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REVIEW

Early cardiovascular abnormalities in newly diagnosed obstructive sleep apnea

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Abstract: Obstructive sleep apnea (OSA) is associated with high cardiovascular morbidity and mortality. Recent studies have shown that it is associated with atherosclerosis and left ventricular dysfunction markers. The aim of this study was to assess the cardiovascular effects of OSA depending on its severity, in patients without clinically diagnosed cardiovascular disease. One hundred thirty newly diagnosed, nondiabetic OSA patients (mean age 49 ± 10 years), without vasoactive treatment were included. They underwent clinical and ambulatory blood pressure measurements, echocardiography, carotid ultrasound examination, and a carotid–femoral pulse wave velocity (PWV) measurement. Seventy-five percent of the subjects were hypertensive according to the clinical or ambulatory measurement. More patients with the most severe forms (respiratory disturbance index >37/hour) had a nondipper profile (52% vs 34%; $P = 0.025$) and their left ventricular mass was higher (40 ± 7 vs 36 ± 8 g/m, p = 0.014). This last parameter was independently and inversely associated with mean nocturnal oxygen saturation ($P = 0.004$). PWV and carotid intima-media thickness did not differ between one OSA severity group to another, but the prevalence of carotid hypertrophy was higher when mean SaO_2 was below 93.5% (29.5 vs 16%; $P = 0.05$). Our study shows that in OSA patients without clinically diagnosed cardiovascular disease, there is a significant left ventricular and arterial effect, which is even more marked when OSA is severe.

Keywords: obstructive sleep apnea, hypertension, left ventricular hypertrophy, intima-media thickness, arterial stiffness

Introduction

Obstructive sleep apnea (OSA) is a common but underdiagnosed disease[1] that causes increased cardiovascular morbidity and mortality, including arterial hypertension (HT), coronary heart disease, heart rhythm and conduction disorders, heart failure, and stroke.[2–12]

Although OSA is often associated with certain cardiovascular risk factors such as HT, obesity, diabetes, and dyslipidemia, it is legitimate to mention the direct role that OSA plays in the development of atherosclerosis. In fact, repeated episodes of hypoxia, hypercapnia, microarousals, and changes in intrathoracic pressure trigger pathophysiological mechanisms such as sympathetic hyperactivity,[13–15] oxidative stress,[16] systemic inflammation,[17] hypercoagulability,[18] and even endothelial dysfunction.[19] And all these abnormalities combine chronically to bring about the development of vascular lesions. Ultrasonography – a noninvasive, quick and reproducible technique – can be used to evaluate the atherosclerotic process at an early stage.[20] It analyzes vascular remodeling, measures the parietal thickness

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(intima-media thickness [IMT]) and detects atheromatous plaques. Like IMT and carotid plaques, carotid–femoral pulse wave velocity (PWV) is an early and independent marker of cardiovascular morbidity and mortality, notably coronary and cerebral morbidity and mortality.[21–23] PWV is a noninvasive way of assessing aortic stiffness. The large arteries play a crucial role in cardiac structure so increased arterial stiffness contributes independently to arterial pressure and to an increase in left ventricular afterload, thereby promoting left ventricular hypertrophy (LVH).[24]

A few studies have focused on structural and functional modifications to the large arteries in OSA, with the majority of them reporting increases in carotid IMT and PWV.[25–34] Similarly, some studies have found a link between OSA and LVH.[35–38] The link that connects OSA to these cardiovascular abnormalities remains ambiguous due to the frequent presence of confounding factors in the studies.

We performed our study on a large sample of patients with newly diagnosed and untreated OSA, without any known cardiovascular disease or vasoactive treatment. The main aim was to assess arterial structural and functional modifications, as well as remodeling of the left ventricle (LV), in this population. To the best of our knowledge, no study has simultaneously analyzed these three cardiovascular abnormalities in OSA patients without clinically diagnosed cardiovascular disease.

Materials and methods

Study population

The patients included in the study were referred to the Sleep Laboratory at the University Hospital of Grenoble (France) for symptoms indicating OSA between November 2001 and July 2007. The diagnosis of OSA was confirmed using polysomnography or ventilation polygraphy. We did not include patients if they presented a known cardiovascular disease including HT, any pathology affecting arterial blood pressure (BP) regulation (such as heart failure, Parkinson's disease and heart or kidney transplantation), atrial fibrillation or frequent extrasystole (>10/min), chronic respiratory insufficiency or previous treatment of OSA by means of nasal continuous positive airway pressure (nCPAP), maxillofacial surgery or a mandibular advancement prosthesis (oral appliance). We excluded diabetic patients (fasting glycemia ≥7.0 mmol/L or antidiabetic treatment), patients for whom the 24-hour ambulatory BP monitoring (ABPM) was invalid and patients who were on vasoactive drugs. Ethical approval was obtained from the local ethics committee and all of the participants gave their informed consent. The registration number for this study is NCT00764218.

Blood pressure and heart rate measurements

Clinical BP was measured by mercury sphygmomanometer on three occasions in line with European Society of Hypertension–European Society of Cardiology guidelines.[39] Systolic BP (SBP) and diastolic BP (DBP) were assessed. Pulse pressure (PP) was calculated using the following formula: PP = SBP minus DBP. Clinical HT was defined as a clinical SBP ≥140 mmHg and/or a clinical DBP ≥ 90 mmHg.[39] Increased clinical PP was defined as PP ≥ 65 mmHg.[40] Clinical heart rate (HR) was measured by pulse palpation (30 seconds) after the third measurement of BP in a supine position.

ABPM was carried out with a Spacelabs 90207® device (Spacelabs International, Redmond, WA, USA). Measurements were taken every 15 minutes over 24 hours. Daytime (07:00 to 22:00) HT was defined as daytime SBP ≥ 135 mmHg and/or daytime DBP ≥ 85 mmHg, and nocturnal (22:00 to 07:00) HT as nocturnal SBP ≥ 120 mmHg and/or nocturnal DBP ≥ 70 mmHg.[39] Nondipping status was defined as a nocturnal BP reduction of <10%.

Respiratory measurements

Full polysomnography was performed in 94 of the 130 patients (72%). Continuous recordings were taken with electrode positions C3/A2-C4/A1-Cz/01 of the international 10–20 Electrode Placement System, eye movements, chin electromyogram and ECG modified V2 lead. Sleep was scored manually according to standard criteria.[41] Airflow was measured using nasal pressure associated with the sum of buccal and nasal thermistor signals. Respiratory efforts were monitored with abdominal and thoracic bands. An additional respiratory effort signal (ie, pulse transit time) was recorded concurrently. Pulse transit time allowed us to identify "autonomic activations", and as a consequence, microarousals.[42] We were thus able to use the same rules and definition for hypopnea whatever the diagnostic method used for the diagnosis of sleep apnea. Oxygen saturation (SaO_2) was measured using a pulse oximeter (Biox-Ohmeda 3700®; Ohmeda, Liberty Corner, NJ, USA). The same variables were measured in the remaining 36 patients, except for sleep variables which were not recorded. Apnea was defined as a complete cessation of airflow for ≥10 seconds, and hypopnea as a ≥50% reduction in the nasal pressure signal or a 30%–50% decrease associated with either oxygen desaturation of ≥3% or an arousal (defined according to the Chicago report or by autonomic activations on pulse transit time), both lasting for ≥10 seconds.[42,43] Apnea was classified

as obstructive, central or mixed according to the presence or absence of respiratory efforts. The classification of hypopnea as obstructive or central was based on the pulse transit time signal and the shape of the inspiratory part of nasal pressure (flow limited aspect or not). The respiratory disturbance index (RDI) was calculated and defined as the number of episodes of apnea and hypopnea per hour of sleep (full polysomnography) or per hour of recording (polygraphy without electroencephalogram recording). In our study, a diagnosis of OSA was retained if RDI was ≥15 per hour. Subjects were split into two groups depending on the severity of their OSA, using the median RDI: group A (RDI < 37/hour, N = 65) and group B (RDI > 37/hour, N = 65). In an additional analysis, they were then split according to the median of the mean nocturnal SaO_2: group 1 (SaO_2 < 93.5%, N = 65) and group 2 (SaO_2 > 93.5%, N = 65).

Echocardiography

The echocardiogram was carried out using an HP Sonos 2500® (Hewlett Packard, Santa Clara, CA, USA) machine equipped with a 2.5 MHz probe. The examination was performed in M-mode with 2D guidance in the long axis of the left parasternal view. LV internal end-diastolic (LVD) and end-systolic diameters, as well as interventricular septum and posterior wall (LVPW) thicknesses, were measured over five consecutive cycles. Systolic function was assessed by the LV ejection fraction (LVEF) according to the Teicholz formula. LV mass (LVM) was measured according to the Penn convention using the Devereux formula and was normalized for body surface area and $height^{2.7}$ to derive the LV mass index (LVMI and LVMI-$height^{2.7}$).[44,45] LVH was defined as an LVMI of ≥ 111 g/m^2 or ≥ 50 g/$m^{2.7}$ in men and of ≥106 g/m^2 or ≥47 g/$m^{2.7}$ in women.[46,47] LV geometry was analysed according to the presence or absence of LVH and the calculated relative parietal thickness at the end of ventricular diastole (RWT = 2 × LVPW/LVD). All echocardiograms were recorded by the same experienced operator. We were able to perform a complete LV geometry analysis in 116 of the 130 patients (89%).

Carotid ultrasonography

B-mode ultrasonography was performed using an HP Sonos 2500® (Hewlett Packard) machine using a sectorial 7.5 MHz probe. The method used to determine the mean common carotid IMT and luminal diameter has been previously described.[48] Both common carotid arteries were studied consecutively in the long axis with a probe incidence allowing good quality images. The IMT was defined as the distance separating the most internal parts of these lines and the luminal diameter by the distance between the blood–intima interfaces on the anterior and posterior walls. The images were recorded in end-diastole and then analyzed by specific validated software (TIMC laboratory, CHU Grenoble, France). IMT and diameter measurements were carried out on areas free of atheroma and then averaged. The IMT and luminal diameter values for any given subject were the mean values for the two common carotid arteries. Carotid wall hypertrophy was defined as a common carotid IMT above 0.8 mm.[49] A plaque was defined as an echogenic structure encroaching into the vessel lumen with a distinct area and with an IMT more than 50% greater than those of the neighboring sites. Carotid ultrasonography was performed by two operators who were blinded to the other study data. The analysis of carotid parameters using the specific software was performed by the same operator throughout the entire study.

Aortic pulse wave velocity

To determine the carotid-femoral PWV, two pulse transducers were fixed on the skin over the right common carotid and femoral arteries. The time delay was measured with a Complior® device (Artech Medical, Pantin, France), between the feet of simultaneously recorded pulse waves and averaged over 10 consecutive cycles. The carotid-femoral PWV was calculated as the distance between the arterial sites divided by the time delay. Increased PWV was defined as PWV > 12 m/second.[39]

Biological parameters

All of the subjects had plasma assays of total cholesterol (enzymatic colorimetry, normal: 4.62–7.04 mmol/L), triglycerides (enzymatic colorimetry, normal: 0.63–2.58 mmol/L), high-density lipoprotein (HDL) cholesterol (enzymatic colorimetry, normal: 1.0–1.62 mmol/L), low-density lipoprotein (LDL) cholesterol (Friedwald formula, normal: 2.60–4.67 mmol/L), glucose (enzymatic method, normal: 3.8–5.8 mmol/L) and creatinine (enzymatic colorimetry, normal: 62–106 µmol/L).

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS Inc, Chicago, IL, USA). We assessed the normality of data distribution. Continuous data were expressed as mean ± standard deviation (SD). Relationships between continuous variables were evaluated using Pearson's correlation analysis when data were normally distributed and using Spearman's correlation analysis when they were not

normally distributed. Noncontinuous variables, expressed as percentages, were compared using a Chi-squared test. Comparisons between groups for continuous variables were made using a Student's *t*-test (or a Mann–Whitney U test when the data were not normally distributed). We performed multivariate analysis using stepwise regression. Variables included in our analysis were all the variables significantly ($P < 0.05$) associated with the explained variable using univariate analysis. We considered values of $P < 0.05$ significant for all analyses. We have chosen to include all *P* values under 0.20 in the tables.

Results

We included 130 patients (109 men, 84%), with a mean age of 49 ± 10 years. The general characteristics of the population are presented in Table 1. Most of the patients exhibited moderate to severe OSA (63 of the 130 subjects (48%) had a RDI of 30–50 per hour, and 31 (24%) had a RDI upper than 50 per hour). Body mass index (BMI) was 26.5 ± 3 kg/m^2, 73 patients (56%) were overweight and 15 (11.5%) were obese. Groups A and B were comparable in terms of age, sex, smoking status and all biological parameters. Patients with RDI over 37 per hour (ie, Group B) had a significantly higher BMI.

Clinical BP and ABPM parameters, as well as HR, did not vary from group to group (Table 1). Forty-five patients (35%) had clinical HT, 66 (51%) had diurnal HT, and 89 (68%) had nocturnal HT. In total, 98 patients (75%) were hypertensive measured clinically or with ABPM. Out of the 45 patients presenting clinical HT, grades were as follows: 28 HT grade 1 (62%), 13 HT grade 2 (29%) and four HT grade 3 (9%). Eight subjects (18%) had isolated systolic HT, 15 (33%) had isolated diastolic HT, and 22 (49%) had systolo-diastolic HT. Fifty-five patients (42%) had a nondipper profile for either SBP or DBP. There was a trend for a higher prevalence of clinical HT in group B (41% vs 28%, respectively; $P = 0.07$) than in group A, and a nondipper profile was more common in the most severe cases of OSA (Table 2).

Arterial parameters are presented in Table 2. There are no significant differences between groups A and B in any of these parameters. Carotid IMT and PWV were positively correlated with age ($P < 0.0001$), clinical SBP, DBP, and PP ($P < 0.0001$ for all but the correlation between IMT and DBP of $P < 0.01$), as well as with all BP parameters measured using ABPM ($P < 0.05$). Carotid IMT was correlated with mean SaO_2 (r = –0.21, $P = 0.017$; Figure 1) but PWV and PP were not correlated with any respiratory parameters. Clinical PP was positively correlated with age (r = 0.19, $P = 0.03$) and carotid IMT, PWV and clinical PP correlated with each other. In a multivariate analysis, IMT and PWV were independently associated with age and with clinical SBP ($P < 0.0001$). Clinical PP was independently associated with PWV ($P < 0.0001$) and IMT ($P = 0.005$).

Patients presenting carotid parietal hypertrophy were older, had a higher clinical SBP and presented more severe OSA (Table 3). Subjects with carotid atheromatous plaques were older ($P < 0.0001$), presented higher clinical SBP and DBP ($P < 0.001$), and higher total ($P = 0.018$) and LDL ($P = 0.028$) cholesterol.

All of the echocardiographic parameters are summarized in Table 2. LVEF did not change from group to group depending on the severity of the OSA. LVH was present in 5% to 9.5% of the patients depending on the criteria chosen (LVMI or LVMI-height$^{2.7}$), with no significant difference between the two groups. Patients with the most severe OSA had significantly higher LV wall thickness, LVM (before and after indexation) and RWT. LVMI-height$^{2.7}$ was significantly correlated with age (r = 0.19, $P = 0.04$), clinical SBP (r = 0.25, $P = 0.006$), and DBP (r = 0.22, $P = 0.02$), diurnal and nocturnal SBP and PP ($P < 0.05$), mean nocturnal SaO_2 (r = –0.27, $P = 0.003$), minimal SaO_2 (r = –0.19, $P = 0.036$) and $SaO_2 < 90\%$ (r = 0.23, $P = 0.011$), but not with RDI. LVMI-height$^{2.7}$ was also correlated with IMT (r = 0.19, $P = 0.038$) and PWV (r = 0.18, $P = 0.05$). In a multivariate analysis, LVMI-height$^{2.7}$ was independently correlated with clinical SBP ($\beta = -0.25$, $P = 0.01$) and mean nocturnal SaO_2 ($\beta = 0.23$, $P = 0.004$).

Patients with mean $SaO_2 < 93.5\%$ (Group 1) were older ($P = 0.001$) and had a higher BMI ($P = 0.003$). They also tended to have worse HT as evaluated both clinically and measured using ABPM (Table 4) and presented significantly higher LVMI-height$^{2.7}$ ($P = 0.003$) (Figure 2), as well as a greater prevalence of carotid parietal hypertrophy (29.5% vs 16%, $P = 0.05$).

Discussion

HT: a common disease in OSA

The prevalence of HT in OSA patients is estimated to be nearly 50%.[50] Although the link between the two pathologies was long disputed due to the numerous confounding factors, OSA is now recognized as one of the causes of secondary HT.[39,51] In our study, 75% of patients were hypertensive, although at inclusion, none of them were known to be hypertensive. In the general population, the prevalence of undiagnosed HT is around 25%,[52] which is three times

Table 1 General, hemodynamic, biological, and respiratory characteristics of the global population and according to the severity of OSA (RDI)

	Total (N = 130)	Group A RDI < 37 (N = 65)	Group B RDI > 37 (N = 65)	*P* value
Age (years)	49 ± 10	48 ± 10	49 ± 10	NS
Gender (% men)	84	80	88	NS
BMI (kg/m²)	26.5 ± 3	25.6 ± 3	27.5 ± 3.5	**0.001**
Active smoking (N, %)	26 (20)	14 (21)	12 (18)	NS
Clinic SBP (mmHg)	131 ± 16	131 ± 18	132 ± 14	NS
Clinic DBP (mmHg)	86 ± 10	85 ± 11	87 ± 10	NS
Clinic PP (mmHg)	45 ± 11	46 ± 12	44 ± 10	NS
Clinic HR (bpm)	65 ± 10	65 ± 10	65 ± 10	NS
Daytime SBP (mmHg)	128 ± 14	127 ± 13	128 ± 15	NS
Daytime DBP (mmHg)	84 ± 8	84 ± 7	83 ± 9	NS
Nighttime SBP (mmHg)	113 ± 12	111 ± 12	114 ± 13	NS
Nighttime DBP (mmHg)	72 ± 8	71 ± 8	73 ± 8	NS
Total cholesterol (mmol/L)	5.16 ± 1.03	5.32 ± 1.06	5.06 ± 1.01	NS
LDL cholesterol (mmol/L)	3.22 ± 0.86	3.35 ± 0.91	3.02 ± 0.77	NS
HDL cholesterol (mmol/L)	1.55 ± 0.39	1.57 ± 0.37	1.54 ± 0.4	NS
Triglycerides (mmol/L)	1.2 ± 0.56	1.17 ± 0.34	1.24 ± 0.67	0.09
Glucose (mmol/L)	5.02 ± 0.7	5.0 ± 0.8	5.04 ± 0.5	NS
Creatininemia (µmol/L)	88 ± 13	89 ± 15	86 ± 12	NS
RDI (/h)				
Microarousal index (/h)	40 ± 17	28 ± 7	53 ± 14	**<0.0001**
Mean nocturnal SaO_2 (%)	35 ± 14	29 ± 9	42 ± 15	**<0.0001**
Minimal nocturnal SaO_2 (%)	93.5 ± 1.8	94 ± 1.6	93 ± 2	NS
SaO_2 < 90% (%)	84 ± 6	85.5 ± 5	82.6 ± 7	**0.006**
	5.7 ± 11.5	3.5 ± 10	8 ± 13	**0.03**

Note: Results are given as mean ± SD or percentage.

Abbreviation: BMI, body mass index; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HR, heart rate; NS, not significant; OSA, obstructive sleep apnea; PP, pulse pressure; RDI, respiratory disturbance index; SaO_2, oxygen saturation; SaO_2 < 90%, percentage of recording time spent at a SaO_2 < 90%; SBP, systolic blood pressure; SD, standard deviation.

lower than in our population. Our results show the extent to which HT is under-diagnosed in OSA patients. They also serve as a reminder of the utility of ABPM, which is a recommended technique in this pathology.[39] In our study, this OSA-associated HT showed the following characteristics: predominantly nocturnal HT associated with a high prevalence of nondipper status and primarily diastolic HT. This is in line with the data found in the literature. We did not find any difference in BP values according to the severity of the OSA. This is certainly linked to the fact that, despite high prevalence of HT, the population studied was very moderately hypertensive (62% grade 1 HT). In fact, we were studying an OSA population without clinically diagnosed cardiovascular disease, which was consequently not greatly affected by severe HT.

From a pathophysiological point of view, episodes of apnea and hypopnea are responsible for changes in BP. The occurrence of a cortical microarousal leads to a hypertensive peak.[53,54] Moreover, repeated episodes of hypoxia and hypercapnia trigger pathophysiological mechanisms including sympathetic hyperactivity.[13,55] and the secretion of vasoactive substances.[56,57] Finally, each apnea is accompanied by a cycle of desaturation and reoxygenation which leads to the production of free radicals,[58] systemic inflammation,[17] and coagulation abnormalities.[18] These biochemical and cellular modifications contribute to endothelial dysfunction[19,59] and atherosclerotic degeneration. It has been hypothesized that chronic hypoxia has an effect on vascular remodeling on the basis of results from animal and tissue culture experiments.[60,61]

Table 2 Cardiovascular parameters in the global population and according to the severity of OSA (RDI)

	Total (N = 130)	Group A RDI < 37 (N = 65)	Group B RDI > 37 (N = 65)	*P* value
Clinic hypertension (N, %)	45 (35)	18 (28)	27 (41)	0.07
Nondipper SBP (N, %)	49 (38)	18 (28)	31 (48)	**0.015**
Nondipper DBP (N, %)	37 (29)	13 (20)	24 (37)	**0.026**
Nondipper SBP or DBP (N, %)	55 (42)	22 (34)	34 (52)	**0.025**
LVEF (%)	58 ± 6	59 ± 6	57 ± 7	NS
IVS (mm)	8.5 ± 1	8.1 ± 1.1	8.8 ± 1.2	**0.005**
LVPW (mm)	9.0 ± 1.1	8.7 ± 1.2	9.2 ± 1.2	**0.01**
LVM (g)	168 ± 41	159 ± 41	178 ± 38	**0.013**
LVMI (g/m^2)	87 ± 19	83 ± 20	90 ± 18	**0.05**
LVMI-height$^{2.7}$ (g/m)	38 ± 8	36 ± 8	40 ± 7	**0.014**
LVH ind$^{2.7}$ (N, %)	11 (9.5)	4 (7)	7 (12)	0.19
RWT (%)	36 ± 5.5	35 ± 4.6	37 ± 6	**0.039**
RWT > 0.45 (N, %)	7 (6)	2 (3.5)	5 (8.5)	0.16
Clinic PP (mmHg)	45 ± 11	46 ± 12	44 ± 10	NS
Increased clinic PP (N, %)	8 (6)	5 (7)	3 (4.5)	NS
PWV (m/s)	9.1 ± 1.5	8.9 ± 1.6	9.2 ± 1.4	NS
Increased PWV (N, %)	5 (8)	1 (1.5)	4 (6)	0.18
Carotid IMT (mm)	0.65 ± 0.15	0.64 ± 0.16	0.66 ± 0.13	NS
Increased carotid IMT (N, %)	30 (23)	14 (21)	16 (25)	NS
Carotid plaques (N, %)	25 (19)	13 (20)	12 (18)	NS

Note: Results are given as mean ± SD or percentage.

Abbreviations: DBP, diastolic blood pressure; IMT, intima-media thickness; IVS, interventricular septum; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; LVPW, left ventricular posterior wall; NS, not significant; OSA, obstructive sleep apnea; PP, pulse pressure; PWV, pulse wave velocity; RDI, respiratory disturbance index; RWT, relative wall thickness; SBP, systolic blood pressure; SD, standard deviation.

OSA, carotid remodeling, and arterial stiffness

Carotid ultrasonography and evaluation of arterial stiffness are useful for the early detection of atherosclerosis at an asymptomatic stage.[62,63] Increased carotid IMT is a marker of structural vascular damages whereas arterial stiffness, as estimated by PP and PWV, reflects functional modifications on the large arteries. In our study, carotid IMT, PP and PWV values were not very high compared to previous studies conducted on apnea patients. This partly explains the absence of a significant difference between our two OSA severity groups for these arterial parameters. These "normal" values are probably due to the relatively low number of major vascular risk factors in our population.

Almost a quarter of patients presented carotid hypertrophy and 19% had carotid plaques. These values are particularly high for a population potentially considered at low cardiovascular risk, according to the literature.[64] Furthermore, carotid hypertrophy was more common in patients with the most severe OSA (mean SaO_2 < 93.5%) and it was associated with worse respiratory parameters. In line with other studies,[25–30,33] our results suggest that OSA contributes to the genesis of atherosclerosis. However, it remains to be formally demonstrated that the association between OSA and carotid hypertrophy is independent, as the confounding factors are numerous. A few studies state that OSA has a direct effect on IMT.[25,28,30] However, most of these studies have significant limitations as they cover a large number of major vascular risk factors and subject numbers are low, eg, Silvestrini and colleagues studied a sample of 23 obese patients.[25] Similarly, in the study by Schulz and colleagues, 20% of patients were diabetic, 58% were dyslipidemic, and 65% were hypertensive.[30] In contrast, in our study, there were no diabetic patients, only 11.5% were obese, and only 7.5% were dyslipidemic. We recently published a study in 83 OSA patients after exclusion of the majority of confounding factors and found an independent association between IMT and SaO_2, but only in normotensive subjects.[28] In addition to the relatively low number of major vascular risk factors in our study, the relatively young age of the population and

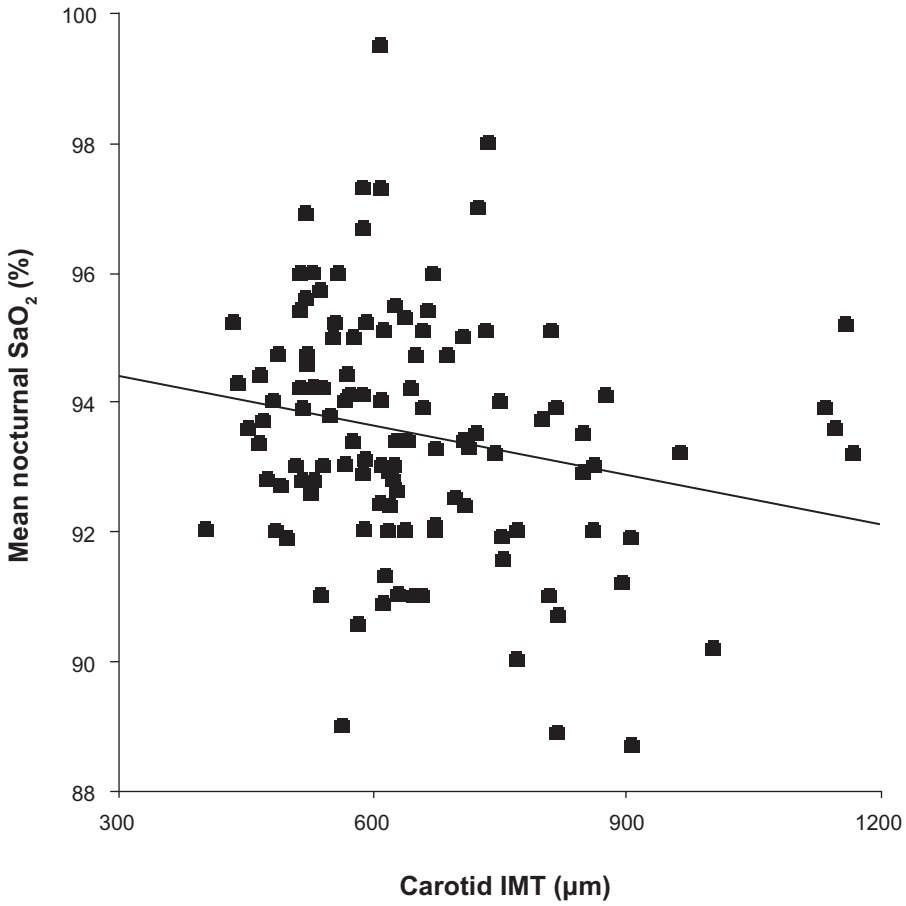

Figure 1 Relationship between carotid IMT and mean nocturnal SaO_2 ($r = -0.21$, $P = 0.017$).
Abbreviations: IMT, intima-media thickness; SaO_2, oxygen saturation.

the recent diagnosis of the OSA potentially contributed to the exclusion of patients with more advanced atherosclerosis. However, our population must not be considered at low cardiovascular risk. This is well demonstrated by the high prevalence of carotid wall abnormalities.

We did not find a significant link between the severity of OSA and aortic stiffness. This is inconsistent with the findings of a number of other studies and can be explained first and foremost by the characteristics of the patients included.[26,28,31,32,34] In fact, whilst in our study OSA was at a mild stage in most subjects and whilst there were few major vascular risk factors, the majority of other studies focusing on PWV looked at very severe OSA.[31,32,34] Although carotid IMT appears to increase early on in the disease, the increase in arterial stiffness could be the consequence of prolonged exposure to OSA.

OSA and cardiac hypertrophy

Our results, like those of other studies, show a link between LVM and the severity of OSA.[35–38,65–67] However, the prevalence of LVH was moderate in our study (9.5%), with no significant difference between the groups of differing OSA severity. In Noda and colleagues' study, prevalence was nearly 40% but the patient population had been suffering from OSA for a longer period of time, was more obese and had worse HT.[67] We can question the independence of the link between OSA and LVM, because OSA patients are more often hypertensive, obese or diabetic, and these are all well-characterized risk factors for LVH. Hedner and colleagues were the first to consider this link, showing that LVM was around 15% higher in normotensive OSA patients than in normotensive control subjects.[65] Similarly, in the study by Cloward and colleagues, HT prevalence was 52% and that of LVH was 88%, suggesting that LVH cannot be explained by HT alone.[37] However, the results of these studies must be analyzed with care because both included obese patients in whom it is well known that it is difficult to measure LVM by ultrasound. Furthermore, neither used ABPM, although 24-hour BP monitoring is more closely associated with LVM. Conversely, a more

Table 3 Factors related to carotid hypertrophy

	Carotid hypertrophy (N = 30)	Normal IMT (N = 100)	*P*
Age (years)	55 ± 8	47 ± 10	**<0.0001**
Clinic SBP (mmHg)	140 ± 18	128 ± 14	**0.002**
Mean nocturnal SaO_2 (%)	92.6 ± 1.7	93.8 ± 1.7	**0.002**
Minimal nocturnal SaO_2 (%)	82.2 ± 8.1	84.7 ± 5.5	0.055
SaO_2 < 90% (%)	10 ± 16	5.5 ± 9.5	**0.020**

Note: Results are given as mean ± SD.
Abbreviations: IMT, intima media thickness; SaO_2, oxygen saturation; SaO_2 < 90%, percentage of recording time spent at a SaO_2 < 90%; SBP, systolic blood pressure; SD, standard deviation.

recent study conducted by Niroumand and colleagues in 533 OSA patients, in whom confounding factors were rigorously controlled for, showed that OSA was not directly involved in the LVM increase.[36] In our study, the link between LVM and mean nocturnal SaO_2 was independent of other factors, suggesting that OSA is directly involved in the occurrence of LVH.

From a pathophysiological point of view, the cardiac changes observed during OSA are linked to an increase in LV afterload, due to a number of different mechanisms. Thus, repeated episodes of nocturnal hypoxia and microarousals – as a result of the sympathetic hyperactivity that they cause – contribute to increase BP.[15] On the other hand, the degree of negative intrathoracic pressure generated by inspiratory effort during OSA has the direct effect of raising transmural pressure and LV afterload, independently of BP.[68–70] Finally, our study, like several others, suggests that arterial stiffness is a possible left ventricular remodeling mechanism during OSA.[71,72]

Study limitations

The main limitation of our study is the absence of a control group. However, several studies have already shown that OSA patients present greater atherosclerotic and cardiac effects than healthy subjects. The aim of our prospective study performed on a large sample of newly diagnosed OSA patients was to determine whether the severity of OSA was associated with the cardiovascular effects independently of traditional major cardiovascular risk factors. As far as we know, this is the first study to have simultaneously evaluated structural and functional cardiovascular parameters in newly diagnosed OSA subjects.

It is difficult to assert that OSA is at an early stage. However, absence of known cardiovascular disease, particularly known hypertension, and absence of former OSA treatment is in favor of a recent disease.

We have used simplified techniques for assessing OSA diagnosis and severity in a subgroup of the included patients. However, in our study, LVM and carotid hypertrophy were

Table 4 Cardiovascular anomalies according to the severity of OSA (mean nocturnal SaO_2)

	Group 1 SaO_2 < 93.5% (N = 68)	Group 2 SaO_2 > 93.5% (N = 62)	*P* value
Clinic hypertension (N, %)	27(40)	18 (29)	0.14
Clinic or ABPM hypertension (N, %)	55 (81)	43 (69)	0.09
Nondipper SBP or DBP	33 (48)	23 (38)	0.13
LVMI-height$^{2.7}$ (g/m)	40 ± 8	36 ± 8	**0.003**
LVH ind$^{2.7}$ (N, %)	8 (12)	3 (4.8)	0.12
Carotid IMT (mm)	0.67 ± 0.14	0.63 ± 0.15	0.13
Increased carotid IMT (N, %)	20 (29.5)	10 (16)	**0.05**
Carotid plaques (N, %)	15 (22)	10 (16)	NS

Note: Results are given as mean ± SD or percentage.
Abbreviations: ABPM, ambulatory blood pressure monitoring; DBP, diastolic blood pressure; IMT, intima media thickness; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; NS, not significant; OSA, obstructive sleep apnea; SaO_2, oxygen saturation; SBP, systolic blood pressure; SD, standard deviation.

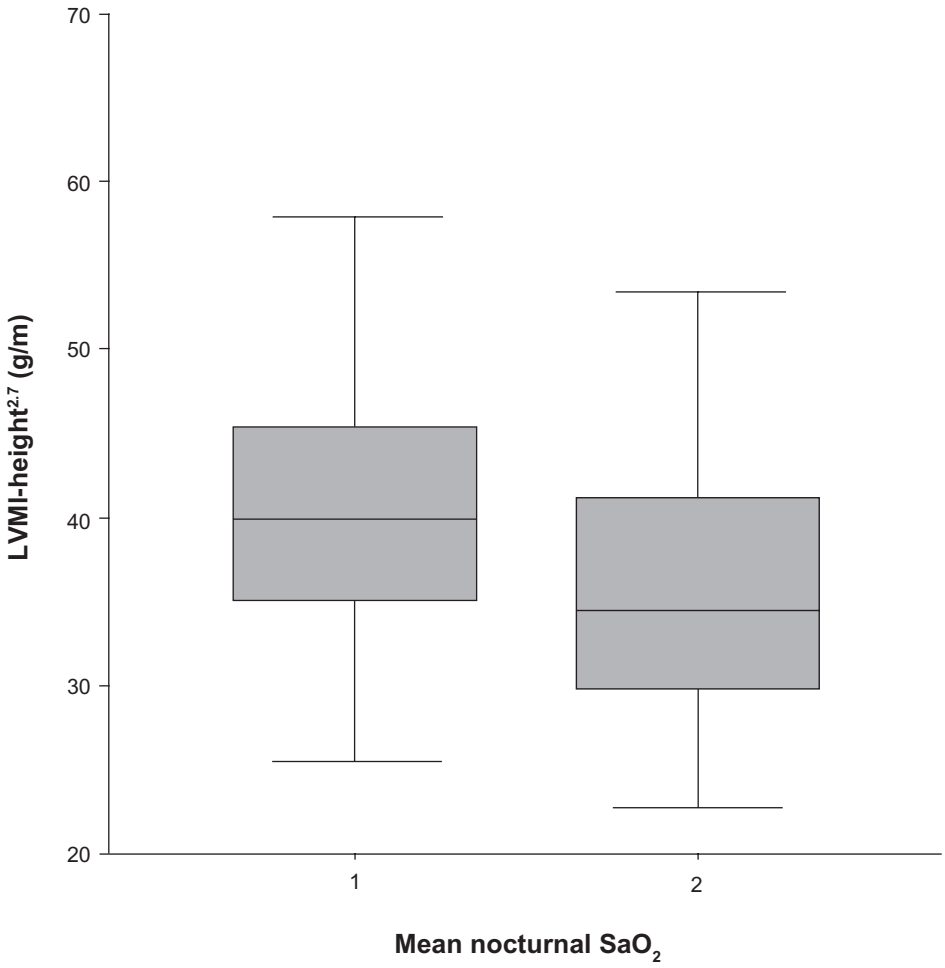

Figure 2 LVMI-height$^{2.7}$ according to the mean nocturnal SaO_2 group (median) ($P = 0.003$ between groups 1 and 2).
Notes: Group 1: mean nocturnal $SaO_2 < 93.5\%$; Group 2: mean nocturnal $SaO_2 \geq 93.5\%$.
Abbreviations: LVMI, left ventricular mass index; SaO_2, oxygen saturation.

mainly correlated with SaO_2 parameters which are properly assessed by simplified sleep studies.

Conclusion

Our population of newly diagnosed OSA patients without clinically diagnosed cardiovascular diseases presented early signs of atherosclerosis and nascent cardiac damage. The severity of the OSA appeared to play more of a role in LV remodeling than in arterial modification. A more systematic study of functional and structural cardiac and arterial modifications in OSA patients could improve the stratification of their cardiovascular risk and help identify candidates for earlier and more aggressive OSA therapy.

Disclosures

The authors report no conflicts of interest in this work.

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