

Left Ventricular Systolic and Diastolic Function in Obstructive Sleep Apnea

Impact of Continuous Positive Airway Pressure Therapy

Mehmood Butt, MRCP*; Girish Dwivedi, MD, MRCP, PhD*; Alena Shantsila, MD; Omer A. Khair, MD, FRCP; Gregory Y.H. Lip, MD, FRCP, FESC, FACC

Background—Previous studies in obstructive sleep apnea (OSA) were limited by study cohorts with comorbidities that confound assessment of left ventricular (LV) systolic and diastolic function. We comprehensively evaluated LV function using 2-dimensional echocardiography (2DE), tissue Doppler imaging (TDI), and 3-dimensional echocardiography (3DE) in subjects moderate-severe OSA, who were compared with disease (patients with hypertension, no OSA) and healthy control subjects.

Methods and Results—A total of 120 subjects (n=40 each of matched OSA, hypertension and healthy cohorts) underwent echocardiographic examination for the assessment of septal and posterior wall thickness, LV mass index, LV volumes and ejection fraction, mitral valve inflow indices (E, A), mitral annular velocity (S, E'), and left atrial volume index (LAVI). OSA subjects were treated with continuous positive airway pressure (mean duration of 26 weeks), after which the echocardiographic parameters were reassessed. Posterior wall thickness and LV mass index were significantly higher in OSA and hypertensive groups compared with healthy. Systolic S velocity was reduced in OSA and hypertensive compared with healthy control subjects ($P<0.05$). Diastolic function (E/A, IVRT, and E/E') was impaired in both OSA and hypertensive groups. On 3DE, mean LAVI was significantly greater in OSA and hypertensive compared with healthy. In OSA patients, continuous positive airway pressure therapy resulted in reduction of the posterior wall thickness ($P=0.02$) and improvement in LV ejection fraction ($P<0.05$), systolic S velocity ($P<0.05$), and diastolic LV impairment parameters.

Conclusions—Moderate to severe OSA causes structural and functional changes in LV function and are comparable to that seen in hypertension. These abnormalities significantly improve after CPAP therapy. (*Circ Heart Fail.* 2012;5:226-233.)

Key Words: obstructive sleep apnea ■ continuous positive airway pressure ■ left ventricle ■ systolic function ■ diastolic function

Obstructive sleep apnea (OSA) is an increasing major public health problem being associated with various cardiovascular disorders.¹⁻³ OSA is characterized by partial or complete recurrent upper airway obstructions during sleep, which results in periods of apnea/hypopnea, oxygen desaturation, periodic nocturnal arousals, and daytime sleepiness. Left ventricular (LV) systolic and diastolic functions are well-established prognostic markers of adverse cardiovascular outcome in a number of conditions. Small studies have reported LV dysfunction of unknown etiology in OSA population.^{4,5} However, due to the commonly accompanying comorbidities with OSA, such as obesity, coronary artery disease, and hypertension that can independently affect LV function, studies assessing LV function in “pure” OSA patients (ie, without other confounding comorbidities) are sparse.

Clinical Perspective on p 233

The majority of data suggest that OSA contributes to the development of some LV systolic and diastolic dysfunction and subsequently heart failure, although some studies have reported otherwise.⁶⁻⁸ Most of these studies have used either M mode or conventional 2-dimensional echocardiography (2DE) with Doppler imaging techniques to evaluate systolic (LV dimensions/volumes and ejection fraction) and diastolic function (transmitral flow velocities and intraventricular relaxation time). Newer echocardiographic techniques such as tissue Doppler imaging (TDI) and 3-dimensional echocardiography (3DE) provide more accurate evaluation of LV function, but limited data are available in OSA, especially with the latter.

Received August 1, 2011; accepted January 11, 2012.

From the University of Birmingham Centre for Cardiovascular Sciences (M.B., G.D., A.S., G.Y.H.L.) and the Department of Respiratory Medicine (O.A.K.), City Hospital, Birmingham, United Kingdom.

*Drs Butt and Dwivedi contributed equally to this work.

Correspondence to G.Y.H. Lip, MD, FRCP, FESC, FACC, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham B18 7QH, UK. E-mail g.y.h.lip@bham.ac.uk

© 2012 American Heart Association, Inc.

Circ Heart Fail is available at <http://circheartfailure.ahajournals.org>

DOI: 10.1161/CIRCHEARTFAILURE.111.964106

Continuous positive airway pressure (CPAP) is established treatment for OSA, but the studies investigating the effect of CPAP on LV function in moderate to severe OSA are limited with contradictory data, with some reporting improvement in LV function, with others showing no change with CPAP.^{8–12}

To address these unresolved issues, we performed a comprehensive LV assessment with the use of 2DE, TDI, and 3DE in otherwise healthy subjects with moderate-severe OSA and compared the results with matched “disease control subjects” and healthy control subjects in a cross-sectional analysis. We also assessed the effect of CPAP therapy on LV function in OSA subjects. We tested the hypothesis that LV function abnormalities exist in normotensive OSA subjects compared with healthy control subjects. Second, we hypothesized that optimal CPAP therapy would reverse LV function abnormalities in OSA patients. Of note, vasodilator stress myocardial contrast echocardiography (in addition to wall motion analysis) was also used to noninvasively exclude significant coronary artery disease, as part of our comprehensive echocardiographic assessment in all three study groups.

Methods

We recruited 40 consecutive subjects with a confirmed diagnosis of moderate-severe OSA [Apnea-Hypopnea Index (AHI) >15, diagnosed by multichannel polysomnography; FSI Gray Flash recorder Stowood Scientific Instruments Ltd, Oxford, UK], from the sleep laboratory in City Hospital Birmingham, United Kingdom. These OSA patients were compared with matched disease control subjects (otherwise healthy patients with essential hypertension) and healthy control subjects (n=40 each) for a cross-sectional comparison. OSA was excluded from both control groups (AHI <5) by multichannel sleep study.

All study participants were deemed otherwise healthy by careful history, clinical examination, baseline blood tests, 12-lead ECG and transthoracic echocardiography. Patients with comorbidities such as those with preexisting diabetes mellitus (defined according to World Health Organization criteria; fasting plasma glucose >7.0 mmol/L, or 2-hour postprandial plasma glucose of >11.1 mmol/L, and/or the patient taking on antidiabetic treatment such as insulin or oral therapy or on dietary management), hyperlipidemia (defined as patients taking antidyslipidemic drugs such as statins and/or fibrates), and coronary artery disease (eg, previous myocardial infarction or revascularization procedure) were excluded. Patients with known structural heart disease, LV dysfunction, previous cerebrovascular event, malignancy, connective tissue or inflammatory disease, acute/chronic infection, and hepatic or renal impairment were also excluded from the study. Using the method described previously by our group, we used vasodilator stress myocardial contrast echocardiography to exclude coronary artery disease (a strong confounding factor for adverse cardiac remodeling) in our study patients.¹³ Ethical approval was granted by local research ethics committee and written informed consent was provided.

All study subjects fasted for 12 hours and abstained from smoking, alcohol, tea, and coffee for 24 hours before the study. Hypertensive subjects were advised to omit their medications on the study day, as prolonged treatment omission was deemed unethical. Blood pressure measurements were performed before any scanning, from right arm while subjects were rested for 15–20 minutes in supine position. All scans were performed in a quiet, darkened, temperature-controlled room.

After baseline measurements, the OSA subjects were prescribed and autotitrated with an automated CPAP device (REMstar Pro M Series with C-Flex–Phillips Respironics, Youngwood, PA). CPAP compliance was monitored/recorded throughout the study at regular intervals. Satisfactory CPAP compliance was defined as a minimum usage of 4 hours per night for at least 75% of the week’s nights (ie,

>5 nights per week). After a mean duration of 26 weeks on CPAP therapy, all available OSA subjects (n=37) completed followed-up.

Echocardiography

All subjects underwent M-mode, 2DE, TDI, and 3DE using Phillips iE33 ultrasound machine (Bothel, WA). Modern off-line QLAB software [Xcelera, Phillip (iE33) Ultrasound Quantification Module, DA Best, The Netherlands] was used for quantification of LV function. The interobserver and intraobserver variability for echocardiography parameters by blinded reviewers was assessed (n=10) and calculated as 11% and 6.8%, respectively.

M-Mode, TDI, and 2D Echocardiography

Resting images of parasternal long-axis, short-axis (at aortic valve level, mitral leaflet level, papillary muscle level, and apex), apical 4-chamber, apical 5-chamber, apical 2-chamber, and apical 3-chamber views were acquired during transthoracic echocardiography. The relevant American Society of Echocardiography (ASE) guideline recommendations were used during M-mode, TDI, and 2DE image acquisition and calculation of various parameters.^{14–16} Area-length method was used to calculate left atrial (LA) volume on 2DE. LA volume was indexed to body surface area to obtain LA volume index (LAVI).

Three-Dimensional Echocardiography

Three-dimensional echocardiography was performed in apical views. Three-dimensional LV and LA images were taken by wide-angled acquisition (full-volume method) during end expiration. Off-line QLAB software was used for displaying and quantifying 3-dimensional images. The LV and LA volumes were measured using a semiautomatic tracing of endocardial border at systole and diastole at each frame during 1 cardiac cycle¹⁷; however, automatic tracings were manually modified if necessary. LA appendage and pulmonary vein aperture were excluded from LA volume calculations.

LV Parameters

Septal wall thickness, posterior wall thickness, and LV mass index (all obtained on M-mode) were used to assess LV structural parameters. LV ejection fraction (LVEF), LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV) were assessed using the modified Simpson biplane method, M-mode, and 3DE. LV volumes, LVEF, and mitral annular systolic velocity (S) (mean of lateral and septal) were used to assess LV systolic function. Acute diastolic functional assessment was performed by evaluating E/A (mitral inflow indices), E/E’ (early mitral inflow velocity/TDI derived early septal mitral annular diastolic velocity), and intra ventricular relaxation time (IVRT). LAVI provided a measure of chronic diastolic function.

Power Calculation

Based on previous studies that compared cardiac structural and functional parameters of OSA patients with normal control subjects and evaluated response to CPAP therapy in the OSA group, we calculated that a sample size of 35 patients in each group would have an 80% power to detect a significant difference.^{10–12} We anticipated that 5 OSA patients would be CPAP-noncompliant and therefore aimed to recruit 40 patients in each group.

Statistical Analysis

After a test of statistical normality, data were expressed as mean±SD for normally distributed data or median and interquartile range (IQR) for nonnormally distributed data. Cross-sectional comparisons between the 3 groups (OSA, hypertensive, and healthy control subjects) were analyzed by 1-way ANOVA or Kruskal-Wallis test, with Tukey post hoc test (after log transformation for nonnormal data), as appropriate. Paired comparisons before versus after CPAP were performed using paired *t* test or paired Wilcoxon test, as appropriate. Using univariate and multivariate regression

Table 1. Clinical Characteristics of Obstructive Sleep Apnea Patients, Hypertensive Control Subjects, and Healthy Control Subjects

Variable	OSA (n=40)	Hypertensive Control Subjects (n=40)	Healthy Control Subjects (n=40)	P Value
Male/female	33/7	31/9	30/10	
Age, y	50 (10)	49 (11)	46 (9)	0.12
AHI	39 (22)*‡	4 (2)‡	3 (2)*	<0.0001
Body mass index	34 (8)	32 (6)	32 (6)	0.12
Systolic blood pressure, mm Hg	142 (16)	150 (20)†	135 (15)†	<0.0001
Diastolic blood pressure, mm Hg	83 (11)	85 (10)	82 (9)	0.22
No. of current smokers	14	12	16	
Comorbidities				
Treated hypertension	0	40	0	
Treated dyslipidemia	0	0	0	
Known coronary artery disease	0	0	0	
Diabetes mellitus	0	0	0	
Past stroke/TIA	0	0	0	
Current drug therapy				
ACE inhibitors	0	23	0	
ARB	0	20	0	
Calcium channel blockers	0	20	0	
β-blockers	0	15	0	
Aspirin	0	34	0	
Diuretics	0	7	0	

Values are described as mean (standard deviation) and median (interquartile range). $P<0.05$ considered statistically significant.

OSA indicates obstructive sleep apnea; TIA, transient ischemic attack; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; AHI, Apnea-Hypopnea Index; BMI, body mass index; CPAP, continuous positive airway pressure.

*Significance between OSA and healthy subjects.

†Significance between hypertensive and healthy subjects.

‡Significance between OSA and hypertensive subjects.

analyses, predictive models of changes in echocardiographic parameters of systolic and diastolic function with CPAP therapy in the OSA group were evaluated as a function of sleep (ie, change in Epworth score) and clinical variables (ie, changes in systolic and diastolic blood pressure). All analyses were performed using Minitab v 15 for Windows (Minitab Inc, State College, PA) and Analyze-It Software (version 1.62), Leeds, United Kingdom. A value of $P<0.05$ was considered statistically significant.

Results

Subjects were comparable in age, sex, and body mass index (BMI) among the 3 groups (Table 1). Hypertensive subjects had significantly higher systolic blood pressure compared with the healthy group ($P<0.0001$).

CPAP compliance was achieved in all 40 OSA patients, of which 37 were available for follow-up examination (mean follow-up of 26 weeks). A modestly elevated ($>140/80$ mm Hg) mean baseline blood pressure was noted, and,

Table 2. Clinical Features in Obstructive Sleep Apnea Patients Undergoing CPAP Treatment

	Before CPAP	After CPAP	P Value
n	37	37	
BMI, kg/m ²	34±7	34±8	0.18
Epworth score	13±6	5±6	<0.0001
Systolic BP, mm Hg	144±16	133±13	<0.0001
Diastolic BP, mm Hg	83±11	80±7	0.02

Values are described as mean±SD. $P<0.05$ was considered statistically significant.

CPAP indicates continuous positive airway pressure; BMI, body mass index; BP, blood pressure.

after CPAP therapy, there was a significant drop in systolic ($P<0.0001$) and diastolic pressure ($P=0.04$) (Table 2). A significant reduction in Epworth score was seen ($P<0.0001$).

LV Structural Parameters

The posterior wall thickness ($P<0.0001$) and LV mass index ($P=0.009$) were higher in the OSA and hypertensive group compared with normal control subjects (Table 3 and Figure 1). After CPAP, there was significant reduction in septal ($P<0.0001$) and posterior wall thickness ($P=0.02$) (Table 4).

LV Systolic Function Parameters

Systolic S velocity on TDI was significantly reduced in OSA and hypertensive groups ($P<0.0001$). No other differences in LV systolic function parameters were evident between the three groups on M mode, 2DE, or 3DE (Table 5). After CPAP in the OSA group, systolic function parameters, such as LV ejection fraction (on M-mode, 2D, and 3DE) and systolic S velocity on TDI ($P=0.01$), improved significantly (Table 6 and Figure 2).

LV Diastolic Function Parameters

Acute diastolic function parameters (E/A, IVRT) were suggestive of diastolic impairment in both OSA and hypertensive groups, compared with healthy subjects (all $P<0.05$). E/E' was only significantly different between hypertension and healthy control subjects. All measured acute diastolic indices were comparable between OSA and hypertension (Table 7).

The mean LAVI on 2DE and 3DE, a surrogate for chronic diastolic dysfunction, was significantly greater in OSA and hypertensive groups compared with normal control subjects.

Table 3. Left Ventricular Structural Parameters in Study Population (Cross-Sectional Comparison)

	OSA	Hypertension	Healthy	P Value
n	40	40	40	
IVSd, cm	1.1±0.2	1.2±0.2	1.3±0.7	0.8
LVPWd, cm	1.2±0.2*	1.2±0.2†	1±0.2*†	<0.0001
LV mass index, g/m ²	124±34*	121±35†	102±33*†	0.009

OSA indicates obstructive sleep apnea; IVSd, interventricular septal thickness in diastole; LVPWd, posterior wall thickness in diastole; LV, left ventricle. Values are mean±SD. $P<0.05$ considered statistically significant.

*Statistical significance lies between OSA and healthy subjects.

†Statistical significance lies between hypertensive and healthy subjects.

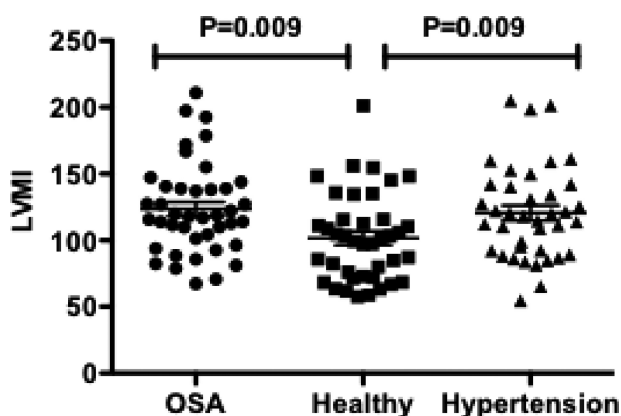


Figure 1. Left ventricular mass index in obstructive sleep apnea, healthy control subjects, and hypertensive patients. OSA indicates obstructive sleep apnea; LVMI, left ventricular mass index.

Only mean LAVI using 2DE (but not 3DE) was higher in the OSA group compared with the hypertensive group (Table 7).

Significant improvements in the E/A, IVRT, E/E', and LAVI were noted after CPAP therapy in the OSA group (Table 8 and Figures 3 and 4).

On multivariable linear regression analyses of the predictive models of various echocardiographic parameters, we found that LV systolic and diastolic markers did not significantly correlate with changes in either systolic [(3DE LVESV: $P=0.94$), (3DE LVEDV: $P=0.29$), (3DE EF: $P=0.65$), (E/E': $P=0.71$), (LAVI-3DE: $P=0.93$)] or diastolic blood pressure [(3DE LVESV: $P=0.52$), (3DE LVEDV: $P=0.31$), (3DE EF: $P=0.86$), (E/E': $P=0.24$), (LAVI-3DE: $P=0.61$)] after CPAP treatment in OSA patients. The change in the Epworth score predicted an improvement in 3DE EF ($P=0.01$) on univariate analysis, with a trend ($P=0.09$) for improvement being seen on multivariate linear regression analysis.

Discussion

To the best of our knowledge, this is the first study that has provided a comprehensive assessment of LV structural and functional parameters using 2DE, TDI, and 3DE in moderate-severe OSA patients who were free of other concomitant confounder morbidities. Moreover, we have shown the positive effect of CPAP intervention on echocardiographic parameters. These observations highlight the value of CPAP

Table 4. Effect of Continuous Positive Airway Pressure Therapy on Left Ventricular Structural Parameters in Obstructive Sleep Apnea Patients

	Before CPAP	After CPAP	P Value
n	37	37	
IVSd, cm	1.1±0.2	0.99±0.2	<0.0001
LVPW, cm	1.2±0.2	1.1±0.2	0.02
LV mass index, g/m ²	127±34	125±47	0.831

CPAP indicates continuous positive airway pressure; IVSd, interventricular septal thickness in diastole; LVPWd, posterior wall thickness in diastole; LV, left ventricle.

Values are mean±SD. $P<0.05$ considered statistically significant.

Table 5. Left Ventricular Systolic Function Parameters (Cross-Sectional Comparison)

	OSA (n=40)	Hypertension (n=40)	Healthy (n=40)	P Value
M-Mode				
LVEDV, mL	112.5±37.08	104.3±30.38	111.8±35.80	0.49
LVESV, mL	42±20.22	34.8±16.08	36.7±17.14	0.17
LVEF, %	64.1±7.84	67.4±8.52	67.4±9.8	0.15
2D				
LVEDV, mL	88±24	81±20†	93±26†	0.05
LVESV, mL	30.6±13.04	28.4±12	34.4±14.13	0.11
LVEF, %	65.9±9.61	65.8±8.92	64±7.77	0.55
TDI				
S velocity	6±1*	6±1†	7±1†	<0.0001
3D				
LVEDV, mL	84±25	88±23	84±24	0.78
LVESV, mL	29±11	29±10	29±11	0.98
LVEF, %	66±8	67±7	66±7	0.58

Values are mean±SD. $P<0.05$ considered statistically significant.

OSA indicates obstructive sleep apnea; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; 2D, 2-dimensional echocardiography; TDI, tissue Doppler imaging; 3D, 3-dimensional echocardiography.

*Statistical significance lies between OSA and healthy subjects.

†Statistical significance lies between hypertensive and healthy subjects.

therapy on cardiovascular structure and function in OSA patients.

Previous studies that did not fully control for confounding variables suggested that OSA is associated with changes in cardiac structure and function.^{18,19} For example, Usui et al²⁰

Table 6. Effect of Continuous Positive Airway Pressure Therapy on Left Ventricular Systolic Function Parameters in Obstructive Sleep Apnea Patients

	Before CPAP (n = 37)	After CPAP (n = 37)	P Value
M-Mode			
LVEDV, mL	114±34	136±40	<0.0001
LVESV, mL	43±18	37±18	0.08
LVEF, %	64±7	74±8	<0.0001
2D			
LVEDV, mL	89±25	91±27	0.64
LVESV, mL	32±13	28±12	0.09
LVEF, %	65±9	70±7	0.007
TDI			
S velocity	6±1	7±1	0.01
3D			
LVEDV, mL	86±25	93±27	0.05
LVESV, mL	30±11	30±12	0.88
LVEF, %	66±8	71±9	0.02

Values are mean±SD. $P<0.05$ considered statistically significant.

CPAP indicates continuous positive airway pressure; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; 2D, 2-dimensional echocardiography; TDI, tissue Doppler imaging; 3D, 3-dimensional echocardiography.

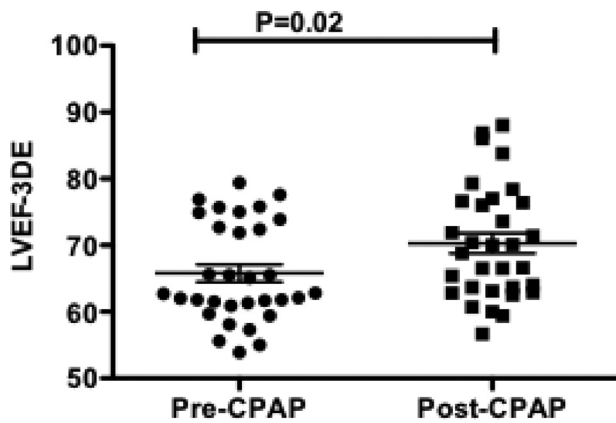


Figure 2. Comparison of left ventricular ejection fraction by real-time 3-dimensional echocardiography in obstructive sleep apnea patients before and after continuous positive airway pressure therapy. LVEF indicates left ventricular ejection fraction; 3DE, 3-dimensional echocardiography; and CPAP, continuous positive airway pressure.

reported that OSA was associated with an increased prevalence of LV hypertrophy in patients with nonischemic dilated cardiomyopathy. Our finding of increased posterior wall thickness and LV mass index extends these findings by showing early structural changes are seen in OSA patients with no overt cardiovascular disease. Interestingly, we found no significant difference in the cardiac structural findings between the OSA and hypertensive groups. The reduction in LV thickness is in accord with other studies and may have long-term prognostic implications.²¹

LV Systolic Function

Our finding of preserved LV systolic remodeling parameters is consistent with other small OSA studies, although none of them used 3DE, the current gold standard technique.⁶⁻⁸ In our study, we performed 3DE to estimate LV remodeling parameters, which is known to be more accurate in patients with abnormal LV geometry, a finding expected in OSA patients.¹⁸⁻¹⁹ Moreover, many of the previous studies included OSA patients of varying severity, with confounder comorbidities being present. In 1 small technetium-99m ventriculography-based study, for example, a lower LVEF was

Table 7. Left Ventricular Diastolic Function Parameters (Cross-Sectional Comparison)

	OSA (n=40)	Hypertension (n=40)	Healthy (n=40)	P Value
E/A	1.01±0.35†	1.1±0.89*	1.5±0.45*†	<0.0001
E/E', septal	9.5±3.93	10±3.52*	8.2±2.21*	0.05
IVRT, ms	0.10±0.02†	0.10±0.03*	0.08±0.02*†	0.002
LAVI-2D, mL/m ²	28.1±9.50†	23.7±5.74*†	18.6±4.93*†	<0.0001
LAVI-3D, mL/m ²	26.3±8.04†	23.1±5.32*	18.2±4.33*†	<0.0001

Values are described as mean±SD. P<0.05 considered statistically significant. OSA indicates obstructive sleep apnea; E, mitral early inflow peak velocity; A, late inflow peak velocity; IVRT, isovolumetric relaxation time; LAVI, left atrial volume index; 2D, 2-dimensional echocardiography; 3D, 3-dimensional echocardiography.

*Statistical significance lies between hypertensive and healthy subjects.

†Statistical significance lies between OSA and healthy subjects.

Table 8. Effect of Continuous Positive Airway Pressure Therapy on Left Ventricular Diastolic Function Parameters in Obstructive Sleep Apnea Patients

	Before CPAP	After CPAP	P Value
n	37	37	
E/A	1.0±0.4	1.4±0.4	<0.0001
E/E', septal	9±4	8±2	0.02
IVRT, ms	0.09±0.02	0.07±0.02	<0.0001
LAVI-2D, mL/m ²	28±9	23±6	<0.0001
LAVI-3D, mL/m ²	26±8	22±7	<0.0001

CPAP indicates continuous positive airway pressure; E, mitral early inflow peak velocity; A, late inflow peak velocity; IVRT, isovolumetric relaxation time; LAVI, left atrial volume index; 2D, 2-dimensional echocardiography; 3D, 3-dimensional echocardiography.

demonstrated in the OSA population (53±7%) compared with healthy subjects (61±6%).⁸ In obese OSA patients, technetium-99m radionuclide ventriculography could have serious limitations that are more exaggerated because of variable soft tissue attenuation. In the present study, we also found reduced mitral annular S velocity in the OSA and hypertensive groups, suggesting that as seen in hypertension, the longitudinal systolic function is much affected earlier than other systolic parameters in OSA. There were also significant improvements in LVEF and the S velocity on TDI after CPAP treatment, consistent with other small studies that were based on older echocardiographic assessment techniques.^{8-9,11-12,22}

The exact mechanisms by which CPAP improves LV systolic function are unclear. By reducing the blood pressure, hypoxia, rapid intrathoracic pressure changes, and secondary hemodynamic disturbances, CPAP treatment may have a positive impact on LV systolic remodeling parameters.²³ Improvement in subendocardial ischemia and enhanced oxy-hemoglobin levels could also have important roles to play in improving LV hemodynamics and systolic function.²⁴

LV Diastolic Function

Our study has shown deranged indices of acute diastolic function in moderate to severe OSA and hypertension pa-

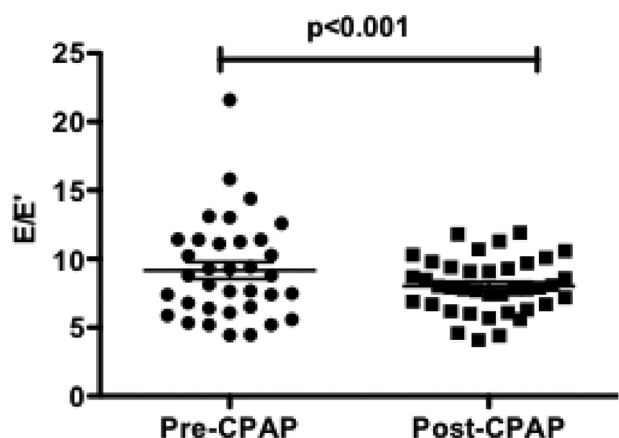


Figure 3. Comparison of E/E' (representing left ventricular filling pressure) in obstructive sleep apnea patients before and after continuous positive airway pressure therapy. CPAP indicates continuous positive airways pressure.

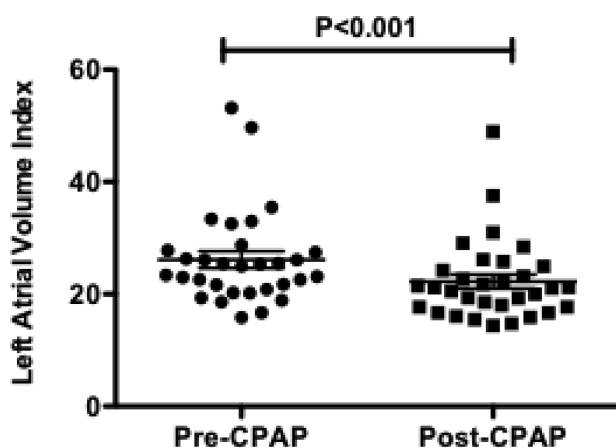


Figure 4. Comparison of left atrial volume index in obstructive sleep apnea patients before and after continuous positive airway pressure therapy. CPAP indicates continuous positive airways pressure.

tients compared with healthy subjects, with the indices being comparable between the OSA and hypertensive cohorts. These findings are consistent with other studies,^{7,25} although Niroumand et al²⁶ found conflicting results perhaps due to patients in their study having milder OSA.

LAVI has been considered as the “morphophysiological expression” of chronic diastolic dysfunction, reflecting the duration and the severity of increased LA pressure. We found a greater LAVI, both on 2DE and 3DE in the OSA group, which is in accord with some limited studies.^{27–28} An enlarged left atrium is an independent risk factor for atrial fibrillation and other cardiovascular events such as heart failure and mortality.^{29–31} Therefore, the enlarged LAVI could explain high prevalence of AF in the OSA population that has been previously recognized.

Due to previously demonstrated age-related LA remodeling, abnormal flow dynamics and impaired early diastolic filling, we recruited middle-aged, sex- and BMI-matched multi-ethnic population to avoid these biases. Moreover, the LAVI was estimated using 3DE in our study, which provides more accurate (taking into account that LA can enlarge eccentrically) and possibly quicker results as compared with 2DE techniques.³²

CPAP therapy resulted in improvement of both acute as well as chronic diastolic function parameters, consistent with other studies.^{9–10,27} The potential mechanisms leading to abnormalities of diastolic function and their improvement after CPAP therapy remain to be established. Endothelial dysfunction, surges in blood pressure, hypoxia, and hypercapnia with over activation of sympathetic system and increased preload by intermittent negative intrathoracic pressure all contribute to the development of diastolic dysfunction in OSA,^{33–36} and the correction of some or all of these may account for reversal of LV diastolic dysfunction parameters seen in the OSA group after CPAP treatment.

Effect of CPAP Treatment on Blood Pressure

An elevated blood pressure is a common sequelae of OSA and has been confirmed both in epidemiological and hospital-based studies.^{37–39} This is independent of obesity and the

other common risk factors for hypertension that are seen in OSA patients. In a landmark randomized, control trial, Pepperell et al⁴⁰ have shown that therapeutic CPAP reduces mean arterial ambulatory blood pressure by 2.5 mm Hg. This benefit was demonstrated both in both systolic and diastolic blood pressure and during both sleep and wake periods. Of note, only a very small subset of patients in their study had preexisting hypertension or were receiving antihypertensive medications, the blood pressure lowering was greater in patients with more severe sleep apnea and was independent of the baseline blood pressure. Furthermore, the blood pressure fall with CPAP was consistent above and below the median of the baseline blood pressures studied.⁴⁰ Thus, Pepperell et al⁴⁰ concluded that CPAP corrects the sleep apnea effect which is seen equally in patients with elevated or normal blood pressure.

Our study confirms and extends the interpretation of the findings by Pepperell et al.⁴⁰ In our study—to avoid the confounding effect of hypertension—we excluded OSA patients with diagnosed hypertension or on antihypertensive treatment. We recorded a significant effect of CPAP treatment on both systolic as well as diastolic blood pressure. From previous large, prospective studies, such a significant fall in blood pressure would be expected to be associated with a significant reduction in stroke and coronary artery disease risk.⁴¹

Limitations

Our study was unblinded and therefore observer bias cannot be fully excluded. The OSA group had patients with higher BMI albeit insignificant compared with the other disease and healthy control groups, which may be of some relevance. Indeed, obesity is implicated in the development of LV diastolic dysfunction,⁴² but recent work confirms our observations that impact of OSA on LV remodeling is beyond obesity per se.²⁸ Another limitation of our study is that despite using strict inclusion/exclusion criteria, the mean systolic blood pressure in the OSA group was 141 mm Hg. The study protocol did not mandate use of 24-hour ambulatory blood pressure monitoring, and we relied on multiple prior blood pressure recordings (in community, home readings, and specialized clinics) to exclude masked hypertension (or white coat hypertension) in the OSA and normal control groups as per current existing United Kingdom clinical practice. Therefore, the chance of OSA and normal control subjects having masked hypertension is small but cannot be excluded altogether. Last, significant improvement in systolic and diastolic blood pressure was observed in the OSA group after CPAP therapy that may have partly contributed to favorable LV remodeling changes.

On multivariable linear regression analyses, the improvement in blood pressure did not predict improvement in LV parameters, although a trend for improvement was observed for change in the Epworth score after CPAP treatment. Moreover, as none of the subjects in the OSA group received antihypertensive therapy during the study period, favorable LV remodeling changes could only be due to CPAP (irrespective of the mechanism) treatment, which confirms our hypothesis that the abnormal LV changes respond to CPAP treatment. Due to the sample size, evaluation of other

demographics and anthropomorphic factors (such as age, BMI, and sex) was not performed on multivariate linear regression analyses as it would have caused overfitting in the model. Due to very short interval of the CPAP trial, changes in these parameters are likely to be negligible and should have no major effect on our study results and interpretation.

Conclusions

Moderate to severe OSA causes structural and functional changes in LV function on echocardiography comparable to that seen in hypertension, with both acute and chronic LV diastolic dysfunction parameters impaired. A marked improvement was observed in both parameters, associated with concurrent drop in systolic and diastolic arterial blood pressure after 6 months of CPAP use. This may imply that OSA could be crucial in development of LV diastolic dysfunction that may lead to heart failure and increased mortality if left untreated. Further large prospective studies including 24-hour ambulatory blood pressure monitoring would be needed to explore this hypothesis and the precise mechanism(s) of LV function improvement.

Sources of Funding

This study was supported by a Phillip Poole-Wilson seed corn fund grant from the BUPA Foundation, UK. Funding for the Sonovue contrast was provided by Bracco Research SA, Switzerland.

Disclosures

None.

References

- Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;154:1217–1239.
- Butt M, Dwivedi G, Khair O, Lip GY. Obstructive sleep apnea and cardiovascular disease. *Int J Cardiol*. 2010;139:7–16.
- Leung RS, Bradley TD. Sleep apnea and cardiovascular disease. *Am J Respir Crit Care Med*. 2001;164:2147–2165.
- 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.
- Malone S, Liu P, Holloway R, Bradley TD. Obstructive sleep apnea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. *Lancet*. 1991;338:1480–1484.
- Kim SH, Cho GY, Shin C, Lim HE, Kim YH, Song WH, Shim WJ, Ahn JC. Impact of obstructive sleep apnea on left ventricular diastolic function. *Am J Cardiol*. 2008;101:1663–1668.
- Kraiczi H, Caidahl K, Samuelsson A, Peker Y, Hedner J. Impairment of vascular endothelial function and left ventricular filling. *Chest*. 2001;119:1085–1091.
- Alchanatis M, Tourkhoriti G, Kosmas EN, Panoutsopoulos G, Kakouros S, Papadima K, Gaga M, Jordanoglou JB. Evidence for left ventricular dysfunction in patients with obstructive sleep apnea syndrome. *Eur Respir J*. 2002;20:1239–1245.
- Akar Bayram N, Ciftci B, Durmaz T, Keles T, Yeter E, Akcay M, Bozkurt E. Effects of continuous positive airway pressure therapy on left ventricular function assessed by tissue Doppler imaging in patients with obstructive sleep apnea syndrome. *Eur J Echocardiogr*. 2009;10:376–382.
- Alchanatis M, Paradellis G, Pini H, Tourkhoriti G, Jordanoglou J. Left ventricular function in patients with obstructive sleep apnea syndrome before and after treatment with nasal continuous positive airway pressure. *Respiration*. 2000;67:367–371.
- Bellone A, Etteri M, Vettorello M, Berruti V, Maino C, Mariani M, Clerici D, Nessi I, Gini G, Natalizi A, Brunati P. The effects of continuous positive airway pressure on plasma brain natriuretic peptide concentrations in patients presenting with acute cardiogenic pulmonary edema with preserved left ventricular systolic function. *Am J Emerg Med*. 2010;28:230–234.
- Haruki N, Takeuchi M, Kanazawa Y, Tsubota N, Shintome R, Nakai H, Lang RM, Otsuji Y. Continuous positive airway pressure ameliorates sleep-induced subclinical left ventricular systolic dysfunction: demonstration by two-dimensional speckle-tracking echocardiography. *Eur J Echocardiogr*. 2010;11:352–358.
- Shantsila A, Dwivedi G, Shantsila E, Butt M, Beevers DG, Lip GY. Persistent macrovascular and microvascular dysfunction in patients with malignant hypertension. *Hypertension*. 2011;57:490–496.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
- Quiñones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA; Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002;15:167–184.
- Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107–133.
- Poutanen T, Jokinen E, Sairanen H, Tikanoja T. Left atrial and left ventricular function in healthy children and young adults assessed by three dimensional echocardiography. *Heart*. 2003;89:544–549.
- Shivalkar B, Van de Heyning C, Kerremans M, Rinkevich D, Verbracken J, De Backer W, Vrints C. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. *J Am Coll Cardiol*. 2006;47:1433–1439.
- Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnea. *J Hypertens*. 1990;8:941–946.
- Usui K, Parker JD, Newton GE, Floras JS, Ryan CM, Bradley TD. Left ventricular structural adaptations to obstructive sleep apnea in dilated cardiomyopathy. *Am J Respir Crit Care Med*. 2006;173:1170–1175.
- Moro JA, Almenar L, Fernández-Fabrellas E, Ponce S, Blanquer R, Salvador A. Hypertension and sleep apnea–hypopnea syndrome: changes in echocardiographic abnormalities depending on the presence of hypertension and treatment with CPAP. *Sleep Med*. 2009;10:344–335.
- Bendjelid K, Schütz N, Suter PM, Fournier G, Jacques D, Fareh S, Romand JA. Does continuous positive airway pressure by face mask improve patients with acute cardiogenic pulmonary edema due to left ventricular diastolic dysfunction? *Chest*. 2005;127:1053–1058.
- Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA*. 1996;275:1557–1562.
- Scharf SM. Effects of continuous positive airway pressure on cardiac output in experimental heart failure. *Sleep*. 1996;19(Suppl 10):S240–S242.
- Fung JW, Li TS, Choy DK, Yip GW, Ko FW, Sanderson JE, Hui DS. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *Chest*. 2002;121:422–429.
- 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.
- Oliveira W, Campos O, Cintra F, Matos L, Vieira ML, Rollim B, Fujita L, Tufik S, Poyares D. Impact of continuous positive airway pressure treatment on left atrial volume and function in patients with obstructive sleep apnea assessed by real-time three-dimensional echocardiography. *Heart*. 2009;95:1872–1878.
- Otto ME, Belohlavek M, Romero-Corral A, Gami AS, Gilman G, Svaticova A, Amin RS, Lopez-Jimenez F, Khandheria BK, Somers VK. Comparison of cardiac structural and functional changes in obese oth-

- erwise healthy adults with versus without obstructive sleep apnea. *Am J Cardiol.* 2007;99:1298–1302.
29. Parkash R, Green MS, Kerr CR, Connolly SJ, Klein GJ, Sheldon R, Talajic M, Dorian P, Humphries KH. Canadian Registry of Atrial Fibrillation: the association of left atrial size and occurrence of atrial fibrillation; a prospective cohort study from the Canadian Registry of Atrial Fibrillation. *Am Heart J.* 2004;148:649–654.
 30. Pritchett AM, Jacobsen SJ, Mahoney DW, Rodeheffer RJ, Bailey KR, Redfield MM. Left atrial volume as an index of left atrial size: a population-based study. *J Am Coll Cardiol.* 2003;41:1036–1043.
 31. Takemoto Y, Barnes ME, Seward JB, Lester SJ, Appleton CA, Gersh BJ, Bailey KR, Tsang TS. Usefulness of left atrial volume in predicting first congestive heart failure in patients ≥ 65 years of age with well-preserved left ventricular systolic function. *Am J Cardiol.* 2005;96:832–836.
 32. Artang R, Migrino RQ, Harmann L, Bowers M, Woods TD. Left atrial volume measurement with automated border detection by 3-dimensional echocardiography: comparison with magnetic resonance imaging. *Cardiovasc Ultrasound.* 2009;7:16.
 33. Carlson JT, Hedner J, Elam M, Ejjnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest.* 1993;103:1763–1768.
 34. Hall MJ, Ando S, Floras JS, Bradley TD. Magnitude and time course of hemodynamic responses to Mueller maneuvers in patients with congestive heart failure. *J Appl Physiol.* 1998;85:1476–1484.
 35. Leuenberger U, Jacob E, Sweer L, Waravdekar N, Zwillich C, Sinoway L. Surges of muscle sympathetic nerve activity during obstructive apnea are linked to hypoxemia. *J Appl Physiol.* 1995;79:581–588.
 36. Schulz R, Schmidt D, Blum A, Lopes-Ribeiro X, Lücke C, Mayer K, Olschewski H, Seeger W, Grimminger F. Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnea: response to CPAP therapy. *Thorax.* 2000;55:1046–1051.
 37. 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.
 38. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study: Sleep Heart Health Study. *JAMA.* 2000;283:1829–1836.
 39. Davies CW, Crosby JH, Mullins RL, Barbour C, Davies RJ, Stradling JR. Case-control study of 24 hour ambulatory blood pressure in patients with obstructive sleep apnea and normal matched control subjects. *Thorax.* 2000;55:736–740.
 40. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, Mullins R, Jenkinson C, Stradling JR, Davies RJ. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnea: a randomised parallel trial. *Lancet.* 2002;359:204–210.
 41. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease, part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet.* 1990;335:765–774.
 42. Mureddu GF, de Simone G, Greco R, Rosato GF, Contaldo F. Left ventricular filling pattern in uncomplicated obesity. *Am J Cardiol.* 1996;77:509–514.

CLINICAL PERSPECTIVE

Structural and functional abnormalities in otherwise healthy patients with obstructive sleep apnea may contribute to their cardiovascular morbidity. Previous small studies in obstructive sleep apnea were limited by other comorbidities that confound assessment of cardiac structure and function. Continuous positive airway pressure therapy may benefit cardiac structure and function in such patients. In the present study, we demonstrate that otherwise healthy moderate to severe obstructive sleep apnea patients have structural and functional changes in left ventricular function on echocardiography comparable to that seen in overt hypertension. These abnormalities were significantly improved after continuous positive airway pressure therapy. Such improvement in left ventricular function would be expected to be associated with a significant reduction in stroke and coronary artery disease risk.

Left Ventricular Systolic and Diastolic Function in Obstructive Sleep Apnea: Impact of Continuous Positive Airway Pressure Therapy

Mehmood Butt, Girish Dwivedi, Alena Shantsila, Omer A. Khair and Gregory Y.H. Lip

Circ Heart Fail. 2012;5:226-233; originally published online March 13, 2012;

doi: 10.1161/CIRCHEARTFAILURE.111.964106

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2012 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circheartfailure.ahajournals.org/content/5/2/226>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Heart Failure* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation: Heart Failure* is online at:
<http://circheartfailure.ahajournals.org/subscriptions/>