Pulmonary Hypertension, Hypoxemia, and Hypercapnia in Obstructive Sleep Apnea Patients*

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To define the parameters of respiratory insufficiency in OSA, 114 consecutive patients (108 men, six women) were prospectively studied. In addition to standard polysomnography, they underwent pulmonary function tests, right heart catheterization, and ventilatory response tests to hypercapnia. Nineteen patients (19 percent) had a resting PAF ≥ 20 mm Hg. Multiple regression analysis showed that FEV, and PaCO₂ (both with a negative coefficient) and PaCO₂ (with a positive coefficient) significantly contributed to PAF. Thirteen patients (12 percent) had a PaCO₂ ≥ 45 mm Hg. A multiple regression analysis showed that FEV₁ and the minute ventilation at PtcCO₂ = 60 mm Hg (both with a negative coefficient) and the cumulative apnea duration (with a positive coefficient) significantly contributed to the presence of hypercapnia and diffuse airway obstruction, but not to the severity of sleep apneas or nocturnal desaturation.

Although it is generally acknowledged that the obstructive sleep apnea (OSA) syndrome was first described as the pickwickian syndrome, characterized by daytime somnolence, obesity, cyanosis, polycythemia, hypoventilation, and cor pulmonale, it is clear that many, if not most, sleep apnea patients do not show the signs of the pickwickian syndrome. However, surprisingly few studies have investigated the frequency and mechanisms of respiratory insufficiency and right heart failure in OSA patients.

One study in a group of 50 patients concluded that daytime hypoxemia and/or hypercapnia were necessary conditions for the development of right heart failure. This study denied a contributing role for the severity of sleep apneas. However, clinical signs of right heart failure may be a late stage of progression of the disease; therefore, the investigation of the factors of pulmonary hypertension may be of more clinical and therapeutic interest. In a study of 65 patients, Podzus et al found daytime pulmonary hypertension in 20 percent of the patients, not related to the number or duration of apneas. More recently, Weitzenblum et al in a series of 46 patients found that pulmonary hypertension was present in 20 percent of patients and was related to the presence of hypercapnia.

OSA = obstructive sleep apnea; PAF = pulmonary artery pressure; EOG = electro-oculogram; PHT = pulmonary hypertension

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PaCO₂. Thirty-seven patients (33 percent) had a PaO₂ ≤ 65 mm Hg. A multiple regression analysis showed that FEV₁ (with a positive coefficient) and the hypopnea + apnea index (with a negative coefficient) significantly contributed to PaO₂. These data confirm that impaired daytime pulmonary function (diffuse airway obstruction) contributes to the development of daytime pulmonary hypertension, hypoxemia, and hypercapnia in OSA patients. They show that the amount of sleep-related breathing disorders also plays a significant role.

(Chest 1989; 96:729-37)
Table 1—Morphometric, Respiratory Function, Right Heart Catheterization, and Polysomnographic Data of the Total Patient Population

<table>
<thead>
<tr>
<th>Age</th>
<th>BMI</th>
<th>SBP</th>
<th>DBP</th>
<th>pHO₂</th>
<th>pHCO₃</th>
<th>PAPm</th>
<th>PAPex</th>
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<tbody>
<tr>
<td>N</td>
<td>114</td>
<td>114</td>
<td>114</td>
<td>114</td>
<td>112</td>
<td>112</td>
<td>100</td>
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<tr>
<td>Mean</td>
<td>52.71</td>
<td>31.67</td>
<td>144.25</td>
<td>86.63</td>
<td>71.65</td>
<td>38.79</td>
<td>15.81</td>
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<tr>
<td>SE</td>
<td>0.94</td>
<td>0.54</td>
<td>1.99</td>
<td>1.37</td>
<td>1.06</td>
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<tr>
<th>TLC, L</th>
<th>F EV, L</th>
<th>FEV₁/FVC</th>
<th>FVC, L</th>
<th>%FVC/pred</th>
<th>VCO₂, L</th>
<th>WSaO₂</th>
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<tbody>
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<td>N</td>
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<td>112</td>
<td>112</td>
<td>112</td>
<td>112</td>
<td>71</td>
</tr>
<tr>
<td>Mean</td>
<td>5.49</td>
<td>2.61</td>
<td>71.10</td>
<td>3.62</td>
<td>90.08</td>
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<td>0.08</td>
<td>0.99</td>
<td>0.09</td>
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<th>AMD</th>
<th>ACD</th>
<th>Mm SaO₂</th>
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<td>61.88</td>
<td>23.51</td>
<td>25.44</td>
<td>86.96</td>
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<td>3.23</td>
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<td>1.73</td>
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<table>
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<tr>
<th>N Arousals</th>
<th>TST</th>
<th>% St1 + 2</th>
<th>% St3 + 4</th>
<th>% REM</th>
<th>Sleep Eff</th>
</tr>
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<tbody>
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<td>114</td>
<td>114</td>
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<tr>
<td>Mean</td>
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<td>11.72</td>
<td>9.21</td>
<td>0.96</td>
<td>0.60</td>
<td>0.58</td>
</tr>
</tbody>
</table>

BMI = body mass index, kg/m²; SBP = systolic blood pressure, mm Hg; DBP = diastolic blood pressure, mm Hg; PAPm = pulmonary artery pressure at rest, mm Hg; PAPex = pulmonary artery pressure during 40-W exercise, mm Hg; V Pco₂, L = minute ventilation at end-tidal Pco₂ = 60 mm Hg; W SaO₂ = wake SaO₂ (%); AHI = apnea plus hypopnea index, no./h; Ai = apnea index, no./h; AMD = mean apnea duration, s; ACD = mean cumulative apnea duration in 1 h, min/h; Mm SaO₂ = mean minimal SaO₂ during sleep, %; M SaO₂ = mean SaO₂ during sleep, %; m SaO₂ = minimal SaO₂ during sleep, %; TST = total sleep time, min; % St1 + 2 = % of stages 1 + 2 non-rapid eye movement (NREM) sleep; % St3 + 4 = % of stages 3 + 4 NREM sleep; % REM = % of REM sleep; Sleep Eff = sleep efficiency.

Patients and Methods

Patients

As part of the evaluation of the severity of OSA before adequate treatment, 114 consecutive OSA patients (106 men, six women) referred to our Sleep Laboratory for symptoms evocative of OSA, including daytime somnolence (74 patients), snoring (25 patients), respiratory failure without a clear origin (eight patients), and observation of respiratory arrests during sleep (seven patients), underwent standard polysomnography (n = 114), pulmonary function tests (n = 112), right heart catheterization (n = 100), and respiratory response to hypercapnia (n = 71, this investigation being available only later during the course of the study). All patients gave informed consent to the investigations.

The evaluation was performed at least six weeks after a possible episode of acute cardiorespiratory failure. None of the patients had a history of overt chronic lung disease such as asthma, pulmonary fibrosis, sarcoidosis, or emphysema, but patients with a history of tobacco smoking, whether associated or not with chronic cough and sputum, were not excluded.

Polysomnography

The polysomnographic recording, preceded by an unrecorded adaptation night, was performed according to previously described methods. Briefly, it included a standard EEG, EOG, and EMG of chin muscles; breathing during sleep was analyzed with a Fleisch 2 pneumotachograph and electronic integrator (Godart Statham) attached to a soft Silastic facial mask (Bird 3434) and either thoracic and abdominal mercury-filled elastic strain gauges or an esophageal balloon. Transcutaneous oxygen saturation (SaO₂) was also recorded (Ohmeda Biox III).

Central, obstructive, and mixed apneas were defined according to the usual criteria. Hypopneas were defined as a 50 percent fall in tidal volume from its value during quiet wakefulness, without a major change in respiratory rate. Only patients with more than five apneas per hour of sleep, more than 80 percent of them being of the obstructive type, were included. Ear oximeter readings below 40 percent were regarded as equal to 40 percent because of the strong linearity of the measurements in this range.

The following parameters were computed from the polysomnographic recordings: apnea index (number of apneas per hour of sleep), apnea + hypopnea index, percentage of central, obstructive and mixed apneas, mean cumulative duration of apneas per hour of sleep, and mean apnea duration. Four SaO₂ parameters were analyzed: the mean SaO₂ during 5 min of wakefulness just prior to sleep onset (wake SaO₂), the minimal SaO₂ during sleep (minimal SaO₂), the mean SaO₂, and the mean of the minimal SaO₂ observed after each apnea (mean minimal SaO₂).

In one patient, SaO₂ readings were not reliable (dark skin). Another patient did not tolerate the face mask; apneas were identified with a thermistor, but their duration could not be assessed as reliably as with the pneumotachograph; apnea duration measurements from this patient were therefore discarded.

Pulmonary Function Tests

Conventional spirometry was performed with a 10-L closed-circuit spirometer. Static lung volumes were measured by the closed-circuit helium dilution method. The reference values used were those of the European Community. Right heart catheterization was performed as previously described in 100 patients. The hemodynamic measurements were always done while the patient was awake. For the purposes of this study, we used small-diameter floated catheters, either Grandjean flexopulmocaths (F 4) or Swan-Ganz catheters (F 5). The catheters were introduced percutaneously into an antecubital vein. The 14 patients in whom the right heart catheterization had not been performed differed from the 100 patients in whom it had been done in that they were more overweight (BMI = 35.47 ± 2.25 vs 31.39 ± 1.16 kg/m², p < 0.01) and had a lower TLC (4.72 ± 0.32 vs 4.82 ± 0.29 L, p < 0.02), suggesting that these patients' condition was more severe. However, the individual reasons for not performing right heart catheterization were not systematically related to...
the severity of the patients' condition (refusal by the patient, n = 10; failure of the catheterization, n = 2; or contraindication to catheterization, n = 2). Almost all of the patients (91 of 100) underwent an 8-min steady-state exercise on a bicycle ergometer in the supine position. The load was 40 W. Hemodynamic measurements were performed during the last minute of exercise.

In the last 71 patients studied, awake ventilatory responses to progressive normoxic hypercapnia were tested using rebreathing techniques modified from Read. Airflow was measured by pneumotachography and end-tidal CO (PETCO2) by a rapid infrared analyzer. The slopes of minute ventilation vs PETCO2 were computed. The level of minute ventilation at PETCO2 = 60 mm Hg was measured or extrapolated.

**Statistical Analysis**

The patient population was split into subgroups defined as hypercapnic (PaCO2 ≥ 45 mm Hg) vs nonhypercapnic, hypoxemic (PaO2 ≤ 65 mm Hg) vs nonhypoxemic, and pulmonary hypertensive (resting pulmonary artery pressure ≥ 20 mm Hg) vs nonpulmonary hypertensive. These subgroups were compared by means of Student's t tests for unpaired values.

Since these comparisons showed differences between patient subgroups in parameters which were intercorrelated, a multiple regression analysis with stepwise variable selection was performed with PaO2, PaCO2, and PAP successively as the dependent parameter to determine which of the parameters significantly contributed to the variance of PAP, PaO2, and PaCO2. To validate the regression analysis, the normality of the distribution of the parameters was checked (Kolmogorov-Smirnov test). To further picture the relationships between the variables, single regression analyses were performed between PAP, PaO2, and PaCO2, and each of the variables contributing to the multiple regression models. The regression model was tested with 18 patients investigated after this study was completed.

**RESULTS**

The patients' anthropometric and main respiratory function, right heart catheterization, and polysomnographic data are given in Table 1. As a group, their values were within the normal range for all parameters studied except BMI. The individual values covered a wide range, from normal to pathologic (Fig 1). None of the observed distributions was significantly different from normal except that of mean minimal SaO2.

**Pulmonary Hypertension**

Nineteen patients (19 percent) had a PAP at rest ≥ 20 mm Hg. Fourteen among them were hypoxemic and five were hypercapnic. Among the five nonhypoxic patients, only one had an FEV1/FVC ratio > 0.65. This patient was morbidly obese (BMI = 38 kg/m2). Twelve pulmonary hypertensive patients (63 percent) had a FEV1/FVC below 0.65, while only 11 (14 percent) nonhypertensive patients did.

As a group, pulmonary hypertensive patients differed from nonpulmonary hypertensive patients in that they had a lower PaO2, higher PaCO2, and lower...
FIGURE 3. Multiple regression for pulmonary artery pressure (PAP, upper panel) and single regression analyses with parameters contributing to PAP.

FIGURE 4. Plots of the predicted values (obtained using the multiple regression model established in 114 patients) vs observed values of PAP, PaCO₂, and PaO₂ in 18 prospectively studied patients.

FIGURE 5. Comparison of anthropometric, pulmonary function, right heart catheterization, and polysomnographic parameters in hypercapnic and nonhypercapnic OSA patients. * = p<0.05; ** = p<0.01; *** = p<0.001.

TLC, FEV₁, FEV₁/FVC, FVC, and %FVC predicted. They also had higher apnea+hypopnea and apnea indices, and lower wake, mean minimal, mean, and minimal SaO₂ (Fig 2).

The multiple regression parameter selection was, in decreasing order of the contribution (percent) to the model for PAP: FEV₁, and PaO₂ (77.7 percent and 16.82 percent, respectively, both with a negative coefficient), and PaCO₂ (5.48 percent, with a positive coefficient). The r² value for the model was 0.44, with df=95 and p<0.0001. Figure 3 shows the multiple regression model and the single regression analyses for PAP vs each of the selected parameters. When this model was applied to 18 newly investigated patients, the predicted PAP correlated with the observed PAP (r=0.70, p=0.005). Figure 4 shows predicted vs observed values in these patients. The mean difference between predicted and observed values was 0.24 mm Hg, ranging from −6.0 to 0.5 mm Hg.

**Hypercapnia**

Thirteen patients (12 percent) were hypercapnic (PaCO₂ ≥ 45 mm Hg). Nine of them had a FEV₁/FVC ratio below 0.65. The other four had normal FEV₁/
FVC and normal FVC, but three of them had a BMI greater than the mean of the hypercapnic group.

As a group, hypercapnic patients differed from nonhypercapnic patients in that they had a higher diastolic blood pressure, lower PaO₂, higher rest and exercise PAP, and lower FEV₁, FEV₁/FVC, FVC and %FVC predicted; they also had a higher hypopnea + apnea index and lower wake, mean minimal, mean, and minimal SaO₂ (Fig 5).

When all parameters were allowed to enter the regression analysis, PaO₂ appeared to be the strongest contributor (with a negative coefficient) to PaCO₂; however, because of the physiologic links between PaO₂ and PaCO₂, this statistical correlation was predictable and does not help explain the determinants of PaCO₂ in OSA patients; therefore, PaO₂ (and the various SaO₂ parameters) were excluded from the regression analysis for PaCO₂, and conversely.

The multiple regression analysis then selected as contributing factors to the variance of PaCO₂, in decreasing order of the contribution (percent) to the model: FEV₁ (59.66 percent, with a negative coefficient), the cumulative apnea duration (20.25 percent, with a positive coefficient), and the minute ventilation at P₆CO₂ = 60 mm Hg (20.09 percent, with a negative coefficient; Fig 6).

The r² value for the model was 0.41, with df=66, p<0.0001. Only 70 observations were fitted, because of the limited number of patients in whom ventilatory responses to hypercapnia had been tested. However, when ventilatory responses to hypercapnia were excluded from the independent parameters to increase the number of fitted observations, no model with a higher r² value was obtained. Figure 6 shows the multiple regression model and the single regression analyses for PaCO₂ vs each of the selected parameters. When this model was applied to the 18 newly investigated patients, the predicted PaCO₂ correlated with the observed PaCO₂ (r=0.79, p<0.0002). Figure 4 shows predicted vs observed values in these patients.
The mean difference between predicted and observed values was 0.11 mm Hg, ranging from –7.5 to 6.9 mm Hg.

**Hypoxemia**

Thirty-seven patients (33 percent) were hypoxemic (PaO2 ≤ 65 mm Hg). Less than half of them (15) had an FEV1/FVC ratio ≤0.65. Twenty-nine (78 percent) had a BMI greater than 30 kg/m2, while only 40 (53 percent) nonhypoxemic patients did.

As a group, hypoxemic patients differed from nonhypoxemic patients in that they were older and had a higher PaCO2, higher rest and exercise PAP, lower TLC, FEV1, FEV1/FVC, FVC, and %FVC predicted; they also had higher apnea + hypopnea index and lower wake, mean minimal, mean, and minimal SaO2 (Fig 7).

The stepwise parameter selection for PaO2 included, in decreasing order of the contribution (percent) to the model: FEV1 (86.09 percent, with a positive coefficient), and the hypopnea + apnea index (13.91 percent, with a negative coefficient). The r² value for the model was 0.31, with df=106, p<0.0001 (109 observations fitted). Figure 8 shows the multiple regression model and the single regression analyses for PaO2 vs each of these parameters. When this model was applied to the 18 newly investigated patients, the predicted PaO2 correlated with the observed PaO2 (r = 0.70, p<0.002). Figure 4 shows predicted vs observed values in these patients. The mean difference between predicted and observed values was 2.35 mm Hg, ranging from –15.6 to 19.5 mm Hg.

**DISCUSSION**

In this group of 114 unselected OSA patients, 19 of 100 (19 percent) had daytime pulmonary hypertension, 37 of 112 (33 percent) had daytime hypoxemia, and 13 of 112 (12 percent) had daytime hypercapnia. Pulmonary hypertension may have been slightly underestimated because the 14 patients who did not undergo right heart catheterization were more overweight and had lower TLC, which may be contributory factors to pulmonary hypertension. However, using the model to predict the missing PAP values yielded only two additional patients with a PAP ≥ 20 mm Hg; ie, a final number of 21 pulmonary hypertensive patients of 114 patients (18 percent). These percentages are similar to the 20 percent pulmonary hypertensive patients as well as to the 14 percent hypercapnic patients reported in other studies.5,6,8 Leech et al9 reported a higher percentage of hypercapnic patients (37 percent) in a group of 111 patients. However, their patient sample was probably not representative of the general OSA patient population, as indicated by the high percentage of women (32 percent), far higher than the usual proportion of about 10 percent women in OSA populations.15

Our study shows that OSA patients with signs or complications of respiratory insufficiency, be it pulmonary hypertension, daytime hypoxemia, or hypercapnia, are clearly distinct from OSA patients without respiratory insufficiency. The differences mainly involve respiratory function tests, severity of hypoxemia during sleep, and the number of episodes of sleep-disordered breathing.

However, because of the complex relationships among the parameters involved, the comparison of subgroups with or without respiratory insufficiency does not allow a further interpretation of the observed differences. Therefore, we performed multiple regression analyses, which selected among the intercorrelated independent parameters those that explain the highest amount of variance of the dependent parameter.

**Pulmonary Artery Pressure**

The demonstration in our patients of a relationship between the degree of pulmonary hypertension and FEV1, PaO2, and PaCO2 is in agreement with the
finding by Bradley et al. of a relationship between clinical signs of right heart failure and daytime hypoxemia and/or hypercapnia associated with impaired lung function, if one accepts that pulmonary hypertension is the first step in the development of cor pulmonale.

The contributing role of daytime PaO₂ and PaCO₂ to PAP is in agreement with the known relationships among hypoxemia, hypercapnia, and PHT in diseases other than OSA, namely, COPD. However, it is noteworthy that daytime hypoxemia and hypercapnia appear to be only secondary factors, after FEV₁, in the model for PAP in our study and that nighttime hypoxemia does not appear to contribute at all, once the contribution of FEV₁ and daytime PaO₂ has been taken into account. This demonstrates the primary role of diffuse airway obstruction in the development of PHT in OSA patients. However, it should be emphasized that 7/19 (35 percent) patients with PHT did not have obstructed lower airways had an FEV₁/FVC ratio greater than 0.65.

The overall predictive value of the selected model, although highly significant, remains relatively low. It is possible that the descriptors of daytime or nighttime hypoxemia that we included were not the relevant ones. A more continuous evaluation of daytime hypoxemia, including exercise and taking into account the variability of PaO₂, may have been more adequate. It may also be that the number of falls of SaO₂ below a given level during sleep, or the slope of the decrease in SaO₂ would have been better predictors of PAP than the mean, the minimal, and mean minimal SaO₂. Alternatively, the role of factors other than hypoxemia, such as the changes in hemodynamic conditions related to the drastic changes in intrathoracic pressures during sleep apneas, combined with impaired airway and lung mechanics, may be hypothesized. We are not aware of any experimental work investigating the possible long-term effect of changes in intrathoracic pressures on pulmonary artery pressure.

\[ PaCO₂ \]

The parameters related to PaCO₂ give an indication...
as to the possible factors of hypoventilation in OSA patients. The strongest relationship was found with FEV₁, again emphasizing the contributory role of diffuse airway obstruction to the development of hypercapnia. The second contributing factor was the cumulative apnea duration, showing that the severity of sleep apnea by itself may contribute to hypercapnia. The third contributing factor related to PaCO₂ was the level of minute ventilation at FETCO₂ = 60 mm Hg, which reflects the degree of ventilatory response to hypercapnia. A relationship between daytime hypercapnia and decreased ventilatory response to hypercapnia was previously reported.₃,₁⁰ This indicates either that an impaired ventilatory response to CO₂ plays a role in the development of hypercapnia or that chronic hypercapnia may decrease the chemosensitivity to CO₂. The rapid improvement in the ventilatory response to hypercapnia observed in OSA patients treated with nasal CPAP¹⁷ and the more progressive one after tracheostomy¹⁸,¹⁹ suggest that the presence of apneas during sleep may contribute to an impairment of the ventilatory response to CO₂.

In a similar study of 111 patients, Leech et al²⁰ found PaCO₂ to be related to PaO₂, because of the physiologic relationship between PaO₂ and PaCO₂, such a statistical correlation was predictable and does not help explain the mechanisms of hypercapnia in OSA patients. Only in the subgroup of 41 hypercapnic patients, did Leech et al²⁰ also find PaCO₂ to be related to the apnea + hypopnea index and to the percent predicted of FVC. Because of the small number of hypercapnic patients in our population, we did not try to perform separate correlation analyses, which, in addition, would have introduced an artificial threshold in an otherwise continuously varying parameter. The differences between the study by Leech et al and ours may be due to differences in patient selection; the high percentage of women (32 percent) in those authors’ study, which was even higher among hypercapnic patients (54 percent) suggests that their patients were not representative of the general OSA population. In addition, they did not include ventilatory response to hypercapnia among the parameters studied.

Our results are in keeping with those of Bradley et al,²¹ who also found hypercapnia to be correlated with the degree of diffuse airway obstruction and of ventilatory response to hypercapnia in 50 OSA patients.

PaO₂

More patients were found to be hypoxemic than hypercapnic, showing that hypoventilation was not the sole mechanism of hypoxemia in these patients. The FEV₁ was again found to be the main contributor to PaO₂, suggesting that diffuse airway obstruction, or lung volume restriction due to obesity, played a contributing role through a ventilation/perfusion mis-match. However, 22/37 (59 percent) hypoxemic patients had FEV₁/FVC > 0.65, suggesting that the lower airway obstruction need not be very important for daytime hypoxemia to develop. It is also possible that other factors, eg, obesity-hypoventilation, play a role; yet the BMI was not found to contribute significantly to daytime PaO₂ in these patients.

The PaO₂ was also found to be related to the hypopnea + apnea index, suggesting that the number of disordered breathing episodes during sleep contributes to the development of daytime hypoxemia.

Globally, the model for daytime hypoxemia explained only 31 percent of the variance of PaO₂. This low figure suggests that the relevant parameter was not included among the independent parameters. It may be connected with the clinical observation of a large day-to-day variability in PaO₂ without any apparent change in the patients’ condition, which shows that in OSA patients, the determining factors of daytime PaO₂ are ill-defined.

Our data show that impaired daytime lung function plays the major role in the development of respiratory insufficiency and pulmonary hypertension in OSA patients. The aggravating role of COPD in OSA syndromes was previously stressed on a clinical basis by Flenley,²² who coined the term “overlap syndrome” to describe this association. Conversely, it has been shown that in COPD patients who had concurrent OSA, the hemodynamic status was more severe than in patients with “pure” COPD with a similar degree of respiratory function impairment.²³ However, since in our patients all studied parameters varied continuously, from normal to pathologic, the described correlations suggest that even mild alterations in any of the contributing parameters may play a role in the development of respiratory insufficiency and cor pulmonale. This should be a further incentive in OSA patients to avoid factors compromising pulmonary function (ie, obesity, tobacco smoking). It also suggests that the aim of the treatment of OSA patients should be the elimination of sleep apneas, rather than only their reduction in number or the suppression of subjective symptoms.

ACKNOWLEDGMENTS: The authors are grateful to Annie Peter, Béatrice Fillius, Claire Bonigen, and Evelyne George for the care they take of their patients, and to Dr. Florence (Département d’Informatique de la Faculté de Médecine de Strasbourg) for his contribution to the statistical analysis of their data.

REFERENCES