Egyptian Journal of Chest Diseases and Tuberculosis (2016) 65, 233–237

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Egyptian Journal of Chest Diseases and Tuberculosis

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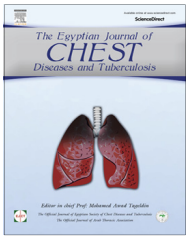

ORIGINAL ARTICLE

Study of sleep related respiratory disorders in patients with idiopathic pulmonary arterial hypertension

H. Shaarawy [a,*], **A. Elhawary** [b]

[a] *Chest Disease Department, Faculty of Medicine, Alex. University, Egypt*
[b] *Chest Disease Department, Faculty of Medicine, Zagazig University, Egypt*

Received 27 June 2015; accepted 14 December 2015
Available online 4 January 2016

KEYWORDS

Pulmonary arterial hypertension;
Obstructive sleep apnea;
Nocturnal desaturation

Abstract The effects of sleep-disordered breathing (SDB) and nocturnal hypoxemia on pulmonary hemodynamics have long interested physicians who manage patients with pulmonary arterial hypertension. The aim of the present study is to study the prevalence and identify the types of sleep related breathing disorders in patients with IPAH in the state of Kuwait.

Patients and methods: 36 patients(32 females and 4 males) were included, the mean age was 35.2 ± 17.3 years, all patients were non-smokers and non-obese. All patients were subjected to routine investigations, Echocardiography, CT pulmonary angiography and full night polysomnography. All cases pulmonary hypertension related to cardiac disease or collagenic vascular disease or Thromboembolic disease were excluded.

Results: The mean AHI was 13.8 ± 8.3/h of sleep with OSA proved in 5 patients (13.9%) and CSR/CSA proved in 2 patients (5.56%). Nocturnal desaturation was more pronounced in the studied patient as 27 patients (75%) showed nocturnal desaturation. There was a significant correlation between SDB measures and baseline oxygen saturation, lowest oxygen saturation during walking and mean PAP.

Conclusion: SDB is significant in patients with IPAH and can affect the disease progression and the quality of life of those patients. All patients should undergo sleep study to identify patients who are in need of nocturnal oxygen therapy or in need for CPAP therapy in case of OSA.

Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure ⩾25 mm Hg at rest, measured during right heart catheterization. There is still insufficient evidence to add an exercise criterion to this definition [1]. The term pulmonary arterial hypertension (PAH) describes a subpopulation of

* Corresponding author.

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

http://dx.doi.org/10.1016/j.ejcdt.2015.12.011

patients with PH characterized hemodynamically by the presence of pre-capillary PH including an end-expiratory pulmonary artery wedge pressure (PAWP) ⩽15 mm Hg and a pulmonary vascular resistance >3 Wood units. Right heart catheterization remains essential for a diagnosis of PH or PAH [2,3].

Primary pulmonary hypertension (PPH) is a rare disease characterized by elevated pulmonary artery pressure with no apparent cause. PPH is also termed precapillary pulmonary hypertension or, as is currently preferred, idiopathic pulmonary arterial hypertension (IPAH) [4].

The effects of sleep-disordered breathing (SDB) and nocturnal hypoxemia on pulmonary hemodynamics have long interested physicians who manage patients with pulmonary arterial hypertension (PAH). SDB, a term that encompasses the spectrum of Cheyne-Stokes respiration/central sleep apnea (CSR/CSA), obstructive sleep apnea (OSA) and nocturnal desaturation, is a common condition in the United States and western nations [5].

Sleep causes a profound effect in individuals with severe pulmonary disease, by its influence on the respiratory drive, airway stability, and ventilatory mechanics [6,7]. Reported sleep disturbances in patients with pulmonary disease include unsuspected obstructive sleep apnea and a high prevalence of insomnia, excessive daytime sleepiness, and nightmares compared to the general population, in addition, patients with COPD, kyphoscoliosis, and neuromuscular disorders have been shown to frequently desaturate, especially during rapid eye movement (REM) sleep [8–10]. Nocturnal hypoxemia can lead to polycythemia, respiratory failure, and pulmonary hypertension. Hypoxemia causes pulmonary vasoconstriction and elevated pulmonary artery pressures. In patients with PPH, untreated and unsuspected nocturnal hypoxemia can have deleterious effects and may worsen the pulmonary hypertension.

Aim of the work

The aim of the present study was to study the prevalence and identify the types of sleep related breathing disorders in patients with IPAH in the state of Kuwait.

Patients and methods

This study was carried out at the Pulmonary Rehabilitation Center – Pulmonary Hypertension Unit which is the only specialized unit to mange IPAH patients in the Ministry of Health, state of Kuwait.

The study was a retrospective study including all patients with IPAH seen in the unit in the last 6 years from Jan 2009 to Dec 2014 and still under follow up in the outpatient clinic. Study was approved by the ethics committee in the MOI, state of Kuwait.

This study was performed on (36) 1PH patients (4) males and (32) females with age ranging from 18 to 65 years.

Inclusion criteria

Adult patients proved to have IPAH without any co-morbidity at the time of diagnosis.

Exclusion criteria

- Patients with BMI >35.
- Patient with COPD or chronic lung disease.
- Patient with Connective tissue diseases.
- Patient with Thromboembolic disease.
- Patients with PH secondary to heart disease or patients with congestive heart failure.
- Patients already diagnosed with SDB or on long term oxygen therapy.

- PEulmonary hypertension was confirmed by right heart catheterization and was defined as a mean pulmonary artery pressure of >25 mm Hg at rest or >30 mm Hg during exercise [4].
- Functional class was estimated according to New York Heart Association (NYHA) classification [11].

To diagnose IPH, secondary causes of pulmonary hypertension were ruled out in all patients by

- Full history taking with stress on: chest symptoms, special habits especially smoking, cardiac symptoms.
- Physical examinations.
- Chest radiographs.
- High-resolution CT scans and CT pulmonary angiography.
- Pulmonary function studies.
- Transthoracic echocardiograms and transesophageal echocardiograms.
- Ventilation–perfusion scans.
- Right and left heart catheterization.
- Screening for connective tissue diseases.

For evaluation of sleep related breathing disorders patients were subjected to

- Thorough history taking about sleep symptoms.
- Physical examinations with stress on: Neck circumference.
- Body mass index (BMI). 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 [12].
- BMI = weight (kg)/height^2 (m^2).
- Epworth sleepiness scale (ESS) [13].
- Arterial blood gases.
- The 6-min walk test [14].
- Oxygen saturation by pulse oximetry (SpO_2) was measured at rest and during ambulation.
- Polysomnography (PSG): Full night polysomnography involving the recording of electroencephalography (EEG) electro-oculography (EOG), submental and anterior tibial electromyography (EMG), electrocardiography (ECG), respiratory effort (abdominal and thoracic effort), nasal airflow sensor and oxygen saturation (pulse oximetry) and position detection camera. Polysomnography used in this study is a full night polysomnography (Alice 4 Respironics), according to polysomnography OSA was diagnosed if the Apnea/Hypopnea index (AHI) is more than 5/h of sleep with more than 50% of all apneas occurring during sleep are of obstructive nature, CSR/CSA was diagnosed if there

are at least 3 cycles of hyperventilation followed by central apnea associated with the absence of thoracic or abdominal movements and attack lasting for more than 10 sec and the patient is diagnosed as having morbid CSA if attacks are more than 10/h of sleep, nocturnal desaturation was diagnosed if the oxygen desaturation index 4% (ODI 4%) was more than 10/h of sleep (it means that the oxygen saturation drops by more than 4% from the baseline) associated with the time of sleep spent with oxygen saturation $<90\%$ (D90) equals to 10% or more from the total sleep time [15].

Statistical analysis

All statistical analyses were conducted using the software package SPSS 20.0 for Windows® (SPSS Inc., Chicago, IL, USA). All data are tabulated and presented as mean ± standard deviation. Spearman's correlation was done to correlate between the polysomnography data and the general and ECHO data of the patients. Significant results were detected at $p < 0.05$.

Results

Table 1 shows that the number of patients included in the study was 36 patients, and the mean age was 35.2 ± 17.3 years, 32 females and 4 males. All patients were non smokers, non obese (the mean BMI was 24.2 ± 6.3, ESS was less than 10 in all patients denoting no significant signs of day time sleepiness (mean was 6.1 ± 2.8). The mean six minute walking distance for the patients was 368.2 ± 105.9 m with base line SaO_2 was 93.6 ± 5.4% during wakefulness and the lowest SaO_2 reached during walking was 82.6 ± 11.1%. As regards the PFTs of the studied patients the mean FEV1% pred. was 78.3 ± 3.64, mean FVC% pred. was 73.6 ± 6.5 while the mean FEV1/FVC was 83.4 ± 2.3 denoting the presence of mild restrictive pattern in the studied patients with no signs of airway obstruction. On the other hand the mean FEF_{25-75}% pred. was 62.3 ± 6.8 denoting small airway disease. As regards the NYHA class there were 2 patients in class 1, 24 patients in class 2 and 10 patients were in class 3. None of the studied patients were in class 4. Lastly the mean PAP of the studied patients was 48.4 ± 12.9 mm Hg and the cardiac index was 3.2 ± 0.5 L/min/m^2.

Table 1 General criteria of the patients.

Character	Mean ± SD
No. of patients	36
Age in years	35.2 ± 17.3
Smoking status	0/36
Female/male ratio	32/4
Body mass index (Kg/m^2)	24.2 ± 6.3
Epworth Sleepiness Scale (ESS)	6.1 ± 2.8
Six minute walking distance in m	368.2 ± 105.9
Base line SaO_2 during wakefulness	93.6 ± 5.4
Lowest SaO_2 during walking	82.6 ± 11.1
PFT	
FEV1% pred.	78.3 ± 3.64
FVC% pred.	73.6 ± 6.5
FEV1/FVC	83.4 ± 2.3
FEF_{25-75}% pred.	62.3 ± 6.8
NYHA class (no. of patients)	
Class 1	2
Class 2	24
Class 3	10
Class 4	0
Mean PA pressure in mm Hg	48.4 ± 12.9
Cardiac index L/min/m^2	3.2 ± 0.5

Table 2 Polysomnography data of the patients.

Character	Mean ± SD
Total sleep time (TST) in min.	358.1 ± 3.5
Sleep efficiency	72.4 ± 3.25
Non REM sleep time as % from TST	75.3 ± 6.8
REM sleep time as % from TST	20.4 ± 2.9
Arousal index/h	23.5 ± 7.9
AHI/h	13.8 ± 8.3
No. of OSA patients	5/36 (13.9%)
No. of CSR/CSA patients	2/36 (5.56%)
Lowest SaO_2 during sleep	77.2 ± 11.3
D90 as % from TST	28.6 ± 9.4
Oxygen desaturation index 4%	23.6 ± 6.5
No. of patients with nocturnal desaturation	27/36 (75%)

REM: Rapid Eye Movement, AHI: Apnea/Hypopnea Index.

Table 2 shows that the TST of the studied patient was 358.1 ± 3.5 minutes with sleep efficiency of 72.4 ± 3.25%. The percentage of non REM sleep from the TST was 75.3 ± 6.8%, while the percentage of REM sleep from the TST was 20.4 ± 2.9%. The mean arousal index during sleep was markedly increased denoting disturbed sleep in these patients (23.5 ± 7.9/h) which can affect the quality of life. As regard measures of SDB the total AHI during sleep was 13.8 ± 8.3/h which is bigger than normal in comparison to the general population with the no. of OSA patients was 5 patients, all were females (13.9%) denoting increased incidence of OSA in this group of patients more than in the general population. The no. of CSR/CSA patient was 2 (5.56%) and these 2 patients were in NYHA class 3. As regards the measures of nocturnal desaturation the lowest oxygen saturation reached during sleep was 77.2 ± 11.3%, mean ODI4% was 23.6 ± 6.5/h of sleep and the mean D90 was 28.6 ± 9.4% from the TST. According to the definition of nocturnal desaturation stated above the no. of nocturnal desaturators in this study was 27 patients (75%) denoting a significant prevalence of this phenomena in these patients with its consequences on the disease and the negative effect on the quality of life in these patients. On using Spearman's correlation coefficient (Table 3), there was a significant correlation between the baseline oxygen saturation during rest and all parameters of nocturnal desaturation including the lowest oxygen saturation reached during sleep ($p = 0.003$), D90 ($p = 0.006$) and the ODI4% ($p = 0.04$), also the baseline oxygen saturation during rest showed a significant correlation with the arousal index during sleep ($p = 0.04$). On the other hand the lowest oxygen saturation reached during walking showed a significant correlation with the Lowest SaO_2 during sleep ($p = 0.005$), D90 ($p = 0.004$) and the arousal index ($p = 0.03$). The mean PAP showed a significant correlation with D90 ($p = 0.005$), the AHI ($p = 0.04$) and the

Table 3 Positive correlations detected between the general criteria and polysomnography criteria of the patients.

General criteria	Polysomnography criteria	*P* value
Base line SaO_2	Lowest SaO_2 during sleep	0.003
	D90	0.006
	ODI4%	0.04
	Arousal index	0.04
Lowest SaO_2 during exercise	Lowest SaO_2 during sleep	0.005
	D90	0.004
	Arousal index	0.03
Mean PAP	D90	0.005
	AHI	0.04
	Arousal index	0.03

D90: time spent with oxygen saturation below 90% as percentage from total sleep time, ODI4%: oxygen desaturation index/h of sleep, PAP: Pulmonary Artery Pressure.

arousal index ($p = 0.03$). It is worth noting that Age, BMI and ESS or any of the parameters of pulmonary function testing did not show any significant correlation with the AHI or any of the parameters of nocturnal desaturation in the studied patients.

Discussion

The aim of the present study was to estimate the prevalence and define the different types of sleep disordered breathing in patients with Idiopathic PAH. The most encountered type of SDB observed was the nocturnal desaturation which was present in 27 patients (75%). Nocturnal desaturation was present irrespective of the presence of any other event like hypopnea or apnea giving the possibility of V/Q mismatch as a reasonable explanation. This abnormality is well known in patients with PAH and its cause is not only due to obliteration of small pulmonary arterioles which increases pulmonary physiologic dead space, but also to narrowed distal airways [16–18]. In this field it is worth noting that the $FEF_{25–75}$ was decreased (62.3 ± 6.8% pred.) denoting the small airways were affected but $FEF_{25–75}$ did not show any correlation to the parameters of SDB in the present study. On the other hand nocturnal desaturation was correlated with baseline oxygen saturation at rest, lowest oxygen saturation reached during walking and mean PAP. As regard the AHI it was elevated in this group of patients (13.8 ± 8.3/h of sleep) with 5 female cases proved to have OSA (13.9% of all cases and 15.6% from female patients alone) which is more than estimated for the general population in which the incidence is in the range of 9% for adult females [5], these patient were not obese and did not complain of day time sleepiness denoting the importance of doing sleep study in such group of patients to uncover the hidden OSA which can add to the poor prognosis of these patients. Changes in ventilation during sleep, such as mild hypoventilation, [19,20] decreased functional residual capacity, [21] blunted responses to hypoxemia and hypercapnia, [22] and increased upper airway resistance, are well established [23]. Such ventilatory changes are mild and well tolerated in healthy individuals but may exhibit more profound gas exchange abnormalities in patients with PAH; the presence of nocturnal desaturation or OSA in these patients will cause pulmonary vasoconstriction which is a direct response to alveolar hypoxia in a physiologic attempt to minimize ventilation perfusion mismatch. The recurrence of hypoxemic episodes in sleep apnea results in repetitive increases in pulmonary artery pressures; however, about 1 in 5 patients develop sustained pulmonary hypertension during the daytime [24]. More severe OSA and hypoxia may lead to right ventricular hypertrophy culminating in daytime pulmonary hypertension and right ventricular failure in the presence of hypercapnia and chronic alveolar hypoventilation [25]. Although the idea of the present study is not new it adds more information and evidence about the presence of SDB in patients with IPAH which is a rare disease and at the same time it is one of the few studies done in the middle east in this field; the results of the present study are in agreement with the result of many researchers, who worked in the same field. Rafanan in 2001 [26] studied 13 patients with IPAH through single night full polysomnography and found that Seventy-seven percent of patients with IPAH have significant nocturnal hypoxemia that is unrelated to apneas and hypopneas. Nocturnal desaturation occurs more frequently in patients with higher P (A–a) O_2 values and lower FEV1 values, resting arterial PaO_2 and SpO_2 values, and walking SpO_2 values. Schulz in 2002 [27] investigated the presence of periodic breathing in 20 patients with IPAH by pulmonary function testing, right heart catheterization and full night polysomnography, they found that Periodic breathing occurs in patients with advanced primary pulmonary hypertension and can be reversed by nocturnal nasal oxygen. The clinical and prognostic significance of periodic breathing in primary pulmonary hypertension needs to be determined by further studies. It is worth noting that in the present study there were 2 patients suffering from CSR/CSA and the 2 patients were belonging to NYHA class 3, so the presence of CSR/CSA in these 2 patients was possibly attributed to have an effect on the cardiac condition. Ulrich in 2008 [28] studied 38 patients with pulmonary hypertension (23 patients with IPAH and 15 patients with chronic Thromboembolic disease) with full night polysomnography and ambulatory cardiorespiratory studies. They concluded that in patients with pulmonary hypertension, CSR/CSA is common, but obstructive sleep apnea also occurs. Sleep-related breathing disorders are not associated with excessive sleepiness but affect the quality of life. They should be evaluated by polysomnography or cardiorespiratory sleep studies because pulse oximetry may fail to detect significant sleep apnea. Prisco in 2011 [29] studied the Correlation of pulmonary hypertension severity with metrics of comorbid sleep-disordered breathing. The study included 28 patients with pulmonary hypertension (32% of idiopathic origin and 68% associated with other diseases). They concluded that SDB comprising obstructive apneas, hypopneas, and nocturnal hypoxemia is prevalent in PH and cannot be accurately predicted by sleep apnea signs and symptoms or diurnal rest and exercise SaO_2. The association of AHI and T90% with mPAP suggests a potential relationship between the pathophysiology of sleep-disordered breathing and PH. Jilwan in 2013 [30] studied 46 patients with pulmonary hypertension (29 patients with IPAH and 17 patients with Thromboembolic disease) with full night polysomnography and trans-cutaneous capnography. They found that nocturnal desaturation was present in 82.6% of patients with pulmonary hypertension with the main mechanism of V/Q mismatch either alone or in association with obstructive events as Apnea or Hypopnea, and the mean PAP not the clinical symptoms was

predictive of nocturnal desaturation. They concluded that the occurrence of nocturnal hypoxemia is high in PH and should be screened for systematically. Further studies are needed to determine the impact of nocturnal hypoxemia on the outcome of patients with PH.

Conclusion

SDB is significant in patients with IPAH and can affect the disease progression and the quality of life of those patients. All patients should undergo sleep study to identify patients who are in need of nocturnal oxygen therapy or in need for CPAP therapy in case of OSA.

Conflict of interest

There is no conflict of interest.

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