Cardiorespiratory consequences of sleep apnoea syndrome in patients with massive obesity

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ABSTRACT: Assessment of cardiorespiratory consequences of sleep apnoea syndrome (SAS) is difficult owing to confounding factors, especially obesity, that are strongly associated with SAS. This study was designed to assess the cardiorespiratory consequences of SAS by comparing the results of a comprehensive cardiorespiratory evaluation in apnoeic and nonapnoeic patients with massive obesity.

In a retrospective chart-review study, we studied 60 patients with massive obesity defined by a body mass index (BMI) $>40 \text{ kg}\cdot\text{m}^{-2}$, presenting no chronic respiratory disease, who underwent an extensive assessment of cardiorespiratory consequences of obesity, including overnight polysomnography, lung function tests, arterial blood gas analysis, evaluation of vascular risk factors, myocardial scintigraphy with dipyridamole stress-test, isotopic ventriculography, Doppler echocardiography and Holter electrocardiogram recording.

SAS defined by an apnoea + hypopnoea index (AHI) ≥ 10 was diagnosed in 42% of patients (25 out of 60). Mean $\pm$ SD AHI of SAS-positive (SAS+) patients was 38 ± 24 . Age, BMI, ventilatory function parameters, prevalence of smoking history and diabetes mellitus did not differ significantly in SAS+ versus SAS-negative (SAS-) groups. The following complications were observed more frequently in SAS+ than in SAS- patients: daytime hypoxaemia (35 vs 9%, $p < 0.02$), pulmonary arterial hypertension (36 vs 7%, $p < 0.05$) and increased interventricular septal thickness (50 vs 15%, $p < 0.03$). No association was found between SAS on the one hand and systemic arterial hypertension, coronary artery disease, left ventricular dysfunction and nocturnal cardiac arrhythmias on the other.

Nocturnal apnoeas in massive obesity may thus be associated with moderate daytime hypoxaemia, mild pulmonary arterial hypertension and moderate left ventricular hypertrophy, but not with severe cardiorespiratory complications.

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Sleep apnoea syndrome (SAS) has been reported to be associated with excess mortality [1, 2] and a wide range of cardiac and respiratory sequelae [3–5]: daytime alveolar hypoventilation, pulmonary arterial hypertension, systemic arterial hypertension, left ventricular hypertrophy and dysfunction, cardiac arrhythmias and ischaemic heart disease. However, conflicting data have been published on the cardiorespiratory consequences of SAS. This might be due to the fact that most studies did not take sufficient account of the potential effects of confounding variables, such as age, smoking, and obesity [6]. Obesity is a major confounding factor as it is strongly associated with SAS [7, 8], and may yield the same cardiorespiratory complications as SAS. Therefore, observing cardiac and respiratory abnormalities in an obese patient with SAS does not necessarily imply a causal association between nocturnal apnoeas and cardiorespiratory morbidity.

Another confounding factor is the association of chronic obstructive pulmonary disease (COPD), which may explain certain conflicting results on the role of SAS in

the development of daytime alveolar hypoventilation and pulmonary arterial hypertension [9–11].

The aim of the present study was to assess the cardiorespiratory consequences of SAS by comparing the results of a comprehensive cardiorespiratory evaluation in apnoeic and nonapnoeic patients with a similar degree of obesity, *i.e.* massive obesity and without COPD. This study investigated the role of SAS in the development of daytime alveolar hypoventilation, pulmonary arterial hypertension, systemic arterial hypertension, left ventricular dysfunction, left ventricular hypertrophy and dilatation, cardiac arrhythmias and coronary artery disease.

Patients and methods

Study population

The study population included morbidly obese patients admitted consecutively over a 3 yr period to the Nutrition department of Hôtel-Dieu Hospital for an extensive

assessment of obesity-related complications including a comprehensive evaluation of heart and respiratory systems. All of these patients, whether or not presenting the typical clinical features of obstructive SAS, underwent polysomnography, lung function tests, arterial blood gas analysis, radionuclide ventriculography, myocardial scintigraphy with dipyridamole test, Doppler echocardiography and Holter electrocardiogram (ECG) recording. Inclusion criteria for the present study were: 1) massive obesity defined by a body mass index (BMI) $>40 \text{ kg}\cdot\text{m}^{-2}$; 2) absence of COPD defined by the usual criteria [12] and absence of restrictive respiratory disease other than that related to obesity, namely pulmonary fibrosis, sequelae of pulmonary tuberculosis and chest wall disease; 3) absence of respiratory failure or bronchopulmonary infection during the previous 2 months; and 4) absence of congestive heart failure or acute coronary event in the previous 2 months.

A total of 60 patients meeting these criteria were included in this retrospective chart-review study.

Methods

Polysomnography

Overnight polygraphic sleep study was carried out in our sleep laboratory using standard recording techniques. Sleep was monitored with an electroencephalogram, an electro-oculogram and a chin electromyogram (Alvar, Medical Equipment International, Paris, France). The sleep was analysed manually by 30 s epochs according to the interpretation manual of RECHTSCHAFFEN and KALES [13]. At the time of the study, computerized systems for storing data were not available in our laboratory, so recordings were made on paper.

Air flow recording by means of an oronasal thermistor detected apnoea, defined as cessation of air flow for at least 10 s. Apnoea index (AI) was calculated as the number of apnoeas per hour of sleep. The type of apnoea was defined by analysis of thoraco-abdominal movements, that were recorded by respiratory inductive plethysmography using mercury strain gauge (Volucapt, Vickers, Bordeaux, France). The transducers were placed around the chest and abdomen.

Arterial oxyhaemoglobin saturation (Sa_2O_2) was recorded by means of a pulse oximeter (Oxyshuttle, Sensor Medics Inc., Anaheim, USA).

Hypopnoea was defined as a decrease in ventilation exceeding 50% associated with Sa_2O_2 drop by $\geq 4\%$, for at least 10 s. Apnoea + hypopnoea index (AHI) was calculated as the number of apnoeas and hypopnoeas per hour of sleep.

Several parameters of oxyhaemoglobin desaturation were computed: 1) minimal Sa_2O_2 ; 2) percentage of total sleep time (TST) spent at $\text{Sa}_2\text{O}_2 < 90\%$ (% TST- $\text{Sa}_2\text{O}_2 < 90\%$); 3) percentage of TST spent at $\text{Sa}_2\text{O}_2 < 80\%$ (% TST- $\text{Sa}_2\text{O}_2 < 80\%$); and 4) percentage of TST during which Sa_2O_2 drops by $\geq 4\%$ from the nocturnal baseline (% TST- Sa_2O_2 dip $\geq 4\%$).

The patients were divided up into two groups according to AHI: patients with SAS (SAS+ group) were defined

by an AHI ≥ 10 episodes $\cdot\text{h}^{-1}$, and patients without SAS (SAS- group) were defined by an AHI < 10 episodes $\cdot\text{h}^{-1}$.

Nutritional assessment

Anthropometric measurements. Weight, height and waist-to-hip ratio were measured. Waist circumference was measured at the level of the umbilicus and hip circumference at the greater trochanters with the subject upright.

Biological measurements. These included measurements of fasting and postprandial blood glucose. Diabetes mellitus was defined by a fasting blood glucose level $\geq 7.7 \text{ mmol}\cdot\text{L}^{-1}$, a postprandial blood glucose level $\geq 11 \text{ mmol}\cdot\text{L}^{-1}$, or by the history of regular treatment for previously-known diabetes. In addition, total blood cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoprotein A₁, and apolipoprotein B were measured using enzymatic methods on a fasting sample.

Lung function tests

Pulmonary volumes and flows were measured by means of a wet spirometer PULMONET III (Sensor Medics). Results were expressed as percentages of reference values.

Assessment of cardiorespiratory consequences

The following six methods of assessment were performed.

Arterial blood gas analysis. Partial pressures of oxygen (Pa_2O_2) and carbon dioxide (Pa_2CO_2) were measured in an arterial blood sample taken during daytime wakefulness, with the patient in semi-recumbent position (Instrumentation Laboratory 1306, Milan, Italy). Hypoxaemia was defined as $\text{Pa}_2\text{O}_2 < 9.3 \text{ kPa}$ ($< 70 \text{ mmHg}$) and hypercapnia as $\text{Pa}_2\text{CO}_2 \geq 6.0 \text{ kPa}$ ($\geq 45 \text{ mmHg}$).

Measurement of arterial blood pressure. Arterial blood pressure was measured in the morning with the patient in supine position. Six recordings of blood pressure were obtained on each patient during their hospitalization. Systemic arterial hypertension was defined as a systolic blood pressure $\geq 160 \text{ mmHg}$ or a diastolic blood pressure $\geq 95 \text{ mmHg}$, observed over at least three recordings. Patients with a history of regular antihypertensive medication for a known systemic arterial hypertension were also considered as hypertensive.

Single-photon-emission computed tomography (SPECT) myocardial study. SPECT myocardial study with a dipyridamole stress-test was performed, using an intravenous infusion of dipyridamole ($0.6 \text{ mg}\cdot\text{kg}^{-1}$). An intravenous injection of 111 MBq of thallium-201 or of 296-740 MBq of technetium-99m methoxy-isobutyl-isonitrile (MIBI) (depending on patient's weight) was followed by a SPECT acquisition: 30 frames on a 180° arc extending from 45° right anterior oblique to 45° left posterior oblique position (30 s per frame, matrice 64×64). Horizontal long-axis, short-axis and vertical long-axis slices were reconstructed

using filtered back-projection. Myocardial segment activity was assessed on a short-axis slices bull-eye, where the maximum count per pixel of each cut was normalized to a value of 100%. A new acquisition using the same procedure was performed following a rest injection, 240 min later for thallium-delayed imaging, 2 days later for MIBI rest imaging.

Myocardial ischaemia was defined by the presence of a myocardial perfusion defect on the dipyridamole images, that disappeared or markedly decreased on the rest images.

Radionuclide ventriculography. Multiple-gated equilibrium cardiac imaging was performed following a standard procedure: 1 GBq of technetium-99m was injected after *in vivo* (or *in vitro*) labelling of red blood cells. Data were acquired in the left anterior oblique (LAO) view, using the degree of obliquity that provided the best separation between both ventricles and the atria. Sixteen frames per cycle were acquired (minimum 200,000 counts per frame, matrice 64 × 64, Tomo camera Elscint 609, Haifa, Israel, or Acti CGR, Sopha-Médical, Buc, France) and processed with special computer systems (Elscint Apex SP 1 or S4000, Sopha-Médical).

The left ventricular ejection fraction (LVEF) was calculated by both automatic and semi-automatic programmes, after generation of Fourier phase and amplitude images, and definition of end-diastolic and end-systolic left ventricular images. Left ventricular dysfunction was defined by an LVEF <55%.

Doppler echocardiography. Doppler echocardiography was performed in all patients, using an echocardiograph (77020-CF; Hewlett-Packard, Andover, USA).

In the assessment of left ventricular wall thickness and diameters, the following parameters were measured: left ventricular posterior wall diastolic thickness (LV-PWT), diastolic interventricular septal thickness (Septum-T), left ventricular end-diastolic diameter (LV-EDD), and left ventricular end-systolic diameter (LV-ESD).

Left ventricular hypertrophy was defined by a LV-PWT >11 mm and/or a Septum-T >11 mm. Left ventricular dilatation was defined by a LV-EDD >56 mm and/or a LV-ESD >40 mm.

In the assessment of pulmonary artery pressure (P_{pa}), systolic P_{pa} was evaluated by measuring tricuspid regurgitant blood flow peak velocity by means of continuous-wave Doppler echocardiography. If tricuspid regurgitation was absent, mean P_{pa} was estimated from the early diastolic pulmonary regurgitant blood flow peak velocity in continuous-wave Doppler echocardiography. If both tricuspid and pulmonary regurgitations were absent, P_{pa} was evaluated by measuring acceleration time of pulmonary blood flow recorded by means of pulsed Doppler echocardiography. Pulmonary arterial hypertension was defined by an estimated systolic P_{pa} >35 mmHg, an estimated mean P_{pa} >20 mmHg or a pulmonary acceleration time <90 ms [14].

24 h Holter ECG monitoring. A 24 h Holter ECG recording (Anatec S612, Ela Medical, Montrouge, France) was performed in all patients in order to screen cardiac arrhythmias. Two recording periods were defined: a "nocturnal" period from 22:00 to 08:00 h, and a "daytime" period from 08:00 to 22:00 h.

Physicians who performed and interpreted the various cardiological and respiratory investigations were not informed about the results of polysomnography.

Statistical analysis

Quantitative data were compared in the SAS- versus SAS+ groups using Student's t-test, and percentages using Chi-squared test.

Regression analysis and multivariate analysis were made by multiple linear regression (BMDP program P1R; Statistical Solutions Ltd, Cork, Ireland) looking for a correlation between the AHI on the one hand and the different cardiorespiratory parameters on the other.

Results are given as mean ± SD.

Results

Polysomnography (table 1)

SAS (AHI ≥10) was diagnosed in 42% of patients (25 out of 60). AHI of SAS+ patients was 38 ± 24. Apnoea index of SAS+ patients was 33 ± 23, with predominance of obstructive or mixed-type apnoeas (77% of total number of detected apnoeas) and an average duration of 22 ± 5 s.

The values of nocturnal oxyhaemoglobin desaturation parameters are summarized in table 1. No patient exhibited Cheyne-Stokes respiration.

General characteristics (table 2)

A significantly higher percentage of males was found in the SAS+ than in the SAS- group. Age did not differ in the two groups nor did it correlate significantly with AHI. The percentage of patients with smoking history and the number of cigarette pack-years did not differ between SAS- versus SAS+ patient groups. The percentages of patients with excessive daytime somnolence or observed

Table 1. – Polysomnography data in SAS+ versus SAS- patients

Polysomnographic parameter	SAS- AHI <10 (n=35)	SAS+ AHI ≥10 (n=25)	p-value
AHI episodes·h ⁻¹	2±3	38±24	<0.001
AI episodes·h ⁻¹	1±2	33±23	<0.001
% TST-Sa _o ₂ <90%	22±26	67±31	<0.001
% TST-Sa _o ₂ <80%	3±7	32±34	<0.001
% TST-Sa _o ₂ dip ≥4%	25±22	60±29	<0.001
Minimal Sa _o ₂ %	77±12	60±17	<0.001

Values are mean ± SD. SAS-: without sleep apnoea syndrome; SAS+: with sleep apnoea syndrome; AHI: apnoea + hypopnoea index; AI: apnoea index; Sa_o₂: arterial oxyhaemoglobin saturation; % TST-Sa_o₂ <90%: percentage of total sleep time (TST) spent at Sa_o₂ <90%; % TST-Sa_o₂ <80%: percentage of TST spent at Sa_o₂ <80%; % TST-Sa_o₂ dip ≥4%: percentage of TST during which Sa_o₂ dropped by ≥4% from nocturnal baseline.

Table 2. – General characteristics of SAS+ versus SAS- patients

Characteristic	SAS- AHI <10 (n=35)	SAS+ AHI ≥10 (n=25)	p-value
Age ⁺ yrs	43±10	47±10	NS
Male %	26	58	<0.02
Smoking			
Current %	29	33	NS
Pack-years ⁺	18±11	29±16	NS
Snoring %	82	92	NS
Excessive daytime somnolence %	29	71	<0.01
Observed apnoeas %	13	57	<0.01
ACE inhibitors %	19	16	NS
Beta-blockers %	13	17	NS
Calcium-channel blockers %	13	12	NS
Prior AMI %	10	8	NS

Values are percentages of patients. ⁺: mean±SD. ACE: angiotensin-converting enzyme; AMI: acute myocardial infarction; NS: nonsignificant. For further definitions see legend to table 1.

apnoeas were significantly higher in the SAS+ than in the SAS- group, but the prevalence of snoring did not differ in the two groups. No significant difference was found between SAS- and SAS+ patients regarding the regular use of angiotensin-converting enzyme inhibitors, beta-blockers, or calcium-channel blockers. The percentage of patients with a history of prior myocardial infarction did not differ in SAS- versus SAS+ groups (10 versus 8%).

Nutritional parameters (table 3)

Weight, BMI and waist-to-hip ratio showed no significant difference between SAS- and SAS+ groups. No significant correlation was found between AHI on the one hand, and weight, BMI or waist-to-hip ratio on the other.

Table 3. – Nutritional parameters in SAS+ versus SAS- patients

	SAS- AHI <10 (n=35)	SAS+ AHI ≥10 (n=25)	p-value
Weight kg	139±30	143±32	NS
BMI kg·m ⁻²	50.9±10	49.7±9.4	NS
W/H ratio			
male	0.98±0.1	1.01±0.14	NS
female	0.95±0.12	0.92±0.13	NS
Fast. gluc. mM	6.8±2.8	6.4±1.2	NS
PP gluc. mM	7.9±3.4	8±2.3	NS
Diabetes % [#]	28	30	NS
Total chol. g·L ⁻¹	2.1±0.5	2.2±0.4	NS
HDL chol. g·L ⁻¹	0.4±0.1	0.4±0.1	NS
Trigly. g·L ⁻¹	1.7±1	1.6±0.8	NS
Apo A ₁ g·L ⁻¹	1.4±0.3	1.5±0.2	NS
Apo B g·L ⁻¹	1.3±0.5	1.4±0.4	NS

Values are mean±SD. [#]: percentage of patients. BMI: body mass index; W/H: waist to hip; Fast. gluc.: fasting blood glucose level; PP gluc.: postprandial blood glucose level; chol.: blood cholesterol level; HDL: high-density lipoprotein; Trigly.: blood triglycerides level; Apo A₁ and Apo B: blood levels of Apolipoprotein A₁ and B, respectively; NS: nonsignificant. For further definitions see legend to table 1.

None of the patients had unusual forms of obesity, especially those known to be associated with sleep apnoea such as genetic syndromes (e.g. Prader-Willi).

The percentage of patients with diabetes mellitus was not significantly different in SAS- versus SAS+ groups. Blood concentrations of fasting and postprandial glucose, cholesterol, HDL cholesterol, triglycerides and apolipoproteins A₁ and B were not significantly different in SAS- versus SAS+ groups. Regression analysis found no correlation between AHI and any of those parameters.

Lung function tests (table 4)

Forced expiratory volume in one second (FEV₁), slow vital capacity (VC), FEV₁/VC ratio, residual volume (RV), expiratory reserve volume (ERV), functional residual capacity (FRC) and total lung capacity (TLC) values showed no significant difference between SAS- and SAS+ groups. AHI did not correlate significantly with any of those ventilatory parameters.

An important decrease in ERV and FRC was found in the two groups, but mean values of TLC, VC, FEV₁ and FEV₁/VC were within normal range.

Assessment of cardiorespiratory consequences

Daytime Pa,O₂ and Pa,CO₂ measurements (table 5). Arterial blood gas analysis was available in 95% of patients (57 out of 60). Arterial puncture was not possible in the remaining three patients for obesity-related technical difficulties.

Pa,O₂ was significantly lower in the SAS+ than in the SAS- group. The percentage of patients with hypoxaemia, defined as Pa,O₂ <9.3 kPa (<70 mmHg) was significantly larger in SAS+ group (35%) than in SAS- group (9%).

Pa,CO₂ was slightly higher in SAS+ than in SAS- group, but the difference was not statistically significant (p=0.08). Hypercapnia, defined as Pa,CO₂ ≥6.0 kPa (≥45 mmHg) was observed more often in SAS+ (22%) than in SAS- group (6%), but the difference did not reach a significant level (p=0.08).

Univariate analyses revealed a negative correlation between AHI and Pa,O₂ (r=-0.30, p<0.03), and a positive

Table 4. – Lung function tests in SAS+ versus SAS- patients

		SAS- AHI <10 (n=35)	SAS+ AHI ≥10 (n=25)	p-value
FEV ₁	% pred	96±20	91±19	NS
VC	% pred	100±16	96±18	NS
FEV ₁ /VC	% pred	99±10	95±11	NS
RV	% pred	87±24	77±20	NS
ERV	% pred	43±23	40±21	NS
FRC	% pred	70±18	63±16	NS
TLC	% pred	94±15	88±14	NS

Values are mean±SD. FEV₁: forced expiratory volume in one second; VC: vital capacity; RV: residual volume; ERV: expiratory reserve volume; FRC: functional residual capacity; TLC: total lung capacity; % pred: percentage of the predicted value; NS: nonsignificant. For further definitions see legend to table 1.

Table 5. – Daytime hypoxaemia, hypercapnia, and pulmonary arterial hypertension in SAS+ versus SAS- patients

Parameter	Patients n	SAS- AHI <10	SAS+ AHI $\geq$ 10	p-value
P_{a,O_2} <70 mmHg %	57*	9	35	<0.02
P_{a,O_2} mmHg		86.8 $\pm$ 13.2	77 $\pm$ 15.3	<0.02
P_{a,CO_2} $\geq$ 45 mmHg %	57*	6	22	NS
P_{a,CO_2} mmHg		38.5 $\pm$ 5.3	41.2 $\pm$ 5.9	NS
PAH %	28**	7	36	<0.05

*: patients in whom arterial blood gas analysis could be performed; **: patients in whom pulmonary artery pressure could be estimated by Doppler echocardiography in satisfactory technical conditions; +: mean $\pm$ SD. P_{a,O_2} : arterial partial pressure of oxygen; P_{a,CO_2} : arterial partial pressure of carbon dioxide; PAH: pulmonary arterial hypertension; SAS: sleep apnoea syndrome; AHI: apnoea + hypopnoea index. 1 mmHg=0.133 kPa.

correlation between AHI and P_{a,CO_2} ($r=0.29$, $p<0.04$). However, in multivariate analysis, no correlation was found between AHI and either P_{a,O_2} or P_{a,CO_2} .

Systemic arterial hypertension (table 6). The prevalence of systemic arterial hypertension showed no significant difference between the SAS- and SAS+ groups (47 versus 42%). Most of hypertensive patients were receiving anti-hypertensive medication at the time of presentation, with no significant difference between the SAS- and SAS+ groups (87 versus 80% of hypertensive patients).

SPECT myocardial study (table 6). This investigation was carried out in satisfactory technical conditions in 88% (53 out of 60) of patients. Percentages of positive aspects of myocardial ischaemia on scintiscan were comparable in the SAS- versus SAS+ groups (23 versus 24%).

Left ventricular function evaluation by radionuclide angiography (table 6). LVEF was measured in satisfactory technical conditions in 98% of patients (59 out of 60). LVEF showed no significant difference between the SAS- group (59.6 $\pm$ 8.4%) and the SAS+ group (57.3 $\pm$ 9.7%), and the two groups did not differ significantly in the percentage of patients (26 versus 33%, respectively) with left ventricular dysfunction defined by LVEF <55%.

Evaluation of left ventricular wall thickness and diameters by echocardiography (table 7). Echocardiographic study of the left ventricle (LV) was carried out reliably in only

Table 6. – Systemic arterial hypertension, myocardial ischaemia and left ventricular dysfunction in SAS+ versus SAS- patients

Parameter	Patients n	SAS- AHI <10	SAS+ AHI $\geq$ 10	p-value
Hypertension % [#]	60	47	42	NS
Myocardial ischaemia % [#]	53*	23	24	NS
%LVEF <55% [#]	59**	26	33	NS
LVEF % ⁺		59.6 $\pm$ 8.4	57.3 $\pm$ 9.7	NS

*: percentage of patients; +: mean $\pm$ SD; *: patients in whom single-photon-emission computed tomography myocardial study could be performed in satisfactory technical conditions; **: patients in whom radionuclide ventriculography could be performed in satisfactory technical conditions. NS: nonsignificant; LVEF: left ventricular ejection fraction. For further definitions see legend to table 1.

Table 7. – Left ventricular hypertrophy and dilatation in SAS+ versus SAS- patients

	SAS- AHI <10	SAS+ AHI $\geq$ 10	p-value
Septum-T >11 mm % [#]	15	50	<0.03
Septum-T mm ⁺	9.7 $\pm$ 1.8	11.3 $\pm$ 2.4	<0.04
LV-PWT >11 mm % [#]	0	12	NS
LV-PWT mm ⁺	8.9 $\pm$ 1.3	9.6 $\pm$ 1.7	NS
LV-EDD >56 mm % [#]	18	15	NS
LV-EDD mm ⁺	51.8 $\pm$ 5.8	51.1 $\pm$ 4.4	NS
LV-ESD >40 mm % [#]	6	17	NS
LV-ESD mm ⁺	32 $\pm$ 5.1	32.9 $\pm$ 5.6	NS

The data presented concern the 37 patients in whom echogenicity was good enough to allow echocardiographic measurements of LV wall thickness and diameter. #: percentages of patients; +: mean $\pm$ SD. LV: left ventricular; Septum-T: diastolic interventricular septal thickness; PWT: posterior wall diastolic thickness; EDD: end-diastolic diameter; ESD: end-systolic diameter; NS: nonsignificant. For further definitions see legend to table 1.

62% of patients (37 out of 60), because of poor echogenicity related to massive obesity in the remaining patients.

Diastolic interventricular septal thickness was significantly larger in the SAS+ (11.3 $\pm$ 2.4 mm) than in the SAS- group (9.7 $\pm$ 1.8 mm). The percentage of patients with a diastolic interventricular septal thickness >11 mm was significantly higher in the SAS+ than in the SAS- group (50 versus 15%). Univariate analysis showed a significant correlation between AHI and septal thickness ($r=0.37$, $p<0.03$), but this correlation was not found in multivariate analysis.

LV-PWT, LV-EDD and LV-ESD did not differ in SAS- versus SAS+ groups, and did not correlate significantly with the AHI. No significant difference was found between percentages of patients with abnormally high values of LV-PWT, LV-EDD and LV-ESD in the SAS- group and the respective percentages in the SAS+ group.

Evaluation of P_{pa} by Doppler echocardiography (table 5). It was possible to estimate P_{pa} by Doppler echocardiography in only 47% of patients (28 out of 60) essentially because of problems related to poor echogenicity.

Pulmonary arterial hypertension (PAH) was observed significantly more often in SAS+ than in SAS- patients (36 versus 7%), and was only moderate.

Detection of nocturnal cardiac arrhythmias by 24 h Holter ECG recording (table 8). An interpretable recording was obtained in only 78% of patients (47 out of 60) because of recording defect ($n=4$), insufficient recording period ($n=5$) or bad-quality ECG signal ($n=4$).

The number of nocturnal premature ventricular beats and premature supraventricular beats per hour was not significantly different in the SAS- versus the SAS+ group, and did not correlate significantly with the AHI. The SAS- and SAS+ groups showed no significant difference in the prevalence of nocturnal multifocal premature ventricular beats. No patient presented nocturnal ventricular or supra-ventricular tachycardia. Nocturnal sinus arrest for >2 s was recorded in one patient in SAS- group and in one patient in SAS+ group. No patient presented nocturnal sino-atrial or atrioventricular block.

No significant difference was found by comparing nocturnal with daytime arrhythmias in either group.

Table 8. – Nocturnal cardiac arrhythmias in SAS+ versus SAS- patients

	SAS- AHI <10	SAS+ AHI ≥10	p-value
PVB beats·h ⁻¹ +	18±53	6±19	NS
PVB >10 beats·h ⁻¹ % [#]	10	11	NS
PVB >30 beats·h ⁻¹ % [#]	10	5	NS
Multifocal PVB % [#]	7	16	NS
VT % [#]	0	0	NS
PSVB beats·h ⁻¹ +	7±6	7±6	NS
PSVB >10 beats·h ⁻¹ % [#]	17	21	NS
PSVB >30 beats·h ⁻¹ % [#]	0	0	NS
SVT % [#]	0	0	NS
Sinus arrest >2 s % [#]	3	5	NS
SA block % [#]	0	0	NS
II or III AV block % [#]	0	0	NS

The data presented concern the 47 patients in whom an interpretable 24 h Holter electrocardiogram recording was obtained.

[#]: percentage of patients; +: mean±SD. PVB: premature ventricular beat; PSVB: premature supraventricular beat; VT: ventricular tachycardia; SVT: supraventricular tachycardia; SA block: sino-atrial block; II or III AV block: second degree or third degree atrioventricular block; NS: nonsignificant. For further definitions see legend to table 1.

Discussion

The present study carried out in patients with massive obesity and without COPD, shows that SAS is not associated with severe cardiorespiratory complications, but produces only minor consequences *e.g.* moderate daytime hypoxaemia, mild pulmonary arterial hypertension and moderate hypertrophy of the interventricular septum. No association was found between SAS on the one hand, and systemic arterial hypertension, left ventricular dysfunction or dilatation, coronary artery disease, and cardiac arrhythmias on the other. The major difficulty in investigating the cardiorespiratory effects of sleep apnoeas lies in adjusting for the effects of confounding factors that are closely associated with sleep apnoeas [6]. In the present study, the apnoeic and nonapnoeic patient groups did not differ with regard to the main confounding factors, *i.e.* severity and type of obesity, other vascular risk factors, age and impairment of lung function, so that it was possible to evaluate the cardiorespiratory complications that were specifically related to nocturnal apnoeas.

Some criticism could be addressed as regards the sleep studies of the present work. The arousal frequency was not routinely computed at the time that the sleep studies were performed. Although arousals are recognized to be important correlates of rises in sympathetic activity that occur with abnormal respiratory events during sleep [4], the specific role of arousals in the cardiorespiratory complications of SAS is not yet fully understood and should be studied prospectively. Some patients in the SAS- group exhibited moderate nocturnal desaturation. None of the SAS- patients had Cheyne-Stokes respiration. Those nocturnal desaturations that occurred most often in the absence of hypopnoeas might be related to the mechanical respiratory consequences of massive obesity, exaggerated during sleep [15]. As we did not measure arousal frequency or oesophageal pressure, some patients with the upper airway resistance syndrome might have been missed

and included in the SAS- group. However, to our knowledge, the cardiovascular consequences of the upper airway resistance syndrome have not yet been evaluated.

The present study shows that the only cardiorespiratory complications of SAS were daytime hypoxaemia, pulmonary arterial hypertension and interventricular septal hypertrophy. Daytime hypoxaemia was observed in 35% of the SAS+ and in only 9% of the SAS- patients, while no patient had COPD. The exclusive role of obesity in the mechanism of daytime hypoxaemia can be ruled out as the severity and type of obesity, and its repercussions on ventilatory function, did not differ significantly in the SAS- versus the SAS+ group. The mechanism of daytime hypoxaemia is probably alveolar hypoventilation induced by impairment of ventilatory control that results from nocturnal apnoeas [16, 17].

Nocturnal apnoeas may lead to peaks of pulmonary arterial hypertension which results essentially from hypoxaemic pulmonary vasoconstriction [5]. Whether permanent pulmonary arterial hypertension could result solely from apnoea-induced nocturnal repeated hypoxaemias still remains a much-debated question. It is usually stated that the development of pulmonary arterial hypertension is often associated with daytime hypoxaemia that is principally related to an associated COPD [10, 18]. The present data suggest that SAS may be complicated by pulmonary arterial hypertension in the absence of associated COPD. However, great care needs to be taken in the interpretation of the results as Doppler estimation was not possible in approximately 50% of patients because of obesity-related echogenicity problems. Invasive haemodynamic studies are therefore warranted to confirm these results.

The present study demonstrates a moderate interventricular septal hypertrophy in 50% of SAS+ and in only 15% of SAS- patients. Septal hypertrophy was not associated with a significant increase in left ventricular posterior wall thickness. Although right ventricular wall thickness was not measured because of echogenicity problems, it is unlikely that the increase in interventricular septum thickness was related to right ventricular hypertrophy because pulmonary hypertension, when observed, was always moderate. So the increased septal thickness probably represents an initial stage of left ventricular hypertrophy, as has been demonstrated in patients with borderline hypertension [19]. Septal hypertrophy was observed more often in apnoeic than in nonapnoeic patients, although the two groups did not differ with regard to the prevalence of systemic arterial hypertension, and the severity of obesity. These results are in accordance with those of HEDNER *et al.* [20] who showed that, in obese patients with normal blood pressure, the left ventricular mass is larger in apnoeic patients than in weight-paired nonapnoeic patients. Obstructive apnoeas may lead to left ventricular hypertrophy *via* several mechanisms: an increase in left ventricular afterload during apnoeas that results from systemic vasoconstriction and high intrathoracic negative pressures, and a permanent rise in sympathetic activity [5].

This study finds no association between SAS on one hand, and systemic arterial hypertension, coronary artery disease, left ventricular dysfunction and cardiac arrhythmias on the other. Nocturnal apnoeas may lead to paroxysmic peaks of systemic blood pressure [4], but evidence for a causal association between nocturnal apnoeas and daytime arterial hypertension is still lacking because

obesity as a confounding factor has not been assessed adequately in most studies [6, 21]. In the present study concerning patients with massive obesity, the prevalence of daytime arterial hypertension was high, but did not differ significantly in apnoeic *versus* nonapnoeic patients. However, our results should be cautiously interpreted as most hypertensive patients were already receiving antihypertensive medication.

An association between sleep apnoeas and coronary artery disease has been reported, but in those studies, diagnosis of SAS was made after that of ischaemic heart disease [6, 22]. In the present cross-sectional study, patients were systematically screened for coronary artery disease using SPECT myocardial scintigraphy with dipyridamole stress-test which has been shown to have high sensitivity and specificity for that diagnosis [23]. The prevalence of coronary artery disease was found to be relatively high but it was not significantly different in apnoeic *versus* non-apnoeic patients.

LVEF did not differ significantly in apnoeic *versus* nonapnoeic patients in the present study. The main point is that this result was observed in two groups of patients which were comparable with regard to the confounding factors, *i.e.* severity and type of obesity, prevalence of coronary artery disease, systemic arterial hypertension and diabetes mellitus. Similar results were reported by HANLY *et al.* [24] who have shown, in moderately obese patients, that systolic left ventricular function was not different in apnoeic patients *versus* nonapnoeic snorers. However, in patients presenting SAS associated with idiopathic dilated cardiomyopathy, reversal of nocturnal apnoeas by nasal continuous positive airway pressure may lead to significant improvement in left ventricular function [25].

The present study demonstrates that prevalence of nocturnal cardiac arrhythmias is not significantly different in apnoeic *versus* nonapnoeic patients. Comparable results have been reported by FLEMONS *et al.* [26] who showed that prevalence of cardiac arrhythmias was low in apnoeic patients without serious cardiac or respiratory co-morbidity and was similar to their prevalence in healthy subjects.

The results of the present work should be interpreted with the knowledge that the study population consisted of patients referred for a comprehensive evaluation of obesity-related complications. These patients were investigated independently of the presence of clinical features of sleep apnoeas. Patients with recent respiratory and cardiac failure were excluded as well as those with a recent acute coronary event. Thus, patients with troublesome symptoms of SAS or severe cardiovascular disease may have taken an alternative clinical route and so not been included. Therefore, the patients who were studied would represent the mild end of the spectrum and any differences from those obese patients with no respiratory sleep disease minimized. However, we did not exclude patients with significant heart disease unless they had presented an acute event in the previous 2 months. Approximately 10% of the included patients suffered from a prior myocardial infarction. In both apnoeic and nonapnoeic patient groups, the percentages of patients with systemic arterial hypertension or myocardial ischaemia were high despite their relatively young age, which suggests that the potential for selection bias was not major.

In conclusion, the present study shows that, in patients with massive obesity, sleep apnoeas do not yield severe cardiorespiratory complications, but only minor complications such as moderate daytime hypoxaemia, mild pulmonary arterial hypertension and moderate left ventricular hypertrophy. No association was found between nocturnal apnoeas on the one hand, and systemic arterial hypertension, coronary artery disease, left ventricular dysfunction and cardiac arrhythmias on the other. However, this study does not exclude the possibility that more severe cardiorespiratory complications could be observed in older patients, in patients with higher apnoea + hypopnoea index or more profound nocturnal hypoxaemia, or in severely symptomatic patients presenting for assessment and management of sleep apnoea.

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