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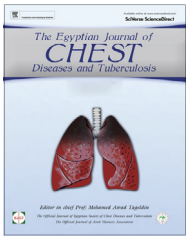

ORIGINAL ARTICLE

Pulmonary hypertension in obstructive sleep apnea hypopnea syndrome

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KEYWORDS

OSA;
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Abstract *Background:* There has been uncertainty until recently whether OSA, is sufficient to cause persistent daytime pulmonary hypertension and right ventricular dysfunction.

Objectives: The aims of this study, were to investigate whether OSA by itself without any other cardiac or lung disease can lead to pulmonary hypertension, and to assess the effect of CPAP therapy on pulmonary artery pressure.

Subjects and methods: The study was performed on 54 OSA patients. All patients were subjected to thorough history taking including Epworth sleepiness scale and Berlin questionnaire, physical examinations, calculation of BMI, plain chest X-ray pulmonary function tests, polysomnography and echocardiography. Ten patients out of 24 patients of OSA with PH have been treated with CPAP for six months.

Results: Pulmonary hypertension (PH) was present in (44.4%) of OSA patients. There were significantly higher PASP and mPAP in severe OSA patients versus non severe OSA patients. There were significant higher BMI, neck circumference, AHI and ODI in OSA patients with PH compared to OSA patients without PH. Awake SaO_2 and minimum SaO_2 were significantly lower in OSA patients with PH compared to OSA patients without PH. There were significant reduction in both mPAP and PASP after 6 months of CPAP treatment ($p = 0.007$, 0.005 respectively).

Abbreviations: ODI, oxygen desaturation index; PH, pulmonary hypertension; AHI, apnea hypopnea index; mPAP, mean pulmonary artery pressure; PASP, pulmonary artery systolic pressure; BMI, body mass index

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Conclusion: OSA is associated with pulmonary hypertension, improvement of pulmonary hypertension through controlling OSA by CPAP therapy signifies that OSA plays a crucial role in the pathogenesis of pulmonary hypertension.

Recommendations: CPAP therapy should be advised to all OSA patients with pulmonary hypertension.

Introduction

Obstructive sleep apnea (OSA) is a disorder that is characterized by obstructive apneas and hypopneas due to repetitive collapse of the upper airway during sleep [1].

OSA is associated with repetitive nocturnal arterial O_2 desaturation and intrathoracic negative pressure swings and an acute increase in pulmonary artery pressure. Experimentally induced intermittent hypoxemia in rodents, have been proved to develop pulmonary vascular remodeling and sustained PH and right ventricular hypertrophy. Until recently, however, it was unclear whether episodic nocturnal hypoxemia associated with OSA was sufficient to cause similar changes in humans [2].

Due to the lack of population-based studies, the true prevalence of PH is not known [3]. Many of the studies that discussed the consequences of untreated OSA are looking for associations between the prevalence of a cardiovascular consequence at a given time with the severity/presence of OSA [4].

This controversy appears to have been resolved by several recent studies that have shown pulmonary hypertension in 20–40% of patients with OSA in the absence of other known cardiopulmonary disorders and reductions in pulmonary artery pressure in patients with OSA after nocturnal continuous positive airway pressure (CPAP) treatment [2,5].

Aim of the work

The aims of this study, were to investigate whether OSA by itself without any other cardiac or lung disease can lead to pulmonary hypertension, and to assess the effect of CPAP therapy on pulmonary artery pressure.

Subjects and methods

This study was carried out at the Sleep-Disordered Breathing Unit, Chest Medicine Department, Mansoura University Hospitals in the period between June 2009 and September 2011. The study was performed on 54 OSA patients (29 males and 25 females with age ranged from 30 to 67 years), with >5 and without any heart or lung diseases.

Inclusion criteria

Middle-aged adults with OSA and no other concomitant heart and lung diseases that may affect pulmonary hemodynamics enrolled in the study fulfilled the following inclusion criteria:

1. Polysomnographic diagnosis of OSA with an apnea–hypopnea index (AHI) $>$ 5 with symptoms suggestive of OSA (e.g. excessive day time sleepiness, snoring, nocturnal chocking and witnessed apnea).
2. normoxemia and normocapnia based on ABGs.
3. Absence of chronic lung disease, cor pulmonale, myocardial, pericardial, valvular heart disease or arrhythmias based on clinical and laboratory tests (chest X-ray, electrocardiogram, echocardiography).

Exclusion criteria

Other causes of pulmonary hypertension: COPD patients, chronic thromboembolic disease, connective tissue diseases, interstitial lung diseases, mitral valve diseases or congestive heart failure.

Patients subgroups

The selected patients were classified according to AHI into two groups:

(I) Severe OSA patient with AHI $>$ 30 [6] (38 cases, 22 males and 16 females with mean age 46.34 $\pm$ 6.56)

(II) Non severe OSA patient with AHI $\leqslant$ 30 (16 cases, 7 males and 9 females with mean age 46.13 $\pm$ 6.98).And also were classified according to pulmonary artery pressure measurement into two groups:

(a) OSA patients with pulmonary hypertension (i.e. mPAP $>$ 25 mmHg) [7].

(b) OSA patients without pulmonary hypertension (i.e. mPAP $\leqslant$ 25 mmHg).

All patients were subjected to

1. *Thorough history taking with stress on:* Age, chest symptoms, special habits especially smoking and alcohol intake, cardiac symptoms, evaluation of excessive day time sleepiness using the Epworth sleepiness scale [8] and sleep disordered breathing symptoms such as snoring, nocturnal choking, witnessed apnea at night, and Berlin questionnaire [9].
2. *Physical examinations with stress on:* Neck circumference. Body mass index (BMI). Chest and heart examination.
3. *Calculation of Body mass index (BMI):* The used method for estimation of the body mass index was the weight–height index according to the following equation (BMI = weight (kg)/height^2 (m^2).
4. Plain chest X-ray.
5. *Laboratory tests:* Awake arterial blood gases prior to polysomnogram session, complete blood picture, Liver function tests, Serum creatinine, and random blood sugar.

6. *Pulmonary function tests:* Forced vital capacity (FVC% of predicted), forced expiratory volume in the first second (FEV1% of predicted), and FEV1/FVC% ratio were measured by the standard spirometric technique (Spiro-Jaeger, Germany), the highest value from at least three spirometric maneuvers was selected .
7. *Polysomnography (PSG):* Full night polysomnography involves the recording of electroencephalography (EEG) electro-oculography (EOG), submental and anterior tibial electromyography (EMG), electrocardiography (ECG), respiratory effort (abdominal and thoracic effort), nasal and oral airflow sensor and oxygen saturation (pulse oxymetry). Polysomnography used in this study is a full night polysomnography (Jaeger Sleep Screen).
8. *Echocardiography:* To exclude left sided heart diseases (e.g. mitral valve diseases or congestive heart failure) and for the assessment of pulmonary artery systolic pressure and mean pulmonary artery pressure (PASP–mPAP):
   (a) *PASP measurement:* PASP can be reliably determined from peak TR jet velocity, using the simplified Bernoulli equation and combining this value with an estimate of the RA pressure: PASP = 4(*V*)2 + RA pressure where *V* is the peak velocity (in meters per second) of the tricuspid valve regurgitant jet [10,11].
   (b) *mPAP:* mPAP can be measured by acceleration time (AT) of the pulmonary velocity flow measured by a pulsed Doppler of the pulmonary artery in systole, whereby mean PA pressure = 79 – (0.45 × AT) [11, 12]. The same group also found that in patients with ATs < 120 ms, the formula for mean PA pressure is 90 _ (0.62 _ AT) and performed better [13].
9. *CPAP therapy:* All OSA patients with pulmonary hypertension were advised to use the CPAP therapy. Only 14 patients agreed to use the CPAP therapy, and follow up echocardiography was done to them after 6 months and only 10 patients have completed the study. CPAP pressure was adjusted according to the following equation: Auto-CPAP setting: reference pressure (Pref) = 0.193 × BMI + 0.077 × neck circumference + 0.02 × apnea + hypopnea index – 0.611 and Pref −4 to Pref + 3 cm H_2O pressure limits [14].

Some modification according to each patient's comfort and limitation of side effects was done to the pressure adjustment. CPAP therapy at least 6 h/day was documented by patients' bed partner in a sleep diary. The follow up sessions were done at 7, 30, and 60 days after the initiation of the CPAP therapy with a phone call by the patient in between sessions and written information about any trouble shouting problems during CPAP use.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) version 10. Qualitative data were presented as number and percent. Comparison between groups was done by the Chi-square test. Quantitative data were tested for normality by the Kolmogrov–Smirnov test. Normally distributed data were presented as mean ± SD. Student's *t*-test was used to compare between two groups. Non parametric variables were presented as Median (min – max) and the Mann–Whitney test (*U* test) was used to compare between two groups. $P < 0.05$ was considered to be statistically significant.

Results

The study included 29 male and 25 female OSA patients; mean age was 46.28 ± 6.62. The mean of BMI was 30.28 ± 3.72, the median AHI was 57.55 (9.2 – 132.6) and the median of mPAP was 25 (10 – 42). Severe OSA with AHI > 30 was present in (70.3%) and included 38 cases, 22 males and 16 females with mean age 46.34 ± 6.56. Non severe OSA with AHI < 30 was present in (29.7%) and included 16 cases, 7 males and 9 females with mean age 46.13 ± 6.98. In this study the selected patients' spirometric pulmonary function (FEV1, FVC, FEV1/FVC) of all the studied OSA patients were nearly within the

Table 1 Comparison between severe OSA patients VS non severe OSA patients according to age, sex, anthropometric measurements, Epworth scale and Berlin questionnaire, PFT and awake ABGs.

	Non-severe OSA (AHI < 30) (*n* = 16)	Severe (AHI ⩾ 30) (*n* = 38)	*P* value
Age	46.13 ± 6.98	46.34 ± 6.56	0.914
Sex			
Male	7 (43.8%)	22 (57.9%)	0.341
Female	9 (56.3%)	16 (42.1%)	
BMI	26.81 ± 2.07	31.74 ± 3.28	< 0.001
Neck_cm	38.81 ± 2.20	43.47 ± 1.96	< 0.001
Epworth_Scale	8.25 ± 1.53	13.34 ± 2.21	< 0.001
Berlin questionnaire	2.00 ± 0.00	2.82 ± .39	< 0.001
*AHI	15.75 (9.20–30.0)	70.25 (35.20–132.60)	< 0.001
FEV1	79.22 ± 10.31	79.84 ± 7.63	0.810
FVC	87.86 ± 12.20	86.44 ± 7.71	0.610
FEV1/FVC	90.57 ± 4.44	90.29 ± 5.32	0.857
PaO_2	86.46 ± 3.86	80.51 ± 6.59	< 0.001
$PaCO_2$	37.33 ± 2.84	40.45 ± 6.75	0.082
SaO_2	96.63 ± 2.18	92.77 ± 3.33	< 0.001

* AHI = Apnea–hypopnea index, Median (min – max) and Mann–Whitney *U* test was used for data with non-parametric distribution, $P < 0.05$ significant.

Table 2 Distribution of pulmonary hypertension among the studied OSA patients.

	No	%
OSA with pulmonary hypertension (*mPAP > 25)	24	44.4
OSA without pulmonary hypertension (*mPAP < 25)	30	55.6

* mPAP = Mean pulmonary artery pressure.

normal range (mean 79.69 ± 8.4, 86.86 ± 9.17, 90.38 ± 5.04 respectively).

There were no significant differences in spirometric pulmonary function tests (FEV1, FVC, FEV1/FVC) between severe OSA patients compared to non severe OSA patients, and there were no significant differences in spirometric pulmonary function testes as regards FEV1, FVC, and FEV1/FVC in pulmonary hypertensive patients versus non pulmonary hypertensive patients. There were significantly higher BMI, neck circumference, Epworth scale, Berlin questionnaire and AHI in severe OSA patients Vs non severe OSA patients (p = <.001). There were significantly lower awake SaO_2 and PaO_2 in severe versus non severe OSA patients (p = <.001) (Table 1).

Pulmonary hypertension (PH) i.e. mPAP > 25 mmHg was present in 44.4% of OSA patients. (Table 2).

There were significantly higher PASP and mPAP in severe OSA patients versus non severe OSA patients (Table 3).

There were significantly more nocturnal oxygen desaturation (significant lower basal SaO_2, minimum SaO_2 and higher desaturation index p = <.001) in severe OSA patients compared to non severe OSA patients (Table 4).

There were significantly higher BMI, neck circumference and AHI in OSA patients with PH compared to OSA patients without PH. Awake SaO_2 was significantly lower in OSA patients with PH compared to OSA patients without PH (Table 5).

There was significantly higher ODI in OSA patients with PH versus OSA patients without PH (Table 6).

There were significant positive correlations between AHI and (BMI, ODI, PASP and mPAP) (p < 0.001 for each). Also there were positive correlations between mPAP and (BMI, ODI). However, there were significant negative correlations between AHI and (PaO_2, Basal SaO_2 and Minimum SaO_2) (P < 0.001 for each), there were significant negative correlations between mPAP and (PaO_2 and Minimum SaO_2) (P = 0.005, P < 0.001 respectively) (Table 7).

There were significant reductions in both mPAP and PASP after 6 months of CPAP treatment (p = 0.007 0, 0.005 respectively) with percentage of reduction after 6 months of CPAP therapy in both mPAP, PASP (26.91% and 23.11% respectively) (Table 8).

Discussion

There has been uncertainty until recently as to whether OSA, is sufficient to cause persistent daytime PHT and right ventricular dysfunction. Some studies have concluded that PHT and right heart disease, if occur in OSA, are always attributable to other coexisting conditions such as COPD or morbid obesity that resulted in chronic hypoxemia secondary to pulmonary ventilation–perfusion inequality, alveolar hypoventilation, or both. However, these studies were conducted among patients with a mixture of OSA and chronic lung disease, making it difficult to determine the relative contributions of sleep apnea-related intermittent hypoxia to PHT and right heart disease [15].

This study was carried out on 54 patients of OSA and no other concomitant heart or lung diseases that may affect pulmonary hemodynamics.

Our study revealed that Epworth sleepiness scale (ESS) and Berlin questionnaire were significantly higher in severe OSA versus non severe OSA (p = .001 for each, Table 1), which signify that both questionnaire may be a predictor of severity of OSA Sharma et al. [6] had reported Berlin questionnaire as a predictor to high risk category of OSA with high sensitivity (86%) and specificity (95%). Also, Steven [6] has found a significant positive correlation between ESS and AHI and concluded that if ESS was more than 10, sleep related breathing disorders (SRBDs) should be suspected. They also advised to assess ESS in SRBDs to rule out or prove OSA and hence manage it early in the course of the disease. In our study there were significantly higher BMI and neck circumference in severe OSA patients compared to non severe OSA patients and there

Table 3 Comparison between severe OSA patients VS non severe OSA patients according to mPAP and PASP.

	Non-severe OSA (AHI < 30) (n = 16)	Severe (AHI ⩾ 30) (n = 38)	P value
PASP	25 (20–49)	40.5 (20–50)	<0.001
mPAP	12 (10–35)	30 (10–42)	<0.001

*PASP = Pulmonary artery systolic pressure, mPAP = Mean pulmonary artery pressure. Median (min – max) and Mann–Whitney U test was used for data with non-parametric distribution, P < 0.05 significant.

Table 4 Comparison between severe OSA patients VS non severe OSA patients according to parameters of nocturnal O_2 desaturation.

	Non-severe OSA (AHI < 30) (n = 16)	Severe (AHI ⩾ 30) (n = 38)	P value
Basal SaO_2	93.76 ± 1.52	90.50 ± 2.94	<0.001
*ODI	8.47 ± 7.11	64.53 ± 26.17	<0.001
Minimum SaO_2	85.23 ± 4.96	72.74 ± 7.88	<0.001

* ODI = Oxygen desaturation index.

Table 5 Comparison between OSA patients with and without pulmonary hypertension according to age, sex, anthropometric measurements, Epworth scale and Berlin questionnaire, PFT and awake ABGs.

	Non-PH (n = 30)	PH (n = 24)	P value
Age	46.43 ± 7.65	46.08 ± 5.21	0.849
Sex			
Male	16 (53.3%)	13 (54.2%)	0.951
Female	14 (46.7%)	11 (45.8%)	
BMI	28.77 ± 2.71	32.17 ± 4.00	< 0.001
Neck_cm	40.93 ± 2.83	43.54 ± 2.43	0.001
*mPAP	13.5 (10–25)	35 (28–42)	< 0.001
*AHI	33.7 (9.2–107.3)	83.65 (27.9–132.6)	< 0.001
FEV1	80.29 ± 9.73	78.87 ± 6.53	0.543
FVC	87.49 ± 11.35	86.08 ± 5.50	0.579
FEV1/FVC	89.68 ± 5.37	91.25 ± 4.55	0.260
PaO_2	83.64 ± 5.53	80.55 ± 7.26	0.081
$PaCO_2$	38.21 ± 2.87	41.17 ± 8.24	0.072
SaO_2	94.93 ± 3.05	92.63 ± 3.67	0.015

* mPAP = Mean pulmonary artery pressure, AHI = Apnea–hypopnea index. Median (min – max) and Mann–Whitney U test was used for data with non-parametric distribution, $P < 0.05$ significant.

Table 6 Comparison between OSA with and without pulmonary hypertension according to parameters of nocturnal O_2 desaturation and AHI.

	Non-PH (n = 30)	PH (n = 24)	P value
Basal SaO_2	91.81 ± 3.29	91.04 ± 2.56	0.353
*ODI	35.50 ± 31.07	65.83 ± 30.06	0.001
Minimum SaO_2	78.91 ± 8.24	73.35 ± 9.42	0.025

* ODI = Oxygen desaturation index.

Table 7 Correlation between AHI and (BMI, PaO_2, Basal CO_2, ODI, Min O_2, PASP and mPAP).

	AHI		mPAP	
	R	P	r	P
BMI	0.685	< 0.001	0.433	0.001
PaO_2	−0.657	< 0.001	−0.379	0.005
$PaCO_2$	0.264	0.053	0.259	0.058
Basal SaO_2	−0.727	< 0.001		
*ODI	0.947	< 0.001	0.484	< 0.001
Minimum SaO_2	−0.748	< 0.001	−0.343	0.011
**PASP	0.600	< 0.001		
***mPAP	0.546	< 0.001		

* ODI = Oxygen desaturation index.
** PASP = Pulmonary artery systolic pressure.
*** mPAP = Mean pulmonary artery pressure.

were significantly higher BMI and neck circumference in patients with PH patients versus non PH patients. Fishman et al. [16] concluded that neck circumference greater than 40 cm predicts OSA with sensitivity of 61% and specificity of 93%, regardless of gender. Also, Young and his colleagues reported that neck circumference was the most powerful predictor of OSA among all anthropometric variables studied, suggesting that the central obesity rather than generalized distribution of body fat is important for the development of OSA [17]. Obesity leads to increased amount of fat in the neck which plays the greatest role in OSA [18]. It is presumed that increased fat deposition in the neck region or adjacent to the upper airway on the pharyngeal wall can impinge on the pharyngeal lumen and predispose its collapse during sleep. There is a link between obesity and PH which may be attributed to the relative deficiency of release of adiponectin, which has an important role in pulmonary vascular inflammation suppression by inhibiting vasoconstricting substances [19].

In this study there was a significant positive correlation between AHI and BMI and also there was a significant positive correlation between mPAP and BMI (Table 7). This was in agreement with Chaouat et al. [20] who have reported a significant positive correlation between AHI and BMI, and Arias et al. [21] who reported high BMI in OSA patients with PH compared to OSA without PH.

The prevalence of pulmonary hypertension (PH) i.e. (mPAP > 25 mmHg) [7] in the studied OSA patients was 44.4% (24 out of 54 patients, Table 2), and the median of mPAP of total group of patients was 25 (10 – 42, Table 1). OSA alone may cause mild to moderate pH, but coexisting day time hypoxia is typically required for sustained severe pH and cor pulmonale [22]. Minai et al. [23] reported that mild, moderate and even severe PH (i.e. mPAP ⩾ 40 mmHg) can occur in patients with OSA. Moreover, Fletcher et al. [24] had reported pulmonary hypertension in severe OSA in the absence of hypoxemic lung disease.

The incidence of PH in OSA patients has been estimated to be 20–40%. [2,5]. Our result was close to Laks et al. [25] who reported PH in 42% of OSA patients and Saijkov et al. [26] who reported PH in 41% of OSA patients. OSA is characterized by episodes of apnea and hypopnea during sleep, these episodes are caused by partial or complete upper airway obstruction. Episodes of oxygen desaturation cause a transient increase in pulmonary artery and pulmonary wedge pressures and permanent PH Marrone and Bonsignore [27] Diurnal PH was elucidated by the sustained hypoxia which results in remodeling of the pulmonary vasculature, with intimal smooth muscle thickening, endothelial perforation, and fibroelastosis [28].

Daytime hypoxemia has been reported to develop in patients with OSA [29,30]. In our study OSA patients were without resting hypoxemia but there were significantly lower awake PaO_2 and SaO_2, in severe OSA patients versus non severe OSA patients ($P < 0.001$, for each, Table 1). Meanwhile there was no significant difference in awake $PaCO_2$ in severe OSA versus non severe OSA patients (Table 1). This was in agreement with Fanfulla et al. [31] who found significantly lower PaO_2 and SaO_2 in severe OSA versus non severe OSA and no significant difference in $PaCO_2$ in severe OSA versus non severe OSA. In this study, there was no significant correlation between AHI and $PaCO_2$ ($P = 0.053$, Table 7). This was in agreement to Ayappa et al. [32] who demonstrated no significant correlation between $PaCO_2$ and OSA severity.

In our study there was significantly lower awake SaO_2 in the pulmonary hypertensive group versus the non pulmonary hypertensive group ($P = 0.015$, Table 5) this was in agreement

Table 8 mPAP and PASP before and after 6 months of CPAP treatment.

	N	Pre	Post	*P* value	Percentage of improvement
mPAP	10	35 (28–40)	26 (20–35)	0.007	26.91 (0–37.14)
PASP	10	45 (40–50)	35 (30–42)	0.005	23.11 (11.11–33.33)

*PASP = Pulmonary artery systolic pressure, mPAP = Mean pulmonary artery pressure, Median (min – max) and Mann–Whitney *U* test was used for data with non-parametric distribution, $P < 0.05$ significant.

with most of the other studies [23,21,33] who reported a significant reduction in daytime SaO_2 in the pulmonary hypertensive group versus teh non pulmonary hypertensive group. Also in this study both awake PaO_2 and $PaCO_2$ were not significantly different between the pulmonary hypertensive group and the non pulmonary hypertensive group (Table 5). These were in agreement with Alchanatis et al. [33] and Leech [34].

OSA patients without resting hypoxemia had frequent episodes of nocturnal desaturation (saw-tooth pattern) that are more in REM and abolished by CPAP [35]. In this study there were significantly more nocturnal oxygen desaturation (significant lower basal SaO_2, minimum SaO_2 and higher desaturation index $p = <.001$) in severe OSA patients compared to non severe OSA patients (Table 4). This was as in agreement with Fanfulla et al. [31]. Also in this study there were significant negative correlations between AHI and (PaO_2, basal SaO_2 and minimum SaO_2) and significant positive correlation between AHI and ODI, Table 7). This was in accordance to Chaouat et al. [20] who have reported that AHI was significantly negatively correlated with (PaO_2, basal SaO_2 and minimum SaO_2).

Nocturnal hypoxemia may be crucial to the development of pulmonary hypertension [25]. The mechanisms by which alveolar hypoxia leads to PH are probably both, pulmonary vasoconstriction and remodeling of pulmonary vascular bed [36]. It has been hypothesized that isolated nocturnal hypoxemia (without significant daytime hypoxemia) could lead to pulmonary hypertension [26]. In this study patients were without daytime hypoxemia, in the same time the rate of PH encountered in our OSA patients was high (44.4%), denoting that repeated nocturnal hypoxemia alone is the leading factor in the pathogenesis of PH.

Chronic intermittent hypoxia activates homeostatic mechanisms in the respiratory system that induce changes in gene expression by mediation of several transcription factors, such as hypoxia-inducible factors (HIF), both HIF-1α and HIF-2α, are involved in physiological responses of pulmonary arterioles to chronic intermittent hypoxia, collectively producing hypertrophy of the pulmonary arteriolar smooth muscle [31,37].

In this study there were significantly higher ODI and significantly lower minimum SaO_2 in the pulmonary hypertensive group than the non pulmonary hypertensive group (Table 6). This was in agreement with [25,21]. Also in this study there was a significant positive correlation between mPAP and ODI, and there was a significant negative correlation between mPAP and PaO_2 and minimum SaO_2. These were in agreement with Arias et al. [21].

In this study mPAP and PASP were significantly higher in severe OSA patients versus non severe OSA patients (Table 3). Also, in our study AHI was significantly positive correlated with mPAP and PASP (Table 7). Leech [34] had concluded that the severity of OSA is correlated to pulmonary artery pressure.

These could be explained according to Han et al. [2] who stated that severe OSA is associated with repetitive nocturnal arterial O_2 desaturation and intrathoracic negative pressure swings with an acute increase in pulmonary artery pressure and also intermittent hypoxemia for several hours per day developed pulmonary vascular remodeling and sustained pulmonary hypertension.

In our study, 10 out of 24 patients of OSA with PH who have been treated with CPAP for 6 months, without medical treatment of PH, have remarkably lowered mPAP (from 35 (28–40) to 26 (20–35), $P = 0.007$), and also lowered PASP (from 45 (40–50) to 35 (30–42), with percentage of reduction in both mPAP and PASP 26.91, 23.11 respectively (Table 8). This was in agreement with Alchanatis et al. [33] study which also demonstrated a marked reduction in mPAP after effective treatment of CPAP therapy for 6 months. Also, in accordance to Arias et al. [21] who have reported a reduction in PASP in OSA patients with PH after effective treatment with CPAP therapy for 6 months. More recently, Oliveira et al. [38] have reported the beneficial effect of CPAP treatment in reducing the risk of developing pulmonary hypertension and right ventricular failure in OSA patients. These findings signify that there is a causal relationship between OSA and PH.

Conclusion

OSA is associated with pulmonary hypertension which increased with severity. Nocturnal O_2 desaturation and increased BMI are important risk factors in the pathogenesis of pulmonary hypertension in OSA patients. Improvement of pulmonary hypertension through controlling OSA by CPAP therapy signifies that OSA plays a crucial role in the pathogenesis of pulmonary hypertension.

Recommendations

CPAP therapy should be advised to all OSA patients with pulmonary hypertension. All patients with pulmonary hypertension should be screened for the presence of associated SRBDs.

References

[1] B.G. Philips, V.K. Somers, Sleep disordered breathing and risk factors for cardiovascular disease, Curr. Opin. Pulm. Med. 8 (2002) 516–520.
[2] M.K. Han, V.V. McLaughlin, G.J. Criner, et al, Pulmonary diseases and the heart, Circulation 116 (2007) 2992–3005.
[3] R.E. Girgis, S.C. Mathai, Pulmonary hypertension associated with chronic respiratory disease, Clin. Chest Med. 28 (1) (2007) 219.

[4] A.B. Platt, S.T. Kuna, S.H. Field, et al, Adherence to sleep apnea therapy and use of lipid-lowering drugs: a study of the healthy user effect, Chest 137 (2010) 102–108.
[5] N.S. Marshall, K.K. Wong, P.Y. Liu, et al, Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study, Sleep 31 (2008) 1079–1085.
[6] S. Redline, V.K. Kapur, M.H. Sanders, S.F. Quan, D.J. Gotlieb, D.M. Rapoport, et al, Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment, Am. J. Respir. Crit. Care Med. 161 (2000) 369–374.
[7] G. Simonneau, I. Robbins, M. Beghetti, R.N. Channick, M. Delcroix, C.P. Denton, C.G. Elliott, S. Gaine, M.T. Gladwin, Z.C. Jing, M.J. Krowka, D. Langleben, N. Nakanishi, R. Souza, Updated clinical classification of pulmonary hypertension, J. Am. Coll. Cardiol. 54 (2009) S43–S54.
[8] D. Stevens, Sleep Medicine Secrets, Hanley & Belfus Inc., 2004.
[9] S.K. Sharma, C. Vasudev, S. Sinha, A. Banga, R.M. Pandey, K.K. Handa, Validation of the modified Berlin questionnaire to identify patients. At risk for the obstructive sleep apnoea syndrome, Indian J. Med. Res. 124 (2006) 281–290.
[10] M.R. Fisher, P.R. Forfia, E. Chamera, et al, Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension, Am. J. Respir. Crit. Care Med. (2009) (Epub ahead of print).
[11] L.G. Rudski, W.W. Lai, J. Afilalo, et al, Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography, J. Am. Soc. Echocardiogr. 23 (2010) 685–713.
[12] G. Mahan, A. Dabestani, J. Gardin, A. Allfie, C. Burn, W. Henry, Estimation of pulmonary artery pressure by pulsed Doppler echocardiography, Circulation 68 (1983) 367.
[13] A. Dabestani, G. Mahan, J.M. Gardin, K. Takenaka, C. Burn, A. Allfie, et al, Evaluation of pulmonary artery pressure and resistance by pulsed Doppler echocardiography, Am. J. Cardiol. 59 (1987) 662–668.
[14] O. Marrone, A. Salvaggio, S. Romano, G. Insalaco, Automatic titration and calculation by predictive equations for the determination of therapeutic continuous positive airway pressure for obstructive sleep apnea, Chest 133 (2008) 670–676.
[15] N. Dursunoglu, D. Dursunoglu, M. Kilic, Impact of obstructive sleep apnea on right ventricular global function: sleep apnea and myocardial performance index, Respiration 72 (278–284) (2005) 3.
[16] A.P. Fishman, Pulmonary circulation, in: A.P. Fishman, A. Fisher (Eds.), Handbook of Physiology, Sec. 3: The Respiratory System: Circulation and Nonrespiratory Functions, American Physiological Society, Bethesda, MD, 2007, pp. 93–166.
[17] T. Young, P. Peppard, M. Palta, Population based study of sleep disordered breathing as risk factor for hypertension, Arch. Intern. Med. 157 (1997) 1746–1752.
[18] R.J. Schwab, A.N. Goldberg, A.I. Pack, Sleep apnea syndromes, in: A.P. Fishman (Ed.), Pulmonary Diseases and Disorders, third edition., McGraw-Hill, 1998, p. 1617, Chapter 102.
[19] R. Summer, K. Walsh, B.D. Medoff, Obesity and pulmonary arterial hypertension: is adiponectin the molecular link between these conditions?, Pul Circ. 1 (4) (2011) 440–447.
[20] A. Chaouat, E. Weitzenblum, J. Krieger, et al, Pulmonary hemodynamics in the obstructive sleep apnea syndrome: results in 220 consecutive patients, Chest 109 (1996) 380–386.
[21] M.A. Arias, F. García-Río, A. Alonso-Fernández, et al, Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study, Eur. Heart J. 27 (2006) 1106–1113.
[22] B.G. Judde, S. Liu, M.J. Sateia, Cardiovascular abnormalities in sleep-disordered breathing, Semin. Respir. Crit. Care Med. 24 (2003) 315–322.
[23] O.A. Minai, B. Ricaurte, R. Kaw, J. Hammel, M. Mansour, K. McCarthy, J.A. Golish, J.K. Stoller, Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome, Am. J. Cardiol. 104 (2009) 1300–1306.
[24] E.C. Fletcher, J.M. Schaaf, J. Miller, et al, Long term cardiopulmonary sequelae in patients with sleep apnea and chronic lung disease, Am. Rev. Respir. Dis. 135 (1997) 525–533.
[25] L. Laks, B. Lehrhaft, R.R. Grunstein, C.E. Sullivan, Pulmonary hypertension in obstructive sleep apnoea, Eur. Respir. J. 8 (1995) 537–541.
[26] D. Sajkov, R.J. Cowie, A.T. Thornton, et al, Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome, Am. J. Respir. Crit. Care Med. 149 (1994) 416–422.
[27] O. Marrone, M.R. Bonsignore, Pulmonary hemodynamics in obstructive sleep apnea, Sleep Med. Rev. 6 (2002) 175–193.
[28] R.L. Doyle, Surgical treatment/interventions for pulmonary arterial hypertension: ACCP evidence based clinical practice guidelines, Chest 126 (2004) 63–71.
[29] E. Bady, A. Achkar, S. Pascal, et al, Pulmonary arterial hypertension in patients with sleep apnea syndrome, Thorax 55 (2000) 934–949.
[30] A. Chaouat, E. Weitzemblum, J. Krieger, T. Ifoundza, M. Oswald, R. Kessler, Association of chronic obstructive pulmonary disease and sleep apnea syndrome, Am. J. Respir. Crit. Care Med. 151 (1995) 82–86.
[31] F. Fanfulla, M. Grassi, A.E. Taurino, N.D. Lupo, R.T. Tch, The relationship of daytime hypoxemia and nocturnal hypoxia in obstructive sleep apnea syndrome, Sleep 31 (2) (2008) 249–255.
[32] I. Ayappa, K.I. Berger, R.G. Norman, B.W. Oppenheimer, D.M. Rapoport, Hypercapnia and ventilatory periodicity in obstructive sleep apnea syndrome, Am. J. Respir. Crit. Care Med. (2002) 1112–1115.
[33] M. Alchanatis, G. Tourkohoriti, S. Kakouros, E. Kosmas, S. Podaras, J.B. Jordanoglou, Daytime pulmonary hypertension in patients with obstructive sleep apnea, Respiration 68 (2001) 566–572.
[34] J.A. Leech. Right ventricular dysfunction relates to nocturnal hypoxemia in patients with sleep apnea syndrome, 2002.
[35] J.S. Richard, M.G. Andrew, J.P. Allam, Sleep apnea syndromes, in: A.P. Fishman, J.A. Elias, J.A. Fishman, et al. (Eds.), fourth ed., Fishman's Pulmonary Diseases and Disorders, vol. 102, McGraw Hill, 1998, pp. 1617–1637.
[36] M.R. Adrian, The stages of the sleep, in: A.P. Fishman, J.A. Elias, J.A. Fishman, et al. (Eds.), fourth ed., Fishman Pulmonary Diseases and Disorders, vol. 4, McGraw Hill, 2008, pp. 1686–1697.
[37] G.L. Semenza, O_2-regulated gene expression: transcriptional control of cardiorespiratory physiology by HIF-1, J. Appl. Physiol. 96 (2004) 1173–1177.
[38] W. Oliveira, D. Poyares, F. Cintra, M.L.C. Vieira, C.H. Fischer, V. Moises, S. Tufik, A. Carvalho, O. Campos, Impact of continuous positive airway pressure treatment on right ventricle performance in patients with obstructive sleep apnoea, assessed by three-dimensional echocardiography, Sleep Med. 13 (2012) 510–516.