Obstructive sleep apnea syndrome and the pulmonary circulation

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The pulmonary hemodynamic consequences of obstructive sleep apneas have been investigated by several groups during the last 30 years. The earlier data have been obtained by measuring the intravascular pulmonary arterial pressure (PAP) and have shown a rise of PAP during apneas, the highest PAP being observed at the end of apneas. Actually, during obstructive apneas the only reliable measurements are those of transmural PAP which increases throughout the apneas, as a consequence of hypoxic vasoconstriction, and decreases after ventilation has resumed. The link between episodic (nighttime) and permanent (daytime) pulmonary hypertension is poorly understood. Recent studies have clearly indicated that daytime hypoxemia, generally due to an associated chronic airflow obstruction, is the major determinant of permanent pulmonary hypertension and cor pulmonale, and that nocturnal hypoxemia is not sufficient *per se*.

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In recent years, with the development of sleep laboratories and polysomnography, a great number of studies have been devoted to obstructive sleep apnea syndrome (OSAS). Since alveolar hypoxia induces pulmonary vasoconstriction, it can be expected that a sleep-related episode of hypoxemia will be accompanied by peaks of pulmonary hypertension. In fact, there have been few hemodynamic investigations during sleep in OSAS patients and the number of patients who could be investigated was rather restricted in all the published studies. This is probably accounted for by the fact that hemodynamic investigations are not easily performed during sleep.

Another important question is that of the development of permanent (diurnal) pulmonary hypertension in patients with OSAS: does sleep-related (episodic) pulmonary hypertension lead to daytime (permanent) pulmonary hypertension? What is the real prevalence of permanent pulmonary hypertension in a population of OSAS subjects and what are the mechanisms leading to permanent pulmonary hypertension?

Acute effects of obstructive sleep apneas on the pulmonary circulation

The first studies on the pulmonary circulation in OSAS patients were performed in 1972: Coccagna et al.[1] in Bologna, and Lonsdorfer et al.[2], in Strasbourg, were probably the first to measure continuously mean pulmonary artery pressure (PAP) during sleep in OSAS patients. They used small floated catheters and these investigations were combined with polysomnography. Both groups of authors observed large oscillations in PAP due to intrathoracic pressure swings and noticed that mean PAP was higher following the apneas when ventilation had resumed. The increase in PAP was higher during REM sleep[1]. PAP returned to baseline values with awakening in the morning. There was a concomitant rise in systemic arterial pressure[1].

These results have been confirmed by the group of Stanford[3]: 10 out of 12 patients developed rises in PAP which were severe in 5 of them. PAP returned to control levels if several minutes of normal ventilation occurred, but conversely PAP gradually increased in the case of repeated apnea episodes in close sequence. Furthermore, Buda et al.[4] from the same group found that in those patients in whom they could be recorded pulmonary artery wedge pressures were also increased, but to a lesser degree. There is an agreement on the fact that the highest PAP is observed in the immediate post-apnea period[1,2,5].

In fact, the measurements of intravascular pressures, related to the atmospheric pressure, are not reliable during apneas be-

cause of the considerable variations of intrathoracic pressure. Obstructive apneas can be assimilated to a Müller maneuver (inspiratory effort against a closed glottis) and the PAP reflects the changes in intrathoracic pressure; the latter may decrease by as much as 30 mmHg during an obstructive apnea, with a subsequent fall of PAP which decreases to negative values[5]. In this instance the only significant variable is the transmural pressure (intravascular minus intrathoracic pressure) which can be obtained by simultaneously measuring PAP and intrathoracic pressure, i.e. the esophageal pressure, obtained from an esophageal balloon.

Transmural pressures in OSAS patients have been measured by Marrone et al.[6]. They have observed that transmural pressures show a trend to increase throughout the apneas and to decrease after ventilation has resumed, while pressures referenced to atmosphere had an opposite behavior. In most of their patients (5/7) there was a significant negative correlation between transmural PAP and arterial oxygen saturation (SaO_2).

In a further study, Marrone et al.[7] have observed that transmural systolic PAP shows rapid changes, which reflect esophageal pressure variations, and slower changes which are likely to be caused by changes in SaO_2. Using the same methodology we have observed[8] that in a sample of apneas randomly chosen among the longest ones, transmural PAP followed a biphasic evolution with an initial decrease and a final increase. Transmural PAP was correlated with SaO_2, but also with heart rate and esophageal pressure. We therefore suggested that transmural PAP decreases during the initial part of an obstructive apnea, due to the decrease in cardiac output and heart rate and increases during the final part due to hypoxic vasoconstriction.

Studies based on the measurement of transmural PAP[6-8] have shown that markedly hypertensive values of PAP are not the rule in OSAS patients during sleep, which is somewhat different from the results of earlier studies[1-3] but it must be underlined that the latter have included "Pickwickian" patients with severe obesity (and daytime alveolar hypoventilation) whereas more recent studies have included "usual" OSAS patients without daytime respiratory insufficiency. The results of Marrone et al.[6,7] have been recently confirmed by Schäfer et al.[9] who observed that systolic transmural PAP increased from 28.0 ± 12.1 mmHg (beginning of apnea) to 38.6 ± 15.5 mmHg (end of apnea); this change was significant ($p < 0.0001$) but not indicative of marked pulmonary hypertension. The change in transmural PAP was significantly correlated with the change in SaO_2 ($p < 0.0001$).

The cardiac output has been measured by Guilleminault et al.[10], by the thermodilution method, in 17 OSAS patients, and they have found it to decrease regularly during apneas, by 35% of its baseline value as a mean, and to increase at the resumption of ventilation. An increased pulmonary artery wedge pressure has been observed by Buda et al.[4], suggesting that an impaired left ventricular function could play a role in the increase of PAP. The results by Guilleminault et al.[10] and Buda et al.[4] could not be confirmed since no other studies, to our knowledge, have investigated cardiac output and pulmonary artery wedge pressure during obstructive apneas.

Thus, its seems that the increase of transmural PAP during an obstructive apnea is the consequence of the interaction of multiple factors including negative intrathoracic pressure, variations in heart rate, cardiac output and, possibly, left heart filling pressure, but the major factor seems to be hypoxic vasoconstriction. The elevation of transmural PAP is most often mild to moderate and markedly hypertensive values of PAP during sleep are very unusual, except in some patients who exhibit daytime respiratory insufficiency.

From nocturnal to daytime pulmonary hypertension

Is permanent (daytime) pulmonary hypertension a feature of OSAS patients? Cor pulmonale is indeed a classical feature of the "Pickwickian" syndrome which was described by Burwell et al.[11] 50 years ago but "Pickwickian" syndrome and OSAS are not synonymous and it is presently accepted that most of OSAS patients do not exhibit in fact pulmonary hypertension.

In the study by Chaouat et al.[12], performed in our department, 220 consecutive unselected OSAS patients underwent right heart catheterization (Table I). Pulmonary hypertension, defined by a resting mean PAP ≥ 20 mmHg, was observed in only 37 patients (17%) which confirmed previous results from our department[13,14] and those of Podszus et al.[15]. Our results are in agreement with the earlier findings by Bradley et al.[16] who showed that cor pulmonale was infrequent (6/50 patients) in OSAS and was exclusively observed in patients exhibiting daytime alveolar hypoventilation and an obstructive ventilatory defect (Table I). We have also observed[12] that pulmonary hypertension was generally associated with daytime hypoxemia (24/37 patients) and less often with hypoxemic hypercapnia (15/37 patients). Hypoxemia and hypercapnia were strongly linked to the presence of an obstructive ventilatory defect (chronic obstructive pulmonary disease) and were also observed in some patients with a restrictive defect (severe obesity)[12]. Taken together these data do not support the hypothesis that pulmonary hypertension can develop in OSAS patients in the absence of daytime hypoxemia.

However, there is still controversy in this field and other results[17-20] have indicated that diurnal pulmonary hypertension could be observed, in OSAS patients, in the absence of hypoxemia and of lung disease. Sajkov et al.[17,21] have noticed the presence of pulmonary hypertension in about 30% of OSAS patients without associated pulmonary or heart disease (Table I). Their

Table I. Prevalence of pulmonary hypertension in obstructive sleep apnea patients from several studies of the literature.

Author	No. patients	Sex (M/F)	Selection of the patients	Pulmonary hypertension
Bradley et al.[16]	50	44/6	Unselected	6 (12%)
Podszus et al.[15]	65	61/4	?	13 (20%)
Weitzenblum et al.[13]	46	42/4	Unselected	9 (20%)
Krieger et al.[14]	114	108/6	Unselected	21 (19%)
Chaouat et al.[12]	220	204/16	Unselected	37 (17%)
Laks et al.[18]	100	?	Unselected	42 (42%)
Sanner et al.[19]	92	81/11	Clinically significant lung disease was excluded	18 (20%)
Sajkov et al.[17]	27	26/1	No associated cardiac or lung diseases	11 (41%)
Sajkov et al.[21]	32	30/2	No associated cardiac or lung diseases	10 (31%)
Bady et al.[20]	44	37/7	No associated lung diseases	12 (27%)

cohort was relatively small and PAP was not measured by right heart catheterization but estimated from pulsed Doppler recording. Laks et al.[18] have found pulmonary hypertension in 42/100 patients (Table I), 6 of whom had a normal arterial partial oxygen pressure (≥ 80 mmHg) but the wedge pressure was not measured and pulmonary hypertension could have been of the post-capillary type in some of their markedly overweight patients (mean body mass index 38 kg/m^2). More recently, Bady et al.[20] have observed pulmonary hypertension in 12/44 patients without chronic obstructive pulmonary disease; the pulmonary hypertension group differed by a lower arterial partial oxygen pressure (but hypoxemia was very mild) and by the presence of marked obesity (body mass index 37.4 ± 6.0 kg/m^2).

Thus, permanent pulmonary hypertension may be present in some OSAS patients without significant daytime hypoxemia, but the majority of OSAS patients never develop pulmonary hypertension. The risk of pulmonary hypertension is indeed increased in those OSAS patients who exhibit an associated chronic obstructive pulmonary disease or a severe obesity or a combination of both. Interestingly, there is no relationship between the severity of OSAS, expressed by the apnea-hypopnea index and the presence of pulmonary hypertension[12,16,18,22]. Almost all studies agree on the fact that pulmonary hypertension is generally of mild degree in OSAS patients (PAP most often in the range 20-35 mmHg)[12,18,20,22], which is very similar to chronic obstructive pulmonary disease. However, pulmonary hypertension worsens during exercise and in our series[12] PAP increased from 26.0 ± 5.8 (rest) to 46.7 ± 12.0 mmHg (steady state exercise) in the small subgroup with pulmonary hypertension; this marked increase was partly explained by an abnormally high wedge pressure during exercise[12].

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