV	*Left atrial volume*
LVM	*Left ventricular mass*
OSAS	*Obstructive sleep apnea syndrome*
PAS	*Pulmonary artery stiffness*
SPAP	*Systolic pulmonary artery pressure*

Subjects were consecutively evaluated by echocardiography combining M-mode, two-dimensional Doppler, and tissue Doppler imaging, and their clinical and laboratory data were obtained.

The study was approved by the Ethics Committee of the Harran University Faculty of Medicine according to ethical criteria for human investigation outlined in the Second Declaration of Helsinki. All subjects provided informed written consent.

Demographics, clinical data, and blood samples

Systolic and diastolic blood pressure, and demographic measurements including height and weight were obtained according to standard protocols. Body mass index was calculated as weight divided by height squared. Blood samples were collected on the morning following polysomnography after at least 10 hours of fasting. Serum C-reactive protein (CRP) levels were determined by spectrophotometric methods using a Cobas Integra 800 chemistry analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

Polysomnography and classification of obstructive sleep apnea

Polysomnographic assessment was conducted using a 55-channel Alice 5 Diagnostic Sleep System (Philips Healthcare, Bothell, WA, USA) in the sleep laboratory. Electrocardiogram, electroencephalogram, electromyogram, electrooculogram, pulse oximetry, nasal air flow, snoring, leg movements, thoracic and abdominal movements, and body position were continuously monitored and analyzed.

Polysomnographic records were assessed via computer-assisted manual scoring according to American Academy of Sleep Medicine criteria by physicians certificated in sleep disorders and polysomnography. OSAS was identified by the number of of apneic and hypopneic events per hour during sleep. Apnea was defined as an absence of airflow lasting at least 10 seconds. Hypopnea was defined as a reduction of airflow with 4% oxygen desaturation lasting at least 10 seconds with subsequent arousal. Subjects with fewer than 5 apnea-hypopnea index (AHI) events per hour were identified as normal, those with 5–15 AHI events per hour were defined as identified as having mild OSAS, and those with more than 15 AHI events per hour were identified as having as moderate to severe OSAS.[16,17]

Echocardiography, aortic stiffness, and pulmonary artery stiffness

All echocardiographic assessments were implemented based on guidelines of the American Society of Echocardiography.[18,19] Echocardiography was performed in the left lateral decubitus position using a GE Vivid S6 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway) with an M4S-RS (1.5–3.6 MHz) cardiac transducer. All measurements were taken by two experienced cardiologists who were unaware of patient data, and calculated using averages of 5 consecutive cycles. All Doppler echocardiographic records were made at a sweep rate of 100 mm/s.

Left and right ventricular diameters, and thicknesses of interventricular septum and posterior wall were measured on M-mode tracking at the level of the papillary muscles in parasternal long-axis view, according to established standards. Left and right ventricular ejection fractions were calculated using modified Simpson's rule.[18] Systolic pulmonary artery pressure (SPAP) was calculated throughout tricuspid regurgitated flow, based on American Society of Echocardiography guidelines.[20]

Transmitral flow was recorded by pulsed-wave Doppler placed between the mitral leaflet tips in apical 4-chamber view. Peak early (E) and late (A) diastolic velocities, ratio of early to late peak velocities (E/A), deceleration time of E velocity (DT), and isovolumic relaxation time (IVRT) were measured. Left ventricular tissue Doppler imaging was evaluated using pulsed-wave Doppler recording at the lateral side of the mitral annulus in the apical 4-chamber view. Early (E') and late (A') diastolic and systolic annular myocardial velocities were measured.[19]

LVM was calculated using modified formula of Devereux et al., and LVM index was normalized for body surface area.[21] Left atrial volume (LAV) was calculated according to standard criteria based on American Society of Echocardiography recommendations, and LAV index was also normalized for body surface area.[18]

Aortic systolic and diastolic diameters were measured on M-mode tracking at 3 centimeters above aortic valves in parasternal long-axis view and used to calculate aortic stiffness parameters, the formulas of which are presented below.

Aortic strain (AS, %) = 100 x (aortic systolic diameter - aortic diastolic diameter) / aortic diastolic diameter.

Aortic distensibility (AD, cm^{-2} $dyn^{-1}10^{-6}$) = 2 x (aortic strain) / (systolic blood pressure - diastolic blood pressure).

Aortic stiffness (β) index (ASI) = ln (systolic blood pressure / diastolic blood pressure) / aortic strain.

PAS was assessed using pulmonary pulsed-wave Doppler recordings at 1 centimeter distal to the pulmonic valve in parasternal short-axis view, and was calculated using the formula below, proposed by Görgülü et al.[12]

PAS (kHz / sec) = maximal frequency shift of pulmonary flow / pulmonary acceleration time.

Statistical analysis

Data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages, and continuous variables were expressed as mean±SD. A one-sample Kol-

mogorov-Smirnov test was used to evaluate normalization of data distribution. Comparison of variables between groups was established using independent samples t-test or Mann-Whitney U test (for data with normal or abnormal distribution, respectively). In addition, bivariate correlation analysis was used to determine correlation between variables. After scatter plot assessment of variable pairs, Pearson correlation was used for variable pairs with linear distribution, and Spearman correlation was used for variable pairs with abnormal distribution. In addition, multiple stepwise linear regression analyses were used to determine independent predictors. Aortic stiffness parameters were separately analyzed for CRP and PAS with linear regression analyses. Left ventricular diastolic dysfunction parameters (E/A, E', E'/A', and E/E'), LVM index, and SPAP were also analyzed for prediction of PAS with linear regression analyses. Variables considered to be clinically relevant and statistically significant were included in regression analyses, and ASI with abnormal distribution was included by altering logarithmic transformation. Statistical significance among variables was considered a two-tailed p value of less than 0.05.

RESULTS

A total of 66 subjects without coexisting disorders, consisting of a patient group of 31 subjects with OSAS and a control group of 35 subjects without OSAS, were included. Demographic, clinical and laboratory parameters were similar in both groups. However, C-reactive protein (CRP) level was higher in OSAS group than in control group (p=0.034) (Table 1).

Left ventricular and right ventricular diameters and ejection fractions were similar between the groups (p>0.05 for all). PAS and SPAP were significantly higher in the OSAS group than in the control group (p<0.001 for all). Regarding diastolic parameters, E/A ratio, E'/A' ratio, and E' were significantly lower in the OSAS group, compared to the control group (p<0.001 for all), and E/E' ratio and LVM index were higher in the OSAS group than in the control group (p=0.002 and p=0.003, respectively). DT, IVRT, and LAV index were higher, though not statistically significant, in the OSAS group, compared to the control group (p>0.05 for all). Results demonstrate that AS and AD were lower in the OSAS group than in the control group (p<0.001 for both), but that ASI was higher in the OSAS group than in the control group (p<0.001) (Table 1).

Bivariate correlation analyses showed a positive correlation between PAS and AHI, SPAP, CRP, ASI, E/E' ratio, and LVM index (p=0.047, p<0.001, p=0.039, p<0.001, p=0.040, and <0.001, respectively), and a negative correlation between PAS and AS, AD, E/A ratio, E'/A' ratio, and E' (p<0.001 for all). Analysis also demonstrated that CRP was positively correlated with AHI, PAS, LVM index, and ASI (p=0.011, p=0.039, p=0.016, and p<0.001, respectively), and negatively correlated with E', E'/A', AS, and AD (p=0.008, p=0.045, p=0.001, and p<0.001, respectively) (Table 2; Figure 1, 2). Moreover, a strong correlation between aortic stiffness parameters and left ventricular parameters was demonstrated in separate linear correlation analysis (p<0.01 for all) (Table 3).

Multiple linear regression analyses demonstrated that CRP and PAS were independent predictors for AS, AD, and ASI (p<0.05) (Table 4). However, PAS was the most important independent predictor for aortic stiffness parameters (p<0.001 for all) in the final model. In addition, the second multiple linear regression analysis showed that only SPAP and LVM index were independent predictors for PAS (p=0.001 for each) (Table 5). In final model, SPAP was the most important predictor for PAS estimation (p<0.001).

DISCUSSION

The present study was the first to investigate the association of PAS with aortic elastic properties, left ventricular diastolic parameters, and LVM index among patients with newly diagnosed moderate to severe OSAS. Primary results were, first, that elastic properties of pulmonary artery and aorta were significantly impaired and correlated in patients with OSAS, second, that the deterioration of most left ventricular diastolic parameters and LVM index correlated to an increase in PAS, third, that PAS and CRP were correlated with AHI and aortic stiffness, and were independent predictors for aortic stiffness, and fourth, that SPAP and LVM index were independently associated with PAS.

It is widely known that OSAS patients are at risk for various cardiovascular disorders, including atherosclerosis and systolic or diastolic ventricular dysfunction.[4] However, controversial left ventricular

Table 1. Clinical, demographic, laboratory, and echocardiographic characteristics of all subjects

Characteristics	OSAS group (n=31)	Control group (n=35)	*p*
Age (years)	45.5±6.6	43.0±6.4	0.114
Male, n (%)	25 (71.4)	23 (74.2)	0.174
Body mass index (kg/m^2)	26.7±2.1	26.2±3.2	0.443
Systolic blood pressure at rest (mmHg)	127.2±15.4	120.7±14.0	0.075
Diastolic blood pressure at rest (mmHg)	77.3±8.9	73.7±9.2	0.059
Heart rate at rest (beats/min)	80.7±6.9	77.1±8.3	0.068
Apnea-hypopnea index (events/hour)	45.4±28.1	–	–
Laboratory parameters			
C-reactive protein (mg/dl), median (IQR)	0.30 (0.01–0.80)	0.24 (0.01–0.50)	0.034*
Glucose (mg/dl)	89.7±5.1	87.9±6.5	0.231
Urea (mg/dl)	29.9±4.2	29.3±3.8	0.532
Creatinine (mg/dl)	0.8±0.1	0.8±0.1	0.688
Aspartat aminotransferase (U/L), median (IQR)	21.00 (15.00–36.00)	22.00 (16.00–38.00)	0.101*
Alanine aminotransferase (U/L), median (IQR)	24.00 (18.00–48.00)	24.00 (14.00–43.00)	0.964*
Total cholesterol (mg/dl)	190.2±19.0	183.2±19.1	0.151
Low-density lipoprotein cholesterol (mg/dl)	118.7±20.7	111.7±18.7	0.152
High-density lipoprotein cholesterol (mg/dl)	40.6±5.1	41.6±4.0	0.366
Triglyceride (mg/dl)	168.9±39.0	159.6±39.4	0.340
White blood cells (10^3/mm^3)	9.1±1.6	8.5±1.2	0.145
Hematocrit (%)	47.5±4.0	45.9±2.7	0.082
Platelet (10^3/mm^3)	286.4±57.7	301.6±63.7	0.314
Thyroid-stimulating hormone (mIU/L)	1.7±0.4	1.8±0.3	0.280
Echocardiography			
Left ventricle end-diastolic diameter (mm)	48.6±4.0	47.4±2.5	0.150
Left ventricle end-systolic diameter (mm), median (IQR)	32.00 (24.00–40.00)	31.00 (27.00–35.00)	0.319*
Left ventricular ejection fraction (%)	63.5±4.5	65.3±4.2	0.091
Mitral deceleration time (ms)	189.3±16.3	183.5±16.4	0.155
Mitral isovolumic relaxation time (ms)	88.1±11.4	83.3±14.7	0.148
E' (m/s)	11.4±2.6	17.0±4.7	<0.001
E/A ratio	0.9±0.2	1.3±0.3	<0.001
E'/A' ratio	0.9±0.3	1.6±0.6	<0.001
E/E' ratio, median (IQR)	6.17 (3.47–14.14)	4.76 (3.39–14.00)	0.002*
Left atrial volume index (cm^3)	15.1±3.7	14.4±3.2	0.389
Left ventricular mass index (cm^3)	94.8±26.0	77.6±18.6	0.003
Aortic strain (%)	4.9±2.4	14.6±3.7	<0.001
Aortic distensibility (10^{-6} cm^2 dyn^{-1})	2.1±1.2	6.5±2.2	<0.001
Aortic stiffness β index, median (IQR)	13.59 (4.16–21.02)	3.47 (2.13–6.24)	<0.001*
Pulmonary artery stiffness (kHz/s)	28±5	18±4	<0.001
Systolic pulmonary artery pressure (mmHg)	34±8	22±5	<0.001
Right ventricle end-diastolic diameter (mm)	32.5±2.8	31.5±1.8	0.075
Right ventricle ejection fraction (%)	48.9±5.2	50.7±4.1	0.122

E': Tissue Doppler early annular myocardial diastolic velocities; E/A: Ratio of E wave to A wave throughout trans-mitral flow; E'/A': Ratio of E' wave to A' wave on mitral lateral annular tissue Doppler flow; E/E': Ratio of E wave to E' wave; IQR: Interquartile range; OSAS: Obstructive sleep apnea syndrome. *p values of Mann-Whitney U test.

Table 2. Bivariate analyses of variables associated with pulmonary artery stiffness and C-reactive protein

Variables	Pulmonary artery stiffness		C-reactive protein	
	r	p	r	p
Apnea-hypopnea index	0.359	0.047	0.497	0.011
Systolic pulmonary artery pressure	0.522	<0.001	0.217	0.143
E/A ratio	-0.543	<0.001	-0.162	0.216
E'	-0.452	<0.001	-0.342	0.008
E'/A' ratio	-0.537	<0.001	-0.262	0.045
E/E' ratio	0.253	0.040	0.213	0.102
Left ventricular mass index	0.419	0.001	0.316	0.016
Aortic strain	-0.684	<0.001	-0.412	0.001
Aortic distensibility	-0.671	<0.001	-0.494	<0.001
Aortic stiffness β index	0.730	<0.001	0.441	<0.001
C-reactive protein	0.268	0.039	–	–

E': Tissue Doppler early annular myocardial diastolic velocities; E/A: Ratio of E wave to A wave throughout trans-mitral flow; E'/A': Ratio of E' wave to A' wave on mitral lateral annular tissue Doppler flow; E/E': Ratio of E wave to E' wave; PAS: Pulmonary artery stiffness.

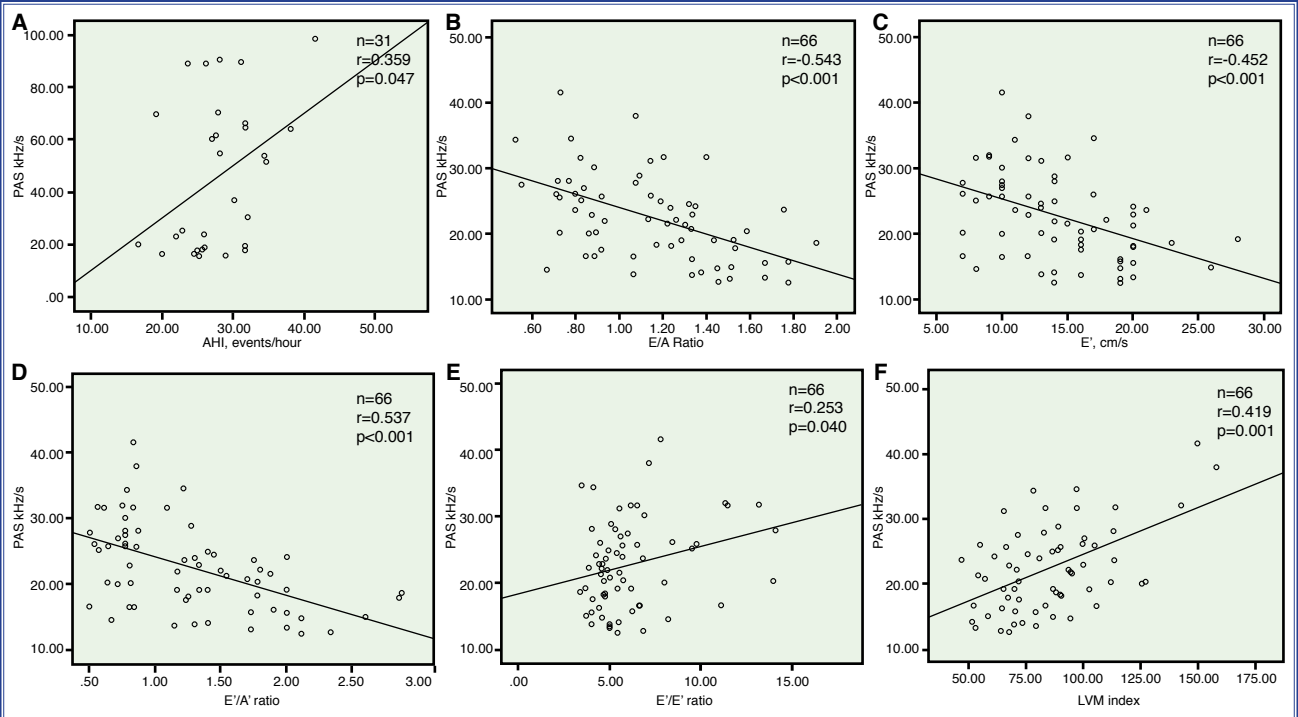

Figure 1. Scatter graph showing correlations between PAS and **(A)** apnea-hypopnea index, **(B)** E/A ratio, **(C)** E' wave, **(D)** E'/A' ratio, **(E)** E/E' ratio, and **(F)** left ventricular mass index. AHI: Apnea-hypopnea index; E': Tissue Doppler early annular myocardial diastolic velocities; E/A: Ratio of E wave to A wave throughout trans-mitral flow; E'/A': Ratio of E' wave to A' wave on mitral lateral annular tissue Doppler flow; E/E': Ratio of E wave to E' wave; LVM: Left ventricular mass; PAS: Pulmonary artery stiffness.

diastolic dysfunction and left ventricular hypertrophy data from OSAS patients has been reported.[8–11] While some studies have demonstrated impaired left ventricular diastolic function and increased LVM in OSAS cases,[9–11] no change was observed by Varol et al.[8] One reason for this discrepancy may be that OSAS patients usually have coexisting disorders such as hypertension, diabetes, metabolic syndrome, and obesi-

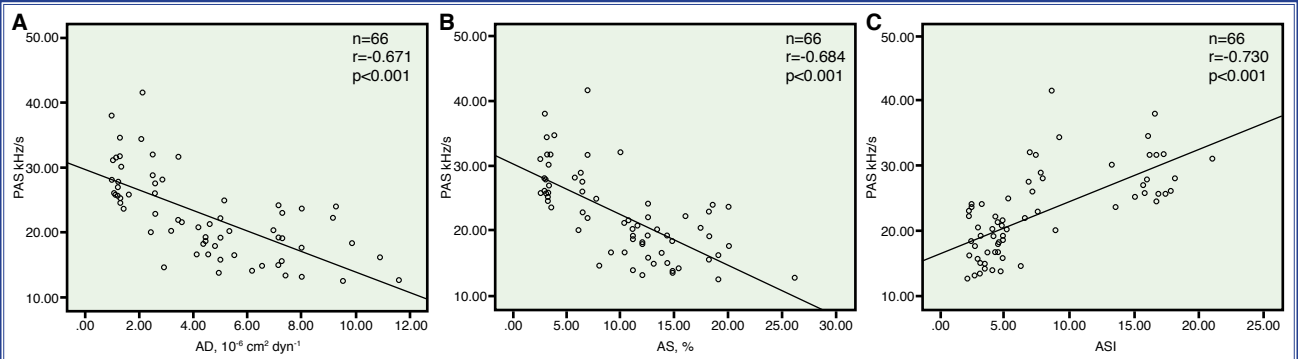

Figure 2. Scatter graph showing correlations between PAS and **(A)** aortic distensibility, **(B)** aortic strain, and **(C)** aortic stiffness β index. AD: Aortic distensibility; AS: Aaortic strain; ASI: Aortic stiffness index; PAS: Pulmonary artery stiffness.

ty, which potentially affect ventricular diastolic functions and hypertrophy. An increase in LVM index and deterioration in left ventricular diastolic dysfunction parameters in OSAS subjects were determined in the present study, while no significant changes were observed in DT and IVRT, E/A, E'/A', and E' significantly decreased, and E/E' considerably increased. Some studies found no changes of DT in OSAS,[9–11,22,23] while others reported an increase.[24–26] The results of the present study were consistent with the former, demonstrating a slight impairment in well-selected cases of OSAS without coexisting clinical conditions. Similarly, no significant increase in LAV index was determined in the present study, as it was in others.[6,9] Left ventricular hypertrophy has been another subject of debate. While the present study and that of Aslan et al. found increased LVM index irrespective of confounding factors,[10] Varol et al. reported no significant left ventricular hypertrophy in patients with moderate to severe OSAS but without hypertension, diabetes, and obesity.[8] An increase in aortic stiffness has been reported in OSAS patients.[7,26–28] Aortic stiffness leads to left ventricular afterload increase, which may impair general diastolic functions. A correlation between aortic stiffness and left ventricular diastolic functions has also been demonstrated.[26,29] Consistent with these findings, impaired elastic aortic properties and a significant association of aortic stiffness with left ventricular diastolic parameters were found in the present study.

CRP, a marker of inflammation, is closely associated with aortic stiffness and atherosclerosis, and is a powerful predictor of cardiovascular risk.[30,31] However, conflicting findings have been reported regarding the association of CRP and OSAS.[10,31–36] Schiza et al. demonstrated a statistically significant correlation between CRP levels and AHI in patients with moderate to severe OSAS.[33] Another study reported that CRP was correlated with intermittent hypoxia, but not with AHI in moderate to severe OSAS.[34] Aslan et al. reported no difference in CRP levels between moderate to severe OSAS subjects and those with mild

Table 3. Correlation analyses between aortic stiffness and left ventricular parameters

Variables	Aortic strain		Aortic distensibility		Aortic stiffness β index	
	r	p	r	p	r	p
E/A ratio	0.615	<0.001	0.599	<0.001	-0.573	<0.001
E'	0.636	<0.001	0.645	<0.001	-0.609	<0.001
E'/A' ratio	0.678	<0.001	0.713	<0.001	-0.682	<0.001
E/E' ratio	-0.414	0.001	-0.447	<0.001	0.401	0.001
LVM index	-0.384	0.002	-0.444	<0.001	0.429	<0.001

E': Tissue Doppler early annular myocardial diastolic velocities; E/A: Ratio of E wave to A wave throughout trans-mitral flow; E'/A': Ratio of E' wave to A' wave on mitral lateral annular tissue Doppler flow; E/E': Ratio of E wave to E' wave; LVM: Left ventricular mass.

Table 4. Multiple linear regression analysis (stepwise) in prediction of aortic stiffness parameters

	Aortic strain						
	Unstandardized coefficients		Standardized coefficients			95% confidence interval	
	B	Std. Error	β	t	p	Lower	Upper
Model I (R^2=0.506)							
PAS	-0.682	0.089	-0.711	-7.703	<0.001	-0.859	-0.505
Model II (R^2=0.551)							
PAS	-0.601	0.091	-0.627	-6.576	<0.001	-0.784	-0.418
CRP	-7.023	2.918	-0.229	-2.407	0.019	-12.867	-1.179
	Log-aortic stiffness β index						
Model I (R^2=0.542)							
PAS	0.037	0.004	0.736	8.290	<0.001	0.028	0.045
Model II (R^2=0.678)							
PAS	0.029	0.004	0.591	7.323	<0.001	0.021	0.037
CRP	0.628	0.128	0.397	4.913	<0.001	0.372	0.885
	Aortic distensibility						
Model I (R^2=0.444)							
PAS	-0.313	0.046	-0.666	-6.806	<0.001	-0.405	-0.221
Model II (R^2=0.514)							
PAS	-0.264	0.047	-0.563	-5.666	<0.001	-0.357	-0.171
CRP	-4.242	1.487	-0.283	-2.853	0.006	-7.219	-1.265

Dependent variables= Aortic strain, aortic stiffness β index, and aortic strain; Predictors for model I= PAS; Predictors for model II= PAS and CRP (for tree analysis). CRP: C-reactive protein; PAS: pulmonary artery stiffness.

Table 5. Multiple linear regression analysis for prediction of PAS

	Unstandardized coefficients		Standardized coefficients			95% confidence interval	
	B	Std. Error	β	t	p	Lower	Upper
Model I (R^2=0.260)							
SPAP	0.415	0.102	0.510	4.064	<0.001	0.209	0.620
Model II (R^2=0.410)							
SPAP	0.336	0.095	0.413	3.543	0.001	0.145	0.527
LVM index	0.102	0.030	0.399	3.418	0.001	0.042	0.162

Dependent variable= PAS; Predictor for model 1= SPAP; Predictors for model 2= SPAP and LVM index. LVM: Left ventricular mass; PAS: Pulmonary artery stiffness; SPAP: Systolic pulmonary artery pressure.

OSAS.[10] Likewise, CRP levels in all OSAS stages were found to be similar in a study conducted by Kurt et al.[35] A recent meta-analysis indicated that obesity might be an underlying factor for elevated CRP levels in OSAS. Significantly increased CRP levels demonstrating a significant correlation with AHI and aortic stiffness parameters were observed in the present study. It is known that intermittent hypoxia gives rise to oxidative stress and activation of inflammation, causing the release of inflammatory mediators such

as CRP.[37,38] Our findings support this causative association between hypoxia and inflammation, as OSAS patients tend to be hypoxic, compared to normal population.

Furthermore, increased PAS indicates impaired elasticity of the pulmonary artery, and reflects the status of the pulmonary vascular bed. Previous studies have demonstrated a close association between right ventricular functions and PAS.[12–15] However, whether PAS has any effect on left ventricular diastolic parameters has yet to be determined. A study conducted with bicuspid aortic valve patients reported that PAS had deteriorated with aortic stiffness. The authors hypothesized that the aorta and the pulmonary artery are affected at a similar rate because they originated from the same embryonic stem, rather due to the presence of acquired conditions such as hypoxia or lung diseases.[39] The present study investigated whether the arteries were simultaneously affected by hypoxic status in moderate to severe OSAS and found that, indeed, both aortic and pulmonary arterial stiffness had significantly deteriorated in subjects and that PAS was an independent predictor of aortic stiffness. More importantly, stepwise regression analyses indicated that PAS was a stronger independent predictor of AS, AD, and ASI than CRP. In addition, multiple linear regression analyses indicated that SPAP and LVM index were independent predictors of PAS. The underlying mechanisms linking PAS with aortic stiffness may be intermittent hypoxia and oxidative stress due to their potential effect on both the pulmonary and aortic vascular beds. On the other hand, intrathoracic pressure oscillations, increase in intermittent blood pressure, and sympathetic activation may be responsible for the deterioration of left ventricular diastolic functions, even in patients without hypertension.[10,27,40] In addition, raised right ventricular pressure may impair left ventricular filling. As expected, a positive correlation between SPAP and PAS was determined. Considering that that elastic properties of the pulmonary artery are impaired before the development of pulmonary hypertension, it may be speculated that PAS can indicate properties of left ventricular diastolic filling and left ventricular hypertrophy. On the other hand, although changes in blood pressure and heart rate during each apneic and hypopneic event were not recorded, it appears likely that raised blood pressure and heart rate due to hypoxia, and changes in intrathoracic pressure may lead to aortic stiffness, left ventricular hypertrophy, and left ventricular diastolic dysfunction. While it has been established that moderate to severe OSAS typically appears between the ages of 50 and 60,[41] the average age in the population of the present study was approximately 46 years, suggesting that OSAS may have been detected early, just before the onset of cardiovascular and metabolic disorders. The results of the present study speak to the importance of early OSAS diagnosis.

The present study has demonstrated that OSAS is a complex clinical condition associated with inflammation, aortic and pulmonary artery stiffness, left ventricular hypertrophy, and diastolic dysfunction. Given these findings, improved understanding of underlying pathological processes may provide optimization of treatment strategies.

Limitations

This study had some limitations, primarily small sample size. Duration of OSAS was not clearly defined by patients, and thus was not included. Body mass indexes were not completely within normal limits. Finally, assessments were noninvasively performed by echocardiography rather than magnetic resonance imaging, computed tomography, or catheterization.

Conclusion

Results demonstrate that elevated PAS was associated with impaired aortic stiffness, left ventricular diastolic parameters, and LVM index in OSAS patients, and that PAS may be a better indicator of aortic stiffness than CRP in cases of OSAS.

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