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Pulmonary haemodynamics in patients with OSAS or an overlap syndrome

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ABSTRACT: ***Pulmonary haemodynamics in patients with OSAS or an overlap syndrome. I. Hawryłkiewicz, P. Śliwiński, D. Górecka, R. Pływaczewski, J. Zieliński.***

Background. **Alveolar hypoxia is the most important mechanism leading to pulmonary arterial vasoconstriction, remodelling and pulmonary hypertension. Patients with Obstructive Sleep Apnoea Syndrome (OSAS) experience multiple short periods of alveolar hypoxia during apnoeic episodes. However, the question as to whether these hypoxic episodes are responsible for the development of permanent pulmonary hypertension is still debatable. We aimed to investigate the relationship between the episodes of nocturnal desaturation and pulmonary haemodynamics in two distinct group patients: with pure OSAS or an overlap syndrome.**

Methods**: We studied 67 patients with severe OSAS (means: age 45±8 years, AHI 62±22, FEV_1 3.6±0.8 L = 97±16% of predicted PaO_2 72±10 mmHg, $PaCO_2$ 40±4 mmHg) and 17 patients with an overlap syndrome (OS), means: age 51±5 years, AHI 64±19, FEV_1 1.5±0.7 = 43±16% of predicted PaO_2 57±9 mmHg). All subjects underwent pulmonary artery catheterisation with pressure and flow recordings and an overnight full sleep study.**

Results**. On average patients with OSAS had nocturnal desaturation (mean overnight SaO_2 = 87±5%) and normal PPA (15.8±4.6 mmHg). Only 11 out of 67 subjects (16%) presented with pulmonary hypertension. Patients with OS had nocturnal desaturation (mean overnight SaO_2 = 80.2±8.5%) and mild pulmonary hypertension (PPA 24.2±7.4 mmHg). Only three out of 17 patients had normal pulmonary arterial pressure.**

Conclusions. **In patients with severe OSAS, pulmonary hypertension is rare (16%) and is related best to the severity of the disease and to obesity. In OS patients diurnal pulmonary hypertension is frequent but does not correlate with the severity of nocturnal desaturation.**
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Keywords: Nocturnal hypoxaemia, pulmonary hypertension, obstructive sleep apnoea syndrome, overlap syndrome.

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Introduction

Although first reports on Obstructive Sleep Apnoea Syndrome (OSAS) included pulmonary arterial pressure recordings and demonstrated an increase in pulmonary arterial pressure during apnoeic episodes [1, 2], the question - are multiple apnoeic episodes responsible for development of permanent pulmonary hypertension in patients with OSAS? - is a matter of constant debate.

Results of majority of studies have suggested that pulmonary hypertension develops in OSAS patients only when signs of COPD are present or they suffer from extreme obesity [3-7]. However, other authors found pulmonary hypertension also in patients with pure OSAS or those patients who are not extremely obese [8-10].

Recently, McGuire and Bradford [11] demonstrated the development of pulmonary hypertension in rats exposed to short bursts of hypoxia and hypercapnia imitating apnoeic episodes. Fagan [12] studied the effect of intermittent hypoxia in mice and also concluded that mice develop pulmonary hypertension in response to the repetitive hypoxia-reoxygenation.

Clinical investigations on OSAS usually encompass patients with varying severities of the underlying disease and those frequently suffering from other confounding diseases. The aim of this study was to perform prospective investigations on pulmonary haemodynamics in a consecutive series of patients admitted to our Sleep Laboratory who were diagnosed to have either: 1) severe form of OSAS (AHI>40), and were free from symptoms and signs of COPD; or 2) severe form of OSAS (AHI>40) and moderate or severe COPD (an overlap syndrome - OS).

Material and methods

Patients with Obstructive Sleep Apnoea Syndrome (OSAS)

Sixty-seven patients; 64 males and 3 females, aged 45 ± 8 years were investigated. The diagnosis of COPD was excluded by negative history, physical examination, chest-X-ray and spirometry showing FEV_1/FVC ratio higher than 85% of the initial prediction [13]. Diagnosis of OSAS was established during full polysomnography [14]. Athropometric, lung function data of the studied group are shown on table 1 and apnoea/hypopnoea index (AHI) on table 3.

Table 1. - Anthropometric and pulmonary function data in 67 OSAS patients

Variable	Mean ± SD
Age (years)	45.3 ± 8.2
BMI (kg/m^2)	35.4 ± 6.8
FVC (L) (% of predicted)	4.6 ± 0.9 (98 ± 15)
FEV_1 (L) (% of predicted)	3.6 ± 0.8 (97 ± 16)
FEV_1 % FVC	78 ± 5
PaO_2 (mmHg)	72 ± 10
$PaCO_2$ (mmHg)	40 ± 4
TLC (L) (% of predicted)	6.9 ± 0.8 (101 ± 11)
R tot (kPa.s/L)	0.26 ± 0.13

Patients with Overlap Syndrome (OS)

Seventeen male patients, aged 51 ± 8 years with confirmed OSAS and clinically significant (stage II or III) COPD [13] were investigated. All presented with a severe form of OSAS, mean AHI = 64 ± 19. Anthropometric and lung function data of that group is shown on table 2.

Lung function tests

Spirometry was performed using dry spirometer Vitalograph (Vitalograph, Maidenhead, UK) or Lungtest 1000 (MES, Kraków, Poland) according to the ATS guidelines [15], and referred to ECCS normal values [16]. Arterial blood gases were measured using Corning 168 semiautomatic blood gas analyser (Corning, Medfield, US). Total lung capacity and total pulmonary resistance were measured in a body pletysmograph Masterlab (Jaeger, Würzburg, Germany).

Pulmonary haemodynamics

Pulmonary artery catheterisation was performed in the supine position using Swan - Ganz thermodilution catheter F 7 (Edwards Labs, Irvine, US) introduced by the Seldinger method via antecubical or subclavian vein. Intravascular pressures were measured using Siemens Elema 746 or P23XL Viggo-Spectramed (Oxnard, US) pressure transducer and registered on Mingograph 34 (Siemens - Elema, Solna, Sweden) or Recor (Siemens - Elema, Solna Sweden) recorders. The zero reference level was established at 5 cm below the sternal angle. The following pressures were recorded: right atrial mean pressure (PRA), right ventricle systolic (RVSP) and end-diastolic (RVEDP) pressures, mean pulmonary arterial pressure (PPA) and mean pulmonary wedge pressure (PW). All recordings were performed when patient breathed quietly and instantaneous values were averaged over three respiratory cycles. Cardiac output (CO) was measured in triplicate using a cardiac output computer (COM - 1, Edwards Labs, Irvine, US). Pulmonary vascular resistance (PVR) was calculated.

Table 2. - Anthropometric and pulmonary function data in 17 patients with an overlap syndrome (OS)

Variable	Mean ± SD
Age (years)	51.4 ± 8.3
BMI (kg/m^2)	37 ± 4
FVC (L) (% of predicted)	2.7 ± 0.7 (59 ± 16)
FEV_1 (L) (% of predicted)	1.5 ± 0.7 (43 ± 16)
FEV_1 % FVC	54 ± 13
PaO_2 (mmHg)	57 ± 9.5
$PaCO_2$ (mmHg)	47 ± 10

Sleep study

Full polysomnography was performed using Somnostar Alpha polysomnograph (SensorMedics, Yorba Linda, Ca, US). Details of the procedure were described elsewhere [17]. Diagnosis of OSAS was based on ATS recommendations [14]. Sleep stages were classified according to Rechtschaffen and Kales [18]. From pulse oximetry recording following variables were analyzed: SaO_2 mean = mean overnight SaO_2, SaO_2 minim. = the lowest SaO_2 recorded. Time spent in SaO_2 below 90% (T 90) was also calculated.

The study was approved by the Ethics Committee of the Institute of Tuberculosis and Lung Diseases. All subjects gave their informed consent.

Statistical analysis

All data was analysed using Sigma Stat 1992-1995 Statistical Software Version 2,0 Jandel Corporation. Means ± SD were calculated. Relations between studied variables were analysed using Anova (mono and poly), Student's *t* test or Mann - Whitney Rank Sum and linear regression analysis. The level of significance was set at p value < 0.05.

Results

OSAS patients

Patients with OSAS as a group presented with normal spirometry, lung mechanics and blood gas values (table 1). Results of their pulmonary haemodynamics and of overnight pulse oximetry recording are shown on table 3. Right heart and pulmonary arterial pressures in the group as a whole were within normal range. Cardiac output and pulmonary vascular resistance were also normal. All patients presented with nocturnal desaturation, spending half of the night in saturation below 90%.

There were negative correlations between SaO_2 mean and: mean PPA (r=-0.37 p= 0.003) and PVR (r=-0.37 p=0.007). Positive correlations were found between mean PPA and BMI (r=0.45, p.<0.001) and T90 (r=0.37 p=0.008). No correlation between AHI and mean PPA was found.

In the OSAS group there were 11 subjects with pulmonary hypertension (mean PPA >20 mmHg). Comparisons of anthropometric, pulmonary function and polysomnographic data of patients with

Table 3. - Pulmonary haemodynamics data, AHI and nocturnal pulse oximetry in 67 OSAS patients

Variable	Mean ± SD
PRA (mmHg)	4.2 ± 2.7
PRVS/ED (mmHg)	28.1/5 ± 7.1/3.3
PPA mean (mmHg)	15.8 ± 4.6
PW mean (mmHg)	6.8 ± 3.1
CO (L/min)	5.6 ± 2.2
PVR (dynes.sec.cm^{-5})	150 ± 83
AHI	62 ± 22
SaO_2 mean (%)	87.4 ± 5.4
SaO_2 minim. (%)	57.4 ± 15.9
T 90 (%)	48.3 ± 25.4

normal or elevated PAP are shown in table 4. The subjects with pulmonary hypertension were significantly younger, more obese and a had higher number of apnoeic episodes per hour of sleep.

Overlap syndrome patients

Seventeen patients with OS presented with severe obstructive ventilatory defect. They presented also with signs of respiratory failure (table 2). Pulmonary artery catheterization revealed, in the group as a whole, elevated mean PPA and PVR, and normal PW and CO (table 5). In three patients pulmonary arterial pressure was normal, mean 12 ± 3 mmHg. In 14 patients pulmonary hypertension was found (mean PPA = 27 ± 5 mmHg). Statistical analysis did not show any correlation between PPA and other studied variables.

All patients with the overlap syndrome presented with nocturnal desaturations. In this group we did not find correlations between nocturnal desaturation and pulmonary haemodynamic data. Comparison of studied variables in patients with

Table 4. - Anthropometric, pulmonary function data and AHI in 56 OSAS patients with normal PPA (Group A) and in 11 OSAS patients with elevated PPA (Group B)

Variable	Group A	Group B
PPA mean (mmHg)	14.2 ± 2.8	23.9 ± 3.6 ***
Age (years)	46.5 ± 8	39.5 ± 6 **
BMI(kg/m^2)	34 ± 6	42 ± 6 ***
AHI	57 ± 19	88 ± 18 ***
Ht (%)	47 ± 5	52 ± 5 *
FVC %N	100 ± 14	84 ± 12 **
FEV_1 % N	100 ± 15	82 ± 12 ***
FEV_1 % FVC	78 ± 5	78 ± 6 NS
TLC % N	102 ± 11	89 ± 8 **
R tot (kPa.s/L)	0.26 ± 0.13	0.31 ± 0.07 **
PaO_2 (mmHg)	72.4 ± 9	70.2 ± 15 NS
$PaCO_2$ (mmHg)	39.1 ± 3.4	43.2 ± 6.6 NS
SaO_2 mean (%)	88 ± 5	84 ± 7 NS
SaO_2 minim. (%)	58 ± 15	51 ± 21 NS
T 90 (%)	48 ± 26	71 ± 24 *

Legend: * p < 0.05, ** p < 0.01, *** p < 0.001, NS = non significant.

Table 5. - Pulmonary haemodynamics and polysomnographic data in 17 patients with OS

Variable	Mean ± SD
PRA (mmHg)	3.2 ± 3
PRVS/ED (mmHg)	37.6/4.1 ± 10.2/3.1
PPA mean (mmHg)	24.2 ± 7.4
PW mean (mmHg)	9.1 ± 7.3
CO (L/min)	5.6 ± 2.3
PVR (dynes.sec.cm^{-5})	229 ± 97
AHI	64 ± 19
SaO_2 mean (%)	80.2 ± 8.5
SaO_2 minim. (%)	50.7 ± 19.7
T 90 (%)	76.9 ± 25.7

and without pulmonary hypertension (table 6) did not show any statistically significant difference between both groups. There was no difference in the severity of the disease (AHI), BMI, PaO_2 and nocturnal desaturation. It is important to note that the difference in severity of airflow limitation did not reach significance level.

Discussion

The largest non-selected series of patients with OSAS was published by Chaouat *et al.* [5]. Our study seems to be the first one assessing pulmonary haemodynamics in a large group of patients with severe OSAS not complicated by COPD. The main finding was that, in general, even in a severe form of the disease, in the majority of patients there is no permanent Pulmonary Hypertension (PH). The best correlation between pulmonary arterial pressure and other studied variables was found for BMI. We did not find differences in severity of nocturnal desaturation between patients with normal versus elevated pulmonary artery pressure except for the weak difference in the time spent in desaturation. Correlations between mean overnight SaO_2 and pulmonary arterial pressure and vascular resistance, although statistically significant, seem to be of no clinical importance considering normal pulmonary arterial pressure in majority of subjects.

Our results are in keeping with those reported by Weitzenblum group who studied pulmonary

Table 6. - Comparison of patients with overlap syndrome: with normal pulmonary arterial pressure (PPA) and with patients with pulmonary hypertension (PH)

Variable	Normal PPA	PH
Number of patients	3	14
PPA (mmHg)	12 ± 3	27 ± 5 ***
AHI	64 ± 34	64 ± 16 NS
BMI (kg/m^2)	38 ± 2	37 ± 5 NS
PaO_2 (mmHg)	54 ± 14	58 ± 9 NS
FEV_1 % N	57 ± 16	41 ± 16 NS
SaO_2 mean (%)	83 ± 12	79 ± 8 NS

Legend: *** p < 0.001, NS = non significant.

haemodynamics in the largest series of patients with OSAS ever published [5]. Among 220 patients with OSAS, pulmonary hypertension was present in 17%. The majority of patients having pulmonary hypertension presented with signs of COPD. This probably contributed to the development of pulmonary hypertension. In others, PH could be explained by obesity induced hypoventilation and hypoxia.

Similar findings have been reported by Sanner *at al*. [10]. They found PH in 20% of OSAS patients without concomitant lung disease. Patients with PH presented with restrictive impairment of ventilatory reserves. Permanent hypoventilation in severely obese patients with OSAS may be the main cause of development of pulmonary hypertension [19].

In contrast Laks found pulmonary hypertension in 42% of one hundred investigated patients with OSAS [9]. Patients with PH were older, had higher arterial carbon dioxide tension, lower arterial oxygen tension and lower forced expiratory volume in one second. Such constellation of signs suggests that some of those patients may have suffered from the overlap syndrome.

Some authors have suggested that a relationship exists between obesity, hypoventilation and the development of pulmonary hypertension [20]. The differences in the lifestyle, extreme obesity [7] or genetic predisposition to excessive hypoxic pulmonary vasoconstriction [21] may also contribute to development of PH in some patients with OSAS.

The disorders of ventilation and concomitant hypercapnia in OSAS patients were observed in alcohol abusers [22, 23]. Chan suggested that a heavy alcohol intake may be an important mechanism in causing depressed respiratory drive which results in hypercapnic respiratory failure in patients with severe OSAS leading to pulmonary hypertension [24].

How can the discrepancy between clinical observations and the results of recent animal studied showing development of PH after exposure to short repetitive episodes of hypoxia similar to those observed in patients with OSAS [11, 12] be explained? Early studies on animal models demonstrated that short amounts of exposure, lasting only few hours per day, to hypoxia may imitate nocturnal desaturation in COPD patients which has also resulted in the development of permanent PH [25, 26]. However, the rat is a poor animal model of hypoxic pulmonary hypertension in man [27]. In the rat pulmonary arterial wall remodeling is concentrated on hypertrophied medial muscular coat leading to severe pulmonary hypertension. In man the development of subendothelial longitudinal muscle fibres and endothelial proliferation leading to intimal fibroelastosis prevails.

In conclusion, we investigated relations between nocturnal arterial blood desaturation and pulmonary haemodynamics in two distinct groups of patients; patients with pure, severe obstructive sleep apnoea and patients with OSAS complicated by the clinically important COPD (OS). In patients with OSAS pulmonary hypertension was rare and related best to severity of the disease and obesity. In patients with OS, pulmonary hypertension was present in the majority of subjects. Factors contributing to the development of PH were difficult to isolate. However, our findings do not support the hypothesis that isolated nocturnal hypoxia plays an important role in the development of hypertension in patients with OSAS.

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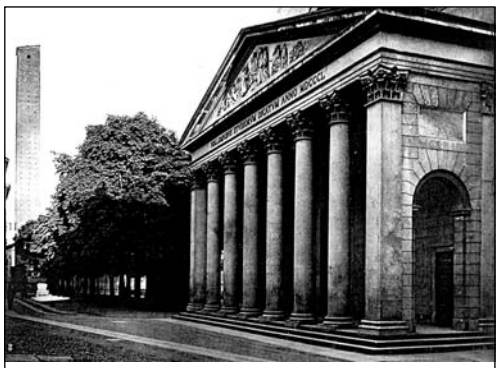

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