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RETRACTION

Urgent Announcement From the Editor-in-Chief Regarding Duplicate Publication

Hiroaki Shimokawa MD, PhD

The editorial team of Circulation Journal recently confirmed that the manuscript written by Halil Tanriverdi et al, published in the June 2006 issue of Circulation Journal (*Circ J* 2006; **70:** 737–743), was a duplicate publication of their previously published paper (*Respiration* 2006; **73:** 741–750).

Halil Tanriverdi, Harun Evrengul, Asuman Kaftan, Cuneyt Orhan Kara, Omur Kuru, Seyhan Tanriverdi, Sibel Ozkurt, Ender Semiz. Effect of obstructive sleep apnea on aortic elastic parameters: Relationship to left ventricular mass and function. *Circ J* 2006; **70:** 737–743.

Halil Tanriverdi, Harun Evrengul, Cuneyt Orhan Kara, Omur Kuru, Seyhan Tanriverdi, Sibel Ozkurt, Asuman Kaftan, Mustafa Kilic. Aortic stiffness, flow-mediated dilatation and carotid intima-media thickness in obstructive sleep apnea: Non-invasive indicators of atherosclerosis. *Respiration* 2006; **73:** 741–750.

This is an obvious violation of the following "Instructions to Authors":

Submission of a manuscript to the Circulation Journal implies that the article is original and that no portion (including figures or tables) is under consideration elsewhere or has been previously published in any form other than as an abstract. Previous publication includes publishing as a component of symposia, proceedings, transactions, books (or chapters), articles published by invitations or reports of any kind, as well as in electronic data bases of a public nature.

Therefore, we have decided to retract the paper from Circulation Journal.

As Editor-in-Chief, I regret the time that peer reviewers and others spent evaluating this paper.

I sincerely hope and trust that there will be no repetition of this kind in the future.

Hiroaki Shimokawa, MD, PhD
Editor-in-Chief
Circulation Journal

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Circ J 2006; **70:** 737–743

Effect of Obstructive Sleep Apnea on Aortic Elastic Parameters

—— Relationship to Left Ventricular Mass and Function ——

Halil Tanriverdi, MD; Harun Evrengul, MD; Asuman Kaftan, MD; Cuneyt Orhan Kara, MD*; Omur Kuru, MD; Seyhan Tanriverdi, MD**; Sibel Ozkurt, MD†; Ender Semiz, MD

Background Obstructive sleep apnea (OSA) syndrome has a critical association with cardiovascular mortality and morbidity. Aortic elastic parameters are important markers for left ventricular (LV) function and are deteriorated in cardiovascular disease.

Methods and Results Aortic elastic parameters and LV functions and mass were investigated in 40 patients with OSA (apnea–hypopnea index (AHI) ≥5) (mean age 51.3±9 years, 32 males) and 24 controls (AHI <5) (mean age 51.9±5.2 years, 19 males). All subjects underwent polysomnographic examination and recordings were obtained during sleep. They also underwent a complete echocardiographic examination and systolic and diastolic aortic measurements were noted from M-mode traces of the aortic root. There were no significant differences in the demographic data of the patients with OSA and the controls. Subjects with OSA demonstrated higher values of aortic stiffness (7.1±1.88 vs 6.42±1.56, p=0.0001), but lower distensibility (9.47±1.33 vs 11.8±3.36, p=0.0001) than the controls. LV ejection fraction was significantly lower in patients with OSA when compared with the control group (61.3±5.2% vs 65.9±8.4%, p=0.0001). LV diastolic parameters were also compared and were worse in the subjects with OSA than in the control subjects (mitral E/A: 0.91±0.42 vs 1.35±0.66, p=0.001; Em/Am: 0.86±0.54 vs 1.23±0.59, p=0.021). Respiratory disturbance index had a positive correlation with aortic stiffness (r=0.63, p=0.0001 and negative correlation with distensibility (r=–0.41, p=0.001).

Conclusion Aortic elastic parameters are deteriorated in OSA, which has an extremely high association with cardiovascular disease. Increased aortic stiffness might be responsible for the LV systolic and diastolic deterioration in OSA syndrome. (*Circ J* 2006; **70:** 737–743)

Key Words: Aortic elastic properties; Left ventricular function; Obstructive sleep apnea; Stiffness

Obstructive sleep apnea (OSA) is characterized by periodic complete or partial upper airway obstruction during sleep, causing intermittent cessation of breathing (apnea) or reduction in airflow (hypopnea) despite ongoing respiratory effort. This disorder has been described for decades, but its recognition has remained a problem. OSA appears to be an independent cardiovascular risk factor; several epidemiologic studies have identified OSA syndrome as an independent risk for systemic hypertension, coronary artery disease, stroke, and cardiac arrhythmias[1–4]

There are conflicting data in the literature on the association between OSA and left ventricular (LV) hypertrophy. Although some investigators have reported that patients with OSA develop LV hypertrophy independently of hypertension[5], others have found no difference between patients with OSA and control subjects in LV mass (LVM)[6,7] LV diastolic dysfunction is regarded as an early sign of myocardial disease and an important determinant of symptoms and clinical outcome in patients with cardiovascular disease[8] It has been shown recently that impaired LV diastolic filling occurs in OSA patients with no other active pulmonary or cardiac disease[9] Clearly, it is important to know whether OSA alone constitutes an independent risk factor for the development of LV dysfunction and hypertrophy, and thus for increased cardiovascular morbidity and mortality.

Aortic elastic properties are important determinants of blood pressure (BP) and LV function. The aorta functions not only as a conduit delivering blood to the tissues but also as an important modulator of the entire cardiovascular system, buffering the intermittent pulsatile output from the heart to provide steady flow to the capillary beds. By virtue of its elastic properties, the aorta influences LV function, structure and coronary blood flow[10]

Consequently, we hypothesized that OSA affects the functional and structural properties of large arteries, contributing to impaired LV function and changes in the LV geometry.

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*Departments of Cardiology, *Otorhinolaryngology, **Radiology and †Chest Disease, Pamukkale University School of Medicine, Denizli, Turkey*

Mailing address: Halil Tanriverdi, MD, Pamukkale Üniversitesi Tip Fakültesi Kalp Merkezi, Kinikli/Denizli, Turkey. E-mail: drhaliltanriverdi@yahoo.com.tr

Methods

Study Protocol

We selected 64 patients who were referred between March 2004 and April 2005 for evaluation of snoring and possible sleep apnea. All patients came to the sleep laboratory for a diagnostic overnight sleep study. Before the sleep study, each patient completed a questionnaire regarding medical and sleep history and current medications. This information was subsequently reviewed by a physician during a follow-up visit to the sleep clinic. Additional data collected on the night of the sleep study included demographics and anthropomorphic measurements. Furthermore, all subjects underwent a routine cardiological evaluation (BP measurement, electrocardiogram) in order to rule out primary heart disease. None of the study patients had a history of either arterial hypertension or use of antihypertensive medications. Supine systolic and diastolic BP were measured with the cuff method after at least 10 min of undisturbed rest. Hypertension was defined as BP >140 mmHg or equal to 140 mmHg systolic and/or 90 mmHg diastolic pressure. On the morning after the sleep study, each patient underwent Doppler echocardiography. Both the sonographer and the reporting cardiologist were unaware of the patient's sleep study findings. The study was approved by the local Ethic's Committee, and written informed consent was given by each participant.

Exclusion Criteria

Exclusion criteria were as follows: (1) unstable cardiorespiratory status, defined as the occurrence of respiratory failure, bronchopulmonary infection, or congestive heart failure in the previous 2 months; (2) coronary artery disease, defined as typical angina pectoris, prior myocardial infarction, positive exercise test result, positive myocardial scintigraphy or positive coronary angiography findings; (3) valvulopathy, permanent atrial fibrillation, congenital heart disease; (4) hypertension, diabetes, dyslipidemia, use of drugs (antihypertensives, antidiabetics, lipid lowering treatment); and (5) chronic severe alcoholism and smoking.

Sleep Studies

Overnight polysomnography was performed for all patients. The equipment consisted of a Compumedics (Abbotsford, Victoria, Australia) P series system, which recorded the following channels: central electroencephalogram, electrooculogram, chin electromyogram, pulse oximeter, chest and abdominal excursion, airflow (by oronasal thermistry), single bipolar electrocardiogram, and body position. The respiratory disturbance index (RDI) was defined as the number of apneas plus hypopneas per hour of sleep time. Apnea was defined as a reduction in airflow to <25% of baseline for >10 s, and hypopnea was defined as a decrease in airflow to <70% of baseline or thoracoabdominal excursion for >10 s, associated with a 3% fall in oxyhemoglobin saturation. Sleep staging was performed according to Rechtschaffen and Kales criteria![11] OSA was defined in patients with an apnea–hypopnea index (AHI) ≥5, and controls as an AHI <5.

Echocardiographic Measurements

M-mode, 2-dimensional and Doppler echocardiography were performed while the subjects were in the left lateral decubitus position, using a Vivid 7 Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) with 2.5 MHz probe. Echocardiographic tracings were recorded on super VHS videotapes at a sweep speed of 50 mm/s. LV dimensions in diastole and systole, and the thickness of the interventricular septum and posterior wall were measured by the M-mode technique. LVM was calculated using Devereux's formula:[12] $LVM = 0.8 \times [1.04 \times (\text{septal thickness} + \text{posterior wall thickness} + \text{LV end-diastolic diameter})^3 - (\text{LV end-diastolic diameter})^3] + 0.6$ g. LVM was divided by body surface area to obtain the LVM index (LVMI). The LV diameters, volumes and systolic functions were measured according to the recommendations of the American Society of Echocardiography![13] LV ejection fraction (LVEF) was calculated as (diastolic volume – systolic volume)/(diastolic volume) by Simpson's method. Early (E) and atrial (A) transmitral maximal flow velocities, the E/A ratio and deceleration time of the E wave were registered. The following measurements of diastolic function were determined by pulse Doppler tissue imaging (DTI). Pulsed DTI of the LV basal inferior wall was performed in the apical 2-chamber view. Early (Em) and atrial (Am) diastolic waves (cm/s), peak velocity of the myocardial systolic wave (Sm) (cm/s), Em/Am ratio, Em-wave deceleration time (DTm in ms) were measured. The pulmonary venous flow parameters were defined as follows: S-wave, peak systolic flow velocity in the pulmonary vein; D-wave, peak diastolic flow velocity in the pulmonary vein; and duration of pulmonary-atrial reversal signal. Diastolic function of the LV was divided into 4 patterns: normal, abnormal relaxation, pseudonormal, and restrictive filling.

The aortic diameter was recorded by M-mode echocardiography at a level 3 cm above the aortic valve![14] Internal aortic diameters were measured in systole and diastole by means of a caliper as 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 the time of full opening of the aortic valve, and diastolic (AoD) diameter was measured at the peak of QRS. Ten consecutive beats were measured routinely and averaged. The AoS and AoD indexes (AoS-I and AoD-I) for each subject were calculated by dividing the AoS and AoD by the body surface area. The percentage change of the aortic root was calculated as $\%Ao = 100 \times (AoS - AoD)/AoD$ to obtain the aortic strain. All recordings were analyzed by the same investigator without knowledge of the patient's category. For intraobserver variability, video recordings of echocardiographic examinations were analyzed again within 1 week by the same echocardiographer using Vingmed analysis software. Intraobserver variability was minimal (coefficient of variation for echocardiographic parameters ranged from 6% to 8%).

BP

All patients had BP measured with a mercury sphygmomanometer while supine. Korotkoff phases I and V were used to determine the systolic and diastolic pressures, respectively, and the average of 3 readings was regarded as the clinical BP. Pulse pressure (PP) was obtained as systolic minus diastolic BP, and the following indexes of the elastic properties of the aorta were calculated: (1) aortic root distensibility $= 2 \times (AoS - AoD)/PP \times AoD$, in cm^2/dynes, and (2) aortic stiffness index = ln (systolic blood pressure (SBP)/diastolic blood pressure (DBP))/(AoS – AoD)/AoD (pure number), where DBP is the diastolic BP, SBP is systolic BP, and PP is PP![15–17] LV meridional systolic wall stress was estimated by modifying previously published methods,

Table 1 Comparison of Patients With OSA and Controls

	OSA patients (AHI ≥5) (n=40)	*Controls (AHI <5) (n=24)*	*p value*
Demographic characteristics			
Age (years)	*51.3±9*	*51.9±5.2*	*NS*
Gender (M/F)	*32/8*	*19/5*	*NS*
Weight (kg)	*84.6±12*	*83.2±7.4*	*NS*
Height (cm)	*1.67±5.2*	*1.68±9*	*NS*
BMI (kg/m^2)	*29.8±5.3*	*29.4±3.9*	*NS*
SBP (mmHg)	*128.5±7.5*	*125.4±11.2*	*NS*
DBP (mmHg)	*77.4±8.4*	*80.3±7.7*	*NS*
Pulse pressure	*51.1±8.2*	*45.1±11*	*0.015*
Polysomnographic findings			
AHI	*25.3±11.4*	*3±1.5*	*0.0001*
RDI	*46.5±22.4*	*5.8±2.8*	*0.0001*
Lowest SaO_2 (%)	*67.2±12.4*	*90.3±8.7*	*0.0001*
Mean SaO_2 (%)	*87.2±2.6*	*94.6±3.4*	*0.022*
SaO_2 <%90 (%TST)	*26.3±23.3*	*1.2±2.1*	*0.0001*
Echocardiographic parameters			
IVS diastolic thickness (cm)	*1.13±0.12*	*1.01±0.11*	*0.0001*
PW diastolic thickness (cm)	*1.03±0.07*	*0.91±0.13*	*0.0001*
LV diastolic diameter (cm)	*5.31±0.57*	*5.14±0.42*	*NS*
LV systolic diameter (cm)	*3.48±0.38*	*3.26±0.46*	*0.011*
LV mass index (g/m^2)	*117.2±18.4*	*94.3±18.7*	*0.0001*
LV ejection fraction (%)	*61.3±5.2*	*65.9±8.4*	*0.0001*
Doppler parameters			
Diastolic dysfunction (+/–)	*21/19*	*5/29*	*0.0001*
Peak E/A ratio	*0.91±0.42*	*1.35±0.66*	*0.001*
Em/Am ratio	*0.86±0.54*	*1.23±0.59*	*0.021*
Aortic elastic parameters			
Systolic diameter (cm)	*3.48±0.53*	*3.42±0.45*	*NS*
Diastolic diameter (cm)	*2.81±0.43*	*2.78±0.38*	*NS*
Distensibility ($cm^2 \cdot dyn^{-1} \cdot 10^{-6}$)	*9.47±1.33*	*11.8±3.36*	*0.0001*
Strain (%)	*23.8±3.65*	*25.7±6.5*	*NS*
Stiffness index	*7.1±1.88*	*6.42±1.56*	*0.0001*
End-systolic wall stress (kdyne/cm^2)	*64.8±14.8*	*56.5±11.6*	*0.025*

OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RDI, respiratory disturbance index; SaO_2 <%90 (%TST), the percentage of the total sleep time that oxygen saturation was less than 90%; IVS, interventricular septum; PW, posterior wall; LV, left ventricular; E, early diastolic peak flow velocity; A, late diastolic peak flow velocity; Em, early myocardial Doppler peak velocity; Am, late myocardial Doppler peak velocity.

assuming that LV geometry is spherical and wall thickness is uniform![8]

$$\text{End-systolic wall stress (kdyne/cm}^2) = 0.334 \times \text{SBP} \times \text{LVDS}/[\text{PWS} \times (1 + \text{PWS}/\text{LVDS})]$$

where LVDS = systolic LV diameter and PWS = systolic posterior wall thickness.

Statistical Analysis

All analyses were performed with the SPSS 11.5 package program (Chicago, IL, USA). Results are given as mean ± standard deviation. Student's t-test or 1-way ANOVA, as appropriate, was used to compare continuous variables, and the chi-square test was used to compare proportions among groups. Linear regression analysis with Pearson's coefficients was used to assess the strength of association between variables. Multivariate regression analysis was used to identify determinants of aortic stiffness and distensibility and to evaluate the interaction between indices of OSA [RDI and saturation of oxygen (SaO_2) (during sleep)] and known determinants of stiffness. The strength of these relationships was expressed as the β coefficient and p value. A p-value of <0.05 was considered statistically significant.

Results

Basic Characteristics of Subjects

The characteristics of the subjects are summarized in Table 1. There was no statistically important difference among the patients with OSA and controls ($p>0.05$), according to age, gender, height, weight, body mass index (BMI), SBP or DBP.

Echocardiographic Parameters

Table 1 also shows the echocardiographic data of the groups. We compared the LVMI of the patients with OSA and without OSA. Analysis of the 64 patients revealed that LVMI was significantly greater in patients with OSA than in controls. The potential determinants of LVMI included age, BMI, RDI, SBP and SaO_2 <90% (% of the total sleep time (%TST)). LVMI was positively correlated with RDI ($\beta=0.281$, $p=0.04$) and Sao_2 <90% (%TST) ($\beta=0.263$, $p=0.032$). No significant correlation was found between LVMI and age, BMI or SBP.

None of the patients had LV systolic dysfunction. LVEF was significantly higher in controls than in patients with OSA ($p=0.0001$). LV diastolic dysfunction was present in 21 of the 40 OSA patients and in 5 of the 24 control subjects ($p=0.0001$). Impaired relaxation was by far the most common abnormal pattern in both groups (16 and 4 patients, respectively). Pseudonormal pattern was observed

Table 2 Correlations Between Aortic Elastic Parameters and LV Diastolic Parameters

	Aortic stiffness index		*Aortic distensibility*	
	Coefficent	*p value*	*Coefficent*	*p value*
E	*–0.43*	*0.007*	*0.33*	*0.021*
A	*0.31*	*0.008*	*–0.31*	*0.03*
E/A ratio	*–0.4*	*0.001*	*0.27*	*0.023*
DT	*0.21*	*NS*	*–0.27*	*NS*
Em	*–0.34*	*0.005*	*0.24*	*0.028*
Am	*0.26*	*0.033*	*–0.21*	*NS*
Em/Am ratio	*–0.33*	*0.002*	*0.33*	*0.008*
DTm	*0.22*	*0.04*	*–0.27*	*0.005*
Sm	*–0.38*	*0.001*	*0.37*	*0.005*

DT, deceleration time of E wave; DTm, Em-wave deceleration time; Sm, peak velocity of myocardial systolic wave. Other abbreviations see in Table 1.

Table 3 Correlations Between Severity of OSA and Aortic Elastic Parameters, Blood Pressures, LV Function and Mass

	RDI		*SaO_2 <%90 (%TST)*	
	Coefficent	*p value*	*Coefficent*	*p value*
Aortic stiffness index	*0.63*	*0.0001*	*0.33*	*0.021*
Aortic distensibility	*–0.41*	*0.001*	*–0.31*	*0.03*
LVEF	*–0.34*	*0.006*	*–0.28*	*0.009*
LVMI	*0.45*	*0.0001*	*0.37*	*0.007*
SBP	*0.26*	*NS*	*0.24*	*0.038*
DBP	*–0.2*	*NS*	*–0.21*	*NS*
E/A ratio	*–0.28*	*0.04*	*–0.33*	*0.008*
Em/Am ratio	*–0.21*	*NS*	*–0.27*	*0.006*

LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index. Other abbreviations see in Tables 1,2.

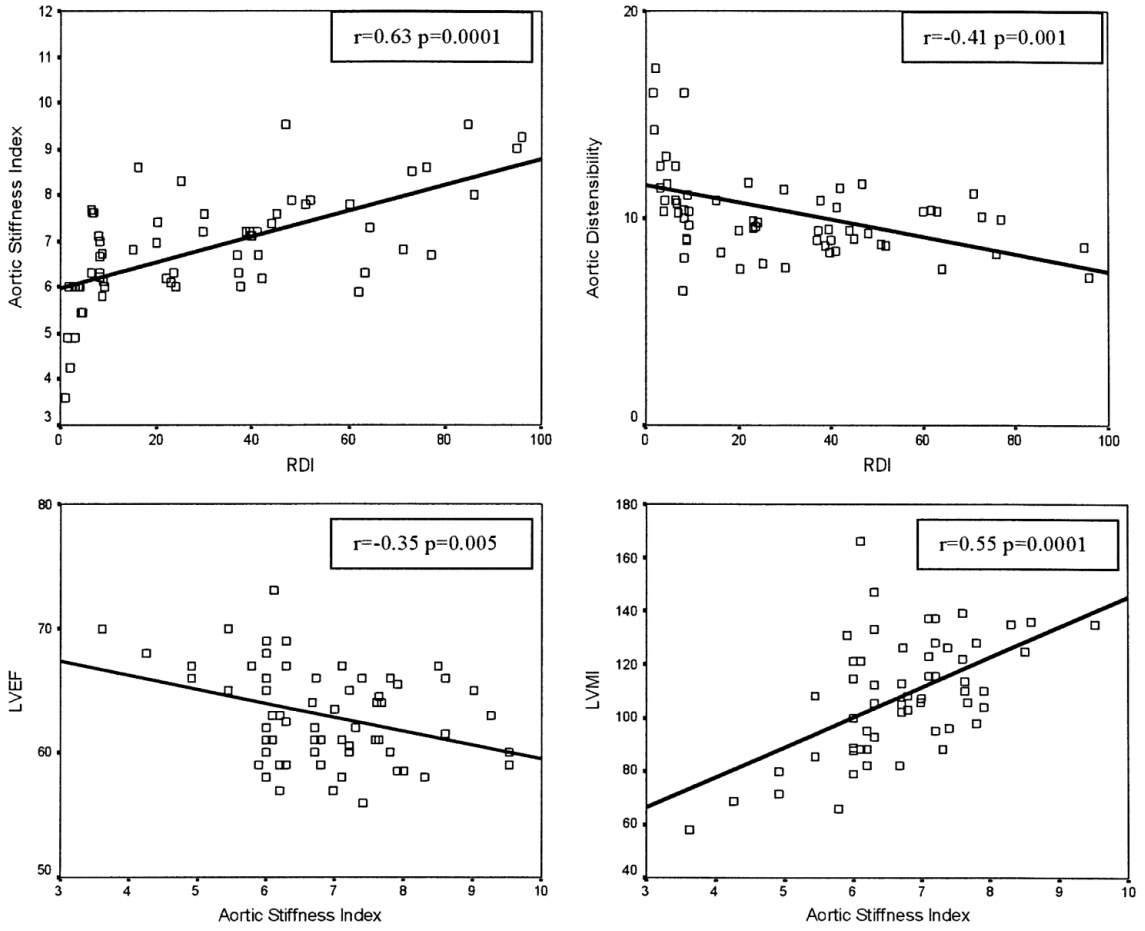

Fig 1. Correlation between respiratory disturbance index (RDI), aortic stiffness index, aortic distensibility ($cm^2 \cdot dyn^{-1} \cdot 10^{-6}$), left ventricular ejection fraction (LVEF, %) and left ventricular mass index (LVMI, g/m^2).

in 4 of the OSA patients and in 1 of the 24 control subjects, and restrictive filling pattern was documented in only 1 among all patients with OSA. LV diastolic parameters were also compared and were observed to be worse in patients with OSA (Table 1). Diastolic cardiac function, when expressed as the E/A and Em/Am ratios, were deteriorated with increased severity of nocturnal hypoxemia (measured with RDI and %TST, Table 3). E/A and Em/Am ratios were inversely and significantly correlated with the aortic stiffness index (Table 2).

The AoS, AoD and aortic strain were similar between the 2 groups (Table 1). Aortic distensibility was significantly lower in patients with OSA than in controls (p=0.0001). The aortic stiffness index and LV end-systolic wall stress were significantly greater in OSA patients than in controls (Table 1).

We found that in the correlation analyses the RDI showed a positive correlation with aortic stiffness and LVMI, and negative correlation with distensibility and LVEF (Table 3). Aortic stiffness index correlated with

Table 4 Potential Determinants of Structural and Functional Left Ventricular Changes

	LVMI		*End-systolic wall stress*		*LVEF*	
	β	*p value*	β	*p value*	β	*p value*
Aortic stiffness index	*0.32*	*0.011*	*0.34*	*0.008*	*–0.27*	*0.002*
RDI	*0.16*	*0.042*	*–0.15*	*0.038*	*–0.14*	*0.034*
SaO_2 <%90 (%TST)	*0.12*	*0.058*	*0.14*	*0.048*	*–0.13*	*0.056*
Age	*0.02*	*0.85*	*0.11*	*0.52*	*–0.18*	*0.04*

Abbreviations see in Tables 1,3.

LVEF and LVMI (Fig 1). Potential determinants of aortic stiffness were evaluated by performing multivariate regression analysis between transformed values of the aortic stiffness (dependent variable), and transformed values of BMI, age, RDI, and SaO_2 <90% (%TST) (independent variables). Tests for multicollinearity were also performed which found no evidence that relationships between the independent variables may lead to inaccurate results. Aortic stiffness was positive correlated with RDI (β=0.357, p=0.012) and duration of SaO_2 <90% (β=0.312, p=0.026), but was not significantly correlated with BMI and age. Multiple regression analysis was performed for potential determinants of LV structural and functional changes (Table 4).

Discussion

The main findings of this study are: (1) patients with OSA syndrome exhibited a mild decrease in LV systolic function, deteriorated diastolic function and increased LVMI; (2) systolic and diastolic LV dysfunction in the OSA patients could not be attributed to the usual causes of LV functional disturbances, such as coronary artery disease, congestive heart failure because of cardiomyopathy or valvular heart disease (for systolic LV dysfunction), chronic systemic hypertension, hypertrophic cardiomyopathy or aortic stenosis; (3) LVEF and LVMI correlated with the severity of OSA (according to RDI and/or the severity of nocturnal arterial desaturation) and the aortic stiffness index; and (4) elastic properties of the aorta were deteriorated in patients with OSA.

There has been much study of the association between OSA and LV hypertrophy and LV function,[5,6,9,19–24] and the current findings are in close agreement with those other reports. We found that decreased LVEF and impaired LV filling pattern in the present patients with OSA without any cardiac or pulmonary disease. Niroumand et al found that the E/A ratio was marginally lower (indicating more impaired LV diastolic function) in patients with OSA than in those without OSA, although the difference did not reach statistical significance.[22] In our study we used mitral and pulmonary Doppler flow and tissue Doppler parameters for determining the diastolic function, and those methods might be more reliable for the detection of diastolic dysfunction. Noda et al found that hypertension was the most important factor in the development of cardiac hypertrophy in OSA patients;[24] however, their study data suggested that severity of OSA correlated with LVM. In agreement with our result, Hedner et al found that LV structural changes were independent of hypertension in patients with OSA, and they suggested that cardiac hypertrophy not explained by hypertension may be related to increased sympathetic stimulation in OSA or to repeated short-term increases in afterload caused by apnea.[5]

Increased aortic stiffness might be an important factor in assessing the effects of OSA on LV function and mass. Jelic et al have shown reversible increases in arterial stiffness associated with obstructive apneas and hypopnea in sleep and they claim that the timing of the major increase in arterial stiffness, during late apnea but before EEG arousal, suggests that asphyxia of the obstructive event, or the mechanical stimulus of increasingly negative intrathoracic pressure, is likely to contribute to this change.[25] It has been suggested that the chronic intermittent hypoxia associated with obstructive apneas during sleep may contribute to arterial endothelial damage and dysfunction, leading to reversible perturbations in vascular tone and blood flow.[26–28] In the current study, the severity of the decrease in SaO_2 associated with the obstructive events was significantly correlated with the degree of aortic stiffness, suggesting that the hypoxia of the obstructive event played a significant role in the change in aortic elastic properties. However, increased arterial stiffness in OSA is unlikely to reflect a response to hypoxia alone. Apnea-related hypoxemia and arousals from sleep increase sympathetic nervous system activity, which results in systemic vasoconstriction.[29] Forced inspiration against increased airway resistance during wakefulness raises aortic transmural pressure, thereby increasing aortic stiffness and LV systolic load.[30] Increased aortic stiffness over several hours of apnea may cumulatively lead to LV dysfunction and LV hypertrophy. Hypoxemia related to apnea can also increase aortic stiffness and impair LV function.

Previous studies have shown that a less compliant aorta may affect both LV systolic energies and mechanics. When the aorta was experimentally stiffened, there was an increase in cardiac energetic cost for a given stroke volume.[31] Moreover, in isolated prepared hearts and in dogs, stroke volume varied inversely with aortic stiffness.[10,32] In addition, a stiffer aorta with higher pulse wave velocity may have a detrimental effect on the systolic function of an already depressed LV through changes in the reflected waves that arise from the periphery.

Stiffer central vessels may influence LV relaxation,[33] and the association between increased aortic stiffness and a more restrictive mitral filling pattern is consistent with this. A link between greater aortic stiffness and a restrictive mitral filling pattern could occur as a result of cardiac hypertrophy, changing the properties of both the myocytes and the interstitium, which is known to be a factor that influences LV diastolic filling.[34]

A reduction in aortic distensibility may worsen the burden of a weakened heart through changes in BP. The consequences of aortic stiffening during the aging process with preserved LV systolic function are higher SBP and lower DBP.[35] In the present subjects, higher SBP and lower DBP were associated with a stiffer aorta. A possible explanation could be in the earlier reflections merging with the incoming wave during systole instead of diastole, thus

decreasing aortic diastolic pressure, which might impair coronary perfusion. In experimental models, greater aortic stiffness was associated with subendocardial ischemia through a reduction in DBP.[36] Recently, increased PP in cardiac heart failure was associated with DBP reduction rather than SBP increase.[37] Because PP results from both cardiac and arterial factors,[35] we speculate that the absence of a significant relationship between aortic stiffness and PP in the present study population might be a consequence of impaired LVEF.

Increased stiffness can be a potential factor for wall stress. When afterload is increased, an increased intraventricular pressure has to be generated, first to open the aortic valve and then during the ejection phase these increases in afterload and intraventricular pressure lead to an increase in myocardial wall stress. In animal models, loss of aortic distensibility directly affects the mechanical performance of the LV, with increases noted in LV systolic pressure and wall tension.[38]

Study Limitation

We ruled out hypertension by clinical BP measurement. However, OSA patients tend to have increased BP during the night, even if they are normotensive when assessed in the outpatient setting during the day. Previewing ambulatory BP measurements of our study group would have eliminated cases with possible nocturnal hypertension.

Conclusions

The present study has demonstrated that a significant proportion of OSA patients without any other active lung or cardiac disease develop LV systolic and diastolic dysfunction, compared with non-apneic snorers of similar BMI. Our data suggest a possible mechanism whereby aortic stiffness may affect LV function and mass in patients with OSA. A stiffer aorta may interfere with both systolic and diastolic function. Changes in aortic stiffness may be a clinically important parameter in predicting LV function and mass in OSA and there is a need to investigate that effect of nasal continuous positive airway pressure treatment on changes in aortic elasticity.

References

1. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *N Engl J Med* 2000; **342:** 1378–1384.
2. Schafer H, Koehler U, Ewig S, Hasper E, Tasci S, Luderitz B. Obstructive sleep apnea as a risk marker in coronary artery disease. *Cardiology* 1999; **92:** 79–84.
3. Koskenvuo M, Kaprio J, Telakivi T, Partinen M, Heikkila K, Sarna S. Snoring as a risk factor in ischemic heart disease and stroke in men. *Br Med J* 1987; **294:** 16–19.
4. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep induced apnea syndrome: Prevalence of cardiac arrhythmia and their reversal after tracheostomy. *Am J Med* 1977; **63:** 348–358.
5. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnea. *J Hypertens* 1990; **8:** 941–946.
6. Davies RJ, Crosby J, Prothero A, Stradling JR. Ambulatory blood pressure and left ventricular hypertrophy in subjects with untreated obstructive sleep apnea and snoring, compared with matched control subjects, and their response to treatment. *Clin Sci* 1994; **86:** 417–424.
7. Hanly P, Sasson Z, Zuberi N, Alderson M. Ventricular function in snorers and patients with obstructive sleep apnea. *Chest* 1992; **102:** 100–105.
8. Shen WF, Tribouilloy C, Rey JL, Baudhuin JJ, Boey S, Dufosse H, et al. Prognostic significance of Doppler-derived left ventricular diastolic filling variables in dilated cardiomyopathy. *Am Heart J* 1992; **124:** 1524–1533.
9. Alchanatis M, Paradellis G, Pini H, Tourkohoriti G, Jordanoglou J. Left ventricular function in patients with obstructive sleep apnoea syndrome before and after treatment with nasal CPAP. *Respiration* 2000; **67:** 367–371.
10. Urschel CW, Covell JW, Sonnenblick EH, Ross J Jr, Braunwald E. Effects of decreased aortic compliance on performance of the left ventricle. *Am J Physiol* 1968; **214:** 298–304.
11. Rechtschaffen, A, Kales A. A manual of standardized terminology: Techniques and scoring system for sleep stages of human subjects. Washington, DC: National Institutes of Health, US Government Printing Office, 1968; 204.
12. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. *Circulation* 1977; **55:** 613–618.
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; **2:** 358–367.
14. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: Comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J* 1990; **11:** 990–996.
15. Stratos C, Stefanadis C, Kallikazaros I, Boudoulas H, Toutouzas P. Ascending aorta distensibility abnormalities in hypertensive patients and response to nifedipine administration. *Am J Med* 1992; **93:** 505–512.
16. Greenfield JC, Patel DJ. Relation between pressure and diameter in the ascending aorta of man. *Circ Res* 1962; **10:** 778–781.
17. Stefanadis C, Wooley CF, Bush CA, Kolibash AJ, Boudoulas H. Aortic distensibility abnormalities in coronary artery disease. *Am J Cardiol* 1987; **59:** 1300–1304.
18. Douglas PS, Reichek N, Plappert T, Muhammad A, St John Sutton MG. Comparison of echocardiographic methods for assessment of left ventricular shortening and wall stress. *J Am Coll Cardiol* 1987; **9:** 945–951.
19. Krieger J, Grucker D, Sforza E, Chambron J, Kurtz D. Left ventricular ejection fraction in obstructive sleep apnea: Effects of long-term treatment with nasal continuous positive airway pressure. *Chest* 1991; **100:** 917–921.
20. Fung JW, Li TS, Choy DK, Yip GW, Ko FW, Sanderson JE, et al. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *Chest* 2002; **121:** 422–429.
21. Banno K, Shiomi T, Sasanabe R, Otake K, Hasegawa R, Maekawa M, et al. Sleep-disordered breathing in patients with idiopathic cardiomyopathy. *Circ J* 2004; **68:** 338–342.
22. Niroumand M, Kuperstein R, Sasson Z, Hanly PJ. Impact of obstructive sleep apnea on left ventricular mass and diastolic function. *Am J Respir Crit Care Med* 2001; **163:** 1632–1636.
23. Meguro K, Adachi H, Oshima S, Taniguchi K, Nagai R. Exercise tolerance, exercise hyperpnea and central chemosensitivity to carbon cioxide in sleep apnea syndrome in heart failure patients. *Circ J* 2005; **69:** 695–699.
24. Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest* 1995; **107:** 1538–1544.
25. Jelic S, Bartels MN, Mateika JH, Ngai P, DeMeersman RE, Basner RC. Arterial stiffness increases during obstructive sleep apneas. *Sleep* 2002; **25:** 15–20.
26. Dean RT, Wilcox I. Possible atherogenic effects of hypoxia during obstructive sleep apnea. *Sleep* 1993; **16:** 15–22.
27. Kato M, Roberts-Thomson P, Phillips BG, Haynes WG, Winnicki M, Accurso V, et al. Impairment of endothelium-dependent vasodilation of resistance vessels in patients with obstructive sleep apnea. *Circulation* 2000; **102:** 2607–2610.
28. Ohike Y, Kozaki K, Iijima K, Eto M, Kojima T, Ohga E, et al. Amelioration of vascular endothelial dysfunction in obstructive sleep apnea syndrome by nasal continuous positive airway pressure. *Circ J* 2005; **69:** 221–226.
29. Fletcher EC. Sympathetic activity and blood pressure in the sleep apnea syndrome. *Respiration* 1997; **64**(Suppl 1)**:** 22–28.
30. Virolainen J, Kupari M. Age-dependent increase in aortic stiffness during negative intrathoracic pressure in healthy subjects. *Am J Cardiol* 1993; **71:** 878–882.
31. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ven-

tricle. *Circ Res* 1992; **71:** 490–502.
32. Wilcken DE, Charlier AA, Hoffmann JI, Guz A. Effects of alterations in aortic impedance on the performance of the left ventricles. *Circ Res* 1964; **14:** 283–293.
33. Chen CH, Nakayama M, Nevo E, Fetics BJ, Maughan WL, Kass DA. Coupled systolic-ventricular and vascular stiffening with age: Implications for pressure regulation and cardiac reserve in the elderly. *J Am Coll Cardiol* 1998; **32:** 1221–1227.
34. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991; **83:** 1849–1865.
35. Nichols WW, O'Rourke MF. Vascular impedance. *In*: McDonald's blood flow in arteries: Theoretical, experimental and clinical principles, 4th edn. London: Edward Arnold; 1998; 54–97, 243–283, 347–395.
36. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol* 1993; **21:** 1497–1506.
37. Mitchell GF, Tardif JC, Arnold JM, Marchiori G, O'Brien TX, Dunlap ME, et al. Pulsatile hemodynamics in congestive heart failure. *Hypertension* 2001; **38:** 1433–1439.
38. Kelly RP, Tunin R, Kass DA. Effect of reduced aortic compliance on cardiac efficiency and contractile function of in situ canine left ventricle. *Circ Res* 1992; **71:** 490–502.