Pulmonary Hypertension in Obstructive Sleep Apnea Syndrome


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Introduction

Cor pulmonale has a well-described association with chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung diseases.[1] This association is felt to be the result of chronic hypoxic pulmonary vasoconstriction as well as a complex interaction of molecular pathways culminating in pulmonary vascular remodeling. The WHO clinical classification of pulmonary hypertension (PH) includes these patients in WHO Class III (PH associated with lung diseases and/or hypoxemia), which also incorporates patients with sleep disordered breathing.[2] Obstructive sleep apnea (OSA)/hypopnea syndrome is the most widely studied of all sleep disordered breathing syndromes, occurring in approximately 10% of adult men and 5% of middle-aged women.[3] It is becoming increasingly clear that, in addition to excessive daytime sleepiness and snoring, OSA is associated with a variety of chronic cardiovascular sequelae, including hypertension, stroke, coronary artery disease, and sudden death.[4] Pulmonary hypertension is a less appreciated complication of the physiologic changes associated with OSA.[5-8] Patients with OSA have been shown to have transient, sometimes severe, elevations in pulmonary arterial pressures (PAP) during sleep;[9] however, daytime, fixed PH has received less attention. Several factors associated with OSA may produce PH,[5-8] including chronic hypoxia, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, intermittent intrathoracic pressure changes, and associated comorbidities. This review is devoted to permanent, daytime PH in patients with OSA.

Definition of Pulmonary Hypertension in Obstructive Sleep Apnea

Pulmonary hypertension is defined by the presence of resting mean PAP (mPAP) >25 mmHg during right heart catheterization (RHC).[10,11] However, previous studies on PH in patients with COPD and OSA have defined PH as mPAP >20 mm Hg. Pulmonary arterial hypertension (PAH) is a subgroup further defined by the presence of pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg and both PAH (PCWP ≤15 mm Hg) and pulmonary venous hypertension (PVH; PCWP >15 mm Hg) have been reported in patients with OSA.[7,12,13] Severe PH remains poorly defined and the suggested definition of resting mPAP ≥40 mm Hg has several limitations.[7,14]

Pulmonary Hemodynamics in Sleep

Several hemodynamic alterations have been described in association with normal sleep, including a decrease in systemic blood pressure and heart rate.[15] However, limited data suggest that normal sleep has minimal impact on pulmonary hemodynamics.[16,17] This relationship is dramatically altered during episodes of apnea. Several studies have described significant increases in PAP from the middle of the apnea to the end of the apnea, which reaches a maximum during the first few breaths once the obstruction is relieved (postapneic hyperventilation).[16,18-21] These acute changes are more pronounced during rapid eye movement (REM) sleep than in non-REM sleep,[9,18,20-22] and are felt to be related to acute changes in intrathoracic pressure, hypoxia, and reflex mechanisms. Repeated apneic episodes with attendant hypoxia can produce a sustained augmentation of the pressor response of the pulmonary arterial system, which escalates progressively during the night.[9,18,23] It may be that the marked oxygen desaturation in REM sleep augments progressive increase in PAP without time to recover to baseline in the event of consecutive prolonged apneic episodes with short interapneic intervals.[17]

Epidemiology of Awake Pulmonary Hypertension in Obstructive Sleep Apnea

Similar to patients with chronic lung diseases, PH in the setting of OSA generally appears to be mild to moderate,[24,25] with severe PH being less common.[7,24,25] Largely as a result of concern over the invasive nature of RHC, the true prevalence of PH in OSA is not known due to a lack of large, population-based studies. Prevalence data on resting, awake PH in OSA is based primarily on retrospective case series or prospective cohort studies with poorly defined entry criteria (**Table 1**).[7,12,13,18,22-37] This literature is further confounded by several limitations—the most important among which are a lack of consistency in defining PH, the varying methods used to detect its presence, and the lack of exclusion of other secondary causes with proper evaluation. It is generally accepted that measurement of PH in obese patients with OSA is especially prone to error when performed by Doppler echocardiography (DE),[5,10,38,39] and although DE estimates of right ventricular systolic pressure (RVSP) correlate strongly with systolic PAP measured by RHC, there is large variation among individual pa-

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Table 1. Prevalence of Resting, Awake Pulmonary Hypertension in Obstructive Sleep Apea

Study	N	Method of diagnosis	Definition of PH (mm Hg)*	Cardio-pulmonary diseases excluded	PH prevalence (%)	mPAP (mm Hg)	mPAP in PH (mm Hg)#	Mean FEV1 % pred*	Mean AHI or RDI/h*	Mean Awake PaO_2*	Mean BMI kg/m^2 or % IBW*
Tilkian et al, 1976[18]	12	RHC	ND	No	67	21	25	-	-	77	-
Schroeder et al, 1978[26]	22	-	mPAP >20	Yes	59	21	25	-	-	80	-
Podszus et al, 1986[27]	65	RHC	ND	No	20	19	29	-	-	-	§122±16
Fletcher et al, 1987[28]	24	RHC	mPAP >20	No	79	29	30	62	66	66	§~156
Weitzenblum et al, 1988[29]	46	RHC	mPAP ≥20	No	20	16	23	66	-	73	145±27
Krieger et al, 1989[30]	114	RHC	mPAP ≥20	Yes	19	16	-	65 ~	90	72	31.7±5.8
Apprill et al, 1991[31]	46	RHC	mPAP ≥20	Yes	20	-	23	^70	89	73	§~144
Laks et al, 1995[25]	100	RHC	mPAP ≥20	No	42	21	29	^76	64	74	37 (24-54)
Chaouat et al, 1996[24]	220	RHC	mPAP ≥20	No	17	-	26	-	78	73	-
Sanner et al, 1997[13]	92	RHC	mPAP ≥20	Yes	20	15	22	92	40	83	31.4±5.1
Sforza et al, 1998[23]	7	RHC	mPAP ≥20	Yes	43	23	26	>80	84	81	38.7±1.6
Niijima et al, 1999[22]	19	RHC	mPAP >20	No	53	20	28	82	54	72	35.1±7.7
Bady et al, 2000[12]	44	RHC	mPAP >20	Yes	27	20	28	92	53	81	37.4±6.0
Alchanatis et al, 2001[32]	29	RHC	mPAP ≥20	Yes	21	17	26	92	63	90	41.0±7.0
Minai et al, 2009[7]	83	RHC	mPAP >25	No	70	34	40	66	31	-	34.3±8.8
Sajkov et al, 1994[33]	27	echo	mPAP ≥20 or PASP ≥30	Yes	41	18	23	89	55	75	~30
Laaban et al, 1998[34]	25	echo	mPAP >20 PASP >35	Yes	36	-	-	91	38	77	49.7±9.4
Sajkov et al, 1999[35]	32	echo	mPAP ≥20	Yes	34	26	24	103	46	78	~31
Yamakawa et al, 2002[36]	37	echo	ND	Yes	22	-	-	-	48	-	~29
Arias et al, 2006[37]	23	echo	PASP >30	Yes	43	22	28	111	44	-	33.6±4.4

AHI = apnea-hypopnea index; BMI = body mass index; FEV1 = forced expiratory volume in 1 second; IBW = ideal body weight; mPAP = mean pulmonary arterial pressure; N = sample size; ND = not defined; OSA = obstructive sleep apnea; PaO_2 = partial pressure of oxygen in arterial blood; PASP = pulmonary arterial systolic pressure; PH = pulmonary hypertension; RDI = respiratory disturbance index; RHC = right heart catheterization.

* Refers to mean values of all patients with OSAHS in the study.
# Refers to mPAP in the group of patients with PH as defined in each study. PH is defined based on resting PAP.
^ FEV1/FVC ratio is used since FEV1 % was not available.
§ IBW is used if BMI is not available.

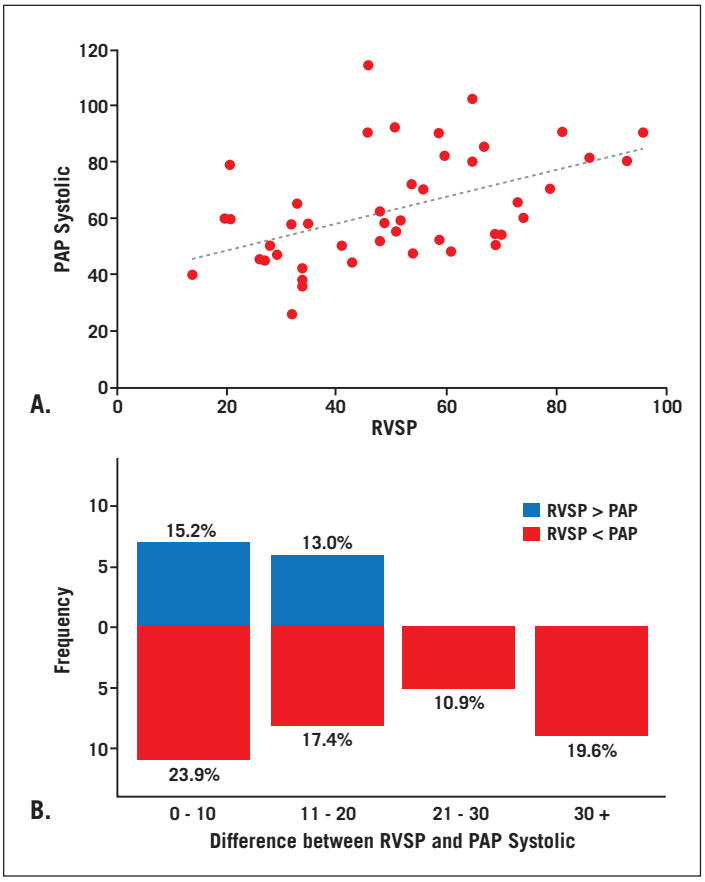

Figure 1: Correlation between pulmonary artery systolic pressure (PASP) measured by RHC and RVSP measured by transthoracic echocardiography *(A)* in a cohort of 83 patients with OSA. *(B)* Degree of agreement in individual patients showing inaccuracy of RVSP from TTE compared to PASP by RHC. Adapted from Minai et al[7] with permission.

tients (**Figure 1**).[7] Despite these limitations of DE in making a diagnosis of PH in this population,[5,7] several studies have used this methodology (**Table 1**). In addition, several comorbidities including left-sided cardiac disease, COPD, and obesity may have an impact on the occurrence of PH and were not always excluded.

The prevalence of PH determined by RHC or DE in patients with OSA, in studies excluding cardiopulmonary disease, ranges from 17% to 41% (**Table 1**). In the largest series published to date, 17% of a sample of 220 patients with OSA met diagnostic criteria for PH.[10,24] The true gender distribution of PH in OSA patients is unknown. Female preponderance has been described in several other forms of PH and has been attributed to genetic predisposition, the role of estrogen, and higher prevalence of autoimmune disease in females.[10] Two recent studies of PH in patients with OSA have reported a higher prevalence of PH among females than males.[7,24] The accuracy and significance of this finding, if any, requires larger studies in view of the predominantly male nature of the OSA population.

Coexistence of underlying chronic lung disease increases the risk of developing PH, and most studies showing a >50% prevalence of PH in patients with OSA have not excluded patients with chronic cardiopulmonary disease.[7,18,22,28] Studies have indicated that the presence of obstructive[8,28,40] or restrictive[7] ventilatory defects on spirometry indicate a group at higher risk. On the other hand, even studies of patients without significant cardiopulmonary disease have included patients with small airway abnormalities[35] or mild hypoxemia.[12,32] In a European population with lower body mass index (BMI) (32±6 kg/m^2),[30] a lower prevalence of PH was reported than an Australian population with a higher BMI (37 [range 24-54 kg/m^2]).[25] Other studies have reported no association between the prevalence or severity of PH and BMI in patients with OSA.[7,33]

Exercise-induced PH has also been described in patients with OSA.[18,24,41,42] In a cohort of 49 consecutive patients with OSA, Hetzel et al[41] found that 6 (12%) patients had resting PH (mPAP >20 mm Hg), whereas 39 (80%) patients had PH during exercise (mPAP >30 mm Hg). All patients had normal pulmonary vascular resistance, and the main contributors to PH were elevated BMI, total lung capacity, and elevated PCWP.

Right Ventricular Hypertrophy and Right Heart Failure in Obstructive Sleep Apnea

Early studies in patients with OSA reported on the occurrence of clinical cor pulmonale.[28,43] However, it is not clear that cor pulmonale equates to RV systolic failure in this population since RV diastolic dysfunction and solute and water retention may produce similar clinical findings. O'Hearn et al and Whyte et al[44,45] found lower extremity edema to be a highly specific indicator of right heart failure in OSA patients with a BMI >40 kg/m^2. Unlike patients with PAH who have chronic RV pressure overload and markedly elevated pulmonary vascular resistance, OSA patients may have chronic volume overload with milder elevation in pulmonary vascular resistance, suggesting that these patients may not have a large decrease in the cross-sectional area of the pulmonary vasculature.[44,46]

Cineradiographic observation in humans has demonstrated a progressive enlarging of the heart size throughout apnea.[47] Thus, RV hypertrophy and dilation could stem from the mechanical effect of long-term, recurrent upper airway obstruction.[48] The Framingham Heart Study found a small but significant increase in RV wall thickness using DE, suggestive of elevated PAP, in patients with severe OSA.[48] Thickness of the RV wall was independently and positively correlated with the severity of OSA. The prevalence of RV abnormalities has varied widely between 0% and 71% among studies (**Table 2**).[28,43,44,49-55] The validity and clinical significance of this observation remains poorly defined given the obvious limitations of DE in imaging the RV in morbidly obese patients with OSA.

Following the Framingham Heart Study, several studies reported decreased RV contractility and RV failure in patients with severe OSA.[56-58] Right ventricular dysfunction, however, appears to be less common compared to PH alone and is frequently associated with coexisting left heart or chronic lung diseases with daytime hypoxemia.[44,54,55] Echocardiographic studies in OSA patients without significant pulmonary comorbidities found elevated awake arterial partial pressure of carbon dioxide ($PaCO_2$), apnea-hypopnea index (AHI) >40,[55] and obesity to be important risk factors for reduced RV ejection fraction.[59] Mild abnormalities in RV function have been reported in the absence of daytime, resting PAH and may presumably occur as a consequence of the nocturnal hypoxia and attendant hemodynamic alterations. Current evidence, however, suggests that the occurrence of RV systolic failure in OSA requires the presence of additional comorbidities such as chronic lung disease or left ventricular dysfunction.[24,43,60]

Pathogenesis and Pathophysiology (Figure 2)

The role of apnea and hypoxia

Patients with OSA have normal gas exchange when awake and

Table 2. Prevalence of Right Ventricular Dysfunction and Right Ventricular Hypertrophy in Obstructive Sleep Apnea

Study	N	RVD defined by	Mean BMI kg/m^2 or % IBW*	Mean AHI or RDI/h*	Cardiopulmonary disease excluded	RVD or RVH prevalence (%)	Mean RVEF (%)
Hedner et al, 1990[49]	61	2DE (RVH)	-	-	Normal daytime ABGs	0	75
Hanly et al, 1992[50]	30	2DE (RVH)	32.8±7.2	-	Normal daytime ABGs, no AMI	0	-
Berman et al, 1991[51]	24	2DE (RVH)	-	27	No	71	-
Noda et al, 1995[53]	51	2DE (RVH)	46.7±19.4	51	Excluded HOCM, heart valve disease	12	-
#Davidson et al, 1995[52]	-	2DE (RVH)	-	-	-	-	-
Bradley et al, 1985[43]	50	clinical & ECG (cor pulmonale)	§186 ±12	57	No	12	-
Fletcher et al, 1987[28]	24	clinical (cor pulmonale) and/or radionuclide ventriculography <45% and/or RHC mPAP >20 mm Hg with PVR >100 dyne/s/cm^{-5}	§163±21	64	Yes	75	45±15
Sanner et al, 1997[54]	107	radionuclide ventriculography RVEF <45%	30±6	40 (all pt)	Yes	18	38±4
O'Hearn et al, 2009[44]	70	radionuclide ventriculography RVEF <40%	40±8	68	Yes	29	32.5±8
Nahmias et al, 1996[55]	112	radionuclide ventriculography RVEF <40%	§174±7	53	Yes	31	31±1

2DE = 2-dimensional echocardiogram; ABG = arterial blood gas; AHI = apnea-hypopnea index; AMI = acute myocardial infarction; BMI = body mass index; ECG = electrocardiogram; HOCM = hypertrophic obstructive cardiomyopathy; IBW = ideal body weight; mPAP = mean pulmonary arterial pressure; N = sample size; ND = not defined; OSA = obstructive sleep apnea; PVR = pulmonary vascular resistance; RDI = respiratory disturbance index; RHC = right heart catheterization; RVEF = right ventricular ejection fraction; RVD = right ventricular dysfunction; RVH = right ventricular hypertrophy.

* Refers to mean values of all patients with RVD and RVH in the study.
# Conclude that RV thickness is related to severity of AHI and PAP.
§ IBW is used if BMI is not available.

only become hypoxemic during sleep.[61] Animal experiments have shown that intermittent hypoxia (4-8 hours per day) is sufficient to induce a sustained rise in PAP and RV hypertrophy.[62-66] Coccagna and colleagues[20] have demonstrated occurrence of PAP elevation with sleep-related hypoxemia, and acute rise in PAP during obstructive events has been shown to correlate inversely with the degree of oxygen desaturation.[9,16,65] The mild increase in PAP during a respiratory event is due to an interplay of multiple factors including hypoxic pulmonary vasoconstriction, mechanically induced negative intrathoracic pressure from heightened inspiratory muscle response against an occluded airway, and direct effect on the vasculature from reflex mechanisms inducing variations in heart rate, cardiac output, and increased left-sided filling pressures. However, most studies have reported no association between severity of OSA (as measured by AHI) and the presence or severity of PH.[3,7,48,66-68]

It is well established that chronic daytime hypoxia can lead to PH and cor pulmonale.[69] Hypoxic pulmonary vasoconstriction improves ventilation-perfusion matching by shunting blood to better-ventilated lung zones and induces a rise in PAP.[70] The deleterious effects of episodic hypoxia on pulmonary hemodynamics have been extensively described;[62-64,71] however, the mechanisms by which chronic hypoxia leads to pulmonary vascular remodeling are complex and poorly understood. In addition to causing vasoconstriction and shear stress, chronic hypoxia exerts its effect on the vascular endothelium and smooth muscle cells (mainly the

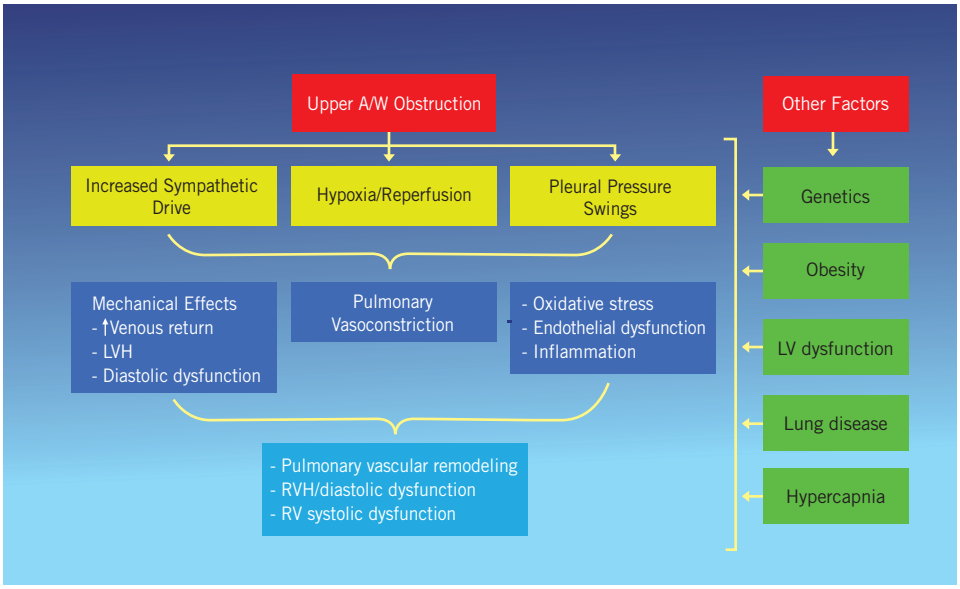

Figure 2: Pathophysiology of pulmonary hypertension in obstructive sleep apnea.

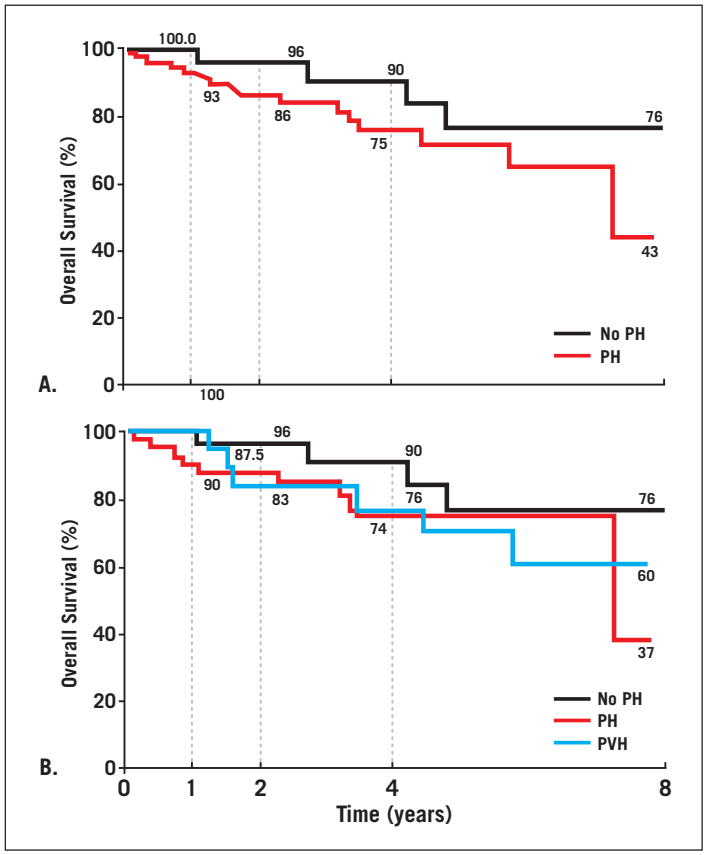

Figure 3: Kaplan-Meier survival estimates in 83 patients with OSA *(A)* with and without PH and *(B)* those without PH compared to those with PAH and PVH. Adapted from Minai et al[7] with permission.

small muscular pulmonary arteries and nonmuscular precapillary arterioles) to release vasoconstrictive, pro-proliferative, and mitogenic mediators. Several mediators including endothelin-1, vascular endothelial growth factor, angiotensin II, nitric oxide, endothelial apoptotic factors, angiotensin converting enzyme, inflammatory mediators (IL-8, IL-6), reactive oxygen species, and various transcription factors such as hypoxia-inducible factor-1 have been implicated in this process.[72] These events lead to angiogenesis, promote muscle and fibroblast proliferation, produce extension of smooth muscle into nonmuscularized vessels, and increase vascularity.[72] The pathologic features of hypoxic vasculopathy include concentric intimal thickening secondary to proliferation of endothelial cells, smooth muscle cells, and myofibroblasts, medial hypertrophy with longitudinally oriented smooth muscle bundles of the muscular pulmonary arteries, adventitial proliferation, and abnormal extracellular matrix deposition.[72-74] There is muscularization of the arterioles, with well-developed distinct elastic laminae and medial muscle layer extending to the smaller vessels. Extreme capillary proliferation may also be seen in some patients with severe OSA and RV hypertrophy.[72]

Controversy remains over whether intermittent hypoxia (such as that produced by apneic events during sleep) is adequate to produce pulmonary vascular remodeling resulting in awake, resting PH. Individual variation in ventilatory responsiveness to hypoxia demonstrated in awake OSA patients[75] could also modulate the magnitude of PAP changes,[17] although its role in PH remains controversial. So far it has not been convincingly demonstrated that a reduced chemosensitivity, possibly secondary to repetitive nighttime hypoxemic and hypercapnic episodes, can lead to daytime hypoxemia or PH.[30, 76] Although hypercapnia is known to potentiate the hypoxic response, evidence does not support it being a major factor for OSA-associated PAP changes. Whether the repetitive upper airway collapse and large intrathoracic negative pressure swings with nocturnal oxygen desaturation and hypercapnia leading to marked variation in PAP underlies the chronic PAP elevation in OSA requires further study.[18,20,21,23,27,77]

The hypothesis that isolated nocturnal hypoxemia may lead to permanent PH is supported by studies demonstrating PH in patients with normal daytime PaO_2[25] or very slight hypoxemia.[33] A decrease in PAP after 3-6 months of nighttime continuous positive airway pressure (CPAP) therapy without an associated improvement in spirometry or awake blood gases[32,37,78] further strengthens this hypothesis.

The role of comorbidities

Several studies have shown that OSA patients with PH often have concomitant cardiac or pulmonary disease, leading to the speculation that such comorbidities are a prerequisite for the development of significant PH and RV failure in OSA. It has been suggested that PH in association with OSA is mainly precapillary in nature;[8] however, given the prevalence of morbid obesity, hypertension, and left ventricular systolic and diastolic dysfunction in this population, it is likely that postcapillary factors[37,50,56,79-82] play an important role. Diastolic dysfunction and left ventricular hypertrophy with elevated PCWP have been demonstrated in OSA patients without any other evidence of underlying cardiac disease and may contribute to the diagnosis of PH during rest and exercise.[58,83-85] Diastolic dysfunction can produce elevated PCWP in severely obese OSA patients with normal left ventricular function.[41,44,54] Chaouat et al[24] demonstrated a rise in mPAP from 26.0±5.8 to 46.7±12 mm Hg during submaximal steady-state

Table 3: Effects of Pulmonary Arterial Pressure Therapy in Obstructive Sleep Apnea on Pulmonary Hemodynamics and Biochemical Markers

Study	Method of diagnosis of PH	Endpoint	Sample size	Mean AHI	Mean PaO_2 (mm Hg)	PAP therapy duration (months)	Mean PAP use, (h/day)	Treatment response
Hemodynamics								
Sfozar et al, 1990[59]	RHC	PH	54 (overall) 8 (PH)	91 -	70 -	12 -	5.3±1.8 -	mPAP 15±1 → 15±1 (NS) mPAP 23±1 → 21±1 (NS)
Chaouat et al, 1997[99]	RHC	PH	65 (overall) 11 (PH)	87 -	71 -	60 -	5.2 -	mPAP 16±5 → 17±5 (NS) mPAP 24±.5 → 20±5 (NS)
Archanatis et al, 2001[32]	echo	PH	29 (overall) 6 (PH) 23 (nonPH)	54 63 51	90 81 92	5.4 - -	 - -	mPAP 17.2±5.2 → 13.2±3.8 (P<0.001) mPAP 25.6±4.0 → 19.5±1.6 (P<0.001) mPAP 14.9±2.2 → 11.5±2.0 (P<0.001)
Sajkov et al, 2002[78]	echo	PH	20 (overall)	-	-	4	5.1±0.3	mPAP 16.8±1.2 → 13.9±0.6 (P<0.05) *ΔmPAP/∅SaO_2 10.0±1.6 à 6.3±0.8 (P<0.05)
Arias et al, 2006[37]	echo	-PH -Blood pressure -Urinary catecho-lamines	23 (overall) 10 (PH) 13 (nonPH)	44 69 25	- - -	3 - -	6.2±1.1 - -	PASP 28.9±8.6 → 24.0±5.8 (P<0.0001) No change in blood pressure or levels of urinary catecholamines
Other Markers								
Collop et al, 1996[98]	echo	Awake SaO_2	1	-	32	4	-	Awake SaO_2 62% → 95% on room air
Nahmias et al, 1996[55]	nuclear ventricu-lography	RVEF	7 (RVD subset)	53	67	6-24	-	RVEF 30±3 → 39.3±3 (P=0.01)
Kita el al, 1998[90]	-	Cardiac natriuretic peptides	14	61	77	1 night	-	Reduction in morning plasma natriuretic peptide levels (ANP and BNP) (P<0.001)
Schulz et al, 2000[91]	-	Plasma NOx lost to	13 (excluding follow-up patients)	37	-	2 nights	7.1±1.8	Increase in plasma NOx level (P<0.01) Level remain constant compared to level after 2 nights of use

AHI = apnea-hypopnea index; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; mPAP = mean pulmonary arterial pressure; NOx = derivatives of nitric oxide; ie, nitrate and nitrite; OSA = obstructive sleep apnea; PaO_2 = partial pressure of oxygen in arterial blood; PAP = positive airway pressure; PASP = pulmonary arterial systolic pressure; PH = pulmonary hypertension; RHC = right heart catheterization; RVD = right ventricular dysfunction (refers to systolic and diastolic flattening of the interventricular volume septum); RVEF = right ventricular ejection fraction; SaO_2 = arterial oxygen saturation.

*Refers to measure of pulmonary vascular response to hypoxia consistent with right ventricular pressure and overload on echo finding.

exercise, partly explained by an exercise-induced rise in PCWP. Two other studies have reported similar findings, suggesting that PVH due to diastolic dysfunction is an important factor in patients with OSA.[18,42] Whether exercise-induced PH identifies a subgroup of OSA patients at higher risk of developing resting PH requires further study.

Patients with both COPD and OSA (also known as "overlap syndrome") are at a higher risk of developing PH than patients with either condition alone. Chronic obstructive pulmonary disease is often the primary cause of alveolar hypoventilation in OSA.[8] Studies have clearly demonstrated that presence of airway obstruction predicts hypoxemia-hypercapnia and PH.[7,8,14,24,28,40,86,87] In these patients with PH, bronchial obstruction is usually mild-moderate, and the degree of blood gas disturbances may not be severe.[8]

The role of obesity

The likelihood of PH in morbid obesity is increased considerably when OSA is present.[34,44] Bady et al demonstrated that the severity of obesity and the associated changes in lung function play an important role in the pathogenesis of PH in patients with OSA.[12] Another study showed that greater age and increased BMI distinguished OSA patients with mild PH from those without PH.[32] However, other studies[7,25,33] have not found a significant difference in body weight in OSA patients with and without PH. Discrepancies in the findings among the series in the literature could be accounted for by the differences in the prevalence of severe obesity in each series and across continents where these studies were conducted.[8] Obesity hypoventilation syndrome, which is defined by a clinical triad of obesity, awake chronic hypercapnia, and OSA, is associated with a higher prevalence of PH and greater PAP levels.[88,89] Whether obesity confers an added risk for PH over and above that due to OSA and the associated comorbidities needs to be better defined.

Role of humoral factors

The effect of humoral factors on awake PAP remains speculative. Increased natriuretic peptides and decreased nitric oxide have been found in OSA patients[90] and levels improved with CPAP treatment.[91] Both circulating humoral substances and genetic factors could influence individual responsiveness to hypoxia and therefore the levels of PAP reached after obstructive events causing similar degree of oxygen desaturations.[17]

Clearly we are in need of studies to better define the role of pulmonary vasoconstriction, vascular remodeling, and preclinical changes in pulmonary circulation and the impact of genetic factors on changes in pulmonary hemodynamics due to OSA.

Predictors of Pulmonary Hypertension in Obstructive Sleep Apnea

The presence of comorbidities such as COPD and left-sided cardiac disease increases the likelihood of PH in patients with OSA. Studies have shown that the development of PH is correlated with lower daytime baseline arterial oxygen tension (PaO_2) and longer duration of nocturnal hypoxemia (SaO_2 <90%), which are important surrogate markers of severity in OSA.[12,13,24,33] In a recent study, younger age, female gender, obesity, and increased duration of nocturnal desaturation were found to be associated with the presence of PH.[7] However, presumably because of the small sample size and the relatively low prevalence of PH in this population, no prediction models based on demographics and polysomnographic variables had been reported until recently.

Clinical Significance of Pulmonary Hypertension in Obstructive Sleep Apnea

Pulmonary hypertension can lead to functional decline and poor prognosis in several diseases, including connective tissue diseases, pulmonary fibrosis, and COPD.[92] Previous studies of PH in patients with OSA have not addressed this association, largely because of the small numbers of patients with PH and the short-term nature of these studies.[5] A recent report found that OSA patients with PH had lower functional capacity (as measured by 6-minute walk distance) and more dyspnea compared to OSA patients without PH.[7] This association did not reach statistical significance largely due to the small sample size. This study further showed that mortality was increased in patients with PH (**Figure 3**) and that in addition to factors such as age, forced expiratory volume in 1 second, diffusion capacity for carbon monoxide, and AHI, pulmonary hemodynamics were important correlates of increased mortality in patients with OSA.[7] The only other report to examine the hemodynamic predictors of mortality in OSA did not find resting mPAP to be a predictor of mortality on multivariate analysis.[93]

Management of Obstructive Sleep Apnea – Pulmonary Hypertension

The American College of Chest Physicians consensus panel has recommended that patients with PH should be evaluated for OSA but did not recommend routine screening for PH in patients with OSA.[5]

Given the likelihood of comorbidities, an important initial step should be to look for and manage comorbidities, including diastolic dysfunction and COPD. In addition, exertional and nocturnal hypoxia should be corrected with oxygen supplementation or CPAP therapy as appropriate. Oxygen supplementation has been shown to reduce PAP in patients with COPD and nocturnal hypoxemia.[94] In dog models of artificially-induced recurrent episodes of obstructive apnea, blunting of PAP elevation results from restoration of arterial oxygen saturation following O_2 supplementation.[95,96] Tracheostomy has also been shown to cause a dramatic reduction in PAP in OSA patients with sleep-related oxygen desaturation.[20,97]

Treatment of OSA with CPAP has been shown to lower systolic blood pressure, improve quality of life, and improve arterial oxygen saturation in patients without concomitant COPD. It is unclear whether the mild PH found among OSA patients without concomitant cardiopulmonary diseases requires treatment. In addition to relieving the upper airway obstruction and minimizing the intrathoracic pressure swings, long-term treatment with CPAP can produce significant improvement in daytime arterial oxygenation,[98] raising the expectation of improvement or stabilization of PH, similar to that seen in COPD patients receiving long-term oxygen supplementation.[94] Studies examining the effect of nasal CPAP treatment on PH in patients with OSA are sparse and have reported conflicting results (**Table 3**).[32,37,55,59,78,90,91,98,99] Prevention of high PAP peak through application of CPAP during sleep was first demonstrated by Marrone et al.[100] Studies by Sforza et al and Chaouat et al[59,99] did not demonstrate a change in PAP following nasal CPAP use for 1 and 5 years respectively. These studies were limited by the very small subset of patients with PH in the OSA group (N=8 and 4 respectively). Two small, uncontrolled studies addressed the positive impact of CPAP therapy on pulmonary hemodynamics in OSA patients with PH. Collop and coworkers[98] showed that treatment of OSA with nasal CPAP reverses PH in morbidly obese women without clinically significant lung disease. A prospective, uncontrolled, single-center case series by Sajkov et al[78] showed significant decrease in the daytime PAP and pulmonary vascular response to hypoxia after 4 months of nasal CPAP treatment in 5 of the 20 OSA patients with mild PH. These were followed by larger prospective, controlled trials. Alchanatis et al,[32] in a study of OSA patients (N=29) without other pulmonary or cardiac disease, reported a reduction in mPAP in both groups of OSA patients with (N=6) and without PH (N=23) after 6 months of CPAP treatment. Arias and colleagues[37] demonstrated a reduction in systolic PAP after CPAP therapy in 10 obese patients in the first placebo-controlled trial of OSA treatment in PH.

Based on the current limited data, we can conclude that CPAP

therapy has a modest role in improving pulmonary hemodynamics in OSA and is less likely to normalize the more severe elevations in PAP.[5] The role of additional vasomodulatory agents in this setting requires further study. It had been reported that the response of RV function to OSA treatment is better than that of PAP.[28,55,101] Right ventricular ejection fraction has been shown to improve significantly after long-term CPAP treatment in both pediatric and adult populations.[28,55,101]

Dramatic weight reduction brought about by surgical options may also play a role in improving pulmonary hemodynamics in OSA. Matilde et al[102] showed a significant improvement in pulmonary hemodynamics following a marked reduction in body weight and resolution of OSA following bariatric surgery. In their study, the PAP completely normalized in 4 out of 28 patients with mPAP ranging from 31 to 80 mm Hg. There was also a significant reduction in mean systolic PAP in the group of obese patients in whom OSA resolved post-surgery (mean systolic PAP 61±16 mm Hg before to 43±9 mm Hg after surgery).

Summary

Obstructive sleep apnea modestly increases the risk of PH and causes mild elevation of PAP as compared to PAH. Development of PH is likely multifactorial, involving both precapillary and postcapillary processes. Due to a lack of population-based studies, the true prevalence of PH is not known; however, it is clear that patients with comorbidities are at higher risk. In patients with milder elevations in PAP, CPAP therapy has the potential to improve pulmonary hemodynamics, although the role of adjunctive vasomodulatory therapy should be explored in those with more significant elevations. Longer-term studies of various treatment options with an emphasis on functional improvement, quality of life, and survival are required to properly assess their role.

References

1. Girgis RE, Mathai SC. Pulmonary hypertension associated with chronic respiratory disease. *Clin Chest Med*. 2007;28(1):219.
2. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009;54S(1 Suppl):43.
3. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med*. 2002;165(9):1217-1239.
4. McNicholas WT. Cardiovascular outcomes of CPAP therapy in obstructive sleep apnea syndrome. *Am J Physiol Regul Integr Comp Physiol*. 2007;293(4):R1666-R1670.
5. Atwood CW Jr, McCrory D, Garcia JG, Abman SH, Ahearn GS; American College of Chest Physicians. Pulmonary artery hypertension and sleep-disordered breathing: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 Suppl):72S-77S.
6. Sajkov D, McEvoy RD. Obstructive sleep apnea and pulmonary hypertension. *Prog Cardiovasc Dis*. 2009;51(5):363-370.
7. Minai OA, Ricaurte B, Kaw R, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am J Cardiol*. 2009;104(9):1300-1306.
8. Kessler R, Chaouat A, Weitzenblum E, et al. Pulmonary hypertension in the obstructive sleep apnoea syndrome: Prevalence, causes and therapeutic consequences. *Eur Respir J*. 1996;9(4):787-794.
9. Marrone O, Bonsignore MR, Romano S, Bonsignore G. Slow and fast changes in transmural pulmonary artery pressure in obstructive sleep apnoea. *Eur Respir J*. 1994;7(12):2192-2198.
10. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 Suppl):14S-34S.
11. Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2004;43(12 Suppl S):40S-47S.
12. Bady E, Achkar A, Pascal S, Orvoen-Frija E, Laaban JP. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. *Thorax*. 2000;55(11):934-939.
13. Sanner BM, Doberauer C, Konermann M, Sturm A, Zidek W. Pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Arch Intern Med*. 1997;157(21):2483-2487.
14. Chaouat A, Bugnet AS, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;172(2):189-194.
15. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. *N Engl J Med*. 1993;328(5):303-307.
16. Marrone O, Bellia V, Ferrara G, et al. Transmural pressure measurements. Importance in the assessment of pulmonary hypertension in obstructive sleep apneas. *Chest*. 1989;95(2):338-342.
17. Marrone O, Bonsignore MR. Pulmonary haemodynamics in obstructive sleep apnoea. *Sleep Med Rev*. 2002;6(3):175-193.
18. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Hemodynamics in sleep-induced apnea. Studies during wakefulness and sleep. *Ann Intern Med*. 1976;85(6):714-719.
19. Podszus T, Greenberg H, Scharf S. Influence of sleep state and sleep disordered breathing on cardiovascular function. In: Saunders NA, Sullivan CE, eds. *Sleep and Breathing*. 1st ed. New York: Marcel Decker; 1994:257.
20. Coccagna G, Mantovani M, Brignani F, Parchi C, Lugaresi E. Continuous recording of the pulmonary and systemic arterial pressure during sleep in syndromes of hypersomnia with periodic breathing. *Bull Physiopathol Respir (Nancy)*. 1972;8(5):1159-1172.
21. Lonsdorfer J, Meunier-Carus J, Lampert-Benignus E, et al. Hemodynamic and respiratory aspects of the pickwickian syndrome. *Bull Physiopathol Respir (Nancy)*. 1972;8(5):1181-1192.
22. Niijima M, Kimura H, Edo H, et al. Manifestation of pulmonary hypertension during REM sleep in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 1999;159(6):1766-1772.
23. Sforza E, Laks L, Grunstein RR, Krieger J, Sullivan CE. Time course of pulmonary artery pressure during sleep in sleep apnoea syndrome: role of recurrent apnoeas. *Eur Respir J*. 1998;11(2):440-446.
24. Chaouat A, Weitzenblum E, Krieger J, Oswald M, Kessler R. Pulmonary hemodynamics in the obstructive sleep apnea syndrome. Results in 220 consecutive patients. *Chest*. 1996;109(2):380-386.
25. Laks L, Lehrhaft B, Grunstein RR, Sullivan CE. Pulmonary hypertension in obstructive sleep apnoea. *Eur Respir J*. 1995;8(4):537-541.
26. Schroeder JS, Motta J, Guilleminault C. Haemodynamic studies in sleep apnea. In: Guilleminault C, Dement WC, eds. *Sleep Apnea Syndromes*. New York: Alan R. Liss; 1978:177.
27. Podszus T, Bauer W, Mayer J, Penzel T, Peter JH, von Wichert P. Sleep apnea and pulmonary hypertension. *Klin Wochenschr*. 1986;64(3):131-134.
28. Fletcher EC, Schaaf JW, Miller J, Fletcher JG. Long-term cardiopulmonary sequelae in patients with sleep apnea and chronic lung disease. *Am Rev Respir Dis*. 1987;135(3):525-533.
29. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am Rev Respir Dis*. 1988;138(2):345-349.
30. Krieger J, Sforza E, Apprill M, Lampert E, Weitzenblum E, Ratomaharo J. Pulmonary hypertension, hypoxemia, and hypercapnia in obstructive sleep apnea patients. *Chest*. 1989;96(4):729-737.
31. Apprill M, Weitzenblum E, Krieger J, Oswald M, Kurtz D. Frequency and mechanism of daytime pulmonary hypertension in patients with obstructive sleep apnoea syndrome. *Cor Vasa*. 1991;33(1):42-49.
32. Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S, Jordanoglou JB. Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics. *Respiration*. 2001;68(6):566-572.
33. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. *Am J Respir Crit Care Med*. 1994;149(2 Pt 1):416-422.
34. Laaban JP, Cassuto D, Orvoen-Frija E, et al. Cardiorespiratory consequences of sleep apnoea syndrome in patients with massive obesity. *Eur Respir J*. 1998;11(1):20-27.
35. Sajkov D, Wang T, Saunders NA, Bune AJ, Neill AM, Douglas Mcevoy R. Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. *Am J Respir Crit Care Med*. 1999;159(5 Pt 1):1518-1526.
36. Yamakawa H, Shiomi T, Sasanabe R, et al. Pulmonary hypertension in patients with severe obstructive sleep apnea. *Psychiatry Clin Neurosci*. 2002;56(3):311-312.
37. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous posi-

tive airway pressure: a randomized, controlled cross-over study. *Eur Heart J*. 2006;27(9):1106-1113.
38. Scharf SM, Iqbal M, Keller C, et al. Hemodynamic characterization of patients with severe emphysema. *Am J Respir Crit Care Med*. 2002;166(3):314-322.
39. Minai OA, Budev MM. Diagnostic strategies for suspected pulmonary arterial hypertension: a primer for the internist. *Cleve Clin J Med*. 2007;74(10):737-747.
40. Fletcher EC, Luckett RA, Miller T, Costarangos C, Kutka N, Fletcher JG. Pulmonary vascular hemodynamics in chronic lung disease patients with and without oxyhemoglobin desaturation during sleep. *Chest*. 1989;95(4):757-764.
41. Hetzel M, Kochs M, Marx N, et al. Pulmonary hemodynamics in obstructive sleep apnea: frequency and causes of pulmonary hypertension. *Lung*. 2003;181(3):157-166.
42. Hawrylkiewicz I, Cieslicki JK, Palasiewicz G, Koziej M, Mankowski M, Zielinski J. Pulmonary circulation at rest and during exercise in patients with obstructive sleep apnea before and after one year of treatment with CPAP. *Pneumonol Alergol Pol*. 1996;64(9-10):638-643.
43. Bradley TD, Rutherford R, Grossman RF, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. *Am Rev Respir Dis*. 1985;131(6):835-839.
44. O'Hearn DJ, Gold AR, Gold MS, Diggs P, Scharf SM. Lower extremity edema and pulmonary hypertension in morbidly obese patients with obstructive sleep apnea. *Sleep Breath*. 2009;13(1):25-34.
45. Whyte KF, Douglas NJ. Peripheral edema in the sleep apnea/hypopnea syndrome. *Sleep*. 1991;14(4):354-356.
46. Barratt-Boyes BG, Wood EH. Cardiac output and related measurements and pressure values in the right heart and associated vessels, together with an analysis of the hemo-dynamic response to the inhalation of high oxygen mixtures in healthy subjects. *J Lab Clin Med*. 1958;51(1):72-90.
47. Lugaresi E, Cirignotta F, Coccagna G, Montagna P. Clinical significance of snoring. In: Saunders NA, Sullivan CE, eds. *Sleep and Breathing*. New York: Basel: M. Dekker Inc.; 1984:283.
48. Guidry UC, Mendes LA, Evans JC, et al. Echocardiographic features of the right heart in sleep-disordered breathing: The Framingham heart study. *Am J Respir Crit Care Med*. 2001;164(6):933-938.
49. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens*. 1990;8(10):941-946.
50. Hanly P, Sasson Z, Zuberi N, Alderson M. Ventricular function in snorers and patients with obstructive sleep apnea. *Chest*. 1992;102(1):100-105.
51. Berman EJ, DiBenedetto RJ, Causey DE, et al. Right ventricular hypertrophy detected by echocardiography in patients with newly diagnosed obstructive sleep apnea. *Chest*. 1991;100(2):347-350.
52. Davidson WR. Ventricular hypertrophy in sleep apnoea. *J Sleep Res*. 1995;4(S1):176-181.
53. Noda A, Okada T, Yasuma F, Nakashima N, Yokota M. Cardiac hypertrophy in obstructive sleep apnea syndrome. *Chest*. 1995;107(6):1538-1544.
54. Sanner BM, Konermann M, Sturm A, Muller HJ, Zidek W. Right ventricular dysfunction in patients with obstructive sleep apnoea syndrome. *Eur Respir J*. 1997;10(9):2079-2083.
55. Nahmias J, Lao R, Karetzky M. Right ventricular dysfunction in obstructive sleep apnoea: reversal with nasal continuous positive airway pressure. *Eur Respir J*. 1996;9(5):945-951.
56. Otto ME, Belohlavek M, Romero-Corral A, et al. Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. *Am J Cardiol*. 2007;99(9):1298-1302.
57. Romero-Corral A, Somers VK, Pellikka PA, et al. Decreased right and left ventricular myocardial performance in obstructive sleep apnea. *Chest*. 2007;132(6):1863-1870.
58. Dursunoglu N, Dursunoglu D, Kilic M. Impact of obstructive sleep apnea on right ventricular global function: sleep apnea and myocardial performance index. *Respiration*. 2005;72(3):278-284.
59. Sforza E, Krieger J, Weitzenblum E, Apprill M, Lampert E, Ratamaharo J. Long-term effects of treatment with nasal continuous positive airway pressure on daytime lung function and pulmonary hemodynamics in patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1990;141(4 Pt 1):866-870.
60. Hawrylkiewicz I, Palasiewicz G, Plywaczewski R, Sliwinski P, Zielinski J. Comparison of pulmonary hemodynamics in patients with COPD and patients with overlap syndrome with similar severity of airway obstruction and gas exchange. *Pol Arch Med Wewn*. 1999;102(5):961-966.
61. Coccagna G, Pollini A, Provini F. Cardiovascular disorders and obstructive sleep apnea syndrome. *Clin Exp Hypertens*. 2006;28(3-4):217-224.
62. Kay JM, Suyama KL, Keane PM. Effect of intermittent normoxia on muscularization of pulmonary arterioles induced by chronic hypoxia in rats. *Am Rev Respir Dis*. 1981;123(4 Pt 1):454-458.
63. McGuire M, Bradford A. Chronic intermittent hypercapnic hypoxia increases pulmonary arterial pressure and haematocrit in rats. *Eur Respir J*. 2001;18(2):279-285.
64. Nattie EE, Bartlett D Jr, Johnson K. Pulmonary hypertension and right ventricular hypertrophy caused by intermittent hypoxia and hypercapnia in the rat. *Am Rev Respir Dis*. 1978;118(4):653-658.
65. Schafer H, Hasper E, Ewig S, et al. Pulmonary haemodynamics in obstructive sleep apnoea: time course and associated factors. *Eur Respir J*. 1998;12(3):679-684.
66. Morera J, Hoadley SD, Roland JM, et al. Estimation of the ratio of pulmonary to systemic pressures by pulsed-wave Doppler echocardiography for assessment of pulmonary arterial pressures. *Am J Cardiol*. 1989;63(12):862-866.
67. Catterall JR, Douglas NJ, Calverley PM, et al. Transient hypoxemia during sleep in chronic obstructive pulmonary disease is not a sleep apnea syndrome. *Am Rev Respir Dis*. 1983;128(1):24-29.
68. Veerman DP, Imholz BP, Wieling W, Wesseling KH, van Montfrans GA. Circadian profile of systemic hemodynamics. *Hypertension*. 1995;26(1):55-59.
69. Garcia J, Malik A. Pulmonary circulation and regulation of fluid balance. In: Saunders NA, ed. *Murray and Nadel's Textbook of Respiratory Medicine*. 4th ed. Philadelphia: Elsevier; 2005.
70. Voelkel NF. Mechanisms of hypoxic pulmonary vasoconstriction. *Am Rev Respir Dis*. 1986;133(6):1186-1195.
71. Widimsky J, Ostadal B, Urbanova D, Ressl J, Prochazka J, Pelouch V. Intermittent high altitude hypoxia. *Chest*. 1980;77(3):383-389.
72. Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. *Circ Res*. 2006;99(7):675-691.
73. Voelkel NF, Tuder RM. Hypoxia-induced pulmonary vascular remodeling: a model for what human disease? *J Clin Invest*. 2000;106(6):733-738.
74. Sartore S, Chiavegato A, Faggin E, et al. Contribution of adventitial fibroblasts to neointima formation and vascular remodeling: from innocent bystander to active participant. *Circ Res*. 2001;89(12):1111-1121.
75. Laks L, Lehrhaft B, Grunstein RR, Sullivan CE. Pulmonary artery pressure response to hypoxia in sleep apnea. *Am J Respir Crit Care Med*. 1997;155(1):193-198.
76. Block AJ. Respiratory disorders during sleep. Part I. *Heart Lung*. 1980;9(6):1011-1024.
77. Bonsignore MR, Marrone O, Insalaco G, Bonsignore G. The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms. *Eur Respir J*. 1994;7(4):786-805.
78. Sajkov D, Wang T, Saunders NA, Bune AJ, Mcevoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2002;165(2):152-158.
79. Robbins IM, Newman JH, Johnson RF, et al. Association of the metabolic syndrome with pulmonary venous hypertension. *Chest*. 2009;136(1):31-36.
80. Fung JW, Li TS, Choy DK, et al. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *Chest*. 2002;121(2):422-429.
81. Alchanatis M, Paradellis G, Pini H, Tourkohoriti G, Jordanoglou J. Left ventricular function in patients with obstructive sleep apnoea syndrome before and after treatment with nasal continuous positive airway pressure. *Respiration*. 2000;67(4):367-371.
82. Alchanatis M, Tourkohoriti G, Kosmas EN, et al. Evidence for left ventricular dysfunction in patients with obstructive sleep apnoea syndrome. *Eur Respir J*. 2002;20(5):1239-1245.
83. Cloward TV, Walker JM, Farney RJ, Anderson JL. Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. *Chest*. 2003;124(2):594-601.
84. Rochester DF, Enson Y. Current concepts in the pathogenesis of the obesity-hypoventilation syndrome. mechanical and circulatory factors. *Am J Med*. 1974;57(3):402-420.
85. Sukhija R, Aronow WS, Sandhu R, et al. Prevalence of left ventricular hypertrophy in persons with and without obstructive sleep apnea. *Cardiol Rev*. 2006;14(4):170-172.
86. Bradley TD, Rutherford R, Lue F, et al. Role of diffuse airway obstruction in the hypercapnia of obstructive sleep apnea. *Am Rev Respir Dis*. 1986;134(5):920-924.
87. Chaouat A, Weitzenblum E, Krieger J, Ifoundza T, Oswald M, Kessler R. Association of chronic obstructive pulmonary disease and sleep apnea syn-

drome. *Am J Respir Crit Care Med*. 1995;151(1):82-86.
88. Sugerman HJ, Baron PL, Fairman RP, Evans CR, Vetrovec GW. Hemodynamic dysfunction in obesity hypoventilation syndrome and the effects of treatment with surgically induced weight loss. *Ann Surg*. 1988;207(5):604-613.
89. Kessler R, Chaouat A, Schinkewitch P, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest*. 2001; 120(2):369-376.
90. Kita H, Ohi M, Chin K, et al. The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnoea and its response to therapy with nasal continuous positive airway pressure. *J Sleep Res*. 1998;7(3):199-207.
91. Schulz R, Schmidt D, Blum A, et al. Decreased plasma levels of nitric oxide derivatives in obstructive sleep apnoea: response to CPAP therapy. *Thorax*. 2000;55(12):1046-1051.
92. Ruiz-Cano MJ, Escribano P, Alonso R, et al. Comparison of baseline characteristics and survival between patients with idiopathic and connective tissue disease-related pulmonary arterial hypertension. *J Heart Lung Transplant*. 2009;28(6):621-627.
93. Chaouat A, Weitzenblum E, Krieger J, et al. Prognostic value of lung function and pulmonary haemodynamics in OSA patients treated with CPAP. *Eur Respir J*. 1999;13(5):1091-1096.
94. Fletcher EC, Levin DC. Cardiopulmonary hemodynamics during sleep in subjects with chronic obstructive pulmonary disease. The effect of short- and long-term oxygen. *Chest*. 1984;85(1):6-14.
95. Iwase N, Kikuchi Y, Hida W, et al. Effects of repetitive airway obstruction on O_2 saturation and systemic and pulmonary arterial pressure in anesthetized dogs. *Am Rev Respir Dis*. 1992;146(6):1402-1410.
96. Schneider H, Schaub CD, Chen CA, et al. Neural and local effects of hypoxia on cardiovascular responses to obstructive apnea. *J Appl Physiol*. 2000; 88(3):1093-1102.
97. Motta J, Guilleminault C, Schroeder JS, Dement WC. Tracheostomy and hemodynamic changes in sleep-inducing apnea. *Ann Intern Med*. 1978; 89(4):454-458.
98. Collop NA. Refractory hypoxemia in a morbidly obese 28-year-old woman. *Chest*. 1996;109(4):1101-1102.
99. Chaouat A, Weitzenblum E, Kessler R, et al. Five-year effects of nasal continuous positive airway pressure in obstructive sleep apnoea syndrome. *Eur Respir J*. 1997;10(11):2578-2582.
100. Marrone O, Milone F, Ferrara G, Romano L, Bellia V. Transmural pulmonary artery pressure during CPAP in obstructive sleep apnoea syndrome. *Eur Respir J Suppl*. 1990;11:544s-545s.
101. Tal A, Leiberman A, Margulis G, Sofer S. Ventricular dysfunction in children with obstructive sleep apnea: radionuclide assessment. *Pediatr Pulmonol*. 1988;4(3):139-143.
102. Valencia-Flores M, Orea A, Herrera M, et al. Effect of bariatric surgery on obstructive sleep apnea and hypopnea syndrome, electrocardiogram, and pulmonary arterial pressure. *Obes Surg*. 2004;14(6):755-762. ■