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**PULMONARY ARTERY HYPERTENSION AND SLEEP
DISORDERED BREATHING: AN ACCP EVIDENCE-BASED
CLINICAL PRACTICE GUIDELINE**

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ABSTRACT

The objective of this article is to review the available data on the relationship between sleep disordered breathing (SDB) and pulmonary arterial hypertension (PAH), with a focus on the prevalence of SDB in patients with idiopathic pulmonary arterial hypertension (IPAH); the prevalence of pulmonary arterial hypertension (PAH) in patients with SDB; and the effects of SDB treatment on PAH.

The evidence to date suggests that PAH may occur in the setting of SDB, although the prevalence is low. However, pulmonary hypertension in SDB is most strongly associated with other risk factors, such as left-sided heart disease, parenchymal lung disease, nocturnal desaturation, and obesity. The limited data available also suggest that SDB is uncommon in IPAH. CPAP treatment of SDB may lower pulmonary artery pressures when the degree of pulmonary hypertension is mild.

KEY WORDS

Pulmonary Arterial Hypertension

Sleep Disordered Breathing

Hypoxemia

Evidenced based review

Clinical guideline

Continuous Positive Airway Pressure Therapy

ABBREVIATIONS

IPAH=idiopathic pulmonary arterial hypertension

SDB=sleep disordered breathing

SAS=sleep apnea syndrome

OSA=obstructive sleep apnea

CPAP=continuous positive airway pressure

PAH= pulmonary arterial hypertension

BMI= body mass index

AHI=apnea – hypopnea index

EEG= electroencephalography

EMG= electromyography

INTRODUCTION

The effects of sleep disordered breathing and nocturnal hypoxemia on pulmonary hemodynamics have long interested physicians who manage patients with pulmonary arterial hypertension (PAH). Sleep disordered breathing (SDB), a term that encompasses the spectrum of sleep related breathing disorders that include central and obstructive sleep apnea (OSA) and nocturnal desaturation, is a common condition in the United States and western nations. Epidemiological studies estimate the prevalence of sleep apnea syndrome to be 4% in middle-aged men and 2% in middle-aged women ¹.

Obstructive sleep apnea is diagnosed by overnight sleep studies that measure sleep EEG, EMG in selected muscle groups, eye movements, oronasal airflow, EKG, respiratory effort, and oxygen saturation. These studies should be performed when clinical findings, such as history of loud snoring, poor quality or restless sleep, or excessive daytime sleepiness suggest the presence of SDB. Obesity and recent weight gain are associated with SDB but are not necessary for it to be present ².

Sleep apnea is strongly associated with cardiovascular morbidity. The Sleep Heart Health Study and the Wisconsin Sleep Cohort Study found that OSA is a risk factor for hypertension, myocardial infarction, heart failure, and stroke ^{3,4}. Randomized, placebo controlled treatment trials have shown that treatment of OSA with Continuous Positive Airway Pressure (CPAP) lowers systolic blood pressure and improves quality of life ^{5,6}.

Several studies have examined the relationship between OSA and PAH, but the literature in this field has been difficult to interpret. Many of these studies have failed to control for the presence of concurrent heart and lung disease, which may independently affect pulmonary artery pressures. Additionally, the hemodynamic definition of pulmonary hypertension used in most of these studies (a mean pulmonary artery pressure >20 mm Hg) is lower than the widely used definition (mean pulmonary artery pressure >25 mm Hg).

The purpose of this review is to critically and systematically assess the literature of PAH and SDB to better understand the relationship between the two conditions.

METHODS

The American College of Chest Physicians (ACCP) Committee on Clinical Practice Guidelines for Pulmonary Arterial Hypertension formulated three key questions to be answered by a comprehensive critical review of the published evidence regarding sleep disordered breathing (SDB) and pulmonary arterial hypertension:

- 1) What is the prevalence of SDB among patients with idiopathic pulmonary arterial hypertension (IPAH)?
- 2) What is the prevalence of PAH among patients with SDB?
- 3) Does treatment of OSA affect pulmonary hemodynamics in patients with OSA

and PAH?

To address these questions, we conducted a computerized search of the MEDLINE bibliographic database from 1992 to October 2002. We searched using the term “hypertension, pulmonary” combined with “Sleep Apnea Syndromes” and subheadings and “Sleep Apnea, Obstructive” and subheadings. We limited the search to articles concerning human subjects that were published in English and accompanied by an abstract. In addition, we searched the reference lists of included studies, practice guidelines, systematic reviews, and meta-analyses, and consulted with clinical experts to identify relevant studies undetected by the search strategy or published before 1992.

We considered studies conducted among patients with known or suspected idiopathic IPAH, as well as populations with known or suspected SDB. We excluded studies of neonates and studies of patients with chronic obstructive pulmonary disease (COPD) or coronary artery disease. We accepted polysomnography or 4-channel cardiopulmonary sleep studies to ascertain the presence or absence of sleep disordered breathing. We accepted right heart catheterization or echocardiography for the diagnosis of PAH and the evaluation of hemodynamic response to treatment. We accepted continuous positive airways pressure (CPAP) or surgical intervention as recognized treatments for OSA. We excluded case series with fewer than 10 subjects.

Two physicians, one with methodological expertise and one with content area expertise, reviewed the abstracts of candidate articles and selected a subset for review in full text.

Full-text articles were reviewed by both physicians to determine whether they were original investigations or review articles and whether they were pertinent to at least one of the key questions.

RESULTS and DISCUSSION

Prevalence of SDB in PAH

A single study with 13 patients ⁷ has reported the prevalence of SDB among patients with PAH. The subjects in this study had marked pulmonary hypertension, with a mean resting pulmonary artery pressure of 60.8 ± 15 mmHg. Ten of 13 (77%) demonstrated nocturnal desaturation, which was defined as spending >10% of the total sleep time with a $\text{SaO}_2 < 90\%$. However, sleep apneas and hypopneas measured during polysomnography were rare.

Nocturnal desaturation was strongly associated with lower FEV_1 values, lower resting oxygenation status, and higher alveolar-arterial oxygen gradients. Three of 10 patients with nocturnal desaturation were hypoxemic at rest, and 7 desaturated with exercise. No differences were found between those with or without desaturation in body mass index (BMI), 6-minute walk test distance, or pulmonary artery pressures measured at right heart catheterization.

Although the sample size was small, this study suggests that nocturnal hypoxemia may occur commonly in IPAH and is primarily related to underlying disturbances in gas

exchange rather than sleep apnea. Since few of these subjects had been treated for nocturnal hypoxemia prior to the study, these data also suggest that nocturnal desaturation may be under-recognized in IPAH. Based on limited data, SDB in the form of nocturnal desaturation appears to be common in PAH, while OSA is uncommon.

As noted in the section of these guidelines dealing with medical therapy, the goal of supplemental oxygen in PAH is to maintain an oxygen saturation > 90% in adults and > 92% in infants and children, including during sleep⁸. The clinical consequences of nocturnal desaturation are not well understood, although it is likely that hypoxia-induced pulmonary vasoconstriction would exacerbate the pre-existent pulmonary hypertensive state. Use of standard oxygen prescribing guidelines, such as those derived from the Nocturnal Oxygen Treatment Trial, are also recommended for hypoxemic patients with PAH⁹.

Recommendation

1. In the evaluation of patients with PAH, an assessment of sleep-disordered Breathing (SDB) is recommended.

Quality of Evidence: Low; Net benefit: small/weak;

Strength of recommendation: C.

2. In the evaluation of a patient with PAH for sleep disordered breathing, a polysomnogram is recommended if OSA is suspected as the etiology, if a screening test for OSA is positive, or if a high clinical suspicion for OSA is present.

Quality of Evidence: Expert opinion; Net benefit: Intermediate;

Strength of recommendation: E/B.

The prevalence of pulmonary artery hypertension in sleep apnea

Twelve studies have estimated the prevalence of PAH in OSA¹⁰⁻²¹(Table 1): Ten of these defined PAH as a mean PAP greater than or equal to 20 mmHg; two studies did not specify the definition of PAH^{17,21}. Ten studies used right heart catheterization to determine PA pressures, while two relied on echocardiographically derived estimates. In general, pulmonary hypertension associated with OSA was mild. The average mean PA pressure in each of these studies was < 30 mm Hg, and in most it was <25 mm Hg.

Prevalence estimates of PH ranged from 17% to 53%.

There are several limitations to the conclusions that can be derived from the data in the literature regarding the relationship between SDB and PAH. Studies examining the relationship between PAH and OSA have largely been retrospective case studies and prospective cohort studies. In addition, the criteria used to enroll subjects into these studies were not always clearly defined. Finally, cohort studies are subject to selection bias.

Many studies tested a variety of variables as predictors of the presence of PAH in the setting of OSA. Four studies reported a higher BMI in PAH compared with non-PAH patients. Lower daytime pO₂ and oxygen saturation during sleep were consistent

predictors of PAH in sleep apnea^{10,11,13-15,19-21}. Of the SDB-related variables, the apnea-hypopnea index was predictive of PAH in 2 of the studies^{13,14}.

Spirometric abnormalities have also been strongly associated with PAH in OSA^{11,13-16,20}.

Several studies attempted to control for the potential confounding influence of concurrent cardiopulmonary disease^{12,19}. Bady and colleagues¹² studied 44 patients with OSA, defined as an AHI > 5, and found 12 with a mean pulmonary pressure >20mmHg and a pulmonary capillary wedge pressure less than 15mmHg, consistent with pre-capillary PH. Patients with spirometric evidence of airflow obstruction were excluded. The group mean PAm pressure in this subgroup was 28.5 ± 6.2 mm Hg, indicative of mild PAH. Patients with and without PAH were similar in age, smoking history, and gender. However, as reported by others, the BMI in the PAH group was significantly greater compared to the non-PAH group (37.4 ± 6.0 vs. 30.3 ± 6.7). The prevalence of PAH in this study of patients with OSA was 27%.

Similar findings have been reported by Sanner¹⁹ and by Sajkov¹⁸, in which consecutive sleep apnea patients were evaluated with sleep studies, pulmonary function tests, and right heart catheterization. These studies reported prevalences of PAH in OSA of 34% and 29%, respectively. Neither of these studies, however, found significant differences in BMI between those with or without PAH.

In general, patients with OSA and PAH tended to be older, heavier and have worse lung function compared to OSA patients without PAH. Sleep apnea parameters such as AHI

were weak predictors of PAH when compared with age, weight and lung function parameters. Nocturnal desaturation, another important measure of OSA severity, was a determinant of the presence of PAH in OSA.

The degree of pulmonary hypertension associated with SDB is not as severe as that associated with IPAH or many other forms of PAH. In the setting of SDB, the stimulus for pulmonary hypertension is thought to be hypoxic pulmonary vasoconstriction and subsequent vascular remodeling²². Recent studies have highlighted the role of increased tone of the autonomic nervous system²³, inflammatory mediators²⁴, and reactive oxygen species²⁵ in the upregulation of peripheral vascular tone in patients with SDB. Ip and colleagues have recently demonstrated that nitric oxide activity is suppressed in OSA, and that this reduction in nitric oxide expression is rapidly reversible with CPAP therapy²⁶. In addition to the aforementioned pathogenic stimuli, a genetic susceptibility may also contribute to a PAH predisposition in response to the chronic sustained or intermittent hypoxia that occurs in SDB.

Recommendation

3. In the management of patients with OSA, routine evaluation for the presence of pulmonary artery hypertension is not recommended.

Quality of Evidence: Low; Net benefit: None; Strength of recommendation: I

Effect of sleep apnea therapy on Pulmonary Artery Hypertension

Few studies have addressed the impact of OSA treatment on pulmonary hemodynamics in PAH due to OSA. Two small, uncontrolled studies evaluated the effects of nasal CPAP treatment on hemodynamic measures in patients with OSA and PAH^{10,27}.

Sajkov and colleagues²⁷ reported a prospective, uncontrolled single center case series in which they tested the impact of CPAP on pulmonary hemodynamics in patients with OSA. Twenty-two OSA patients with normal lung function and without cardiac disease were treated with CPAP for 4 months. The mean AHI for the cohort was 48.6 ± 5.2 , indicative of significant OSA. Pulmonary hemodynamic measurements were made prior to and after treatment. The baseline mean PA pressure for the cohort was 16.8 ± 1.2 mmHg at baseline. After 4 months of CPAP treatment, the mean PA pressures decreased to 13.9 ± 0.6 mmHg ($p < 0.05$) and pulmonary vascular resistance decreased from a baseline of 231 ± 88 dynes \cdot sec/cm⁵ to 186 ± 55 dynes \cdot sec/cm⁵ ($p < 0.05$). Of the 20 patients used for the final analysis (2 patients were noncompliant with CPAP and were not analyzed), 5 met the study's criteria for an increased mean pulmonary artery pressure of >20 mm Hg (range: 20-31 mmHg) after treatment, although these patients also manifested the greatest decline in PA pressure with CPAP therapy.

These authors also examined the responses to hypoxia by comparing the hemodynamic effects of breathing inspired fractions of oxygen of 0.11, 0.21, and 0.50 at baseline and after the 4 months of CPAP therapy. They found that CPAP therapy resulted in significant decreases in mean PA pressure and pulmonary vascular resistance at all levels

of FIO₂. These findings suggest that treatment of sleep apnea with CPAP improves PH and decreases responsiveness to pulmonary vasoconstrictor stimuli that may be present in this setting.

Alchanatis and colleagues¹⁰ also examined the effects of CPAP therapy on pulmonary hemodynamics in a prospective, quasi-controlled study of OSA patients without other pulmonary or cardiac disease. Forty-seven patients with OSA were enrolled but only 29 completed the study, consisting of 6 months of CPAP therapy. Doppler echocardiography and sleep studies were performed in both study patients and in a “control” group of 12 subjects without sleep apnea or PAH.

At baseline, the mean AHI in the OSA group was 54 ± 19 and 9 ± 2 in the “control” group. Of the 29 OSA subjects, 6 met the authors’ criteria for PAH (mean PA pressure ≥ 20 mmHg). The group mean PAm pressure in the OSA patients with and without PAH were 25.6 ± 4.0 vs. 14.9 ± 2.2 mmHg, respectively. Compared to the OSA group without PAH, the PAH group was significantly older (62 ± 4 vs. 48 ± 15 years), had a greater BMI (41 ± 7 vs. 32 ± 4 kg/m²), and a lower resting PaO₂ (81 ± 9 vs. 92 ± 9 mmHg).

After treatment with CPAP for 6 months, mean PA pressures decreased in both the PAH and the non-PAH groups: Mean PA pressures were reduced to 19.5 ± 1.6 mmHg in the PAH group and to 11.5 ± 2.0 mmHg in the non-PAH group ($p > 0.001$ for change from baseline). Body mass index was stable over the 6 month CPAP treatment period.

Based on the limited data available, we can conclude that the severity of the PAH in OSA patients is mild, and that CPAP therapy is moderately effective in reducing pulmonary arterial pressure in this setting. No data have been reported on functional improvement, quality of life, or other patient-level outcomes in patients with OSA and PAH.

Recommendation

4. In patients with OSA and PAH, treatment of OSA with positive airway pressure therapy should be provided with the expectation that pulmonary pressures will decrease, although they may not normalize, particularly when PAH is more severe.

Quality of Evidence: Low; Net benefit: small/weak; Strength of recommendation: C.

FUTURE DIRECTIONS

Our current understanding of OSA and PAH is that OSA is a moderate risk factor for PAH. The level of PH seen in association with OSA is milder than the PH observed in IPAH. The presence of other pulmonary disease appears to be a mediating factor; that is, it influences the degree of PH elevation but is not necessary for its presence. Despite the moderate number of observation studies, and fewer intervention studies, which have shaped our current knowledge about OSA and PAH, we have no longer-term outcome studies. Similarly, we have little information about the short-term effects of elevated pulmonary artery pressure on patient quality of life or other clinically important aspects of OSA.

Studies examining the role of OSA in pulmonary vasoconstriction, vascular remodeling, and pre-clinical changes in the pulmonary circulation are needed. Basic studies of pulmonary vascular biology using animal models of OSA are needed to understand changes at the cellular and molecular level. Finally, studies examining genetic susceptibility factors to OSA-related changes in pulmonary hemodynamics are needed.

SUMMARY OF RECOMMENDATIONS

Based on the available evidence, the following recommendations were accepted by the ACCP Guidelines committee for the evaluation of sleep disordered breathing in the setting of IPAH, for the evaluation PAH in the setting of OSA, and for the treatment of OSA and its effect on PAH.

1. In the evaluation of patients with PAH, an assessment of sleep-disordered Breathing (SDB) is recommended.

Quality of Evidence: Low; Net benefit: small/weak;

Strength of recommendation: C.

2. In the evaluation of a patient with PAH for sleep disordered breathing, a polysomnogram is recommended if OSA is suspected as the etiology, if a screening test for OSA is positive, or if a high clinical suspicion for OSA is present.

Quality of Evidence: Expert opinion; Net benefit: Intermediate;

Strength of recommendation: E/B.

3. In the management of patients with OSA, routine evaluation for the presence of pulmonary artery hypertension is not recommended.

Quality of Evidence: Low; Net benefit: None; Strength of recommendation: I

4. In patients with OSA and PAH, treatment of OSA with positive airway pressure therapy should be provided with the expectation that pulmonary pressures will decrease, although they may not normalize, particularly when PAH is more severe.

Quality of Evidence: Low; Net benefit: small/weak; Strength of recommendation: C.

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