Pulmonary Hypertension and Obstructive Sleep Apnea

Not so Strange Bedfellows

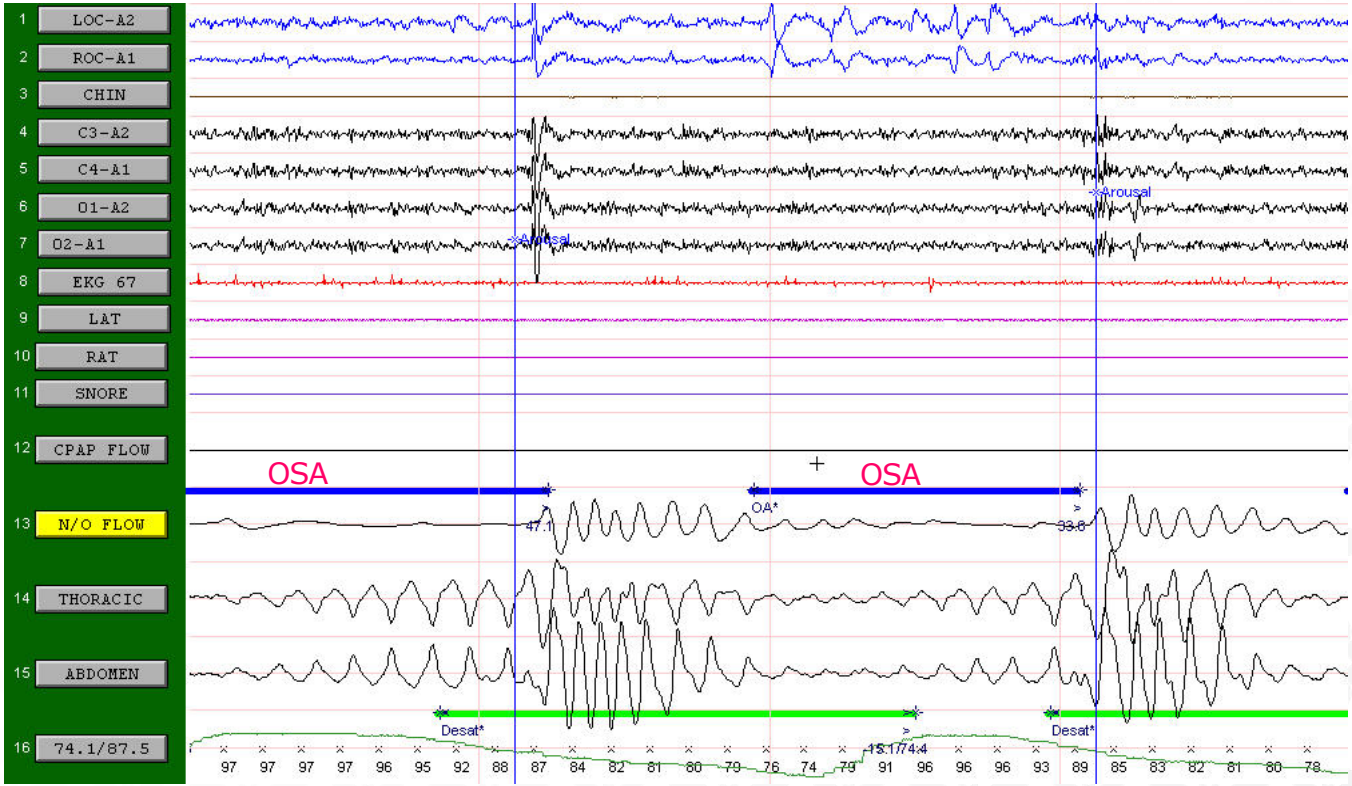
Vahid Mohsenin, M.D., FCCP, FAASM
Professor of Medicine
Section of Pulmonary, Critical Care and & Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut, USA

CHEST® Congress 2019
Thailand
Bangkok | 10-12 April

Disclosures

None to declare

Recurrent upper airway obstruction during sleep



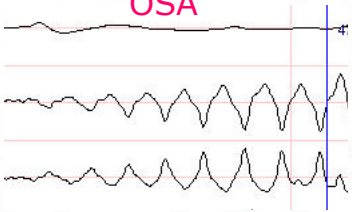
60-second epoch

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

OSA

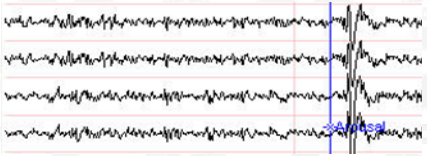


Hypoxia with pulmonary vasoconstriction

OSA

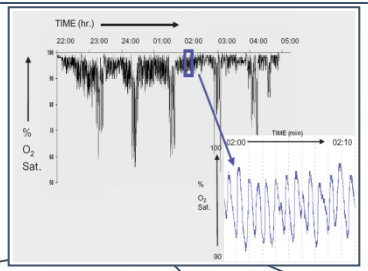
Repeated arousals

OSA



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

Apnea

Arousal

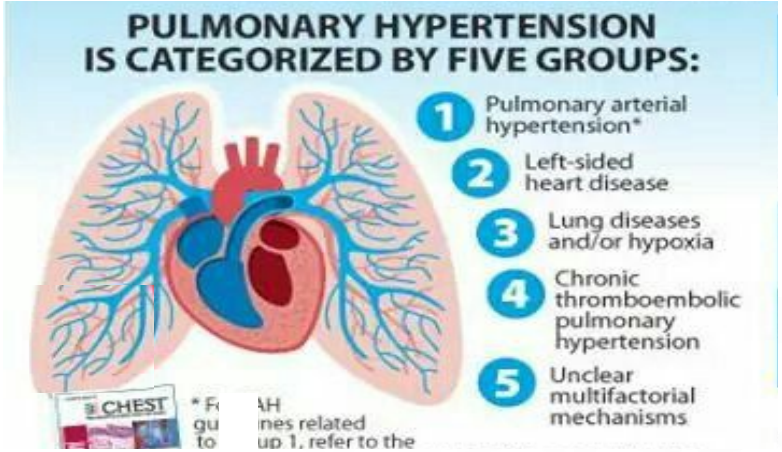
Acute

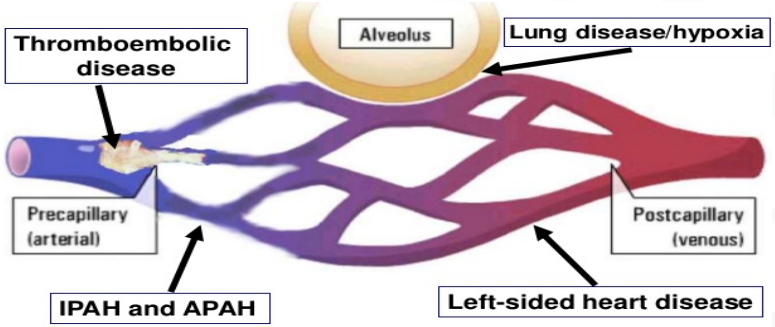
- Hypoxemia
- Hypercapnia
- Arrhythmias
- Vasoconstriction
  - pulmonary
  - systemic

Chronic

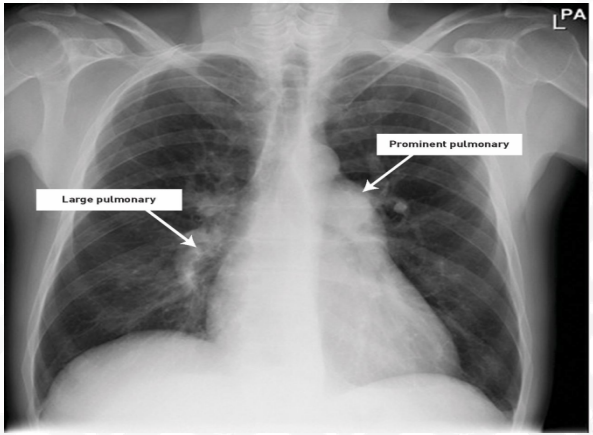
- Hypertension
  - systemic
  - pulmonary
- Coronary Disease
- Cor pulmonale
- Diabetes mellitus
- Stroke
- Death

Types and Symptoms of Pulmonary Hypertension





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



Kholdani…Mohsenin. *Pulm Circ 2015*

Predictive Accuracy of Echocardiography in PH

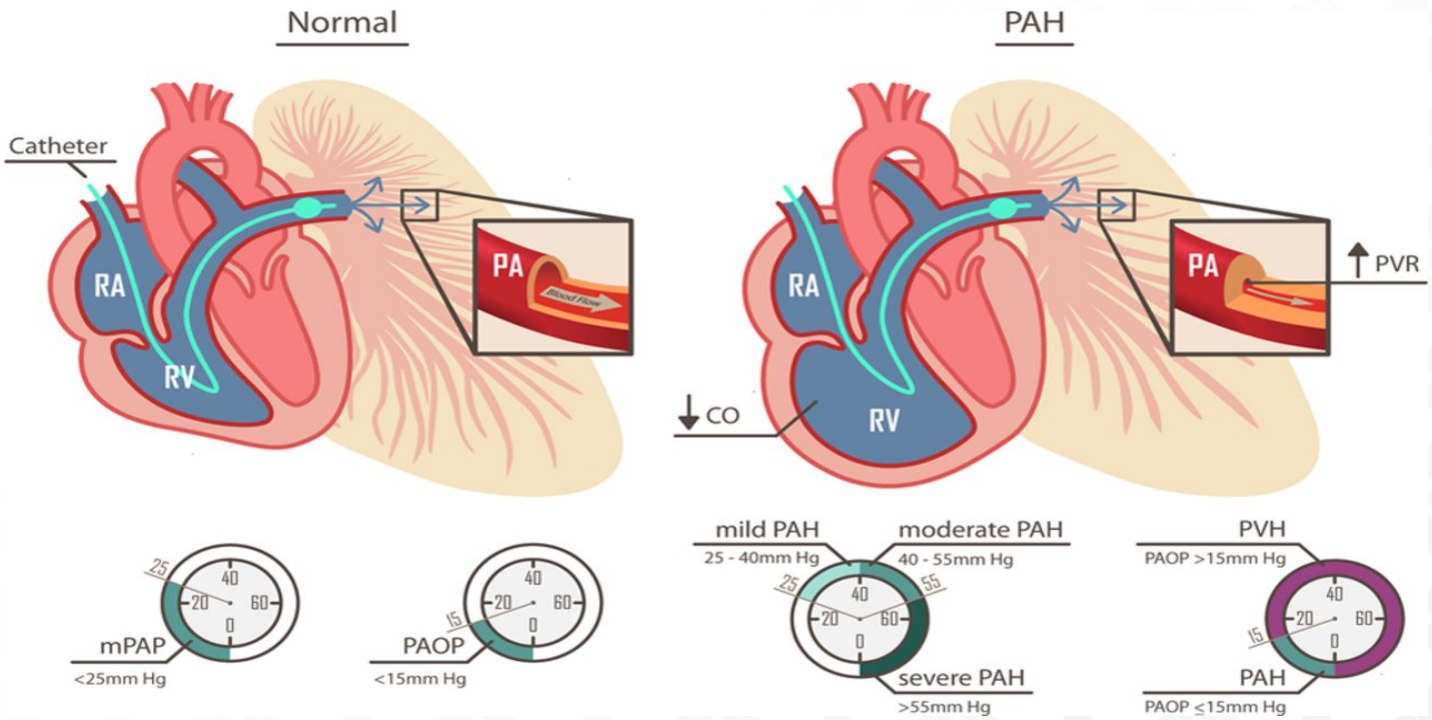
137 patients with systemic sclerosis were prospectively studied as part of a screening program.
All had Doppler echocardiography (tricuspid gradient, TG, for estimating right ventricular systolic pressure, RVSP) performed within 3 months of a right cardiac catheterization.

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
<45 vs ≥45	**47**	**97**	**98**	**41**

Mukerjee...Coghlan. ***Rheumatology 2004***

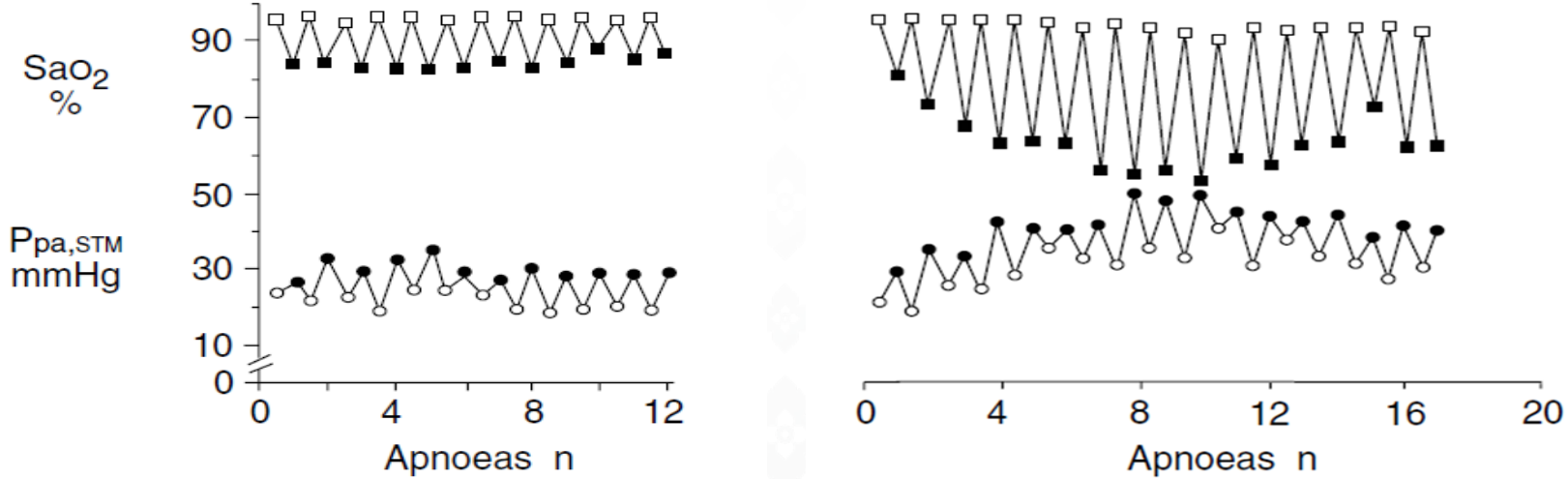
Diagnosis of Pulmonary Hypertension by Right Heart Catheterization

The only way



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

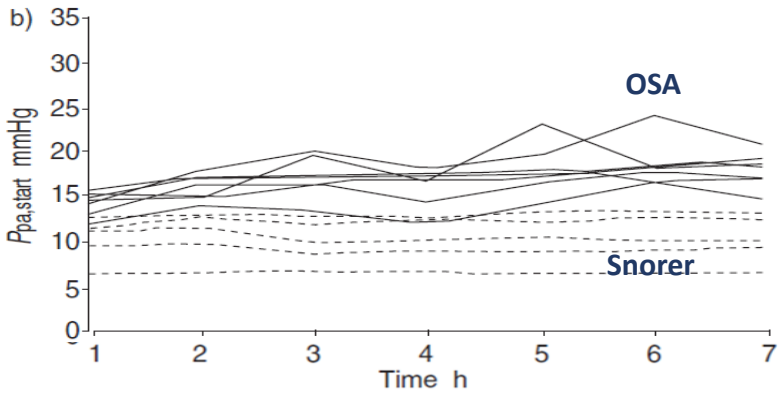
Consecutive values of SaO2 and simultaneous values of trans pulmonary artery systolic pressure ($P_{pa\ STM}$) in the sequences of apneic cycles



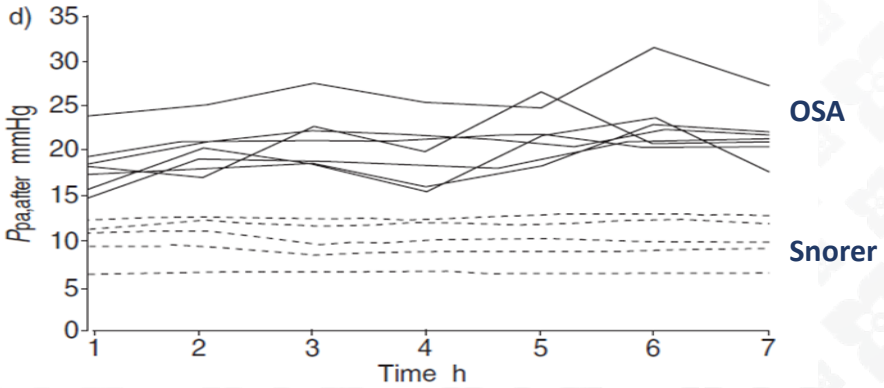
- Increasing pulmonary artery pressure during obstructive apnea with highest level after apnea
- Pulmonary artery occlusion pressure increases progressively during apnea (not shown)

Marrone…Bonsignore. ***Eur Respir J 1994***

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

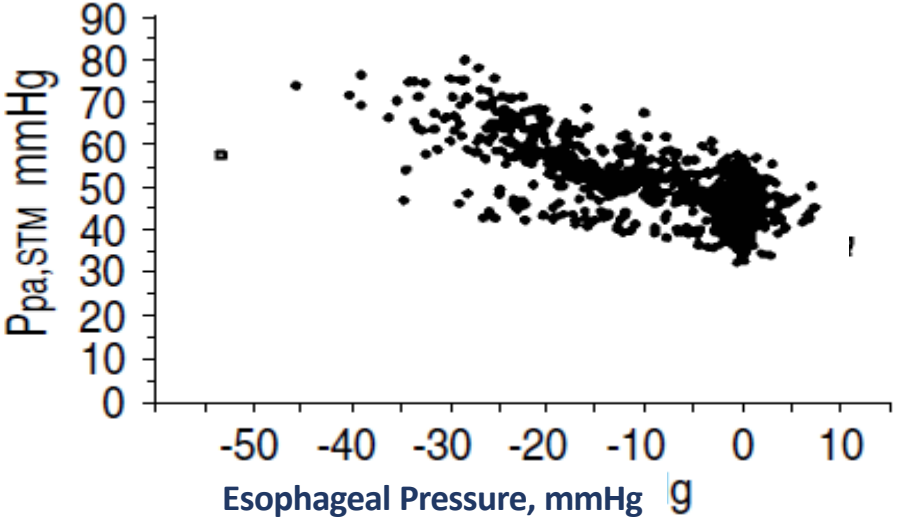


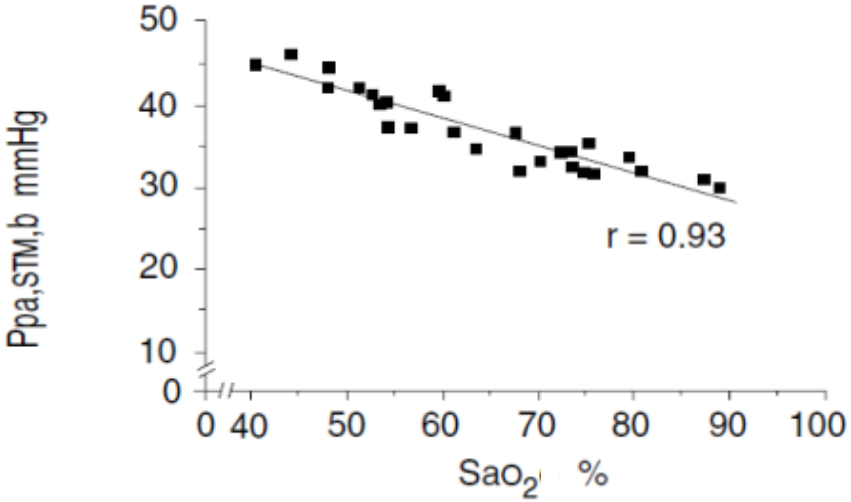
Ppa after each apnea during the night

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

Sforza…Sullivan. *Eur Respir J 1998*

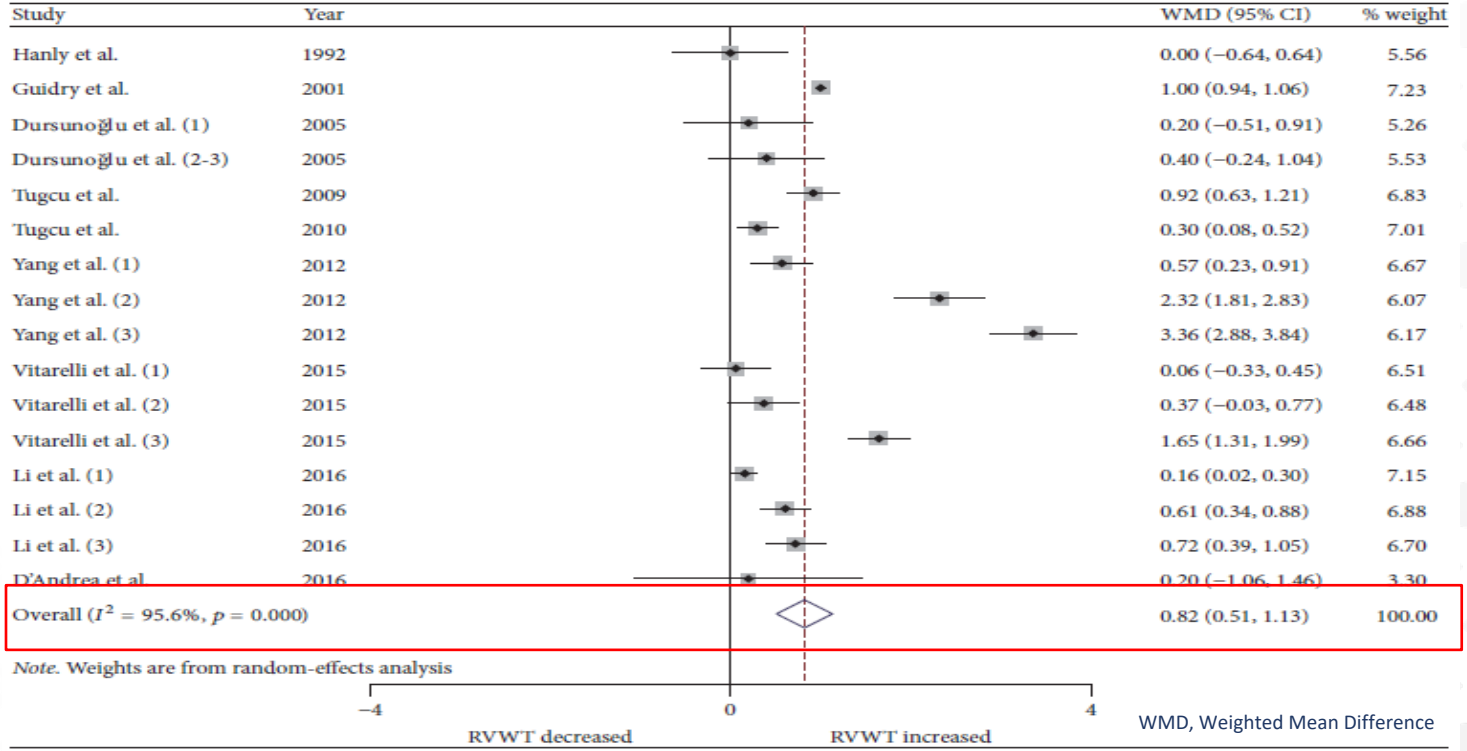
The more the negative intrathoracic pressure and oxygen desaturation during obstructive apneas the higher the pulmonary artery systolic pressure





Marrone…Bonsignore. *Eur Respir J 1994*

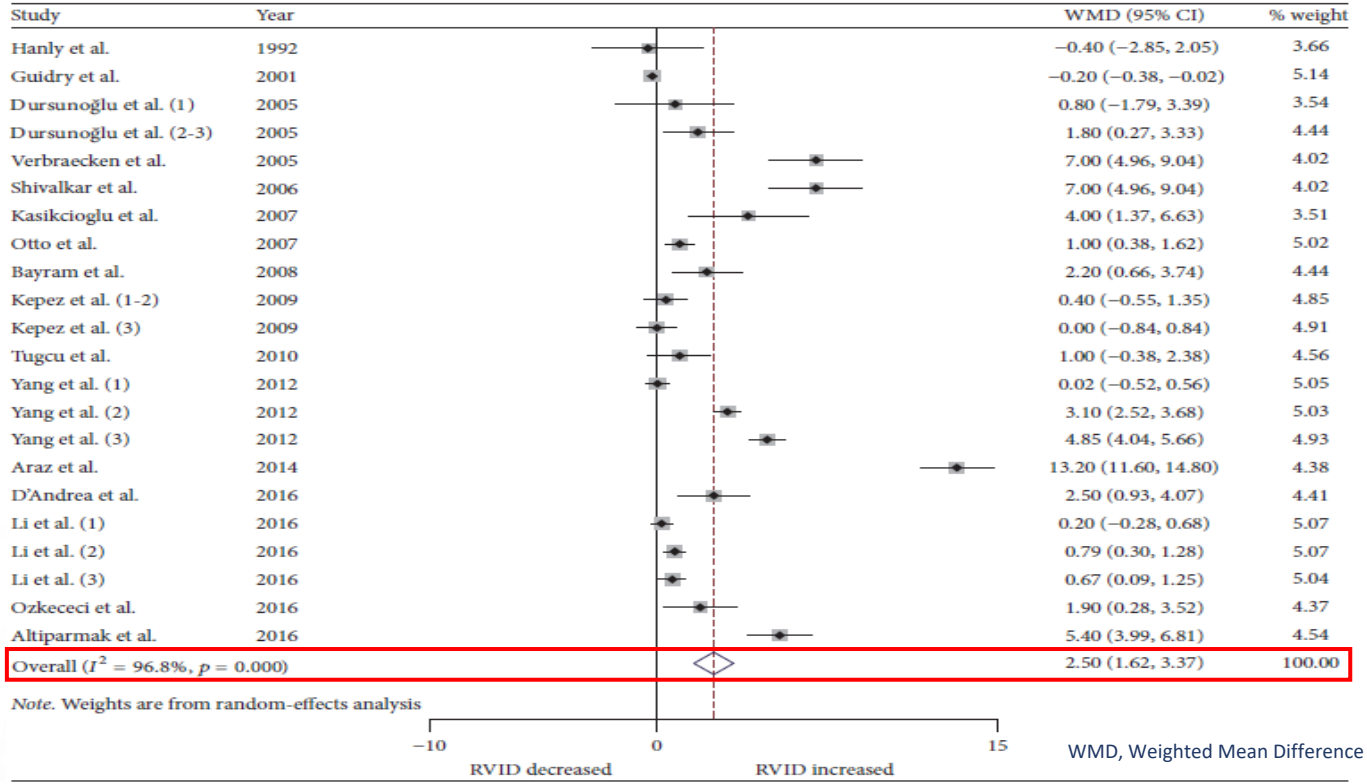
Increased right ventricular free wall thickness in OSA patients aka: RV hypertrophy



WMD, Weighted Mean Difference

Maripov…Sarybaev. Can Respir J 2017

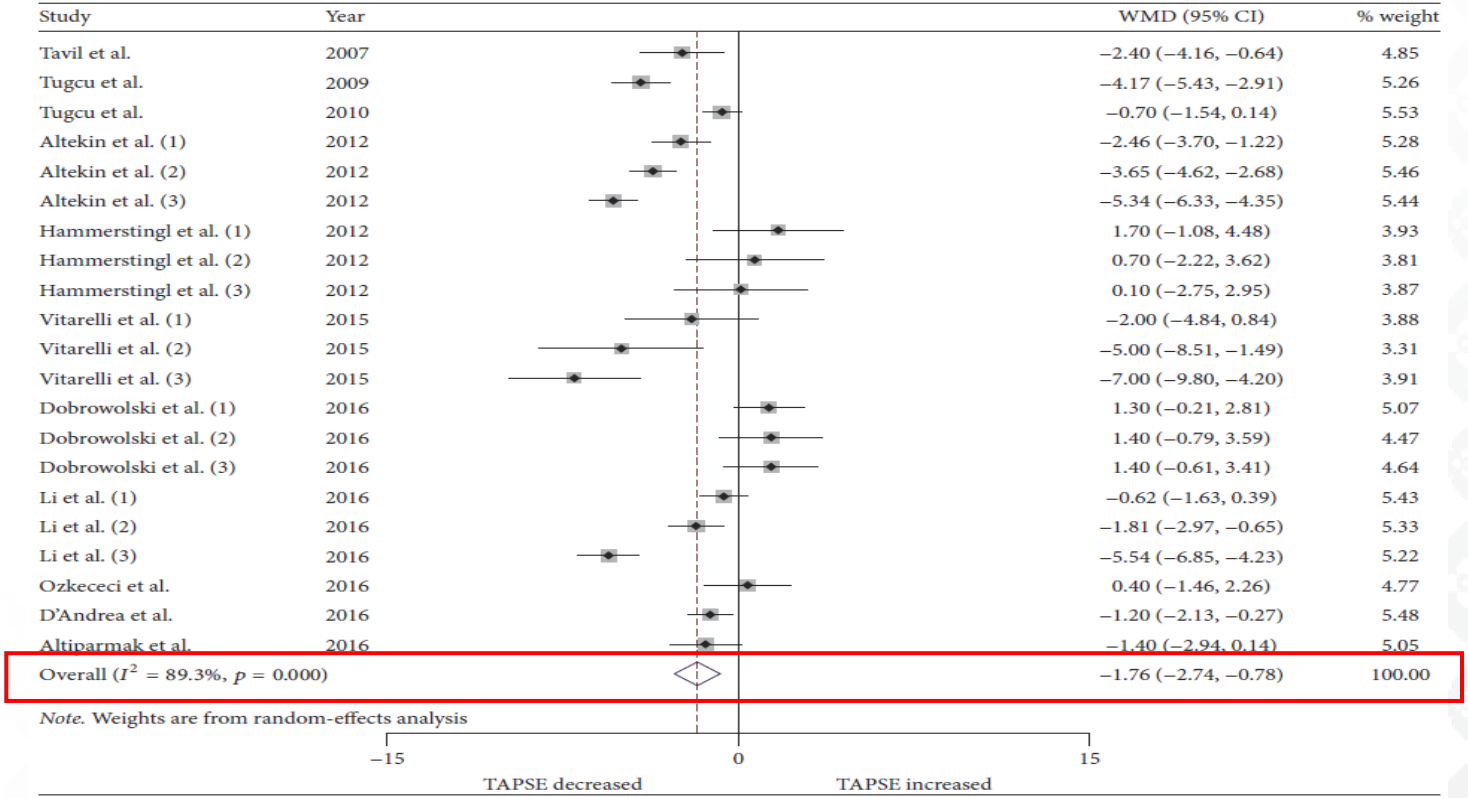
Increased right ventricular internal diameter at diastole in OSA patients aka: RV enlargement



WMD, Weighted Mean Difference

Maripov…Sarybaev. Can Respir J 2017

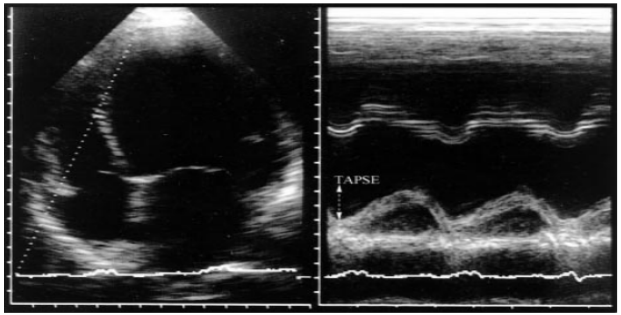
Decreased right ventricular function (reduced TAPSE) in obstructive Sleep apnea



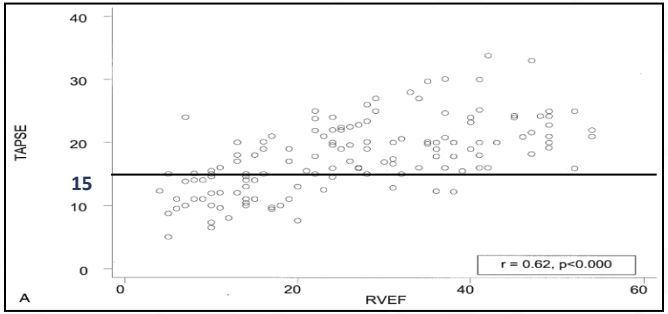
Tricuspid Annular Plane Systolic Excursion

Maripov…Sarybaev. Can Respir J 2017

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±SD 14.7
Mean capillary artery wedge pressure (mmHg) 9.8±SD 4.9

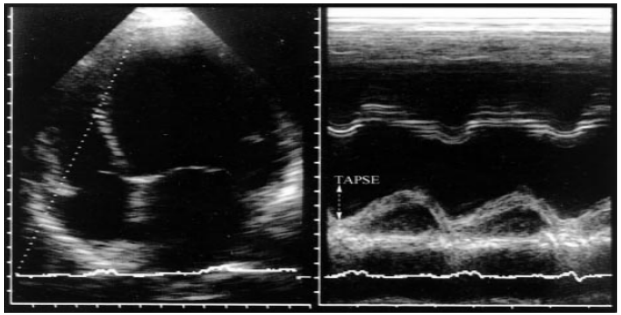
Mortality rate for 100-person-year

TAPSE as an Indicator of RV Function

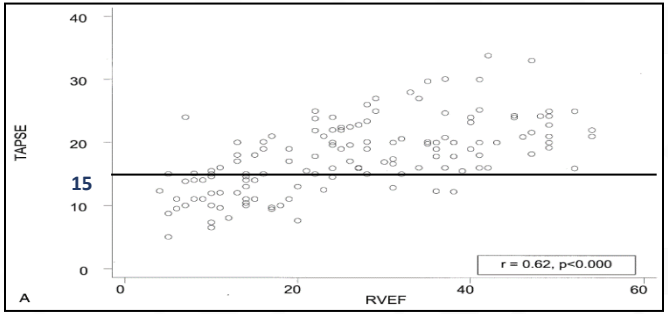
>15 mm	≤15 mm
6.5	**20.8**
(95%CI 3.1-13.7)	(95%CI 16.8-30.4)

Ghio…Tavazzi. Am J Cardiol 2000

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±SD 14.7
Mean capillary artery wedge pressure (mmHg) 9.8±SD 4.9

Mortality rate for 100-person-year

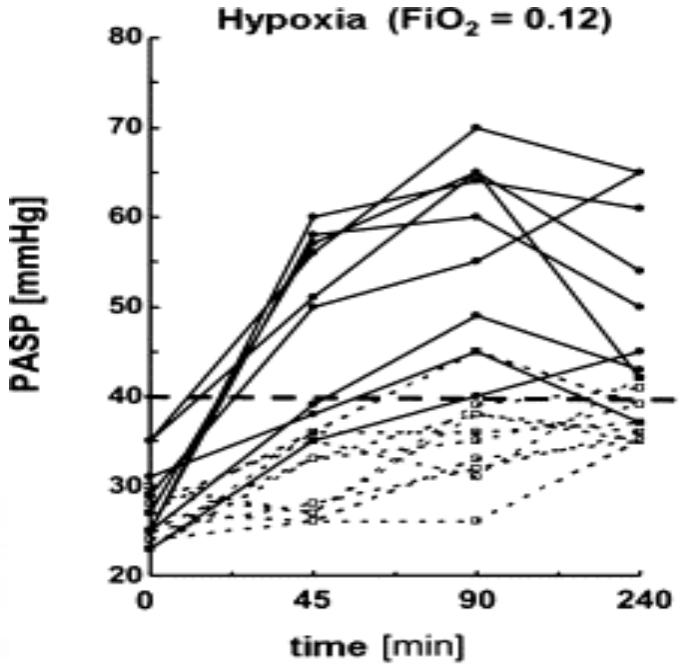
TAPSE as an Indicator of RV Function

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

Ghio…Tavazzi. Am J Cardiol 2000

Prevalence of Pulmonary Hypertension in OSA

It has been shown that inter-individual differences in the magnitude of the pulmonary vascular response to hypoxia may account for the variable development of chronic pulmonary hypertension in subjects exposed to high altitude.

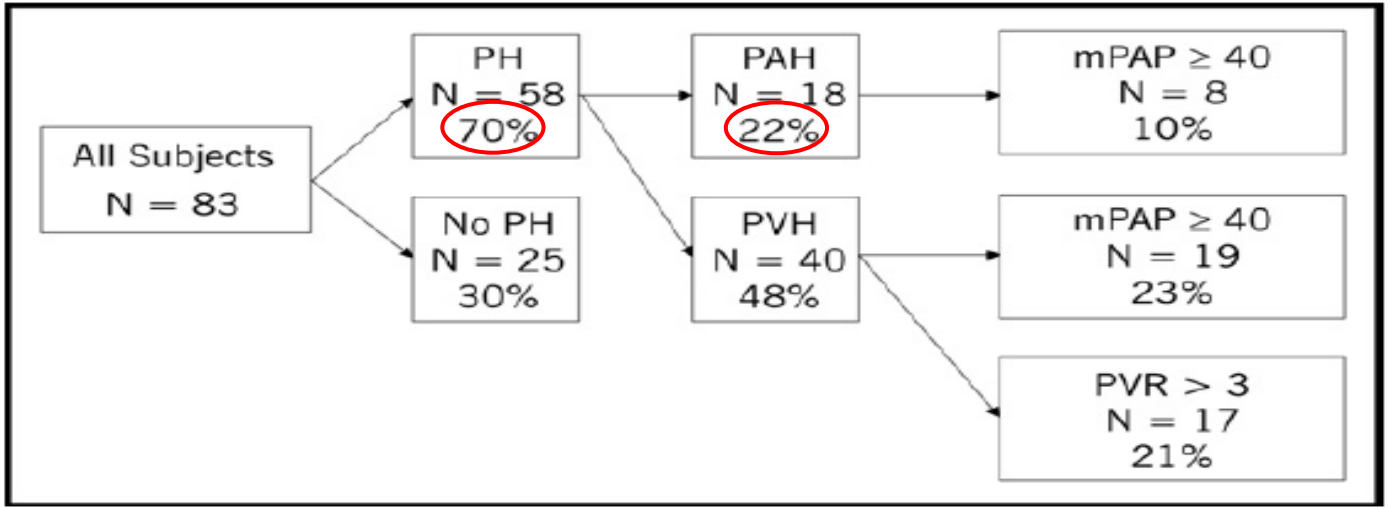


This inter-individual difference in pulmonary vascular response to hypoxia is likely the reason for variable susceptibility to PH in OSA

non- susceptible

Dehnert…Bartsch. *Respir Physiol Neurobiol* 2007

Prevalence of Pulmonary Hypertension in OSA



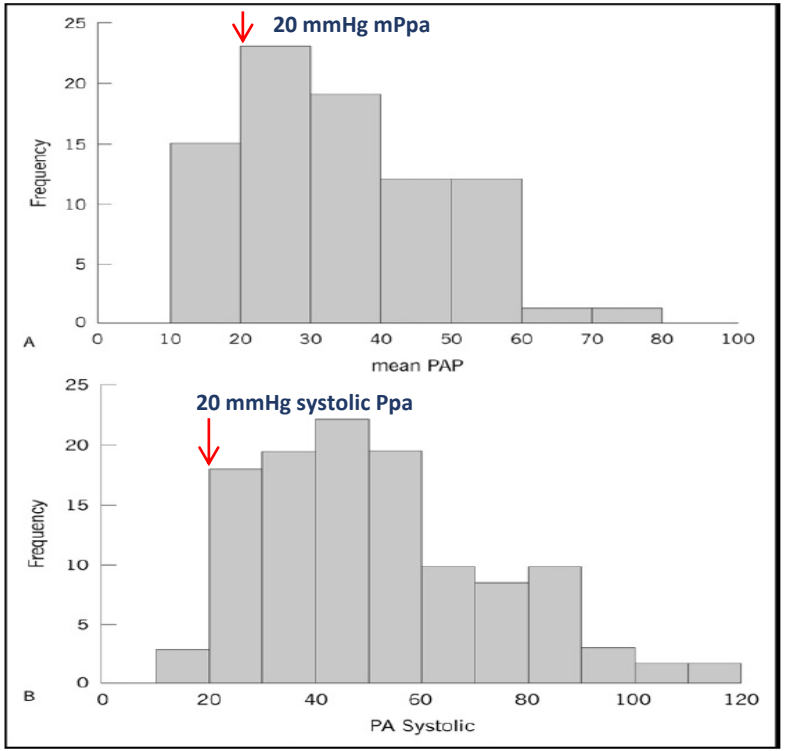
All consecutive subjects with a recent diagnosis of OSA (AHI>5/hr) underwent RHC were included in the present study.

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%

Minai…Stoller. ***Am J Cardiol 2009***

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.



Minai…Stoller. *Am J Cardiol 2009*

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^2)	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^2)	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

Minai…Stoller. *Am J Cardiol 2009*

The combination of female gender, age <49 and RVSP ≥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

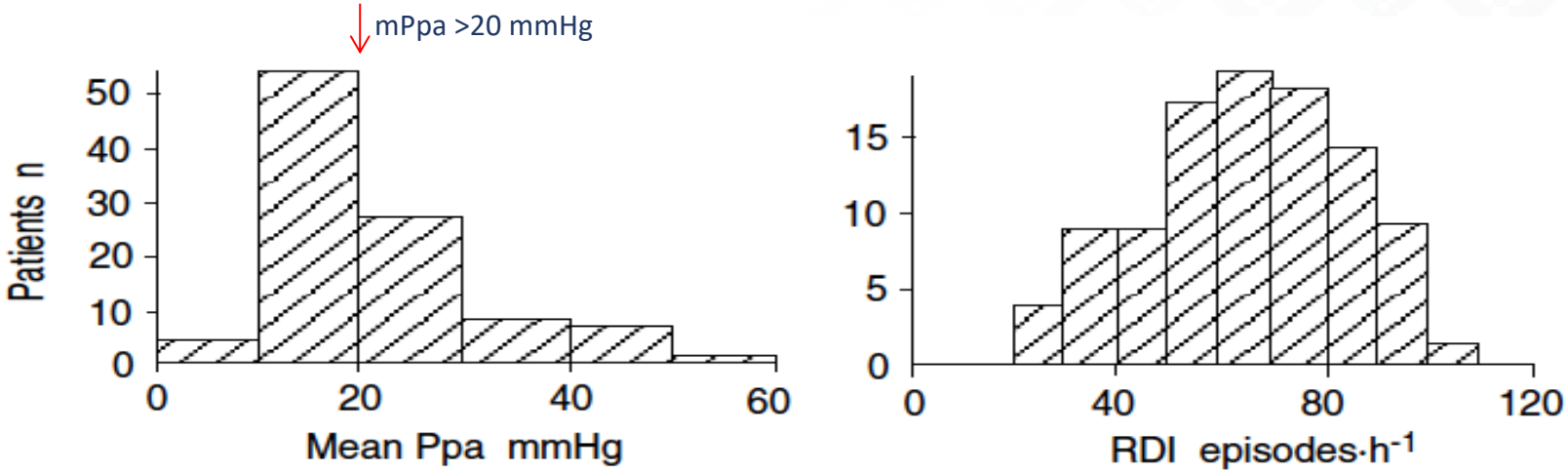
Variable	Parameter Estimate	Standard Error	p Value	Odds Ratio (95% CI)	Scoring System Points
Intercept	0.878	1.072			
Women	1.583	0.730	0.030	4.87 (1.16–20.3)	1
Age <49 years	1.679	0.764	0.028	5.36 (1.20–24.0)	1
Body mass index ≥26 kg/m^2	1.458	0.848	0.086	4.30 (0.82–22.6)	1
RVSP ≥30 mm Hg	4.152	1.136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

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

Minai…Stoller. *Am J Cardiol 2009*

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.

Laks…Sullivan. ***Eur Respir J 2009***

Obesity Hypoventilation Syndrome

- Definition:
  The combination of obesity (BMI >30 kg/m^2) and hypoventilation (awake PaCO2 >45 mmHg), after the exclusion of other disorders associated with hypoventilation.

- The majority of patients also have associated OSA (up to 90%).

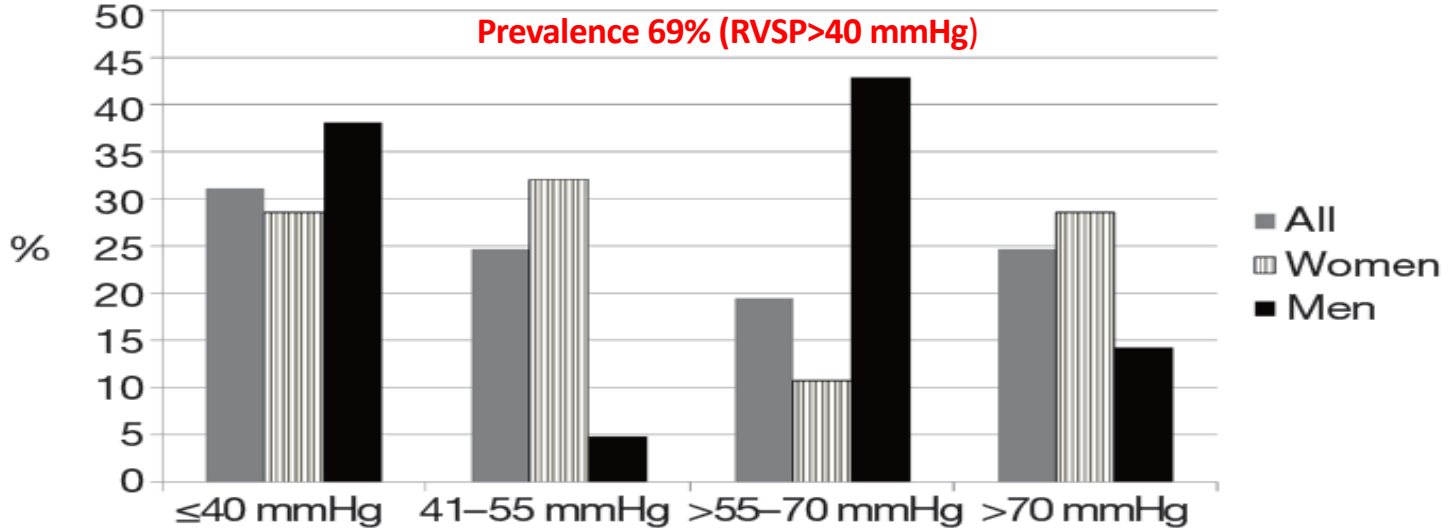
- In two different studies, the prevalence of PH was 58% and 88% (mPAP >20 mmHg).

- The prevalence of severe PH (mPAP >40 mmHg) was 31%.

Mokhlesi…Evans. *Sleep Breath* 2007; Kessler…Chaouat. *Chest* 2001; Sugerman…Vetrovec. *Ann Surg* 1988.

Prevalence of PH in Obesity Hypoventilation Syndrome

Prospective study. Echocardiography for assessment of RVSP.



PaCO2 55.7±9.2 (mmHg); BMI 43.2±0.4 (kg/m^2); AHI 66±45 (events/hr)
OHS definition: awake hypercapnia (PaCO2 >45 mmHg), based on arterial PaCO2; obesity (BMI >30 kg/m2); 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).

Almeneessier…BaHammam. ***J Thorac Dis 2017***

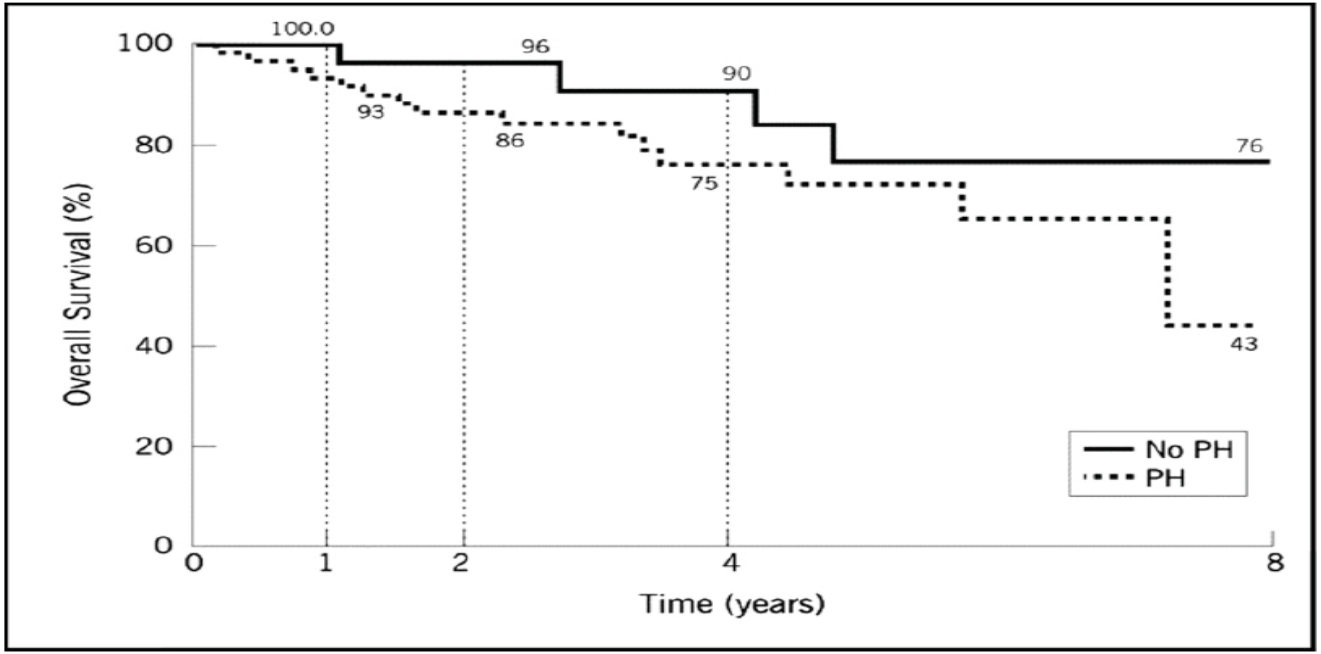
Prevalence of OSA in Pulmonary Hypertension

Study/Year (Type)	No.	Diagnosis of PH	Type of SDB	Prevalence of SDB (%)	BMI, kg/m²	Evaluation of Ventilatory Function	Evaluation of LV Dysfunction	Statistically Significant Variables Associated With SDB (P Value)
Jilwan et al[21]/2013 (prospective)	46	mPAP > 25 mm Hg, PCWP < 15 mm Hg Patients with IPAH or CTEPH	AHI > 5/h Nocturnal hypoxemia (time Sao_2 < 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_1, FVC < 60% predicted	PCWP > 15 mm Hg excluded from study	Nocturnal desaturators: lower Pao_2 (.006), lower resting Spo_2 (.019); higher A-a gradient (.039); lower FEV 25%-75% (.003); higher AHI (.05)
Prisco et al[22]/2011 (prospective)	28	mPAP > 25 mm Hg, PCWP < 18 mm Hg IPAH, or WHO Groups IV, V	AHI > 5/h Nocturnal hypoxemia (%TST Sao_2 < 90%)	OSA (AHI > 5) 14 of 28 patients (50) CSA: 0 of 28 patients %TST < 90%: Sao_2 30.6 ± 36	31.3 ± 9.3	FEV_1, % 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[23]/2008 (prospective)	38	mPAP > 25 mm Hg, PCWP < 15 mm Hh	AHI > 10/h Nocturnal hypoxemia (> 10% TST-Sao_2 < 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[24]/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_1, % 88.0 ± 3.3	PCWP (mean 5 ± 0.4 mm Hg)	Periodic breathing: lower resting Pao_2 (.05); lower DLCO (.05); higher PAP, PVR (.05); lower CO, CI, RVEF (.01)
Rafanan et al[25]/2001 (retrospective)	13	mPAP > 25 mm Hg (rest); mPAP > 30 mm Hg (exercise)	AI > 5 Nocturnal hypoxemia > 10% TST-Spo_2 < 90%	0 of 13 patients with AI > 5 10 of 13 patients (77) nocturnal hypoxemia	30.1 ± 7.3	FEV_1, % 76.5 ± 83.5	NR	Nocturnal desaturators: lower resting Pao_2 (.048); lower Spo_2 (.038); higher $P(A-a)O_2$ (.002); lower FEV_1 (.002)

Prevalence of OSA in PH: 11%-89%

Ismail…Hill. *Chest 2015*

Survival estimates in 83 patients with OSA with and without PH

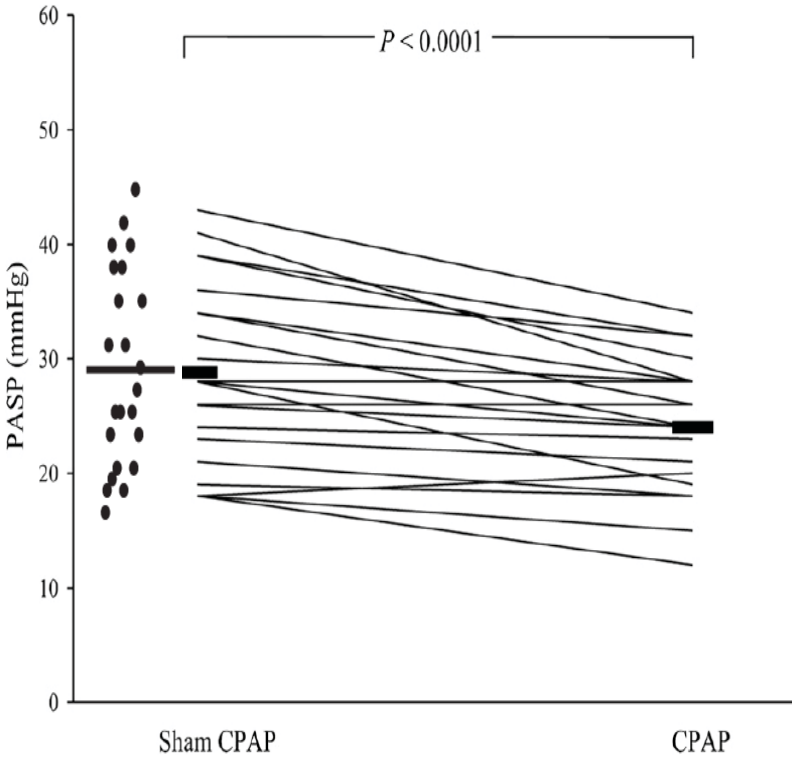


Presence of PH increases mortality in patients with OSA

Minai…Stoller. *Am J Cardiol 2009*

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±24.9/hr
- PH was defined by PASP >30 mmHg (Echo)
- **Effective CPAP therapy reduced PASP by 4.9±3.9 mmHg or 15%**
- Average night usage was similar between effective CPAP (6.2) and sham CPAP (5.8).



Arias…Villamor. *Eur Heart J* 2006

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.

Join colleagues from around the region to gain access to the CHEST learning and training experience at our regional congress. This unique program will go beyond the classroom-style setting to connect you to leading experts who will teach and develop you and your team.

Learn More: athens.chestnet.org

CHEST®
Regional Congress

ATHENS 2019
GREECE | 27-29 JUNE

ΕΛΛΗΝΙΚΗ ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
HELLENIC THORACIC SOCIETY

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.