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Pulmonary hypertension in obstructive sleep apnoea

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ABSTRACT: To determine the frequency and correlates of pulmonary hypertension in sleep-disordered breathing, pulmonary artery pressure, lung function and arterial blood gases were measured in 100 consecutive patients with obstructive sleep apnoea (OSA) (respiratory disturbance index (RDI) of >20 episodes·h^{-1}). Twenty six of the patients had significant chronic airflow limitation (CAL).

Overall, 42% of patients had awake pulmonary artery pressure >20 mmHg. Patients with pulmonary hypertension were older, had higher arterial carbon dioxide tension (Pa_{CO_2}), lower arterial oxygen tension (Pa_{O_2}) and lower forced expiratory volume in one second (FEV_1) values compared with normotensive patients. Pa_{O_2}, Pa_{CO_2} and FEV_1 were correlated with the levels of pulmonary artery pressure (correlation coefficient (r^2) 0.50, 0.46 and 0.49, respectively). These three factors combined could explain 33% of the variability in pulmonary artery pressure. Six patients had pulmonary hypertension despite a Pa_{O_2} in excess of 10.7 kPa (80 mmHg).

We conclude that pulmonary hypertension is common in patients with moderate and severe sleep apnoea, especially those with coexisting chronic airflow limitation. The presence of daytime hypoxaemia is not a prerequisite in the development of pulmonary hypertension in these patients.

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Transient pulmonary hypertension in response to acute episodes of hypoxaemia in sleep has been well documented [1]. However, there is only a weak correlation between daytime pulmonary hypertension and the severity of obstructive sleep apnoea (OSA), defined by either apnoea/hypopnoea index (AHI), respiratory disturbance index (RDI) or level of desaturation [2]. In addition, it has been suggested that pulmonary hypertension and clinical signs of right ventricular failure develop in patients with OSA only in the presence of daytime hypoxaemia secondary to either clinically significant chronic obstructive pulmonary disease or obesity [3, 4]. In contrast, our clinical experience has suggested that some patients with OSA but without daytime hypoxaemia may have pulmonary hypertension.

The largest studies investigating pulmonary hypertension in OSA have examined sleep clinic cohorts that included a substantial number of patients with milder forms of obstructive sleep apnoea [3, 5–8]. Moreover, patients with obstructive sleep apnoea and significant chronic obstructive pulmonary disease were excluded from these studies, although these two entities frequently coexist. In most of the above studies, the prevalence of pulmonary hypertension was estimated at 10–20% of the cohort studied. In one small study, 55% of patients with moderate and severe sleep apnoea had pulmonary hypertension [9], but respiratory function was not reported.

There is increasing recognition that sleep-breathing disorders contribute to cardiovascular morbidity and mortality [10–12], and it is well-established that pulmonary hypertension is associated with increased mortality in patients with chronic airflow limitation [13, 14].

Recently, FLETCHER *et al.* [15] reported increased mortality in patients with chronic airflow limitation and a daytime arterial carbon dioxide tension (Pa_{O_2}) of more than 8.0 kPa (60 mmHg) who had oxyhaemoglobin desaturation during rapid eye movement (REM) sleep. Notably, the daytime Pa_{O_2} overall was lower in the group of nonsurvivors. These patients also had higher mean pulmonary artery pressures compared with a matched group without nocturnal desaturations. As the presence of pulmonary hypertension in patients with OSA may have similar prognostic significance, its occurrence and correlates are of interest.

We measured pulmonary artery pressure and respiratory function in a large group of patients with confirmed severe sleep apnoea, in order to estimate the frequency and correlates of pulmonary hypertension in such patients. In particular, we were interested in identifying whether patients with severe sleep apnoea but normal awake respiratory function may have elevated daytime pulmonary artery pressure.

Methods

Patients

Consecutive patients referred to the Sleep Disorders Centre at Royal Prince Alfred Hospital between November 1989 and March 1992 and found to have RDI of

>20 episodes·h-1, were considered for pulmonary artery catheterization. Patients with isolated left ventricular failure, renal and liver failure were excluded. A small number of patients were not investigated due to either logistic problems or technical difficulties in performing the catheterization procedure. One hundred patients underwent pulmonary artery catheterization.

The study was approved by the University of Sydney Faculty of Medicine Ethics Committee and informed consent was provided by patients.

Sleep studies

All patients underwent a full overnight polysomnographic sleep study in the Sleep Disorders Centre, Royal Prince Alfred Hospital, using a standard protocol [16]. Sleep stages were classified by standard criteria [17]. Apnoeas were scored as cessation of airflow for at least 10 s (with Sa_{O_2} undefined), or less than 10 s with Sa_{O_2} decrease of >4%. Hypopnoeas were scored as at least 10 s reduction from baseline of >50% in airflow or thoracoabdominal wall movements (with Sa_{O_2} undefined), or less than 10 s with a reduction in Sa_{O_2} of >4%. These changes in flow were accompanied by a continuous recording activity of diaphragmatic electromyographic activity (EMG) and thoracoabdominal wall movements.

Respiratory function

The tests were performed in the Respiratory Function Laboratory, Royal Prince Alfred Hospital. Lung volumes were measured using the closed circuit helium dilution technique (Morgan, Chatham, Kent, UK). Carbon monoxide diffusing capacity was determined by the single breath technique (Medgraphic, St. Paul, MN, USA). Arterial blood gases and acid/base status were measured by automatically calibrated 178 pH/ blood gas analyser (Ciba Corning Medfield, Ma, USA).

Pulmonary artery catheterization

Catheterization was performed with patients in a semi-recumbent position, at rest, breathing room air. A single lumen, 4F pulmonary microcatheter (Pulmoflex, Vygon, Germany) was introduced under the control of distally obtained pressure curves [18] continuously recorded on a Hewlett-Packard pressure monitor (H-P 78353B, USA) and a Mingograph 400/700 System (Siemens, Stockholm, Sweden) recorder.

Following the placement of the catheter, patients rested for 15 min, and were asked to breathe normally and avoid conversation. Prior to the recording of the pulmonary artery pressure, the calibration of the recorder was performed using a mercury manometer. The pressure was then recorded

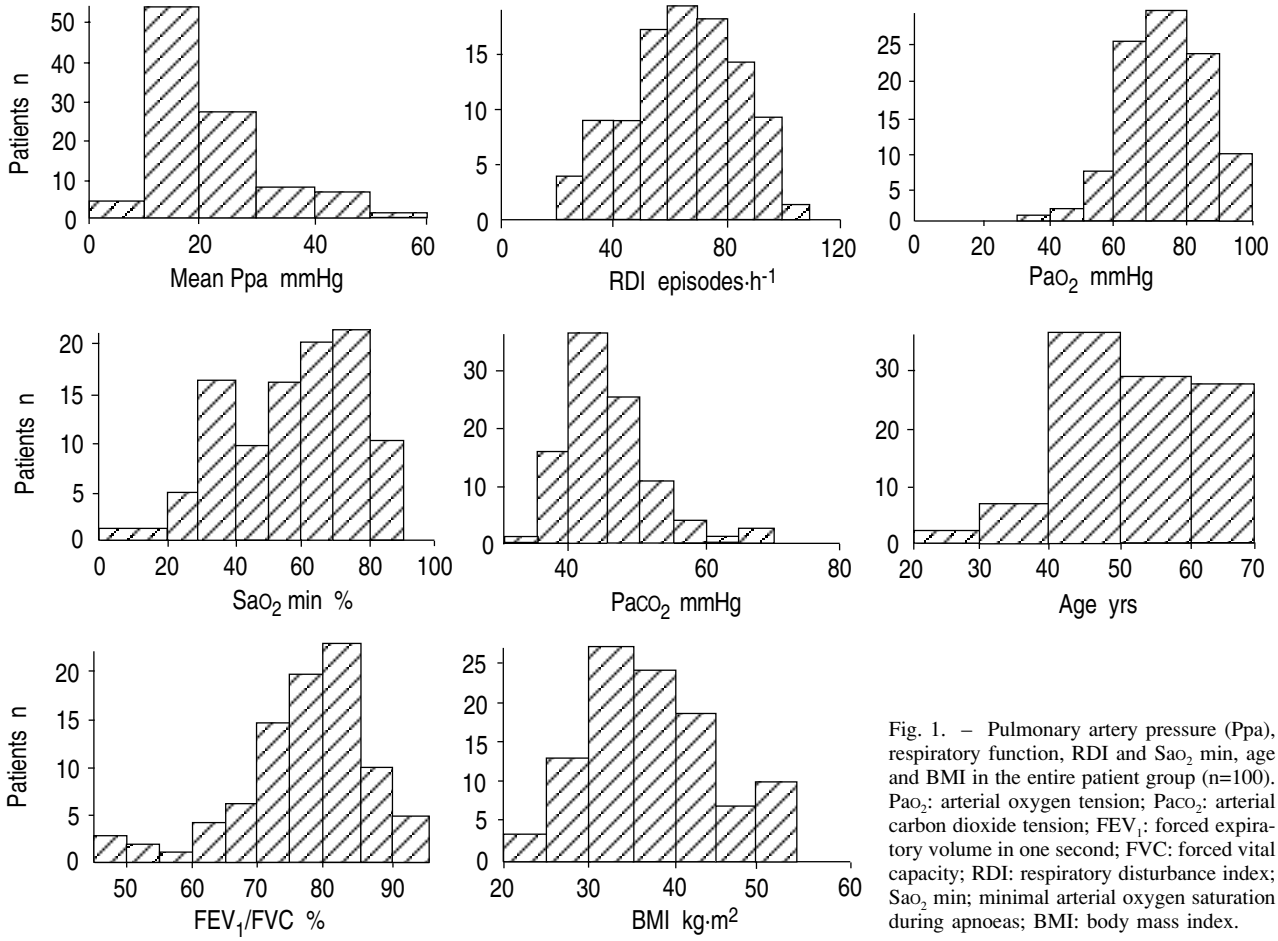

Fig. 1. – Pulmonary artery pressure (Ppa), respiratory function, RDI and Sa_{O_2} min, age and BMI in the entire patient group (n=100). Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RDI: respiratory disturbance index; Sa_{O_2} min; minimal arterial oxygen saturation during apnoeas; BMI: body mass index.

with the transducer placed 5 cm below the sternal angle (manubriosternal joint). At least five respiratory cycles were included in order to obtain mean values for systolic and diastolic pulmonary artery pressure.

Mean pulmonary arterial pressure (Ppa) was calculated from the following equation: mean Ppa = (mean systolic pressure + 2 × mean diastolic pressure) ÷ 3. Mean pulmonary artery pressure of ≥20 mmHg was defined as pulmonary hypertension [14]. After the recordings were completed the catheter was withdrawn. Pressures in the right ventricle and right atrium were recorded, in order to confirm the position of the catheter and exclude a transvalvular gradient between the right ventricle and pulmonary artery.

Statistics

Data are mean (range) unless otherwise specified. Between-group comparisons were performed by unpaired t-test. Univariate regression and Pearsons correlation coefficients were calculated with pulmonary artery pressure as the dependent variable. Significant univariate predictors were then entered into a multiple linear regression model to identify independent predictors of pulmonary artery pressure.

Results

The data for age, body mass index (BMI), lung function and arterial blood gases for the entire patient group are presented in table 1, and the distribution of these factors is shown in figure 1.

Forty two of the patients had pulmonary hypertension. Six patients with normal daytime Pa_{O_2} (≥10.7 kPa (80mmHg)) and pulmonary hypertension were identified; data for this group are shown separately in table 1.

Table 1. – Age, BMI, lung function and arterial blood gas data for the entire patient group (Total, n=100) and subgroup (n=6) with Ppa >20 mmHg and Pa_{O_2} ≥10.7 kPa (≥80 mmHg)

	Total (n=100)	Subgroup (n=6)
Age yrs	52 (29–73)	52 (41–73)
Ppa mmHg	21 (8–52)	32 (20–52)
Pa_{O_2} kPa	9.9 (5.2–13.1)	11.3 (10.7–13.1)
mmHg	74 (39–98)	85 (80–98)
Pa_{CO_2} kPa	6.0 (4.5–8.7)	5.6 (4.9–6.3)
mmHg	45 (34–65)	42 (37–47)
FEV_1 *l*	2.5 (0.58–5.06)	2.7 (10.90–4.70)
FEV_1/FVC %	76 (48–95)	75 (52–85)
RDI episodes·h^{-1}	64 (21–105)	53 (32–82)
Sa_{O_2} min %	57 (0–87)	65 (45–78)
BMI kg·m^{-2}	37 (24–54)	33 (24–43)

Data are presented as mean, and range in parenthesis. Ppa: pulmonary artery pressure; Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RDI: respiratory disturbance index; Sa_{O_2} min: minimal arterial oxygen saturation during apnoea; BMI: body mass index.

Table 2. – Data for the patients divided according to pulmonary artery pressure status

	Hypertensive n=42	Normotensive n=58	p-value
Age yrs	54 (40–73)	50 (29–70)	0.1
Ppa mmHg	29 (20–52)	15 (8–19)	
Pa_{O_2} kPa	8.8 (5.2–13.1)	10.5 (7.3–12.9)	
mmHg	66 (39–98)	79 (55–97)	<0.001
Pa_{CO_2} kPa	6.4 (4.8–8.7)	5.7 (4.5–6.9)	
mmHg	48 (36–65)	43 (34–52)	<0.001
FEV_1 *l*	2.1 (0.60–4.7)	2.9 (0.6–5.1)	<0.001
FEV_1/FVC %	73 (48–91)	79 (58–94)	0.03
RDI episodes·h^{-1}	63 (24–105)	64 (21–98)	0.8
Sa_{O_2} min %	51 (0–85)	62 (21–87)	0.01
BMI kg·m^{-2}	38 (24–54)	36 (24–50)	0.2

Data are presented as mean, and range in parenthesis. For abbreviations see legend to table 1.

Correlates of pulmonary artery pressure

Compared with patients with normal awake pulmonary artery pressure, patients with pulmonary hypertension had lower Pa_{O_2}, higher Pa_{CO_2}, lower FEV_1 and Sa_{O_2} min, but similar mean values for age, RDI and BMI (table 2). Univariate regression demonstrated that only decreasing Pa_{O_2}, increasing Pa_{CO_2} and decreasing FEV_1 were correlated with pulmonary artery pressure (correlation co-efficient of 0.50, 0.46 and 0.49, respectively). These three variables were then entered into a stepwise multiple linear regression analysis. Pa_{O_2} and FEV_1 were independent predictors of pulmonary artery pressure (partial r^2 0.064 and 0.071; p-value 0.01 and <0.001, respectively). Partial r^2 for Pa_{CO_2} was 0.035 (p=0.06). These variables explained 33% of the variability in pulmonary artery pressure.

Discussion

This study demonstrates that pulmonary hypertension is a common finding in patients with severe obstructive sleep apnoea. Forty two percent of the 100 patients studied had mean pulmonary artery pressure of 20 mmHg or more, during wakefulness. The pulmonary vascular consequences of sleep apnoea were worse in the presence of abnormal lung function; 73% of patients with FEV_1/FVC ratio of <70% had pulmonary hypertension. The results confirmed previous work [19], suggesting that FEV_1, awake Pa_{O_2} and Pa_{CO_2} are key predictors of pulmonary hypertension in sleep apnoea. However, 6 of the 40 patients with pulmonary hypertension had a resting arterial Pa_{O_2} ≥10.7 kPa (≥80 mmHg), suggesting that daytime hypoxaemia is not an obligatory finding in patients with both sleep apnoea and pulmonary hypertension.

The frequency of pulmonary hypertension in our patient cohort was higher than previously reported but this could be explained by different patient selection. Most previous studies have included patients with mild sleep apnoea (RDI <20 episodes·h^{-1}), who are less likely to have

cardiovascular complications [3, 5–8]. A recent study assessing pulmonary artery pressure by Doppler echocardiography showed that 11 of 27 (40%) patients with sleep apnoea had pulmonary hypertension [20]. Patients with chronic airflow limitation were excluded from this study. In contrast, the present study documents a high prevalence of elevated resting pulmonary artery pressures in a large number of patients with more severe OSA. A much higher prevalence of pulmonary hypertension has been shown in the small populations of patients with OSA and chronic airflow limitation [21]. Our results confirm that the degree of the pulmonary artery pressure elevation is much higher in the presence of abnormal lung function than in OSA alone. More than 70% of patients with a FEV_1/FVC ratio of less than 70% had a pulmonary artery pressure level in 20–40 mmHg range.

A number of studies have emphasized that pulmonary hypertension or right heart failure in sleep apnoea is unlikely to occur in the absence of daytime hypoxaemia [3, 4]. Some of these studies employing direct pulmonary artery pressure recordings have observed that the prevalence of pulmonary hypertension in a sleep apnoea clinic cohort was 10–20%, and also reported that daytime hypoxaemia was a necessary prerequisite for the development of pulmonary hypertension in patients with sleep apnoea [3, 7]. In contrast, we found a group of patients with normal or near normal awake Pa_{O_2} levels with awake pulmonary hypertension. Thus, daytime hypoxaemia was not a prerequisite for the presence of sustained pulmonary hypertension. In this group of patients, nocturnal exposure to hypoxia and/or hypercapnia may be crucial to the development of pulmonary hypertension. Other factors, such as the sensitivity of pulmonary pressor response to hypoxia, may also be involved.

Although transient increases in pulmonary artery pressure during apnoeas are well-recognized, the role of sleep apnoea in producing sustained awake pulmonary hypertension has been more controversial. One previous study has suggested that the severity of sleep-disordered breathing (using apnoea/hypopnoea index) was independently related to pulmonary artery pressure [22], although we were unable to replicate this finding. We found no significant correlations between the levels of daytime pulmonary artery pressure and the severity of sleep apnoea. However, the indices of the severity of sleep apnoea in current use (apnoea/hypopnoea index or RDI and minimal oxyhaemoglobin saturation) may not adequately describe the hypoxic "challenge" in sleep apnoea. More accurate indices, for example an index of "total nocturnal exposure to hypoxia and hypercapnia", are needed.

Pulmonary hypertension and right ventricular failure are associated with increased morbidity and mortality in chronic airflow limitation and other chronic lung diseases. Increased morbidity may be applicable to patients with OSA and pulmonary hypertension. Patients with moderate and severe sleep apnoea and chronic airflow limitation have a high prevalence of pulmonary hypertension, but elevated pulmonary artery pressure may occur in the absence of any lung disease or awake hypoxaemia. It is important to extend this work and re-examine patients with various degrees of severity of sleep apnoea, and particularly with coexisting chronic airflow limitation.

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