The Relationship of Daytime Hypoxemia and Nocturnal Hypoxia in Obstructive Sleep Apnea Syndrome

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Question of the study: Prevalence and determinants of daytime hypoxemia in patients with obstructive sleep apnea (OSA) syndrome are not well established. The aims of this study, conducted in a large series of OSA patients, were to estimate the prevalence of daytime hypoxemia, to assess the reciprocal effects between daytime PaO_2 and nocturnal SpO_2, and to investigate the direct and indirect role of sleep apnea severity in determining feedback gas exchange abnormalities.

Materials and methods: In 456 patients a daytime hypoxemia-nocturnal hypoxia feedback structural equations model was designed. PaO_2 adjusted for age (% of predicted), percent sleep time spent with SpO_2 <90% (TST_{90}), oxygen desaturation index and the apnea-hypopnea index, were determined as the measures of daytime hypoxemia, nocturnal hypoxia, and sleep apnea severity, respectively, after adjusting for the severity of obesity and lung volumes.

Results: The TST_{90}-PaO_2 feed-back structural equations modeling showed that daytime PaO_2 was inversely related (P<0.001) to nocturnal hypoxia (−4.0% of PaO_2 per 1 SD of TST_{90}). The severity of OSA (−1.0%) was an indirect determinant of daytime PaO_2 via the TST_{90} pathway. In contrast, daytime PaO_2 did not influence (P>0.05) the extent of nocturnal hypoxia.

Conclusions: In OSA patients, the extent of nocturnal hypoxia seems to be both a direct determinant and a mediator of the indirect effect of sleep apnea on the development of daytime hypoxemia.

Keywords: Sleep apnea, hypoxemia, structural equation model, respiratory function, polysomnography

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SLEEP APNEA IS A CHRONIC CONDITION CHARACTERIZED BY UPPER AIRWAY COLLAPSE DURING SLEEP. THE RESULTING DECREASE OR CESSATION OF airflow is generally associated with recurrent drops in oxyhemoglobin saturation. Gas exchange during sleep may be severely affected in certain patients, especially in those who are grossly obese or have chronic respiratory disorders, such as chronic obstructive pulmonary disease (COPD).[1-2] Daytime hypoxemia has been reported to develop in patients with obstructive sleep apnea (OSA).[3-8] In the past, looking for the physiological determinants of nocturnal arterial oxygenation in OSA patients, it was found that derangements of pulmonary mechanics and awake PaO_2 were of major importance in establishing the severity of nocturnal hypoxemia.[9] Other studies showed that the main determinant of daytime hypoxemia is not the OSA per se but rather concomitant comorbidity such as COPD.[7-8,10] However, all these studies were performed on heterogeneous populations with a very high prevalence of COPD patients, so that airway obstruction and lung hyperinflation had major roles in determining the lower values of PaO_2. Moreover, the PaO_2 level at rest is highly dependent on age, and none of the studies previously cited corrected the level of PaO_2 for age, thus invalidating any comparisons of the level of oxygenation in patients with widely different ages.

The aims of the current study were: (i) to estimate the prevalence of alterations in daytime oxygenation in a very large group of OSA patients with a very broad spectrum of disease severity and obesity; (ii) to assess the reciprocal (feedback) effects between daytime PaO_2 and nocturnal SaO_2, adjusted for comorbidities such as obesity and lung volumes; and (iii) to investigate the direct and indirect role of sleep apnea severity in determining feedback gas exchange abnormalities. Some of the results of this study have been previously reported in the form of an abstract.[11]

METHODS

Patients and Study Design

We studied 456 consecutive patients (49.4 ± 10.7 years, 160 females) who complained of snoring and excessive daytime sleepiness and had been consecutively referred to our laboratory for investigations of possible OSA. These investigations consisted of standard polysomnography and, the day after, determination of static and dynamic lung volumes and blood gas measurements. Patients with previously diagnosed or radiologically evident respiratory diseases, radiologically evident lung lesions (e.g., previous tuberculosis treated physically, pulmonary abscesses, pneumothorax), neuromuscular disorders (e.g., post-polio lesions), chest-wall defects, previous use of appetite suppressants or a clinical history of venous thromboembolic disease, a bronchopulmonary infection, or cardiac or respiratory failure in the preceding 6 months were excluded from the study, as were patients with a previous diagnosis of pulmonary arterial hypertension.

The protocol was submitted to the Technical and Ethical Committees. The former approved the protocol and the latter stated that approval was waived since, on admission to hospital,
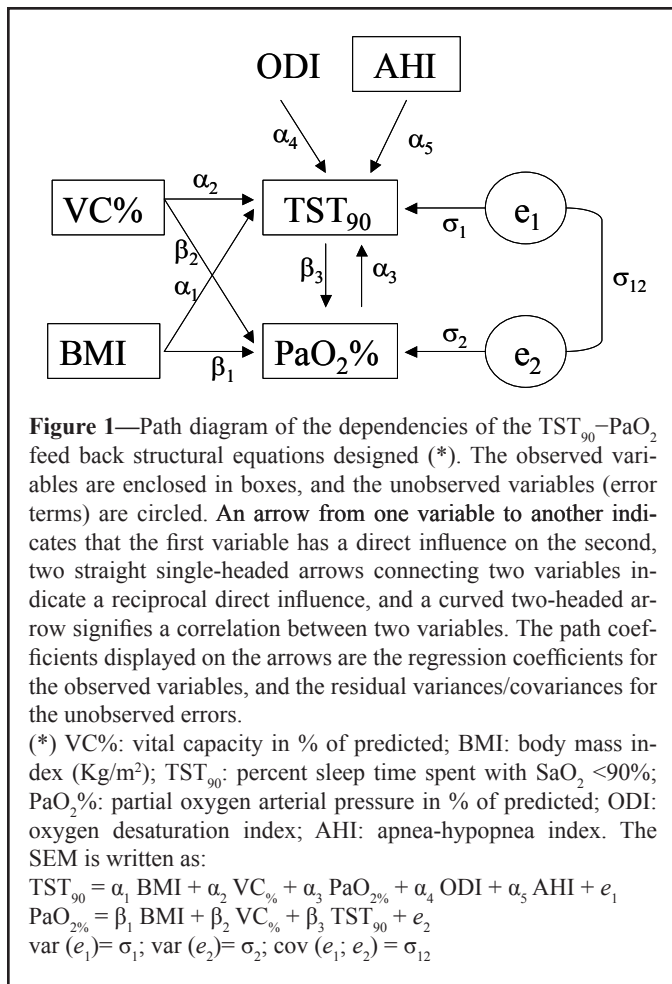
Figure 1—Path diagram of the dependencies of the TST_{90}–PaO_2 feed back structural equations designed (*). The observed variables are enclosed in boxes, and the unobserved variables (error terms) are circled. An arrow from one variable to another indicates that the first variable has a direct influence on the second, two straight single-headed arrows connecting two variables indicate a reciprocal direct influence, and a curved two-headed arrow signifies a correlation between two variables. The path coefficients displayed on the arrows are the regression coefficients for the observed variables, and the residual variances/covariances for the unobserved errors.

(*) VC%: vital capacity in % of predicted; BMI: body mass index (Kg/m²); TST_{90}: percent sleep time spent with SaO_2 <90%; PaO_2%: partial oxygen arterial pressure in % of predicted; ODI: oxygen desaturation index; AHI: apnea-hypopnea index. The SEM is written as:

$$TST_{90} = \alpha_1\,BMI + \alpha_2\,VC_{\%} + \alpha_3\,PaO_{2\%} + \alpha_4\,ODI + \alpha_5\,AHI + e_1$$
$$PaO_{2\%} = \beta_1\,BMI + \beta_2\,VC_{\%} + \beta_3\,TST_{90} + e_2$$
$$\text{var}\,(e_1) = \sigma_1; \ \text{var}\,(e_2) = \sigma_2; \ \text{cov}\,(e_1; e_2) = \sigma_{12}$$

patients are asked to sign whether they consent or not to the use of their medical records and "routine" examination results for research purposes. We analyzed only records of patients who agreed to the use of their data.

Measurements

Sleep Study

Full standard in-laboratory polysomnography (Embla, Medcare, Reykyiavik, Iceland) was performed using current procedures and scored manually according to the criteria of Rechtschaffen and Kales.[12] The polysomnography included: EEG_s (C_3-A_2, C_4-A_1), EOG_s, submental EMG, anterior tibialis electromyograms, nasal cannula airflow signal using a nasal cannula/pressure transducer system, oral thermistor, ECG and body position. SpO_2 was recorded by means of an in-built pulse oximeter (Nonin Medical Inc., Minneapolis, MN, USA) with an Oximax sensor (Nellcore, Pleasanton, CA, USA). The equipment provides both an averaged (4 seconds) and a beat-to-beat SpO_2 value. Respiratory efforts were monitored by the plethysmographic method (X-trace, Medcare, Iceland), so that the sum of thoracic and abdominal activities was obtained.

Arousals were scored according to standard criteria.[13] Apnea was defined as a cessation of airflow for ≥10 seconds, while hypopnea as a clear amplitude reduction of a validated measure of breathing during sleep (but less than a 50% reduction from baseline) associated with an oxygen desaturation of >3% or an arousal.[14]

We determined the apnea-hypopnea index (AHI), and the oxygen desaturation index (ODI), and the percent sleep time spent with SpO_2 <90% (TST_{90}).

Evaluation of Daytime Respiratory Function and Blood Gas Assays

Pulmonary function tests (Masterlab, Jaeger, Hochberg, Germany) were performed as described in the European Respiratory Society statement.[15] Respiratory function data were compared with predicted normal values obtained using the European Community for Steel and Coal (ECSC) 1983 regression equations. Diffuse airway obstruction was defined as a FEV_1 < 70% of predicted and FEV_1/VC <60%, according to a previous study.[6]

Arterial blood-gases were analyzed by an automated, computerized gas analyzer (ABL 550, Radiometer, Copenhagen, Denmark). PaO_2 was adjusted for age and expressed as percent of predicted according to a reference equation for the Italian population.[16] All the measurements were performed between 10:00 and 12:00 a.m. Daytime hypoxemia was defined as PaO_2% <90%, while nocturnal hypoxia was defined as TST_{90} > 1%.

Statistical Analysis

Results are expressed as mean ± SD, and t-tests considering equal or unequal variances were used to compare data among the two groups of patients classified by the dichotomized definitions of TST_{90} and PaO_2. Pearson's r correlation coefficients and forward stepwise regression analyses were performed to evaluate bivariate associations between pairwise variables, and the predictors that explain the variance of continuous measurements of TST_{90} and PaO_2, respectively.

The relationship between daytime hypoxemia and nocturnal hypoxia was investigated by structural equations modeling (SEM).[17,18] This is a statistical multivariate approach based on the use of a system of simultaneous equations to describe a priori relationships of observed (manifest) and unobserved (latent) variables of the physical process that generates the data.

A special type of structural equations modeling is the Path Analysis model in which only observed variables are considered in simultaneous equations. Path Analysis distinguishes three types of effects: direct, indirect, and total effects. The direct effect of an explanatory variable on a response variable is the net effect of a predictor setting all the other predictors in the built-in equations being equal. The indirect effect of an explanatory variable is the effect mediated by the pathway relationships of the other variables built-in the equations. The total effect is the sum of both the direct and indirect effects: total effect = direct effect + indirect effect. The decomposition of effects is always with respect to a specific model.

Based on a preliminary statistical analysis (a stepwise regression analysis), and clinical evidence, a Path Analysis of a TST_{90}–PaO_2% feedback model was designed (Figure 1) to assess the reciprocal effects between TST_{90} and PaO_2%, and the direct and indirect effects of sleep apnea severity (expressed by

Table 1—Anthropometric, Lung Volumes, Blood Gas, and Sleep Data of Patients Classified by the Presence of Daytime Hypoxemia (PaO_2 %<90 of Predicted)

	PaO_2%<90 (n = 372) Mean ± SD	PaO_2%>90 (n = 84) Mean ± SD	P-value (#)
Sex (% (n) male)	63.7 (237)	70.2 (52)	0.311
Age (yr)	48.1 ± 11.9	55.2 ± 12.1	<0.001
BMI (Kg/m^2)	44.3 ± 10.5	35.8 ± 12.1	<0.001
BSA (m^2)	2.36 ± 0.32	2.09 ± 0.26	<0.001
VC (% pred.)	92.9 ± 14.5	99.2 ± 16.1	0.0013
FEV_1 (% of pred.)	91.3 ± 17.1	110.3 ± 18.1	<0.001
FEV_1/VC (abs value)	78.3 ± 8.4	79.4 ± 7.7	0.2531
FRC (% of pred.)	75.5 ± 20.5	83.3 ± 20.6	0.0017
RV (% of pred.)	90.4 ± 23.9	90.1 ± 17.7	0.9162
TLC (% of pred.)	90.7 ± 12.3	94.0 ± 13.4	0.0302
MEF_{50} (% of pred.)	90.9 ± 34.5	96.2 ± 36.3	0.2083
PaO2 (mmHg)	68.9 ± 7.7	83.9 ± 6.4	<0.001
$PaCO_2$ (mmHg)	40.4 ± 4.7	37.0 ± 3.1	<0.001
AHI (event-hour^{-1})	50.7 ± 34.2	38.2 ± 25.7	0.0021
ODI (event-hour^{-1})	52.1 ± 34.2	37.6 ± 25.3	<0.001
TST_{90} (%)	13.1 ± 42.7 §	1.45 ± 15.6 §	<0.001

BMI= body mass index; BSA = body surface area; RV = residual volume; MEF_{50}: expiratory flow at 50% of FVC. AHI = apnea and hypopnea index; ODI = oxygen desaturation index; TST_{90}= total sleep time spent with SaO_2 <90% (% of total sleep time).
# P-values were computed by t-tests of two independent populations with equal or unequal variances, Fisher's exact χ^2 test for sex, and Mann-Whitney U test for TST_{90}.
§ Median ± Interquartile Range

AHI and ODI) in determining $TST_{90}-PaO_2$% feedback, adjusted for obesity (expressed by BMI), and lung volumes (expressed by VC%). A gender stratification analysis was also planned.

The structural equations were fitted using maximum likelihood estimates (MLE). The χ^2 difference test of "fitted" vs. "saturated" models was used for hypothesis testing to evaluate the appropriateness of the feed-back model; large P-value (P > 0.05) was the criteria for data support. The regression parameter estimates (direct, indirect, and total effects) of simultaneous equations were re-expressed in a standardized form multiplying the unstandardized one by 1 standard deviation (SD) of the explanatory variables. The P-values of the direct, indirect, and total estimates were evaluated by t-tests (=estimate/standard error) using robust standard errors; the level of statistical significance was set at P < 0.05, two-sided.

Descriptive and exploratory statistics were analyzed with SPSS 13.0 software (www.spss.com), while the feedback structural equations modeling was performed with Mplus 3.11 software (www.statmodel.com).

RESULTS

All patients enrolled completed the study. The mean PaO_2 value was lower than expected on the basis of age (80.2% ± 10.7% of predicted). Fourteen patients (3% of 456 patients) had diffuse airway obstruction but they did not differ (P >0.05) from the remaining for PaO_2% of predicted (76.3% ± 12.3% vs. 80.3% ± 10.7%), AHI (46.8 ± 22.3 vs. 48.4 ± 33.4) or TST_{90} (31.2 ± 39.6 vs. 24.2 ± 30.1). As expected, the patients with diffuse airway obstruction were older (age 60.7 ± 6.6 vs. 49.1 ± 12.2 yrs, P<0.001) and less obese (BMI 34.8 ± 6.9 vs. 42.7 ± 10.9 kg/m^2, P = 0.01) than the entire sample.

The great majority of patients (81.6% of the 456 patients, 95% CI: 78.0% to 85.1%) had a PaO_2 <90% of predicted. As shown in Table 1, the subjects with preserved PaO_2 were older, and less obese than the patients with PaO_2 <90% of predicted. The absolute FEV_1/VC ratio was similar in these two groups of patients; while patients with daytime PaO_2 >90% of predicted showed lower mean values of AHI, ODI, and TST_{90} in comparison with patients with daytime hypoxemia.

The great majority of patients (79.4% of the 456 patients, 95% CI: 75.7% to 83.1%) had altered gas exchange during sleep, defined as TST_{90} >1% of total sleep time. As shown in Table 2, patients with nocturnal hypoxia had smaller lung volumes, but similar FEV_1/VC ratio, functional residual capacity and residual volumes. In contrast, they had more severe sleep apnea and more impaired daytime PaO_2.

A stepwise regression procedure included the predictors VC, BMI, AHI, ODI, and PaO_2% in the regression equation of TST_{90} from all the potential predictor variables listed in Table 2; while VC, BMI, and TST_{90} were the selected predictors in the regression equation of PaO_2% from all the potential predictor variables listed in Table 1 (data not shown). The results of separate linear regression models for PaO_2% and TST_{90} were used to define the Path Analysis model with the addition of the feedback loop.

The maximum likelihood estimates and robust 95% CI of the standardized regression coefficient parameters (=average change of the response variable by 1 standard deviation (SD) increment of the explanatory variable) for the TST_{90}-PaO_2 feedback structural equations of Figure 1 are reported in Table 3. The chi-square testing (χ^2 =3.242, df = 1, P = 0.072 NS) provided evidence of the appropriateness of the feedback model given the observed data. The two feedback structural equations

Table 2—Anthropometric, Lung Volumes, Blood Gas, and Sleep Data of Patients Classified by Presence of Nocturnal Hypoxia ($TST_{90} \geq 1$.)

	$TST_{90} < 1\%$ (n=94) Mean ± SD	$TST_{90} \geq 1\%$ (n=362) Mean ± SD	P-value (#)
Sex (% (n) male)	56.4 (53)	67.1 (243)	0.068
Age (yr)	50.5 ± 13.4	49.2 ± 11.9	0.3466
BMI (Kg/m^2)	40.0 ± 12.6	43.4 ± 10.9	0.0086
BSA (m^2)	2.19 ± 0.31	2.34 ± 0.32	<0.001
VC (% pred.)	98.6 ± 15.1	92.9 ± 14.8	<0.001
FEV$_1$ (% of pred.)	96.7 ± 18.1	92.0 ± 17.4	0.0195
FEV$_1$/VC (abs value)	78.5 ± 8.1	78.5 ± 8.4	0.9547
FRC (% of pred.)	80.5 ± 19.6	76.0 ± 21.0	0.0605
VR (% of pred.)	94.0 ± 20.7	89.4 ± 23.4	0.0878
TLC (% of pred.)	94.2 ± 12.4	90.5 ± 12.5	0.0117
MEF$_{50}$ (% of pred.)	92.4 ± 36.4	91.7 ± 34.4	0.8713
PaO2 (mm Hg)	77.3 ± 8.0	70.2 ± 9.3	<0.001
PaCO$_2$ (mm Hg)	37.7 ± 3.7	40.3 ± 4.7	<0.001
AHI (event-hour^{-1})	26.8 ± 23.2	54.0 ± 33.0	<0.001
ODI (event-hour^{-1})	28.4 ± 26.0	54.9 ± 32.8	<0.001
PaO$_2$ (% of pred)	87.0 ± 9.2	78.5 ± 10.4	<0.001

BMI = body mass index; BSA = body surface area; RV = residual volume; AHI = apnea and hypopnea index; ODI = oxygen desaturation index; TST_{90} = total sleep time spent with SaO_2 <90%.
# P-values were computed by *t*-tests of two independent populations with equal or unequal variances, and Fisher's exact χ^2 test for sex.

explained 34.2% and 31.3% of the total variance of continuous measurements of TST_{90} and $PaO_2\%$, respectively, while the residual correlation between TST_{90} and $PaO_2\%$ was fixed to 0 to ensure that the regression parameters of the estimated structural model were identified.

The daytime $PaO_2\%$ of predicted was statistically significantly associated (P<0.001) with the feedback effect of nocturnal hypoxia (TST_{90}) and with the effects of obesity (BMI) and lung volumes (VC%). Specifically, an increment of 1 SD (30.5%) of TST_{90} produced a reduction of 3.96% (95% CI: –2.11% to –5.82%) in the PaO_2 % of predicted; an increment of 1 SD (11.3 kg/m^2) of BMI produced a decline of 3.33% (95% CI: –2.14% to –4.53%); and an increment of 1 SD (15%) of VC% produced a rise of 1.5% (95% CI: +0.59% to +2.41%).

In contrast, the daytime PaO_2 feedback effect did not influence (P = 0.965) the extent of nocturnal hypoxia, which was statistically significantly related with the severity of OSA (P <0.001), and background measurements (BMI, P = 0.020 and VC%, P<0.001). Specifically, an increment of 1 SD (33 events/1 hour) in the AHI or ODI increased TST_{90} by 7.99% (95% CI: +3.63% to +12.3%) or 7.01% (95% CI: +2.45% to +11.6%), respectively; TST_{90} also increased by 3.91% (95% CI: +0.61% to +7.21%) for 1 SD of BMI and declined 4.91% (95% CI: –2.24% to –7.58%) for 1 SD of VC%.

The above described changes were net effects (direct effects); however, the severity of OSA, expressed by AHI and ODI, also had statistically significant indirect effects (P = 0.009) on daytime hypoxia via the nocturnal hypoxia pathway, i.e., TST_{90} is a variable that mediates the effect of OSA on PaO_2 outcome. Specifically, via the TST_{90} path, an increment of 1 SD in the AHI or ODI decreased PaO_2 % of predicted by about 1% (95% CI: –0.25% to –1.81% for AHI, and –0.28% to –1.58% for ODI).

None of the results changed if PaO_2 was considered in absolute values rather than in % of predicted.

Stratification according to gender did not show any major differences in feedback, direct or indirect effects between subgroups (data not shown).

DISCUSSION

The main findings of this study are: (i) patients with OSA, in the absence of lung comorbidity such as diffuse airway obstruction, had lower values of PaO_2 than those expected on the basis of age; and (ii) a feedback model of daytime hypoxemia-nocturnal hypoxia (Figure 1) was not supported, even after adjustment for obesity and lung volume, and gender stratification. An increase of percent sleep time with reduced SpO_2 is associated with a decrease in daytime PaO_2, while the level of nocturnal SpO_2 is not related to the level of daytime PaO_2. Moreover, because nocturnal hypoxia is related to the severity of OSA (expressed by AHI and ODI), the level of nocturnal SaO_2 is also a mediator of the severity of the OSA effect on daytime hypoxemia.

We performed the present study in an attempt to determine the direction of the relationship between daytime hypoxemia and nocturnal hypoxia. This issue is related to an appropriate definition of daytime hypoxemia and an appropriate identification of the population of patients. Firstly, most of the previous papers reported that a normal value of PaO_2 at rest is ≥80 mm Hg, hypoxemia is present when the PaO_2 is below 80 mm Hg, and severe hypoxemia when the PaO_2 is ≤65 mm Hg.[1,3,7,8,10] None of these studies adjusted the PaO_2 values for age, obesity or lung volumes. We corrected the PaO_2 data according to the reference equation for the Italian population, thus defining the PaO_2 as a percent of predicted. In this way, we found that the great majority of subjects had reduced PaO_2 values. Indeed, only 84 (18%) patients had a PaO_2 higher than 90% of predicted. This result did not change when different reference values of PaO_2 published in the literature were applied (data not shown),[19,20] or when the PaO_2 was considered as an absolute value.

Table 3—Maximum Likelihood Estimates, and Robust 95% CI of Direct and Indirect Effect Parameters of the Fitted (*) TST_{90}-PaO_2 Feedback Structural Equations of Figure 1

	TST_{90} (%)		PaO_2 (%)	
	β (95%CI) §	P-value	β (95%CI) §	P-value
Feed-back loop:				
TST_{90} (%)	−	−	−3.96 (−2.11 to −5.82)	<0.001
PaO_2 (%)	+0.15 (−6.35 to +6.65)	0.965	−	−
Cor (TST_{90}; PaO_2)	0 #	0 #		
Direct effects:				
BMI (kg/m²)	+3.91 (+0.61 to +7.21)	0.020	−3.33 (−2.14 to −4.53)	<0.001
Vital capacity (%)	−4.91 (−2.24 to −7.58)	<0.001	+1.50 (+0.59 to +2.41)	0.002
AHI (event-hour⁻¹)	+7.99 (+3.63 to +12.3)	<0.001	−	−
ODI (event-hour⁻¹)	+7.01 (+2.45 to +11.6)	0.003	−	−
Indirect effects:				
AHI (event-hour⁻¹) via TST_{90}	−	−	−1.03 (−0.25 to −1.81)	0.008
ODI (event-hour⁻¹) via TST_{90}	−	−	−0.93 (−0.28 to −1.58)	0.009
R-square	0.342	0.313		

(*) χ^2 = 3.242, df = 1, P = 0.072 NS
(#) Fixed parameter in the structural equations
(§) β = average change of the response variable for an increment of 1 SD in the explanatory variable

The second point regards the choice of the population of the patients. In the present study we included consecutive patients with sleep apnea, so that all biases related to disordered respiratory mechanics could be excluded. This was not the case in the previous studies in which a significant proportion of patients, ranging from 11% to 25%, were affected by concomitant COPD, with the prevalence of COPD, sometimes with FEV_1 < 1 litre.[1,3,7-8,10] In COPD, peripheral airway obstruction, parenchymal destruction, and pulmonary vascular abnormalities reduce the lung's capacity for gas exchange, producing hypoxemia and, later on, hypercapnia.[21] Since daytime PaO_2 data were not corrected for age or lung function and, since subjects with concomitant COPD were older than those with simple OSA, the effect of age and lung function impairment in determining lower values of PaO_2 were mutually enhanced.[22]

We found that TST_{90}, an index of nocturnal hypoxia, was a valuable determinant of the development of daytime hypoxemia, even after adjustment for the degree of obesity, lung volumes and sex stratification. AHI and ODI, expressions of the severity of sleep apnea, were also significant determinants although their effect was mediated through TST_{90}. Of interest, the level of TST_{90} appears independent of daytime PaO_2, because the feedback (reciprocal) effect was not supported. This latter is an intriguing observation since in the past it was hypothesized that a low level of daytime PaO_2 may account for the severity of the nocturnal hypoxia.[10] Indeed, Bradley et al. observed, in a group of OSA patients, that the main predictors of nocturnal desaturation, expressed by the mean value of SaO_2 across the night, were daytime PaO_2, alterations in respiratory mechanics (again mainly related to airway obstruction and the degree of obesity), and the sleep time spent in apnea. On the contrary, our results are in agreement with data, reported by Sanders et al, obtained from the Sleep Heart Health Study.[23] They found that patients with sleep apnea without obstructive airway disease had a 20-fold higher odds ratio for nocturnal desaturation than that of healthy subjects, even after adjustment for age, sex, height, weight, race, smoking status and awake SaO_2.

The development of daytime hypoxemia in OSA patients has generally been related to the presence of subclinical arterial pulmonary hypertension (PH).[3-6] However, this association with pulmonary hypertension is now a matter of discussion since most of the studies produced conflicting results. It should be considered that all the studies that gave negative results were the oldest ones and the ones with a relevant percentage of COPD patients, as stated above.[1-3,7-8,10] There is, however, a growing body of evidence that highlights the role of sleep apnea in the development of daytime gas exchange abnormalities through the pathophysiological effect of chronic intermittent hypoxia. The occurrence of PH in OSA patients without concomitant lung disease ranged from 20% to 43%.[4-6,24] In all these studies PH patients had a more altered nocturnal gas exchange and in two of them a lower level of daytime PaO_2.[6,24]

The increasing of pulmonary arterial pressure has been associated with hypoxia-induced pulmonary vasoconstriction.[5,25,26] Animal models showed increases in right ventricular mass, hematocrit level and pulmonary arterial pressure during exposure to chronic intermittent hypoxia or asphyxia.[27,28] Chronic intermittent hypoxia activates homeostatic mechanisms in the respiratory system that induce changes in gene expression by mediation of several transcription factors, such as hypoxia-inducible factor (HIF).[29] Experimental data showed that hypoxia inducible factors (both HIF-1α and HIF-2α) are involved in physiological responses of pulmonary arterioles to chronic intermittent hypoxia, collectively producing hypertrophy and depolarization of pulmonary arteriolar smooth muscle.[29]

Recent studies suggested that the hypoxia inducible factor-1 pathway response to chronic intermittent hypoxia seems to be activated only in patients with moderate to severe nocturnal gas exchange alterations.[30] These patients showed a significantly increased level of erythropoietin during sleep, differently from patients with less severe OSA.[31] On the contrary, in these latter chronic intermittent hypoxia activated a different pathway mediated through the transcription factor nuclear factor-κB that, in turn, increased the expression of tumor necrosis factor-α, which

may contribute to endothelial dysfunction.[32] Finally, treatment with CPAP has been demonstrated to reduce pulmonary arterial pressure levels also in patients with a pressure <20 mm Hg.[26,33]

However, daytime hypoxemia in OSA patients may develop through mismatching of ventilation and perfusion, as a result of different mechanisms, such as changes in mechanical properties of the lung or development of subclinical interstitial pulmonary edema. An increase in elastance of the whole lung during sleep was found in patients with OSA.[34] Sleep may induce a loss in the mechanical coupling between airways and lung parenchyma which, in turn, allows the airways to narrow more easily.[35] Alternatively, the reduction of lung volumes during sleep could not only decrease parenchymal attachments but also increase the forces arising from surface tension, which would lead to an increase in elastance. Indeed, it was shown that the severity of apnea-induced desaturation was correlated with lung volume, particularly with the difference between supine expiratory reserve volume and seated closing volume.[36] These mechanical modifications may induce closure of some respiratory units during upper airway obstruction, which is reversed at the end of the obstruction. These transient abnormalities in the recruitment of lung units resulting in air space closure reduce the gas exchange capacity of the lungs independently from the level of daytime gas exchange.[34]

Chronic intermittent hypoxia induces proliferation of the vasculature due to angiogenesis but can also change the integrity of vessels, leading to changes in vascular permeability.[37] Fletcher et al., in a canine model of OSA, demonstrated that pulmonary edema can develop after recurrent obstructive apneas.[38] They found a significant deterioration of gas exchange in those animals with histologic and/or electron microscopy evidence of lung edema compared to those without edema and controls and a substantial fall in the amplitude of apnea desaturation related to deterioration of gas exchange. It has been demonstrated that hypoxia induces angiogenesis upregulating the vascular endothelial growth factor (VEGF).[39] Schulz et al. found that the serum levels of VEGF are elevated in severely hypoxic patients with OSA and are related to the degree of nocturnal oxygen desaturation.[40] Of interest, patients with the highest degree of nocturnal desaturation were those with the lowest level of daytime PaO_2.

Recently, Guardiola et al. suggested that the mechanical changes and increased interstitial lung water described above were not immediately reversed since they found that OSA patients had lower PaO_2 values in the morning than in the evening.[41]

A possible limitation of our study, like that of the other studies, is the lack of information about the intensity and duration of exposure to nocturnal hypoxia. Different durations of disease, or, more probably, an early onset of OSA may contribute to explain the variability between the results we obtained and those of the previous studies. One particularly complex methodological issue in characterizing the progression of OSA is the worsening epidemic of obesity in western countries such that it can be very difficult to separate the effects on gas exchange of prolonged OSA from those related to increasing body weight.[42] Indeed, a longitudinal study on sleep disordered breathing performed in a nonclinic population found that changes in the respiratory disturbance index over time do not vary uniformly with age, sex, and weight.[43]

Finally, most of the patients enrolled in our study were obese and therefore caution needs to be exercised regarding the generalizability of our findings. However, all the results were statistically adjusted for the level of obesity so that the effect of this anthropometric parameter in our specific cohort could be minimized.

In conclusion, our data support the evidence that nocturnal hypoxia seems to be both a direct determinant and a mediator of the indirect effect of sleep apnea on the development of daytime hypoxemia. Follow-up studies are needed to evaluate the time course of daytime gas exchange abnormalities and to assess the role of therapy in stopping or slowing down this evolution.

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