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Obstructive Sleep Apnea Syndrome

More Insights on Structural and Functional Cardiac Alterations, and the Effects of Treatment With Continuous Positive Airway Pressure

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OBJECTIVES We studied structural and functional cardiac alterations in obstructive sleep apnea (OSA), their relationship to the severity of OSA, and the effects of treatment with continuous positive airway pressure (CPAP).

BACKGROUND Obstructive sleep apnea may influence the cardiac function by several mechanisms in the awake patient.

METHODS Left and right ventricular morphology and function were studied using echocardiography before and after treatment with CPAP in symptomatic patients (Epworth sleepiness score, 10 ± 4.8) with severe OSA (apnea-hypopnea index [AHI], 42 ± 24). The patients (n = 43, 32 men) had no known cardiac disease and were obese (body mass index, 31.6 ± 5.4 kg/m^2). The same echocardiographic parameters were studied in age-matched overweight patients (n = 40; body mass index, 26.4 ± 2.3 kg/m^2).

RESULTS The patients were hypertensive (systolic blood pressure, 153 ± 25 mm Hg), with a higher resting heart rate (77 ± 10 beats/min, p = 0.008) compared with age-matched control patients (n = 40). There was right ventricular dilatation, hypertrophic interventricular septum, reduced left ventricular stroke volume, tissue Doppler-determined systolic and diastolic velocities of the left and right ventricle, and normal pulmonary artery pressure. The structural and functional parameters were significantly associated with AHI ($p < 0.004$). Multiple stepwise regression showed the interventricular septum thickness, right ventricular free wall, and mitral annulus tissue Doppler systolic velocities to be predictive of a higher AHI ($p < 0.001$). Six months after treatment with CPAP, significant improvements were observed in the symptoms and hemodynamics, as well as left and right ventricular morphology and function.

CONCLUSIONS The structural and functional consequences of OSA on the heart are influenced by the severity of AHI. These effects are reversible if the apneic episodes are abolished. (J Am Coll Cardiol 2006;47:1433–9) © 2006 by the American College of Cardiology Foundation

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder associated with increased risk of cardiovascular disease. The OSA syndrome is characterized by repeated partial or complete closure of the pharynx, gasping episodes, sleep fragmentation, and daytime sleepiness (1). The physiologic consequences of these episodes are repetitive bursts of sympathetic activity, hypoxia, hypercapnia, increased left ventricular afterload, and acute hypertension (2).

It was commonly thought to affect obese middle-aged men (3), but it seems that one-third of the patients are women (2,4). Also, obesity is not a prerequisite, especially in older patients (5) or in those from Southeast Asia (6).

The association of OSA and heart failure is already known (7–9). Recently OSA has been recognized as an independent risk factor for hypertension, and to impose several adverse effects on the heart and cardiovascular system (10). Also, a large proportion (40% to 80%) of stroke patients have OSA, suggesting that it may increase the stroke risk beyond direct effects on blood pressure level and variability (11,12). Furthermore, episodes of nocturnal ischemia, increased incidence of sudden death during sleeping hours, early morning acute coronary events, and increased prevalence of arrhythmias in association with OSA have also been reported (13–17).

Clinical management of OSA patients is primarily done by sleep physicians with a background in respiratory medicine or neurology. Atypical presentations may, however, be common, and patients may remain asymptomatic from apneas, presenting instead with hypertension, arrhythmias, or congestive cardiac failure to a cardiologist (18). Established definitions of OSA are based on respiratory and neurophysiologic parameters; however, recent data show that cardiovascular consequences may be more important. Additional, technically simple diagnostic approaches involving study of cardiovascular structural and functional param-

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Abbreviations and Acronyms

AHI = apnea-hypopnea index
BMI = body mass index
CPAP = continuous positive airway pressure
EEG = electroencephalogram
ESS = Epworth sleepiness scale
OSA = obstructive sleep apnea

eters could therefore be useful. Left ventricular hypertrophy with systolic and diastolic dysfunction have been reported (19,20), however, there are few and inconsistent data on structural and functional changes of the right heart. It seems feasible that both left and right ventricles could be affected by the effects of hypoxia and the increased sympathetic drive.

We hypothesized that left and right ventricular morphology and function are affected by the effects of obstructive apnea. We further sought to assess the relationship of possible structural and functional alterations to the severity of obstructive apneas, and observed the effects of treatment with continuous positive airway pressure (CPAP) after six months on these parameters.

METHODS

Patients. Forty-three (32 male) consecutively eligible patients between the ages of 29 and 77 years (mean, 55.2 ± 11.6 years) were included in the study. All patients had a history of snoring, a variable degree of daytime sleepiness, were without evidence of cardiac problems, and were generally in good health (see Table 1 for patient characteristics). Obstructive sleep apnea was confirmed by polysomnography. A physical examination and electrocardiogram were performed, as well as complete two-dimensional and Doppler echocardiography. All patients completed a questionnaire to assess the Epworth sleepiness scale (ESS) (18), which is a rapid, validated method for screening of daytime sleepiness and is useful both in clinical practice and in research settings. Informed consent was obtained from all patients, and the study was approved by the institutional ethical committee. Patients were reassessed after 6 months of CPAP treatment given via nasal mask.

Polysomnography. A full polysomnography was performed in all patients. Electrodes for electroencephalogram (EEG) registration were applied according to standard criteria, using frontal, central, and occipital head electrodes with reference electrodes at the mastoids. Central EEG (C4-A1/C3-A2), frontal EEG (C4-F4), and occipital EEG (A1-O2) recordings were obtained. Electro-oculogram electrodes were placed at the outer canthi of the orbits, and an electromyelogram was measured using thermocouples at the nose and mouth. Ribcage and abdominal movements were analyzed by respiratory inductance plethysmography. Oxygen saturation was measured by pulse oximeter (Ohmeda Biox, Louisville, Colorado). Sleep stages were recorded according to the classic Rechtschaffen and Kales criteria (21). Data were analyzed with a semi-automatic system (Oxford Medilog SAC, Oxford Instruments, Oxford, United Kingdom), allowing visual scoring in addition. Apnea was defined as interruption of the oronasal airflow. Hypopnea was defined as a reduction in airflow with a 50% reduction in thoracic and abdominal efforts for at least 10 s, and a 3% drop in oxygen saturation from the preceding stable saturation, and/or arousal. Apnea-hypopnea index (AHI) was the sum of the number of apneas and hypopneas per hour of sleep. Pulmonary function tests were obtained with the patients in a standing position and breathing room air. Forced spirometry was obtained using a pneumotacho-

Table 1. Clinical Characteristics and Baseline Echocardiographic Data

	Patients (n = 43)	Control Patients (n = 40)
Age (yrs), male/female	55 ± 11, 32/11	50 ± 16, 28/12
Body mass index (kg/m^2)	31.6 ± 5.4	26.4 ± 2.3 ($p < 0.001$)
Heart rate (beats/min)	77 ± 10	68 ± 6 ($p = 0.008$)
Systolic/diastolic blood pressure (mm Hg)	153 ± 25/88 ± 17	132 ± 10/78 ± 8 ($p < 0.01$)
Smoking	12/43 (28%)	—
Arterial hypertension	22/43 (51%)	—
Diabetes mellitus	2/43 (0.05%)	—
Chronic obstructive pulmonary disease	—	—
Cardiac disease	—	—
Right ventricle dimension (cm)	3.3 ± 0.43	2.6 ± 0.51 ($p < 0.001$)
Left ventricular ejection fraction, %	62 ± 9	68 ± 5 ($p = 0.012$)
Stroke volume (ml)	66 ± 16	72 ± 12 ($p = 0.008$)
Performance index (left ventricle)	0.31 ± 0.06	0.24 ± 0.03 ($p = 0.005$)
Performance index (right ventricle)	0.29 ± 0.05	0.25 ± 0.03 ($p = 0.008$)
Isovolumic relaxation time (ms)	88 ± 10	74 ± 8 ($p = 0.001$)
Interventricular septum thickness (cm)	1.32 ± 0.11	0.94 ± 0.18 ($p < 0.001$)
Pulmonary artery pressure (mm Hg)	32 ± 10	22 ± 8 ($p = 0.004$)
Mitral annular Sm (cm/s)	8.3 ± 1.7	9.9 ± 1.6 ($p = 0.001$)
Tricuspid annular Sm (cm/s)	13.4 ± 2.1	15.2 ± 2.2 ($p = 0.004$)
Right ventricle Sm (cm/s)	11.4 ± 2.3	13.5 ± 1.8 ($p < 0.001$)

Sm = systolic tissue Doppler velocity.

graph (Alveo-Diffusiontest, Jaeger, Würzburg, Germany). Lung volumes and resistance were determined using body plethysmography (Bodytest, Jaeger). Arterial blood gases were processed immediately in an analyzer.

Echocardiography. All imaging was performed using Sonos 5500 (Philips, Eindhoven, the Netherlands). A standard two-dimensional and Doppler echocardiographic study was performed. Left ventricular ejection fraction was determined in M-mode (Teicholz) at the parasternal short axis. Left ventricular hypertrophy was defined as interventricular septum thickness of ≥1.3 cm. Mitral and tricuspid valve inflow velocities were measured (early rapid filling wave, E; late filling wave, A), as well as deceleration time (mitral valve), isovolumic relaxation time for the left ventricle, and pulmonary vein signals. Pulsed wave tissue Doppler systolic and diastolic (early; late) velocities (unit, cm/s) were obtained from the mitral valve annulus, tricuspid valve annulus, and right ventricular free wall. Gain settings were adjusted carefully, and the direction of motion was aligned with the scan line direction. Signals were obtained from three end expiratory cycles, and averages were made for the systolic and diastolic velocities. Tissue Doppler velocities offer a robust and sensitive assessment of the regional systolic and diastolic function. Because tissue Doppler velocities vary between the left and right heart, and according to age, the systolic and diastolic velocities were compared with those of age-matched control patients. We also assessed the left and right ventricular performance index, which conceptually combines the systolic and the diastolic function and is determined by the ratio of the sum of the isovolumic times divided by the ejection time.

Control patients. Forty healthy age- and gender-matched patients were recruited after informed consent (age range, 26 to 70 years; 28 men). A complete medical history was obtained, and a physical examination and echocardiographic study were performed. Patients were all lifelong nonsmokers without evidence of obstructive pulmonary disease. None had arterial hypertension, diabetes, or hyperlipidemia; had no family history of premature vascular disease; nor took regular medications. There was no polysomnography performed, but the ESS was 0 in all.

Statistical analysis. All data are expressed as mean ± SD. Linear regressions were performed to assess eventual relationships between the various structural, functional, and hemodynamic parameters measured. Stepwise multiple regression was performed to determine whether severity of obstructive apneas could predict changes in structural or functional parameters. Paired Student *t* test was used to compare differences between OSA patients before and after treatment with CPAP. Unpaired or two-sample independent groups *t* test was used to compare differences between OSA patients and control patients. A p value of <0.05 was considered a significant difference. All statistical calculations were performed using Statview 5+ (SAS Institute Inc., Cary, North Carolina).

RESULTS

The clinical characteristics and other data are presented in Table 1. The patients had significant levels of daytime sleepiness (ESS, 10.5 ± 4.6 with a maximum possible score of 24) and severe OSA (AHI, 42 ± 24). The lung function tests did not show obstructive pulmonary disease. The patients were obese, with significantly higher resting heart rate and blood pressure compared with control patients. There were clear morphologic differences in the right and left ventricle between patients and control patients. The right ventricle was dilated and the interventricular septum was thicker compared with control patients ($p < 0.001$). Only 2 of 43 patients had signs of left ventricular hypertrophy on the electrocardiogram. There was no further evidence of ischemia or arrhythmia on the daytime electrocardiogram.

Functional data showed significantly lower left ventricular ejection fraction and stroke volume, as well as lower tissue Doppler-determined systolic and diastolic velocities for the left and right heart in patients compared with control patients (Table 1). The right and left ventricular performance was significantly reduced compared with control patients, and the systolic pulmonary artery pressure was borderline normal (32 ± 10 mm Hg). The arterial blood gas analysis showed normal daytime oxygen saturation (92 ± 4%), with the minimal nighttime oxygen saturations (76 ± 6%) being well below the accepted value of 88%.

We found higher AHI to be strongly associated with increased right ventricular dimension ($r = 0.482$, $p = 0.0009$) and thicker interventricular septum ($r = 0.49$, $p = 0.0009$). Regarding functional parameters, a higher AHI correlated significantly with reduced tissue Doppler-derived velocities measured at the mitral annulus, tricuspid annulus, and right ventricular free wall, as well as lower stroke volume (Fig. 1). A weaker correlation was found with ESS, which reflects complaints of daytime sleepiness of the patient ($r = 0.23$, $p = 0.08$). In the stepwise multiple regression performed using AHI as the independent variable, interventricular septum thickness, right ventricular free wall, and mitral annulus tissue Doppler velocities were the only parameters retained, showing the most significant association with AHI ($p < 0.001$).

Twenty-five of the original 43 patients were evaluated after 6 months of treatment with CPAP (administered during 6.8 h at night). The remaining patients did not follow the treatment plan for various reasons. At 6 months after treatment with CPAP, there was significant reduction in the daytime sleepiness of the patients (ESS = 5.3 ± 4.0, $p = 0.0012$) and improvements in hemodynamic, structural, and functional parameters measured (Table 2, Fig. 2). The changes in tissue Doppler-derived diastolic velocities and the performance indices, however, did not reach significance, because improvement was not invariably observed in all patients.

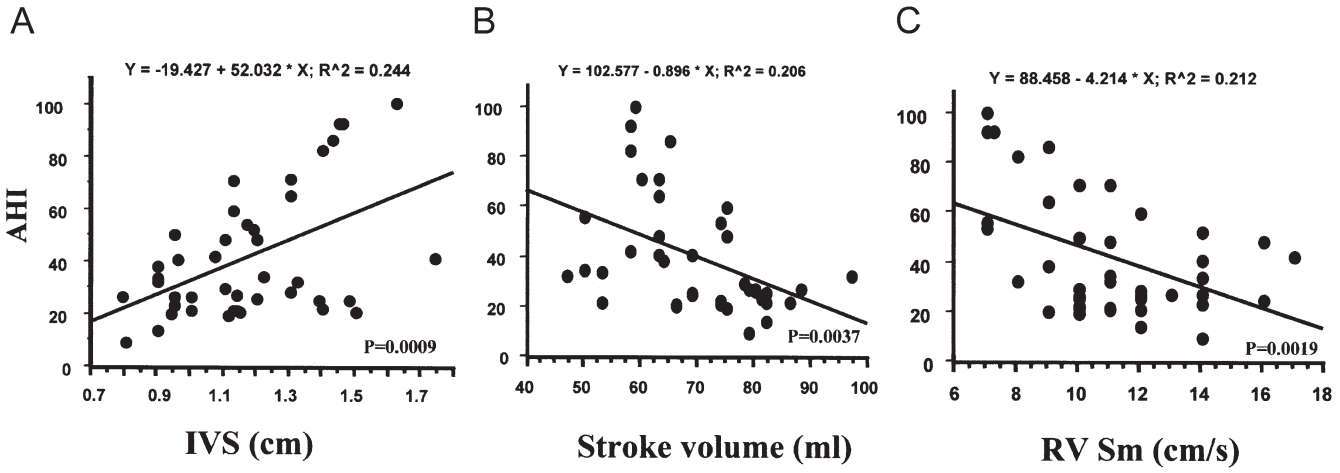

Figure 1. (A) Correlation between apnea-hypopnea index (AHI) and interventricular septum thickness (IVS). **(B)** Correlation between apnea-hypopnea index and left ventricle stroke volume (SV). **(C)** Correlation between apnea-hypopnea index and right ventricular (RV) free wall tissue Doppler systolic velocities (RV Sm).

DISCUSSION

Obstructive sleep apnea is an underdiagnosed and undertreated problem with important cardiovascular consequences. A better understanding and diagnosis of the cardiovascular consequences and improved awareness of physicians is required, but remains a challenge. The pathophysiological effects of obstructive apnea on the cardiovascular system involve complex mechanical, hemodynamic, neurohumoral, and inflammatory mechanisms (2).

We evaluated patients with severe OSA who were obese, had symptoms of daytime sleepiness, had no known cardiac or obstructive pulmonary disease, had daytime hypertension, and had an increased resting heart rate. There is not only increased sympathetic activity during and in the immediate post-apneic periods, but also the daytime sympathetic nervous activity is increased two-fold (15). The association between OSA with occurrence of daytime hypertension (22,23) and loss of nocturnal blood pressure dip (24) is known. Prospective confirmation of the association was reported in the Wisconsin Sleep Cohort Study, in which AHI was a significant independent predictor of daytime hypertension (25). The implications of this study are profound, indicating OSA as a new primary cause of hypertension and the necessity for increased physician awareness.

In our study we found structural and functional cardiac alterations with right ventricular dilatation, left ventricular hypertrophy, and reduced function of both. During apnea the futile inspiratory efforts against the occluded pharynx causes abrupt reductions in the intrathoracic pressure, with enhancement of the venous return, distension of the right ventricle, and leftward shift of the interventricular septum causing a reduced filling of the left ventricle (26,27). There is nocturnal pulmonary hypertension in virtually all patients with OSA (28). These are cyclic increases, associated with apneic episodes and increased right ventricular dimensions. The multiple mechanisms that mediate the nocturnal increase in pulmonary artery pressure include alterations in blood gases, cardiac output, lung volume, intrathoracic pressure, compliance of the pulmonary circulation, and left ventricular diastolic dysfunction (28). There are also early cineradiographic studies in humans and dogs that showed increased right heart size during the apneic episodes (29). In awake patients, right ventricle dilatation, hypertrophy, and dysfunction was usually associated with concomitant lung disease and overt right

Table 2. Patient Data Before and Six Months After Treatment With Continuous Positive Airway Pressure (CPAP)

	Baseline	After CPAP
Heart rate (beats/min)	73 ± 11	67 ± 10 ($p = 0.02$)
Stroke volume (ml)	64 ± 10	71 ± 11 ($p = 0.0037$)
Systolic/diastolic blood pressure (mm Hg)	159 ± 27/92 ± 18	138 ± 28/80 ± 20 ($p < 0.03$)
Pulmonary artery pressure (mm Hg)	32 ± 11	27 ± 9 ($p = 0.009$)
Interventricular septum thickness (cm)	1.32 ± 0.23	0.99 ± 0.21 ($p = 0.001$)
Right ventricle dimension (cm)	3.5 ± 0.45	3.1 ± 0.5 ($p = 0.0014$)
Performance index (right ventricle)	0.30 ± 0.1	0.28 ± 0.15 (p = ns)
Mitral annular Sm (cm/s)	7.9 ± 1.5	8.8 ± 1.0 ($p = 0.0015$)
Tricuspid annular Sm (cm/s)	12.7 ± 1.9	13.9 ± 2.1 ($p = 0.008$)
Right ventricle free wall Sm (cm/s)	10.9 ± 2.1	12.2 ± 1.8 ($p = 0.001$)
Epworth sleepiness score	10.0 ± 4.8	5.3 ± 4.0 ($p < 0.0001$)

Sm = systolic tissue Doppler velocity.

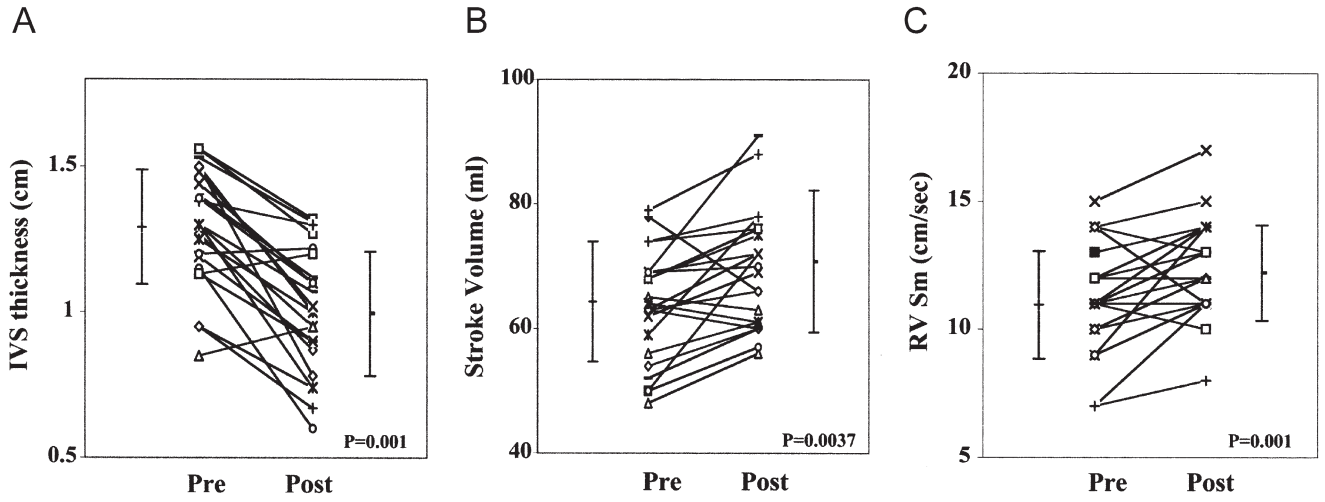

Figure 2. **(A)** Changes in interventricular septum thickness (IVS) before and six months after continuous positive airway pressure treatment. **(B)** Left ventricular stroke volume before and six months after continuous positive airway pressure treatment. **(C)** Right ventricular tissue Doppler systolic velocity (RV Sm) before and six months after continuous positive airway pressure treatment.

heart failure (30,31). However, in the absence of pulmonary disease, radionuclide ventriculography studies of the right ventricle have shown association of reduced right ventricular function with hypercapnia while awake or AHI >40 (32), or sympathetic hyperactivity that is typical of OSA (33). In our patients without evidence of clinically overt right heart failure, associated pulmonary disease, or awake hypercapnia, the right ventricle was dilated with reduced tissue Doppler-determined systolic and diastolic velocities, and we found a significant association between these parameters and the AHI.

Systemic hypertension is the most common risk factor for cardiac hypertrophy and failure in longitudinal studies, and left ventricular hypertrophy is more closely linked to hypertension during sleep than during wakefulness (34). The higher nocturnal blood pressure experienced in hypertensive patients with OSA than in those without may place them at a greater risk for left ventricular hypertrophy (35). We found a highly significant correlation between the interventricular septum thickness and AHI (Fig. 1). The increase in transmural left ventricular pressure (difference between intracardiac and intrathoracic pressure), hence afterload, during OSA episodes, in combination with the reduced filling of the left ventricle, causes a reduction in the stroke volume (2). The stroke volume in our patients was reduced, and once again a significant association was found with the AHI (Fig. 1). The most direct mechanism by which OSA might compromise left ventricular systolic function is through its effect on blood pressure. All left ventricular functional indices (ejection fraction, tissue Doppler systolic velocities, performance index) measured in our patients were reduced. The left and right ventricular diastolic function was invariably altered in all patients.

Data on the coexistence of and association of pulmonary hypertension in OSA are inconsistent (36,37), and little is known of the prognostic implications of pulmonary hypertension in OSA. Alterations of humoral factors (natriuretic peptides, nitric oxide, endothelin) (38–40) and individual predisposition to different remodeling responses of the pulmonary circulation to hypoxia have been implicated. Severe impairment of pulmonary hemodynamics occurs in patients with concomitant lung disease and morbid obesity (31,36,41). Pulmonary hypertension at rest is present in fewer than half of OSA patients, being mild in most cases (41), and right ventricular functional abnormalities are thought to be partly independent of the coexistence of diurnal pulmonary hypertension (33). The daytime oxygen saturation was normal in our patients, and there was no evidence for obstructive lung disease. The pulmonary pressures were borderline normal and showed no significant relationship with AHI. There was, however, consistent right ventricular dilatation and dysfunction in accordance with the severity of the apneas. There was significant improvement in these parameters after treatment with CPAP, providing support for the hypothesis that right ventricular dysfunction may be at least partly independent of pulmonary hypertension and may be a consequence of sympathetic hyperactivity and hemodynamic perturbations related to OSA (33).

The structural and functional involvement of the left and right ventricle without the simultaneous occurrence of significant pulmonary hypertension in patients with OSA could likely be a consequence of the state of hypoxia, increased sympathetic drive, increased oxygen demand, and the mechanical and hemodynamic perturbations. We found a clear relationship between severity of the apneic episodes and these changes. Six months after CPAP treatment, we found consistent improvement in structural and contractile parameters (Table 2, Fig. 2) of both ventricles. The body mass index (BMI) of the patients and the initial treatment strategies remained unchanged. The observed improvements are therefore most likely associated with treatment

with CPAP, which abolishes the apneic episodes and reduces the sympathetic activity. Treatment with CPAP is analogous to the effects of chronic beta-blockade in heart failure. It is, however, achieved nonpharmacologically by reducing the oxygen demand, increasing the oxygen supply, and altering the central sympathetic outflow (2). The CPAP also improves the quality of sleep, decreases daytime sleepiness, and augments neurocognitive function (2). The ESS was clearly improved in our patients. At six months after treatment, changes in the diastolic velocities were variable, with significant improvement in younger patients and variable improvement in older patients. It is possible that improvement in diastolic function requires time (more than six months), or that the presence of other confounding variables (older age, other comorbidity) remains problematic.

To conclude, we present a study showing structural and functional changes of the left and right ventricles that are closely associated with the severity of obstructive apnea, and show significant improvements at 6 months after treatment with CPAP. Cardiovascular physicians could easily use such noninvasive, quantitative, and technically simple methodology to assess cardiac alterations that may, without treatment, have profound cardiovascular consequences for their patients.

Study limitations. We did not have BMI-matched control patients. It is, however, difficult to find healthy, obese, middle-aged patients without the presence of comorbidities (hypertension, metabolic syndrome, diabetes, and so on), which act as confounding factors and would potentially influence all measurements performed in our study. The control patients were age-matched and overweight, with a mean BMI of 26.4 kg/m^2. Furthermore, after 6 months of treatment with CPAP, we found significant improvements in a number of the measured parameters when the BMI and initial treatment strategies remained unchanged. Therefore, to some degree the changes observed in the study seem to be independent of the BMI. Further, the study is small and nonrandomized. There are, however, no large-scale studies involving long-term assessment of cardiovascular alterations before and after various treatment modalities. Also, randomized trials are a difficult issue because of the ethical considerations in withholding CPAP for prolonged periods from control groups.

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REFERENCES

1. The report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–89.
2. Bradley TD, Floras JS. Sleep apnea and heart failure part I: obstructive sleep apnea. Circulation 2003;107:1671–8.
3. Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea and oxygen desaturation in normal subjects: a strong male predominance. N Engl J Med 1979;300:513–7.
4. Edwards N, Wilcox I, Sullivan CE. Sleep apnea in women. Thorax 1998;53 Suppl 3:S12–5.
5. Newman AB, Nieto FJ, Guidry U. Relationship of sleep-disordered breathing to cardiovascular disease risk factors: sleep heart health study. Am J Epidemiol 2001;154:50–9.
6. Ip MS, Lam B, Lauder IJ. A community study of sleep disordered breathing in middle aged Chinese men in Hong Kong. Chest 2001;119: 62–9.
7. Sin DD, Fitzgerald F, Parker JD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999;160:1101–6.
8. Javaheri S, Parker TJ, Liming JD. Sleep apnea in 81 ambulatory male patients with stable heart failure: types and their prevalences, consequences, and presentations. Circulation 1998;97:2154–9.
9. Shahar E, Whitney CW, Redline S. Sleep-disordered breathing and cardiovascular disease: cross sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163:19–25.
10. A Report of the National Commission on Sleep Disorders Research. Wake Up America. A National Sleep Alert. Washington, DC: U.S. Government Printing Office, 1995.
11. Partinen M, Palomaki H. Snoring and cerebral infarction. Lancet 1985;2:1325–6.
12. Hu FB, Willett WC, Manson JE. Snoring and risk of cardiovascular disease in women. J Am Coll Cardiol 2000;35:308–13.
13. Franklin KA, Nilsson JB, Sahlin C, Naslund U. Sleep apnea and nocturnal angina. Lancet 1995;345:1085–7.
14. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005;352: 1206–14.
15. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993;103:1763–8.
16. Hoffstein V, Mateika S. Cardiac arrhythmias, deep snoring and sleep apnea. Chest 1994;106:466–71.
17. Javaheri S. Effects of continuous positive airway pressure on sleep apnea and ventricular irritability in patients with heart failure. Circulation 2000;101:392–7.
18. Lattimore JDL, Celemajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003;41:1429–37.
19. Laaban JP, Pascal-Sebaoun S, Bloch E, Orvoen-Frija E, Oppert JM, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnea syndrome. Chest 2002;122:1133–8.
20. Fung JW, Li TS, Choy DK. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. Chest 2002;121: 422–9.
21. Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring for Sleep Stages of Human Subjects. Los Angeles, CA: Brain Information Service/Brain Research Institute, University of California (UCLA), 1968.
22. Worsnop CJ, Naughton MT, Barter CE, Morgan TO, Anderson AI, Pierce RJ. The prevalence of obstructive sleep apnea in hypertensives. Am J Respir Crit Care Med 1998;157:111–5.
23. Wilcox I, Grunstein RR, Collins FL, Doyle JM, Kelly DT, Sullivan CE. Circadian rhythm of blood pressure in patients with obstructive sleep apnea. Blood Press 1992;1:219–22.
24. Nieto FJ, Young TB, Lind BK. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community based study. Sleep Heart Health Study. JAMA 2000;283:1829–36.
25. Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342:1378–84.
26. Bradley TD, Hall MJ, Ando S. Hemodynamic effects of simulated obstructive apneas in humans with and without heart failure. Chest 2001;119:1827–35.
27. Brinker JA, Weiss JL, Lappe DL. Leftward septal displacement during right ventricular loading in man. Circulation 1980;61:626–33.

28. Young T, Javaheri S. Systemic and pulmonary hypertension. In: Principles and Practice of Sleep Medicine. New York, NY: Elsevier, 2005:1198–202.
29. Tarasluk A, Scharf SM. Cardiovascular effects of periodic obstructive and central apneas in dogs. Am J Respir Crit Care Med 1994;150: 83–9.
30. Bradley TD, Rutherford A, Grossman RF, et al. Role of daytime hypoxia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. Am Rev Respir Dis 1985;131:835–9.
31. Fletcher EC, Schaaf JW, Miller J, Fletcher JC. Long-term cardiopulmonary sequelae in patients with sleep apnea and chronic lung disease. Am Rev Respir Dis 1987;135:525–33.
32. Nahmias J, Lao R, Karetzky M. Right ventricular dysfunction in obstructive sleep apnea: reversal with nasal continuous positive airway pressure. Eur Respir J 1996;9:945–51.
33. Sanner BM, Konermann M, Sturm A, Muller HJ, Zidek W. Right ventricular dysfunction in patients with obstructive sleep apnea syndrome. Eur Respir J 1997;10:945–51.
34. Verdecchia P, Schillaci G, Guerrieri P. Circadian blood pressure changes and left ventricular hypertrophy in essential hypertension. Circulation 1990;81:528–36.
35. Portaluppi F, Provini F, Cortelli P. Undiagnosed sleep-disordered breathing among male nondippers with essential hypertension. J Hypertens 1997;15:1227–33.
36. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1988;138:345–9.
37. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1994;149:416–22.
38. Kita H, Ohi M, Chin K, et al. The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnea and its response to therapy with nasal continuous positive airway pressure. J Sleep Res 1998;7:199–207.
39. Schultz R, Schmidt D, Blum A, et al. Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnea: response to CPAP therapy. Thorax 2000;55:1046–51.
40. Grimpen F, Kanne P, Schultz E, Hagenah G, Hasenfuss G, Andreas S. Endothelin-I plasma levels are not elevated in patients with obstructive sleep apnea. Eur Respir J 2000;15:320–5.
41. Chaouat A, Weitzenblum E, Krieger J, Oswald M, Kessler R. Pulmonary hemodynamics in obstructive sleep apnea syndrome. Chest 1996;109:380–6.