

ORIGINAL ARTICLE

Relationship between obstructive sleep apnea and markers of cardiovascular alterations in never-treated hypertensive patients

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We addressed a question if there is a relationship between severity of newly diagnosed obstructive sleep apnea (OSA) and markers of cardiovascular alterations in middle-aged untreated hypertensive patients. In 121 consecutive patients with never-treated essential hypertension (mean age 35.9 ± 10.1 years; 97 men and 24 women) evaluation of office and ambulatory blood pressure (BP) measurements, metabolic syndrome (MS) components and markers of alterations in cardiovascular system including left ventricular structure and function, carotid artery wall intima-media thickness (cIMT) and urinary albumin excretion (UAE) was performed. OSA was classified as mild (apnea/hypopnea index (AHI) 5–15 events h^{-1}) or moderate-to-severe (AHI > 15 events h^{-1}). Mild and moderate-to-severe OSA were diagnosed in 30% and 20% of patients, respectively. No differences in nighttime BP levels and decline between patients with and without OSA were observed. The patients with moderate-to-severe OSA were characterized by higher cIMT (0.74 ± 0.16 vs. 0.60 ± 0.15 mm; $P = 0.001$), UAE (14.5 ± 6.9 vs. 10.0 ± 8.0 mg $24 h^{-1}$; $P = 0.014$), relative wall thickness (0.42 ± 0.05 vs. 0.39 ± 0.05 ; $P = 0.023$) and by a higher degree of diastolic dysfunction (E'-wave velocity 11.4 ± 3.2 vs. 15.5 ± 3.8 m s^{-1} ; $P < 0.001$) as compared with the patients without OSA. In multivariate analysis, AHI independently of BP and MS components correlated with UAE, relative wall thickness and E'-wave velocity. In the middle-aged never-treated hypertensive patients, moderate-to-severe OSA correlates with markers of cardiovascular alterations independently of BP levels and MS components.

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INTRODUCTION

There is growing evidence that obstructive sleep apnea (OSA) represents a major cardiovascular risk factor and is associated with increased cardiovascular and cerebrovascular morbidity and mortality.^{1,2}

Recent studies have shown that the patients with OSA and hypertension are more likely to display signs of organ involvement—thickening of the carotid wall of the intima-media thickness (cIMT), left ventricular hypertrophy (LVH) and/or microalbuminuria.^{1–3} A major drawback of the studies done so far is that the role of OSA in these changes could not be established unequivocally. Most of the reports evaluating the association of OSA and hypertension with early atherosclerosis included patients with high burden of cardiovascular risk factors including established cardiovascular or cerebrovascular disease, severe obesity or diabetes, or patients receiving varied pharmacological therapy.^{1–3}

However, the relationship between alterations in cardiovascular system and OSA has not been previously studied in middle-aged

patients with never-treated hypertension without overt cardiovascular diseases.^{1–4}

The aim of our study was to evaluate the prevalence of newly diagnosed OSA in middle-aged patients with never-treated essential hypertension stages 1–2 without overt cardiovascular diseases. Moreover, we addressed the question if there is a relationship between the severity of newly diagnosed OSA and alterations in cardiovascular system. Therefore, we evaluated several signs of organ involvement including markers of left ventricular (LV) structure and function, carotid wall thickening and microalbuminuria.

METHODS

Study subjects

In years 2008–2010, 121 consecutive patients with never-treated essential hypertension, age 18–50 years, fulfilling inclusion criteria, attending the outpatient clinic of the Department of Hypertension, Institute of Cardiology, Warsaw, Poland, were asked to enter the study.

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Before entering the study, clinical examination was performed to determine demographics, cardiac history, known duration of hypertension, cardiovascular risk factors and to exclude related comorbidities. Hypertension was diagnosed if office systolic and diastolic blood pressure (BP) levels were 140 and/or 90 mmHg or more and if the mean daytime ambulatory systolic BP and diastolic BP levels were higher than 130 and/or 85 mmHg.⁵ Thus, patients with white-coat hypertension were not included into the study.

Subjects were excluded for any of the following reasons: secondary hypertension and/or related comorbidities including positive history or clinical signs of coronary heart disease, cerebrovascular disease, diabetes mellitus, previous treatment with the hypoglycemic, hypolipemiant and/or antihypertensive agents, neoplastic, hepatic or renal disease, estimated glomerular filtration ratio $<60 \text{ ml min}^{-1}$ per 1.73 m^2 , disabling diseases or refusal to provide an informed consent.

Study design

The protocol included evaluation of: (1) office BP and ambulatory BP measurements, (2) sodium and potassium, lipids, blood count, fasting plasma glucose (FPG), creatinine and uric acid concentrations; (3) OSA: Epworth Sleepiness Scale and full night polysomnography and (4) markers of cardiovascular alterations in all patients. The study was approved by the Ethics Committee of the Institute of Cardiology, Warsaw, Poland and informed written consent was obtained from each patient.

Measurements and definitions

Anthropometric evaluations. All patients underwent standard clinical evaluation. Known duration of hypertension and neck and waist circumferences were recorded. Large neck circumference was defined as $\geq 41 \text{ cm}$ or $\geq 43 \text{ cm}$ for women and men, respectively.⁶ On the basis of weight and height, body mass index was calculated. Abdominal obesity was defined as a waist circumference >102 and $>88 \text{ cm}$ for men and women, respectively.⁵ Current smoking, history of alcoholism, adrenergic medications and oral contraceptives were also documented.

Laboratory methods. Biochemical evaluation of blood samples taken after overnight fasting were determined by routine methods, and included sodium and potassium, lipids, blood count, FPG, creatinine and uric acid concentrations. Estimated glomerular filtration ratio was calculated using the Modification of Diet in Renal Disease formula.⁷ Glucose and lipid metabolism abnormalities as well as metabolic syndrome (MS) were diagnosed on the basis of the 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines—normal FPG: $<5.6 \text{ mmol l}^{-1}$ and impaired FPG: $5.6\text{--}6.9 \text{ mmol l}^{-1}$; increased low-density lipoprotein cholesterol concentration: $>3.0 \text{ mmol l}^{-1}$.⁵ For diagnosis of MS, three of five criteria had to be met: (1) BP $\geq 130/\geq 85 \text{ mmHg}$ —this criterion was met by all patients; (2) abdominal obesity as defined above; (3) high-density lipoprotein cholesterol male $<1.0 \text{ mmol l}^{-1}$, female $<1.2 \text{ mmol l}^{-1}$; (4) triglycerides $>1.7 \text{ mmol l}^{-1}$; and (5) FPG $\geq 5.6 \text{ mmol l}^{-1}$.⁵

Office BP. Office BP was measured by a trained nurse with a patient in the sitting position after a 5-min rest, using an automated device (Omron 705IT, Omron, Kyoto, Japan). Three consecutive readings were performed at two separate visits. If the difference between readings was higher than 10 mmHg, further measurements were taken so as to obtain three consecutive consistent readings at each visit. The average of these readings was recorded.

Ambulatory BP measurements. In all patients, ambulatory BP measurements were recorded using SpaceLabs 90207 or 90217 (Redmond, WA, USA). Readings were obtained every 15 min during the day (0600–2200 hours) and every 30 min during the night (2200–0600 hours). Differentiation between sleep and activity periods was made after recoding, based on data from the patient diary. Nocturnal decrease in BP was quantified as the relative decrease in nocturnal BP for both systolic and diastolic BP: $((\text{daytime pressure} - \text{nighttime pressure})/\text{daytime pressure}) \times 100$ and expressed as a percentage. Subjects were classified as dippers if the proportional decrease from awake to asleep BP was $\geq 10\%$.

Polysomnography. The Epworth Sleepiness Scale was evaluated before the sleep study. In all patients, data regarding mean sleep duration time and snoring were also assessed. The diagnosis of OSA was made by standard attended polysomnography with an Alice 5 (Respironics, Murrysville, PA, USA) device was performed in all subjects. The polysomnography recordings were scored manually using 30-s epochs following Rechtschaffen and Kales' criteria for sleep and wake determination and sleep staging.⁸ Abnormal respiratory events were evaluated according to standard criteria of the American Academy of Sleep Medicine Task Force.⁹

Apnea was defined as the absence of airflow for $\geq 10 \text{ s}$. Hypopnea was scored if there was a $\geq 30\%$ reduction in nasal pressure signal from baseline with a $\geq 4\%$ desaturation for $\geq 10 \text{ s}$. Hypopnea was also scored with $\geq 50\%$ flow reduction associated with arousal. The apnea/hypopnea index (AHI) was the sum of apneas and hypopneas per hour of sleep. OSA was diagnosed as mild OSA (AHI 5–15 events h^{-1}) or moderate-to-severe OSA (AHI >15 events h^{-1}).

Assessment of cardiovascular alterations

Carotid ultrasonography. The carotid ultrasound followed by a duplex color Doppler examination was done with a Phillips ATL 5000 (Philips, Eindhoven, The Netherlands) and a linear probe 7.5–12 MHz. Both left and right carotid arteries were analyzed. Multiple measurements on the distal wall from anterolateral and posterolateral longitudinal views were recorded. cIMT was measured at three points (3 mm apart) in two segments 1 cm from the flow divider caudally (carotid bulb) and 1 cm caudally from the beginning of the common carotid bulb (common carotid). The cIMT value was calculated as an arithmetical mean of 24 measurements from bulb and common carotid segments of both sides.

Echocardiography. Studies were performed with the use of a high-quality commercially available echocardiograph (Vivid 7, GE Healthcare, Little Chalfont, UK) equipped with 2.5 MHz imaging transducer. End-diastolic LV diameter (LVEDd) and end-systolic LV diameter, interventricular septum thickness (IVSTd) and posterior wall thickness (PWTd) were calculated from two-dimensionally guided M-mode tracing from the parasternal long-axis view, in accordance with the American Society of Echocardiography recommendations.¹⁰ LV mass was calculated from end-diastolic measurements using anatomically validated formula,¹¹ and normalized by body surface area–LV mass index. LVH was defined when LV mass index was equal or exceeded 125 g m^{-2} in men and 110 g m^{-2} in women. Relative wall thickness (RWT) was calculated as the PWTd + IVSTd/LVEDd and indicated concentric LV geometry if at least 0.42. LV systolic function was determined by the ejection fraction calculated in M-mode (Teicholz) at the parasternal long-axis and midwall fractional shortening.¹² LV filling was assessed by recording mitral flow by standard pulsed Doppler technique with the sample volume placed at the tips of the mitral leaflets, from the apical four-chamber view. The following parameters were considered: peak early transmitral flow velocity (E), late-diastolic flow velocity (A) and the ratio of the early to late peak (E/A ratio). The pulsed tissue Doppler imaging examination was performed from the apical four-chamber view, with the sample volume placed along the myocardial lateral wall and the left side of interventricular septum, 1 cm above the mitral annulus. Using the average of above two values, we measured myocardial early-diastolic velocity (E'), end-diastolic velocity (A') and their ratio (E'/A'). We evaluated also E/E' ratio. Left atrial size was determined in the parasternal long-axis view as the maximal distance between the posterior aortic root wall and the posterior left atrial wall at end-systole and normalized by body surface area. All calculations were performed during three consecutive cycles.

Other. Urinary albumin excretion (UAE) was assessed using two 24-h urine collections (the average of two collections was recorded). Increased cIMT, LVH and microalbuminuria were defined according to ESH/ESC criteria.⁵

Statistical analysis/analysis

Data analysis was carried out using statistical software PASW Statistics 18 (SPSS, Chicago, IL, USA). The results are presented as mean ± 1 s.d. or median and interquartile range. The values of variables between groups were

compared—continuous and discrete variables: Mann–Whitney test or univariate analysis of variance with *post-hoc* Dunnett's *t*-test or T3 Dunnett's *t*-test depending on Levene's test of homogeneity of variances; categorical variables: χ^2 test or Fisher's exact test. Parameters identified as statistically significant based on univariate analysis ($P < 0.05$) were included in the multivariate logistic or linear regression models in order to determine the combined effect of several variables on the incidence or value of the characteristic. $P < 0.05$ was considered statistically significant.

RESULTS

We evaluated 121 consecutive patients with never-treated essential hypertension (mean age 35.9 ± 10.1 years; 97 men and 24 women). Mild OSA was diagnosed in 36 patients (29.8%) and moderate-to-severe OSA in 24 patients (19.8%). Polysomnography parameters are shown in the Supplementary Table 1. Patients with moderate-to-severe OSA as compared with patients without OSA were characterized by higher frequency of MS and its components (Table 1).

Table 2 presents office BP and ambulatory BP measurement levels across the evaluated groups. Although generally patients with OSA were characterized by higher ambulatory systolic BP as compared with patients without OSA, the difference reached significance only for comparison between patients with mild OSA and without OSA (Table 2). No significant differences in BP profile between the groups were noted (Table 2).

Analysis was performed to determine the predictive value of the clinical variables associated with the moderate-to-severe OSA. Increasing age (odds ratio (OR) 2.00; $P = 0.015$ for 10-year increase),

large neck circumference (OR 3.34; $P = 0.025$) and increased triglycerides levels (OR 3.07; $P = 0.032$) but no other parameters including ambulatory BP measurement levels, nighttime BP decrease and Epworth Sleepiness Scale score predicted independently the presence of moderate-to-severe OSA (Supplementary Table 2). When in this model, components of MS were replaced by the presence of MS—it was the only variable significantly associated with the presence of moderate-to-severe OSA (OR 8.9; 95% CI 3.0–26.2; $P < 0.001$).

The overall frequency of established target organ damage was low—LVH, increased cIMT or carotid plaques and microalbuminuria were observed in 4%, 10% and 5% of patients, respectively. Patients with moderate-to-severe OSA but not with mild OSA were characterized by higher cIMT as compared with patients without OSA (Figure 1). There were significant correlations between AHI, mean saturation and minimal saturation and cIMT ($r = 0.30$; $P = 0.002$; $r = -0.23$; $P = 0.014$; $r = -0.31$; $P < 0.001$, respectively). However, in a multivariate model only age and decreased high-density lipoprotein were significantly and independently correlated with cIMT (Supplementary Table 3).

Patients with moderate-to-severe OSA but not patients with mild OSA were characterized by higher 24-h UAE as compared with patients without OSA (14.5 ± 6.9 vs. 10.0 ± 8.0 mg 24 h⁻¹; $P = 0.014$ and 9.8 ± 4.0 vs. 10.0 ± 8.0 mg 24 h⁻¹; $P = 0.99$, respectively). In a multivariate model, UAE was independently related with FPG and AHI (Supplementary Table 4).

Patients with moderate-to-severe OSA as compared with patients without OSA were characterized by higher indices of LV concentric remodeling as well as by worse indices of diastolic function (Table 3).

Table 1 Clinical characteristics of the studied patients

	Patients without OSA	Patients with mild OSA	Patients with moderate-to-severe OSA	P-value
Subjects (n)	61	36	24	
Men/women	39/22	36/0	22/2	<0.001
Age (years)	35 ± 10	35 ± 10	41 ± 9*	0.019
Known duration of hypertension (years)	1 ± 1	1 ± 1	1 ± 1	0.33
ESS points	6 (3.5–11.5)	6 (2.25–11)	6.5 (3–12)	0.83
BMI (kg m ⁻²)	26.1 ± 4.0	29.0 ± 3.4 [#]	31.2 ± 4.4 [#]	<0.001
Large neck circumference (%)	25	50*	67 [†]	0.001
Abdominal obesity (%)	31	53*	75 [†]	0.001
Metabolic syndrome (%)	21	44*	79 [†]	<0.001
Smokers (%)	23.0%	25.0%	25.0%	0.89
Sodium (mmol l ⁻¹)	141.3 ± 1.9	141.5 ± 1.6	142.3 ± 2.1	0.095
Potassium (mmol l ⁻¹)	4.4 ± 0.4	4.4 ± 0.4	4.6 ± 0.4	0.056
Fasting glucose (mmol l ⁻¹)	5.3 ± 0.6	5.5 ± 0.6	6.3 ± 2.3 [#]	0.004
Increased fasting glucose (%)	23	25	50*	0.039
Total cholesterol (mmol l ⁻¹)	4.9 ± 1.0	5.2 ± 0.9	5.4 ± 1.0	0.080
LDL cholesterol (mmol l ⁻¹)	3.2 ± 0.9	3.4 ± 1.0	3.6 ± 1.0	0.18
HDL cholesterol (mmol l ⁻¹)	1.5 ± 0.4	1.3 ± 0.4	1.2 ± 0.3*	0.015
Decreased HDL level (%)	12	25	33*	0.049
Triglyceride (mmol l ⁻¹)	1.2 ± 0.7	2.0 ± 1.6 [#]	2.3 ± 1.8 [#]	<0.001
Increased triglyceride level (%)	16	39*	63 [†]	<0.001
Creatinine level (μmol l ⁻¹)	85.6 ± 10.3	82.8 ± 10.7	79.7 ± 10.6	0.100
eGFR (ml min ⁻¹ per 1.73 m ⁻²)	101.6 ± 25.7	99.8 ± 15.6	97.8 ± 12.9	0.77
Uric acid level (μmol l ⁻¹)	314.8 ± 80.9	397.4 ± 89.3 [†]	382.5 ± 69.3 [#]	<0.001

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration ratio; ESS, Epworth Sleepiness Scale; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OSA, obstructive sleep apnea.

Data are presented as mean ± s.d. or as median (interquartile range) unless otherwise stated.

Large neck circumference: ≥41 cm female or ≥43 cm male. Abdominal obesity—waist circumference >88 cm female or >102 cm male. Increased fasting glucose concentration: ≥5.6 mmol l⁻¹. Decreased HDL cholesterol concentration: <1.0 mmol l⁻¹ male, <1.2 mmol l⁻¹ female. Increased triglycerides concentration >1.7 mmol l⁻¹. For diagnosis of metabolic syndrome, three of five criteria had to be met: increased blood pressure—this criterion was met for all patients, abdominal obesity, increased fasting glucose, decreased HDL cholesterol and increased triglyceride concentrations as defined above.

* $P < 0.05$; [#] $P < 0.01$; [†] $P < 0.001$ vs. patients without OSA, respectively.

Table 2 Clinic and ambulatory blood pressure levels in relation to the presence of OSA and its severity

	Patients without OSA	Patients with mild OSA	Patients with moderate-to- severe OSA	P-value
Subjects (n)	61	36	24	
Office SBP (mm Hg)	145 ± 9	149 ± 12	147 ± 9	0.14
Office DBP (mm Hg)	94 ± 9	96 ± 13	94 ± 10	0.68
Office heart rate (beats min ⁻¹)	84 ± 16	85 ± 15	83 ± 10	0.75
24-h SBP (mm Hg)	133 ± 7	138 ± 8 [#]	136 ± 7	0.005
24-h DBP (mm Hg)	81 ± 18	84 ± 10	85 ± 8	0.046
24-h heart rate (beats min ⁻¹)	76 ± 9	79 ± 9	79 ± 9	0.21
Daytime SBP (mm Hg)	135 ± 8	140 ± 9 [#]	140 ± 8	0.005
Daytime DBP (mm Hg)	84 ± 8	87 ± 10	88 ± 18	0.098
Daytime heart rate (beats min ⁻¹)	79 ± 9	81 ± 10	81 ± 9	0.34
Nighttime SBP (mm Hg)	120 ± 11	124 ± 10	121 ± 11	0.058
Nighttime DBP (mm Hg)	70 ± 9	73 ± 10	72 ± 10	0.36
Nighttime heart rate (beats min ⁻¹)	65 ± 8	67 ± 8	69 ± 9	0.080
Nocturnal SBP decrease (%)	11 ± 7	11 ± 6	14 ± 5	0.14
Nocturnal DBP decrease (%)	17 ± 8	16 ± 6	19 ± 7	0.22
SBP dippers (%)	52%	50%	75%	0.23
DBP dippers (%)	77%	81%	87.5%	0.62

Abbreviations: DBP, diastolic blood pressure; OSA, obstructive sleep apnea; SBP, systolic blood pressure.

Data are presented as mean ± s.d. unless otherwise stated.

[#]P < 0.01 vs. patients without OSA, respectively.

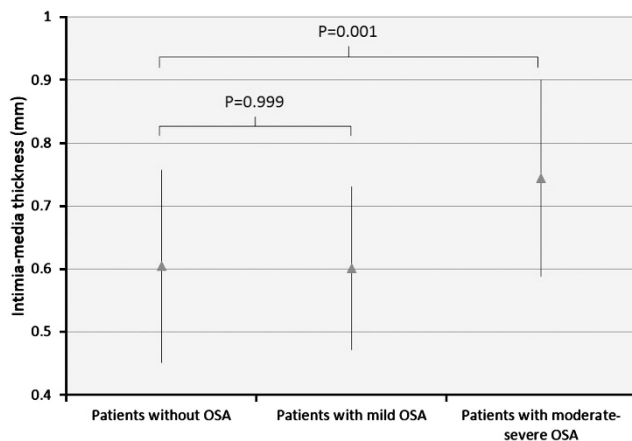


Figure 1 Carotid intima-media thickness according to the presence of obstructive sleep apnea (OSA) and its severity. The data are shown as mean value ± 1 s.d.

There were no differences in parameters describing neither LV systolic function nor in LVM and LV mass index. In separate multivariate analysis, AHI correlated independently of other factors both with RWT and E' (Table 4).

DISCUSSION

First, the novel finding of our study is to document high prevalence of newly diagnosed OSA in middle-aged patients with never-treated hypertension without overt cardiovascular diseases. However, it is difficult to compare our results with those from other studies as in most of them the prevalence of OSA was determined in patients with well-controlled hypertension or drug-resistant hypertension.³

Table 3 Echocardiographic parameters in relation to the presence of OSA and its severity

	Patients without OSA	Patients with mild OSA	Patients with moderate- to-severe OSA	P-value
Subjects (n)	61	36	24	
LVEDd (mm)	49.8 ± 4.6	52.2 ± 3.1*	50.9 ± 5.1	0.035
LVESd (mm)	29.7 ± 3.4	31.8 ± 5.4	29.3 ± 4.7	0.244
IVSTd (mm)	10.2 ± 1.4	10.6 ± 0.8	10.9 ± 1.2*	0.058
PWTd (mm)	9.7 ± 1.2	10.0 ± 0.9	10.6 ± 1.2*	0.005
LAVI (mm m ⁻²)	1.8 ± 0.3	1.9 ± 0.3	1.8 ± 0.2	0.357
EF (%)	69 ± 5	69 ± 6	72 ± 7	0.084
mwFS (%)	18.5 ± 1.9	18.5 ± 2.1	18.2 ± 1.7	0.766
E wave (cm s ⁻¹)	81 ± 17	75 ± 19	71 ± 15	0.084
A wave (cm s ⁻¹)	63 ± 22	58 ± 17	65 ± 14	0.413
E' wave (cm s ⁻¹)	15.5 ± 3.8	14.1 ± 3.1	11.4 ± 3.2 [#]	<0.001
A' wave (cm s ⁻¹)	9.5 ± 2.6	9.9 ± 2.0	10.0 ± 2.0	0.503
E/A ratio	1.35 ± 0.4	1.4 ± 0.5	1.1 ± 0.3*	0.053
E'/A' ratio	1.7 ± 0.6	1.5 ± 0.6	1.2 ± 0.5 [#]	0.004
E/E' ratio	5.4 ± 1.4	5.4 ± 1.4	6.3 ± 1.3*	0.042
RWT	0.39 ± 0.05	0.39 ± 0.05	0.42 ± 0.05*	0.025
RWT ≥ 0.42%	32	22	50	0.08
LVM (g)	184.3 ± 40.1	204.6 ± 30.2*	209.8 ± 45.8*	0.008
LVMI (g m ⁻²)	95.0 ± 16.0	98.2 ± 13.7	97.0 ± 18.6	0.62

Abbreviations: A, late-diastolic flow velocity; A', tissue Doppler of end-diastolic ventricular filling velocity; E, early transmitral flow velocity; E', tissue Doppler of early-diastolic ventricular filling velocity; E/A ratio, ratio of early to late pulsed wave Doppler of diastolic ventricular filling; E'/A' ratio, ratio of early to late tissue Doppler ventricular filling; E/E' ratio, ratio of early-diastolic pulsed wave Doppler to early-diastolic tissue Doppler; EF, ejection fraction; IVSTd, interventricular septum thickness; LAVI, left atrial volume index; LVEDd, end-diastolic left ventricular diameter; LVESd, end-systolic left ventricular diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; mwFS, midwall fractional shortening; OSA, obstructive sleep apnea; PWTd, posterior wall thickness; RWT, relative wall thickness.

Data are presented as mean ± s.d. unless otherwise stated.

*P < 0.05; [#]P < 0.01; *P < 0.001 vs. patients without OSA, respectively.

The non-dipping pattern of BP during the night has been reported as a feature of patients with OSA.³ However, in two recent studies, which included patients with resistant hypertension, no associations between higher nighttime BP levels nor nocturnal dipping pattern and the presence of OSA were reported.^{13,14} Our results also showed no differences in nighttime systolic BP and diastolic BP levels nor in BP nighttime decline between patients with OSA as compared with those without OSA. It is also of interest, that in contrast to some previous studies, blunted nocturnal dip was not correlated with the markers of cardiovascular alterations. Also, in a recent study involving a large group of middle-aged untreated hypertensive patients, Cuspidi *et al.*^{15,16} found that dippers have a similar subclinical cardiac and extra-cardiac organ damage as their nondipper counterparts.

Our study showed that the prevalence of MS was significantly higher in subjects with mild and moderate-to-severe OSA than in patients without OSA. We also found that the MS independently of other factors predicts the presence of moderate-to-severe OSA in hypertensive subjects. Our results support the concept that OSA is tightly linked to MS and represents an independent atherosclerotic burden in this population.¹⁷

Second, what is the novelty of our study, we examined whether there are echocardiographic differences between never-treated hypertensive patients with and without newly diagnosed OSA. Our results confirm this assumption, being in line with the findings of other studies reporting high prevalence of concentric hypertrophy or remodeling in population with hypertension and OSA.¹⁸⁻²¹ In fact, we documented only increased IVSTd and PWTd in patients with

Table 4 Variables related with relative wall thickness (a) and E'-wave velocity (b)—univariate and multivariate linear regression analysis

	Univariate model		Multivariate model	
	Beta	P-value	Beta	P-value
<i>(a) Variables related with relative wall thickness</i>				
Male gender	0.043	0.65		
Age 10 years increase	0.087	0.35		
AHI (events h⁻¹)	0.329	<0.001	0.329	<0.001
Fasting glucose (mmol l ⁻¹)	0.194	0.054		
Abdominal obesity	0.242	0.009		
24-h SBP (mm Hg)	0.012	0.90		
24-h DBP (mm Hg)	-0.030	0.75		
Triglycerides (mmol l ⁻¹)	0.152	0.11		
Decreased HDL cholesterol	0.175	0.06		
<i>(b) Variables related with E'-wave velocity</i>				
Male gender	0.023	0.81		
Age (years)	-0.558	<0.001	-0.444	<0.001
AHI (events h⁻¹)	-0.367	<0.001	-0.223	0.013
Fasting glucose (mmol l⁻¹)	-0.355	<0.001	-0.227	0.009
Abdominal obesity	-0.200	0.039		
24-h SBP (mm Hg)	0.094	0.34		
24-h DBP (mm Hg)	-0.012	0.90		
Triglycerides (mmol l ⁻¹)	-0.189	0.055		
Decreased HDL cholesterol	-0.099	0.31		

Abbreviations: AHI, apnea/hypopnea index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

Abdominal obesity—waist circumference >88 cm female or >102 cm male. Decreased HDL cholesterol: <1.0 mmol l⁻¹ male, <1.2 mmol l⁻¹ female. Only those variables that correlated significantly and were included in the multivariate model are shown in bold.

moderate-to-severe OSA as compared with patients without and with mild OSA. Our analyses also showed positive and independent association between RWT (index of LV geometry) and severity of OSA. Thus, in spite of normal LVM, these patients had a propensity to remodel ventricle in concentric geometry. The association between OSA and LV geometry have been previously investigated in studies conducted in patients with obesity and hypertension.^{21,22} Both overweight and increased BP determine a chronic LV overload and are two of the main factors leading to LVH. However, in our study abdominal obesity and BP levels were not related to RWT in the multivariate analysis, suggesting that severity of OSA had a more relevant effect on LV structure. This is in line with the findings of the study by Cioffi *et al.*,²³ which included 157 patients with suspected OSA undergoing polysomnography. The patients were older as compared with our study and comprised normotensive and both treated and untreated hypertensive subjects. It was also shown that moderate-to-severe OSA was related with increased RWT and concentric geometry independently of BP levels and obesity. The authors proposed that this phenomenon may be related to some consequences of severe OSA including significant hypoxemia, increased sympathetic drive and/or transmural pressure because of the respiratory effort during apneic/hypoapneic event.

In our study, systolic function assessed by ejection fraction was normal in all three groups. What more, midwall fractional shortening did not differ between study groups. It is in contrary to previous studies in which in hypertensive patients systolic shortening is often depressed.^{12,24} It may be explain by relatively normal thickness of LV wall and LV mass index in all three groups. However, diastolic

function differed between study groups. In patients, without evidence of systolic left heart failure, we found a tendency toward diastolic dysfunction. In addition to this, myocardial diastolic function decreased with increasing OSA severity even so all the values were within what is thought to be the 'normal range'.

The previous studies on LV diastolic function in patients with hypertension and/or OSA have yielded conflicting results,^{25–32} depending on methodological approaches and selection of study population. Most studies have reported impaired diastolic function in patients with OSA. However, Niroumand *et al.*²⁹ showed that OSA does not impair LV diastolic function in a large population. In this study, diastolic function was assessed only by conventional Doppler echocardiography (E/A ratio), which have limited value for making diagnosis of LV diastolic function.²⁹

Tissue Doppler imaging-derived parameters seem to be more sensitive in detecting subtle changes in diastolic function in patients with OSA.^{27,28} The findings obtained in this study are in line with previous data obtained by tissue Doppler imaging in patients with essential hypertension^{26,30} or in general population.³² In an outpatient clinic, population conventional Doppler and tissue Doppler imaging demonstrated that patients with hypertension had an impaired LV relaxation and elevated LV end-diastolic pressure, expressed by the E/E' ratio.²⁶ Wachter *et al.*³² in a cross-sectional cohort demonstrated that moderate-to-severe OSA was independently associated with impaired LV filling as assessed by comprehensive echocardiography including tissue Doppler. In our study, E/E' ratio was significantly higher in group with moderate-to-severe OSA comparing with group without OSA. Our results may bring hypothesis that the diastolic disturbances in these patients could likely be the cumulative burden of hypertension and sleep disturbance.

Third, this study showed that in middle-aged, never-treated hypertensive patients with newly diagnosed moderate-to-severe but not mild OSA, cIMT was significantly greater as compared with those without OSA. However, the range of cIMT values observed in most of our patients was below the currently accepted arbitrary cutoff point for increased cIMT. In contrast to our, in some other studies there was a significant difference in cIMT between those with mildly elevated AHI scores and the control groups. In most of the studies, cIMT was evaluated in normotensive subjects with OSA or in patients with OSA and hypertension who were older, had longer known duration of hypertension and were characterized by higher prevalence of target organ damage than those included in our study.

The impact of OSA and hypertension alone compared with the association of both conditions on markers of carotid atherosclerosis is not fully understood. Drager *et al.*³³ showed that the association of OSA and hypertension has additive effects on markers of carotid atherosclerosis. The study showed that cIMT is positively related to systolic BP and AHI indicating that association between OSA and atherosclerosis could be mediated by the presence of hypertension.³³

Silvestrini *et al.*³⁴ were the first to demonstrate that male patients with severe OSA and without any symptoms of cardiovascular and cerebrovascular disease have an increased predisposition to carotid atherosclerosis, independent of the coexistence of the classic vascular risk factors.

It should be noted that our study differs in some ways from the previous reports. In only one study, Bague *et al.*³⁵ characterized cIMT and plaque occurrence in patients with newly diagnosed OSA and never-treated hypertension without known cardiovascular disease. In this group of 83 patients with moderate-to-severe OSA, mean cIMT was 0.67 mm, 30% of subjects had carotid wall hypertrophy and the significant relationship was found between cIMT and plaque

formation and nocturnal oxygen desaturation. However, it is rather difficult to compare our study with those of Baguet *et al.*³⁵ as in contrast to our group, the prevalence of untreated hypertension was 65% and the investigated patients were older.

In our study, a positive correlation was also found between AHI, mean saturation and minimal saturation and cIMT. However, in a multivariate model only age and decreased high-density lipoprotein cholesterol concentration were significantly and independently correlated with cIMT. Most of the studies have shown that cIMT is independently related to the severity of OSA, as expressed by AHI or nocturnal hypoxemia. It has been reported that not only severe OSA, but even mildly elevated AHI scores predispose to early atherosclerosis.

On the contrary, as in our study Kaynak *et al.*³⁶ showed, that although cIMT values and the prevalence of plaque increased with respiratory disturbance index, cIMT was not significantly affected by the severity of OSA.

Fourth, hypertensive patients with moderate-to-severe newly diagnosed OSA but not patients with mild OSA were characterized by higher UAE as compared with patients without OSA. There was a significant correlation between UAE and AHI, which remained significant in a multivariate model. This study showed that AHI correlated with UAE within the normoalbuminuric range.

Recent data indicate that the association of UAE with major cardiac events extends to urine albumin levels below the currently accepted arbitrary cutoff point for microalbuminuria. Our data are in agreement with the results of Ursavas *et al.*,³⁷ who reported that low-grade UAE (0–30 mg g⁻¹) was associated with OSA in normotensive/non-diabetic patients, being independent of age and body mass index. In contrast to our study, subjects with hypertension were excluded from the study.

In another study, Tsioufis *et al.*³⁸ performed in 62 untreated hypertensive patients with OSA, it was documented that UAE was increased within the normal range in hypertensive individuals with OSA as compared with those without OSA proportionally to OSA severity independently of confounders. Supporting our study, in a multivariate model AHI was an independent predictor of UAE. Our study and those of Tsioufis *et al.*³⁸ may indicate that the association of upper-airway dysfunction with albumin excretion may provide an explanatory mechanism for the OSA-related risk in hypertension.

Limitations

We included only middle-aged or younger subjects with never-treated hypertension without a history of diabetes or cardiovascular disease, thus mitigating the potential confounding effects of age and comorbidities on our results. However, our results may not be applicable to the broader population of patients with hypertension.

The absence of a control group may be considered as a study limitation. However, it does not preclude the demonstration of an independent relationship between moderate-to-severe OSA and markers of alteration in cardiovascular system.

Finally, multivariate analysis can only describe the association, but not prove cause and effect. However, data from trials using continuous positive airway pressure in patients with OSA documented that waning of OSA can result in the improvement of markers of cardiovascular alterations.

Summary

In summary, our study documented relatively high prevalence of newly diagnosed OSA in middle-aged never-treated hypertensive subjects. High suspicion of OSA should be particularly raised in patients with MS. Our study showed a relatively low incidence of

established subclinical organ damage. However, patients manifesting moderate-to-severe OSA were characterized by more pronounced markers of alterations in cardiovascular system. This relationship reflects predisposition of middle-aged hypertensive subjects with OSA to develop established target organ damage. It may be postulated that early recognition of OSA in patients with hypertension may prevent the development of organ damage, which reflects an intermediate stage in the continuum of cardiovascular disease and is a determinant of overall cardiovascular risk.

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