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Original Article

The Impact of Sleep Apnea on Conventional Doppler Indices

Ching-Chih Lee[1,2], *Chih-Wei Chen*[2,3]*

[1]*Department of Otolaryngology, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan*
[2]*College of Medicine, Tzu Chi University, Hualien, Taiwan*
[3]*Division of Cardiology, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan*

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Abstract

Objective: To prospectively explore the impact of obstructive sleep apnea (OSA) on conventional Doppler indices and to identify possible negative prognostic factors for left ventricular diastolic dysfunction.
Materials and Methods: All included subjects had overnight polysomnography. All subjects underwent a comprehensive echocardiography examination to evaluate systolic and diastolic function of the left ventricle. A multiple logistic regression model was created to identify potential negative prognostic factors for left ventricular dysfunction.
Results: A significant decrease in the ratio of early and atrial mitral flow velocity (E/A ratio) in OSA patients was found. Patients with moderate-to-severe OSA had a significant increase in the odds ratio for development of an abnormal E/A ratio ($p=0.014$, multivariate logistic regression). There was a significant negative correlation between E/A ratio and apnea-hypopnea index ($p=0.01$). Non-obese OSA patients and obese-OSA patients carried significantly increased odds ratios for the development of a reduced E/A ratio ($p=0.02$ and 0.038, respectively).
Conclusion: Subjects with OSA had reduced mitral E/A ratios, which implies possible impaired diastolic heart function. Further study to reverse impaired diastolic function via lifestyle modifications and treatment with nasal continuous positive airway pressure or surgery is warranted. (*Tzu Chi Med J* 2009;21(3):210–217)

*Corresponding author. Division of Cardiology, Department of Internal Medicine, Buddhist Dalin Tzu Chi General Hospital, 2, Min-Sheng Road, Dalin, Chiayi, Taiwan.
E-mail address: enttcd@hotmail.com

1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive collapse of the upper airway and hypoxemia during sleep. Prevalence reports show that 4% of men and 2% of women are affected by OSA (1). OSA may result in many complications and morbidities. Cardiac arrhythmias, heart failure, impaired neuropsychological ability, and an increased incidence of stroke are closely correlated with OSA (2–4). Cardiovascular disorders are the most important complications associated with OSA, resulting in severe morbidity and mortality. Normally, central sympathetic activity, heart rate, blood pressure, and cardiac output are

reduced during sleep [5]. However, recurrent hypoxia during sleep in OSA patients disrupts the normal sleep cycle and permits surges in blood pressure and heart rate. OSA may contribute to the formation of left ventricular hypertrophy, and severe and moderate OSA results in an increased ventricular mass and left ventricular global dysfunction [6]. Chronic inflammation may be a result of repetitive hypoxemia in OSA patients and may be involved in the development of atherosclerosis and cardiovascular disorders [7].

Diastolic heart failure causes 38–54% of all cases of heart failure [8]. Structural, functional, molecular, and mechanical dysfunction contributes to the formation of diastolic heart failure. Enlarged cardiomyocyte diameter, abnormal titin function, abnormal matrix degradation and increased matrix metalloproteinase-9 are involved in the pathogenesis of cardiovascular diseases [8–10]. These factors increase diastolic resistance and stiffness of the left ventricle. During OSA, exaggerated negative intrathoracic pressure—due to the futile inspiratory effect during upper airway obstruction—leads to an increase in left ventricular transmural pressure, development of cardiac myocyte slippage, adverse ventricular remodeling, and an increase in isovolumic relaxation time [11]. Furthermore, sleep apnea is associated with echocardiographic evidence of increased left ventricular mass and impaired systolic function [12].

Early identification and appropriate treatment of left ventricular diastolic dysfunction is essential to prevent progression to heart failure and death in patients with OSA. Therefore, the purpose of this study was to explore the impact of OSA on left ventricular function and to identify negative prognostic factors for left ventricular dysfunction.

2. Materials and methods

2.1. Subjects

Thirty-five patients with OSA with an apnea-hypopnea index (AHI) ≥ 5 hours^{-1}, and excessive daytime sleepiness (Epworth sleepiness scale >10), and no current drug or mechanical treatment for OSA, were recruited for this study. Patients diagnosed with cancer, angina pectoris, atrial fibrillation, diabetes, chronic renal and/or hepatic disease, chronic pulmonary disease, left ventricular dysfunction (left ventricular ejection fraction $<55\%$) or serum electrolyte imbalances were excluded from the study. Fifteen healthy subjects, who were asymptomatic and underwent a sleep polysomnography for health promotion and disease prevention during annual health checkups, were recruited as control subjects. The criteria used to define normal sleep for this control group were an AHI <5 hours^{-1} and no daytime hypersomnolence (Epworth sleepiness scale <10). The study was approved by the Ethics Committee of the hospital. All subjects provided informed written consent prior to participation.

2.2. Protocol

Peripheral blood samples were drawn from the antecubital vein between 6:00 and 7:00 AM after an overnight fast exceeding 8 hours. Serum cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), glucose, and uric acid levels were measured. A general physical examination was performed in all study participants. In addition, a full evaluation of the status of the upper airway was performed via nasopharyngolaryngoscopy. This included recording the palatal position and tonsil size. Weight and height were measured to calculate the body mass index (BMI). Blood pressure and heart rate were measured in a sitting position with the arm at heart level after 10 minutes of rest. Hypertension was defined as a blood pressure $\geq 140/90$ mmHg or current treatment with antihypertensive medication. All study subjects with hypertension were on regular medication. Impaired glucose tolerance was established on the basis of a previous diagnosis of diabetes mellitus and treatment with diet therapy/antidiabetic medications, or based on the results of two random fasting glucose levels that exceeded 126 mg/dL.

2.3. Polysomnography

All subjects with suspected OSA and all control subjects participated in a sleep study consisting of a one-night portable polysomnography (M-10, Embletta device; Embla, Broomfield, CO, USA), which included a nasal pressure detector consisting of a nasal cannula and pressure transducer system, thoracoabdominal movement detection through two piezoelectric belts, a finger pulse oximeter, and body position detector. Patient with a sleep duration less than 6 hours were excluded.

Apnea episodes were defined as complete cessation of oronasal airflow for ≥ 10 seconds and hypopnea as a $>50\%$ reduction in oronasal airflow accompanied by a $>4\%$ decrease in oxygen saturation measured via pulse oximeter. The oxygen desaturation index was defined as the number of oxygen desaturation events per hour of sleep. Subjects with an AHI ≥ 5 were diagnosed with OSA. On the basis of this test result, the study patients diagnosed with OSA were divided into two groups: those with mild OSA (AHI $=5$–20) and those with moderate to severe OSA (AHI >20).

2.4. Echocardiographic analysis

M-mode, two dimensional, Doppler echocardiography (VIVID 3; GE Medical Systems, Milwaukee, WI, USA) was performed with a 2.5 MHz probe with the subjects in the left lateral decubitus position. The ultrasonographer was blinded to the diagnosis of OSA in all subjects. Left ventricular dimensions during diastole, systole, and left atrial diameters during diastole were measured by the M-mode technique. This was conducted in the parasternal long axis view while dimensions of the right ventricle were measured in the apical four-chamber view. The left ventricular ejection fraction was calculated by the modified Simpson's method using the following equation: (diastolic volume − systolic volume)/diastolic volume.

A truncated ellipsoid method was employed to measure the left ventricular (LV) mass in the apical four-chamber view calculated at the end-diastolic phase. The LV mass index was obtained by the following equation: LV mass/body surface area early (E) and atrial (A) transmitral maximal flow velocities; the E/A ratio was assessed using a pulse wave Doppler technique taken in the apical four-chamber view with a sample volume between the mitral leaflet tip during diastole. The isovolumic relation time (IVRT) was measured using a continuous wave Doppler technique. If tricuspid regurgitation was detected by color Doppler echocardiography, the trans-tricuspid pressure gradient was measured using continuous wave Doppler. Abnormal systolic function was defined as an ejection fraction <55%; abnormal diastolic function was defined as an E/A ratio <1 and/or IVRT >100 ms. The definition of diastolic heart failure requires the presence of signs or symptoms of heart failure, normal or mildly abnormal systolic left ventricular function, and evidence of diastolic left ventricular dysfunction. Diagnostic evidence of diastolic left ventricular dysfunction can be obtained by invasive hemodynamic measurements or noninvasive tissue Doppler examination. This was outlined in a recent consensus statement on the diagnosis of diastolic dysfunction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology [13].

2.5. Statistical analysis

Statistical analysis was performed using SPSS version 12 (SPSS Inc., Chicago, IL, USA). Values are expressed as mean±standard deviation or percentages. Differences between groups were examined by the Kruskal-Wallis test. The Mann-Whitney U test was used for pairwise group comparisons. The correlation between two continuous variables was analyzed with Spearman's correlation coefficient. Pearson's χ^2 test was used to compare proportional data, and multiple logistic regression was used to control for age, sex, and hypertension.

3. Results

The final study sample consisted of 51 subjects, 16 controls, and 35 OSA patients. Basic characteristics of the patients are shown in Table 1. There were no significant differences in their age, sex, smoking history, history of glucose intolerance, systolic blood pressure, or heart rate. The BMI was much higher in

Table 1 — Characteristics and laboratory data in patients with mild, moderate and severe OSA

	Control (n=16)	Mild OSA (n=20)	Moderate-to-severe OSA (n=15)	p
Age (yr)	39±7.8	45±9.5	46±11.9	NS
Sex (male, %)	82	85	100	NS
BMI (kg/m^2)	27±3.8	28±3.3	31±5.1*‡	0.011
AHI per hr	2±1.6	11±4.5	48±21†§	<0.001
ODI per hr	4±3.8	14±7.3	45±21.1	<0.001
Smoking history (%)	44	45	33	NS
Glucose intolerance (%)	6	15	7	NS
Hypertension (%)	19	10	53	0.011
Glucose (mg/dL)	102±27	100±11.4	107±64	NS
Uric acid (mg/dL)	6±1.8	6±1.5	7±1.4	NS
Triglyceride (mg/dL)	179±116	195±102.6	212±149.5	NS
Total cholesterol (mg/dL)	173±57.4	198±40.5	189±46.3	NS
HDL-C (mg/dL)	43±8.6	42±7.8	41±13.8	NS
LDL-C (mg/dL)	125±34.3	133±38.8	124±42.3	NS
SBP (mmHg)	125±21.4	123±14.3	132±16.8	NS
DBP (mmHg)	71±10.2	75±10.5	82±11.8*	0.032
HR (pulse per min)	79±10.7	75±10.5	73±10.1	NS

$^{*}p$<0.05 and $^{†}p$<0.01 versus control; $^{‡}p$<0.05 and $^{§}p$<0.01 versus mild OSA. OSA=obstructive sleep apnea syndrome; NS=not significant; BMI=body mass index; AHI=apnea-hypopnea index; ODI=oxygen desaturation index; HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate.

Table 2 — Left ventricular function by echocardiography in patients with sleep apnea

	Control (n=16)	Mild OSA (n=20)	Moderate-to-severe OSA (n=15)	p
Left atrium (mm)	37±5	37±6.3	38±6.7	NS
IVSD (mm)	9±1.5	9±1.6	10±1.7	NS
LVEDD (mm)	49±4.1	49±4.2	50±2.6	NS
LVESD (mm)	28±3.7	29±2.4	30±3.5	NS
Parameters of systolic function				
Ejection fraction (55–75%)	70±5	70±7.2	69±5.4	NS
Parameters of diastolic function				
E/A ratio	1.3±0.34	1.1±0.36	0.99±0.25*	0.017
IVRT (msec)	90±21.1	99±14.9	96±16.9	NS
Left ventricular mass				
LVM (g)	149±40.9	173±40.4	177±49.8	NS
LVMI (g/m^2)	78±19	91±17.7	86±23.7	NS

*p<0.05 versus control. OSA=obstructive sleep apnea syndrome; IVSD=interventricular septum thickness; LVEDD=left ventricular end-diastolic diameter; LVESD=left ventricular end-systolic diameter; E/A ratio=ratio of early and atrial mitral flow velocity; IVRT=isovolumic relaxation time; LVM=left ventricular mass; LVMI=LVM index; NS=not significant.

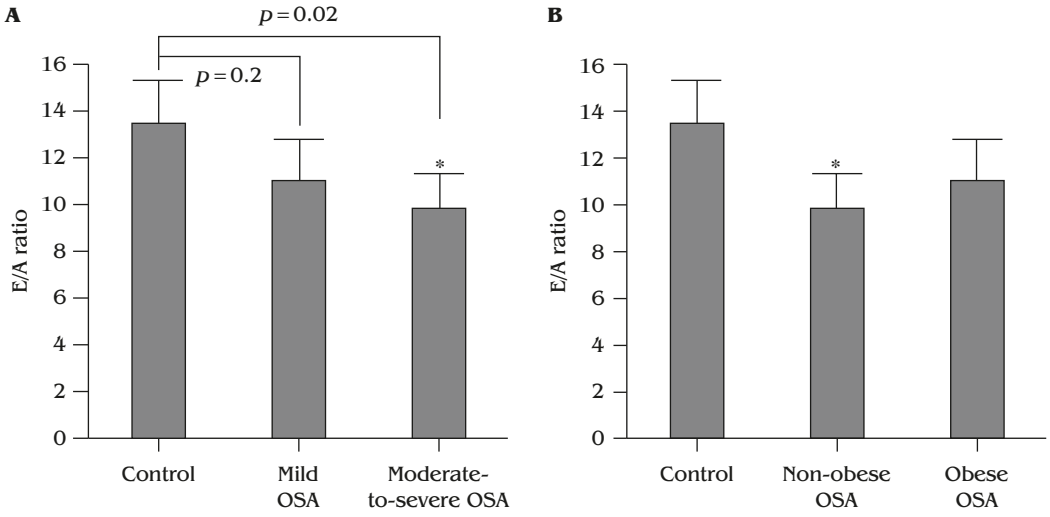

Fig. 1 — (A) Correlation between the ratio of early and atrial mitral flow (E/A ratio) and severity of obstructive sleep apnea (OSA). (B) Cardiac measurement in the control subjects, non-obese OSA, and obese OSA groups. The E/A ratio was significantly decreased in the non-obese OSA group (p=0.032) and borderline decreased in the obese OSA group (p=0.078 *vs.* control group).

patients with moderate-to-severe OSA than the control subjects, or patients with mild OSA (p=0.01). Diastolic blood pressure was higher in patients with moderate-to-severe OSA than the control subjects (p=0.032), and the percentage of those with a history of hypertension was much higher in the moderate-to-severe OSA group (p=0.011). The fasting serum levels of glucose, uric acid, triglycerides, total cholesterol, HDL-C, and LDL-C were not statistically different among the three groups. As shown in Table 2, left ventricular systolic function was not significantly different between the subjects; however, the E/A ratio was significantly lower in subjects with moderate-to-severe OSA (p=0.017; Fig. 1A).

OSA patients were classified into two subgroups according to BMI: non-obese OSA (BMI<27 kg/m^2) and obese OSA (BMI≥27 kg/m^2). The E/A ratios in the non-obese OSA group were still significantly lower than those in the control subjects, although there was no difference in BMI between these two groups (p=0.019; Fig. 1B; Table 3). Fig. 2 shows a negative correlation between E/A ratio and AHI (Spearman's rank correlation coefficient=–0.36, p=0.01), but there was no significant association between E/A ratio and BMI (p=0.68). Fig. 3 shows that 38% of the moderate-to-severe OSA patients, 27% of the non-obese OSA patients, and 29% of the obese OSA patients had reduced E/A ratios and prolonged IVRTs. There was

Table 3 — Left ventricular function by echocardiography in non-obese (BMI<27 kg/m^2) and obese (BMI≥27 kg/m^2) OSA patients

	Control (n=16)	Non-obese OSA (n=11)	Obese OSA (n=24)	p
BMI (kg/m^2)	27±3.8	25±1.2	31±4.8†‡	<0.001
AHI per hr	2±1.6	20±4*	30±25†	<0.001
ODI per hr	4±3.8	18±12.2*	31±23†	<0.001
Parameters of systolic function				
Ejection fraction (55–75%)	70±1.4	69±2.2	69±1.8	NS
Parameters of diastolic function				
E/A ratio	1.3±0.34	0.99±0.31*	1±0.32	0.019
IVRT (msec)	91±3.6	98±5.2	99±4.8	NS
Left ventricular mass				
LVM (g)	149±40.9	164±35.8	180±47.4	NS
LVMI (g/m^2)	78±19	92±17.5	88±21.4	NS

$^*p$<0.05 and $^\dagger p$<0.01 versus control; $^\ddagger p$<0.01 versus mild OSA. BMI=body mass index; OSA=obstructive sleep apnea syndrome; AHI=apnea-hypopnea index; ODI=oxygen desaturation index; E/A ratio=ratio of early and atrial mitral flow velocity; IVRT=isovolumic relaxation time; LVM=left ventricular mass; LVMI=LVM index; NS=not significant.

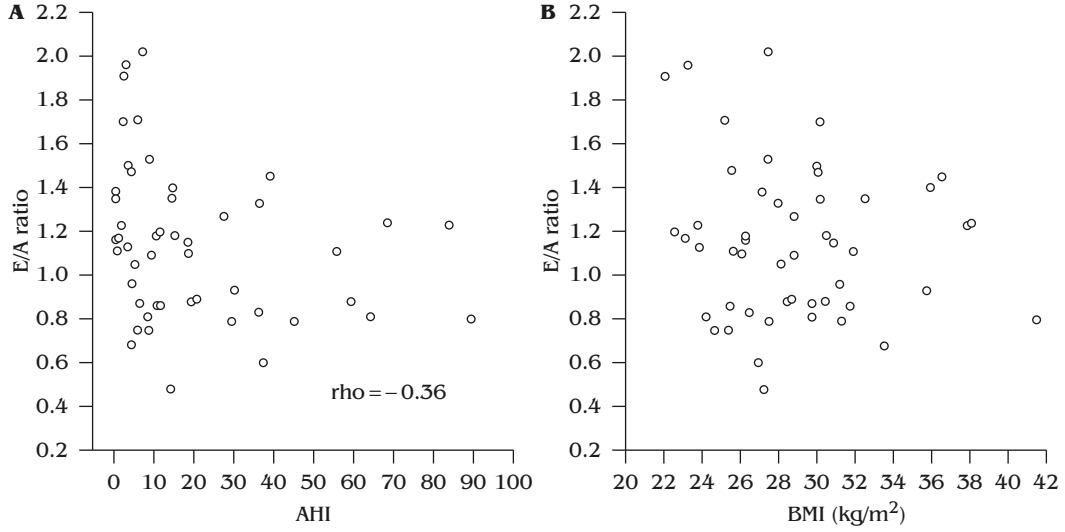

Fig. 2 — (A) Correlation between the ratio of early and atrial mitral flow (E/A ratio) and apnea-hypopnea index (p=0.011). (B) Correlation between the E/A ratio and body mass index (p =0.68). AHI=apnea-hypopnea index; BMI=body mass index.

a significant association between a decreased E/A ratio and prolonged IVRT with severity of OSA (p= 0.043; Fig. 3). Table 4 shows that the moderate-to-severe OSA group had a significantly increased odds ratio for the development of a decreased E/A ratio (p=0.036) after adjusting for age, sex, and hypertension. The non-obese OSA group and obese OSA group had significantly increased risks of developing reduced E/A ratios (p=0.02 and 0.038, respectively).

4. Discussion

This study revealed that individuals with moderate-to-severe OSA have decreased E/A ratios—this impairment may be related to repetitive obstructive apnea events during sleep. However, a close correlation between BMI and AHI was observed. It is possible that the decreased E/A ratio and increased IVRT may be attributed to obesity, rather than repetitive hypoxia. For this reason, the patients with OSA were divided into non-obese and obese OSA groups. The E/A ratios in the non-obese OSA group were still significantly lower than those in control subjects, although there was no significant difference in their BMI. Our results also revealed that there was a significant negative correlation between E/A ratio and AHI, but not between E/A ratio and BMI. This finding suggests that some part of the E/A ratio is decreased independent of obesity. Multivariate logistic regression

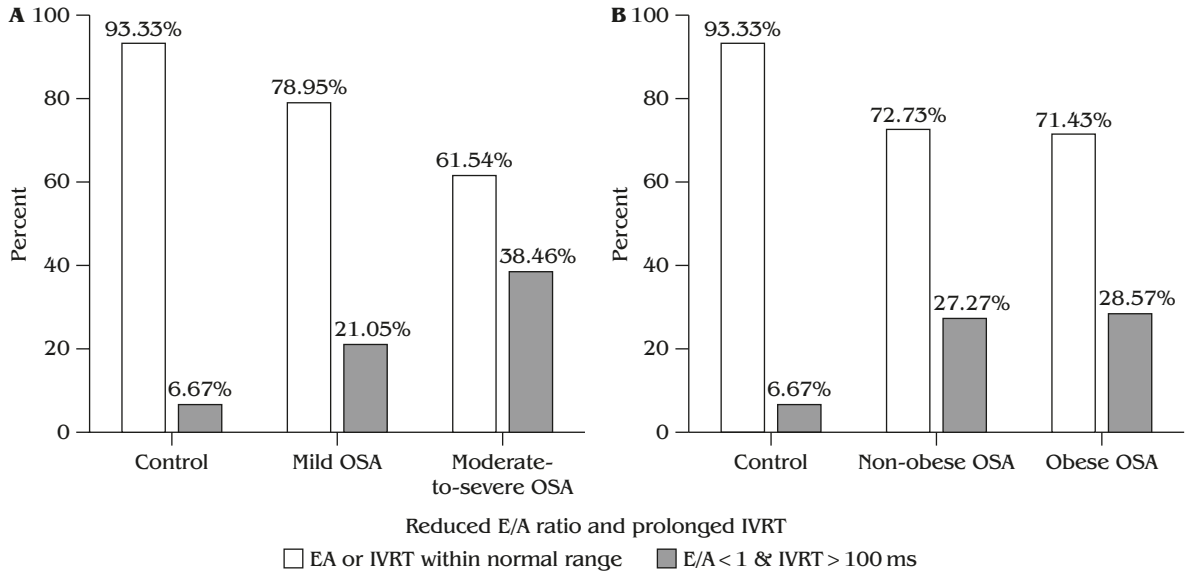

Fig. 3 — Distribution of decreased ratio of early and atrial mitral flow (E/A ratio) and prolonged isovolumic relation time in (A) controls and patients with different severities of obstructive sleep apnea (OSA), and (B) controls and non-obese OSA and obese OSA groups.

Table 4 — Multiple logistic regression analysis adjusted for age, sex, and hypertension

Variables	E/A ratio < 1		IVRT > 100 ms	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sleep apnea classification				
Moderate-to-severe OSA	7.4 (1.1–48)	0.036	2 (0.3–11)	0.521
Mild OSA	5.3 (0.8–32)	0.07	4 (0.7–19)	0.125
Control group	1			
Obesity & sleep apnea				
Obese OSA	4 (1.02–28)	0.038	4.3 (0.7–15)	0.13
Non-obese OSA	11 (1.4–84)	0.02	2 (0.3–11)	0.568
Control group	1		1	

E/A ratio=ratio of early and atrial mitral flow velocity; IVRT=isovolumic relaxation time; OR=odds ratio; CI=confidence interval; OSA=obstructive sleep apnea.

revealed that non-obese patients with OSA and obese OSA patients had significantly increased risks of developing decreased E/A ratios.

The definition of diastolic heart failure requires the presence of particular signs or symptoms. Although diagnostic evidence of diastolic left ventricular dysfunction can be obtained by invasive hemodynamic measurements or noninvasive tissue Doppler, traditional Doppler methods are still popular and widely used. Our findings in this series did not fulfill the criteria of diastolic left ventricular dysfunction by definition, but echocardiographic abnormalities such as decreased E/A ratio were found in patients with sleep apnea.

Niroumand et al [14] reported that E/A ratio is significantly correlated with age, but not with AHI or SaO_2 <90%. However, Arias et al [15] suggested that diastolic dysfunction is only predicted by AHI in multiple logistic regression. Kim et al [16] reported that early diastolic velocity measured by tissue Doppler imaging was inversely correlated with AHI, and there was no significant association between AHI and either E/A ratio or IVRT. In our series, an abnormal E/A ratio was correlated with AHI (Fig. 2), and with the severity of OSA in multivariate logistic regression—after adjusting for age, sex, and hypertension (Table 4).

OSA can induce a series of mechanical, hemodynamic, chemical, neural, molecular, and inflammatory reactions with adverse consequences for the cardiovascular system. Tazaki et al [10] reported that increased matrix metalloproteinase-9 was found in patients with OSA, and an excess of matrix metalloproteinase-9 may be responsible for structural degradation

and atherosclerosis. Exaggerated negative intrathoracic pressure—due to the futile inspiratory effect during upper airway obstruction—leads to an increase in left ventricular transmural pressure, development of cardiac myocyte slippage, adverse ventricular remodeling, and an increase in the isovolumic relaxation time [8,11,17]. Concurrently, enhanced negative intrathoracic pressure increases venous return to the right ventricle—this causes a left shift of the ventricular septum and impaired left ventricular diastolic filling [11,18]. Increased sympathetic nervous activity, which results from the interaction of several excitatory mechanisms, normally dormant during sleep, is a cardinal feature of OSA [5].

Nasal continuous positive airway pressure has been demonstrated to reverse abnormal E/A ratios in OSA patients with impaired diastolic function [15]. OSA patients with elevated inflammation markers—such as tumor necrosis factor-α—treated with nasal continuous positive airway pressure, could experience decreases in inflammatory marker levels [7]. Together, these results imply that cardiac dysfunction and/or inflammation status is reversible in OSA patients and that these patients could benefit from treatment in order to reverse impaired heart function.

The main limitation of our study was the small number of subjects. In addition, we only used simple Doppler echocardiography to evaluate diastolic dysfunction instead of tissue Doppler echocardiography. Tissue Doppler echocardiography is a more sensitive tool for detecting diastolic dysfunction. Additional longitudinal studies are warranted to confirm our results. Nonetheless, this study did identify significant echocardiographic abnormalities in diastolic function in the moderate-to-severe OSA group.

In this study, no significant difference in systolic function among the three groups was found. However, a decreased E/A ratio was noted in the OSA group. Some part of the E/A ratio is decreased independent of obesity. Although a decreased E/A ratio was not enough to detect left ventricular diastolic dysfunction, it did offer some clue to diastolic dysfunction. Diastolic dysfunction is a major risk factor for the development of overt systolic heart failure. These results suggest that some part of impaired diastolic function develops early and deserves more attention in OSA patients.

In conclusion, this study revealed that increased severity of OSA may result in abnormal conventional Doppler indices. This may imply left ventricular diastolic dysfunction. Diastolic dysfunction is a major risk for systolic heart failure and may be combined with systolic function. Individuals with moderate-to-severe OSA have impaired diastolic function and may therefore have an increased risk of overt heart failure. Impaired diastolic function develops early and deserves more attention in OSA patients.

Acknowledgments

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