Use of pulmonary arterial hypertension–specific therapy in overweight or obese patients with obstructive sleep apnea and pulmonary hypertension

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Abstract: Pulmonary hypertension (PH) in overweight or obese patients with obstructive sleep apnea (OSA) may be multifactorial. The effect of pulmonary artery hypertension (PAH)–specific drugs on PH and exercise capacity in such patients is unknown. We performed a retrospective review of overweight or obese patients with OSA and PH who were treated with PAH-specific therapy in our PH clinic. We identified 9 female and 2 male patients. The mean age $\pm$ SD was 54.9 ± 9.3 years. The mean pulmonary artery pressure at the time of diagnosis of PH was 39.8 ± 16.1 mmHg. The right atrial pressure was 11.1 ± 4.5 mmHg, the pulmonary artery wedge pressure was 14.1 ± 2.9 mmHg, the cardiac index was 2.6 ± 0.5 L/min/m², and the pulmonary vascular resistance index was 10.6 ± 7.1 Wood units/m². The indications for use of PAH-specific therapy were dyspnea in association with right heart failure ($n = 4$), persistent PH despite compliance with nocturnal positive airway pressure (PAP) therapy ($n = 4$), or inability to tolerate PAP therapy ($n = 3$). PH was treated with an endothelin receptor antagonist ($n = 8$) or a phosphodiesterase-5 inhibitor ($n = 3$). The 6-minute walk distance (6MWD) improved significantly, from 234 ± 49.7 to 258 ± 54.6 m (24 m [95% confidence interval (CI): 6.5–341.5 m]; $P = 0.014$) over a period of 4.4 ± 1.8 months ($n = 8$) and from 241.7 ± 48.5 to 289.9 ± 91 m (48 m [95% CI: 5.5–90.8 m]; $P = 0.033$) in those with a longer follow-up period of 12.1 ± 6.4 months ($n = 7$). The systolic pulmonary artery pressure dropped significantly, from 64 ± 25.2 to 42 ± 10.4 mmHg (22 mmHg [95% CI: 4–40 mmHg]; $P = 0.024$) over a period of 6.1 ± 4.1 months ($n = 7$). In conclusion, PAH-specific therapy resulted in significant improvement in both PH and 6MWD.

Keywords: pulmonary hypertension, obstructive sleep apnea, therapy.

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INTRODUCTION

More than two-thirds of the US adult population is overweight or obese.¹ Obstructive sleep apnea (OSA), is common among such patients,² and pulmonary hypertension (PH) is a common complication of OSA.³⁻⁹ On the other hand, obesity is common in patients with idiopathic pulmonary arterial hypertension (PAH).¹⁰ Pulmonary hypertension secondary to OSA is usually mild, whereas more severe PH suggests other causes, e.g., obesity hypoventilation syndrome (OHS), chronic obstructive pulmonary disease, left heart disease, chronic thromboembolic PH, and/or idiopathic PAH (IPAH).¹¹ The treatment of PH secondary to OSA, with or without OHS, is nocturnal

positive airway pressure (PAP) therapy and weight loss, including bariatric surgery,¹¹ whereas treatment of IPAH consists of PAH-specific drug therapy and lung transplantation.¹²

The development of PH adversely affects exercise capacity in patients with OSA.¹³ Nocturnal PAP therapy results in modest improvement in pulmonary hemodynamics in patients with OSA;^{9,14,15} however, PH may persist in those in whom PH is more than mild. Moreover, a considerable number of patients may not tolerate nocturnal PAP therapy.¹⁶ Finally, since obesity, OSA, and PH frequently coexist in clinical practice, it may not be

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possible to exclude the possibility of concomitant IPAH even when other causes of PH have been excluded. The effect of PAH-specific therapy on PH and exercise capacity, as measured by 6-minute walk distance (6MWD), in overweight or obese patients with OSA and PH is unknown. We sought to review our experience with the use of such therapy in such patients, who are often seen in practice and present a management dilemma.

METHODS

We performed a retrospective chart review of overweight or obese patients with OSA and PH who were treated with PAH-specific therapy in our PH clinic. The study was approved by our institutional review board (University of Florida Jacksonville Health Science Center [UFJ] 2012–110). We reviewed the records of patients followed in our PH clinic to identify overweight or obese patients with OSA and PH. We included patients if they met the following criteria: (1) PH, defined as resting mean pulmonary artery pressure (mPAP) of >25 mmHg on right heart catheterization (RHC); (2) OSA, defined as an apnea-hypopnea index (AHI) of >5 /hour; (3) body mass index (BMI) ≥ 25 ; (4) no evidence of decompensated left heart disease, pulmonary thromboembolic disease, lung disease, sarcoidosis, or conditions associated with WHO (World Health Organization) group I PAH, i.e., connective tissue disease, human immunodeficiency virus infection, portal hypertension, hemoglobinopathy, and congenital heart disease; (5) no history of anorexigen use; and (6) at least one follow-up visit after initiation of PAH-specific therapy. We collected the following data: demographics, BMI, results of pulmonary function tests, results of sleep study, level of nocturnal PAP therapy used to treat the underlying OSA, results of transthoracic echocardiogram at baseline and follow-up, results of RHC at baseline and follow-up if one was done, results of 6-minute walk test (6MWT) at baseline and follow-up, weight at baseline and follow-up, and drugs used to treat the PH and any adverse drug effects.

We present categorical data as frequencies and percentages and quantitative data as means $\pm$ SD. We compared the change in 6MWD and systolic pulmonary artery pressure (sPAP) between baseline and follow-up by using the paired *t* test. We compared the change in oxyhemoglobin saturation by pulse oximetry between the start and the end of the 6MWT by also using the paired *t* test.

RESULTS

We identified 11 patients: 9 female and 2 male. The mean age was 54.9 ± 9.3 years. The BMI was 42.6 ± 10 kg/m². The AHI was 37.1 ± 40.4 /hour (Table 1). The baseline pulmonary function data are presented in Table 2.

Table 1. Baseline characteristics

Demographics	Value
Age, years	54.9 ± 9.3
Females, <i>n</i> (%)	9 (82)
BMI, kg/m ²	42.6 ± 10
Severely obese (BMI = 35–39.9), <i>n</i> (%)	9 (82)
Morbidly obese (BMI ≥ 40), <i>n</i> (%)	6 (55)
Sleep study	
AHI, per hour	37.1 ± 40.4
CPAP, cm H ₂ O (<i>n</i> = 7)	10.8 ± 1.2
BiPAP, cm H ₂ O (<i>n</i> = 3)	$21 \pm 3.5, 16.3 \pm 2.9$

Note: Data are presented as mean $\pm$ SD unless otherwise noted. BMI: body mass index; AHI: apnea-hypopnea index; CPAP: continuous positive airway pressure; BiPAP: bilevel positive airway pressure.

The mPAP at the time of diagnosis of PH was 39.8 ± 16.1 mmHg. The right atrial pressure was 11.1 ± 4.5 mmHg, the pulmonary artery wedge pressure (PAWP) was 14.1 ± 2.9 mmHg, the cardiac index was 2.6 ± 0.5 L/min/m², and the pulmonary vascular resistance index was 10.6 ± 7.1 Wood units/m² (Table 3).

The indications for use of PAH-specific therapy were dyspnea in association with right heart failure (*n* = 4), persistent PH despite compliance with PAP therapy (*n* = 4), or inability to tolerate PAP therapy (*n* = 3). PH was treated with an endothelin receptor antagonist (*n* = 8) or a phosphodiesterase-5 inhibitor (*n* = 3). There were no adverse effects from the drugs.

The 6MWD improved significantly, from 234 ± 49.7 to 258 ± 54.6 m (24 m [95% confidence interval (CI): 6.5–41.5 m]; *P* = 0.014), over a period of 4.4 ± 1.8 months (*n* = 8) and from 241.7 ± 48.5 to 289.9 ± 91 m (48 m [95% CI: 5.5–90.8 m]; *P* = 0.033) in those with a longer follow-up period of 12.1 ± 6.4 months (*n* = 7; Table 4). There was near-significant desaturation at the end of the 6MWT at baseline that persisted at the first follow-up 6MWT. However, this disappeared by the second follow-up 6MWT, at 12.1 ± 6.4 months (Table 4). There was no significant difference in weight during the follow-up period.

The sPAP dropped significantly, from 64 ± 25.2 to 42 ± 10.4 mmHg (22 mmHg [95% CI: 4–40]; *P* = 0.024) over a period of 6.1 ± 4.1 months (*n* = 7). A follow-up sPAP was not available for one patient, but that patient was evaluated with a noninvasive cardiac output monitor as part of another study, and it showed significant improvement in her cardiac index, from 2.4 to 3.1 L/min/m² over

Table 2. Baseline pulmonary function

Measure	Value
FEV1, L	1.6 ± 0.5
FEV1, % predicted	65.1 ± 18.4
FVC, L	2 ± 0.7
FVC, % predicted	65.4 ± 18.5
TLC, L	3.7 ± 1.2
TLC, % predicted	77 ± 20.9
DLCO, mL/min/mmHg, STPD	15.4 ± 5.9
DLCO, % predicted	66.1 ± 26.1
PaCO ₂ , mmHg (n = 4)	59.8 ± 11.1

Note: Data are presented as mean ± SD. FEV1: forced expiratory volume in first second; FVC: forced vital capacity; TLC: total lung capacity; DLCO: diffusing capacity for carbon monoxide; STPD: standard temperature and pressure, dry; PaCO₂: partial pressure of carbon dioxide in arterial blood.

a period 6 months. The data for 6MWD and sPAP of the individual patients is shown in Table 5.

DISCUSSION

The use of PAH-specific therapy resulted in significant improvement in both 6MWD and PH in overweight or obese patients with OSA and PH in whom PH persisted despite compliance with nocturnal PAP therapy or in those who were unable to tolerate nocturnal PAP therapy. The improvement in 6MWD was more pronounced in those with a longer follow-up period. The improvement of 48 m is also clinically significant, since the minimal clinically important difference in PAH is considered to be 41 m.¹⁷ The significant desaturation noted on the baseline 6MWT disappeared with prolonged use of PAH-specific therapy. There was no significant difference in weight during the follow-up period.

The degree of PH seen in our patients was severe in comparison to the degree of PH usually seen in patients with OSA. The mPAP in our study was ~40 mmHg, whereas it is usually in the 20s in patients with PH secondary to OSA.³⁻⁹ Severe PH (mPAP > 40 mmHg) is rare in patients with OSA. A recent study of patients with OSA reported severe PH in 8 (44%) of the 18 patients with PAH in that study.¹³ However, other cardiopulmonary diseases were not excluded in that study.

The degree of PH in our patients was more severe than usual, probably because most of our patients also had OHS. PH is more common and more pronounced in patients with OSA with OHS than in those with pure OSA.^{18,19} This is probably because hypoxia that is believed to result in

pulmonary vascular remodeling and PH is only nocturnal and intermittent in pure OSA, whereas it is persistent and severe in OHS. Moreover, hypercapnia and acidosis probably also contribute to the development of PH by augmenting hypoxic pulmonary vasoconstriction.²⁰ Unfortunately, arterial blood gases were not available for all our patients. It is also possible that the degree of PH in our patients was more severe than usual because the PH in 3 of our patients was IPAH. The mPAP in these 3 patients was >50 mmHg, which is typical of IPAH.²¹ However, these 3 patients were morbidly obese, with daytime hypercapnia, and the PH was probably secondary to a combination of OSA and OHS rather than to IPAH. Moreover, sleep apneas and hypopneas measured during a formal sleep study are extremely rare in IPAH.²²

It is possible that PH in another 4 of our patients was partly postcapillary and the result of diastolic dysfunction of the left heart, given their borderline high PAWP (16 mmHg in 3 and 17 mmHg in one). However, the borderline high PAWP was unlikely to be from left heart disease, because transthoracic echocardiography revealed right ventricular pressure overload in these patients. More importantly, initiation of PAH-specific therapy did not result in worsening dyspnea or pulmonary edema. It is also possible that PH in 2 of our patients in whom cardiac output was not available was the result of the high-cardiac-output state seen in morbidly obese patients. However, pulmonary vascular resistance corrected for body surface area was abnormally high in the other patients.

Although PH secondary to OSA and OHS falls under the category of PH associated with hypoxia and/or lung disease in the WHO classification of PH,²³ it differs from the majority of other disorders in that group, i.e., chronic

Table 3. Baseline hemodynamics

Measure	Value
RAP, mmHg	11.1 ± 4.5
sPAP, mmHg	59.5 ± 27
dPAP, mmHg	30 ± 12.5
mPAP, mmHg	39.8 ± 16.1
PAWP, mmHg	14.1 ± 2.9
CI, L/min/m ²	2.6 ± 0.5
PVRI, Wood units/m ²	10.6 ± 7.1

Note: Data are presented as mean ± SD. RAP: right atrial pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; CI: cardiac index; PVRI: pulmonary vascular resistance index.

Table 4. Six-minute walk test (6MWT) and weight at baseline and on follow-up

Measure	First follow-up, at 4.4 ± 1.8 months (n = 8)		Second follow-up, at 12.1 ± 6.4 months (n = 7)	
	Baseline	Follow-up	Baseline	Follow-up
6MWD, m	234 ± 49.7	258 ± 54.6 ^a	241.7 ± 48.5	289.9 ± 91 ^b
SpO ₂ at start, %	96.4 ± 2.2	95.1 ± 3.6	96.5 ± 2.4	95.5 ± 4.1
SpO ₂ at end, %	92.4 ± 6.7	88.1 ± 9.4	92.3 ± 7.3	92.3 ± 7.7
Change in SpO ₂ between start and end, %	4	7	4.2	3.2
95% CI, %	−0.2 to 8.2	−0.5 to 14.5	−1.1 to 9.4	−1.2 to 7.4
P	0.06	0.06	0.1	0.12
Supplemental O ₂ , L/min	0.5 ± 1.41	0.5 ± 1.41	0	0
Weight, kg	110 ± 26	112 ± 28	103 ± 23	100 ± 27

Note: Data are presented as mean ± SD. 6MWD: 6-minute walk distance; SpO₂: arterial oxyhemoglobin saturation by pulse oximetry; 95% CI: 95% confidence interval.

^a Change in 6MWD between baseline and first follow-up 6MWT: 24 m (95% CI: 6.5–41.5 m; *P* = 0.014).

^b Change in 6MWD between baseline and second follow-up 6MWT: 48 m (95% CI: 5.5–90.8 m; *P* = 0.033).

obstructive pulmonary disease and interstitial lung disease. Hypoxia and the pulmonary vascular remodeling resulting from it are common to the pathophysiology of PH in both OSA²⁴ and lung diseases.^{25,26} However, there are additional factors that lead to the development of PH in

lung diseases.^{25,26} Since the lung parenchyma is otherwise normal in OSA and OHS, PH secondary to pure OSA or to OSA with OHS is similar to WHO group I PAH, albeit not necessarily pathologically identical. Whether or not an overweight or obese patient with OSA and PH has con-

Table 5. Data of individual patients

Patient	mPAP, mmHg	AHI, per hour	BMI, kg/m ²	6MWD, m			sPAP, mmHg	
				Baseline	First follow-up	Second follow-up	Baseline	Follow-up
A	26	13.3	27	279	300	309	59	54
B	27	24	30	180	207	285	50	37
C	39	19.7	39	240	273	258	62	31
D	31	18.6	37	231	222	240	46	39
E	28	121	38	318	339	315	41	30
F	26	NA	46	255	303	324	60	... ^a
G	51	15	50	189	240	298	70	NA
H	32	7.4	50	180	180	...	48 ^{a,b}	... ^a
I	45	29	40	TSW	TSW	...	75 ^{a,b}	48 ^b
J	76	104	61	TSW	TSW	...	115 ^b	55 ^b
K	57	19.2	51	NA	150	...	91	... ^c

Note: mPAP: mean pulmonary artery pressure on right heart catheterization (RHC); AHI: apnea-hypopnea index; BMI: body mass index; 6MWD: 6-minute walk distance; sPAP: systolic pulmonary artery pressure on transthoracic echocardiogram, unless indicated otherwise; TSW: too sick to walk 6 minutes; NA: not available.

^a No tricuspid regurgitation to estimate sPAP.

^b sPAP on RHC.

^c Cardiac index measured by noninvasive cardiac output monitor (see text).

comitant IPAH, PH in such a patient is therefore expected to respond to PAH-specific therapy with a favorable effect on 6MWD, and this was in fact seen in our study.

Moreover, recent studies have shown that long-standing hypoxia in OSA results in endothelial dysfunction and an imbalance of vasoconstriction and vasodilatation. Continuous PAP therapy in OSA results in enhanced release of nitric oxide by the pulmonary vasculature,²⁷ which suggests that a deficiency of this potent vasodilator exists in patients with OSA. On the other hand, intermittent hypoxia induces increased responsiveness to endothelin-1 in the pulmonary arteries.²⁸ Continuous PAP therapy can reduce nocturnal hypoxia but does not affect endothelin-1 plasma levels.²⁹ These studies also explain the favorable effect of PAH-specific therapy in our study and provide a rationale for considering such therapy in overweight or obese patients with OSA and PH.

There were no adverse effects from the use of PAH-specific therapy. However, left ventricular diastolic dysfunction is common in morbidly obese patients with OSA, and the use of such therapy could result in pulmonary edema. It may be worthwhile to perform a vasodilator challenge or other provocative maneuver during RHC to rule out occult left ventricular diastolic dysfunction before considering PAH-specific therapy in OSA.

Our study suggests that PAH-specific therapy may provide an additional or alternative form of treatment of PH in overweight or obese patients with OSA and PH in whom PH persists despite nocturnal PAP therapy or in those who cannot tolerate nocturnal PAP therapy, respectively. There have been very few studies of the effects of nocturnal PAP therapy on pulmonary hemodynamics in patients with OSA.^{9,14,15} They showed an improvement in the mild PH noted in those studies. Only one excluded patients with other cardiopulmonary disease.⁹ This prospective, quasi-controlled study showed a significant improvement in echocardiogram-estimated mPAP, from 25.6 ± 4 to 19.5 ± 1.6 mmHg ($P < 0.001$) after 6 months of nocturnal continuous PAP therapy in 6 patients with PH secondary to OSA. The AHI was 63 ± 18 /hour, and BMI was 41 ± 7 kg/m² in those patients.⁹ It is unknown whether nocturnal PAP therapy alone can result in significant improvement in the severe degree of PH that was seen in our patients, but persistent PH despite compliance with nocturnal PAP therapy suggests that it is unlikely. On the other hand, one study of the effects of bariatric surgery and weight loss on pulmonary hemodynamics in 18 patients with OHS showed a significant improvement in mPAP, from 36 ± 14 to 23 ± 7 mmHg ($P < 0.0001$) after 3–9 months, and a significant decrease in the percentage of ideal body

weight, from 224 ± 59 to 167 ± 57 ($P < 0.0001$).¹⁸ PH was present in 17 (94.4%) of the 18 patients and was severe in 7 (41%), and the pulmonary artery end-diastolic pressure-to-wedge pressure gradient was >5 mmHg in 13 (76.5%). PH persisted in 10 patients, but it was not severe in any of them.¹⁸ Our study also suggests that PAH-specific therapy may be lifesaving in overweight or obese patients with OSA who are in right heart failure. Finally, PAH-specific therapy may be used to improve the cardiopulmonary status of morbidly obese patients with OSA who wish to undergo bariatric surgery but are considered high risk because of severe PH.

In conclusion, our study suggests that the use of PAH-specific therapy in overweight or obese patients with OSA and PH results in significant improvement in PH and 6MWD. The results of our study should, however, be interpreted with caution, since this is a single-center retrospective case series of a small number of selected patients. The possibility of a placebo effect cannot be excluded in the absence of a control group. The possibility of concomitant IPAH cannot be excluded in a couple of the patients. PAH-specific therapy is costly and could result in adverse consequences, such as pulmonary edema or even death. The management of PH in overweight or obese patients with OSA requires further research, since PH in such cases may be multifactorial and it may be difficult to exclude the possibility of concomitant IPAH.

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