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Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences

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Pulmonary hypertension in the obstructive sleep apnoea syndrome: prevalence, causes and therapeutic consequences. R. Kessler, A. Chaouat, E. Weitzenblum, M. Oswald, M. Ehrhart, M. Apprill, J. Krieger. ©ERS Journals Ltd 1996.

ABSTRACT: "Cor pulmonale" is a classic feature of the "Pickwickian syndrome". Earlier studies have reported a high prevalence of pulmonary hypertension (PH) in obstructive sleep apnoea (OSA) patients, but this has not been confirmed by recent studies with a more adequate methodology, including larger groups of patients.

The first part of this review is devoted to the prevalence of PH in OSA; most recent studies agree on prevalence of 15–20%.

The second (and major) part of the study deals with the causes and mechanisms of PH in OSA. Pulmonary hypertension is rarely observed in the absence of daytime hypoxaemia, and the severity of nocturnal events (apnoea index (AI), apnoea+hypopnoea index (AHI)) does not appear to be the determining factor of PH. Diurnal arterial blood gas disturbances and PH are most often explained by the presence of severe obesity (obesity-hypoventilation syndrome) and, principally, by association of OSA with chronic obstructive pulmonary disease (the so called "overlap syndrome"). Bronchial obstruction is generally of mild-to-moderate degree and may be asymptomatic.

The final part of the review analyses the therapeutic consequences of the presence of PH in OSA patients. Pulmonary hypertension, which is generally mild-to-moderate, does not need a specific treatment. When nasal continuous positive airway pressure (CPAP) fails to correct sleep-related hypoxaemia, supplementary oxygen must be administered. In patients with marked daytime hypoxaemia (arterial oxygen tension (P_{a,O_2}), ≤7.3 kPa (55 mmHg) conventional O_2 therapy (nocturnal + diurnal) is required.

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"Cor pulmonale" is a classic feature of the "Pickwickian syndrome", which was described by BURWELL *et al.* [1] 40 yrs ago. The sleep apnoea syndrome was described later [2–4], and the occurrence of pulmonary hypertension (PH) in sleep apnoea patients has been emphasized [5, 6]. However, these earlier studies involved small numbers of selected (and severe) patients, which probably biased the estimation of the prevalence of PH. In recent years, more adequate studies, including large groups of patients, have investigated the prevalence of cor pulmonale [7] and PH [8–13] in unselected obstructive sleep apnoea (OSA) patients.

In earlier studies using intravascular pressures [5, 14, 15], transient, and sometimes severe, elevations of pulmonary artery pressure (P_{pa}) have been observed during sleep in OSA patients. These findings have been confirmed by more recent transmural measurements of P_{pa} [16–18]. However, we do not definitely know whether sleep-related (episodic) PH leads, with time, to daytime (permanent) PH and, subsequently, to right heart failure.

The present review does not concern the acute haemodynamic aspects of obstructive sleep apnoeas, which have been extensively considered in a state of the art report published recently in the Journal [19]. Instead, it is devoted to daytime (permanent) PH in OSA patients. An attempt will be made to answer the following questions: What is the real prevalence of pulmonary hypertension in OSA patients? What are the mechanisms of permanent pulmonary hypertension and, more specifically, is isolated nocturnal hypoxaemia due to the repetition of apnoeas capable of inducing sustained pulmonary hypertension when daytime arterial blood gases are still normal? Does the presence of pulmonary hypertension require a particular treatment in OSA patients?

Prevalence of pulmonary hypertension in OSA patients

Early studies by the Stanford group [5, 6] found a high prevalence (near 60%) of awake PH defined as a mean P_{pa} >20 mmHg. However, this figure was obtained in a small group (n=22) of OSA patients selected from a larger population, which probably introduced a bias, as mentioned above. Table 1 presents the results of more recent studies, including larger numbers of patients (46–220). Two series must be considered separately, since there are particular ways of selection which undoubtedly bias the results: 1) the series of FLETCHER *et al.* [20], which was restricted to 24 patients, exclusively male, with an associated respiratory disease (which was generally a chronic obstructive pulmonary disease (COPD));

Table 1. – Prevalence of pulmonary hypertension (or cor pulmonale) in several recent studies from the literature

First authors	[Ref.]	Pts n	Sex M/F	Selection of patients	Cor pulmonale n	Cor pulmonale %	PH n	PH %
BRADLEY	[7]	50	44/6	Unselected, consecutive	6	12	-	-
PODSZUS	[8]	65	61/4	Unknown	-	-	13	20
WEITZENBLUM	[9]	46	42/4	Unselected, consecutive	-	-	9	20
KRIEGER	[10]	100	95/5	Unselected, consecutive	-	-	19	19
LAKS	[11]	100	?/?	Unselected, consecutive	-	-	42	42
CHAOUAT	[13]	220	207/13	Unselected, consecutive	-	-	37	17
FLETCHER	[20]	24	24/0	Associated respiratory diseases, male only	18	75	11/15	73
SAJKOV	[21]	27	26/1	No associated lung or cardiac diseases	-		11	41

M: male; F: females; PH: pulmonary hypertension.

and 2) that of SAJKOV *et al*. [21], which was limited to 27 patients without significant lung or cardiac disease associated with the OSA, who underwent pulsed Doppler measurements of P_{pa} but no usual haemodynamic measurements.

BRADLEY and co-workers [7] were probably the first to assess the prevalence of clinical cor pulmonale in unselected OSA patients. They observed that 6 out of 50 (12%) of the patients had cor pulmonale, which is a rather low figure. However, it must be borne in mind that the clinical and electrocardiographic (ECG) signs of cor pulmonale appear later than those of PH assessed by right heart catheterization [22]. In this respect, there is a rather good agreement between this figure and the finding of a 15–20% prevalence of PH in subsequent studies [8–10, 12, 13].

Cor pulmonale is classically defined [23] by the presence of right ventricular hypertrophy. The latter can be assessed by echocardiographic measurements of the right ventricular wall thickness. Controversial results have been reported in the literature: some authors [24] found, by echocardiography, right ventricular hypertrophy in 71% of OSA patients; whereas, others [25] found no evidence of right ventricular enlargement. A very recent Japanese study [26] found right ventricular hypertrophy in 6 out of 51 (12%) OSA patients, which is similar to the prevalence of clinical cor pulmonale reported by BRADLEY and co-workers [7]. In fact, the echocardiographic measurement of right ventricular wall thickness may be difficult in some patients and its precision is discussed, contrasting with the reliability of pulmonary haemodynamic measurements.

It can be seen from table 1 that the results of 4 of the 5 series from the literature [8–10, 13] are quite similar, and indicate that the prevalence of pulmonary hypertension is 17–20%. Indeed, three [9, 10, 13] of these studies originate from the same group, but the number of patients increased from 46 in 1988 to 220 in 1996, and the frequency of PH (17–20%) was remarkably stable over that period. In the recent study by LAKS and co-workers [11], the prevalence of PH was somewhat higher (42%). The Australian patients investigated by LAKS and co-workers [11] had a mean body mass index (BMI) of 37 (range 24–54) $kg \cdot m^{-2}$, indicating the presence of marked obesity in most of the patients, which is in contrast to the European studies, since the mean (±SD) BMI was 32±6 $kg \cdot m^{-2}$ in the 220 patients investigated by CHAOUAT and co-workers [13]. Of interest, the average arterial carbon dioxide tension (P_{a,CO_2}) in the series of LAKS and co-workers [11] was 6.0 kPa (45 mmHg) compared to 5.1 kPa (38.6 mmHg) in the series of CHAOUAT and co-workers [13]. The marked obesity, frequently observed in the patients investigated in Sydney could have favoured the occurrence of alveolar hypoventilation and might explain the relatively high prevalence of PH (42%) when compared to European studies.

A retrospective multicentric study [27], pooling results from Sydney (Australia), Marburg (Germany) and Strasbourg (France), indicated that 111 out of 453 patients, *i.e*. 25% had resting PH. This study included a minority (n=98) of patients from Australia.

Indeed, when OSA is associated with chronic lung disease ("overlap syndrome"), as in the study performed by FLETCHER *et al*. [20], PH is a common finding and clinical cor pulmonale is observed in 75% of the patients, a figure which can be compared with the 12% reported by BRADLEY and co-workers [7] in unselected OSA patients. On the other hand, it is rather surprising that SAJKOV *et al*. [21] observed a high prevalence (41%) of PH in selected patients without clinical or functional evidence of chronic obstructive pulmonary disease (COPD) or other chronic lung diseases and no evidence of any cardiovascular disease, but their study was limited to 27 patients and P_{pa} was not assessed by catheterization but was estimated from pulsed Doppler measurements.

It must be emphasized that in OSA patients PH, when present, is generally of mild degree. In the 42 pulmonary hypertensive patients investigated by LAKS and co-workers [11], P_{pa} ranged 20–52 mmHg but the average value for the group was of only 29 mmHg. Similarly, in the pulmonary hypertensive group of CHAOUAT and co-workers [13], including 37 patients, P_{pa} ranged 20–44 mmHg and exceeded 35 mmHg in only two patients; the average value was 26±6 mmHg. This modest degree of pulmonary hypertension is very similar to that observed in COPD.

Mechanisms and causes of pulmonary hypertension in OSA patients

Pulmonary hypertension is almost always of the precapillary type, since an elevated "capillary" wedge pressure is rarely observed, except when patients are being investigated during an episode of congestive heart failure. In the 37 patients with PH from the series of CHAOUAT and co-workers [13], the pulmonary "capillary" wedge

Table 2. – Anthropometric, functional, gasometric and pulmonary haemodynamic variables in OSA patients with and without pulmonary hypertension, and comparison of the two groups by the t-test

Variable	PH Group (n=37)	Non PH Group (n=183)
Sex M/F	35/2	168/15
Age yrs	52±11	53±9
BMI kg·m^{-2}	34±8	31±5**
VC L	2.8±0.9	3.9±0.8†
VC % pred	74±16	98±14†
FEV1 L	1.8±0.8	2.9±0.7†
FEV1/VC %	64±13	74±9†
P_{a,O_2} kPa	8.6±1.2	10.0±1.3
mmHg	64.4±9.3	74.7±10.0†
P_{a,CO_2} kPa	5.8±0.7	5.0±0.5
mmHg	43.8±5.4	37.6±4†
Haematocrit %	48±6	44±3*
P_{pa} rest mmHg	26.0±5.8	13.7±2.6†
P_{pa} exercise mmHg	46.7±12	27.3±7.5†
PCWP rest mmHg	8.3±2.7	6.0±1.9†
PCWP exercise mmHg	18.3±9	14.1±4.7
PVR rest mmHg·L^{-1}·min	2.8±1.2	1.3±0.5**

Values are presented as mean±SD. PH: pulmonary hypertension; M: male; F: female; BMI: body mass index; VC: vital capacity; PCWP: pulmonary "capillary" wedge pressure; PVR: pulmonary vascular resistance; % pred: percentage of predicted value; FEV1: forced expiratory volume in one second; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; P_{pa}: pulmonary artery pressure; OSA: obstructive sleep apnoea; *,**: p<0.05, 0.01, †: p<0.001. NS: nonsignificant. (From [13]).

pressure, which could be measured at rest in 21 out of 37 patients, never exceeded 13 mmHg, cardiac output was within normal limits, and the increase in P_{pa} was due to the increased pulmonary vascular resistance (table 2).

Pulmonary hypertension worsens during exercise: from 26.0±5.8 to 46.7±12 mmHg in the pulmonary hypertensive patients of CHAOUAT and co-workers [13], who underwent submaximal steady-state exercise (table 2). The increase in P_{pa} during exercise is partly explained by an abnormally high wedge pressure, a fact which was emphasized in an earlier study by TILKIAN *et al*. [5], and has been confirmed in recent reports [13, 28]. In the 20 OSA patients investigated by HAWRYLKIEVICZ *et al*. [28] the wedge pressure increased from 7±3 to 15±7 mmHg during exercise, and the exercising wedge pressure exceeded 20 mmHg in three patients. In the pulmonary hypertensive patients of CHAOUAT and co-workers [13], the wedge pressure increased from 8±3 to 18±9 mmHg during submaximal exercise (table 2). It thus appears that resting PH is almost always of the precapillary type, but that exercising PH could be of the mixed or of the postcapillary type, related to some degree of left ventricular dysfunction during exercise. Left ventricular dysfunction is often found in patients with severe obesity [29], and could be present during exercise in the most obese OSA patients.

Is pulmonary hypertension observed in the absence of daytime hypoxaemia?

It has long been hypothesized that episodic and recurrent hypertension, due to the repetition of apnoeas, could lead to permanent PH [6]. Peaks of PH during sleep have been well-documented in earlier studies measuring intravascular pressures [14, 15] and also in recent, more reliable studies where the simultaneous measurement of intravascular and intrathoracic (oesophageal) pressures allowed the determination of pulmonary artery transmural pressure [16–18]. These transient (and repetitive) elevations of P_{pa} are accounted for by hypoxaemia [16–18], which induces vasoconstriction of the small pulmonary arteries. It is known from animal studies [30–32] that intermittent hypoxia (4–8 h·day^{-1}) may be sufficient to induce permanent PH and right ventricular hypertrophy, but it is not known whether these data are transposable to man. If this is the case, sleep-related hypoxaemia of OSA patients could explain the development of daytime PH.

In fact, there is no proof that OSA alone, in the absence of daytime hypoxaemia, is capable of causing stable PH. Most studies have indicated that PH is observed in hypoxaemic and hypoxaemic-hypercapnic patients [7, 9–11, 13]. Most studies have failed to find a significant relationship between the severity of OSA, expressed by the apnoea index (AI) and the apnoea + hypopnoea index (AHI), and the presence of PH [7, 9, 11, 13, 20].

BRADLEY and co-workers [7] observed that their six patients with cor pulmonale markedly differed from the remainder with regard to arterial blood gas values, whereas the sleep data were similar in the two subgroups. Table 3 shows that hypoxaemia was severe in cor pulmonale patients and absent or mild in the remainder. Similarly, hypercapnia was present in cor pulmonale patients and absent in the remainder. On the other hand, the severity of OSA (AI, AHI, total apnoea time) was identical in patients with and without right heart failure.

Similar results have been observed by WEITZENBLUM *et al*. [9], who compared nine OSA patients with PH to 37 OSA patients without PH. Pulmonary hypertensive patients, as a mean, were hypoxaemic and mildly hypercapnic, whether the remainder had normal or near normal arterial blood gas values. By contrast, the AI and AHI were identical in the two subgroups, as was the time

Table 3. – Comparison between OSA patients with and without right heart failure (RHF)

Variable	OSA With RHF (n=6)	OSA Without RHF (n=44)
Age yrs	49±3	49±2
Weight % ideal	186±12	147±7*
FVC % pred	75±7	105±3†
FEV1 L	1.8±0.3	3.3±0.1†
FEV1/FVC %	56±5	76±1†
P_{a,O_2} kPa	6.9±0.5	10.0±0.3
mmHg	52±4	75±2†
P_{a,CO_2} kPa	6.8±0.3	4.8±0.1†
mmHg	51±2	36±1†
AI n·h^{-1}	30±10	33±4
AHI n·h^{-1}	57±9	60±5
Total apnoea time per h sleep %	22±9	20±7
Mean nocturnal S_{a,O_2} %	76±3	90±1†

Values are presented as mean±SEM. FVC: forced vital capacity; AI: apnoea index; AHI: apnoea-hypopnoea index; S_{a,O_2}: arterial oxygen saturation. *: p<0.05; †: p<0.001. For further definitions see legend to table 2. (From [7]).

Table 4. – Sleep parameters in OSA patients with and without pulmonary hypertension

Variable	PH Group (n=37)	Non PH Group (n=183)
AI $n \cdot h^{-1}$	74±42	59±37*
AHI $n \cdot h^{-1}$	100±33	73±32†
Mean duration of apnoeas s	21±7.3	22.6±7.1
TSA/TST %	27±17	24±18
Mean nocturnal S_{a,O_2} %	89±6	94±3†
Min nocturnal S_{a,O_2} %	64±14	75±16†
Time spent with S_{a,O_2} <90% $min \cdot h^{-1}$	38.4±28.6	11.9±17.9†

Min: minimum; TSA/TST: time spent in apnoea/total sleep time ratio. *: p<0.05; †: p<0.001. For further abbreviations see legend to tables 2 and 3. (From [13]).

spent in apnoea. These results have been confirmed in a very recent study from the same group [13], in which a much higher number of patients were investigated, since 37 patients with PH could be compared to 183 patients without PH: the arterial oxygen tension (P_{a,O_2}) was significantly lower in the former and the P_{a,CO_2} was significantly higher (table 2). Conversely, the differences between sleep parameters, except those relating to nocturnal S_{a,O_2} which is linked to daytime P_{a,O_2} and S_{a,O_2}, were either modest or not significant (table 4). A stepwise multiple regression analysis indicated that P_{pa} was best accounted for by daytime arterial blood gas values; the equation of prediction of P_{pa} did not include any variable representative of the severity of the nocturnal events (table 5).

However, the hypothesis that isolated nocturnal hypoxaemia could lead to permanent PH could be supported by some recent data from the literature: SAJKOV *et al.* [21] observed a very slight hypoxaemia in their pulmonary hypertensive patients (P_{a,O_2} 9.6±1.0 kPa (72.2±7.6 mmHg)) but this group was limited to 11 patients and, as mentioned above, P_{pa} was not measured by right heart catheterization but estimated by pulsed Doppler measurements. LAKS and co-workers [11] observed that six out of 42 patients with PH had a normal daytime P_{a,O_2} (>10.7 kPa (80 mmHg)). However, the capillary wedge pressure was not measured in their study, and it is not possible to rule out that PH was of the postcapillary type in some of these markedly overweight patients (mean BMI = 38 $kg \cdot m^{-2}$).

Thus, most of the data available at present do not support the hypothesis that PH can develop in the absence of daytime hypoxaemia. When present, hypoxaemia is often of a mild degree with a mean P_{a,O_2} in the range 8.0–9.3 kPa (60–70 mmHg) [9–11, 13], but it must be remembered that, even if daytime P_{a,O_2} is over 8.0 kPa (60 mmHg), the mean asleep P_{a,O_2} is indeed much lower. A mean nocturnal P_{a,O_2} of 6.7–7.3 kPa (50–55 mmHg) can be assumed in OSA patients whose mean daytime P_{a,O_2} is about 8.7 kPa (65 mmHg). The combination of marked nocturnal with mild-to-moderate daytime hypoxaemia could explain the development of PH.

The mechanisms by which alveolar hypoxia causes PH are probably similar to those observed in COPD [33], and include both pulmonary vasoconstriction and "remodelling" of the pulmonary vascular bed. In fact there are probably marked interindividual differences in the response of the pulmonary circulation to hypoxia, as in normal individuals [34, 35] and in COPD patients [36]. SAJKOV *et al.* [21] speculated that in "responder" OSA patients repetitive elevation of P_{pa} during sleep may lead, with time, to pulmonary vascular remodelling; and LAKS and co-workers [37] observed that some OSA patients have an exaggerated pulmonary vascular responsiveness to hypoxia and hypercapnia, which may return to normal with long-term treatment.

Causes of arterial blood gas disturbances and of pulmonary hypertension

It has been seen that PH most often develops in the presence of daytime hypoxaemia and (or) hypoxaemia-hypercapnia. The causes of permanent arterial blood gas disturbances in OSA patients will now be considered.

Role of a decreased chemosensitivity to hypoxia and hypercapnia. The hypothesis that a diminished chemosensitivity could account for the presence of daytime hypoxaemia-hypercapnia is certainly an attractive one [38], but has not yet been confirmed. In fact, few studies have included measurements of the ventilatory response to CO_2 and hypoxia in large series of OSA patients [7, 10]. The study by GARAY *et al.* [39] has shown a decrease of the ventilatory response to hypoxia and hypercapnia, respectively in hypoxic and hypercapnic patients,

Table 5. – Stepwise multiple regression analysis of P_{pa}, P_{a,O_2} and P_{a,CO_2} in a large series of OSA patients

1. $P_{pa} = 0.31\ P_{a,CO_2} - 0.0015\ FEV_1 + 0.72\ R_{aw} - 0.26\ \overline{S}_{a,O_2} + 29.98$
   $r^2 = 0.50$. P_{a,CO_2} accounts for 0.32 of the variance, FEV_1 for 0.12, R_{aw} for 0.04, $\overline{S}_{a,O_2}$ for 0.02
   Complete data available for 142 patients. SEE = 4.2 mmHg

2. $P_{a,O_2} = 0.0046\ FEV_1 - 0.052\ AHI - 0.23\ BMI + 72.23$
   $r^2 = 0.23$. FEV_1 accounts for 0.17 of the variance, AHI for 0.04, BMI for 0.02
   Complete data available for 265 patients. SEE = 9.5 mmHg

3. $P_{a,CO_2} = -9.15\ VC + 0.68\ R_{aw} + 0.21\ AI + 43.51$
   $r^2 = 0.30$. VC accounts for 0.21 of the variance, R_{aw} for 0.07, AI for 0.02
   Complete data available for 243 patients. SEE = 4.2 mmHg.

P_{pa}: pulmonary artery pressure; R_{aw}: total airway resistance; $\overline{S}_{a,O_2}$: mean nocturnal arterial oxygen saturation. P_{pa}, P_{a,O_2}, P_{a,CO_2},: mmHg: FEV_1: mL; VC: % of predicted; R_{aw}: $cmH_2O \cdot L^{-1} \cdot s$; $\overline{S}_{a,O_2}$: %; SEE: standard error of the estimate; AHI, AI: $n \cdot h^{-1}$; BMI: $kg \cdot m^{-2}$. For further abbreviations see legends to tables 2 and 3. (From [48]).

but the group was limited to 13 patients who were all obese. The majority of the patients were hypercapnic, whereas hypercapnia is present in only 10–15% of large series of unselected OSA patients [7, 9, 10, 13, 40]. Furthermore, a diminished ventilatory response to CO_2 may be the consequence, and not necessarily the cause, of chronic hypercapnia, a fact which is well-established in COPD patients [41, 42].

The ventilatory response to CO_2 is rapidly improved in patients treated with nasal continuous positive airway pressure (nCPAP) [43]. In OSA patients undergoing tracheostomy, this improvement takes a longer time to occur [44, 45]. These results suggest that repeated apnoeas could favour a diminished ventilatory response to hypoxia and hypercapnia. Indeed, in patients with severe OSA a relatively high percentage of the night is spent in hypoxic and hypercapnic conditions, and this could result, with time, in a blunted chemosensitivity. However, this hypothesis needs to be firmly demonstrated.

RAPOPORT *et al*. [46] have shown that there is, in fact, no parallelism between the changes of P_{a,CO_2} and those of the ventilatory response to CO_2 during nCPAP treatment. Consequently, a diminished ventilatory response to CO_2 does not automatically lead to hypercapnia. Similarly, an improved ventilatory response does not necessarily explain the normalization of P_{a,CO_2} under treatment. For these authors [46], hypercapnia is due rather to a diminished daytime overall ventilation, independent of apnoeas, and these patients are the true "pickwickians".

In summary, it has not, so far, been demonstrated that a diminished chemosensitivity, possibly induced by the repeated episodes of nocturnal hypoxaemia and hypercapnia, is a determining factor of daytime arterial blood gas disturbances. In some patients, efficient treatments of OSA, such as tracheostomy and nCPAP, allow improvement of hypoxaemia and hypercapnia, but it has not been firmly proved that this was accounted for by a normalization of the ventilatory response to hypoxic and hypercapnic stimuli.

Role of obesity. Obesity is a classical cause of alveolar hypoventilation. Historically, the obesity-hypoventilation syndrome has been described as the "pickwickian" syndrome [1]. Obstructive apnoeas have been observed first in "pickwickian" patients with severe obesity [2]. Accordingly, obesity could represent a major cause of respiratory insufficiency and PH in OSA patients.

The data in the literature are rather conflicting, since some studies have shown marked differences with regard to weight between hypercapnic and nonhypercapnic OSA patients [40, 47], and between OSA patients with and without cor pulmonale [7] (table 3); whereas, other studies have not [9, 10]. In two recent studies [11, 13] patients with PH had a higher BMI than the remainder but the difference was rather small and reached the level of significance in only one study [13] (table 2).

In the stepwise multiple regression analysis of P_{a,O_2}, P_{a,CO_2} and P_{pa} performed by CHAOUAT and co-workers [48], BMI is only present in the equation of prediction of P_{a,O_2} (table 5), where it accounts for 2% of the variance. BMI does not appear in the equations of prediction of P_{a,CO_2} and P_{pa}.

It must be emphasized that some series in the literature have included a high percentage of severe obesities [47], which was not the case of other series probably more representative of the "general" population of OSA patients; and that the prevalence of a marked obesity in OSA patients is probably not similar in the USA and Australia when compared to Europe.

Even if an associated COPD represents by far the major cause of hypoxaemia in OSA patients (see below), the role of obesity should not be underestimated: in the study by CHAOUAT and co-workers [13] 37 out of 220 OSA patients had PH. Ten patients exhibiting PH had no obstructive ventilatory pattern or a small airways disease; of these patients six had a pure restrictive ventilatory pattern accounted for by obesity.

In some cases of severe obesity, diurnal alveolar hypoventilation is easily explained by a marked restriction of pulmonary volumes, a decreased thoracic compliance and a reduced inspiratory muscular strength [29]. In other cases of obesity, lung volumes are within normal limits and the cause of hypercapnia is less clear; a diminished chemosensitivity to CO_2 has been advocated but the respective roles of mechanical loading and respiratory neuromuscular control in the pathogenesis of the obesity-hypoventilation syndrome are difficult to define [49].

Role of an associated COPD. Most studies have emphasized the role of an associated COPD in the pathogenesis of hypoxaemia, hypercapnia and PH in OSA patients [7, 9–11, 13, 20, 40, 48]. The coexistence of COPD and OSA, which has been called "overlap syndrome" by FLENLEY [50], is likely to occur in a number of patients, since both COPD and OSA are frequent diseases: a recent study has shown that the prevalence of OSA in middle-aged men is about 5% [51]. In the study by CHAOUAT and co-workers [48] investigating 265 consecutive OSA patients, a permanent bronchial obstruction (forced expiratory volume in one second (FEV_1)/vital capacity ratio (VC) <60%) was observed in 11% of the subjects.

BRADLEY and co-workers [40] have observed that OSA patients with hypoxaemia-hypercapnia (n=7) differed from the remainder (n=43) by the presence of bronchial obstruction; the obstructive ventilatory defect was not severe since the average FEV_1 and FEV_1/forced vital capacity (FVC) were 2.0±0.3 L (±SEM) and 59±5%, respectively, but the differences with the nonhypercapnic group (FEV_1 = 3.3±0.1 L and FEV_1/FVC = 76±1%) were highly significant ($p<0.0001$). The same authors have found very similar results when comparing OSA patients with and without right heart failure [7]: the former exhibited an obstructive ventilatory pattern (table 3) and differed significantly in this regard from the remainder ($p<0.001$).

Our group has reported identical results when comparing OSA patients with and without alveolar hypoventilation [10], and with and without PH [9, 12, 13]. Of interest, our numerical results are very similar to those of BRADLEY and co-workers [7, 40]: in 13 hypercapnic OSA patients [10], the average FEV_1 and FEV_1/VC were 1.9±0.2 L (±SEM) and 63±4%, respectively, *versus* 2.7±0.09 L and 74±1% in the nonhypercapnic patients ($p<0.001$). Identical differences with regard to the presence and degree of bronchial obstruction have been observed between pulmonary hypertensive patients and the remainder [9, 13]. The stepwise multiple regression analysis of

P_{a,O_2}, P_{a,CO_2} and P_{pa} has clearly shown that the indices of bronchial obstruction were the best predictors of arterial blood gas disturbances and of PH [13, 48] (table 5).

In the recent study by LAKS and co-workers [11], patients with PH (n=42) had a lower FEV1 (p<0.001) and a lower FEV1/VC ratio (p=0.03) than the normotensive patients (n=58). SAJKOV *et al*. [21] did not observe significant differences between the pulmonary hypertensive group and the remainder with regard to indices of bronchial obstruction, but their study was limited to 27 patients and P_{pa} was estimated from echo Doppler and not measured (see above). In the study by LEECH *et al*. [47], the hypercapnic patients did not differ from the normocapnic with regard to the FEV1/FVC ratio, However, this series included a high percentage of females (36 out of 111) and of hypercapnic patients (41 out of 111), and most of the patients were markedly obese; accordingly, this series is not representative of a general population of OSA patients.

Another method of investigating the role of chronic airway obstruction in the pathogenesis of arterial blood gas abnormalities is to compare OSA patients with and without an associated COPD. The former ("overlap" patients) markedly differ from the remainder ("simple" OSA patients) with regard to P_{a,O_2} (significantly lower), P_{a,CO_2} (significantly higher), resting and exercising P_{pa} (significantly higher), as can be seen from table 6.

In OSA patients exhibiting permanent PH, bronchial obstruction is generally not severe and the level of hypoxaemia and hypercapnia is modest. In the 37 patients with PH investigated by CHAOUAT and co-workers [13], the average values were: FEV1 1.8 L; FEV1/VC 64%; P_{a,O_2} 8.5 kPa (64 mmHg); and P_{a,CO_2} 5.9 kPa (44 mmHg). In COPD patients with pulmonary hypertension and/or cor pulmonale worse values are generally found: FEV1 ≤1.0 L; FEV1/VC ≤50%; P_{a,O_2} ≤7.3 kPa (55 mmHg) and P_{a,CO_2} ≥6.0 kPa (45 mmHg), and this discordance has been emphasized by several groups [7, 9, 13, 20, 40]. For a given FEV1, P_{a,O_2} is generally lower in OSA patients [7, 20], a fact that could be accounted for by the role of obesity and by a diminished chemosensitivity (see above). Similarly, for a given daytime P_{a,O_2}, P_{pa} is generally higher in OSA patients, a fact which is probably explained by the worsening of P_{a,O_2} during sleep due to the repetition of apnoeas and hypopnoeas.

Thus, an associated COPD is probably the determining factor of alveolar hypoventilation in OSA, but it must be emphasized that the level of bronchial obstruction is most often mild-to-moderate. Furthermore, the chronic airway obstruction may be asymptomatic in some patients, and this stresses the necessity of systematically performing pulmonary function tests (including arterial blood gas measurements) in all patients in whom OSA is assessed by polysomnography.

Table 6. – Comparison of "overlap" patients (OSA with an associated COPD) and remainder (simple OSA) in a large series (n=265) of OSA patients

Variable	"Overlap" patients (n=30)	Remainder (n=235)
Age yrs	58±9	53±10**
Sex M/F	30/0	214/21
VC % pred	82±21	95±16†
FEV1 L	1.6±0.6	2.8±0.8†
FEV1/VC %	50±6	75±7†
P_{a,O_2} kPa	8.8±1.3	9.9±1.3
mmHg	66±10	74±10†
P_{a,CO_2} kPa	5.6±0.8	5.1±0.5
mmHg	42±6	38±4†
P_{pa} rest mmHg	20±6 (n=26)	15±5** (n=194)
PCWP rest mmHg	6±2 (n=16)	6±2 (n=135)
P_{pa} exercise mmHg	37±12 (n=21)	29±10+ (n=180)
PCWP exercise mmHg	13±4 (n=9)	15±5 (n=59)

COPD: chronic obstructive pulmonary disease. +: p=0.01; **: p<0.01; †: p<0.001. For further abbreviations see legends to tables 2 and 3. (From [48]).

Therapeutic consequences

It has been seen that pulmonary hypertension is most often mild-to-moderate in OSA patients, with P_{pa} generally ranging 20–35 mmHg. Such PH does not necessitate specific treatment. On the other hand, the presence of PH indicates that OSA has noticeable consequences and needs appropriate therapeutic measures.

FLETCHER *et al*. [20] have observed that P_{pa} decreased (p=0.05) after 1 and 2 yrs of follow-up in patients with OSA associated with a chronic lung disease treated by tracheostomy: from 36±11 to 25±8 mmHg; but these haemodynamic results were limited to six patients. In the group of patients with isolated OSA (n=5), P_{pa} did not fall but pulmonary vascular resistance did (p<0.005).

At the present time, long-term nCPAP is the "first line" treatment of OSA. Does it have favourable haemodynamic effects in patients with pulmonary hypertension? There are very few data in the literature making it possible to answer this question. SFORZA *et al*. [52] investigated 54 patients treated with nCPAP for at least 1 year. For the group as a whole, P_{pa} was unchanged after a mean follow-up period of 554±28 (±SEM) days. In the small subgroup (n=8) of patients with pulmonary hypertension, P_{pa} did not change significantly (23±1 to 21±1 mmHg). The exercising P_{pa} of the whole group increased slightly but significantly from 30±1 to 33±2 mmHg (p<0.05). These results have been confirmed by a further study from the same group [53], in which the long-term (5 yrs) effects of CPAP were investigated in 48 OSA patients; the number of patients with PH at the onset (n=4) was too limited to allow an estimation of the evolution of P_{pa}. Of interest, both studies [52, 53] have indicated that P_{a,O_2} improved significantly in those patients exhibiting significant hypoxaemia at the onset. If P_{a,O_2} increases with long-term nCPAP treatment, one could expect an improvement, or at least a stabilization, of PH similar to that observed in COPD patients under long-term O_2 therapy [54, 55].

Finally it must be emphasized that if nasal continuous positive airway pressure is efficient in suppressing apnoeas and correcting hypoxaemia in the great majority of obstructive sleep apnoea patients, this may not be the case in some patients with an associated chronic obstructive pulmonary disease and/or obesity-hypoventilation

syndrome. In these patients, apnoeas are abolished by nasal continuous positive airway pressure but some degree of hypoxaemia may persist, particularly during rapid eye movement sleep. Consequently, it is necessary to give supplemental O_2 (1.5–3 $L \cdot min^{-1}$) during sleep or to shift to another mode of nocturnal ventilation, such as bilevel positive airway pressure. In the most severe "overlap" patients and in some obesity-hypoventilation patients, a marked daytime hypoxaemia may persist in spite of the nocturnal treatment of apnoeas. These patients require conventional ($\geq$18 $h \cdot day^{-1}$) oxygen therapy in addition to nasal continuous positive airway pressure or bilevel positive airway pressure ventilation. These patients are the most likely to develop pulmonary hypertension [20] and long-term oxygen therapy may help to decrease or at least stabilize pulmonary artery pressure.

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