Blood pressure, cardiac structure and severity of obstructive sleep apnea in a sleep clinic population

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Objectives **We investigated whether the severity of obstructive sleep apnea (OSA) predicts blood pressure or cardiac left ventricular thickness in a clinical population of OSA patients, if adjustments are made for age, gender, use of antihypertensive agents, smoking, body mass index, history of coronary artery disease, hypercholesterolemia and circulating C-peptide concentrations.**

Design **Relationships in this cross-sectional study were investigated with correlation analysis and multiple regression procedures.**

Patients and methods **Apnea–hypopnea index (AHI, polysomnography) and office systolic and diastolic blood pressures (SBP and DBP) were measured in 81 subjects referred to a university hospital sleep laboratory. Ambulatory blood pressures were recorded during one 24 h cycle. Left ventricular (LV) muscle size was quantified as two-dimensionally directed M-mode-derived end-diastolic thickness of interventricular septum and posterior chamber wall.**

Results **After adjustment for separate or the entire set of covariates, AHI predicted office SBP and DBP as well as daytime ambulatory DBP and night-time ambulatory SBP and DBP, but not daytime ambulatory SBP. In contrast, associations between AHI and LV muscle thickness reflected complex inter-relationships with confounding variables. Smoking and age suppressed, whereas body mass index (BMI) and hypertension inflated the relationship between OSA severity and LV muscle thickness in this study.**

Conclusions **AHI is an independent predictor of several measures of blood pressure. OSA severity and LV muscle thickness appear to be primarily linked via increased blood pressure. *J Hypertens* 19:2071–2078 © 2001 Lippincott Williams & Wilkins.**

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Introduction

Obstructive sleep apnea (OSA) has been hypothesized to cause sustained hypertension [1–3] and cardiac hypertrophy [4–6]. However, inconsistent data resulted from clinic-based studies designed to detect relationships between OSA severity and blood pressure [7–13] or left ventricular (LV) muscle size [14–15] after adjustments for covarying factors, such as age, gender, body mass index (BMI) or use of antihypertensive medication. Thus, it remains uncertain whether the severity of OSA is independently associated with blood pressure and LV muscle thickness in clinical OSA populations characterized by excess comorbidity.

In the current study, we investigated whether office systolic and diastolic blood pressures (SBP and DBP), ambulatory daytime and night-time SBP and DBP as well as echocardiographic measures of LV muscle thickness in sleep-clinic patients are predictable from the severity of OSA as measured by the apnea–hypopnea index (AHI) and the nocturnal oxygen saturation nadir (SATMIN). To reach sufficient study power, we analyzed linear dose–response relationships between continuous rather than categorized variables. Moreover, since age [16,17], gender [16,17], use of antihypertensive agents, smoking [17], BMI [16,17], history of coronary artery disease (CAD) [18], hypercholesterolemia [19,20] and hyperinsulinemia [21,22] may act as confounding factors in this context, we analyzed their effect on associations between OSA severity, blood pressure and LV muscle size by separately adjusting for each covariate and evaluating the significance of respective corrections. Finally, using multiple regression analysis, the marginal contributions of AHI and SATMIN to prediction of blood pressure and LV muscle thickness were evaluated after concomitant adjustment for the entire set of covariables.

Methods

Patients

The present analysis is based on a sample of 81 subjects consecutively referred to the Sleep Laboratory of the Pulmonary Department of Sahlgrenska University Hospital, Gothenburg, Sweden, for either implementation of therapy with continuous positive airway pressure (65 patients) or diagnostic sleep apnea screening (16 patients). Since consideration of patient category did not influence the statistical results, the subjects were considered an undivided sample. Inclusion criteria were willingness to participate in the study and oral informed consent to undergo all study procedures. Intake of medications as prescribed by the referring physician was not changed. 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 2030 h, after a light dinner. Thereafter, intake of food or beverages except water was not permitted until blood sampling next morning. Polysomnography was initiated at approximately 2230 h, after measurement of blood pressure and a routine medical examination. Ventilatory monitoring included recording of oronasal airflow (thermistor Easyflow^{TM}, EPM Systems, Midlothian, Virginia, USA), hemoglobin oxygen saturation by pulse oximetry (Ohmeda Biox 3700e, Louisville, Colorado, USA), respiratory movements of chest and abdomen (Resp-EZ^{TM}, EPM Systems), and body position. Total sleep time (total time spent in sleep stages one to four or rapid eye movement sleep) was obtained from concomitant recordings of electroencephalogram (T3-A2), two electrooculograms 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 (but see [23] 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. The lowest hemoglobin oxygen saturation during the recording (SAT-MIN, as a percentage) was obtained from a separate analysis of the oximetry record.

Blood sampling

Blood samples for analysis of serum concentrations of total cholesterol and C-peptide were obtained in the morning (0620 h), before the patient left the bed, and processed at the hospital laboratory according to routine procedures. Hypercholesterolemia was defined as regular intake of lipid-lowering drugs or a serum cholesterol concentration exceeding 6.5 mmol/l.

Anthropomorphic measures

Body weight and height were averaged from measurements obtained at polysomnography and echocardiography visits. Weight (calibrated balances) and height were measured in indoor clothing and without shoes. BMI was calculated as weight (in kg) divided by height (in m^2).

Blood pressure measurements

Diastolic and systolic blood pressures (DBP and SBP), taken after at least 10 min rest using the cuff method (Kenzomedico, Umedico AB, Stockholm, Sweden), were averaged from two measurements obtained before echocardiography (late afternoon) and in the evening (2100 h $\pm$ 1 h) before polysomnography, respectively. In order to increase generality of the regression relationships between office blood pressures and OSA severity and because the focus on the study was not on absolute blood pressure estimates, measurements were obtained in the supine position before echocardiography and in the sitting position before polysomnography. Cuff size was selected according to the weight of the subject. With the stethoscope placed at the point of maximal artery pulsation, cuff pressure was raised to approximately 30 mmHg above SBP (estimated by palpation) and thereafter reduced at 2–3 mmHg/s. SBP was marked by the point at which repetitive, clear tapping sounds first appeared for at least two consecutive beats. The point where the repetitive sounds finally disappeared (phase 5) indicated the value of DBP. In order to avoid incorrect readings, both investigators measuring blood pressure had been specifically trained by experts in the field of hypertension.

Ambulatory blood pressures were recorded within 1 week after polysomnography, during one 24 h cycle separated from the polysomnography night. Measurements were taken in the non-dominant arm at 20 min intervals using a SpaceLabs 90207 device (Redmond, Washington, USA) [24]. Patients were instructed to cease activity and to keep the measurement arm still during readings. Mean values of DBP and SBP were calculated for predefined daytime (0900–2100 h) and night-time (2330–0530 h) periods using interval-weighted measurement values [25]. At each recording, mean blood pressure (MBP) was computed from SBP and DBP as DBP + (1/3) $\times$ (SBP–DBP).

Echocardiography

The investigators performing echocardiography (K. C. and A. S.) were not aware of the polysomnography results. During echocardiographic examinations subjects rested in the left lateral position. M-mode and two-dimensional echocardiography were performed with an Acuson-128 sonograph (Acuson Computed Sonography, Mountain View, California, USA),

equipped with a 3.5 MHz transducer. Timing of the cardiac cycle was documented by simultaneous recording of the electrocardiogram. Two-dimensional sections were obtained in standard parasternal and apical directions to rule out important vascular abnormalities and regional wall disturbances as well as to guide and verify correctness of M-mode recordings [26]. Two-dimensionally directed M-mode-measurements of interventricular septum and LV posterior wall thickness in diastole (IVSD and PWD) were made from the parasternal short-axis view, in accordance with recommendations of the American Society of Echocardiography [27]. The within-observer variabilities (coefficient of variation) at our laboratory are 5.9 and 6.8% for the IVSD and PWD measurement, respectively. The corresponding between-observer variabilities are 18.6 and 16.0%.

Statistical analysis

Linear relationships between AHI and SATMIN on the one side (explanatory variables) and measures of blood pressure as well as LV muscle thickness (response variables) on the other side were first expressed with simple coefficients of correlation and their P values. With the type of variables selected for the current study, correlation analysis enables reliable inferences despite deviation of some variable distributions from normality [28]. Based on a sample size of $n = 80$ and a significance level of 0.05, a population correlation accounting for 10% or more variability of the respective response variable will give rise to a significant sample correlation with a test power of approximately 80% [29]. After analysis of uncorrected correlations, we re-evaluated all relationships by computing partial correlations separately correcting for age, gender, use of antihypertensives, smoking, BMI, CAD, hypercholesterolemia and C-peptide concentration. The potential of a covariate to change the relationship between OSA severity and blood pressure or LV muscle thickness was evaluated by comparing the uncorrected correlation with the respective part correlation after adjustment for the covariate. Hotelling's t-test was used to test whether such correction altered the relationship to a significant extent [30].

Finally, AHI or SATMIN and the entire set of covariates were concomitantly included as explanatory variables in multiple regression models with measures of blood pressure or LV muscle thickness as response variables. Thus, the additional contributions of AHI and SATMIN to blood pressure or LV muscle size prediction was evaluated after adjustment for the entire set of covariates.

Differences in means of continuously distributed variables between subject categories were compared with the t-test. All tests with correlation- or comparison-wise P values below 0.05 were considered statistically significant.

Results

Subject characteristics

The subject sample included 69 men and 12 women (85.2% men). The proportion of current smokers was 21 of 81 (25.9% smokers). A total of 34 subjects (42.0%) were treated with antihypertensive agents. Out of these, 12 subjects received monotherapy (five with a β-blocker; two with an ACE-inhibitor; four with a calcium antagonist, one with a diuretic). Seventeen subjects received a combination of two agents (three with ACE-inhibitor + diuretic; two with β-blocker + ACE-inhibitor; seven with β-blocker + diuretic; one with ACE-inhibitor + calcium antagonist; three with β-blocker + calcium anatagonist; one with calcium antagonist + diuretic). Five subjects were treated with a combination of three agents (four with β-blocker + ACE-inhibitor + diuretic and one with β-blocker + calcium antagonist + diuretic). Hypercholesterolemia was present in 23 subjects (28.4%), out of which six were treated with lipid-lowering drugs. Ten subjects were known (and treated) diabetics (12.3%) and 17 (21.0%) had a history of coronary artery disease (CAD).

Mean AHI was significantly higher in subjects taking antihypertensive agents ($48.2 \pm 34.0\ h^{-1}$ versus $30.8 \pm 26.8\ h^{-1}$ in subjects not taking antihypertensives, $P = 0.013$), in subjects with CAD history ($53.4 \pm 37.3\ h^{-1}$ versus $34.0 \pm 28.7\ h^{-1}$ in subjects without CAD, $P = 0.023$) and in subjects with hypercholesterolemia ($50.7 \pm 37.9\ h^{-1}$ versus $33.1 \pm 30.4\ h^{-1}$ in those without hypercholesterolemia, $P = 0.022$). Dichotomizations according to gender, diabetes and smoking, yielded groups with insignificantly different mean AHIs: ($40.6 \pm 32.4\ h^{-1}$ in males versus $23.8 \pm 20.6\ h^{-1}$ in females, $P = 0.087$; $35.9 \pm 30.8\ h^{-1}$ in diabetics versus $38.4 \pm 31.7\ h^{-1}$ in non-diabetics, $P = 0.811$; $42.9 \pm 27.4\ h^{-1}$ in smokers versus $36.4 \pm 32.7\ h^{-1}$ in non-smokers, $P = 0.416$). SATMIN was no significant discriminator for any of these categorizations (data not shown).

Continuously distributed characteristics of the study group are outlined in Table 1. The sample represents a wide spectrum of OSA severity, ranging from a few subjects with a small number of respiratory disturbances to patients with a severe breathing disorder during sleep. AHI and SATMIN shared $R^2 = 26.5\%$ common variance ($r = -0.551$, $P = 0.000$), indicating only partial redundancy. Correlations between age, BMI and C-peptide concentration on the one side and measures of OSA severity, blood pressure and LV muscle size on the other side are displayed in Table 2.

Table 1 **Characterization of the study sample**

	n	Mean	Median	Minimum	Maximum	SD
Age (years)	81	56.5	57.4	30.1	74.6	9.99
BMI (kg/m^2)	81	30.1	29.4	21.8	43.8	4.9
C-peptide (nmol/l)	81	0.999	0.830	0.200	4.200	0.726
AHI (per h)	81	38.1	26.4	1.5	128.0	31.4
Lowest saturation (%)	81	79.4	82.0	47.0	92.0	9.0
Office SBP (mmHg)	81	145.5	145.5	118.0	187.5	17.3
Office DBP (mmHg)	81	88.9	90.0	69.5	112.5	9.5
Mean daytime SBP (mmHg)	80	137.0	136.5	109.0	173.4	13.6
Mean daytime DBP (mmHg)	80	86.4	85.7	66.8	108.6	9.5
Mean night-time SBP (mmHg)	76	120.5	119.7	83.8	168.9	14.5
Mean night-time DBP (mmHg)	76	71.0	68.9	46.6	101.1	11.0
Interventricular septum thickness (cm)	66	1.21	1.20	0.70	2.00	0.25
Posterior wall thickness (cm)	71	1.09	1.10	0.60	1.50	0.19

Characterization of the study sample. BMI, body mass index; AHI, apnea–hypopnea index; SBP, systolic blood pressure; DBP diastolic blood pressure; SD, standard deviation.

Table 2 **Correlations between potential confounders and response variables**

	n	Age	BMI	C-peptide
AHI (per h)	81	−0.161 (0.151)	0.278 (0.012)	0.127 (0.258)
SATMIN (%)	81	0.120 (0.284)	−0.102 (0.363)	−0.063 (0.578)
Office SBP (mmHg)	81	0.304 (0.006)	0.124 (0.270)	−0.018 (0.873)
Office DBP (mmHg)	81	−0.090 (0.424)	0.312 (0.005)	0.055 (0.628)
Daytime ambulatory SBP (mmHg)	80	0.061 (0.588)	0.181 (0.107)	0.124 (0.274)
Daytime ambulatory DBP (mmHg)	80	−0.278 (0.013)	0.247 (0.027)	0.136 (0.229)
Night-time ambulatory SBP (mmHg)	76	0.253 (0.027)	0.093 (0.425)	0.128 (0.271)
Night-time ambulatory DBP (mmHg)	76	−0.032 (0.787)	0.026 (0.823)	0.128 (0.272)
Interventricular septum thickness (cm)	66	0.227 (0.067)	0.258 (0.037)	0.062 (0.623)
Posterior wall thickness (cm)	71	0.248 (0.037)	0.316 (0.007)	0.150 (0.213)

AHI, apnea–hypopnea index; SATMIN, minimum oxygen hemoglobin saturation during sleep; SBP, systolic blood pressure; DBP diastolic blood pressure; BMI, body mass index. Corresponding *P* values are shown in parentheses.

Patients receiving antihypertensive treatment had significantly higher office and night-time ambulatory SBP than those not treated with antihypertensive agents ($P = 0.001$ and $P = 0.006$), whereas comparisons for all other measures of blood pressure were associated with *P* values greater than 0.1 (data not shown). IVSD and PWD were increased in patients with antihypertensive medication (IVSD: 1.30 ± 0.28 cm, $n = 26$; PWD: 1.16 ± 0.22 cm, $n = 28$) when compared with patients without antihypertensive treatment (IVSD: 1.16 ± 0.21 cm, $n = 40$, $P = 0.022$; PWD: 1.04 ± 0.16 cm, $n = 43$, $P = 0.011$).

Blood pressure

Without correction for potential confounding variables, AHI was positively and significantly associated with office SBP and DBP, as well as with daytime ambulatory DBP and night-time ambulatory SBP and DBP. As an exception, the correlation between AHI and daytime ambulatory SBP was not significant. Relationships including SATMIN instead of AHI followed the same trend, but were generally weaker (Table 3).

Age, use of antihypertensives, smoking and BMI were identified as variables significantly influencing the correlation of at least one measure of blood pressure with AHI (Table 3, partial correlations for SATMIN not shown). Specifically, adjustment for age strengthened the relationships between AHI and office SBP as well as night-time ambulatory SBP, but weakened the correlation with daytime ambulatory DBP. Moreover, adjustment for smoking significantly strengthened the correlation between AHI and office DBP. In contrast, correction for use of antihypertensive agents reduced correlations involving office and night-time ambulatory SBP, whereas adjustment for BMI only diminished the correlation between AHI and office DBP. With the exception of the relationship between AHI and office SBP, which decreased to a nearly-significant level after control for use of antihypertensive agents (to $r = 0.207$, $P = 0.066$), as well as relationships involving daytime ambulatory SBP, all correlations with AHI remained significant at the 0.05 level after adjustments.

When AHI and the entire set of covariates listed in Table 3 were concomitantly included as explanatory

Table 3 **Partial correlations between obstructive sleep apnea severity and blood pressure**

	Partial correlation between AHI and:					
	Office		Daytime ambulatory		Night-time ambulatory	
Covariate for adjustment	SBP ($n = 81$)	DBP ($n = 81$)	SBP ($n = 80$)	DBP ($n = 80$)	SBP ($n = 76$)	DBP ($n = 76$)
Unadjusted	0.281 (0.011)	0.455 (0.000)	0.166 (0.141)	0.336 (0.002)	0.368 (0.001)	0.438 (0.000)
Age	0.352 (0.001)*	0.448 (0.000)	0.179 (0.115)	0.307 (0.006)*	0.428 (0.000)*	0.439 (0.000)
Gender	0.287 (0.010)	0.452 (0.000)	0.144 (0.205)	0.312 (0.005)	0.340 (0.003)	0.412 (0.000)
Use of antihypertensives	0.207 (0.066)*	0.438 (0.000)	0.124 (0.276)	0.362 (0.001)	0.309 (0.007)*	0.436 (0.000)
Smoking	0.304 (0.006)	0.481 (0.000)*	0.171 (0.133)	0.332 (0.003)	0.391 (0.001)	0.450 (0.000)
BMI	0.260 (0.020)	0.404 (0.000)*	0.123 (0.282)	0.287 (0.010)	0.358 (0.002)	0.448 (0.000)
CAD	0.271 (0.015)	0.450 (0.000)	0.175 (0.124)	0.388 (0.000)	0.348 (0.002)	0.440 (0.000)
Hypercholesterolemia	0.285 (0.011)	0.424 (0.000)	0.207 (0.067)	0.325 (0.003)	0.373 (0.001)	0.399 (0.000)
C-peptide	0.286 (0.010)	0.453 (0.000)	0.153 (0.179)	0.325 (0.003)	0.358 (0.002)	0.429 (0.000)
			Correlation between SATMIN and:			
	Office		Daytime ambulatory		Night-time ambulatory	
	SBP ($n = 81$)	DBP ($n = 81$)	SBP ($n = 80$)	DBP ($n = 80$)	SBP ($n = 76$)	DBP ($n = 76$)
Unadjusted	−0.169 (0.132)	−0.230 (0.039)	−0.145 (0.199)	−0.191 (0.089)	−0.197 (0.088)	−0.238 (0.039)

*Partial correlation is significantly different from unadjusted (zero-order) correlation ($P < 0.05$). SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CAD, coronary artery disease; SATMIN, minimum oxygen hemoglobin saturation during sleep. Corresponding *P* values are shown in parentheses.

variables in multiple regression models, AHI explained a significant additional amount of variability in all measures of blood pressure except daytime ambulatory SBP. In contrast, the marginal predictive power of SATMIN after concomitant inclusion of all covariates into multiple regression models was not significant for any measure of blood pressure (Table 4).

Left ventricular muscle thickness

Uncorrected correlations between AHI and IVSD as well as PWD were positive and significant, indicating increased LV muscle thickness with increasing OSA severity. Without adjustment for covariates, relationships involving SATMIN followed the same trend but were weaker and not significant (Table 5).

Adjustment of the relationship between AHI and IVSD for use of antihypertensive agents as well as adjustment of the relationship between AHI and PWD for gender, use of antihypertensive agents or BMI significantly reduced the respective coefficients of correlation. Some adjustments (AHI versus IVSD for BMI, AHI versus IVSD for CAD and AHI versus IVSD as well as PWD for mean 24 h MBP) resulted in insignificant corrections but, nevertheless, yielded partial correlations that were no longer significant at the 0.05 level (Table 5). In contrast, age, smoking and, to an insignificant extent, hypercholesterolemia acted as suppressor variables, correction for which strengthened all relationships between OSA severity and LV muscle size. Consequently, when the partial correlations between AHI and IVSD or PWD were calculated by primarily adjusting for smoking, the strongest confounder among all covariates, and secondarily for one of the remaining covariates, all

Table 4 **Regression coefficients for apnea–hypopnea index (AHI) and minimum oxygen hemoglobin saturation during sleep (SATMIN) in multiple regression analysis**

Response variable	*n*	Regression coefficient for AHI (95% CI)	*P* value	Regression Coefficient for SATMIN (95% CI)	*P* value
Blood pressure					
Office SBP (mmHg)	81	0.182 (0.048 to 0.316)	0.009	−0.291 (−0.716 to 0.134)	0.176
Office DBP (mmHg)	81	0.116 (0.043 to 0.188)	0.002	−0.169 (−0.402 to 0.064)	0.153
Daytime ambulatory SBP (mmHg)	80	0.070 (−0.046 to 0.186)	0.233	−0.220 (−0.575 to 0.135)	0.221
Daytime ambulatory DBP (mmHg)	80	0.091 (0.015 to 0.167)	0.020	−0.156 (−0.396 to 0.084)	0.200
Night-time ambulatory SBP (mmHg)	76	0.177 (0.065 to 0.290)	0.002	−0.259 (−0.633 to 0.116)	0.172
Night-time ambulatory DBP (mmHg)	76	0.157 (0.071 to 0.243)	0.001	−0.229 (−0.520 to 0.062)	0.121
Cardiac structure					
Interventricular septum thickness (cm)	62	0.0017 (−0.0028 to 0.0037)	0.091	−0.0065 (−0.0124 to −0.0007)	0.030
Posterior wall thickness (cm)	67	0.0015 (−0.0003 to 0.0026)	0.129	−0.0044 (−0.0088 to 0.0001)	0.052

Regression coefficients, their 95% confidence intervals and *P* values for AHI and SATMIN within multiple regression models including AHI or SATMIN in addition to age, gender, use of antihypertensive agents, smoking, body mass index, coronary heart disease, hypercholesterolemia and serum C-peptide concentration as explanatory variables. SBP, systolic blood pressure; DBP diastolic blood pressure; CI, confidence interval.

Table 5 **Partial correlations between obstructive sleep apnea severity and left ventricular muscle thickness**

	Partial correlation between AHI and:		Partial correlation between SATMIN and:	
Covariate used for correction	IVSD	PWD	IVSD	PWD
Uncorrected	0.277 (0.024)	0.299 (0.011)	−0.232 (0.061)	−0.215 (0.071)
Age	0.326 (0.008)*	0.354 (0.003)*	−0.268 (0.031)*	−0.251 (0.036)*
Gender	0.244 (0.050)	0.261 (0.029)*	−0.228 (0.067)	−0.212 (0.079)
Use of antihypertensives	0.216 (0.083)*	0.236 (0.049)*	−0.187 (0.136)*	−0.170 (0.160)*
Smoking	0.347 (0.005)*	0.354 (0.003)*	−0.290 (0.019)*	−0.272 (0.022)*
BMI	0.221 (0.077)	0.231 (0.054)*	−0.214 (0.087)*	−0.197 (0.103)*
CAD	0.228 (0.067)	0.264 (0.027)	−0.215 (0.085)	−0.198 (0.100)*
Hypercholesterolemia	0.323 (0.009)	0.330 (0.005)	−0.261 (0.036)	−0.244 (0.041)
C-peptide	0.271 (0.029)	0.285 (0.017)	−0.229 (0.067)	−0.209 (0.083)
Mean 24 h ambulatory MBP	0.222 (0.086)	0.216 (0.081)	−0.192 (0.139)	−0.175 (0.161)

*Partial correlation is significantly different from uncorrected (zero-order) correlation ($P < 0.05$). Coefficients of unadjusted and partial correlation describing linear relationships between obstructive sleep apnea (OSA) severity, expressed as apnea–hypopnea index (AHI) and lowest oxygen hemoglobin saturation during sleep (SATMIN), and left ventricular muscle thickness, expressed as interventricular septum and posterior wall size. Corresponding P values are shown in parentheses. SBP, systolic blood pressure; DBP diastolic blood pressure; BMI, body mass index; CAD, history of coronary artery disease; MBP, mean blood pressure, IVSD and PWD, interventricular septum and left ventricular posterior wall thickness in diastole.

resulting relationships except those after secondary correction for 24 h MBP were significant (data not shown).

All partial correlations of LV muscle size with SATMIN as marker of OSA severity were weaker and more uncertain than those involving AHI. In contrast, when measures of LV muscle size were concomitantly regressed on age, gender, use of antihypertensives, smoking, BMI, CAD, hypercholesterolemia, serum C-peptide concentration and one of the measures of OSA severity, SATMIN but not AHI explained a significant or nearly significant proportion of the residual variances in IVSD and PWD (Table 4). After additional inclusion of mean 24 h MBP, which absorbed a significant amount of information from both AHI ($r = 0.402$ for correlation between AHI and mean 24 h MBP) and SATMIN ($r = -0.253$ for correlation between SATMIN and mean 24 h MBP), marginal contributions of neither AHI nor SATMIN to IVSD or PWD prediction were significant (AHI versus IVSD: $P = 0.151$; SATMIN versus IVSD: $P = 0.055$; AHI versus PWD: $P = 0.376$; SATMIN versus PWD: 0.137).

Discussion

The present study was performed in OSA patients from a clinic-based population characterized by a relatively high degree of comorbidity. The heterogeneity immanent in the study sample made it possible to estimate the confounding potential of a variety of factors previously suggested to account for part of the relationship between the severity of sleep-disordered breathing and indicators of cardiovascular dysfunction [16–22]. Our results suggest that, in clinical OSA populations, these covariates may not be equally relevant for the prediction of blood pressure and LV muscle size from AHI or SATMIN. In particular, inconsistent relationships between covariates and response variables, as observed in the current population, may result in a complex pattern of confounding influences on the associations between OSA severity and blood pressure or LV muscle thickness. Age, for example, was inversely but comparatively strongly correlated with daytime ambulatory DBP in the present study. As a result, adjustment of the positive association between AHI and daytime ambulatory DBP for age resulted in a weakened partial correlation. In contrast, associations between all remaining response variables and age were insignificant or positive, which explains insignificant corrections or strengthening of partial correlations after adjustment for age.

Several investigations have demonstrated a positive relationship between AHI and office blood pressures [1–3,7,8,16,31]. Those data are corroborated by the present results in a clinical population of OSA patients, showing a strong and robust relationship between OSA severity, as expressed by the AHI, and both office DBP and SBP. Moreover, although confounding effects of factors previously suggested to account for the association between OSA and high blood pressure [16–22] were detectable, their influence was limited. Among all potential confounders considered in the current study, adjustment for use of antihypertensive agents resulted in the largest reduction of the correlation between AHI and office SBP (from $r = 0.281$ to $r = 0.207$), whereas control for BMI had the greatest effect on the association between AHI and DBP (reduction from $r = 0.455$ to $r = 0.404$). However, the resulting partial correlations still indicated an important explanatory power of AHI, suggesting that covariation with single confounders did not fundamentally account for the relationship between AHI and office blood pressure in this clinical population. Moreover, our results from multiple regression

modeling concomitantly adjusting for the entire set of covariates may support the hypothesis that variation in AHI explains an independent proportion of variability in both office SBP and office DBP. Based on the final regression models and their coefficients, office SBP is predicted to increase by 3.6 mmHg [95% confidence interval (CI): 1.0 to 6.3] and office DBP by 2.3 mmHg (95%CI: 0.9 to 3.8) with each additional increase in AHI by 20 h^{-1}, if all confounders are maintained at constant levels. Equivalently, differences in SBP and DBP between the two subjects with the lowest and highest AHIs in the current sample (1.5 versus 128 h^{-1}) would be expected to amount to 23.0 mmHg (95%CI: 6.1 to 40.0) and 14.7 mmHg (95%CI: 5.4 to 23.8), respectively. The regression slopes obtained in the present clinical OSA population are slightly smaller than those previously observed in a community-based, untreated population [16] but larger than those found in a recent, clinic-based study after exclusion of patients with antihypertensive medication (although respective confidence intervals overlap to a large extent) [31]. Nevertheless, the data indicate that a considerable risk for high blood pressure remains detectable after adjustment for the majority of recognized confounding factors, if uncontrolled sleep apnea is present.

The strength of the dose-response relationship between OSA severity and ambulatory blood pressure has previously been estimated in a relatively homogeneous sample of 93 persons with suspected sleep apnea [32]. In that study, the oxygen desaturation index was used as a measure of OSA severity. Blood pressure was recorded in a more controlled environment and, if applicable, at least 3 days after termination of antihypertensive medication. As could be expected from these sampling differences, correlations between OSA severity and daytime and night-time blood pressures were weaker in the present study. However, daytime DBP as well as nighttime DBP and SBP were still significantly correlated with AHI, and these relationships were robust against corrections for age, gender, use of antihypertensive agents, history of CAD, smoking, BMI, hypercholesterolemia and circulating C-peptide concentrations. Combined with the results obtained with the office blood pressure measurements, the present data support the hypothesis that a dose–response relationship between the severity of sleep-disordered breathing and blood pressure level is detectable in heterogeneous clinical populations and, moreover, only in part explainable by covariation with recognized confounding variables. In particular, if sleep apnea is untreated, prescription of antihypertensive agents according to customary treatment routines may not ensure sufficient reduction of daytime or night-time blood pressure in clinical OSA populations, a conclusion which is in agreement with previous data suggesting that severe OSA predicts poor hypertension control [2,33].

It is still a matter of debate whether OSA is independently related to LV hypertrophy. In a previous study from our group, OSA patients had increased LV wall thickness when compared with age- and BMI-matched control subjects. This difference was not explainable by contrasts in office blood pressure [4]. Comparing two groups with low and high apnea indices, 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 [6]. However, the effect of correction for blood pressure and other confounders on this relationship was not reported. In massively obese patients (BMI > 40 kg/m^2), a significant uncorrected correlation between AHI and interventricular septum but not posterior wall thickness was observed [5]. Two studies, one comparing OSA patients with control subjects matched for age, sex, BMI, smoking as well as alcohol intake [14] and one comparing snorers with and without sleep apnea [15], found no relationship between the presence of OSA and LV muscle thickness. In the current study, we observed significant unadjusted exposure–response relationships between AHI and thickness of both the interventricular septum and the LV posterior wall. However, these relationships were partly explainable by specific inter-relationships between measures of OSA severity, LV muscle size and a variety of covariates. Most importantly, muscle thickness was lower in smokers than in non-smokers. This difference, which was not explainable by differences in BMI, outweighed all other relationships involving IVSD and PWD. Since, in addition, OSA was slightly more severe in smokers than in non-smokers, adjustment for smoking strengthened the relationships between OSA severity and LV muscle thickness to an important extent. Addition of the remaining covariates as explanatory variables to the corresponding regression models reduced the marginal information contributed by OSA severity to explanation of cardiac muscle thickness. This may be a consequence of an overall positive association between male gender, use of antihypertensives (indicating previously diagnosed hypertension or cardiac disease), BMI, CAD, C-peptide concentration, 24 h ambulatory MBP and OSA severity, leading to absorption of each other's contributions to variance in LV muscle thickness in the current population. Most obviously, more severe OSA predicted an increased likelihood of antihypertensive treatment as well as higher blood pressure levels, while both use of antihypertensives and blood pressure were linked to increased LV muscle thickness. Therefore, an important part of the relationship between AHI and LV muscle size may be explainable by known hypertension (reflected by the use of antihypertensive agents) and blood pressure. As a consequence, therapeutic apnea reduction might reduce LV muscle size, but such effect might primarily be mediated by concomitant blood pressure reduction [34,35].

In general, the current results suggest that the ability of OSA severity to predict LV muscle thickness depends importantly on the specific constellation of covariates in a given population. Moreover, as indicated by results from animal studies showing that long-term intermittent hypoxia may stimulate cardiac growth more powerfully in spontaneously hypertensive than in Wistar–Kyoto rats [36], genetic traits may be expected to contribute additional interfering influence. Therefore, comprehension of the clinical importance of sleep-disordered breathing for cardiac structure and size may require longitudinal and experimental studies allowing conclusions about causal relationships between cardiac growth, OSA as well as other inherited and acquired patient characteristics.

In conclusion, we found significant exposure–response relationships between AHI and office blood pressures, daytime ambulatory DBP as well as night-time ambulatory SBP and DBP in a clinic-based population of OSA patients. In essence, these relationships were not explainable by confounding effects of age, gender, use of antihypertensive agents, smoking, BMI, CAD, hypercholesterolemia or hyperinsulinemia. Relationships between OSA severity and LV muscle thickness in clinical populations appear to be suppressed by covariation with smoking and age and strengthened by the confounding effects of hypertension and BMI.

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