

Received: 2013.07.27
Accepted: 2013.08.13
Published: 2013.10.23

The incidence and severity of pulmonary hypertension in obstructive sleep apnea with hypothyroidism

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

AB 1 **Omer Araz**
DE 1 **Elif Yilmazel Ucar**
EF 2 **Aslihan Yalcin**
CDF 1 **Didem Pulur**
C 3 **Hamit Acemoglu**
BG 4 **Hakan Tas**
A 1 **Leyla Saglam**
AE 1 **Metin Akgun**
A 5 **Arzu Mirici**

1 Department of Pulmonary Diseases, Ataturk University School of Medicine, Erzurum, Turkey
2 Department of Pulmonary Diseases, Marmara University, Istanbul, Turkey
3 Department of Medical Education, Ataturk University School of Medicine, Erzurum, Turkey
4 Department of Cardiology, Ataturk University School of Medicine, Erzurum, Turkey
5 Department of Pulmonary Diseases, 18 Mart University School of Medicine, Canakkale, Turkey

Corresponding Author: Omer Araz, e-mail: dromeraraz@gmail.com
Source of support: Self financing

Background: Hypothyroidism and obstructive sleep apnea (OSA) are both common health problems and can be seen together. Each of these 2 diseases can cause pulmonary hypertension (PH). We aimed to determine whether hypothyroidism with OSA has a significant effect on the frequency and severity of PH.





Material/Methods: A total of 236 patients were included in the study. Patients were divided into 3 groups: Group I, Obstructive Sleep Apnea (n=149); Group II, Hypothyroidism (n=56); and Group III, Obstructive Sleep Apnea-Hypothyroidism (n=31). All patients underwent polysomnography and echocardiography and serum levels of thyroid-stimulating hormone (TSH) and free thyroxine 4 (FT₄) were analyzed.

Results: There were 167 male and 69 female participants, and the mean age was 47.8±11.5 (Group I: 81.9% male, 18.1% female; Group II: 44.6% male, 55.4% female; Group III: 64.6% male, 35.4% female). Distribution of mean pulmonary arterial pressure on echocardiography was statistically different among the 3 groups ($\chi^2=14.99$, $p=0.006$). When adjusted according to the apnea-hypopnea index (AHI), age, and body mass index (BMI), a significant relation with PH was determined ($p=0.002$).

Conclusions: The combination of hypothyroidism with OSA is associated with an increased frequency and severity of PH. When PH is found out of line with the severity of OSA, thyroid dysfunction should be investigated.

Key words: **obstructive sleep apnea • hypothyroidism • pulmonary hypertension**

Full-text PDF: <http://www.medscimonit.com/download/index/idArt/889619>

 1771  5  —  22

Background

Hypothyroidism and obstructive sleep apnea (OSA) are both common health problems and often occur together [1,2]. An estimated rate for combination of these diseases through patients referred to a sleep laboratory is 1.6–11% [3,4]. Each of these 2 diseases can cause pulmonary hypertension (PH) [5,6].

Despite the growing body of evidence that links OSA to the development of PH, the existence of a direct relationship remains controversial [6]. Hypoxia and related pulmonary vascular changes are the most important causes in the pathogenesis of PH [7,8]. Moreover, hypothyroidism is one of many causes of pulmonary hypertension [9]. The pathophysiological link between thyroid disease and PH remains unclear, but an autoimmune process has been proposed [10]. Although unproven, a potent vasoconstrictor peptide, endothelin-1, has been shown to be significantly higher in tissue with hypothyroidism [11,12].

In this study, we aimed to determine whether routine scanning for hypothyroidism is useful to explain the frequency and severity of PH with OSA.

Material and Methods

Study population

A total of 325 patients were included in the study between January 2011 and January 2012, but 89 were rejected due to the exclusion criteria. The remaining 236 patients were divided into 3 groups: Group I, OSA (n=149); Group II, Hypothyroidism (n=56); and Group III, OSA-Hypothyroidism (n=31). Groups I and III included patients with OSA who had been directly referred to a sleep laboratory; those in Group II were hypothyroidism patients without OSA who were referred from the endocrinology department. Patients with clinical and subclinical hypothyroidism were included in the study. Exclusion criteria were a history of ongoing regular medication for previous hypothyroidism, hypertension, chronic left heart failure, valvular heart disease, coronary artery disease, pericardial disease, collagen vascular diseases, hematological malignancies, HIV infection, hepatobiliary diseases, chronic pulmonary thromboembolism, metabolic disorders, chronic renal disease, and pulmonary disease.

Measurements

After initial clinical evaluation, a questionnaire was used to obtain information about history of snoring, witnessed apnea, and excessive daytime sleepiness. The Epworth Sleepiness Scale (ESS) was used to evaluate sleepiness [13]. Detailed physical examination was carried out and anthropometric measurements, including neck and waist circumference, height, weight, and

body mass index (BMI), were obtained. Chest x-rays, pulmonary function tests, electrocardiograms, and echocardiograms were also obtained. Laboratory tests, including HIV, collagen vascular diseases tests, blood count, and biochemical parameters, were performed.

Hypertension was defined as an average blood pressure of $\geq 140/90$ mmHg – according to the National Heart Lung and Blood Institute criteria [14] – or the current use of antihypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of ≥ 126 mg/dL. Obesity was defined as a body mass index (BMI) ≥ 25 .

A venous blood sample was obtained, and thyroid-stimulating hormone (TSH) and free thyroxine 4 (FT_4) levels were analyzed according to chemiluminescence method via the ACS-180 hormone analyzer system. The normal range for TSH is 0.49–4.6 mIU/L, and for FT_4 it is 0.6–1.8 ng/dl. Arterial blood samples were drawn from the patients included in the study from the radial artery using specially designed heparinized injectors for arterial blood gas analysis. PaO_2 , $PaCO_2$, pH, and SaO_2 measurements were performed according to the ion-selective electrode method via a blood gas analyzer (Cobas® b 221, Mannheim, Germany).

Sleep study

Full polysomnography (PSG) monitoring was performed using the Compumedics E-series Sleep System (Compumedics Sleep: Melbourne, Australia). Electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), and electrocardiography were performed simultaneously. Surface electrodes were used to record EEG channels, right and left EOGs, and submental EMG. Ventilatory flow, either at the nose or at both the nose and mouth, was measured with airflow. Respiratory movements of the chest and abdomen, as well as the body position, were monitored by inductive plethysmography bands. Arterial oxygen saturation was measured transcutaneously with a finger oximeter. Apnea was defined as continuous cessation of airflow for ≥ 10 s, and hypopnea was defined as at least 50% reduction of airflow for ≥ 10 s, with an oxygen desaturation of $\geq 3\%$ or an EEG arousal from sleep. Apneas were classified as obstructive, central, or mixed according to standard criteria of the American Academy of Sleep Medicine [15].

Echocardiography

All patients underwent conventional 2-D and Doppler echocardiographic investigation in addition to tissue Doppler imaging (TDI) by a VIVID 7 (GE, NORWAY) echocardiography device using a 2.5 MHz transducer. In the left lateral decubitus position, echocardiograms were recorded on standard parasternal and apical images. The images were viewed and recorded at end inspiration and end expiration on normal ventilation.

Table 1. Demographic characteristics of all groups.

| | Group I | Group II | Group III |
|-----|----------|----------|-----------|
| Age | 47±12 | 48±11 | 55±13 |
| BMI | 30.2±5.9 | 29.8±2.5 | 36.2±5.8 |
| NC | 41±4 | 38±2 | 42±3 |
| WC | 105±14 | 91±13 | 117±13 |
| ESS | 9±5 | 7±2 | 12±7 |

Data are presented as mean ±SD. BMI – body mass index; NC – neck circumference; WC – waist circumference, ESS – Epworth sleepiness scale.

Table 2. Laboratory findings of all groups.

| | Group I | Group II | Group III |
|-------------------|----------|-----------|-----------|
| TSH | 1.4±0.85 | 14.9±16 | 11.38±3.5 |
| FT4 | 1.3±0.25 | 0.97±0.39 | 0.99±0.20 |
| PaO ₂ | 78±10 | 84±9 | 69±13 |
| PaCO ₂ | 39±5 | 37±2 | 40±3 |
| SatO ₂ | 95±2 | 96±3 | 93±3 |

Data are presented as mean ±SD. TSH – thyroid-stimulating hormone; FT₄ – free T4; PaO₂ – partial pressure of oxygen; PaCO₂ – partial pressure of carbon dioxide; SatO₂ – oxygen saturation.

For each patient, M-mode, B-mode, color flow mapping, and pulse-wave Doppler records were obtained.

Left ventricle diameter (LV), left atrium diameter (LA), right atrium diameter (RA), and right ventricle diameter (RV) were determined with a parasternal long-axis view. Left ventricular ejection fraction (LVEF) was calculated using a modified Simpson method [16]. Systolic pulmonary arterial pressure (sPAP) was calculated by adding estimated right atrial pressure onto the regurgitation gradient through the tricuspid valve. A pressure of over 36 mmHg was defined as pulmonary hypertension [17].

All patients were informed about the study and provided consent to participate. The study was planned according to the ethics guidelines of the Helsinki Declaration, and the study protocol was approved by the local ethics committee (B.30.2.ATA.0.01.00/52).

Statistical analysis

Statistical analysis was performed using SPSS for windows (Version 19.0; SPSS Inc., Chicago, IL). Data are expressed as mean ±SD and percentage. Pulmonary hypertension distribution between groups was analyzed using the chi-squared test. We used ANCOVA to examine the relationship between groups with pulmonary hypertension, adjusting for confounding factors

(apnea-hypopnea index, age, and BMI). Statistical significance was accepted as a P value less than 0.05.

Results

A total of 236 patients were included in the analysis. Of these, 167 were male and 69 were female, with a mean age of 47.8±11.5 (range 18–76 years). There were 122 (81.9%) males and 27 (18.1%) females in Group I; 25 (44.6%) males and 31 (55.4%) females in Group II; and 20 (64.6%) males and 11 (35.4%) females in Group III. Seventy-five patients were smokers and the mean pack-year value was 14.8±2.2.

Demographic characteristics of the groups are shown in Table 1. In Group III, the age and BMI of the patients were higher than in the other groups. Laboratory findings are shown in Table 2 and polysomnography results are shown in Table 3.

The number of patients with a systolic pulmonary arterial pressure (sPAP) of 37–50 mmHg was 32 (74.4%), 6 (66.6%), and 4 (18.2%) in Groups I, II, and III, respectively; there were 11 (25.6%), 3 (33.4%), and 18 (81.8%) patients with a sPAP over 50 mmHg. The echocardiographic characteristics are shown in Table 4. The highest sPAP value was in group III. Distribution

Table 3. Polysomnography results of all groups.

| | Group I | Group II | Group III |
|------|-----------|-----------|-----------|
| AHI | 36±27 | 3±1 | 52±35 |
| MD | 6±4 | 3±1 | 7±4 |
| 90DT | 118±120 | 14±18 | 168±130 |
| AHT | 83.3±66.4 | 3.7±1.9 | 80.6±39.8 |
| SE | 83.3±12.3 | 82.2±16.4 | 83.4±13.8 |

Data are presented as mean ±SD. AHI – apnea-hypopnea index; MD – mean desaturation; DT90 – desaturation time under 90; AHT – apnea-hypopnea time (minutes); SE – sleep efficiency.

Table 4. Echocardiographic measurements of all groups.

| | Group I | Group II | Group III |
|------------|----------|----------|-----------|
| PAP(mm Hg) | 47.5±7.9 | 48.8±7.3 | 62.3±13.3 |
| RA (mm) | 37±4 | 36±2 | 39±10 |
| RV (mm) | 38±4 | 36±2 | 43±8 |
| LV (mm) | 45±5 | 38±2 | 45±4 |
| LA (mm) | 38±4 | 35±3 | 42±6 |
| LVEF | 65±5 | 64±3 | 62±5 |

Data are presented as mean ±SD. PAP – pulmonary artery pressure; RA – right atrium diameter; RV – right ventricle diameter; LA – left atrium diameter; LV – left ventricle diameter; LVEF – left ventricular ejection fraction.

Table 5. Distribution of pulmonary hypertension among groups.

| | Group I n /% | Group II n /% | Group III n /% |
|------------|--------------|---------------|----------------|
| Normal PAP | 106 (71.2) | 47 (83.9) | 9 (29) |
| PH | 43 (28.8) | 9 (16.1) | 22 (71) |
| Total | 149 | 56 | 31 |

PH – pulmonary hypertension. PH distribution between groups was analyzed with chi-square test ($\chi^2=14.99$, $p=0.006$).

of sPAP on echocardiography was statistically different among the 3 groups ($\chi^2=14.99$, $p=0.006$; Table 5). When adjusted according to apnea-hypopnea index (AHI), age, and BMI, a significant relationship with PH was determined ($p=0.002$).

Discussion

The study aimed to investigate whether routine scanning for hypothyroidism can be useful to explain incompatibility of severity of pulmonary hypertension with OSA. Although routine control of thyroid levels for hypothyroidism is not suggested in sleep laboratories [4], in this particular condition, testing for thyroid hormone levels may be carried out.

The pathological changes observed in PH due to hypoxia and OSA include medial hypertrophy and obstructive proliferation of the tunica intima within the distal pulmonary arteries [18]. As the other cause of PH, hypothyroidism is associated with respiratory disorders such as hypoventilation and hypoxia, especially in severe and late presentations, and these disorders can worsen the concomitant PH. Thyroid dysfunction has been linked to vascular reactivity, a phenomenon that can precede PH [19]. It is well known that these 2 diseases, which have similar clinical symptoms [20], can cause PH. However, there is insufficient data on the contribution of these conditions in combination to form PH.

Pulmonary hypertension may occur at different frequencies in OSA (17–53%) and hypothyroidism (10–24%) [7,19]. In our

study, the incidence of PH was similar to that of previous studies when the patient has only 1 of the diseases (Group I and II). It was significantly higher in patients in Group III, who had both conditions (71%). In addition, the mean sPAP in this group was higher than in the other 2 groups. When each group was classified according to sPAP, the rate of patients with a sPAP over 50 mmHg was significantly higher in group III than in the other groups. Both the prevalence and the severity of PH increased in OSA along with hypothyroidism.

In Group III, patients' age, BMI, and AHI were higher than in the other 2 groups. When adjusted according to AHI, age, and BMI, a significant relation with PH was found between the groups. The combination of the 2 diseases, especially when AHI was taken into consideration, showed the effect of occurrence of PH, without regard to the severity of OSA. We believe that this condition should be considered when evaluating PH in OSA patients.

It has been mentioned in previous studies that in OSA patient screening for thyroid function, testing is not cost effective for all age groups; however, this may be done for women and the patients over 60 years [4]. In a different study, the frequency of hypothyroidism in female patients with OSA was not higher than that seen in the general population, and therefore routine screening for thyroid function was not recommended [21]. In our study, mean age was higher in the OSA-hypothyroidism group than in the others, but this was still under 60 years of age. In terms of sex, the number of women in Group III was

higher than in Group I, but lower than in Group II. In our study, the number of women was lower in the OSA-hypothyroidism group than in previous research [22]. Therefore, in terms of demographic characteristics, there was no feature identified in our study that supported the need for additional testing.

The gold standard technique for the measurement of pulmonary arterial pressure is still right heart catheterization. The limitation of the present study is the inaccuracy of the trans-thoracic echocardiogram in determining pulmonary pressure – although a widely used technique, it has a margin of error. However, the use of catheterization is not practical for sleep laboratory patients.

Conclusions

In conclusion, hypothyroidism with OSA precipitates the frequency and severity of PH separately from the severity of OSA. Consequently, when PH is found to be out of line with severity of OSA, defects in thyroid function should be investigated.

Disclosure

The authors received no financial support for the research and/or authorship of this article.

The authors declare that they have no conflict of interest in the publication of this article.

References:

1. Attal P, Chanson P: Endocrine aspects of obstructive Sleep apnea. *J Clin Endocrinol Metab*, 2010; 95: 483–95
2. Grunstein RR, Sullivan CE: Sleep apnea and hypothyroidism: mechanisms and management. *Am J Med*, 1988; 85: 775–79
3. Popovici I, Khawaja I: Efficacy of thyroid function tests in patients suspected of having obstructive sleep apnea. *Chest*, 1997; 112: 149
4. Winkelman JW, Goldman H, Piscatelli N et al: Are thyroid function tests necessary in patients with suspected sleep apnea? *Sleep*, 1996; 19: 790–93
5. Chin RG, Fisher J: Hypothyroidism and pulmonary hypertension: observation and speculation. *Cardiovasc Rev Rep*, 1986; 9: 789–95
6. Houtchens J, Martin D, Klinger JR: Diagnosis and management of pulmonary arterial hypertension. *Pulm Med*, 2011; 2011: 845–64
7. Tuder RM, Abman SH, Braun T et al: Development and pathology of pulmonary hypertension. *J Am Coll Cardiol*, 2009; 54: 3–9
8. Patel R, Aronow WS, Patel L et al: Treatment of pulmonary hypertension. *Med Sci Monit*, 2012; 18(4): RA31–39
9. Li JH, Safford RE, Aduen JF et al: Pulmonary hypertension and thyroid disease. *Chest*, 2007; 132: 793–97
10. Badesch DB, Wynne KM, Bonvallet S et al: Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenetic link? *Ann Intern Med*, 1993; 119: 44–46
11. McAllister RM, Luther KL, Pfeifer PC: Thyroid status and response to endothelin-1 in rat arterial vessels. *Am J Physiol Endocrinol Metab*, 2000; 279: 252–58
12. Lam HC, Wang JP, Lee JK et al: The lung contents of endothelin are altered by thyroid hormone status in rat. *Regul Pept*, 1993; 49: 33–39
13. Johns MW: Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, 1992; 15: 376–81
14. National Heart, Lung and Blood Institute: The seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7). 2004; 26–27
15. Ruehland WR, Rochford PD, O'Donoghue FJ et al: The new AASM criteria for scoring hypopneas: impact on the apnea hypopnea index. *Sleep*, 2009; 32: 150–57
16. Simmons LA, Weidemann F, Sutherland GR et al: Doppler tissue velocity, strain, and strain rate imaging with transoesophageal echocardiography in the operating room: a feasibility study. *J Am Soc Echocardiogr*, 2002; 15: 768–76
17. Galisè N, Hoepfer MM, Humbert M et al: ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J*, 2009; 30: 2493–537
18. Roux F, D'Ambrosio C, Mohsenin V: Sleep-related breathing disorders and cardiovascular disease. *Am J Med*, 2000; 108: 396–402
19. Curnock AL, Dweik RA, Higgins BH et al: High prevalence of hypothyroidism in patients with primary pulmonary hypertension. *Am J Med Sci*, 1999; 318: 289–92
20. Bottini P, Tantucci C: Sleep apnea syndrome in endocrine diseases. *Respiration*, 2003; 70: 320–27
21. Miller CM, Husain AM: Should women with obstructive sleep apnea syndrome be screened for hypothyroidism? *Sleep Breath*, 2003; 7: 185–88
22. Bahammam SA, Sharif MM, Jammah AA, Bahammam AS: Prevalence of thyroid disease in patients with obstructive sleep apnea. *Respir Med*, 2011; 105: 1755–60