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Pulmonary Hypertension and Sleep Apnea

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Prevalence & Severity of PH in OSA

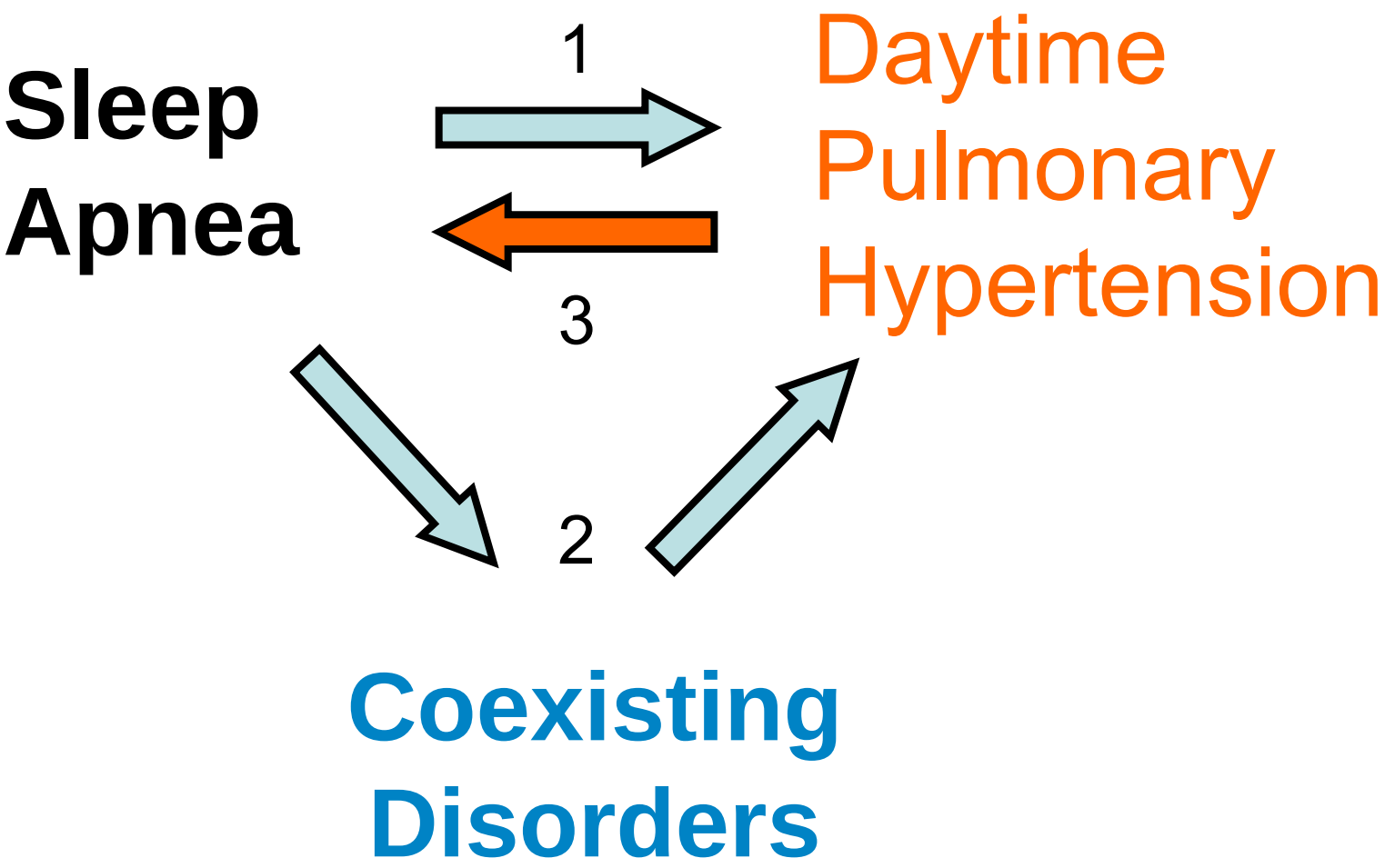
Study	Sample size	PH % prevalence	Entire cohort: mPAP (mm Hg)	In patients with PH: mPAP in PH
Schroeder et al[64]	22	59	21	25
Tilkian et al[28]	12	67	20	23
Fletcher et al[65]	24	79	28	32
Podszus et al[36]	65	20	19	29
Weitzenblum et al[54]	46	20	16	23
Krieger et al[53]	114	19	16	-
Sajkov et al[59]	27	41	18	23
Laks et al[56]	100	42	21	29
Chaouat et al[52]	220	17	-	-
Sanner et al[61]	92	20	15	22
Bady et al[58]	44	27	20	28
Sajkov et al[60]	32	34	18	24
Alchanatis et al[57]	29	21	17	26
Arias et al[63]	23	43	22	28

79%

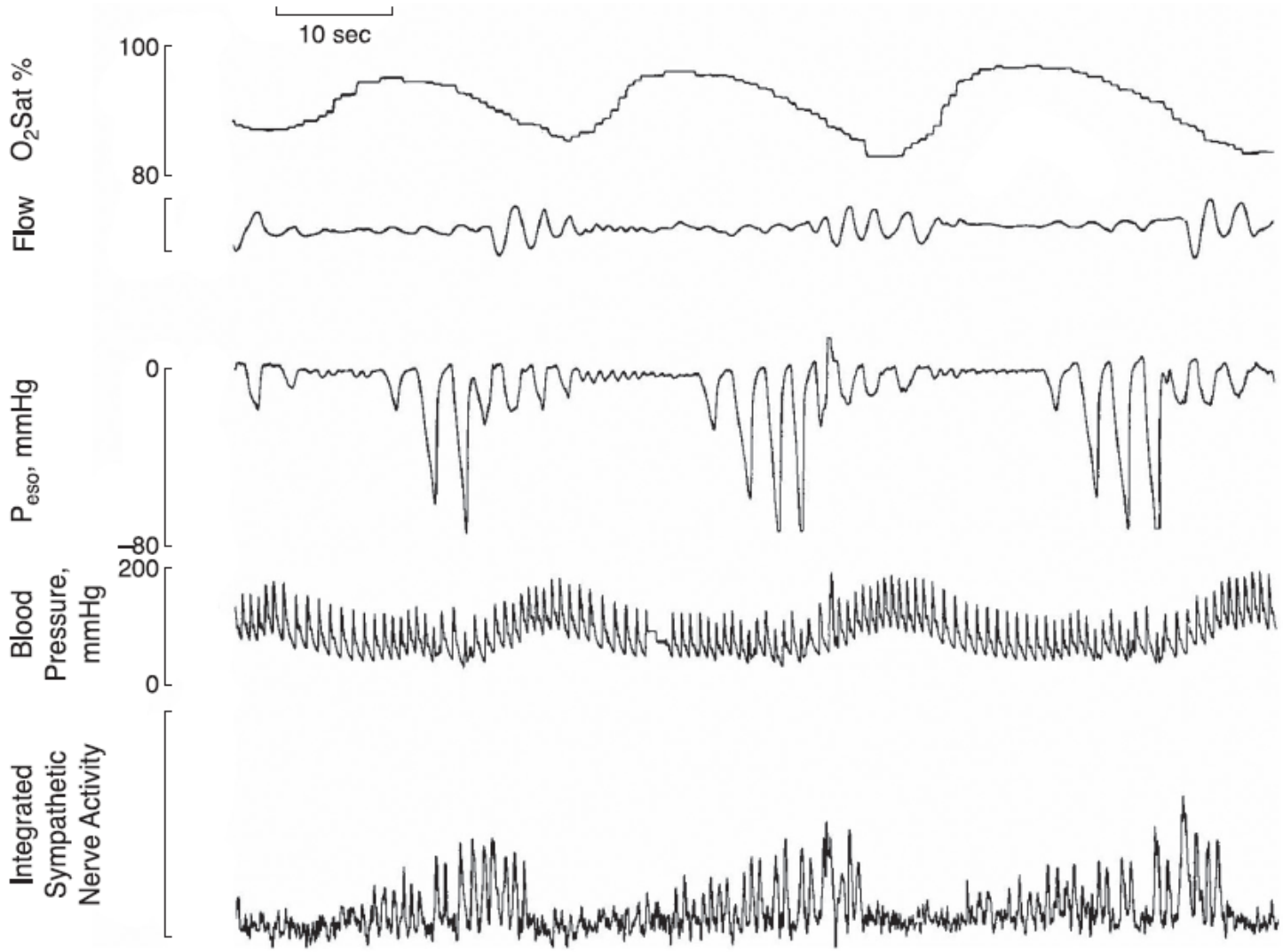
17%

≤32 mmHg

Sakov & McEnvoy. Prog Cardiovasc Dis 2009;51:363

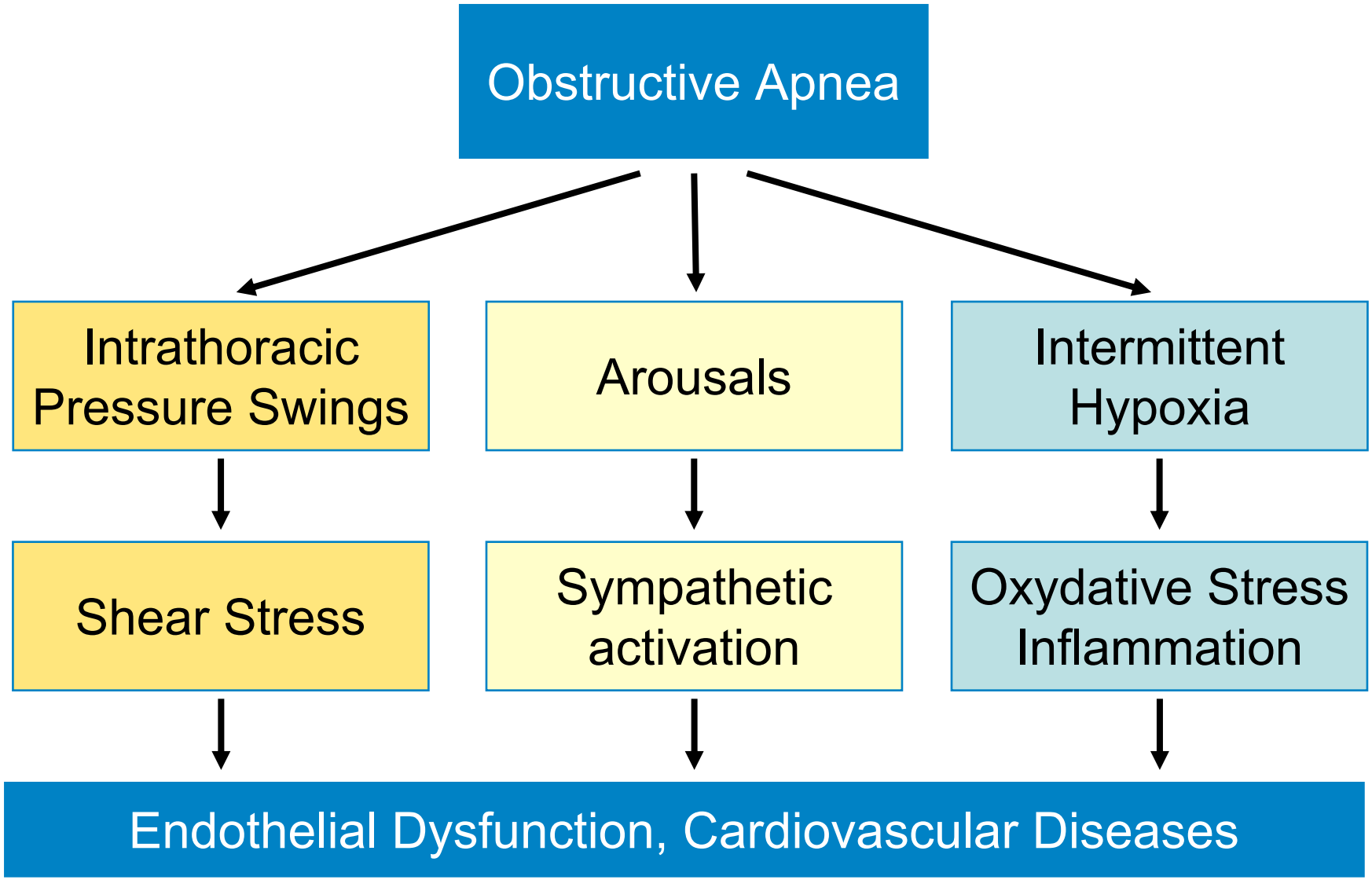

Sleep Apnea
1
3
Daytime Pulmonary Hypertension
2
Coexisting Disorders

Hemodynamic Effects of Sleep Apnea

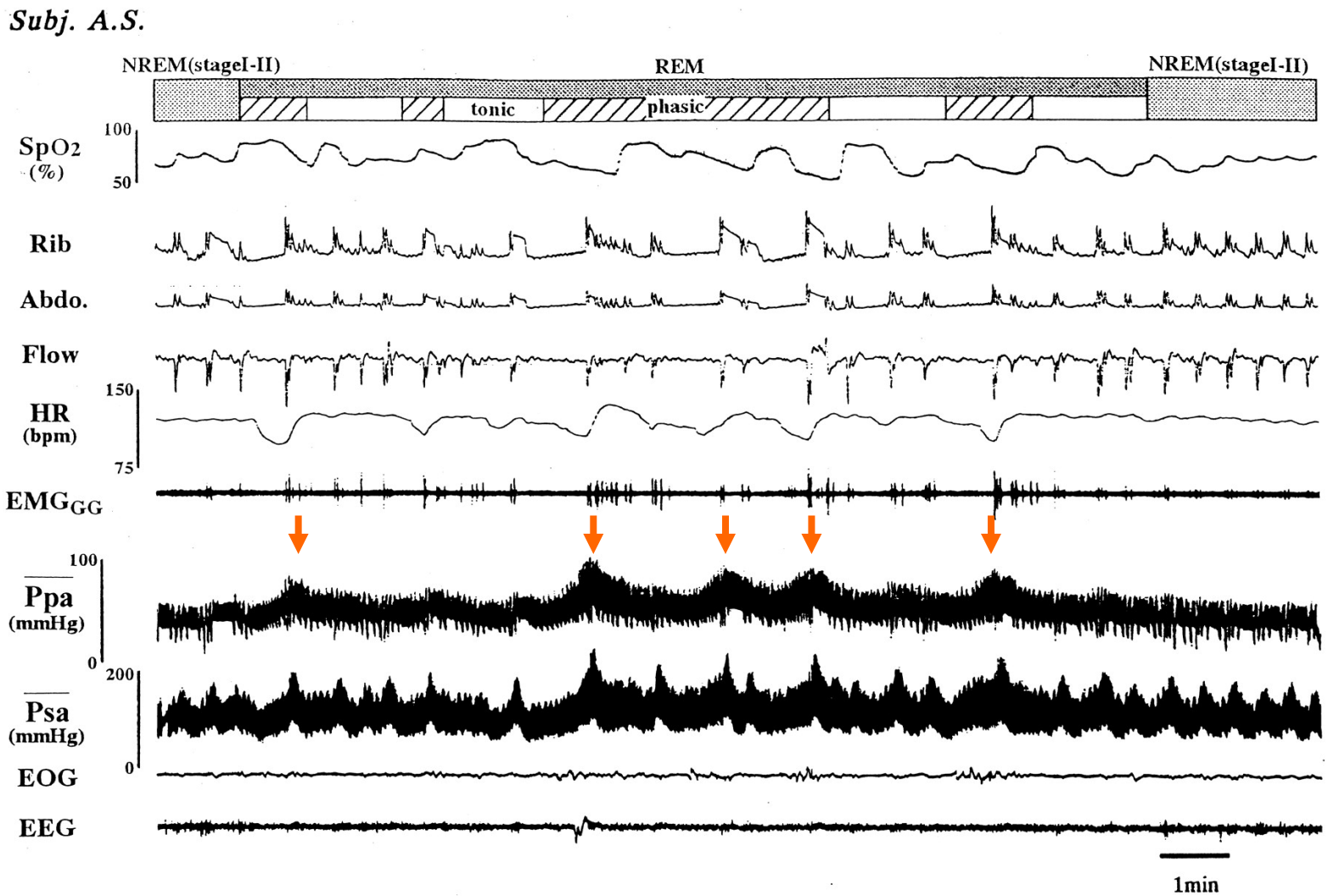


Dempsey et al Physiol Rev 2010;90:47

Cardio-Vascular Consequences of Sleep Apnea



PAP During REM-Sleep OSA



Niijima et al AJRCCM 1999;159:1766

Association of OSA and PH

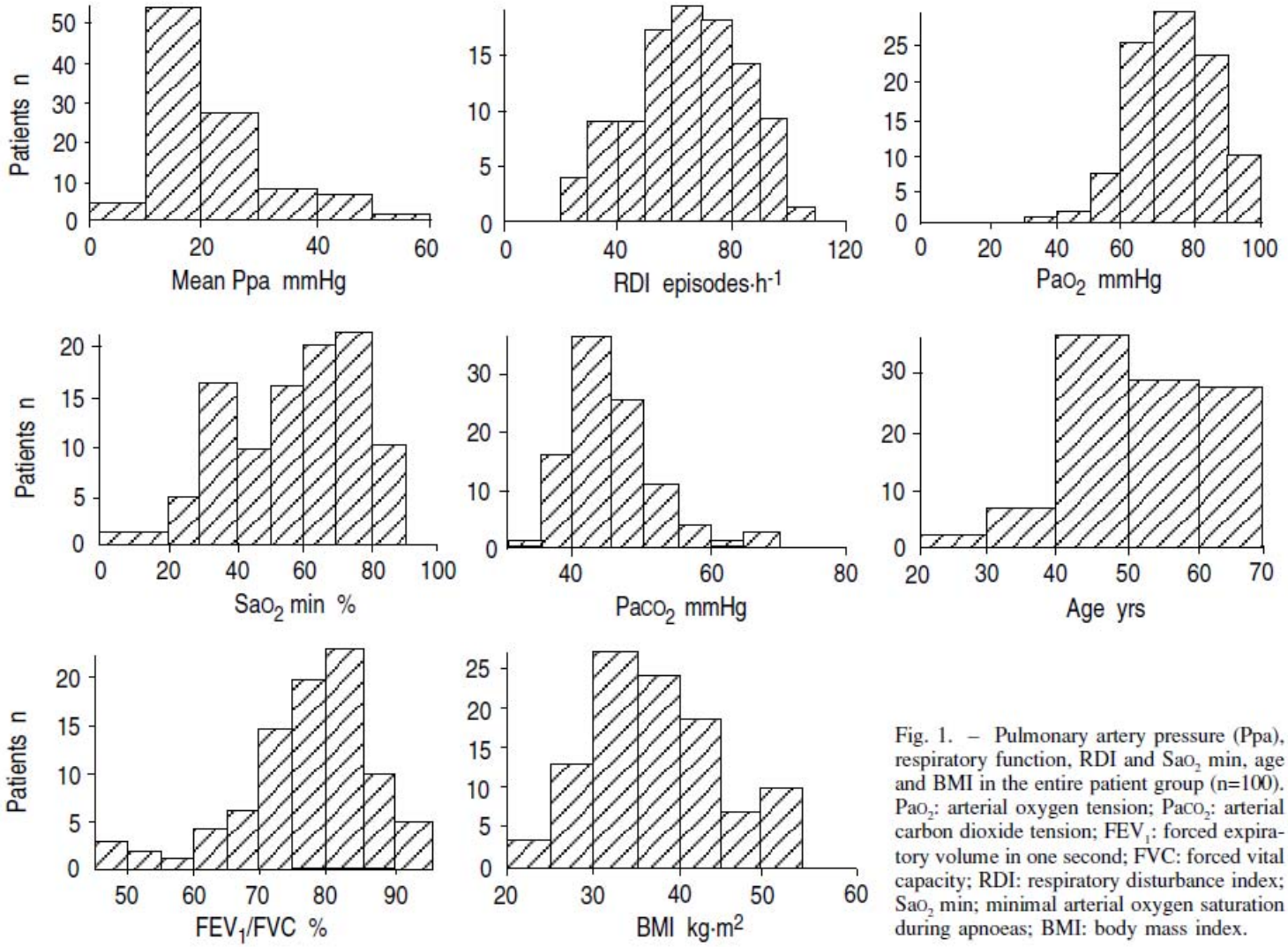


Fig. 1. – Pulmonary artery pressure (Ppa), respiratory function, RDI and Sa_{O_2} min, age and BMI in the entire patient group (n=100). Pa_{O_2}: arterial oxygen tension; Pa_{CO_2}: arterial carbon dioxide tension; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RDI: respiratory disturbance index; Sa_{O_2} min; minimal arterial oxygen saturation during apnoeas; BMI: body mass index.

Laks et al. Eur Respir J 1995;8:537

OSA and PH: Determinants of PAP

Table 6—*Univariate and Multivariate Prediction of PAP**

total n=220, 17% with PAPm>20mmHg

(1) *Linear Correlations Between PAP and Several Variables*			
Age	−0.17 (NS)	BMI	0.23 ($p=0.001$)
VC	−0.51 ($p<0.001$)	VC % predicted	−0.54 ($p<0.001$)
FEV_1	−0.53 ($p<0.001$)	FEV_1/VC	−0.37 ($p<0.001$)
TLC	−0.43 ($p<0.001$)	Raw	0.52 ($p<0.001$)
PaO_2	−0.42 ($p<0.001$)	$PaCO_2$	−0.53 ($p<0.001$)
AI	0.24 ($p<0.001$)	AHI	0.34 ($p<0.001$)
$MSaO_2$	−0.54 ($p<0.001$)	Minimal SaO_2	−0.31 ($p<0.001$)

(2) *Stepwise Multiple Regression Analysis of PAP*

$PAP=0.31\ PaCO_2-0.0015\ FEV_1+0.72\ Raw-0.26\ MSaO_2+29.98$
$r^2=0.50$; $PaCO_2$ accounts for 0.32; FEV_1 for 0.12; Raw for 0.04; $MSaO_2$ for 0.02; Complete set data available for 142 patients.
SEE=4.2 mm Hg.

*For definition of abbreviations: see Tables 1 through 3.
Units: $PaCO_2$, PAP: mm Hg; FEV_1: mL; Raw: cm H_2O/L/s; $MSaO_2$: %.

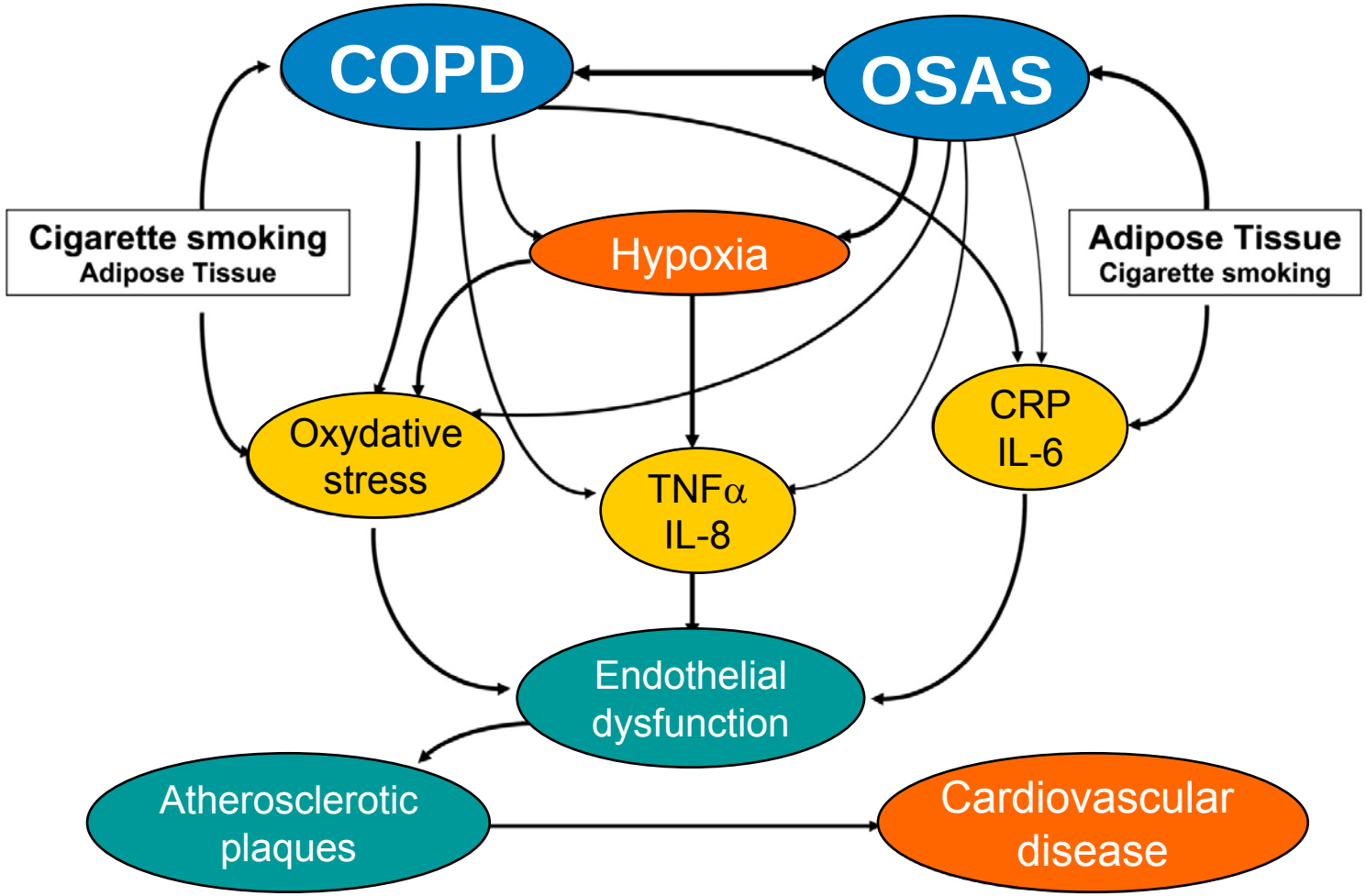
Chaouat et al. Chest 1996;109:380

OSA + COPD: „Overlap Syndrome“

	OSA, normal PFT n=235, 89%	Overlap Syndr. n=30, 11%
FEV1/FVC	75 ±7	50 ±6*
AHI, 1/h (>20/h)	76 ±32	89 ±37
Age, y (males)	53 ±10 (91%)	58 ±9 (100%) *
BMI, kg/m^2	33 ±7	31 ±5
PaO_2, mmHg	74 ±10	66 ±10*
$PaCO_2$, mmHg	38 ±4	42 ±6*
Nocturnal SpO2, %	91 ±4	89 ±4
PAP, mmHg	15 ±5	20 ±6

Chaouat et al. AJRCCM 1995;151:82

Consequences of „Overlap Syndrome“



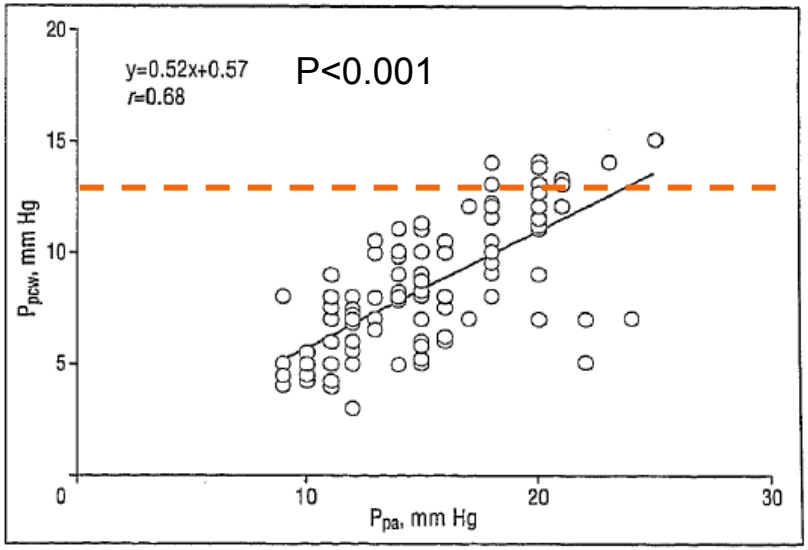
McNicholas. AJRCCM 2009;180:692

OSA&PH And Patients With Normal PFT

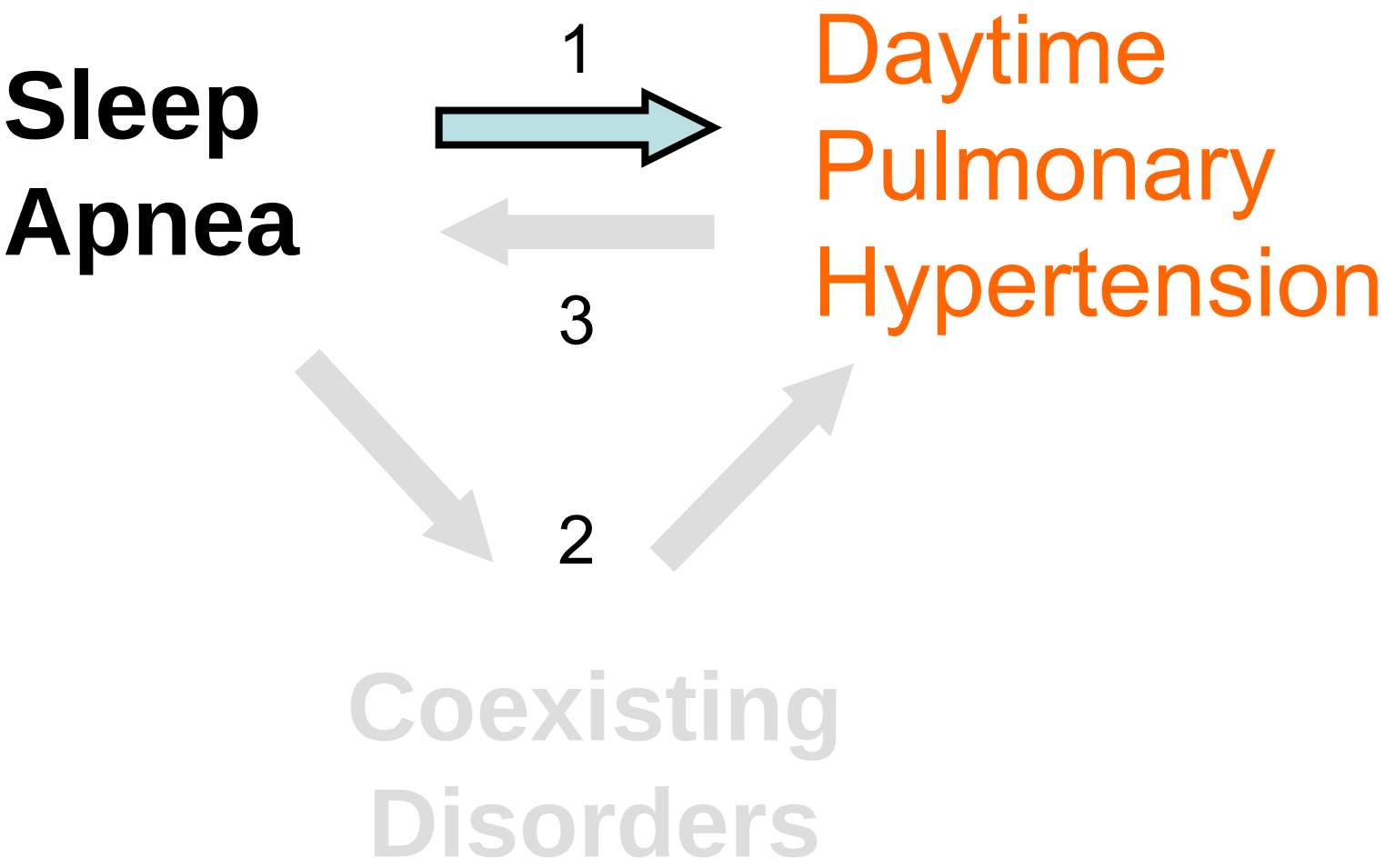
92 OSA patients
AHI>10/h, normal PFT,
Normal daytime ABG

n=74: PH Absent
AHI 39 ±23/h
Time SpO2<90% 19 ±25%

n=18 PAP>20 mmHg
AHI 44 ±28/h
Time SpO2<90% 41 ±37%



Sanner et al. Arch Int Med 1997;157:2483


Sleep Apnea
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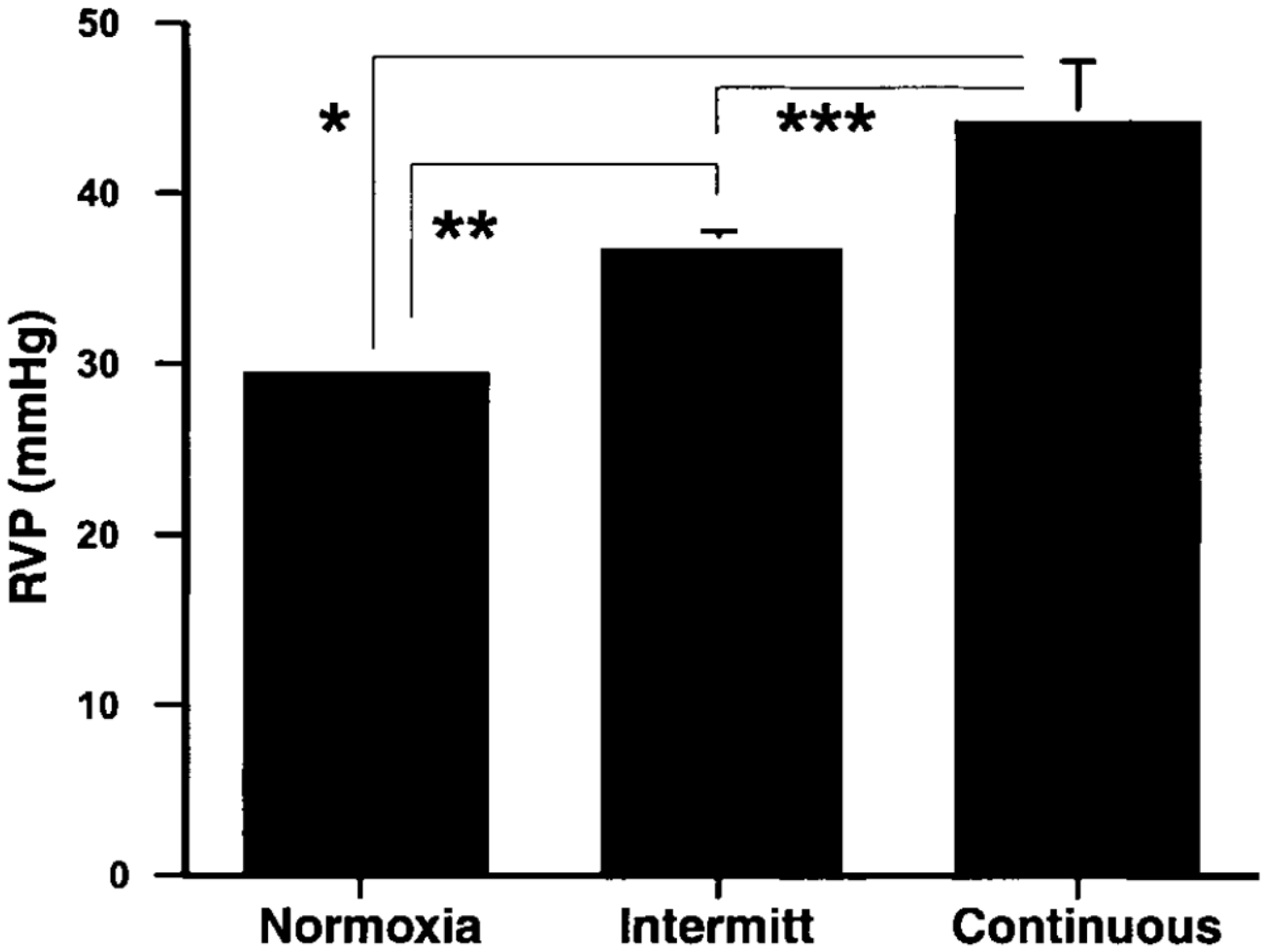
PH in Mice Exposed to Hypoxia



FiO2 21%

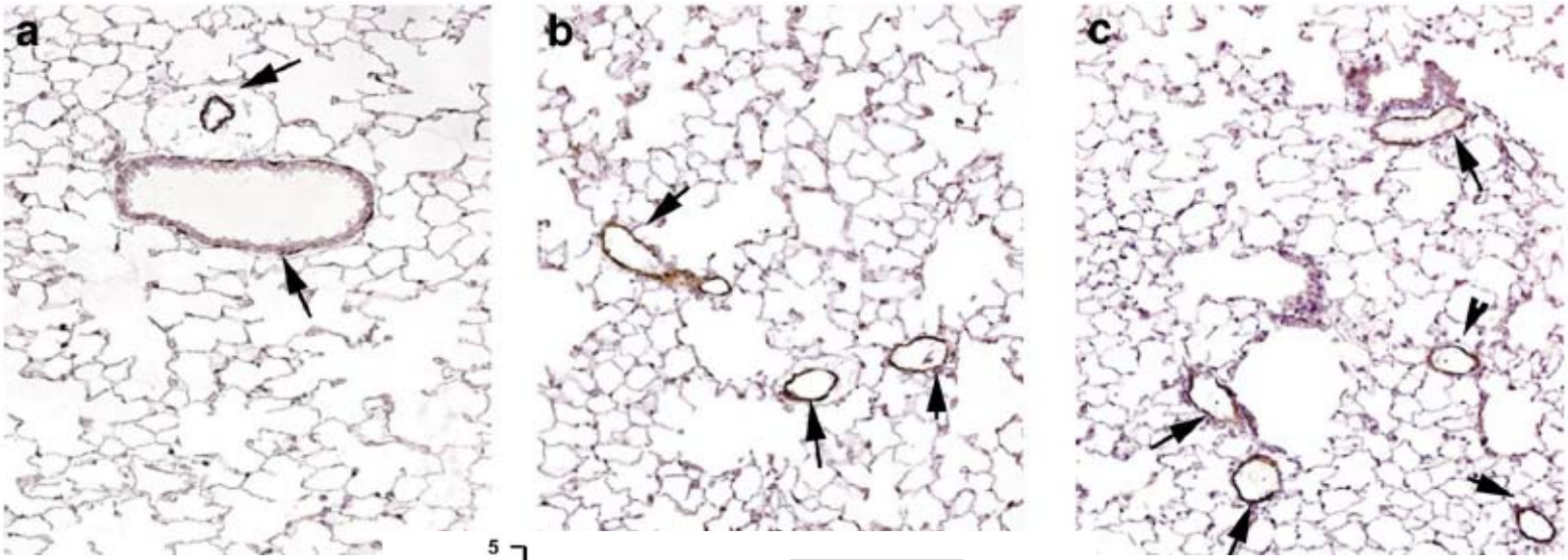
every 2 min FiO2 10% & 21% 2min 8/24h

FiO2 10% (5‘600m)

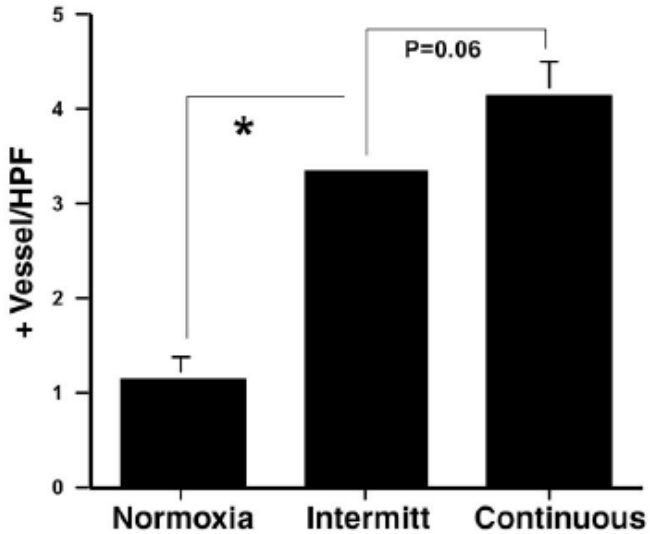
Fagan. JAP 2001;90:2502

Vascular Remodelling in Mice Exposed to Intermittent and Continuous Hypoxia

Normoxia | Intermittent hypoxia | Continuous hypoxia



Number of myosin positive vessels



Fagan. JAP 2001;90:2502

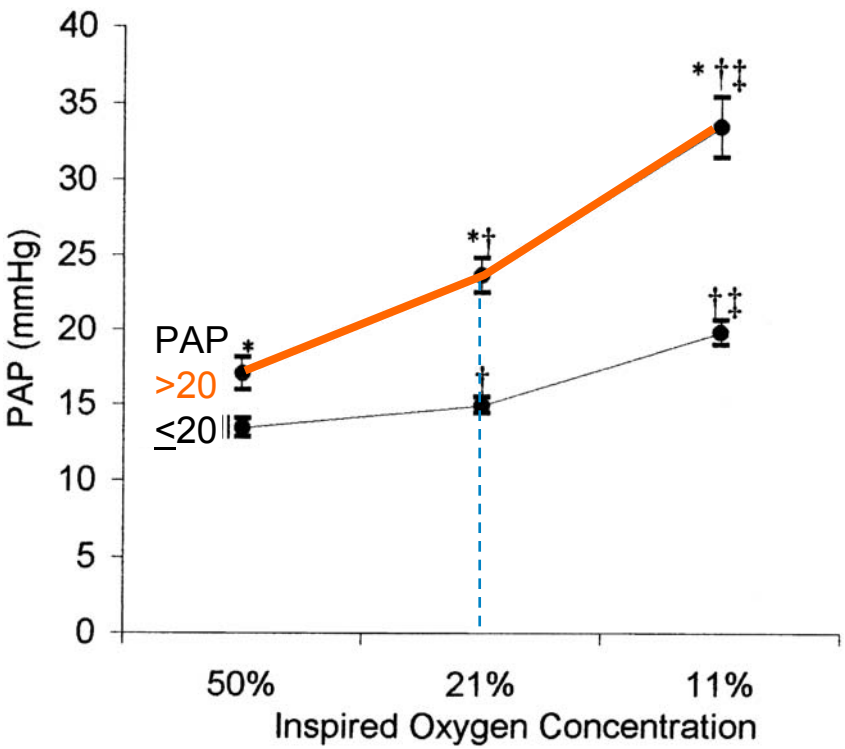
Characteristics of Patients with OSA & PH w/o Cardiopulmonary Disease

	21 OSA Pat. mPAP<20	11 OSA Pat. mPAP≥20
Age, y	49 ±3	54 ±3
BMI, kg/m^2	32 ±1	31 ±1
AHI, 1/h (>10/h)	47 ±5	45 ±7
$tSpO_2$<90, %	34 ±11	38 ±17
PaO_2, $PaCO_2$ mmHg	79 ±2; 41 ±1	77 ±3; 40 ±1
FEV1% (FEV1/FVC>75%)	101 ±2	105 ±4
FRC-Closing Capacity, L	0.27 ±0.09	-0.16 ±0.11*
mPAP, mmHg	15 ±1	24 ±1*

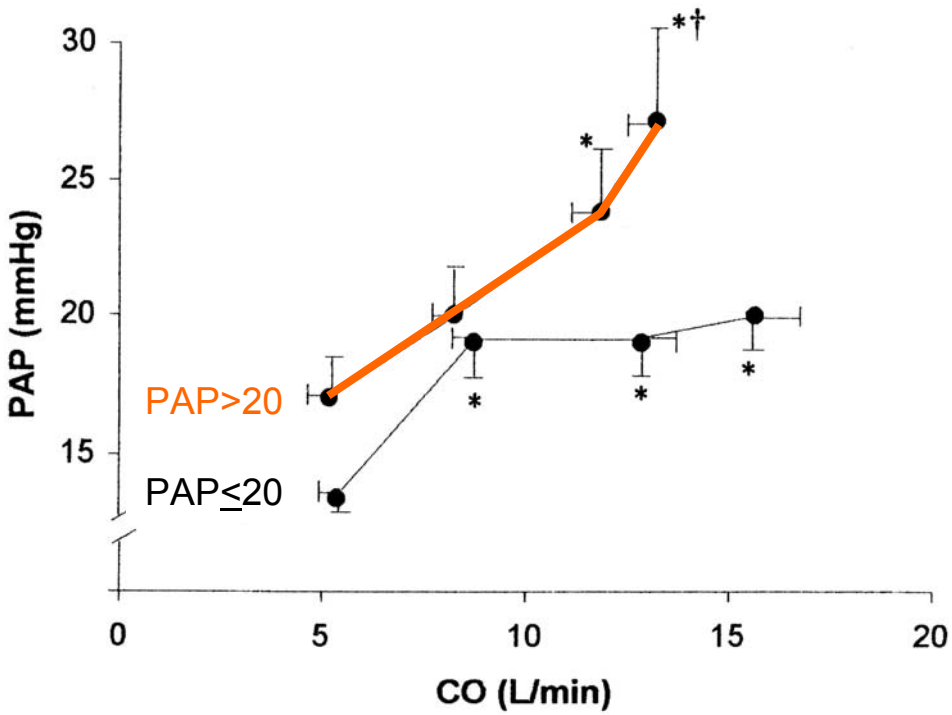
Sajkov et al. AJRCCM 1999;159:1518

Characteristics of Patients with OSA & PH w/o Cardio-Pulmonary Disease

Hypoxic Vasoreactivity

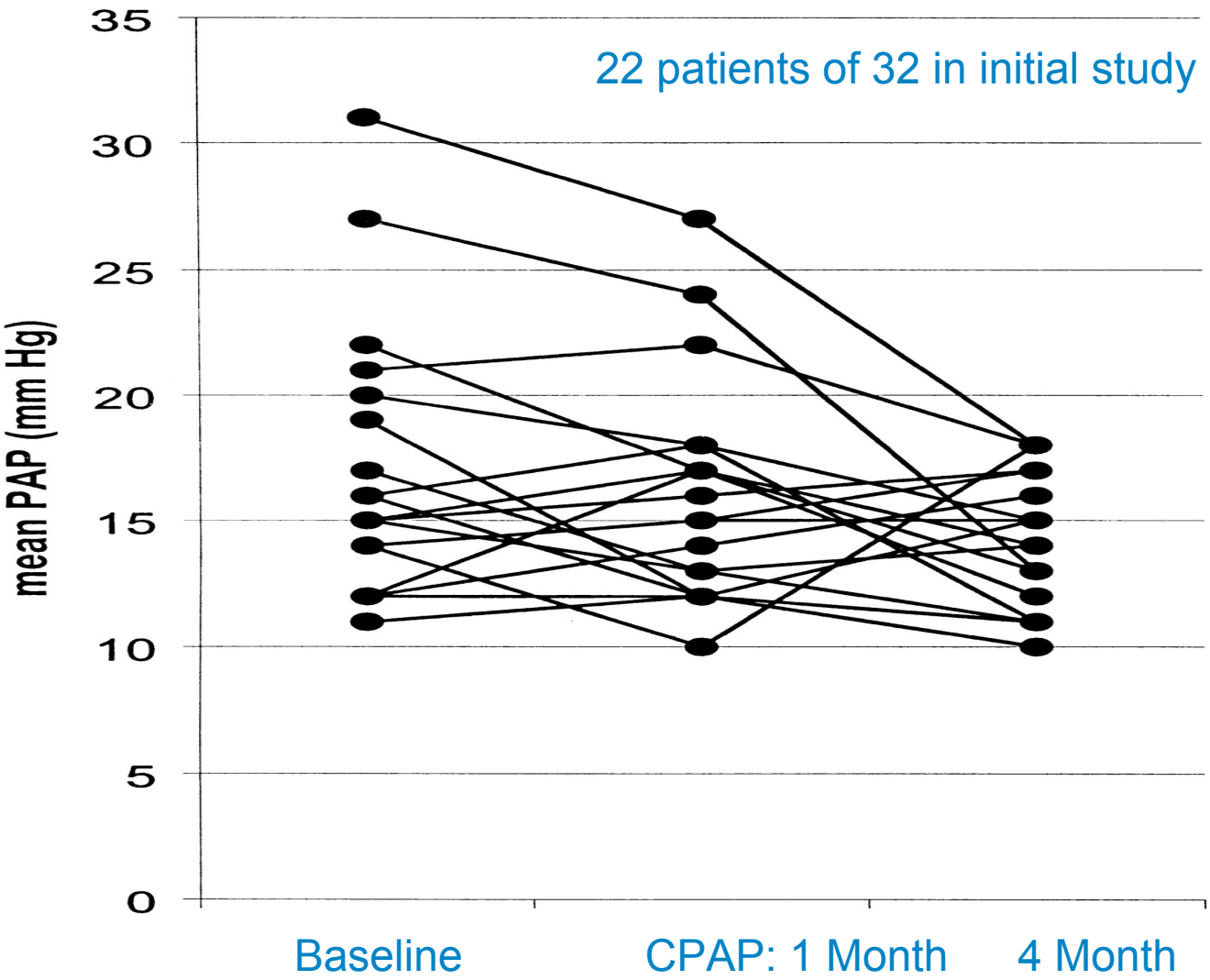


PAP Response to Dobutamin



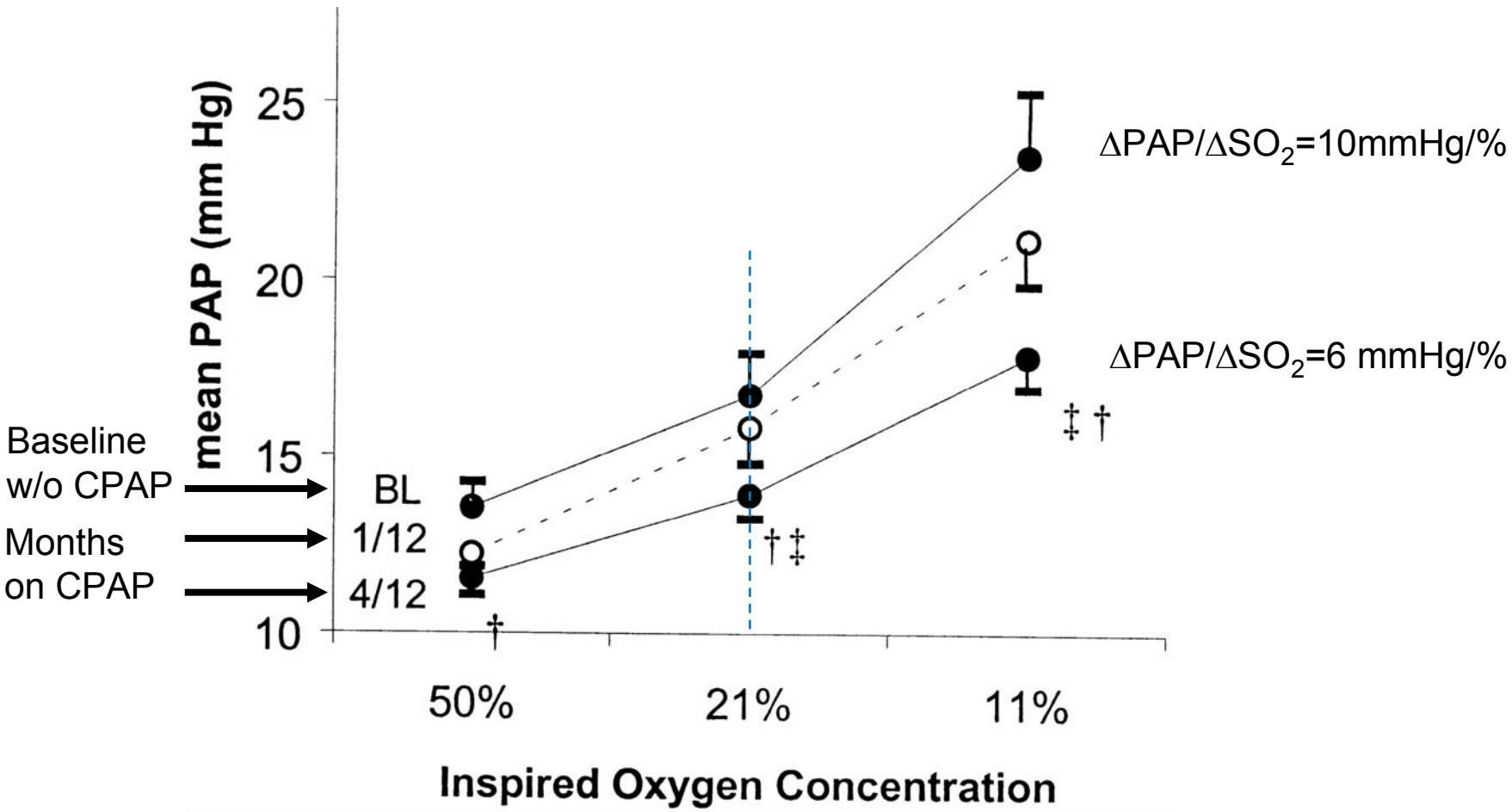
Sajkov et al. AJRCCM 1999;159:1518

Effect of CPAP in OSA with PH



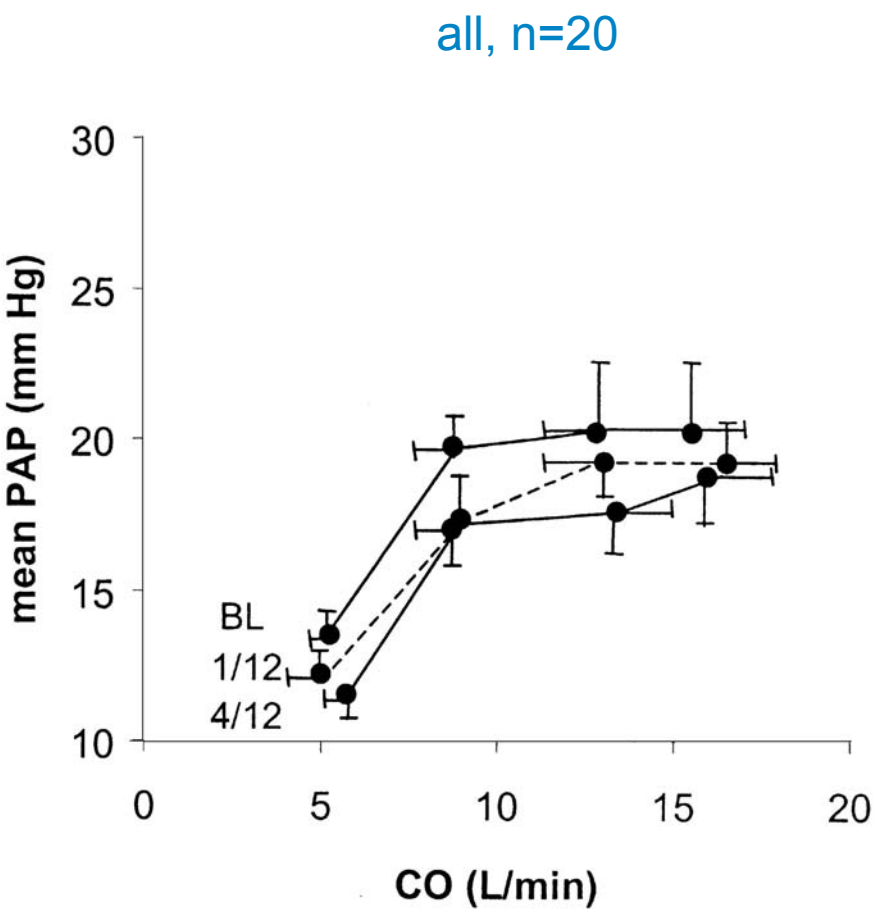
Sajkov et al. AJRCCM 2002;165:152

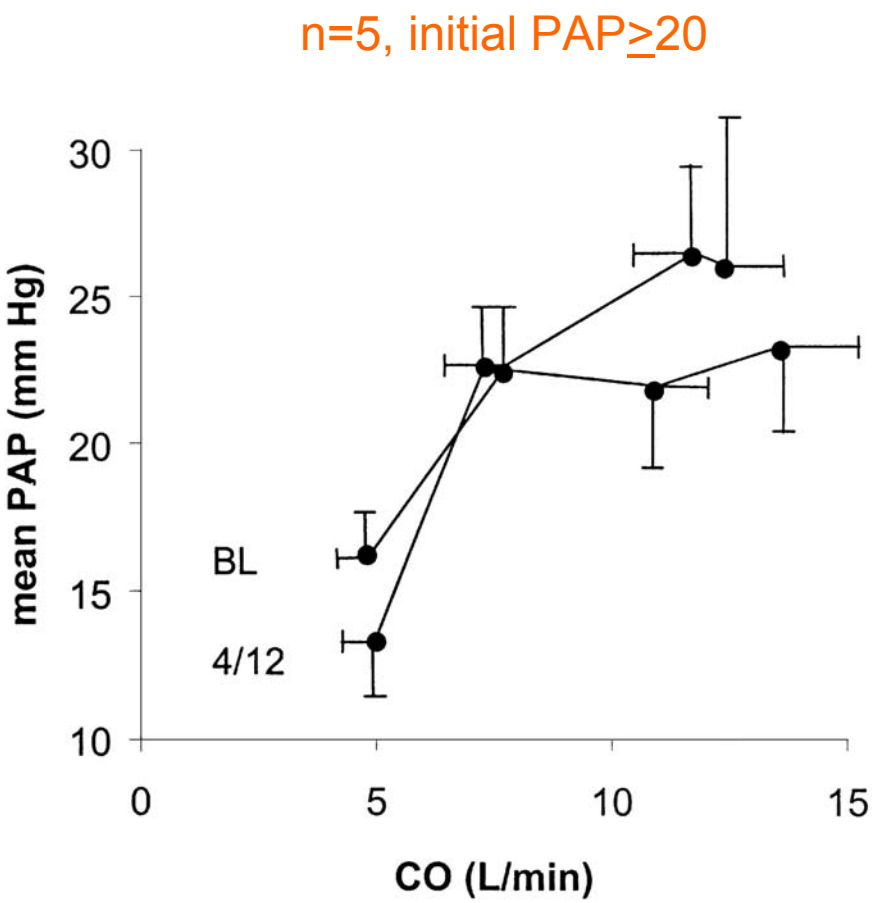
Effect of CPAP on Hypoxic Vasoreactivity



Sajkov et al. AJRCCM 2002;165:152

Effect of CPAP on Pulmonary Flow Reserve





Sajkov et al. AJRCCM 2002;165:152

Randomized Trial on Effect of CPAP on PAP in OSA

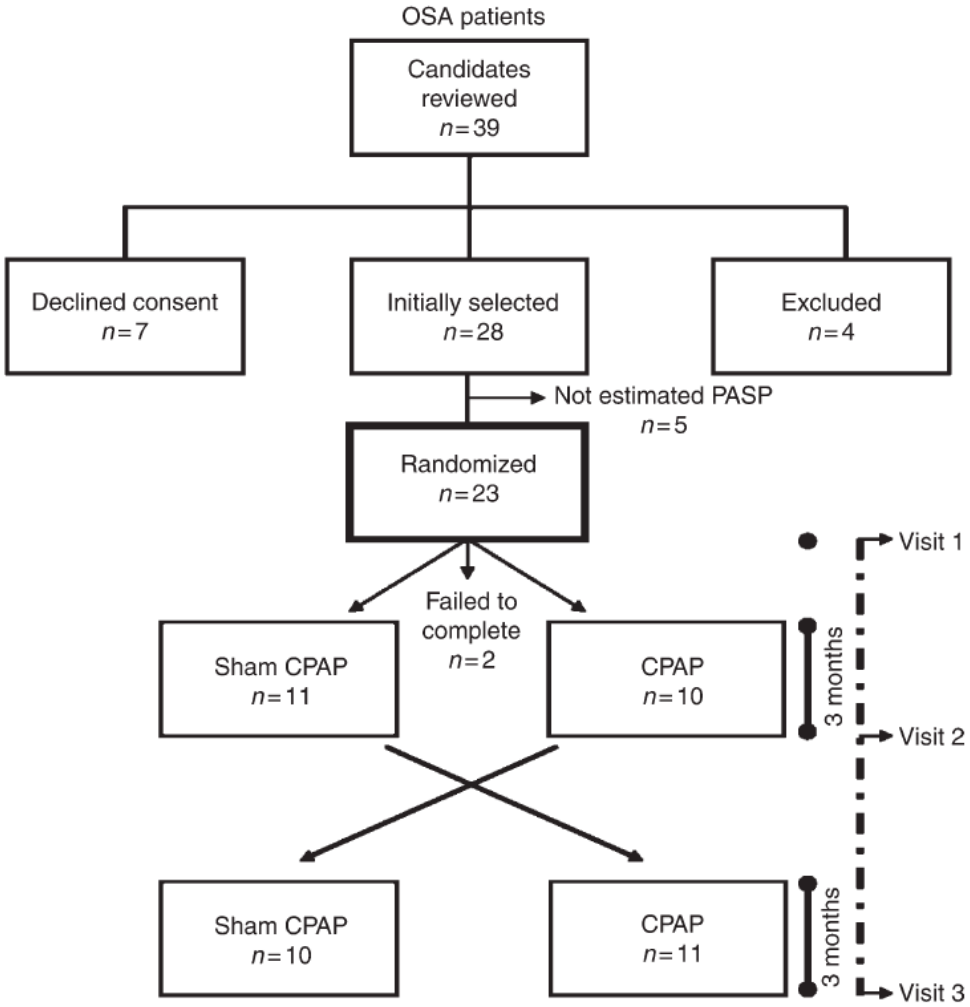


Figure 1 Study protocol.

Inclusion criteria
AHI≥10/h
Epworth≥10

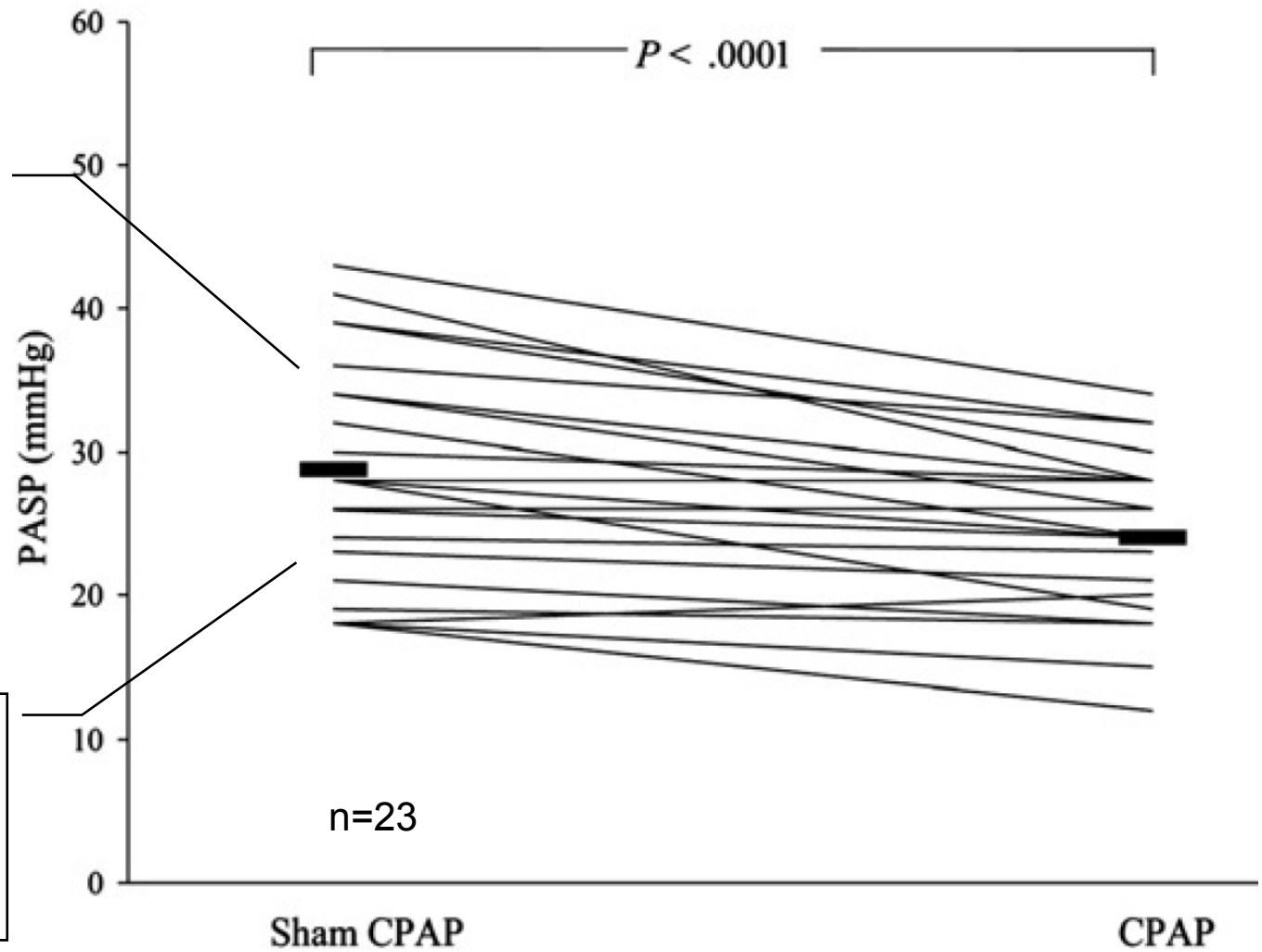
Exclusion criteria
Lung disease
Heart disease
Systemic hypertension
Diabetes

Arias et al. Eur J Cardiol 2006;27:1106

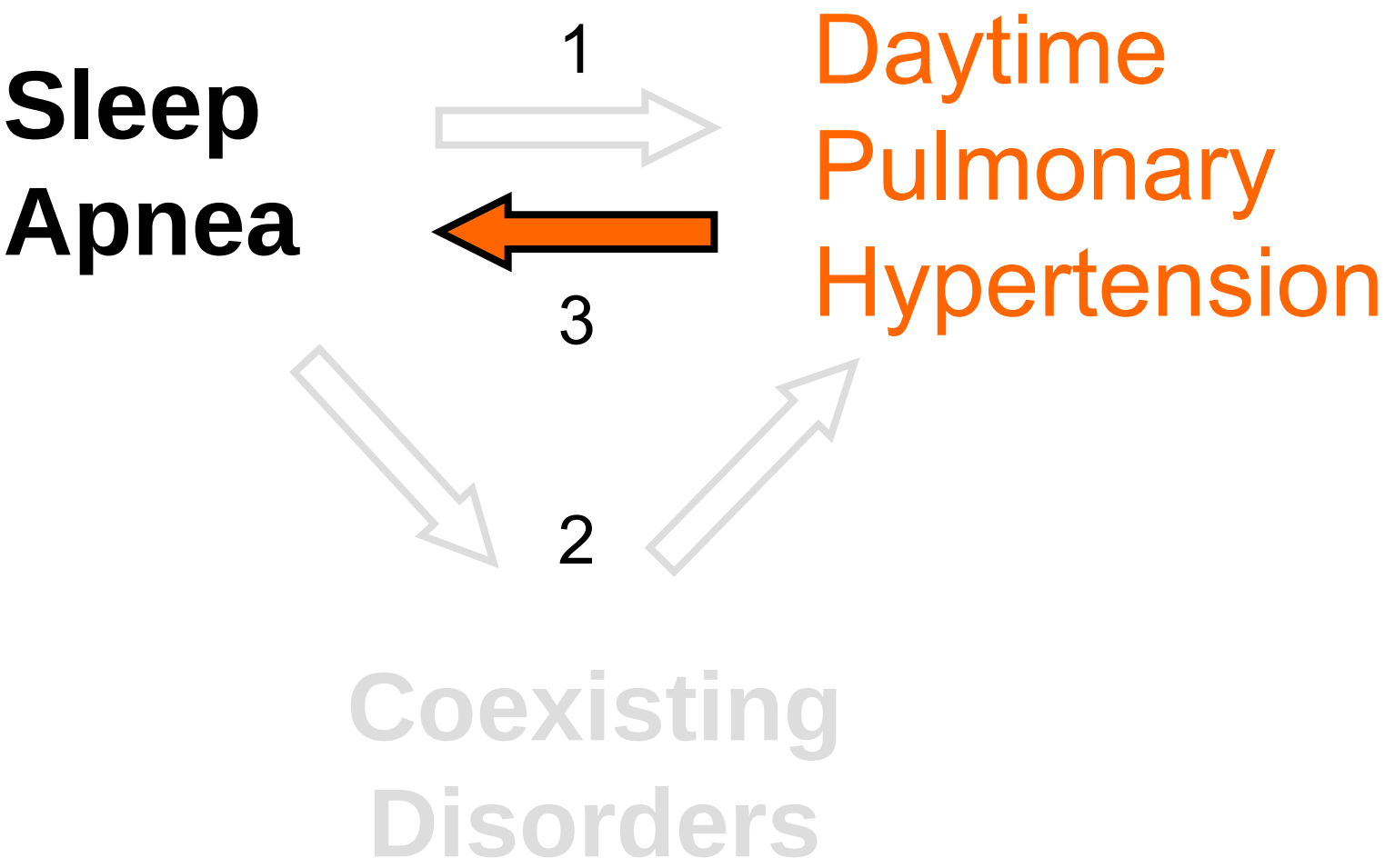
PH in OSA: Effect of CPAP

PAPs>30mmHg
AHI 69 ±25/h
BMI=33.6 ±4.4 kg/m^2
FVC 94 ±12 %pred

PAPs<30mmHg
AHI 25 ±15/h
BMI=28.9 ±2.9 kg/m^2
FVC 117 ±15 %pred
all P<0.05 vs. PAP>30



Arias et al. Eur J Cardiol 2006;27:1106


Sleep Apnea
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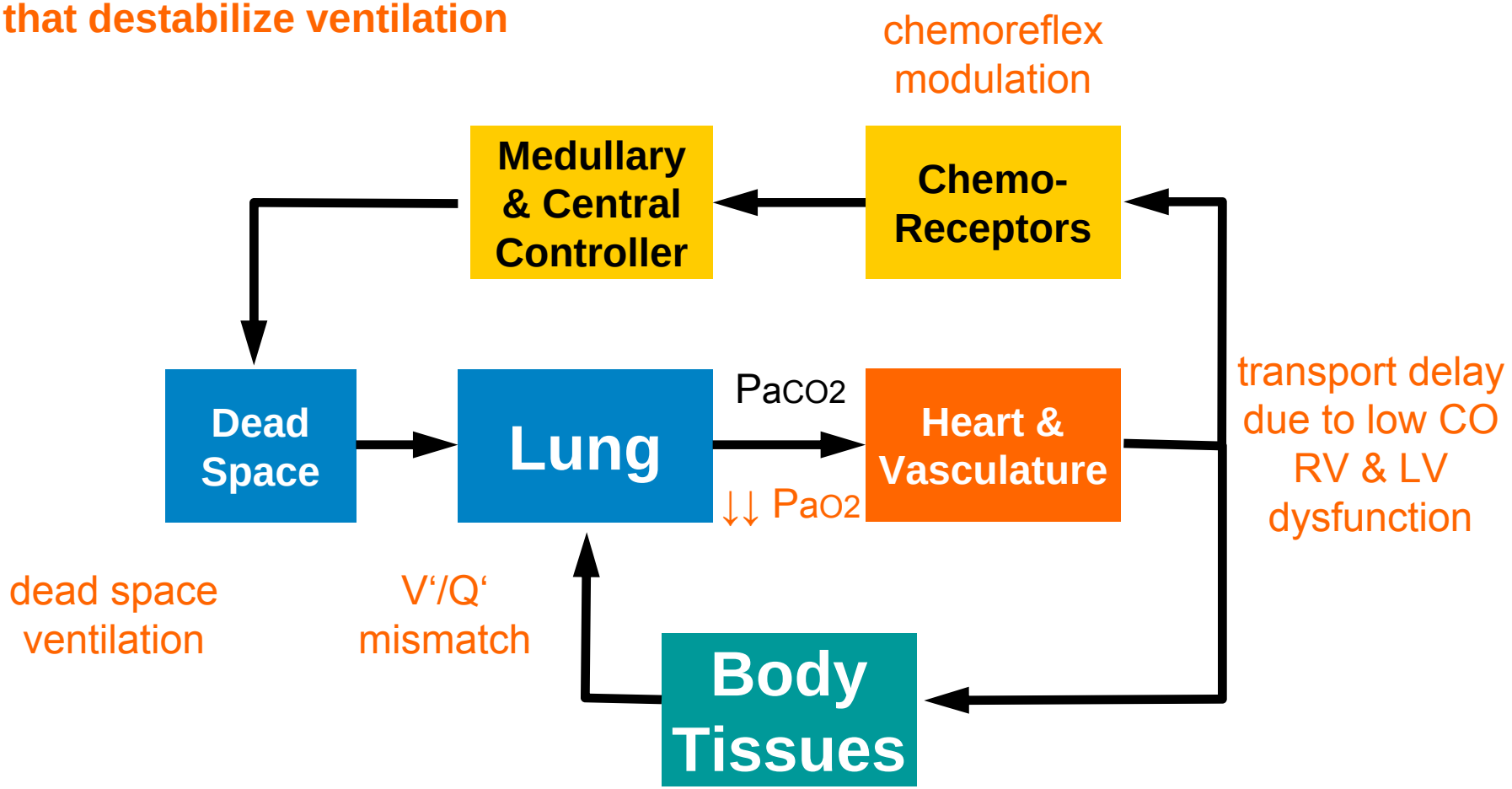
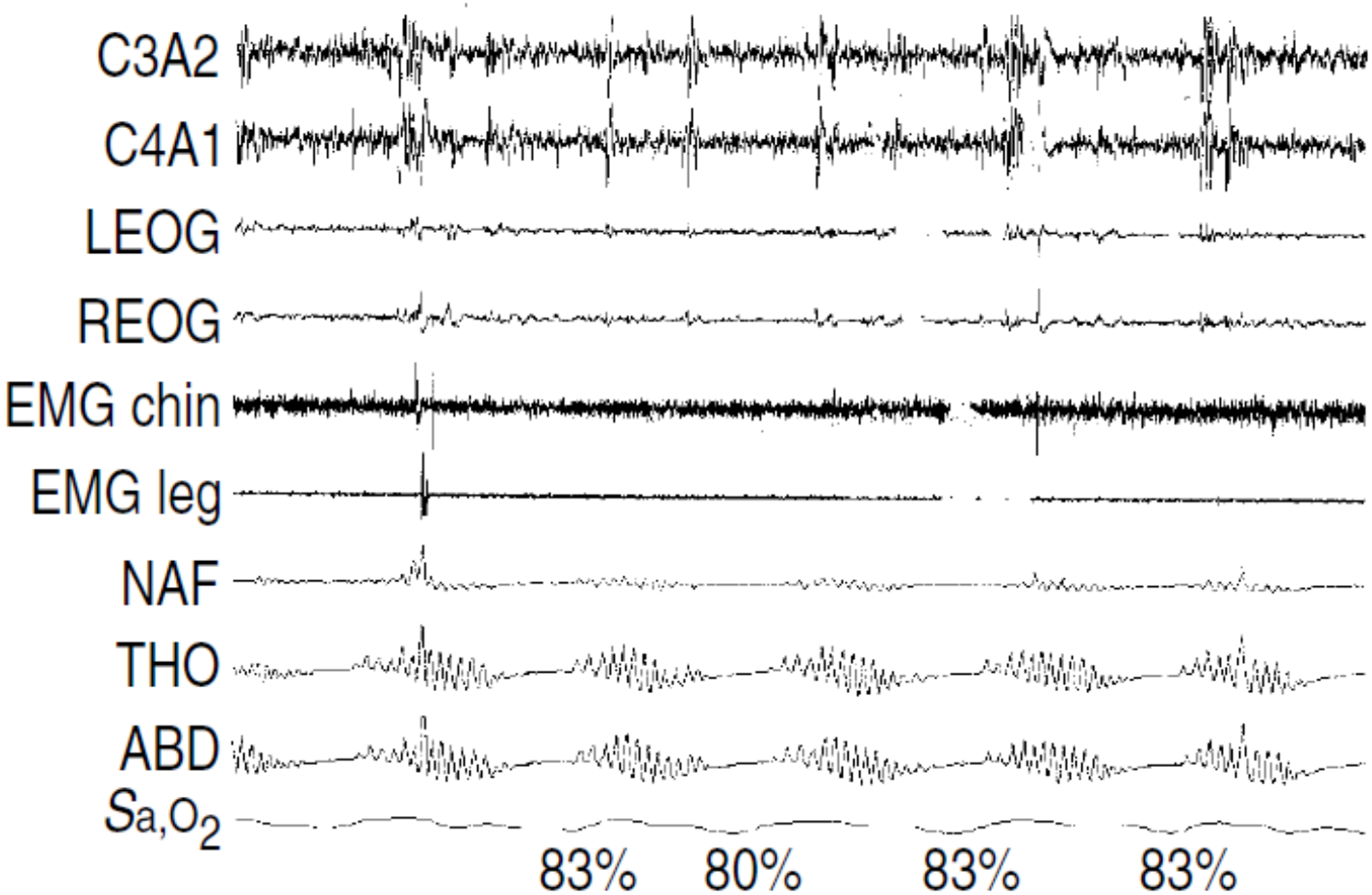
Control of Breathing

Alterations in LV and RV failure that destabilize ventilation



Khoo et al JAP 1982;53:644

Cheyne-Stokes Respiration in IPAH



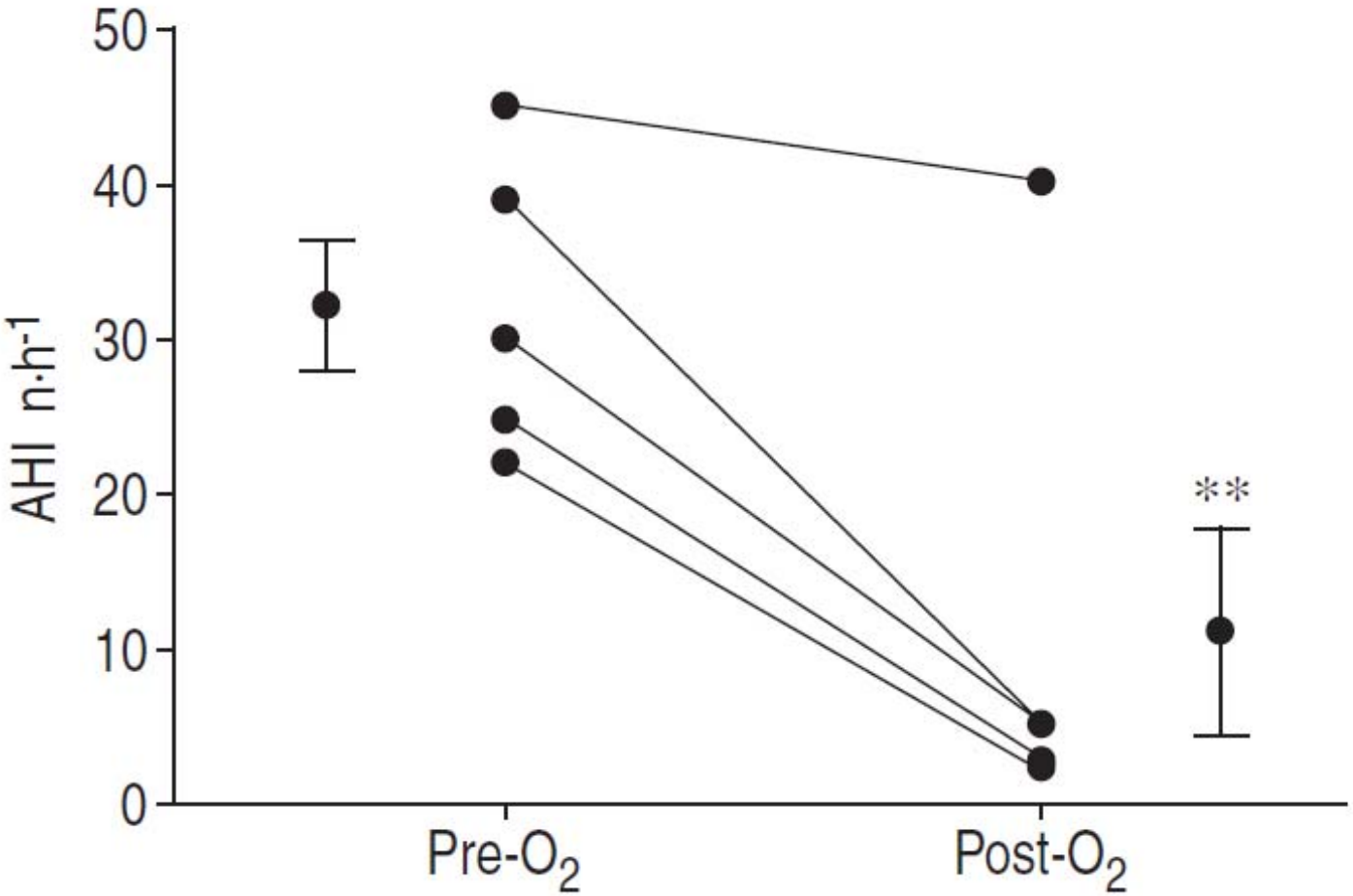
Schulz et al ERJ 2002;19:658

Cheyne-Stokes Respiration in IPAH

	No CSR, n=14	CSR, n=6
PAPm, mmHg	**53 ±4**	**63 ±2***
AHI, 1/h (>20/h)	9 ±3	37 ±5*
Nocturnal SpO_2, %	92 ±1	89 ±1*
DLCO, %pred.	70 ±4	57 ±5*
PaO_2, mmHg	9.1 ±0.7	6.6 ±0.9
$PaCO_2$, mmHg	3.9 ±0.2	3.9 ±0.1
CI, L/min/m^2	2.21 ±0.2	1.38 ±0.1*
RVEF, %	20 ±2	7 ±1%*

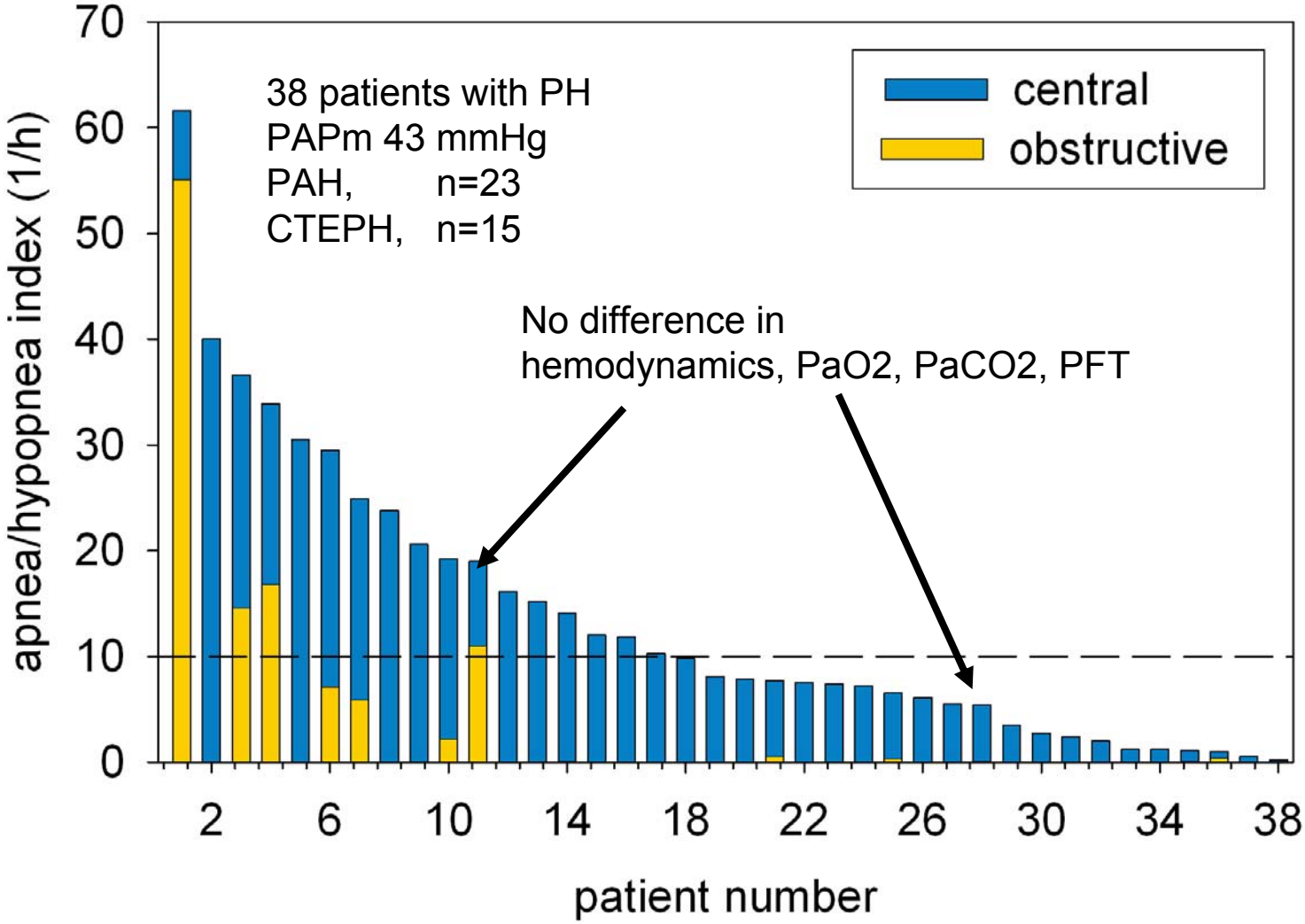
Schulz et al ERJ 2002;19:658

Oxygen Therapy in IPAH with CSR



Schulz et al ERJ 2002;19:658

OSA and CSR in PH



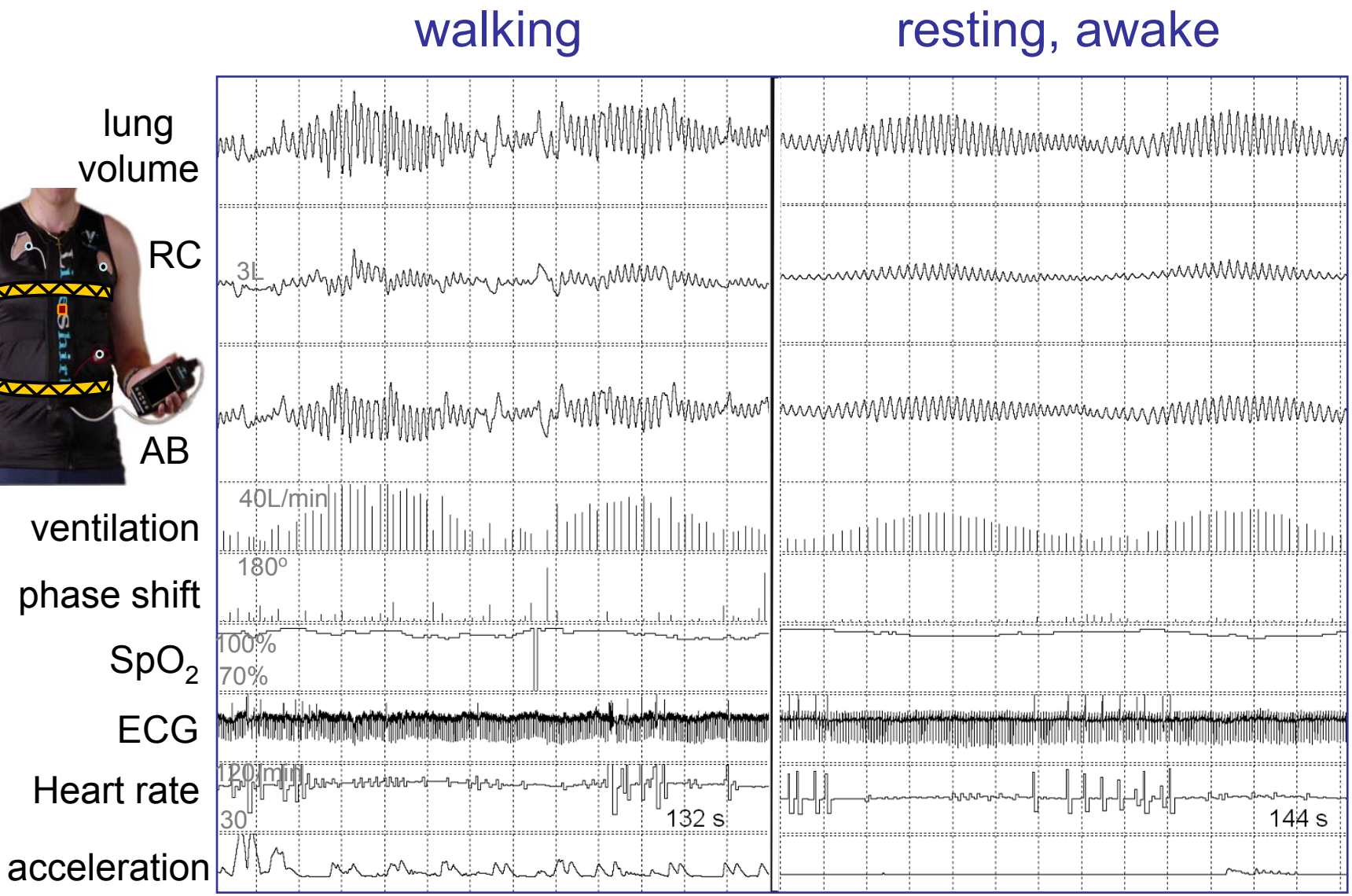
Ulrich et al. Chest 2008;133:1375

QoL in Patients with PH & CSR

	No SA n=19	CSR Central AHI ≥10/h n=15 (39%)
Epworth score	6 (4-10)	8 (7-10)
MSLHF physical emotional	 19 (18-24) 7 (3-16)	 24 (21-28)** 10 (7-14)
SF-36 physical mental	 37 (31-45) 48 (39-59	 29 (26-35)** 55 (46-59)

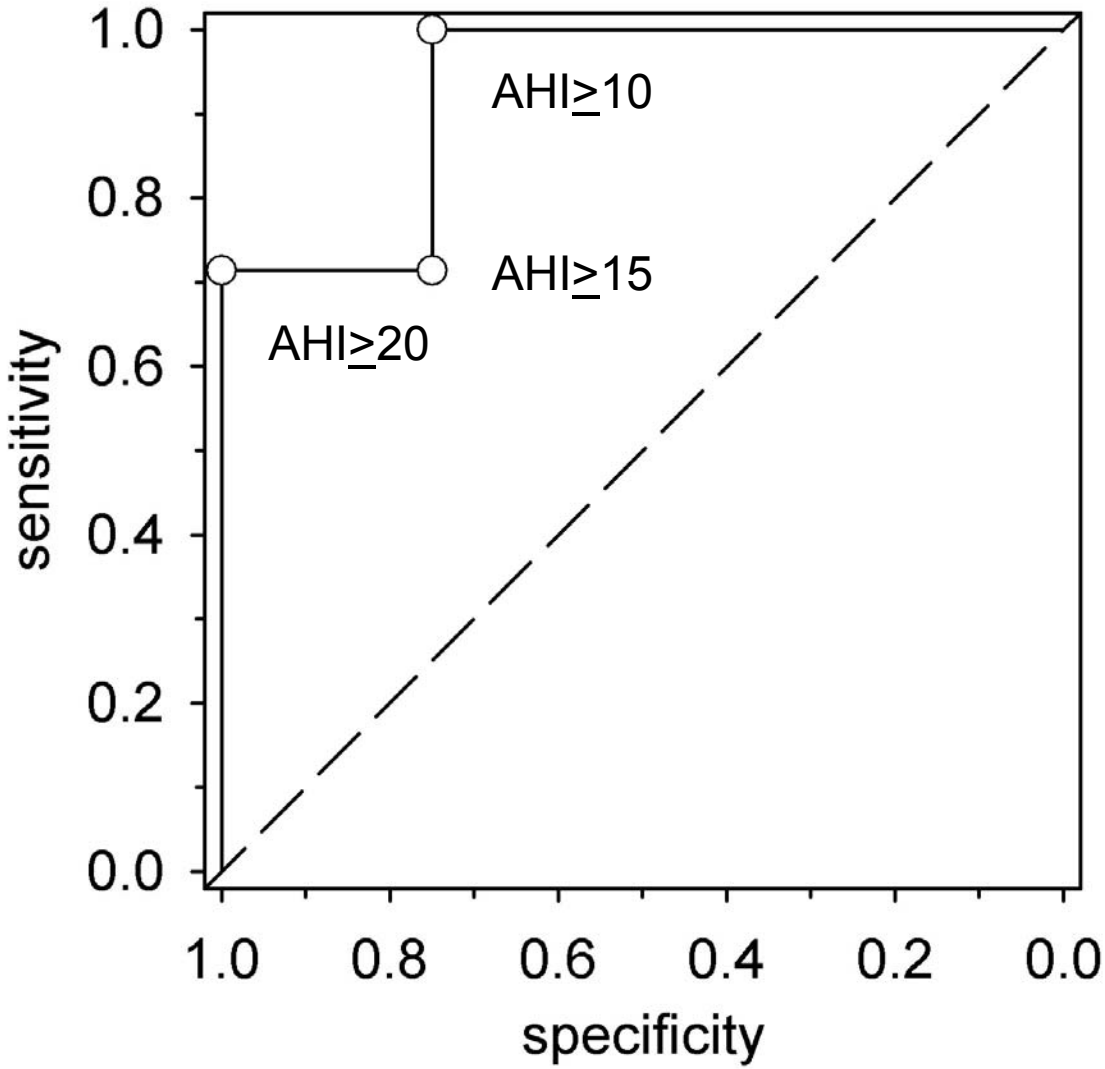
Ulrich et al. Chest 2008;133:1375

Daytime Cheyne-Stokes Respiration in LVF



Brack et al., Chest 2007;132:1463

Diagnostic Performance of Ambulatory Polygraphy Compared to PSG



Performance to predict Polysomnography AHI≥10/h

Polygraphy
ROC area 0.93 ±0.06

Pulse oximetry alone
ROC area 0.66 ±0.16

Ulrich et al. Chest 2008;133:1375

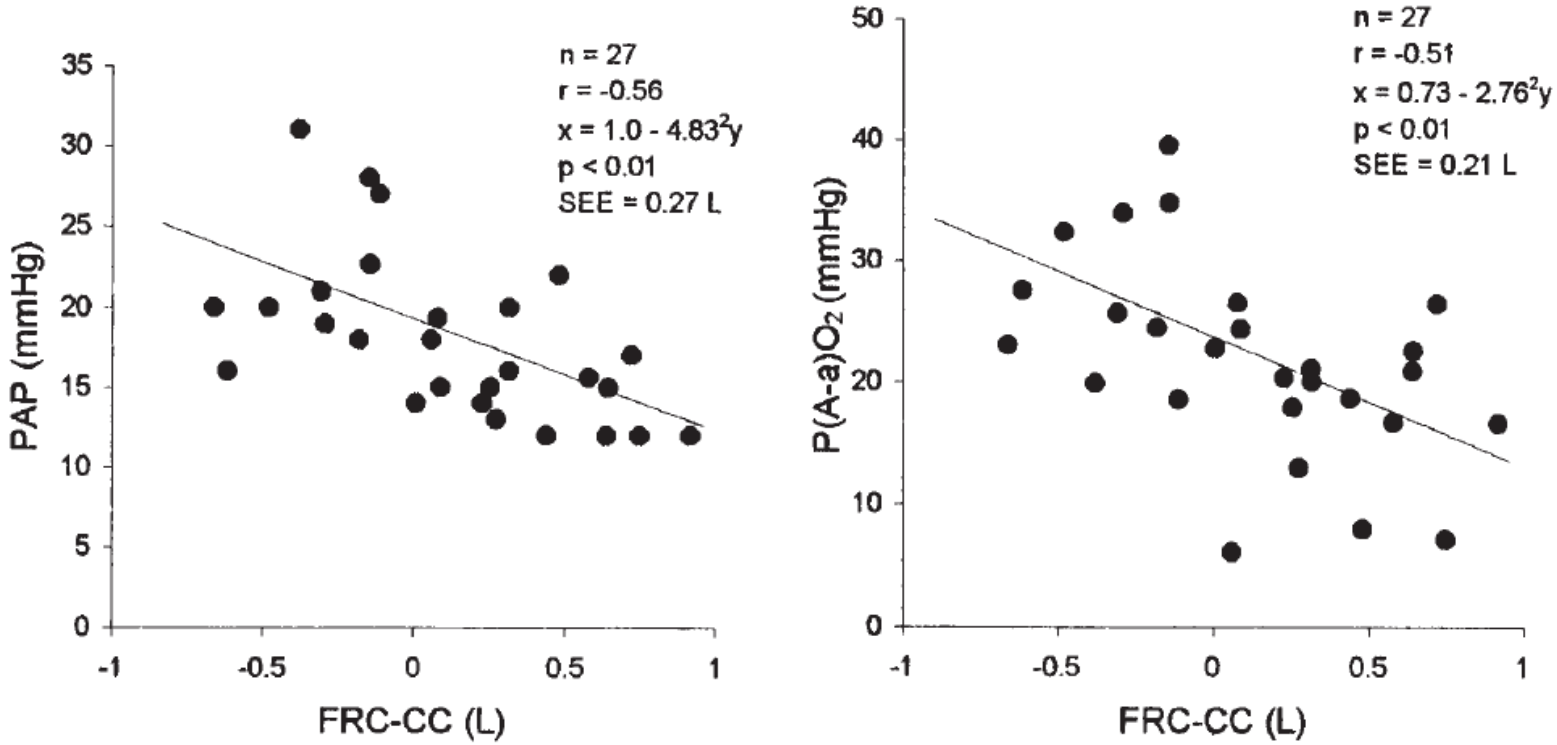
Conclusions OSA & PH

- <20-80% of OSA patients have PH
  - Confounders: obesity, COPD, CHF
  - Predictors: FEV1, PaO_2, $PaCO_2$, BMI
- PH may occur in OSA patients w/o cardiopulmonary disease
  - but is rare and mild
  - poor correlation with AHI
  - associated with increased hypoxic pulmonary vasoreactivity, may lead to vascular remodelling
  - is reversible with CPAP
- PH patients may have CSR and OSA
  - evaluation with ambulatory polygraphy
  - Treatment ? (oxygen)

Summary Cheyne-Stokes Respiration

- CSR and OSA are both common in CHF, stroke, pulmonary hypertension.
- Predictors of nocturnal CSR: age, severe CHF, atrial fibrillation, daytime CSR, low $PaCO_2$.
- CSR in CHF is associated with reduced physical activity and QoL and increased mortality.
- Since symptoms of CSR in CHF are non-specific patients at risk should undergo a sleep study.

Characteristics of Patients with PH and OSA



Sajkov et al. AJRCCM 1999;159:1518

- Pathophysiological link
  - Response of pulmonary circulation to hypoxia
  - OSA as a cause of PHTN
  - PHTN as a cause of CSR
- Clinical relevance PHTN in OSA, causal relationship?
  - Prevalence, association: in general in overlap syndrome
  - Symptoms, QoL
  - First studies in unselected patients: PH associated with poor lung function, impaired gas exchange and obesity
  - Subsequent studies in OSA with normal lung function and normal daytime PO2 also had PH.
  - Some OSA patients may show hyperreactive PA to hypoxia; see also OSA at altitude.
  - Recent studies reveald reduction in PH with CPAP
- Clinical relevance CSR&OSA in PHTN
  - Prevalence
  - Symptoms, QoL
  - Treatment
- Diagnosis

- 35‘max

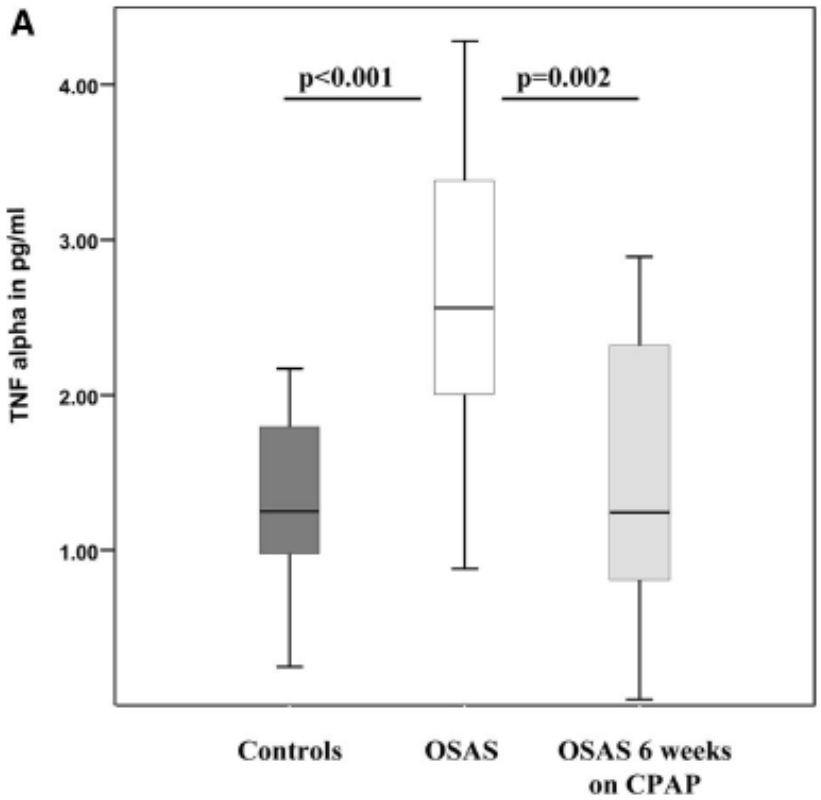
Mechanisms of CSR in Heart Failure

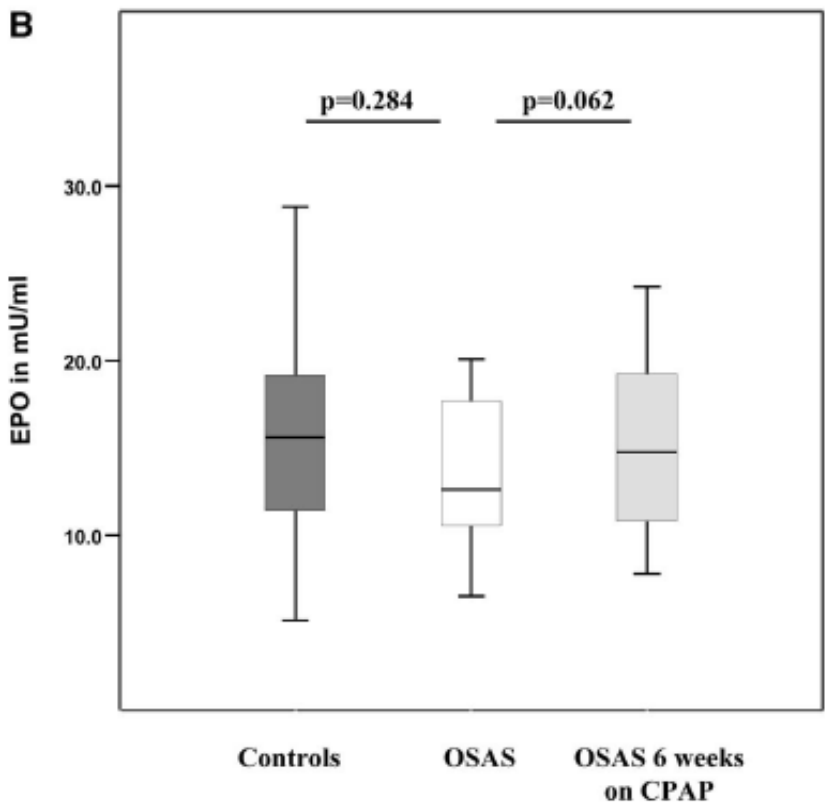
- Increased circulatory delay
- Sympathetic overstimulation
- Modulation of chemoreflex
- Altered gas stores, dead space ventilation
- Supine posture
- Combined LV and RV dysfunction
  elevated PVP

Links between PH and Sleep Apnea

- PH through coexisting disorders
  - OSA, COPD, Obesity-Hypoventilation, Cardiovascular Disease (postcapillary PH)
- PH is induced By OSA
- SA is induced by PH

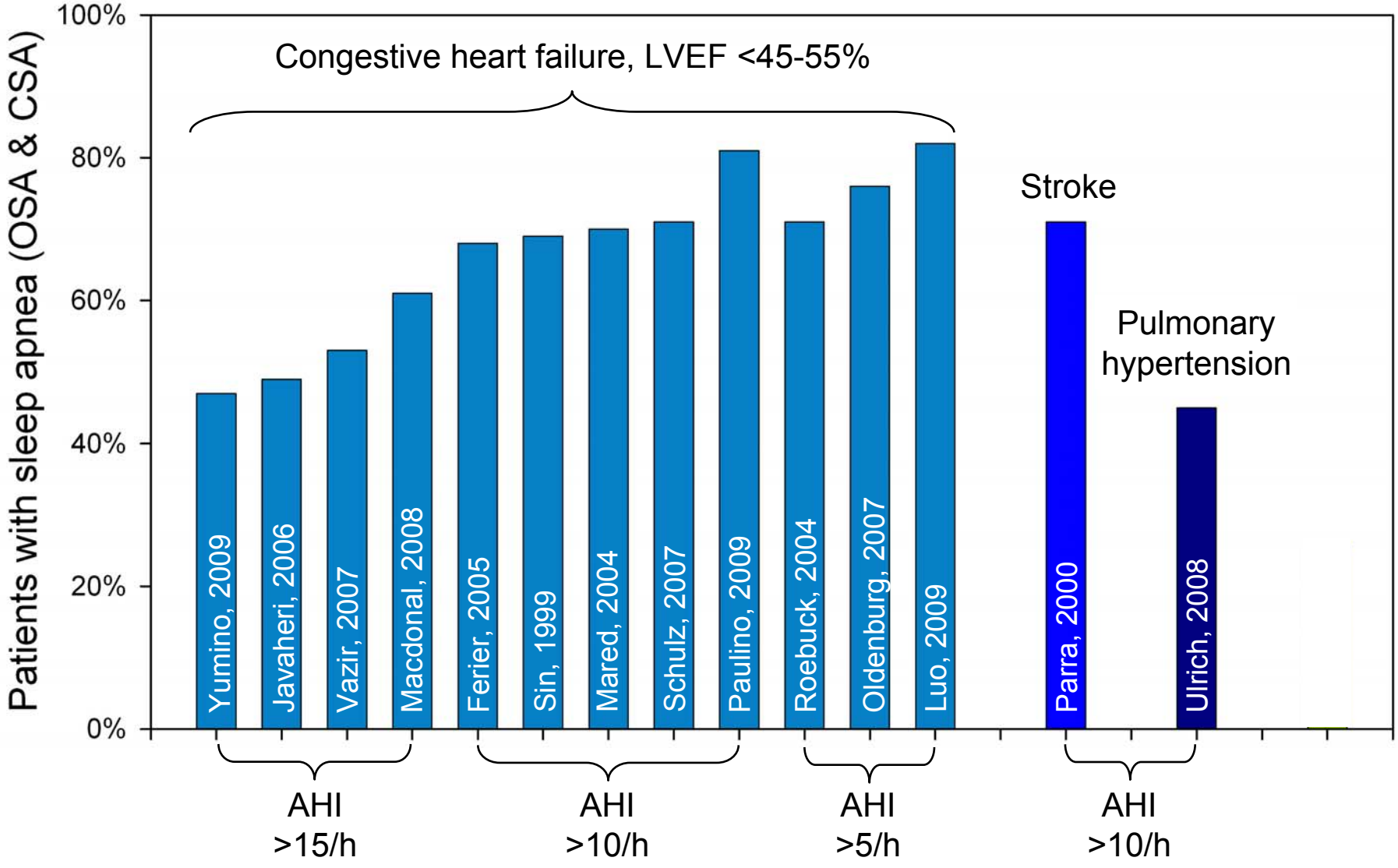
Intermittierende Hypoxie beim OSAS



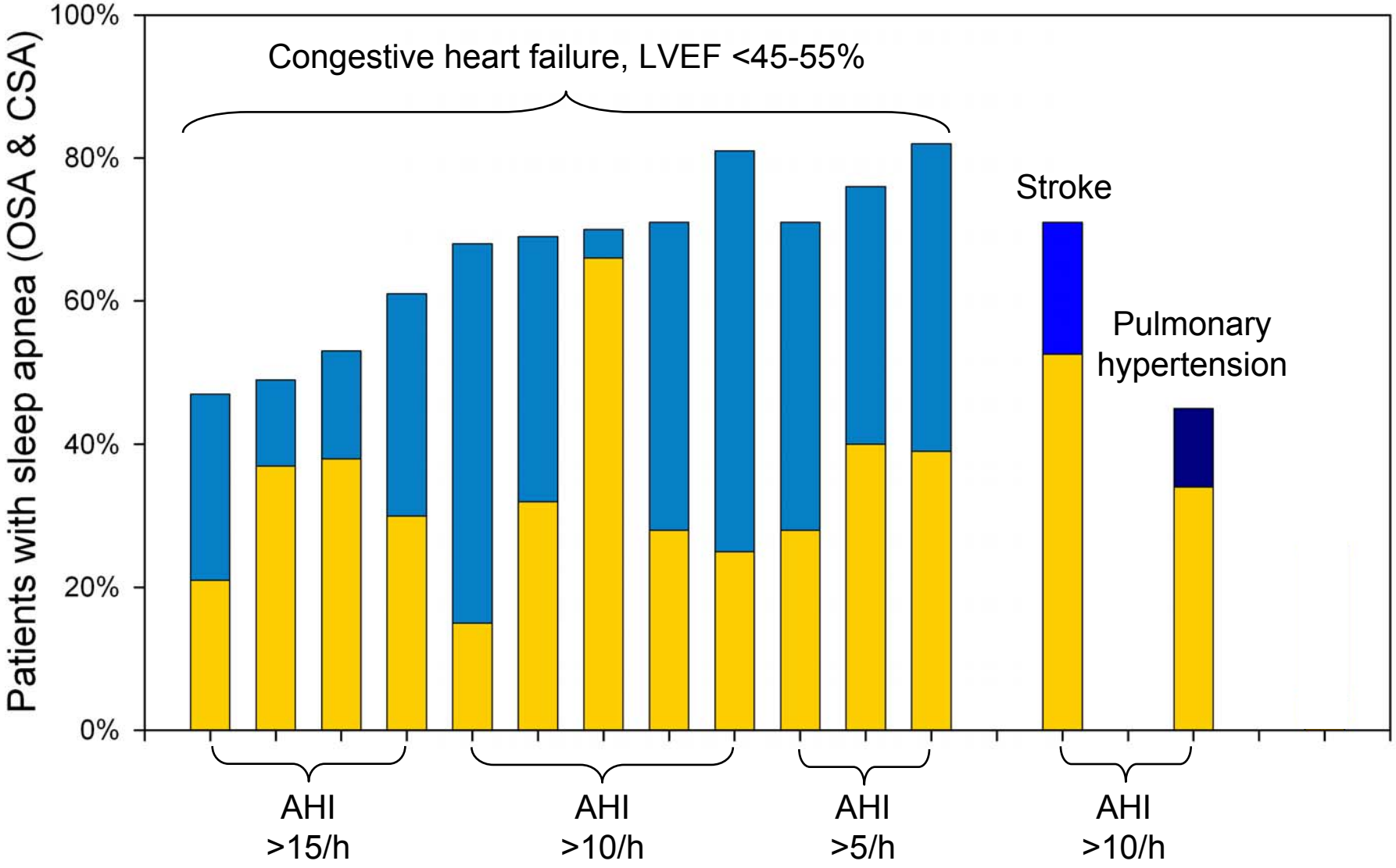


Ryan et al. Circulation 2005;112:2660

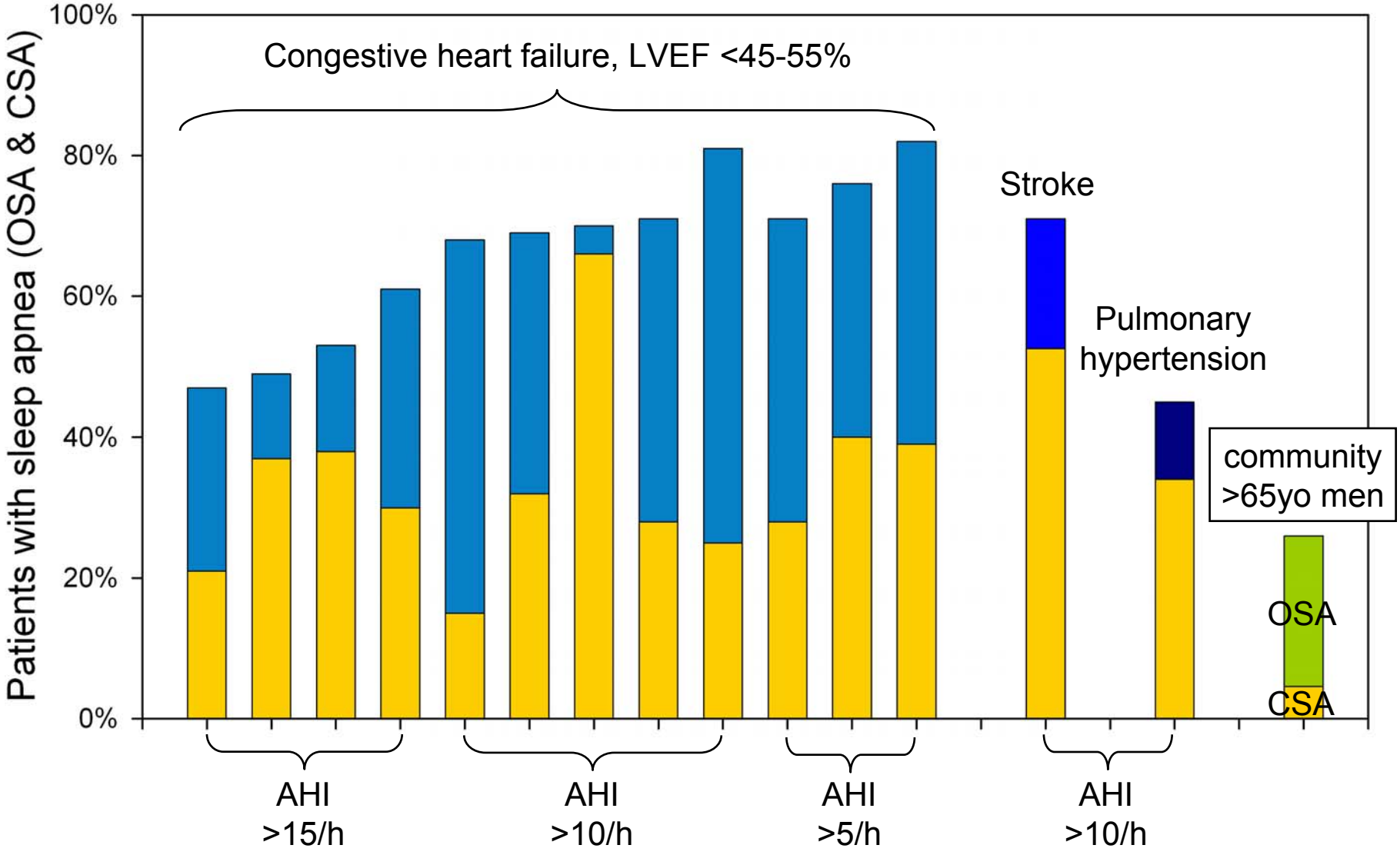
Sleep Apnea in CHF, Stroke & PHTN



Prevalence of CSR/CSA & OSA



Prevalence of CSR/CSA



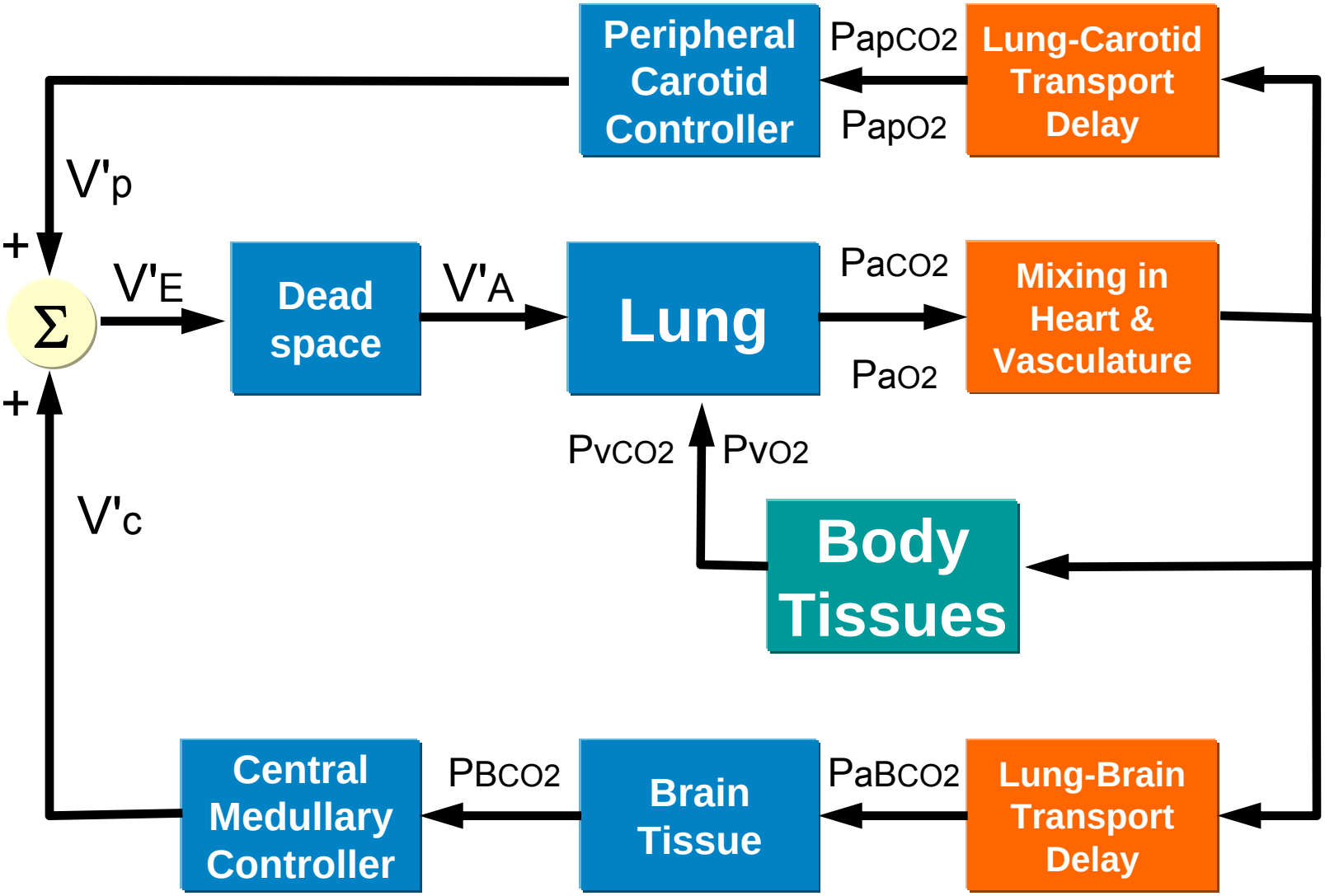
Characteristics of Patients with CHF & CSR

	no SA (AHI<5/h) n=169, 24%	CSR n=278, 40%
AHI	2±2	30±15*
Age, y	61±11	66±11*
Men, %	60	87
BMI, kg/m^2	25.8±3.7	26.3±4.1
NYHA	2.6±0.5	2.9±0.5*
LVEF, % (≤40)	28±7	27±7*
Atrial Fibr., %	14	35
6 min walk, m	377±118	331±111*

* P<0.05

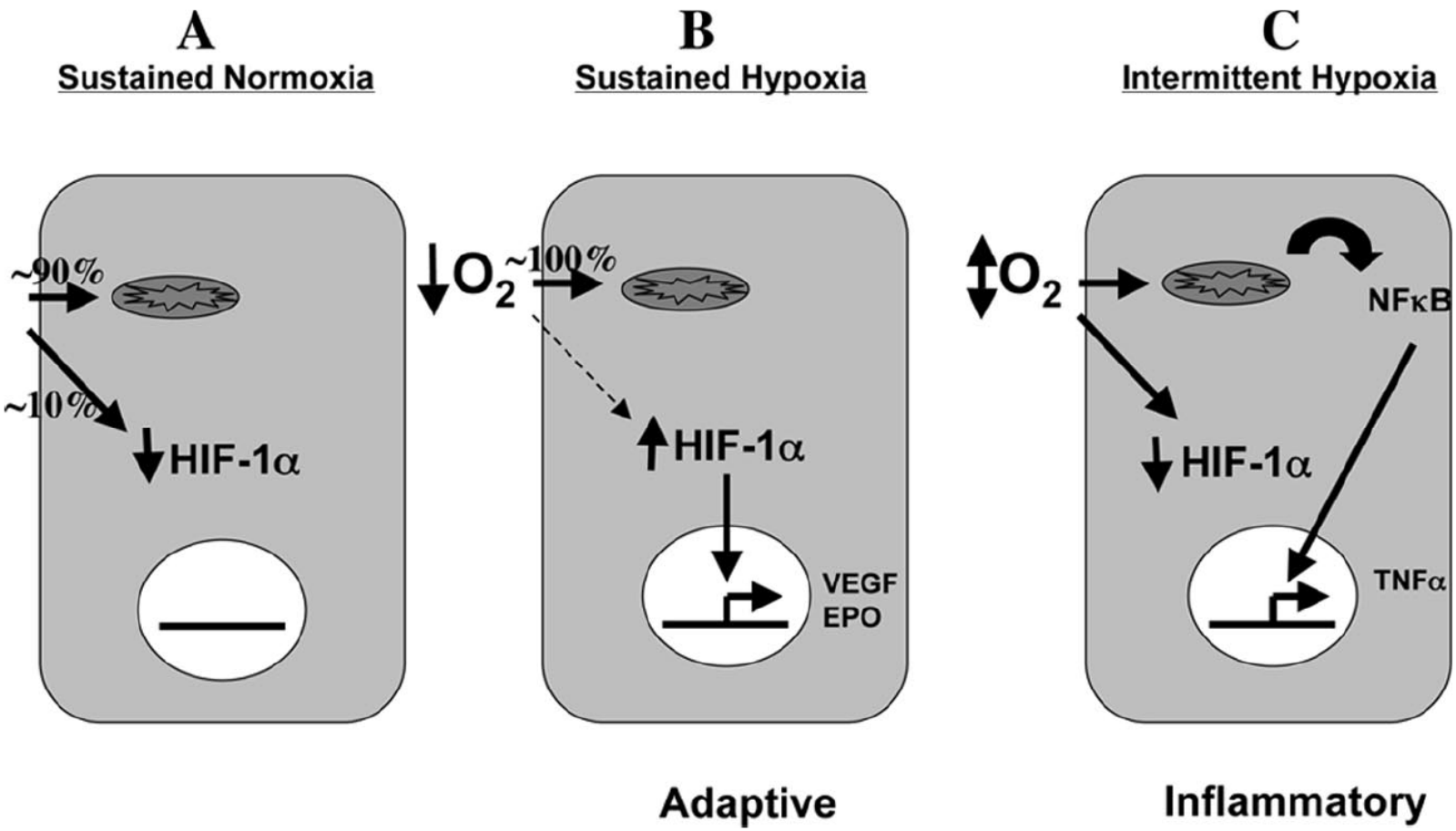
Oldenburg et al. Eur J Heart Fail 2007;9:251

Control of Breathing



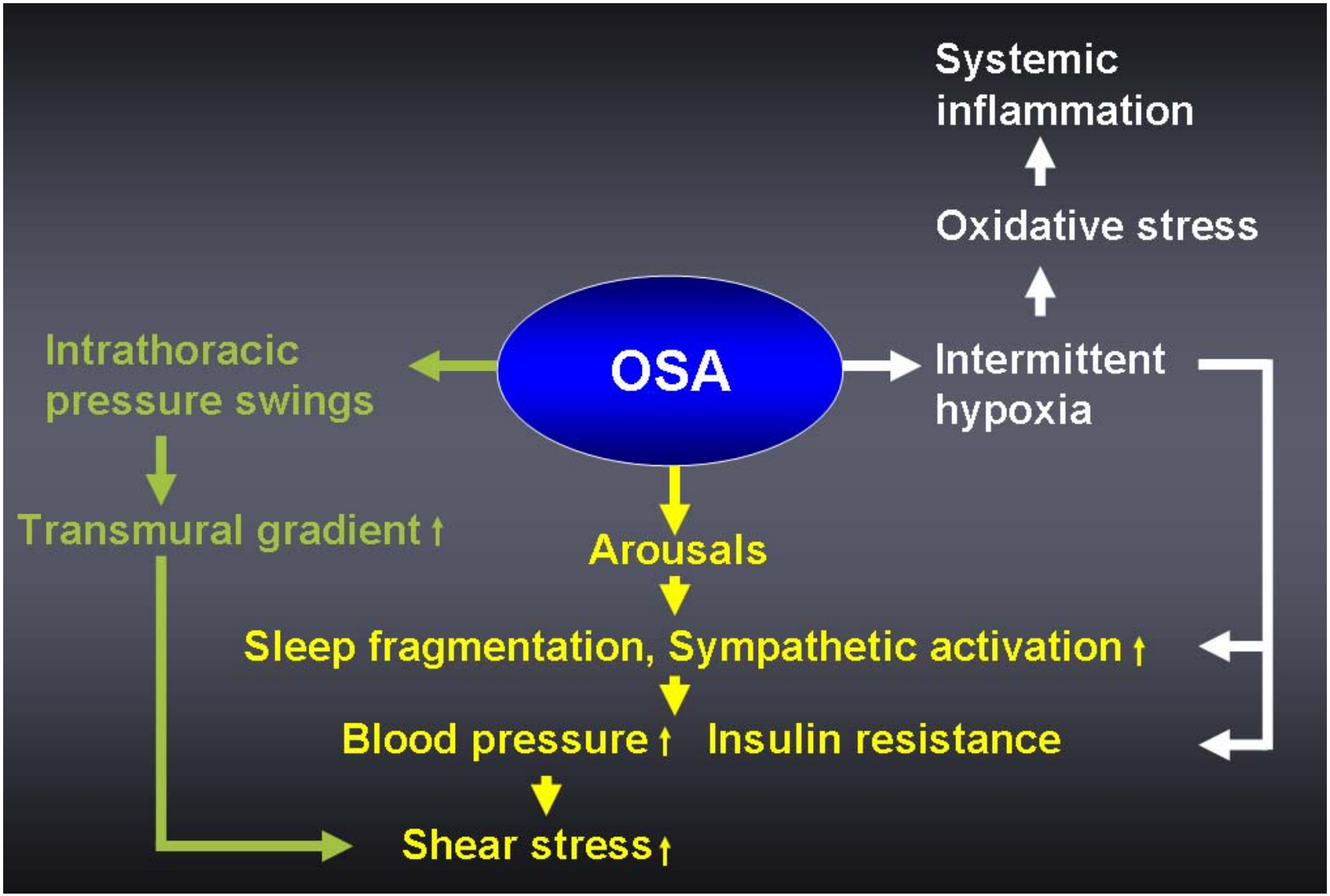
Khoo et al JAP 1982;53:644

Intermittent und Sustained Hypoxia



Ryan et al. Circulation 2005;112:2660

Mechanisms of PH in OSA

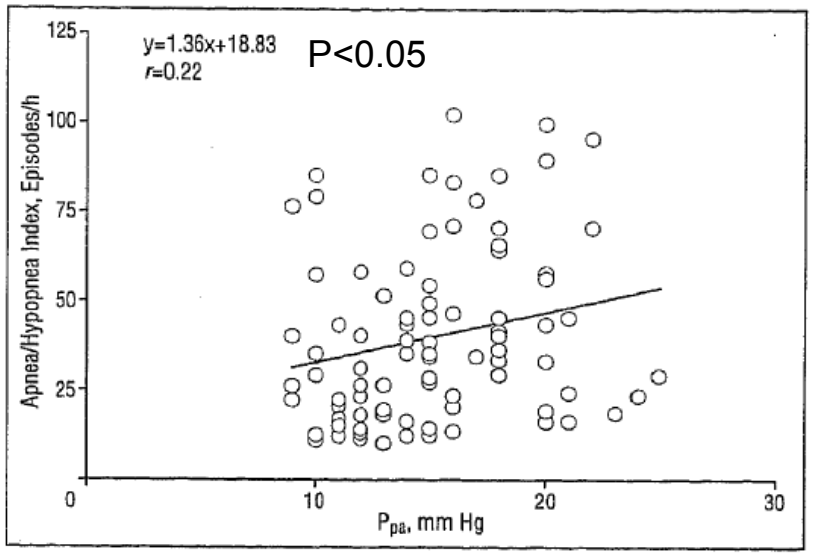


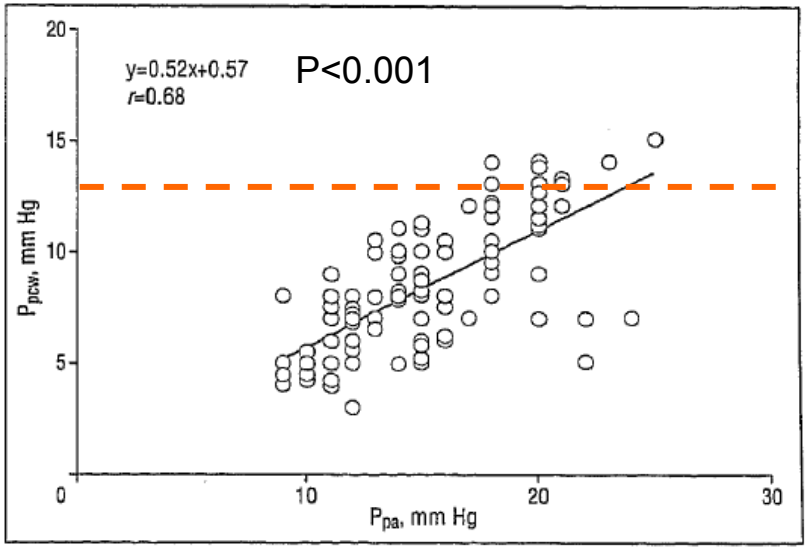
OSA&PH And Patients With Normal PFT

92 OSA patients
AHI>10/h, normal PFT,
Normal daytime ABG

n=74: PH Absent
AHI 39 ±23/h
Time SpO2<90% 19 ±25%

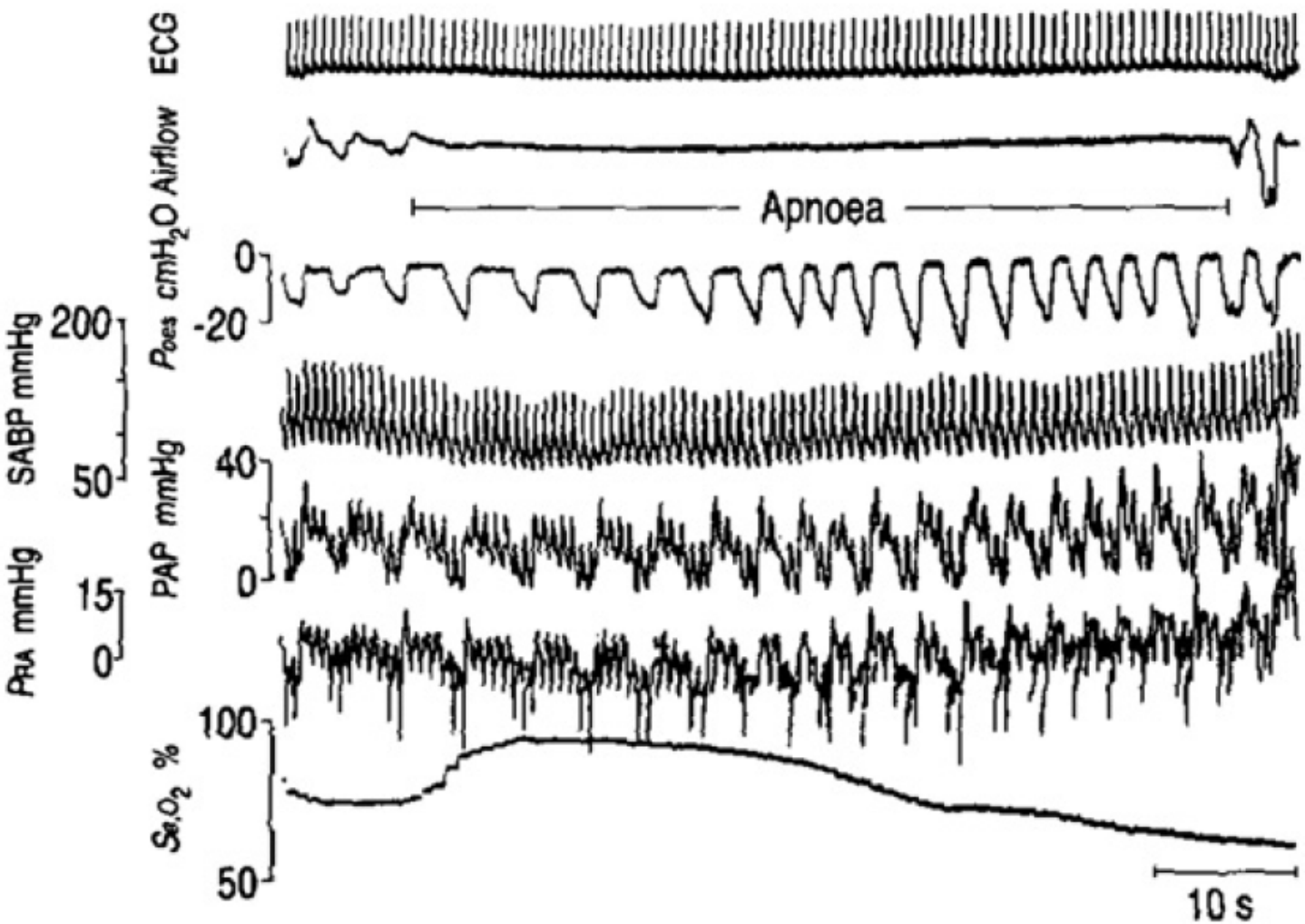
n=18 PAP>20 mmHg
AHI 44 ±28/h
Time SpO2<90% 41 ±37%





Sanner et al. Arch Int Med 1997;157:2483

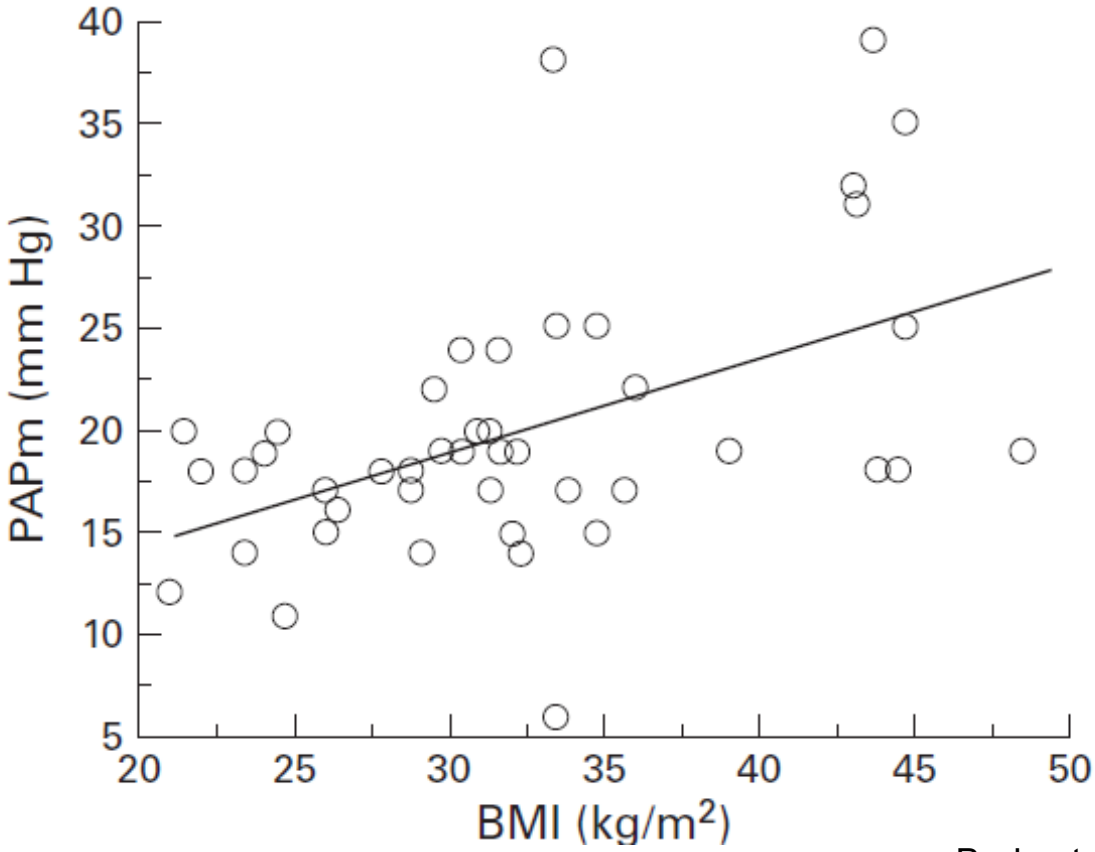
Hemodynamic Effects of Obstructive Apnea



Podzus et al. Marcel Decker, 1994

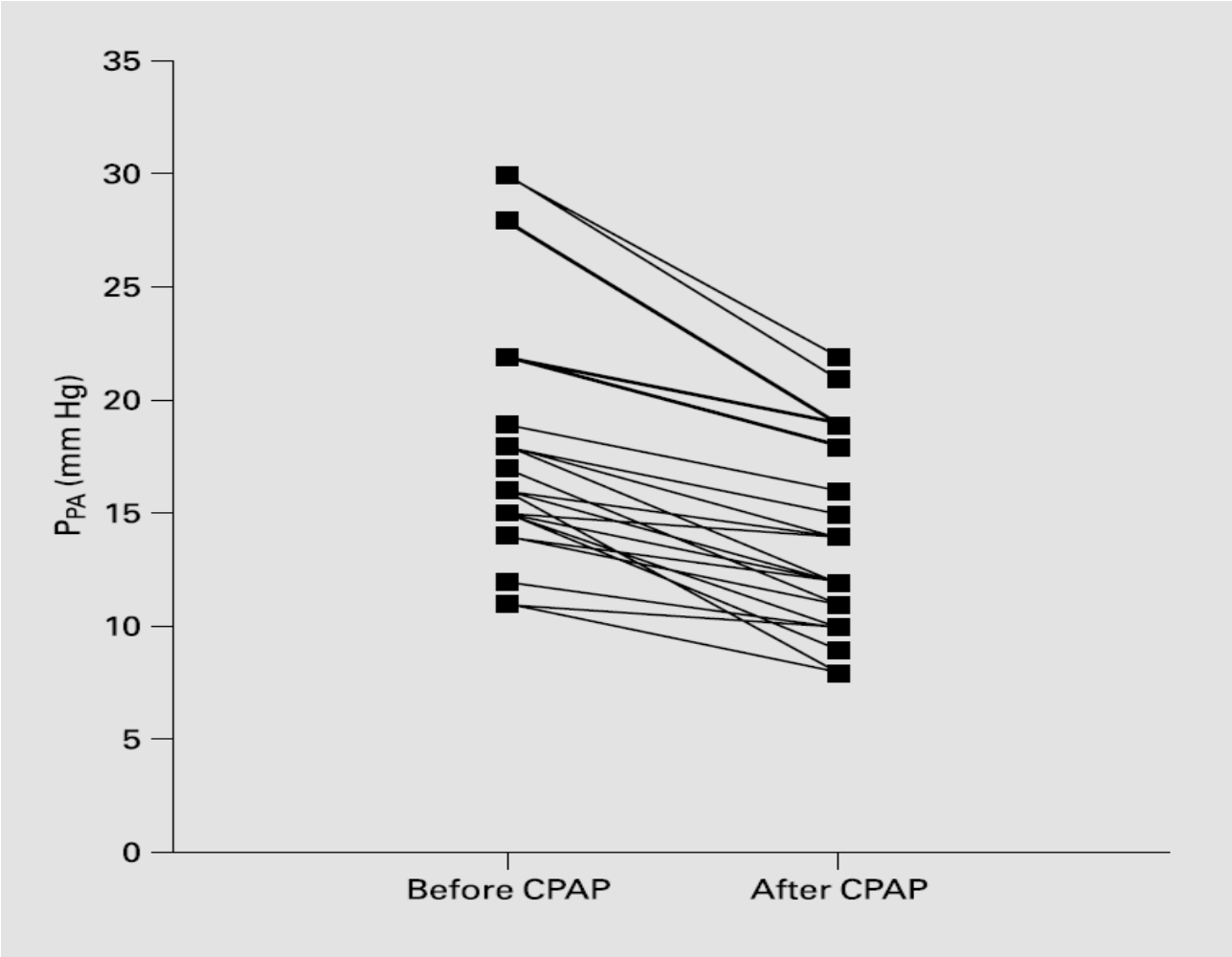
OSA, PH and Obesity

44 OSA patients, AHI>5/h, FEV1>70%, FEV1/FVC>60%
PH associated with: ↑BMI, ↓VC, ↓ERV, ↓PaO2, ↑PaCO2



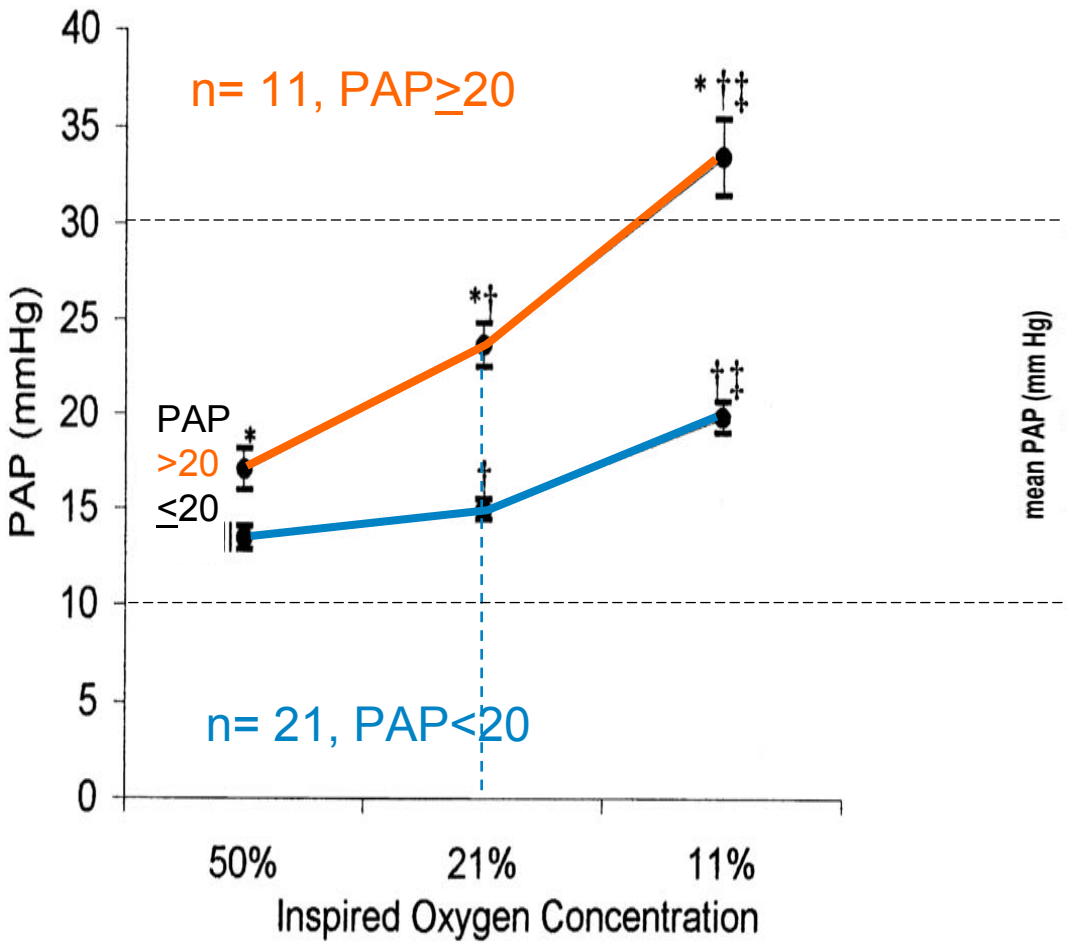
Bady et al. Thorax 2000;55:934

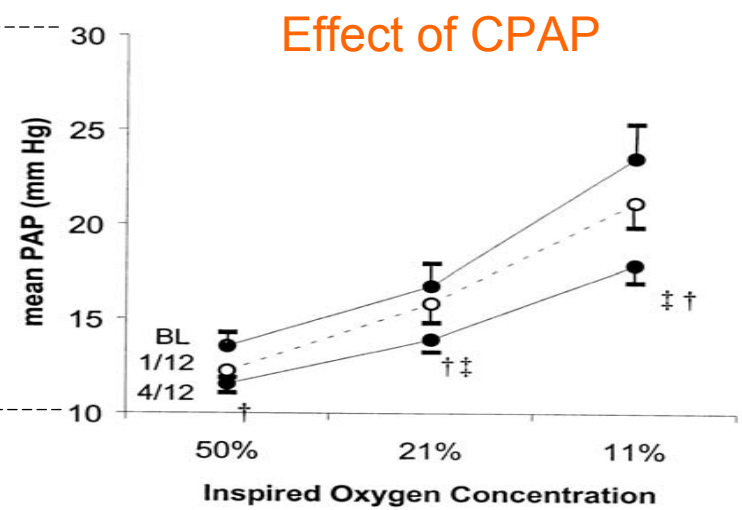
PH in OSA: Effect of CPAP



Alchanatis et al. Respiration 2001;68:566

Effect of CPAP on Hypoxic Vasoreactivity

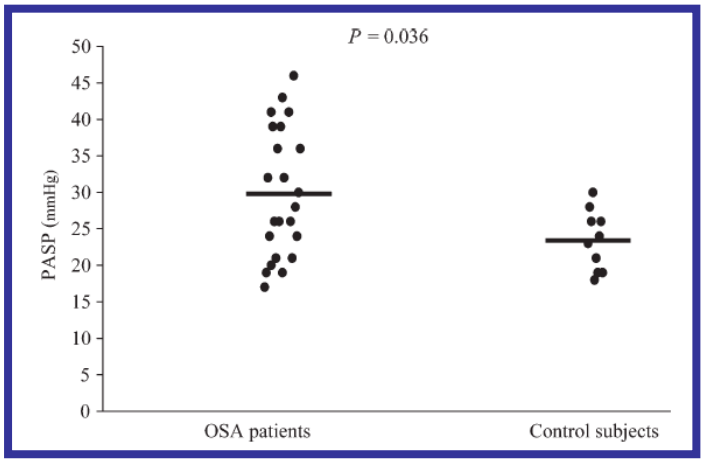




Sajkov et al. AJRCCM 1999;159:1518

Sajkov et al. AJRCCM 2002;165:152

Randomized Trial on Effect of CPAP on PAP in OSA



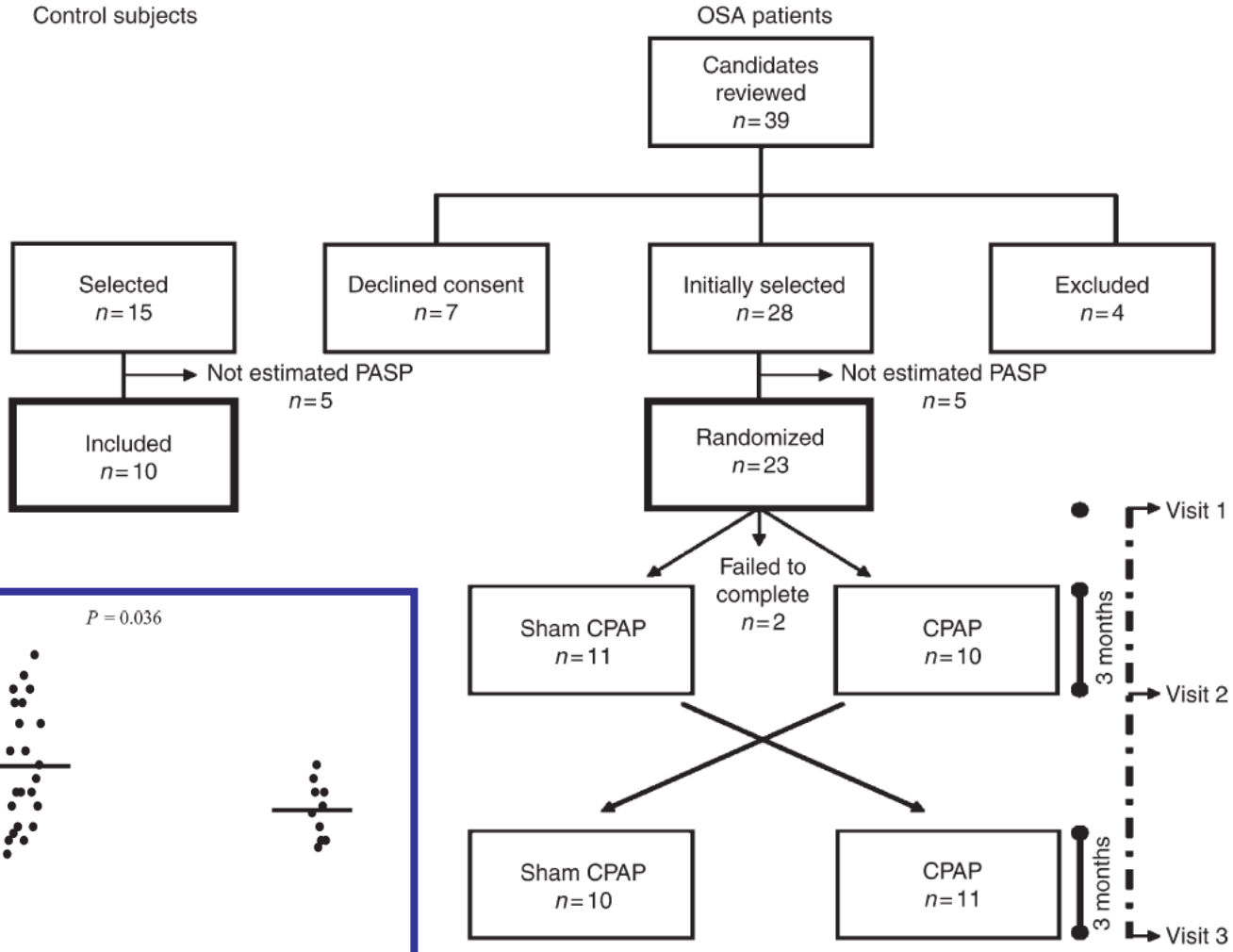


Figure 1 Study protocol.

Arias et al. Eur J Cardiol 2006;27:1106