

Effect of continuous positive airway pressure treatment on pulmonary artery pressure in patients with isolated obstructive sleep apnea: a meta-analysis

Tasnim F. Imran¹ · Marya Ghazipura² · Spencer Liu³ · Tanzib Hossain³ · Hormoz Ashtyani³ · Bernard Kim³ · J. Michael Gaziano¹ · Luc Djousse¹

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Abstract Pulmonary hypertension (PH) can occur in patients with obstructive sleep apnea (OSA) in the absence of cardiac or lung disease. Data on the development and severity of PH, and the effect of continuous positive airway pressure (CPAP) therapy on pulmonary artery (PA) pressures in these patients have been inconsistent in the literature. We sought to determine whether CPAP therapy affects PA pressures in patients with isolated OSA in this meta-analysis. We searched PubMed, Medline, EMBASE and other databases from January 1980 to August 2015. Studies of patients with OSA, defined as an apnea–hypopnea index >10 events/h, and PH, defined as PA pressure >25 mmHg were included. Two reviewers independently extracted data and assessed risk of bias. A total of 222 patients from seven studies (341.53 person-years) had reported PA pressures before and after treatment with CPAP therapy. 77 % of participants were men, with a mean age of 52.5 years, a mean apnea–hypopnea index of 58 events/h, and mean PA pressure of 39.3 ± 6.3 mmHg. CPAP treatment duration ranged from 3 to 70 months. Using fixed effects meta-analysis, CPAP therapy was associated with a decrease in PA pressure of 13.3 mmHg (95 % CI 12.7–14.0) in our study population. This meta-

analysis found that CPAP therapy is associated with a significantly lower PA pressure in patients with isolated OSA and PH.

Keywords Obstructive sleep apnea · Pulmonary artery pressure · Pulmonary hypertension · Continuous positive airway pressure

Introduction

Obstructive sleep apnea (OSA) is a rising health problem that affects up to 2–10 % of the population [1]. OSA has been associated with obesity, hypertension, and left-sided heart disease [2]. Additionally, there is a known association between OSA and pulmonary hypertension (PH) [3]. OSA patients with PH compared to those without PH have been noted to have higher morbidity and mortality [4]. Patients with OSA tend to have repetitive upper airway collapse and oxygen desaturations leading to hypoxemia [5]. Hypoxemia leads to vasoconstriction of the pulmonary vasculature, which can elevate PA pressures over time [5, 6]. Some suggest that PH does not occur in patients with OSA unless they have clinically significant hypoxemic pulmonary disease [7, 8], while others have found that this is not necessarily the case [9–11]. Repetitive hypoxemia during sleep may lead to pulmonary vascular remodeling, thereby impairing recruitment of pulmonary vessels during times of increased pulmonary flow, and ultimately causing sustained PH during the daytime [9].

Despite these proposed mechanisms, the effect of treatment modalities such as continuous positive airway pressure (CPAP) on PH has not been fully elucidated. CPAP is the primary therapy for patients with obstructive sleep apnea, and it has been hypothesized that CPAP may

✉ Tasnim F. Imran
TFImran@partners.org

¹ Department of Medicine, Brigham & Women’s Hospital, VA Boston Healthcare System, Harvard Medical School, 1620 Tremont St, Boston, MA 02120, USA

² Department of Population Health, New York University Langone Medical Center, 650 First Avenue, New York, NY 10001, USA

³ Heart Failure and Pulmonary Hypertension Program, Rutgers, New Jersey Medical School, 30 Prospect St, Hackensack, NJ 07103, USA

reduce pulmonary vascular reactivity to hypoxia, with subsequent reduction in PA pressures [1]. However, data on the effect of CPAP therapy on PA pressures in patients with OSA without comorbid lung or heart disease have been inconsistent. Thus, the purpose of our paper is to conduct a systematic meta-analysis to determine the effects of CPAP therapy on PA pressures.

Methods

Literature search

We performed a literature search (TFI, SL and HA) for all relevant publications using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, Web of Science, the Wiley Cochrane Library, the Cochrane Database, Google Scholar, and clinicaltrials.gov databases. All databases were searched from January 1980 through August 2015 using the following terms: “obstructive sleep apnea”, “sleep apnea/apnea”, “pulmonary hypertension”, “pulmonary artery pressure”, “continuous positive airway pressure”, and “positive pressure airway”. We reviewed articles found as a result of these searches and references cited in these articles. We additionally hand-searched reference lists and contacted investigators of certain studies when necessary. Efforts were made to also include studies not published in the English language.

Inclusion and exclusion criteria

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Materials Statement (PRISMA). Two independent reviewers (TFI and SL) screened and extracted data from full text articles, and Cohen’s kappa was calculated to determine inter-rater reliability. Discrepancies were resolved by reaching consensus through discussion. The studies included in this review met the following inclusion criteria: (1) OSA diagnosed by polysomnography, defined as apnea–hypopnea index >10 events/h, (2) no co-morbid cardiac or pulmonary disease (isolated OSA), (3) PA pressure assessed by Doppler echocardiography or right heart catheterization, represented as mean PA pressure, mean systolic PA pressure, or right ventricular systolic pressure, and (4) pulmonary hypertension diagnosed as mean PA pressure greater than 25 mmHg at rest, with a pulmonary capillary wedge pressure <15 mmHg. The process of selecting studies is outlined in Fig. 1.

Studies with participants having the following characteristics were excluded if: (1) the Apnea–Hypopnea Index (AHI) was <10 events/h or was not reported; (2) PA

pressure was not reported; or (3) patients had co-morbid conditions such as cardiovascular or pulmonary disease.

Data extraction and quality assessment

The following variables were extracted from each study: authors, year of publication, geographic location, age, gender, body mass index (BMI), sample size, mean AHI, method and results of PA pressure measurements, mean daily CPAP usage time, and duration of CPAP therapy. To determine the extent to which we can be confident about our summary estimate, the quality of the included evidence was assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group tool (Fig. 2). This tool determines the quality of the evidence to be high, moderate, low, or very low based on risk of bias, inconsistency, indirectness, imprecision, and publication bias [12]. Six domains were assessed using GRADE: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data (whether the investigators reported all outcome data, including attrition and exclusions, and whether missing data were appropriately accounted for), and selective outcome reported (determined by checking published protocols if available or relying on authors’ methods).

Data synthesis and analysis

The studies were evaluated with regards to similarity of baseline patient characteristics, methods of measurement of PA pressures, and duration of follow-up. The primary endpoint was the change in PA pressures pre- and post-CPAP therapy. A fixed effects meta-analysis was used to calculate the weighted mean difference in PA pressures pre- and post-treatment with CPAP therapy. In a secondary analysis, we also used the random effects meta-analysis model to assess the robustness of our findings. Comprehensive Meta-Analysis version 3.0 was used to create the forest plots. Extracted data were exported to Review Manager version 5.3 (Cochrane Collaboration Software) to determine the GRADE risk of bias [12].

Results

A total of 222 patients (341.53 person-years) from seven pooled studies met our inclusion criteria (Fig. 3). The data are presented as mean \pm SD unless otherwise specified. Table 1 depicts characteristics of the study participants. Based on all reviewed studies, the prevalence of PH in patients with OSA without overt heart or lung disease was approximately 30.6 % [4, 6, 8, 9, 13–20]. Mean age was

Fig. 1 Data search and selection of studies included in the systematic review

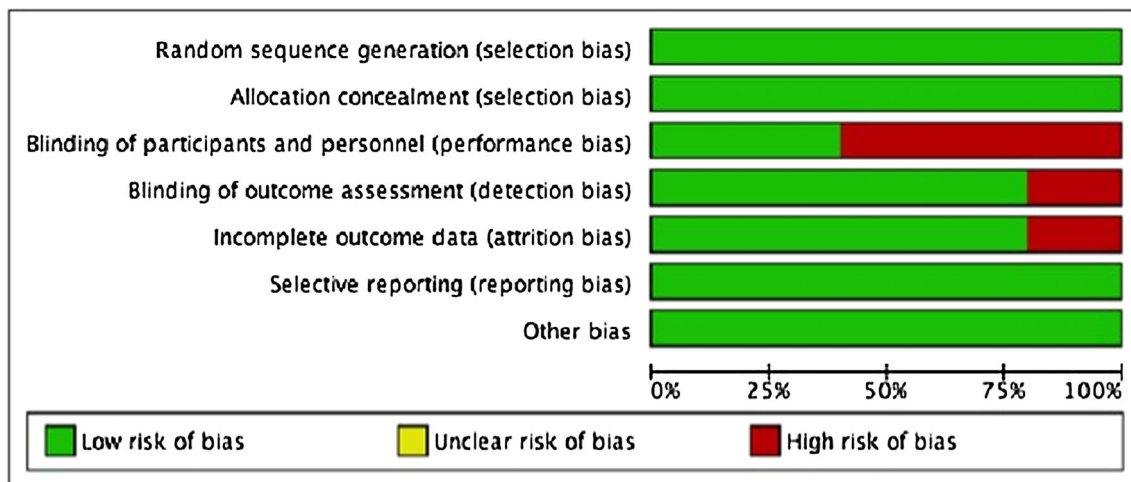
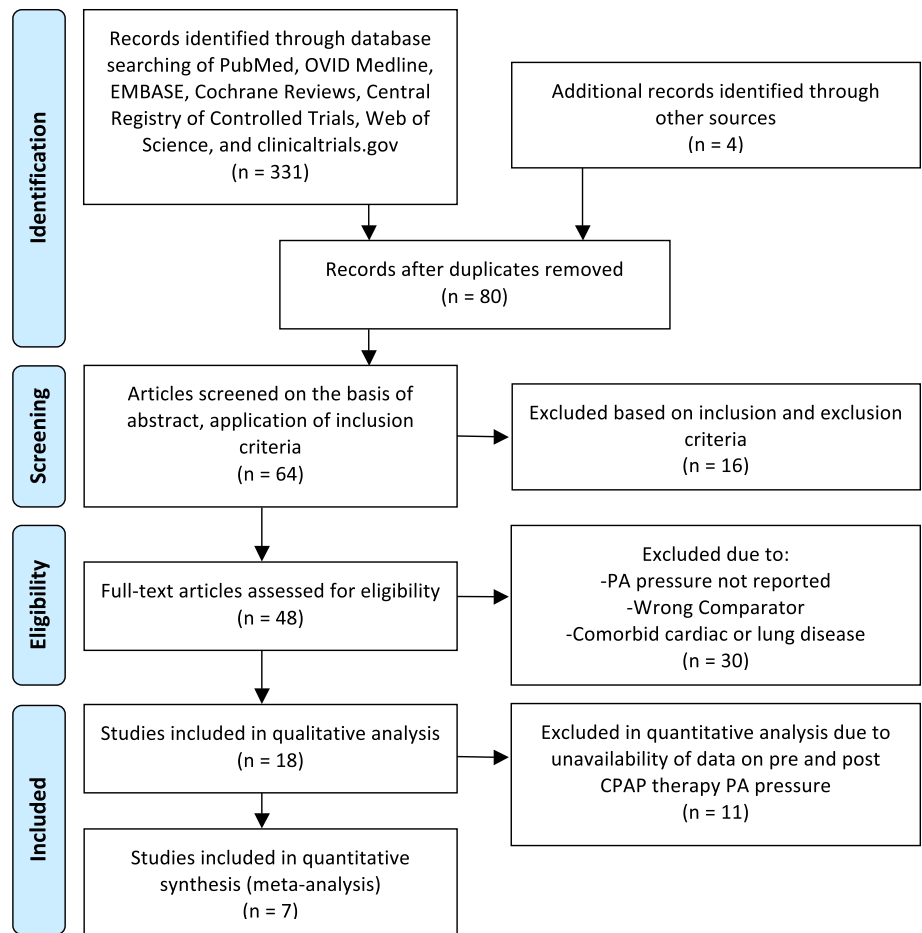
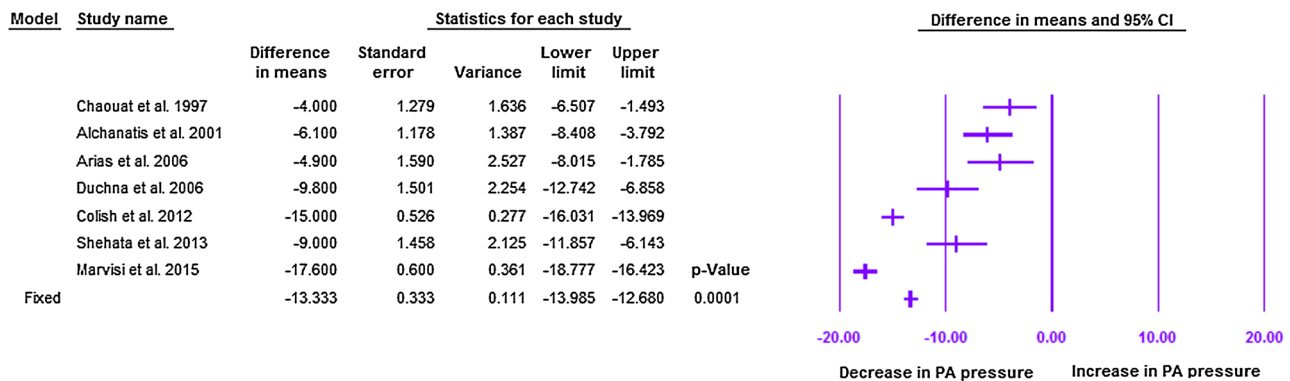


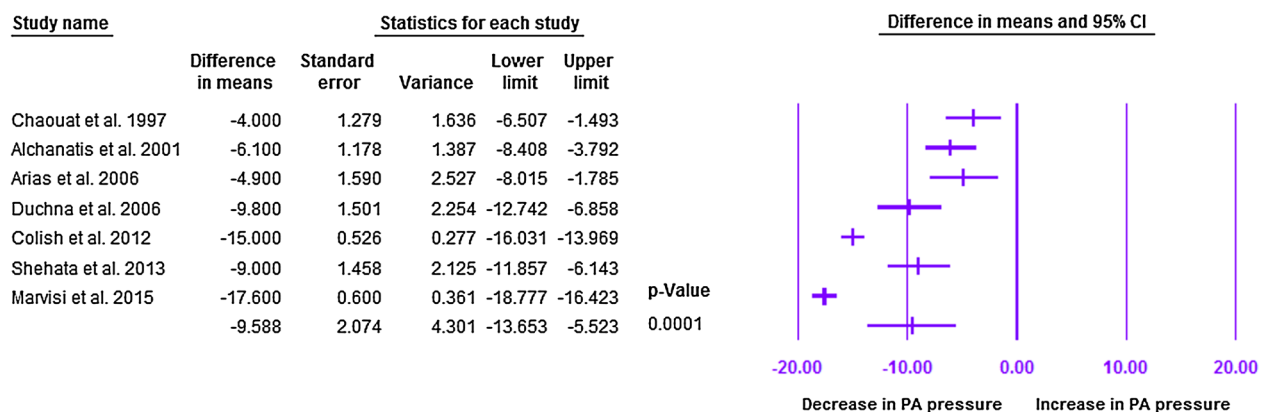
Fig. 2 Risk of bias domains shown as percentages for studies included in the meta-analysis

52.5 years, and 77 % of patients were men. The mean AHI was 58 events/h, and mean PA pressure was 39.3 ± 6.3 mmHg. On average, OSA patients with PH had a BMI 3.3 ± 0.7 units higher compared to OSA patients without PH ($p < 0.0001$). The duration of CPAP treatment

ranged from 3 to 70 months. The mean daily CPAP use was at least more than 4.5 h per night for each study. In pooled analysis, CPAP therapy was associated with a 13.3 mmHg reduction in PA pressure (95 % CI 12.7–14.0; $p < 0.0001$, Fig. 3a), using the fixed model and a

a

Effect of CPAP therapy on PA pressure in patients with isolated OSA - fixed effects model

b

Effect of CPAP therapy on PA pressure in patients with isolated OSA - random effects model

Fig. 3 Meta-analysis of pulmonary artery pressure pre- and post-CPAP therapy, fixed effects model (a), and random effects model (b)

9.6 mmHg reduction in PA pressure (95 % CI 5.5–13.7; $p < 0.0001$, Fig. 3b) using random effects meta-analysis. Figure 4 depicts the cumulative effect of the mean difference in PA pressure over time. There was low evidence of publication bias (Egger's test $p = 0.31$). Overall, the risk of bias was low to moderate, with the majority of the bias revolving around the investigators' inability to blind the participants due to the nature of the intervention (Fig. 2).

Discussion

This meta-analysis demonstrates that CPAP therapy is associated with a 13.3 mmHg reduction in PA pressure in patients with isolated OSA who have pulmonary hypertension ($p < 0.0001$). We found no correlation between severity of OSA and the degree of elevation of PA pressures, as also reported by others [9, 21–23].

Previous studies have found mixed results of CPAP therapy in patients with PH and OSA [15, 24, 25]. A decrease in PA pressures with CPAP has been noted, while others have found no change with CPAP treatment [15, 24, 25]. However, some of these studies included patients with coexisting lung disease and compliance of patients on CPAP may have been difficult to monitor objectively. A previous meta-analysis conducted by Sun et al. [22] found a standardized mean difference in PA pressure of -1.34 mmHg (95 % CI -2.33 to -0.34) in all OSA patients receiving CPAP. Although the effect of CPAP reported by Sun et al. is in the same direction as findings from our meta-analysis, the magnitude of effect is much greater in our study than in the previous meta-analysis. There are several plausible explanations for why this might occur. First, the patient population differs between the two meta-analyses. We specifically included patients with isolated OSA, those without other pulmonary or cardiac co-

Table 1 Characteristics of studies included in the meta-analysis

Study	Location	Study design	Men (%)	Age (years); treatment/control	BMI (kg/m ²); treatment/control	N; treatment/control	AHI (events/h); treatment/control	Time with O ₂ saturation < 90 % (min) or ODI	Method of PA pressure measurement
Chaouat et al. (1997) [15]	France	Prospective cohort	97	53 ± 10	33 ± 6	11	87 ± 33	24 ± 26	Right heart catheterization
						65 total			
Alchanatis et al. (2001) [6]	Greece	Case control	66	62 ± 4	41 ± 7	6	63 ± 18	NR	Doppler echocardiography
Arias et al. (2006) [19]	Spain	Randomized cross-over trial	95	48 ± 15	32 ± 4	23	51 ± 19		
				51 ± 15	33.6 ± 4.4	10	68.7 ± 24.9	30.6 ± 24.6	Doppler echocardiography
				52 ± 12	28.9 ± 2.9	11	25.1 ± 14.5	9.8 ± 10.6	
Duchna et al. (2006) [40]	Germany	Case control	100	57.7 ± 7.3	30.5 ± 3.6	20	37.5 ± 17.6	NR	Doppler echocardiography
				57.2 ± 7.5	31.2 ± 3.3	20	32 ± 19.7		
Colish et al. (2012) [1]	Canada	Prospective cohort	68	51 ± 10	38 ± 9	47	63 ± 30	25.2 ± 10.5	Doppler echocardiography
Shehata et al. (2013) [41]	Egypt	Case control	54	46.1 ± 5.2	30.3 ± 3.7	10	Median: 57.55 (range 9.2–132.6)	65.8 ± 30.1	Doppler echocardiography
				46.4 ± 7.6		14		35.5 ± 31.1 (ODI)	
Marvisi et al. (2015) [42]	Italy	Case control	72	64 ± 20	32 ± 6	17	59.3 ± 24	NR	Doppler echocardiography
				55 ± 16	29 ± 4				

Study	Location	Study design	Mean daily CPAP use (h/night)	Duration of CPAP	PA pressure Pre-CPAP (mmHg)	PA pressure Post-CPAP (mmHg)	p value
Chaouat et al. (1997) [15]	France	Prospective cohort	5.2	64 ± 6 months	24 ± 5 (with PH) 16 ± 5 (total population) *mPAP	20 ± 7 (with PH) 17 ± 5 (total population) *mPAP	0.14
Alchanatis et al. (2001) [6]	Greece	Case control	5.4	7.6 months (range 6.0–10.7)	25.6 ± 4.0 (with PH) 14.9 ± 2.2 (without PH)	19.5 ± 1.6 (with PH) 11.5 ± 2.0 (without PH)	<0.001
Arias et al. (2006) [19]	Spain	Randomized cross-over trial	6.2	>3 months	28.9 ± 8.6	24.0 ± 5.8	<0.0001
Duchna et al. (2006) [40]	Germany	Case control	NR	>6 months	24.1 ± 10.2	14.3 ± 5.4	<0.001
Colish et al. (2012) [1]	Canada	Prospective cohort	>4.5	>12 months	54 ± 6	39 ± 5	<0.05
Shehata et al. (2013) [41]	Egypt	Case control	>6	>6 months	35 (range 28–40) with PH 13.5 (range 10–25) without PH	26 (range 20–35) with PH	0.007
Marvisi et al. (2015) [42]	Italy	Case control	>4	>3 months	39.8 ± 4.1 (with PH) 21.1 ± 3.0 (without PH)	22.2 ± 3	<0.001

*mPAP Mean pulmonary artery pressure, BMI body mass index, AHI apnea hypopnea index, PA pulmonary artery, CPAP continuous positive airway pressure, ODI oxygen desaturation index, NR not reported. For studies that provided separate values for age, BMI and AHI for cases and controls, the top row lists the values for cases and the bottom row lists the values for controls

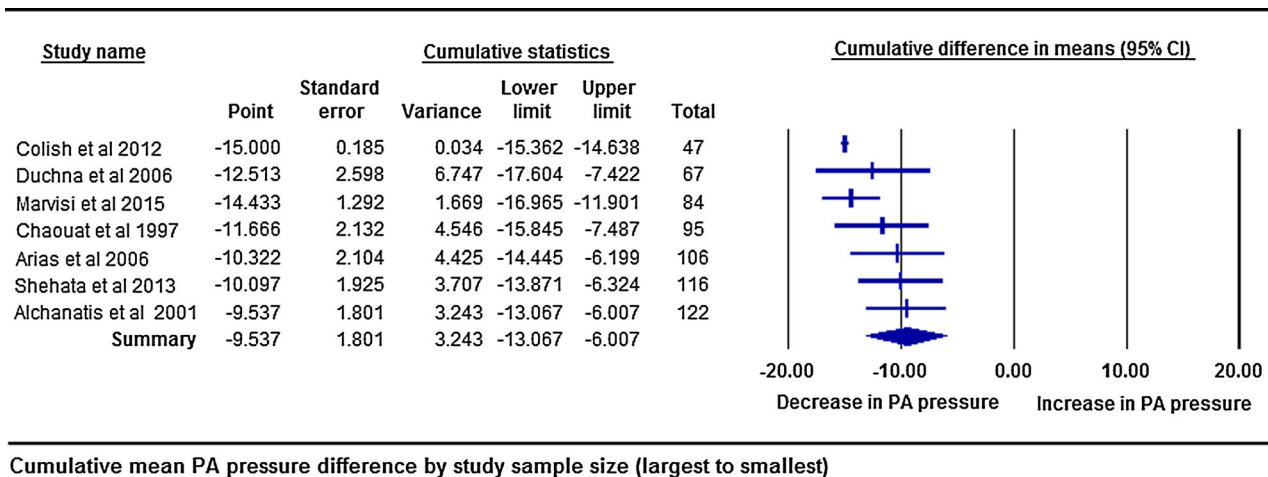


Fig. 4 Cumulative meta-analysis of mean PA pressure difference over time

morbid conditions. This is in contrast with Sun et al., who included all patients with OSA regardless of other diagnoses in their analyses. It is possible that CPAP treatment led to some degree of improvement in PH secondary to OSA in these patients, but that their co-morbid pulmonary disease remained unchanged. Co-morbid conditions such as chronic obstructive pulmonary disease and heart failure can also lead to PH in these patients, and thus, the PA pressure may not be altered significantly after CPAP therapy. Second, the previous meta-analysis included some studies that do not meet the current definition of PH as defined by a PA pressure >25 mmHg at rest. Third, we have included two additional studies that were published after the previous meta-analysis was conducted, which may affect the magnitude of the estimate.

Potential biological mechanisms by which OSA may lead to PH include hypoxic pulmonary vasoconstriction, pulmonary vascular remodeling, and endothelial dysfunction [9, 26]. There may be a genetic predisposition to developing pulmonary vascular remodeling, as not all patients with OSA without lung disease have PH [27]. Genetic variability has been reported in sheep and humans who reside at high altitudes [27]. Patients with baseline arteriolar narrowing may have a heightened response to hypoxia, and they may be at risk for pulmonary vascular remodeling with repetitive episodes of apnea [9]. Chronic hypoxia may also impact the transcription of genes involved in vasoconstriction and smooth muscle proliferation [28]. Decreased oxygen tension increases the production of multiple mitogenic factors for endothelial cells [12–15, 29–32]. Endothelin-1 and serotonin, potent vasoconstrictors, had increased expression when placed in a hypoxic environment [33]. However, nitric oxide, a vasodilator [34] and inhibitor of smooth muscle and fibroblast growth [35, 36], has been shown to have

decreased transcription during hypoxia [37]. It is postulated that CPAP may reduce pulmonary vascular reactivity to hypoxia and improve pulmonary endothelial function, resulting in decreased PA pressures [38]. CPAP has also been shown to improve cardiovascular remodeling as assessed by serial cardiac biomarkers, transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging [1]. TTE in patients undergoing CPAP therapy has demonstrated an improvement in the degree of PH, and related parameters such as right ventricular end-diastolic diameter, left atrial volume index, and right atrial volume index. Cardiac magnetic resonance imaging has revealed a decrease in left ventricular mass, with progressive improvement over the course of a year [1]. Thus, CPAP therapy may lead to resolution of systolic and diastolic abnormalities and improvement in cardiovascular remodeling in OSA patients with PH. Pulmonary hypertension in patients with OSA also portends a worse prognosis and may lead to complications such as right ventricular failure over time [4, 39]. Thus, aggressive therapy with CPAP may be warranted.

The current study has some limitations. First, we analyzed only seven studies in the meta-analysis since the literature on the effects of CPAP on PA pressure for patients with isolated OSA is currently limited. Second, all studies, with the exception of one, utilized TTE to assess PA pressures on follow-up, whereas right heart catheterization may be a more accurate method. However, when patients were followed over months with monitoring of PA pressure at various time intervals, TTE was widely used as it is less invasive and more easily accessible than right heart catheterization. These two methods used to assess PA pressures could have led to misclassification of PA pressure values. Third, most participants (77 %) were men, thereby limiting generalizability of our results to women.

Despite the above limitations, our study has numerous strengths: studies included in this meta-analysis were conducted at various geographic locations; thus, the overall effect may be generalizable to different populations. In addition, adherence to CPAP therapy was optimal, ranging from 87 % (5.4 h/night) in the Alchanatis study to 91 % (6 h/night) in the Arias trial [6, 9, 19]. To maximize the utilization of published data, we also included in our search studies published in languages other than English. Most importantly, our study included only patients with isolated OSA, without other comorbid conditions that can lead to PH, thereby increasing the robustness of the estimate for this patient population.

In conclusion, this meta-analysis provides evidence in support of the efficacy of CPAP therapy for patients with isolated OSA and PH. Further studies, particularly randomized controlled trials, are needed to clearly elucidate the role of this treatment modality. As pulmonary hypertension is an independent predictor of mortality in patients with OSA, reduction in PA pressure may improve survival.

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Compliance with ethical standards

Conflict of interest Dr. Ashtyani has served as an expert witness regarding pulmonary hypertension. All other authors declare no conflict of interest.

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