

# Pulmonary Hypertension and Obstructive Sleep Apnea

## Not so Strange Bedfellows

Vahid Mohsenin, M.D., FCCP, FAASM  
Professor of Medicine  
Section of Pulmonary, Critical Care and & Sleep Medicine  
Yale University School of Medicine  
New Haven, Connecticut, USA



**Thailand**  
Bangkok | 10-12 April

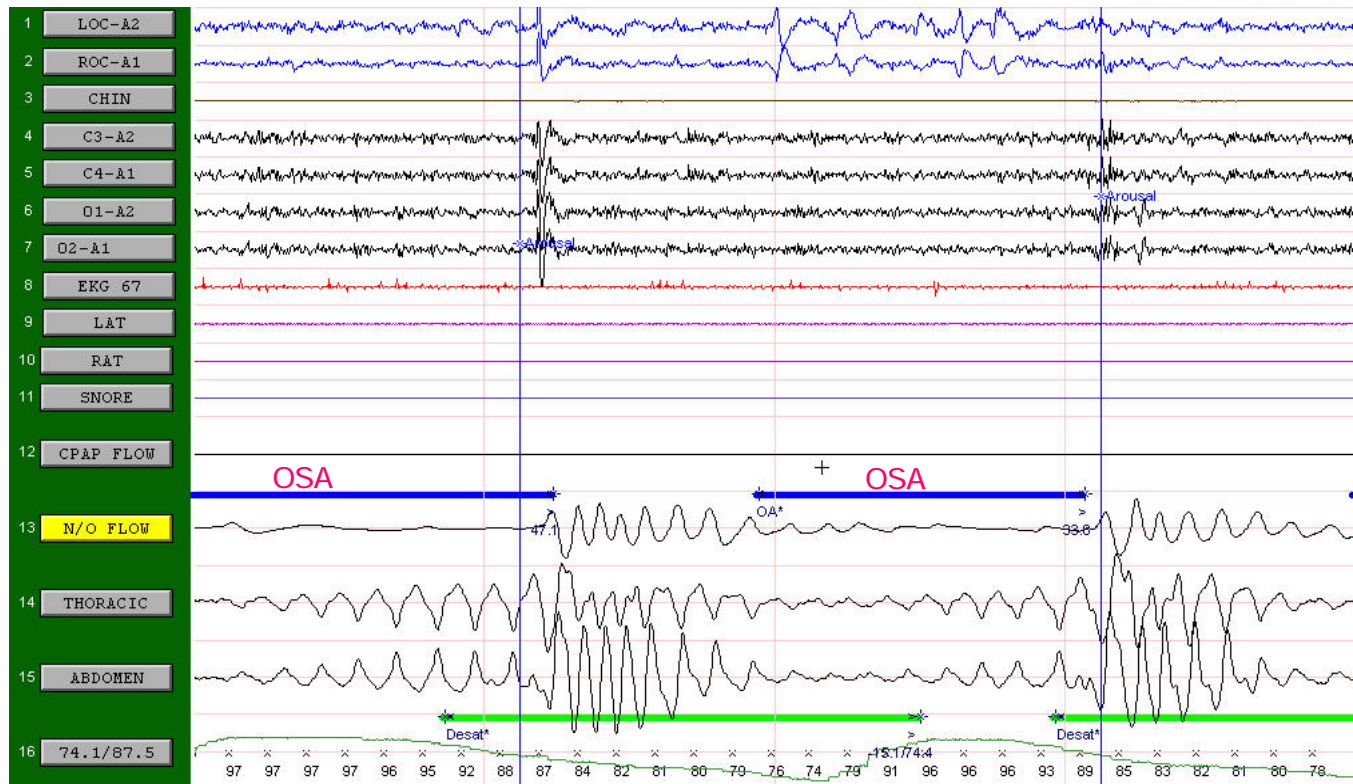


## Disclosures

None to declare



# Recurrent upper airway obstruction during sleep

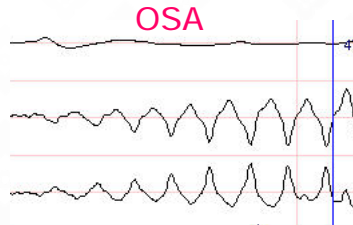


60-second epoch

# Obstructive sleep apnea is associated with:

1. Large swings in intra-thoracic pressure that affect both right and left ventricular functions
2. Alveolar hypoxia causing pulmonary vasoconstriction and increasing RV afterload
2. Sleep apnea is terminated by cortical and subcortical arousals affecting cardiorespiratory function

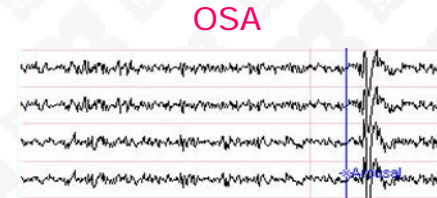
Intra-thoracic pressure swings



Hypoxia with pulmonary vasoconstriction

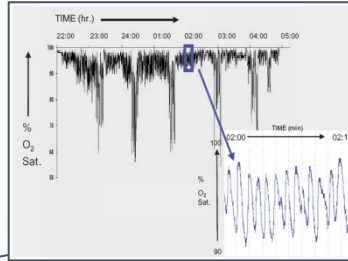


Repeated arousals



# Pathways for Oxidative Stress and Endothelial Dysfunction in OSA

## OSA –Hypoxemia-Reoxygenation



Free radicals

Altered gene expression

↑ Inflammatory products

↑ Adhesion molecules

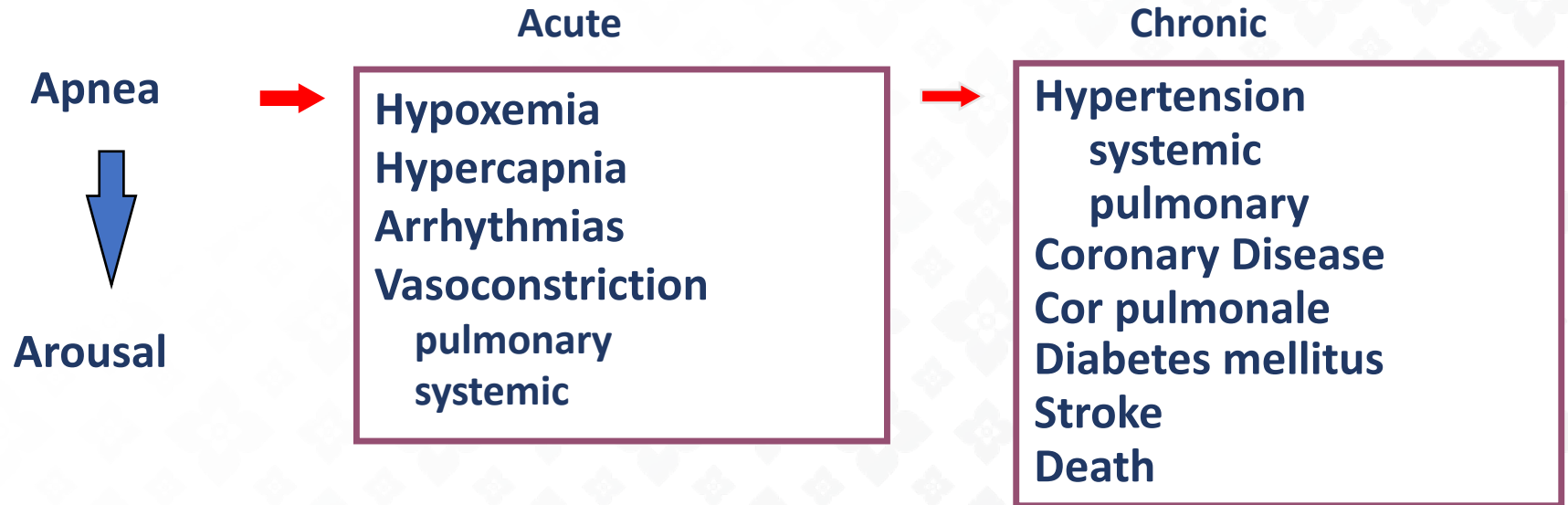
↑ Antiangiogenic proteins

↑ Hemeoxygenase-1

Endothelial Dysfunction

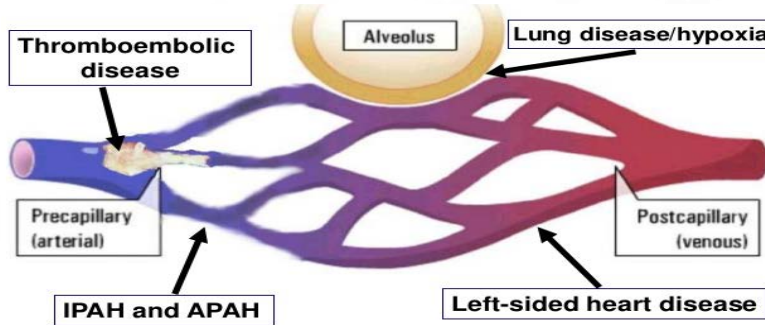
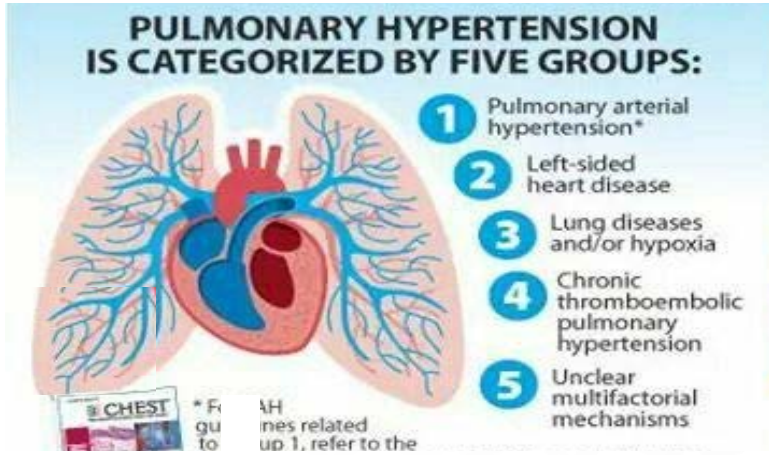
Vascular Complications

# Acute and Chronic Consequences of Sleep Apnea

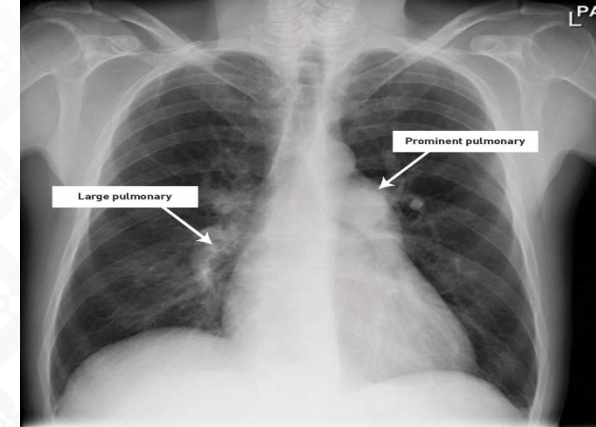




# Types and Symptoms of Pulmonary Hypertension



- Fatigue
- Dizziness or fainting
- Decreased exercise tolerance
- Palpitation
- Chest pain
- Ankle swellings





# Predictive Accuracy of Echocardiography in PH

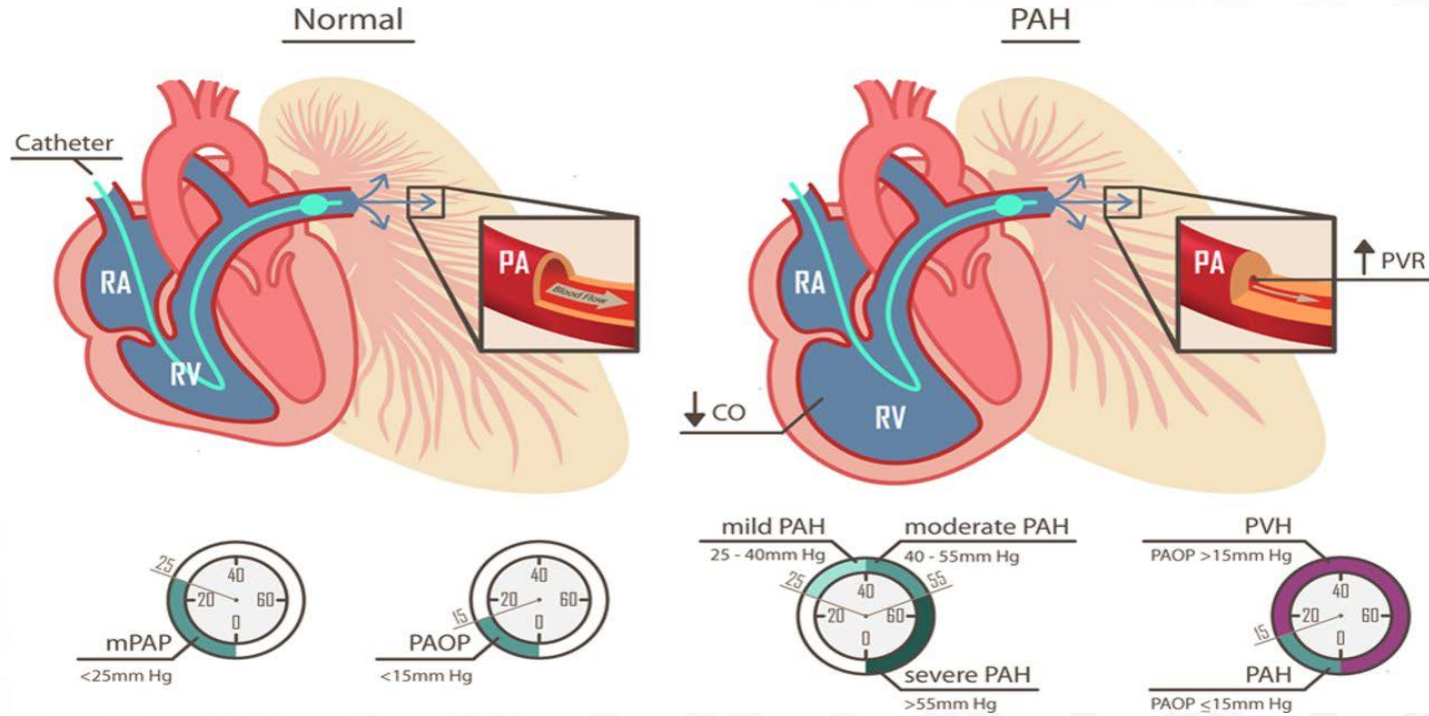
137 patients with systemic sclerosis were prospectively studied as part of a screening program.

All had Doppler echocardiography (tricuspid gradient, TG, for estimating right ventricular systolic pressure, RVSP) performed within 3 months of a right cardiac catheterization.

Echo TG thresholds in mmHg	Sensitivity %	Specificity %	PPV %	NPV %
<30 vs ≥30	88	42	73	57
<35 vs ≥35	75	66	85	50
<40 vs ≥40	58	87	92	44
<b>&lt;45 vs ≥45</b>	<b>47</b>	<b>97</b>	<b>98</b>	<b>41</b>

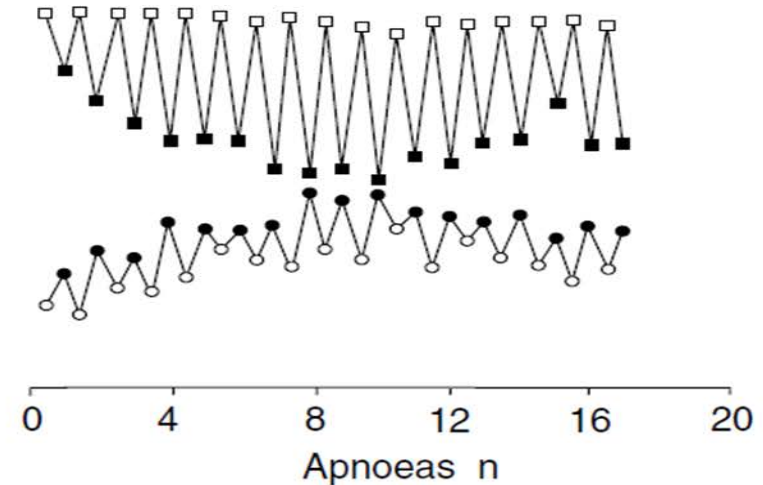
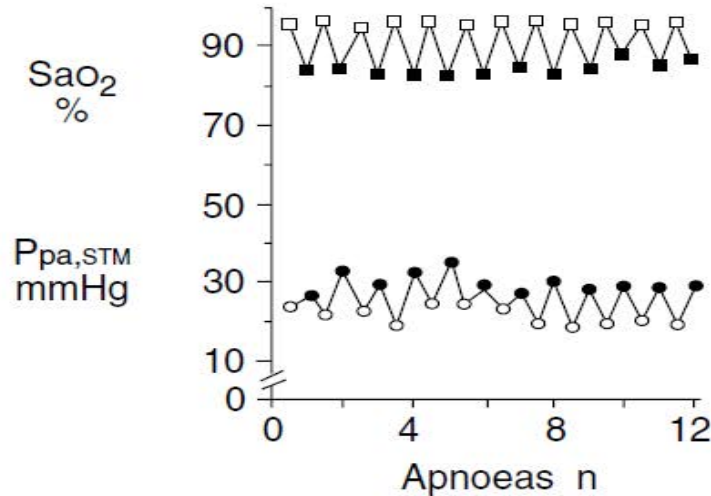
# Diagnosis of Pulmonary Hypertension by Right Heart Catheterization

## The only way



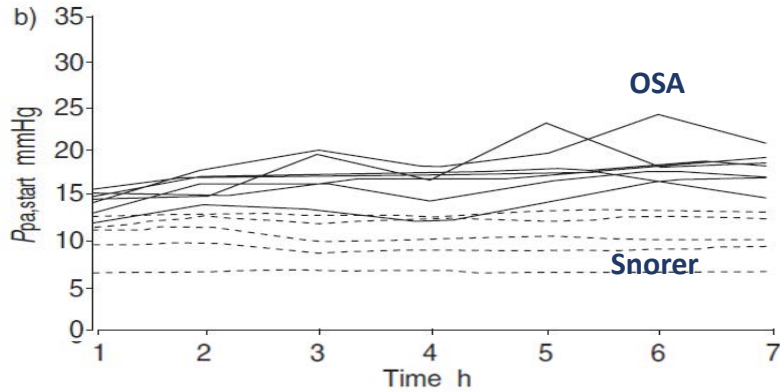
Mean Pulmonary Artery Pressure >20 mm Hg at rest (6<sup>th</sup> World Symposium on PH- 2018)

## Consecutive values of SaO<sub>2</sub> and simultaneous values of trans pulmonary artery systolic pressure (P<sub>pa,STM</sub>) in the sequences of apneic cycles

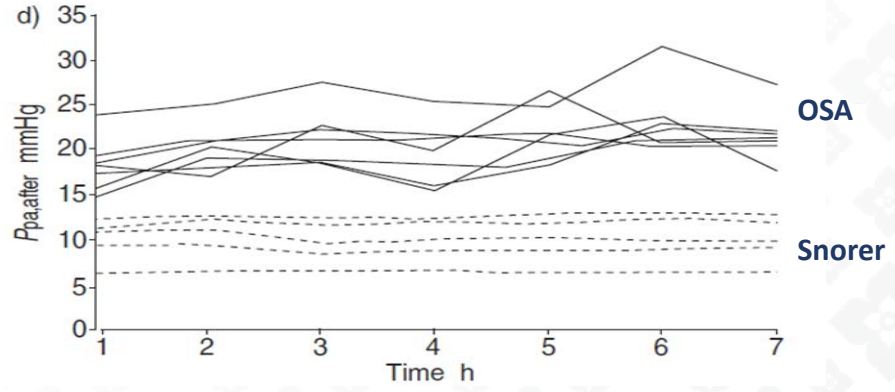


- Increasing pulmonary artery pressure during obstructive apnea with highest level after apnea
- Pulmonary artery occlusion pressure increases progressively during apnea (not shown)

# Mean pulmonary artery pressure (Ppa) at the start of obstructive sleep and after apnea in snorers and OSA



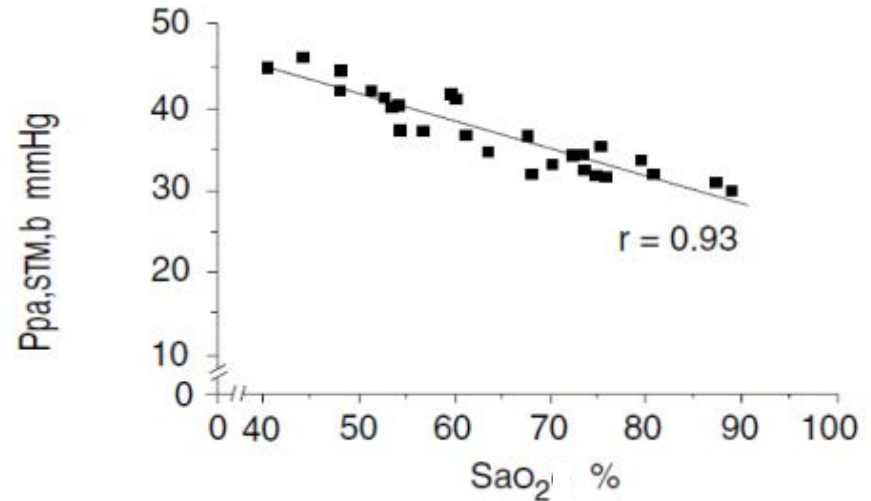
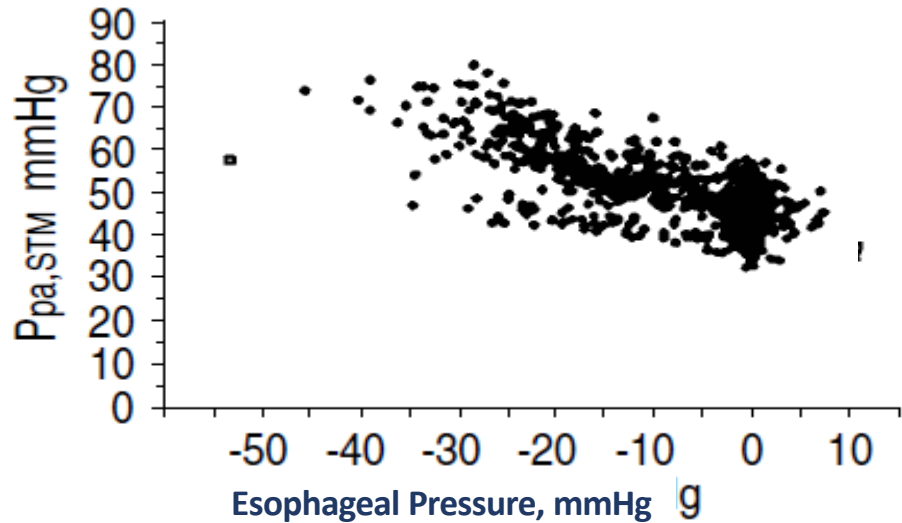
Ppa before each apnea during the night



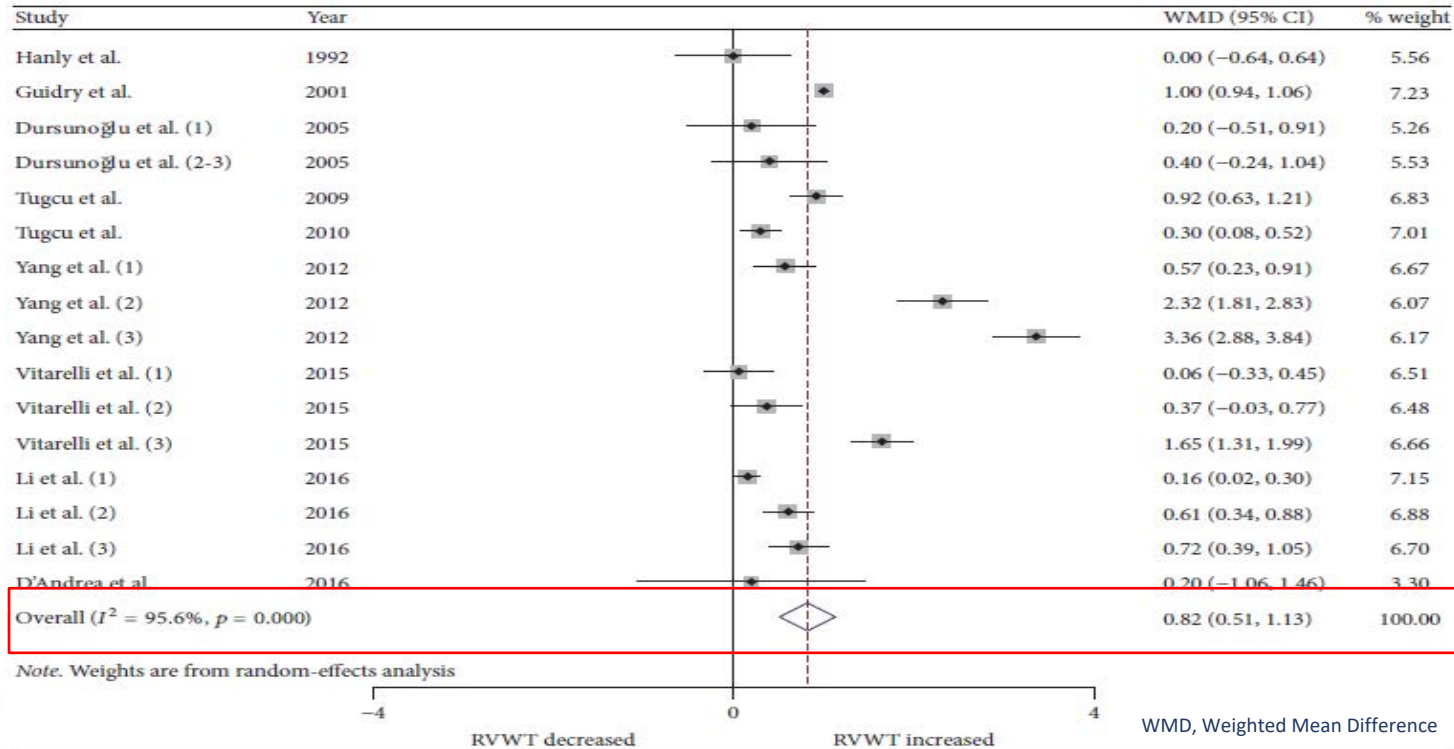
Ppa after each apnea during the night

Compared to snorers, OSA patients showed a small but significant increase in Ppa from the first to the last hour of the night.

The more the negative intrathoracic pressure and oxygen desaturation during obstructive apneas the higher the pulmonary artery systolic pressure

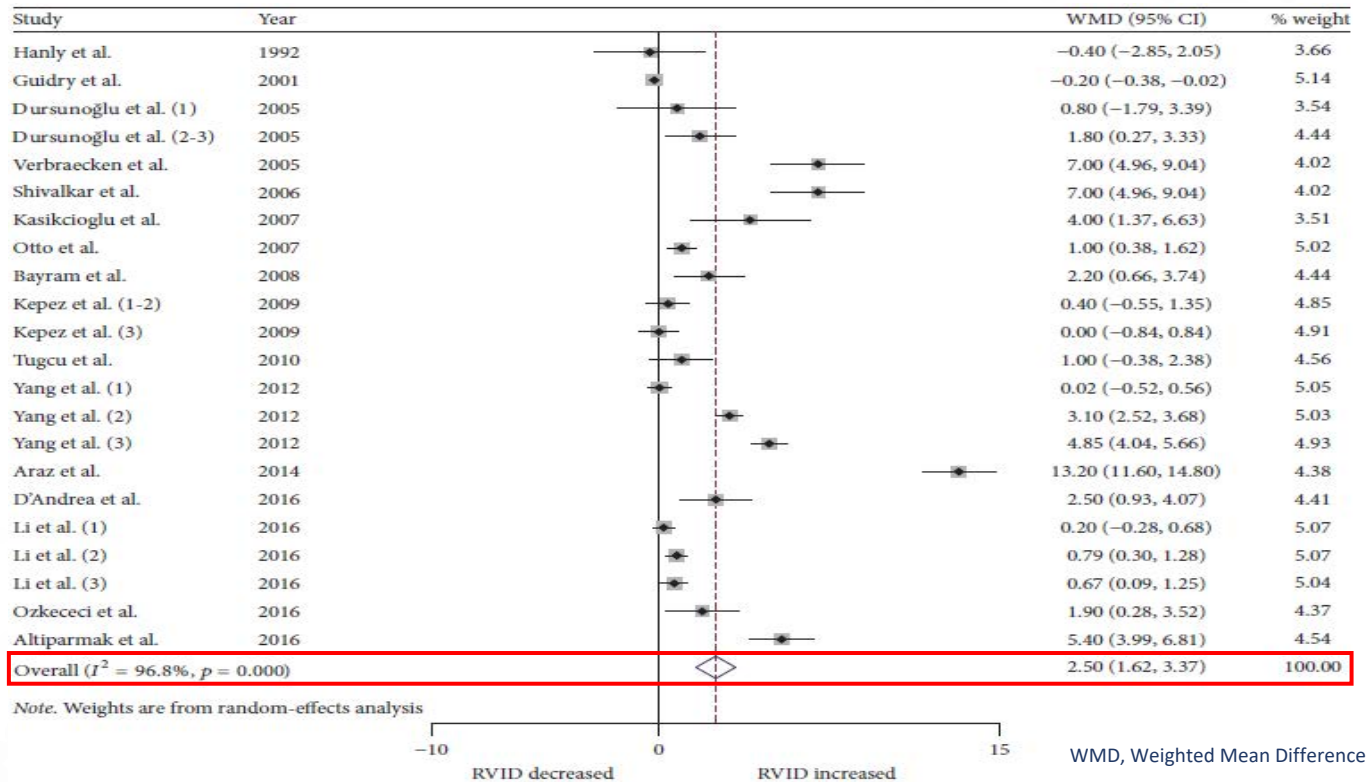


# Increased right ventricular free wall thickness in OSA patients aka: RV hypertrophy



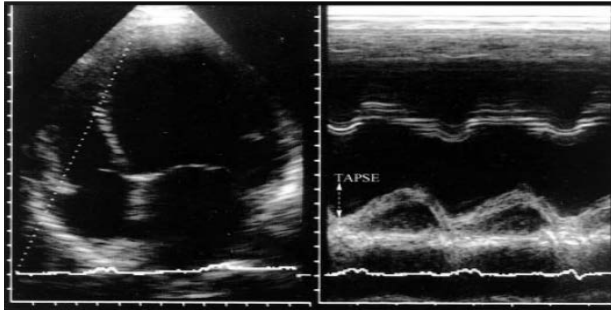


# Increased right ventricular internal diameter at diastole in OSA patients aka: RV enlargement



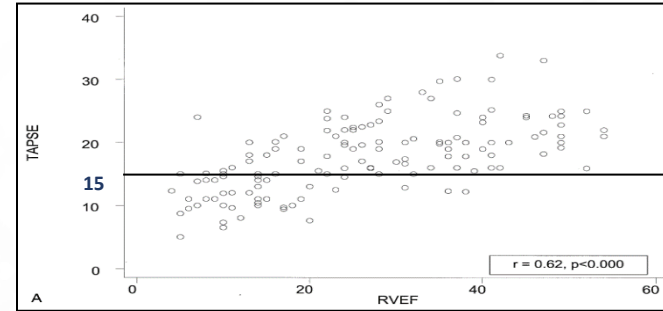


# Decreased TAPSE (decreased RVEF) is associated with increased mortality rate in idiopathic pulmonary arterial hypertension



Left panel: apical 4-chamber view with the M-mode cursor positioned at the lateral portion of the tricuspid annulus.

Right panel: M-mode recording of the TAPSE from the same approach.



Prospective study of 59 patients with PAH followed for 52 months.  
Mean pulmonary artery pressure (mmHg)  $54.5 \pm \text{SD } 14.7$   
Mean capillary artery wedge pressure (mmHg)  $9.8 \pm \text{SD } 4.9$

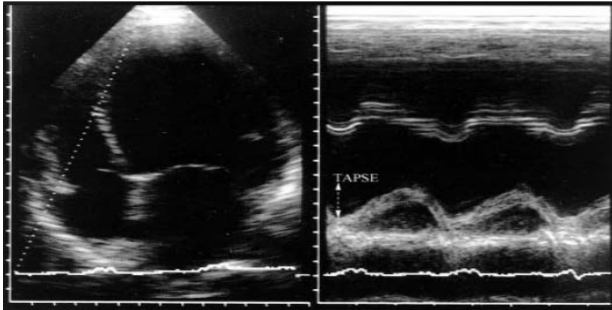
**Mortality rate for 100-person-year**  
TAPSE as an Indicator of RV Function

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>15 mm  
**6.5**  
(95%CI 3.1-13.7)

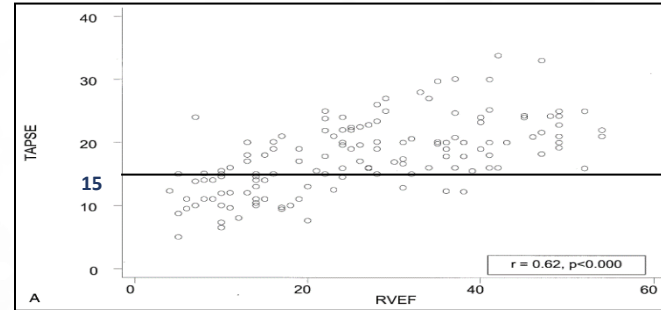
≤15 mm  
**20.8**  
(95%CI 16.8-30.4)

# Decreased TAPSE (decreased RVEF) is associated with increased mortality rate in idiopathic pulmonary arterial hypertension



Left panel: apical 4-chamber view with the M-mode cursor positioned at the lateral portion of the tricuspid annulus.

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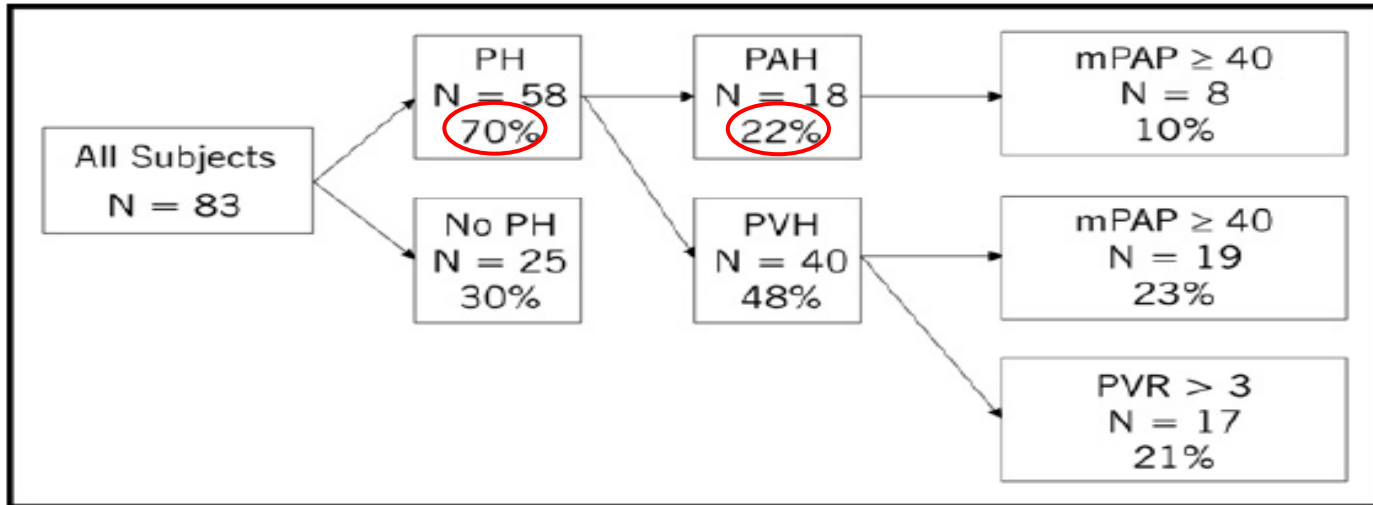
**Mortality rate for 100-person-year**

TAPSE as an Indicator of RV Function

>15 mm	≤15 mm
<b>6.5</b>	<b>20.8</b>
(95%CI 3.1-13.7)	(95%CI 16.8-30.4)



# Prevalence of Pulmonary Hypertension in OSA



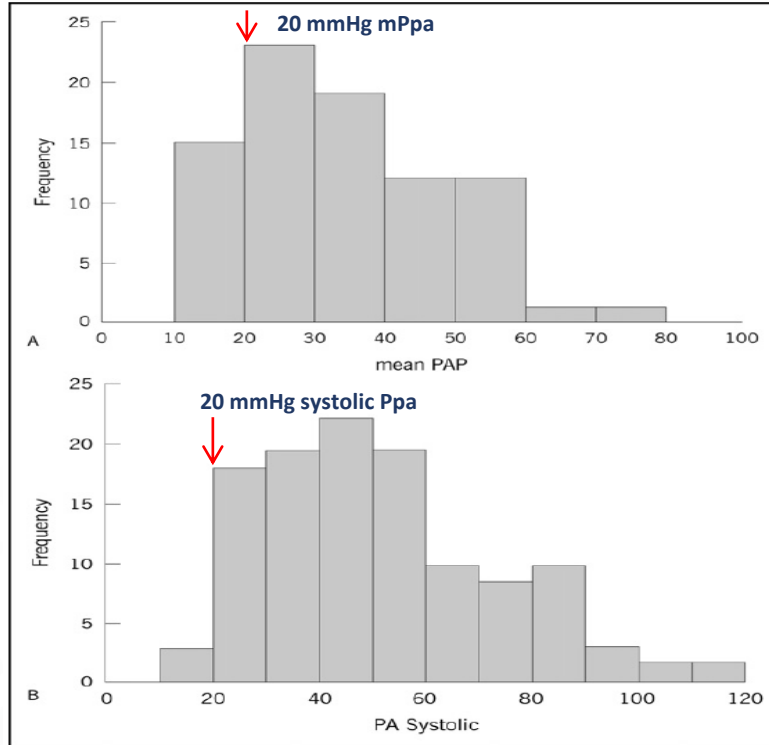
All consecutive subjects with a recent diagnosis of OSA (AHI>5/hr) underwent RHC were included in the present study.

PH was defined as a mean pulmonary arterial pressure of >25 mmHg at rest

Prevalence of pulmonary hypertension (PH) was 70% and pulmonary arterial hypertension (PAH) was 22%



# Frequency distribution of mean pulmonary artery pressure (PAP) and systolic PAP (mmHg) in a cohort of 83 patients with OSA undergoing right-sided heart catheterization.



# Prevalence of Pulmonary Hypertension in OSA

Characteristic	All (n = 83)	Pulmonary Hypertension		p Value*
		No (n = 25)	Yes (n = 58)	
Age (years)	56.7 ± 13	58.4 ± 13.6	55.9 ± 13	0.38
Gender				0.01
Men	48 (57.8%)	20 (42)	28 (58)	
Women	35 (42.2%)	5 (14)	30 (86)	
Body mass index (kg/m <sup>2</sup> )	34.3 ± 8.8	31.2 ± 6.9	35.6 ± 9.3	0.026
Hemoglobin (g/dl)	12.3 ± 1.9	12.3 ± 2.1	12.3 ± 1.9	0.76
Apnea-hypopnea index (events/hour of sleep)	30.8 ± 22.8	34.6 ± 27.8	29.1 ± 21.9	0.52
OSA severity by apnea-hypopnea index				0.42
Mild	39 (47%)	11 (28)	28 (72)	
Moderate	28 (34%)	7 (25)	21 (75)	
Severe	16 (19%)	7 (44)	9 (56)	
Nocturnal oxygen desaturation				0.13
<10% of total sleep time	48 (64%)	17 (35)	31 (65)	
≥10% of total sleep time	27 (36%)	5 (18)	22 (82)	
Not reported	8 (10%)	3 (37.5)	5 (62.5)	
Duration of nocturnal desaturation (% total sleep time)	16.7 ± 25.4	7.4 ± 12.1	20.5 ± 28.5	0.018
Mean pulmonary arterial pressure (mm Hg)	33.8 ± 13.6	18.7 ± 3.5	40.3 ± 11	<0.001
Cardiac index (Fick) (L/min/m <sup>2</sup> )	2.4 ± 1.1	2.65 ± 1.6	2.3 ± 0.9	0.16
Cardiac index <2	26 (35%)	4 (16%)	22 (38%)	0.09
Pulmonary vascular capacitance (ml/mm Hg)	3.0 ± 2.3	4.8 ± 2.9	2.2 ± 1.3	<0.001
Forced vital capacity(% predicted) (n = 51)	68.6 ± 16	75 ± 16	66.8 ± 16	0.042
Forced expiratory volume in 1 s (% predicted) (n = 51)	65.9 ± 17	70 ± 17	64.8 ± 16	0.31
Six-minute walk test (m) (n = 25)	295 ± 136	343 ± 213	285 ± 122	0.5

\* p Value for comparison of patients with and without PH.

Obese females with longer nocturnal oxygen desaturations had higher prevalence of PH

## The combination of female gender, age <49 and RVSP $\geq 30$ mmHg on cardiac echo had high positive predictive value for pulmonary hypertension in obstructive sleep apnea

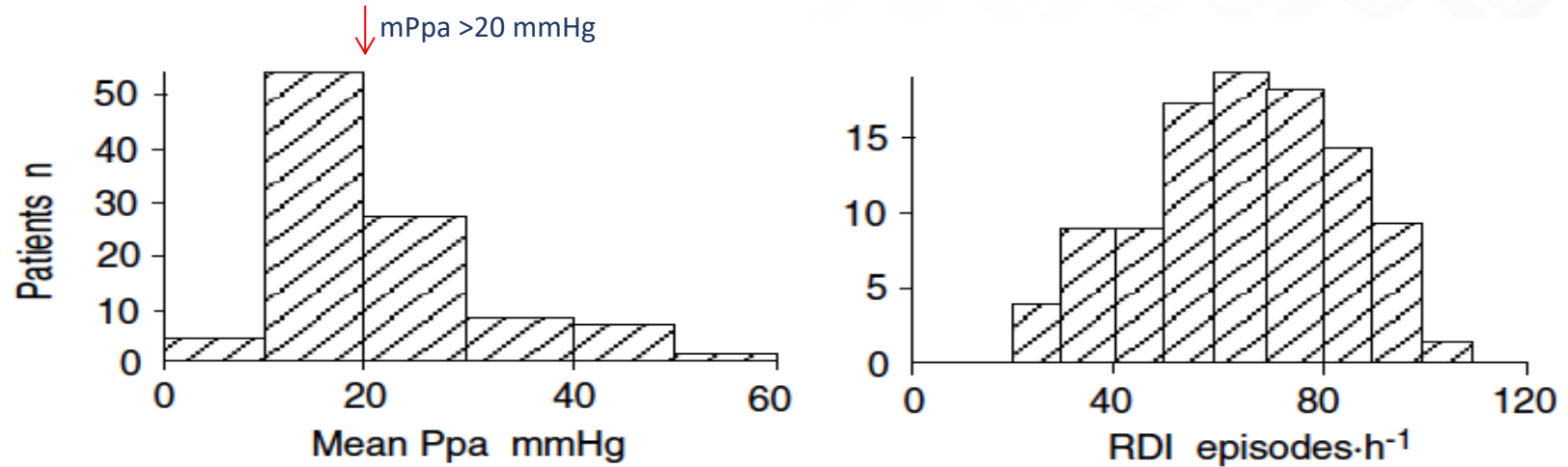
Result of multivariate logistic regression model for pulmonary hypertension

Variable	Parameter Estimate	Standard Error	p Value	Odds Ratio (95% CI)	Scoring System Points
Intercept	0.878	1.072			
Women	1.583	0.730	0.030	4.87 (1.16–20.3)	1
Age <49 years	1.679	0.764	0.028	5.36 (1.20–24.0)	1
Body mass index $\geq 26$ kg/m <sup>2</sup>	1.458	0.848	0.086	4.30 (0.82–22.6)	1
RVSP $\geq 30$ mm Hg	4.152	1.136	<0.001	63.6 (6.87–589)	3

Score	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
$\geq 2$	91.4%	72%	88.3%	78.3%
$\geq 3$	72.4%	96%	97.7%	60%

# Prevalence of Pulmonary Hypertension in OSA

Consecutive patients referred to a sleep disorders center who were found to have RDI of >20/hr, were considered for pulmonary artery catheterization. N=100



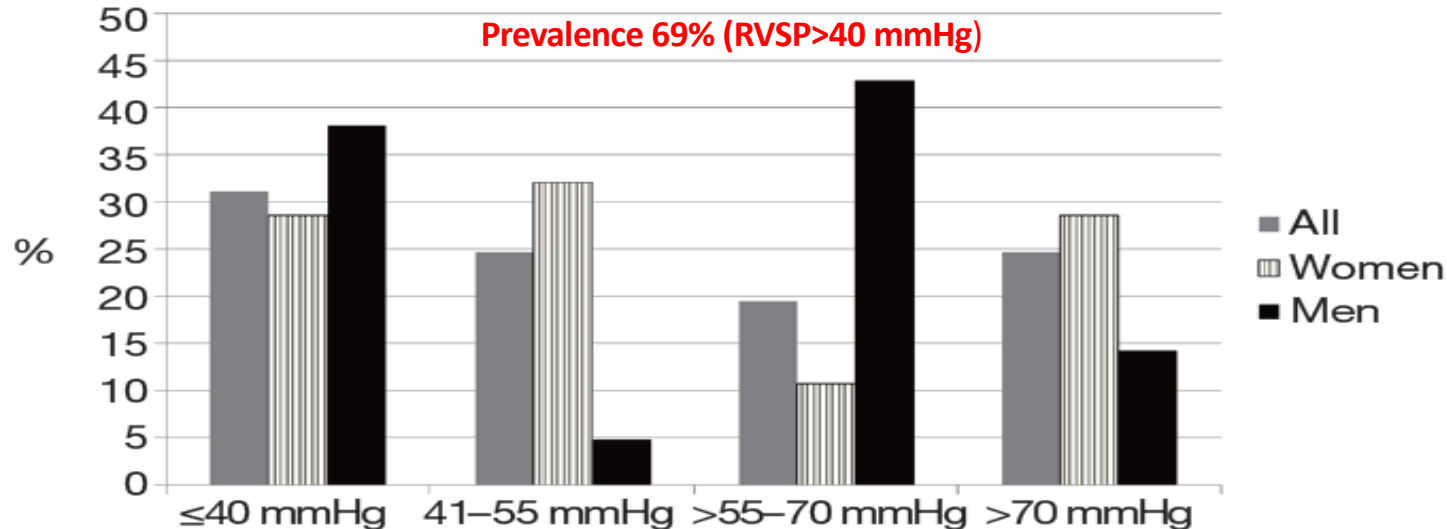
- **Forty-two percent (42%) had Ppa greater than 20 mmHg.**
- More than 70% of patients with a FEV1 /FVC <70% had a pulmonary artery pressure level in 20–40 mmHg range.
- Daytime hypoxemia was not a prerequisite for the presence of sustained pulmonary hypertension.

# Obesity Hypoventilation Syndrome

- Definition:  
The combination of obesity (BMI >30 kg/m<sup>2</sup>) and hypoventilation (awake PaCO<sub>2</sub> >45 mmHg), after the exclusion of other disorders associated with hypoventilation.
- The majority of patients also have associated OSA (up to 90%).
- In two different studies, the prevalence of PH was 58% and 88% (mPAP >20 mmHg).
- The prevalence of severe PH (mPAP >40 mmHg) was 31%.

# Prevalence of PH in Obesity Hypoventilation Syndrome

Prospective study. Echocardiography for assessment of RVSP.



PaCO<sub>2</sub> 55.7±9.2 (mmHg); BMI 43.2±0.4 (kg/m<sup>2</sup>); AHI 66±45 (events/hr)

OHS definition: awake hypercapnia (PaCO<sub>2</sub> >45 mmHg), based on arterial PaCO<sub>2</sub>; obesity (BMI >30 kg/m<sup>2</sup>); and hypoventilation (not primarily due to a chronic lung disease, a chest wall deformity, medication use, a neuromuscular disorder, or a known congenital or idiopathic central alveolar hypoventilation syndrome).

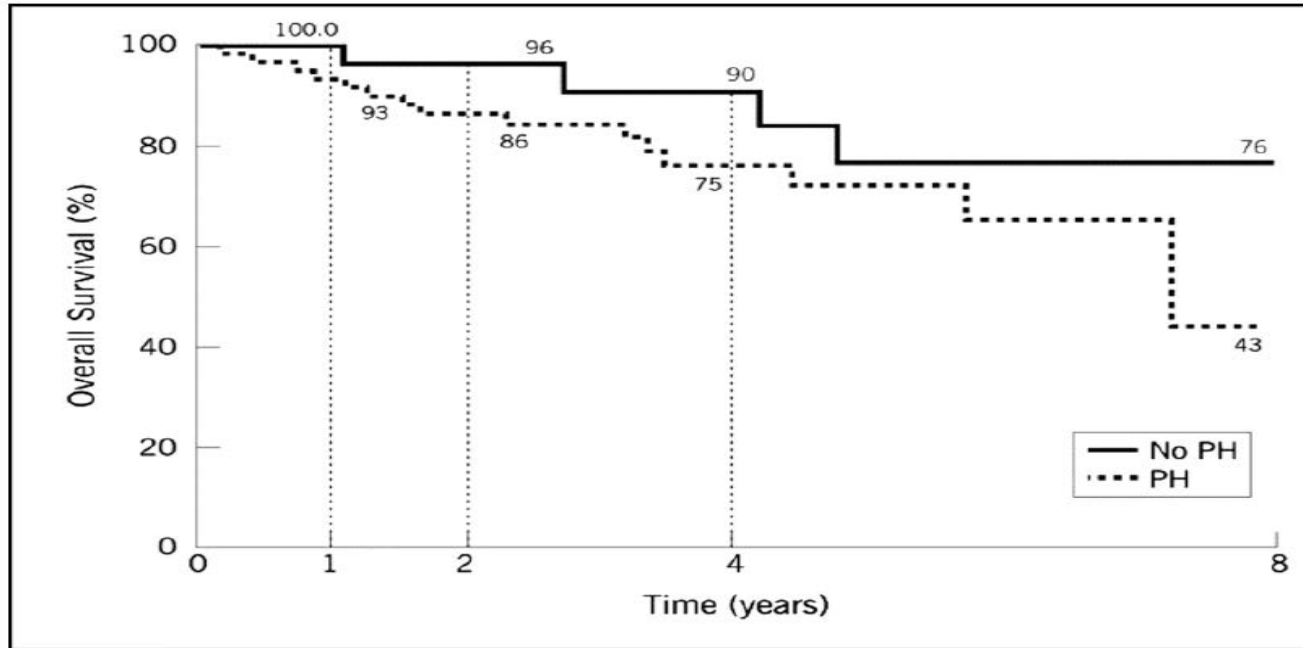


# Prevalence of OSA in Pulmonary Hypertension

Study/Year (Type)	No.	Diagnosis of PH	Type of SDB	Prevalence of SDB (%)	BMI, kg/m <sup>2</sup>	Evaluation of Ventilatory Function	Evaluation of LV Dysfunction	Statistically Significant Variables Associated With SDB (P Value)
Jilwan et al <sup>21</sup> /2013 (prospective)	46	mPAP > 25 mm Hg, PCWP < 15 mm Hg Patients with IPAH or CTEPH	AHI > 5/h Nocturnal hypoxemia (time SaO <sub>2</sub> < 90%) > 60 min	OSA: 41 of 46 patients (89) CSA: 4 of 46 patients (8) Nocturnal hypoxemia: 38 of 46 patients (82.6)	24.6 ± 4.2	Excluded if FEV <sub>1</sub> , FVC < 60% predicted	PCWP > 15 mm Hg excluded from study	Nocturnal desaturators: lower Pao <sub>2</sub> (.006), lower resting Spo <sub>2</sub> (.019); higher A-a gradient (.039); lower FEV <sub>1</sub> 25%-75% (.003); higher AHI (.05)
Prisco et al <sup>22</sup> /2011 (prospective)	28	mPAP > 25 mm Hg, PCWP < 18 mm Hg IPAH, or WHO Groups IV, V	AHI > 5/h Nocturnal hypoxemia (%TST SaO <sub>2</sub> < 90%)	OSA (AHI > 5) 14 of 28 patients (50) CSA: 0 of 28 patients %TST < 90%: SaO <sub>2</sub> 30.6 ± 3.6	31.3 ± 9.3	FEV <sub>1</sub> , % 72.7 ± 20.8	PCWP > 18 mm Hg, evidence of LV dysfunction on TTE, excluded from analysis	OSA: higher mPAP (.005) Nocturnal desaturators: higher mPAP (.038)
Ulrich et al <sup>23</sup> /2008 (prospective)	38	mPAP > 25 mm Hg, PCWP < 15 mm Hg	AHI > 10/h Nocturnal hypoxemia (> 10% TST-SaO <sub>2</sub> < 90%)	CSR/CSA: 15 of 38 patients (39) OSA: 4 of 38 patients (11) Nocturnal hypoxemia (68)	25 (range, 22-29)	NR	PCWP > 15 excluded from analysis	CSR/CSA: lower quality of life by MLHF, SF-36 questionnaires
Schulz et al <sup>24</sup> /2002	20	NR (mPAP 56 ± 2.7 mm Hg)	CSR AHI > 5/h	Cheyne-Stokes respiration 6 of 20 patients (30) OSA: 0 of 20 patients	23.5 ± 1.1	FEV <sub>1</sub> , % 88.0 ± 3.3	PCWP (mean 5 ± 0.4 mm Hg)	Periodic breathing: lower resting Pao <sub>2</sub> (.05); lower DLCO (.05); higher PAP, PVR (.05); lower CO, CI, RVEF (.01)
Rafanan et al <sup>25</sup> /2001 (retrospective)	13	mPAP > 25 mm Hg (rest); mPAP > 30 mm Hg (exercise)	AI > 5 Nocturnal hypoxemia > 10% TST-Spo <sub>2</sub> < 90%	0 of 13 patients with AI > 5 10 of 13 patients (77) nocturnal hypoxemia	30.1 ± 7.3	FEV <sub>1</sub> , % 76.5 ± 83.5	NR	Nocturnal desaturators: lower resting Pao <sub>2</sub> (.048); lower Spo <sub>2</sub> (.038); higher P(A-a)o <sub>2</sub> (.002); lower FEV <sub>1</sub> (.002)

Prevalence of OSA in PH: 11%-89%

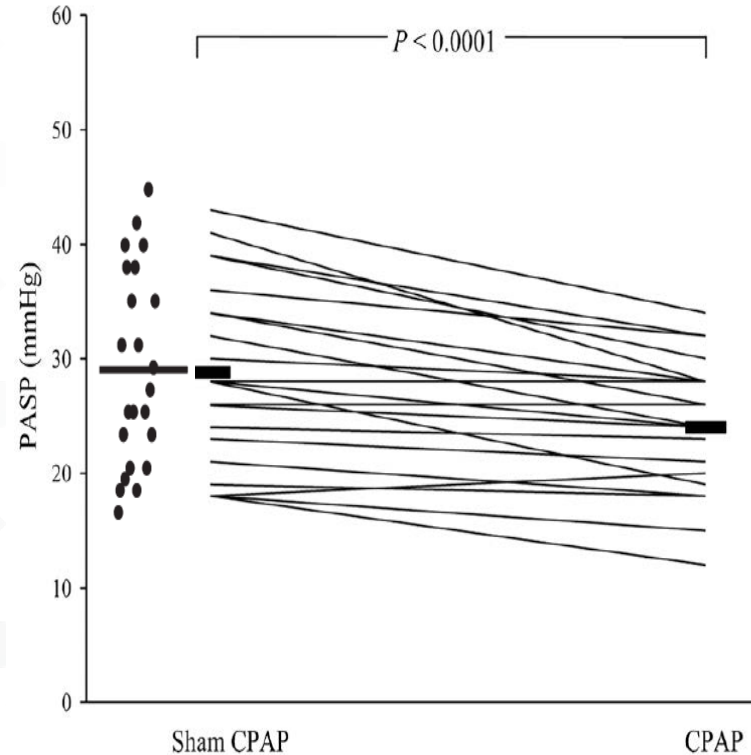
## Survival estimates in 83 patients with OSA with and without PH



Presence of PH increases mortality in patients with OSA

# Non-invasive positive pressure ventilation (CPAP) reduces pulmonary artery pressure in OSA

- A randomized, controlled cross-over study, 12 weeks
- OSA=23, (43% with PH), AHI  $68.7 \pm 24.9$ /hr
- PH was defined by PASP >30 mmHg (Echo)
- **Effective CPAP therapy reduced PASP by  $4.9 \pm 3.9$  mmHg or 15%**
- Average night usage was similar between effective CPAP (6.2) and sham CPAP (5.8).



# Summary

- Significant proportion of patients with OSA undergoing pulmonary artery catheterization have PH, which could be pre-capillary or post-capillary in nature.
- Severe PH can occur in the setting of OSA.
- Patients with OSA and PH may have left ventricular dysfunction as the cause for post-capillary PH.
- Nocturnal hypoxemia can be an important indicator of the presence of PH in this population.
- Treatment of OSA is associated with decreased pulmonary hypertension.

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What is the most common cause of pulmonary hypertension world wide?

- A. Idiopathic pulmonary arterial hypertension
- B. Chronic obstructive lung disease
- C. Left heart disease
- D. Interstitial lung disease



What is the most common cause of pulmonary hypertension world wide?

- A. Idiopathic pulmonary arterial hypertension
- B. Chronic obstructive lung disease
- C. Left heart disease
- D. Interstitial lung disease

Answer: C

Left heart disease is the most common cause of pulmonary hypertension. Heart failure with preserved or reduced ejection fraction and left-sided valvular heart disease can be associated with PH.

Obstructive sleep apnea can be associated with pre-capillary or post-capillary pulmonary hypertension?

- A. True
- B. False

## Obstructive sleep apnea can be associated with pre-capillary or post-capillary pulmonary hypertension?

- A. True
- B. False

Answer: A

Obstructive sleep apnea can be associated with both pre- and post capillary pulmonary hypertension. The latter, post-capillary pulmonary hypertension, in the setting of obstructive sleep apnea is due to left ventricular failure. However, pre-capillary pulmonary hypertension in obstructive sleep apnea can be present in the absence of left heart disease. In general, about 30% of patients with obstructive sleep apnea without left ventricular dysfunction or hypoxemic lung disease have pulmonary hypertension. The prevalence of OSA in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (CTEPH) with New York Heart Association Functional class without COPD or left ventricular dysfunction was 89% (Jiwan et al. Chest 2013).

Patients with obstructive sleep apnea, especially those with daytime hypoxemia and hypercapnia or significant nocturnal oxygen desaturations should be screened for pulmonary hypertension by echocardiography.

- A. True
- B. False

Patients with obstructive sleep apnea, especially those with daytime hypoxemia and hypercapnia or significant nocturnal oxygen desaturations should be screened for pulmonary hypertension by echocardiography.

- A. True
- B. False

Answer: A

The prevalence of severe pulmonary hypertension (mPAP >40 mmHg) in patients with obstructive sleep apnea and daytime hypoxemia and hypercapnia is 31%. Right heart catheterization should be considered for confirmation and better characterization of pulmonary vascular hemodynamic profile.