Impairment of Vascular Endothelial Function and Left Ventricular Filling* 
Association With the Severity of Apnea-Induced Hypoxemia During Sleep

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**Study objective:** To investigate whether a dose-effect relationship exists between the severity of obstructive sleep apnea (OSA) and subclinical indicators of myocardial or vascular dysfunction.

**Design:** Cross-sectional study using correlation analysis.

**Participants:** Twenty subjects referred to our sleep laboratory for screening or therapy of OSA but without regular medication and without known cardiovascular disease.

**Measurements:** Severity of OSA was quantified by polysomnography. Moreover, nocturnal excretion of norepinephrine was determined. Left ventricular (LV) myocardial function was assessed with Doppler echocardiography. Using ultrasonographic measurements, endothelium-dependent and endothelium-independent conduit artery dilation were measured as flow-mediated and glyceryltrinitrate-induced changes in brachial artery diameter.

**Results:** Worsening nocturnal hypoxemia, measured as nocturnal oxygen saturation nadir or percentage of sleep time spent in hypoxemia (< 90% hemoglobin oxygen saturation), predicted increased interventricular septum thickness (corrected for age and body mass index), prolonged isovolumetric relaxation time, decreased ratio between peak early and late mitral flow velocities, as well as reduced endothelium-dependent dilatory capacity of the brachial artery (all relationships corrected for cofactor age and with p < 0.05) were observed. Associations between these cardiovascular function markers and nocturnal excretion of norepinephrine followed the same trend, but relations with interventricular septum thickness and flow-mediated artery dilation missed significance (p = 0.064 and p = 0.061, respectively). LV posterior wall thickness, measures of LV systolic function, early mitral flow deceleration time, and endothelium-independent artery dilation were not significantly related to the degree of nocturnal hypoxemia or norepinephrine excretion. None of the correlations with apnea-hypopnea index were statistically significant.

**Conclusions:** The severity of apnea-related hypoxemia is associated with a gradual deterioration of LV diastolic function as well as large-artery endothelial function. (CHEST 2001; 119:1085–1091)

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Obstructive sleep apnea (OSA) is associated with nocturnal intermittent hypoxia, repetitive activation of the sympathetic nervous system, as well as fluctuations in cardiac output and total peripheral resistance resulting in apnea-related BP oscillations. These phenomena have been suggested as important factors behind the increased prevalence of hypertension and the overall excess cardiovascular risk in OSA. However, if OSA is assumed to play a causal part in the development of hypertension or heart disease, subclinical indicators of myocardial or vascular dysfunction before the emergence of clinical signs of cardiovascular disease might be expected in otherwise healthy subjects with OSA. Moreover, a dose-effect relationship between the degree of apnea-related pathophysiologic and gradual aberrations of respective cardiovascular function markers should be detectable.

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In order to investigate this hypothesis, we included subjects referred to our sleep laboratory for screening or therapy of OSA but without history of diseases directly or indirectly affecting the cardiovascular system and without regular medication. Although functional aberrations clearly indicative of clinical heart or vascular disease may be uncommon in a study sample selected so restrictively, we expected a gradual impairment of cardiovascular function with increasing apnea-hypopnea index (AHI), worsening hypoxemia, or higher activity of the sympathetic nervous system during sleep. Consequently, correlation analysis was used to investigate the association between OSA severity and nocturnal excretion of norepinephrine (NE) on the one side, and echocardiographic measures of left ventricular (LV) myocardial function, as well as endothelium-dependent and independent responsiveness of the brachial artery on the other side. In addition to our narrow inclusion criteria, we made corrections for effects of confounding factors expected to influence respective relationships.

**Materials and Methods**

**Patients**

All male nonsmokers without regular medication and without history of diseases known to affect the cardiovascular system were selected from a total of 81 subjects consecutively referred to the Sleep Laboratory of the Pulmonary Department of Sahlgrenska University Hospital, Gothenburg, Sweden, for either implementation of nasal continuous positive airway pressure therapy or diagnostic sleep apnea screening. None of the participants received continuous positive airway pressure therapy before or during the study. Moreover, we excluded subjects with a fasting plasma triglyceride concentration of \( \geq 4 \) mmol/L or a total cholesterol concentration of \( \geq 8 \) mmol/L. The study was approved by the Ethics Committee of the Medical Faculty of Gothenburg University.

**Sleep Studies**

All participants reported to the sleep laboratory at approximately 8:30 PM, after a light dinner. Thereafter, intake of food or beverages except water was not permitted until blood sampling the next morning. Polysomnography was initiated at approximately 10:30 PM, after a routine medical examination. Ventilatory monitoring included recording of oronasal airflow (Easyflow; EPM Systems; Midlothian, VA), hemoglobin oxygen (HbO\(_2\)) saturation by pulse oximetry (Ohmeda Biox 3700; Ohmeda; Louisville, CO), respiratory movements of chest and abdomen (Resp-EZ; EPM Systems), and body position. Total sleep time (total time spent in sleep stage 1 through stage 4 or rapid eye movement sleep) was obtained from concomitant recordings of ECG (T3-A2), two electro-oculograms, and submental electromyogram (Oxford Medilog System; Oxford, UK). Apneas and hypopneas were defined as episodes lasting at least 10 s with airflow cessation or reductions of the thermistor signal amplitude by at least 50%, respectively. Desaturations or arousals were not considered mandatory for an event to be scored as apnea or hypopnea (see practice parameters outlined by the American Sleep Disorders Association for more recently established clinical criteria for the diagnosis of OSA). The sum of apneas and hypopneas was divided by the total sleep time to obtain the AHI. Hypoxic exposure during sleep was quantified by two different variables. First, a measure of maximal severity of hypoxemia was obtained by averaging the nadir HbO\(_2\) saturations associated with the five severest desaturations during sleep (SATMIN). Averaging was done to increase the robustness of this measure. Secondly, the percentage of total sleep time associated with HbO\(_2\) saturation of \( \leq 90\% \) (HYPOX\(_\%\)) was calculated as a measure of hypoxemia duration. Arousal index was not measured in this study.

**Sampling of Urine and Blood**

Urine collection began immediately before onset of polysomnography, after subjects had voided, and included all urine passed overnight as well as the first morning void. Urine was sampled in 2-L canisters containing 8 mL of 5 M hydrochloric acid. After measurement of urine volume, samples were immediately sent to the hospital laboratory for analysis of NE and creatinine using high-performance liquid chromatography with fluorescence detection and photometry, respectively. NE excretion was expressed as the ratio of NE/creatinine concentrations in the urine sample (mol/mol).

Blood samples for analysis of plasma concentrations of total cholesterol and triglycerides were obtained at wake-up time (6:20 AM) and processed at the hospital laboratory according to routine procedures.

**Anthropomorphic Measures**

Body weight and height were averaged from measurements obtained during polysomnography and sonography visits. Weight (calibrated balances) and height were measured in indoor clothing and without shoes. Body mass index (BMI) was calculated as weight (in kilograms) divided by squared height (in meters).

**BP Measurement and Echocardiography**

The investigators measuring BP and performing echocardiography (K.C. and A.S.) were not aware of the polysomnography results. Supine systolic and diastolic BPs were measured after at least 10 min of undisturbed rest with the cuff method before the beginning of sonographic investigations. Mean BP was computed as diastolic BP + (1/3) × (systolic BP − diastolic BP).

During echocardiographic examinations, subjects rested in the left lateral position. M-mode, two-dimensional, and Doppler echocardiography were performed with an Acuson-128 sonograph (Acuson Computed Sonography; Mountain View, CA), equipped with a 2.0-MHz or 3.5-MHz transducer. Timing of the cardiac cycle was documented by simultaneous recording of the ECG. Valvular abnormalities and regional wall motion disturbances were ruled out in standard parasternal and apical projections.

M-mode measurements of interventricular septum thickness (IVSD) in diastole and LV posterior wall thickness (PWD) in diastole were made from the parasternal short-axis view, in accordance with recommendations of the American Society of Echocardiography. LV systolic function was assessed by fractional shortening (FS) obtained from M-mode recordings of LV systolic and diastolic dimensions as well as by the ejection fraction (EF) estimated from two-dimensional recordings with a modification of Simpson’s rule.
LV diastolic function was assessed by pulsed Doppler echocardiography, which has been validated against radionuclide and contrast angiography. Transmission was observed at the apical view, with the sample volume placed at the level of the mitral valve leaflet tips and the cursor oriented parallel to an imaginary line bisecting the left ventricle from apex to mitral valve. The position of the sample volume was adjusted to obtain a mitral inflow pattern with maximum laminar flow. Variables used to describe LV filling included the ratio between peak early and late LV filling velocities (E/A ratio) and deceleration time (DT), a measure of the rate of deceleration of early diastolic inflow. Isovolumetric relaxation time (IRT) was obtained from M-mode recordings (100 mm/s) and defined as the time between aortic valve closure and mitral valve opening. Each parameter was measured at end expiration and averaged over five consecutive analyzable cardiac cycles.

Brachial Artery Responsiveness

Endothelium-dependent and endothelium-independent reactivity of the brachial artery was assessed according to the method described by Celermajer et al.9 Investigations were performed with subjects in the supine position, using a high-resolution ultrasonographic scanner (Acuson Computed Sonography) equipped with a 7.5-MHz linear-array transducer. The brachial artery was scanned over a longitudinal section 3 cm to 5 cm above the antecubital fossa. When an adequate image was obtained, both arm and probe were secured in position throughout the study using a stereotactic clamp. Arterial diameter was measured at rest, after reactive hyperemia (with increased flow causing endothelium-dependent vasodilation, see below), again at rest, and finally after sublingual administration of glyceryl trinitrate (GTN; an endothelium-independent vasodilator).9 Postischemic artery diameter was recorded at 1 min after rapid deflation of a BP cuff that was held inflated around the forearm with a pressure of 250 mm Hg for 4.5 min. After subsequent 10 min, the second baseline measurement was obtained; GTN, 0.5 mg sublingual, was administered; and, after an additional 4.5 min, a final brachial artery diameter was measured.

Ultrasound images were recorded on videotape, digitized by a high-resolution frame grabber, and stored on a computer. Off-line measurements were performed using dedicated software, averaging the arterial diameter along a 10-mm artery segment. Diameters obtained from five consecutive end-diastolic frames (identified by the ECG R wave) were averaged to yield the brachial artery diameter during respective experimental stages. Flow-mediated artery dilations (FMDs) and GTN-induced dilations were obtained as percentage changes from the preischemia and GTN baselines, respectively.

Data Analysis

Linear relationships between measures of OSA severity (AHI, SATMIN, HYPOX%), NE excretion, and cardiovascular variables were quantified by correlation analysis. Because all variables involved were continuously distributed, this approach may be more efficient in detecting relationships than between-groups comparisons; consequently, our final sample of 20 subjects was expected to be sufficiently sized. Based on a significance level of 0.05 and a sample size of n = 18, a linear association accounting for 35% of the variance of the response variable can be detected with a test power of approximately 80%. All relationships were controlled for the influence of the cofactor age in the sample.9;19

<table>
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<th>Variables</th>
<th>Patients, No.</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>SD</th>
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<td>AHI, events/h</td>
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<td>Age, yr</td>
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<td>65.5</td>
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<td>BMI, kg/m²</td>
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<td>196.6</td>
<td>144.0</td>
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HYPOX% was log normalized before correlation analysis. Correlations involving IVSD or PWD were further controlled for variation in BMI.10;11 Because of skewed distributions, AHI and HYPOX% were log normalized before correlation analysis. Correlation-wise p values < 0.05 were considered statistically significant.

**Table 1—Description of Study Sample**

**Table 2—Correlations (p Values) Between Measures of OSA Severity and Nocturnal NE Secretion**
RESULTS

Sample Characteristics

Characteristics of the study sample are outlined in Table 1. Correlations between measures of OSA severity as well as NE excretion are described in Table 2. While the two measures of hypoxemia were found to be highly redundant ($R^2 = 93.7\%$), their variance explained only between 48.8\% and 67.7\% of the variance in AHI and nocturnal NE excretion. AHI was significantly related to BMI ($r = 0.509$, $p = 0.022$) whereas all remaining correlations between AHI, SATMIN, HYPOX%, or NE excretion on the one side, and age, BMI, serum cholesterol or triglycerides, diastolic or systolic BPs, heart rate, or baseline brachial artery diameter on the other side were not statistically significant (correlations not shown).

Echocardiography

After correction for age and BMI, only SATMIN and HYPOX% were significantly correlated with IVSD. The relationship between NE excretion and IVSD was nearly significant (Table 3). Further corrections for mean BP had only negligible effects on these relationships or their significance levels (data not shown). Sample correlations between OSA severity and PWD were of similar direction but weaker and not statistically significant (correlations not shown).

Systolic cardiac function, measured by M-mode-derived FS as well as two-dimensional-derived EF and corrected for age in both cases, was not significantly related to OSA severity. Despite lacking significance, however, the signs of each of the eight sample correlations (Table 3) invariably indicated reduced function with increasing OSA severity. Diastolic cardiac function, when expressed as IRT or E/A ratio and corrected for age, deteriorated with increasing severity of nocturnal hypoxemia (measured with SATMIN or HYPOX%) and NE excretion. Corresponding correlation coefficients (Table 3) were not importantly changed by further correction for heart rate. (The correlation between HYPOX% and E/A ratio declined [to $r = -0.465$, $p = 0.052$] after controlling for both age and heart rate. All other relationships remained significant.) DT followed the same trend as IRT and E/A ratio, but was not significantly related to the severity of nocturnal hypoxemia or NE excretion. Moreover, although some reduction of diastolic function with increased AHI was indicated by the corresponding sample correlations, none of these relationships were significant.

Brachial Artery Function

FMD was inversely and significantly correlated with the degree of nocturnal hypoxemia. Relationships with AHI and NE excretion followed the same trend but were not significant (Table 3). Further corrections of these relationships for BMI, mean BP, plasma cholesterol, triglycerides, or baseline inner diameter of the brachial artery resulted in negligible changes of the respective correlation coefficients and their p values (not shown). In contrast to the post-ischemic dilatory response, GTN-induced artery dilation did not consistently change in relation with OSA severity or NE excretion.

DISCUSSION

The results of the current study suggest that the severity of apnea-induced HbO$_2$ desaturations in OSA is associated with a gradual but significant tendency toward reduced LV diastolic function and toward an impaired endothelium-dependent dilatory capacity of conduit arteries. Considering the relatively small sample size of the present study, narrow sampling criteria providing a relatively homogeneous study group as well as statistical control of the remaining influence of confounding variables may have enabled sufficient power required to demonstrate subclinical deterioration of cardiovascular function with increasing severity of intermittent nocturnal hypoxemia.
As expected, AHI, SATMIN, HYPOX%, and NE excretion were considerably interrelated in the present study. Consequently, our results do not allow conclusions about the differential contributions of apnea-induced hypoxemia, apneas/hypopneas per se, and nocturnal sympathetic activation to the observed relationships between OSA severity and degree of cardiovascular dysfunction. Moreover, because no arousal index was measured in the current study, the explanatory ability of sleep fragmentation could not be evaluated. However, each of the functional measures significantly related with OSA severity in this study (ie, IVSD, IRT, E/A ratio, and FMD) were more strongly correlated with SATMIN or HYPOX% than with AHI. With one exception (the relatively strong correlation between NE excretion and IRT), superiority of the hypoxemia measures to predict the degree of cardiovascular dysfunction was also seen in comparison with NE excretion. This observation supports findings in patients with isolated diastolic heart failure suggesting a specific relationship between the lowest nocturnal HbO2 saturation, but not AHI, and the extent of diastolic dysfunction. Moreover, animal experiments have shown that long-term intermittent hypoxia in the absence of upper-airway obstructions may modify cardiac size as well as dynamic and steady-state saturation, but not AHI, and the extent of diastolic dysfunction.20 Moreover, animal experiments have shown that long-term intermittent hypoxia in the absence of upper-airway obstructions may modify cardiac size as well as dynamic and steady-state regulation of BP.21–24 As a consequence, intermittent nocturnal hypoxemia in OSA may exert an important biological stimulus to long-term cardiac and artery function, although more longitudinal studies may be required to support this hypothesis. Unfortunately, extrapolation of results from studies on acute or chronic sustained hypoxia to the situation with chronic apnea-related desaturations may not be helpful in this context, because chronic intermittent hypoxia appears to exert a unique effect on cardiovascular homeostasis.21,22,24 Consequently, the mechanisms behind the current findings may require separate investigation.

The relationship between sleep-disordered breathing and LV muscle thickness is still a matter of debate. In a previous study,25 from our group, LV size was increased in OSA patients when compared with age-matched and BMI-matched control subjects, and these changes were independent of resting daytime BP. Comparing two groups with low and high apnea indexes, respectively, another study found a higher prevalence of LV hypertrophy in subjects with more severe sleep apnea and a significant correlation between OSA severity and LV mass. Two studies, one comparing OSA patients with control subjects matched for age, sex, BMI, smoking, as well as alcohol intake, and one comparing snorers with and without sleep apnea, found no relationship between the presence of OSA and LV muscle thickness. In the current investigation, narrower inclusion criteria may have been one factor enabling the detection of a relationship between the degree of nocturnal hypoxemia and IVSD, because cardiac muscle size is influenced by a variety of covariables potentially increasing unexplained variability in more heterogeneous clinical populations.29 However, the absence of a significant relationship between OSA severity and PWD in the current study may illustrate the difficulty to find a consistent association between sleep-disordered breathing and cardiac muscle size. Alternatively, correlation of IVSD but not PWD with the degree of nocturnal hypoxemia may be the result of hypoxemia being related to isolated septal growth. This hypothesis is supported by studies linking septal hypertrophy with a hyperdynamic circulation because of increased sympathetic activity, which is a central characteristic of OSA.20–22 However, studies addressing possible mechanisms behind the permanent overactivity of the sympathetic nervous system in OSA, such as apnea-induced HbO2 desaturations and sleep fragmentation, may be required to elucidate the role of sympathetic overactivity as a promoter of cardiac septal growth in OSA. Moreover, other pathologic mechanisms associated with disturbed breathing during sleep, such as apnea-related increases in afterload and leftwards shifts of the interventricular septum, as well as effects of intermittent hypoxia not mediated by the sympathetic nervous system, may promote septal growth, if persistently present over a longer period of time.

In patients with symptomatic diastolic heart failure, lower E/A ratio and prolonged IRT, both reflecting more severe diastolic dysfunction, are linked to the minimum nocturnal HbO2 saturation induced by sleep apnea.20 Similar results were obtained in the present group of subjects without known heart disease. Although no cause-effect relationships can be derived from these observations, it may be hypothesized that nocturnal HbO2 desaturations result in a deterioration of resting LV function during daytime steady-state conditions. This interpretation is also supported by studies reporting improved global systolic function in patients with congestive heart failure after treatment with continuous positive airway pressure or in patients with OSA after uvulopalatopharyngoplasty.40 Nevertheless, one comparative study using less stringent inclusion criteria (only patients with history of myocardial infarction or daytime hypoxemia or hypercapnia were excluded) than the present investigation was not able to provide evidence for an association between cardiac function and sleep-disordered breathing. As discussed for the relationship between cardiac size and OSA, one explanation for this discrepancy might be that the influence of OSA or its pathophysio
consequences on cardiac function may depend on the composition of the population under consideration. As a consequence, more data identifying clinically important modulators of long-term cardiac function in OSA will be required to solve this problem.

Endothelial function in forearm resistance vessels has been shown to be impaired in OSA patients when compared with healthy subjects. These results are corroborated by the finding of the current study suggesting that flow-mediated dilation in large arteries gradually deteriorates with increasing degree of nocturnal hypoxemia, whereas GTN-induced vasodilation appears unrelated to the severity of desaturations during sleep. Because flow-mediated vascular dilation depends on a high extent on the endothelial generation of nitric oxide while GTN-induced dilation primarily reflects endothelium-independent dilatory function, our findings suggest that the nitric oxide-dependent dilatory capacity of the arterial wall decreases with intensifying apnea-induced hypoxemia. Although this association may reflect a direct or indirect effect of chronic sleep-related intermittent hypoxia on vascular nitric oxide synthesis or degradation, no experimental data on permanent endothelial effects of long-term intermittent hypoxia are, to our knowledge, available to support this hypothesis.

Cofactors potentially relevant for the development of endothelial dysfunction in clinical OSA populations include smoking, hypertension, and hypercholesterolemia. In the current study, however, subjects with a history of any of these factors were excluded. Statistical control of remaining variability in BP or plasma lipid concentrations had no effect on the relationship between nocturnal hypoxemia and FMD. Therefore, it may be concluded that nocturnal hypoxemia may be an independent predictor of impaired endothelial function in OSA. Moreover, because reduced flow-induced brachial artery dilation has been suggested as an early event in the development of atherosclerosis, it may be speculated that endothelial dysfunction is a physiologic or epidemiologic cofactor behind the excess cardiovascular risk in OSA. In conclusion, the severity of apnea-related desaturations in an otherwise healthy population may be associated with subclinical deterioration of cardiovascular function. The prognostic significance of these changes requires further study.

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