Sleep disordered breathing in patients with precapillary pulmonary hypertension (PH)

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Agenda

- Sleep apnea leading to PH
  - Obstructive
  - Hypoventilation

To be differentiated!

- PH with sleep disordered breathing (SDB)
  - Pathophysiology and mechanisms
  - Prevalence
  - Potential treatment strategies

Does Obstructive Sleep Apnea lead to PH?

- Coccagna & Lonsdorfer 1972: catheters during PSG
  - Oscillations in PAP due to intrathoracic pressure swings
  - PAP highest immediate post apnea and in REM-sleep
  - PAP normalized in the morning awake
- Marone 1989 & Schäfer 1998: catheters and esophageal pressure to assess transmural vascular pressure
  - Mildly increased PAP during sleep (SPAP 28 to 38 mmHg), changes significantly correlated to ΔSpO_2
- Guilleminault 1986: catheter in OSAS
  - Marked decrease in cardiac output during apnea (by 35%)

Apnea episodes lead to mild temporary PH

Obstructive Sleep Apnea leading to PH

- Variations in transmural PAP during OSA episodes may be a consequences of multiple factors:
  - variation in intrathoracic pressure
  - variations in heart rate
  - variation in cardiac output
  - possibly variation in left heart filling pressure
- But the major factor for transmural PAP increase during an OSA episodes seems to be:
  - Hypoxic Pulmonary Vasoconstriction (HPV)

Apneas lead to mild temporary PH due to HPV

Weitzenblum & Chaouat 2005

Is permanent PH a feature of OSA?

- Bradely 1985: 50 OSA patients:
  - Cor pulmonale only in 6 patients (12%) with daytime hypoventilation and obstructive ventilatory defect
- Chaouat 1996: catheters in 220 OSA patients:
  - PH defined as mPAP > 20 mmHg found in 37 Pts (17%)
  - 24/37 daytime hypoxemia
  - 15/37 additional hypercapnia, mostly with additional obstructive or restrictive lung disease
  - no correlation of PAP with AHI

The majority of OSA patients without significant daytime hypoxemia will not develop precapillary PH!

CPAP treatment to improve PH in OSA?

- Sajkov AJRCCM 2002: prospective, uncontrolled, 22 patients with OSA, mean AHI 48/min,

N=22	Before CPAP	After CPAP
mPAP mmHg	16.8 ± 1.2	13.9 ± 0.6
PVR dynes*s*cm-5	231 ± 88	186 ± 55

Treatment of OSAS by CPAP is moderately effective in ameliorating pulmonary hemodynamics

Does hypoventilation lead to PH?

- Kessler 2001: PH often found in Obesity - Hypoventilation Syndrome with concomitant daytime hypoxemia and hypercapnia
  - 26 patients, 59% PH
  - 23 concomitant OSA
- Common in PH-clinic (Held M, ERS 2012)
  - 126 PH patients, 19 with OHS
  - mPAP 49mmHg, VO_2max 63 Watt
  - mPAP correlated to $PaCO_2$

Therapy of Obesity Hypoventilation Syndrome

Increase CPAP to eliminate obstructive apneas, hypopneas, and flow limitation

↓

S_{pO_2} persistently below 90% in the absence of obstructive apneas or hypopneas

↓

Switch to bi-level PAP and increase IPAP over the last CPAP pressure that eliminated obstructive apneas until S_{pO_2} > 90%

↓

Add supplemental oxygen if S_{pO_2} is persistently < 90% despite an IPAP – EPAP difference of 8–10 cm H_2O, or try AVAPS

↓

Weight-loss surgery or tracheostomy with or without mechanical ventilation and/or respiratory stimulants in patients who fail positive-airway-pressure therapy

Non-invasive ventilation ameliorates pulmonary hemodynamics in small series

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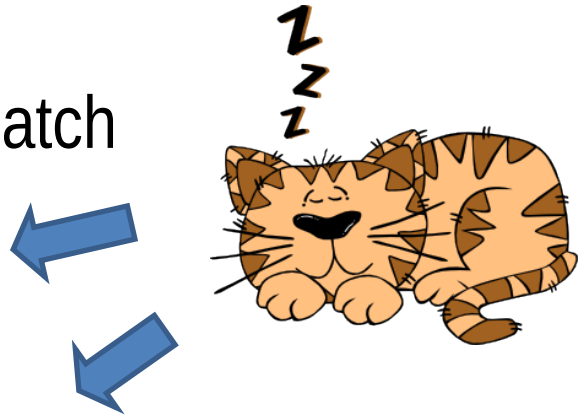
Sleep disordered breathing in PH – potential mechanisms

- Hypoxemia in PH
  - pulmonary capillary bed ↓,V/Q- Mismatch
  - intrapulmonary Shunts
  - respiratory muscle weakness



- Effect of Sleep on lung diseases
  - Respiratory drive ↓, airway stability ↓, ventilation stability ↓ ⟶ sleep disordered breathing

Sleep worsens daytime hypoxemia and may lead to intermittent apnea or periodic breathing

Sleep disordered breathing in PH – different manifestations

- Nocturnal hypoxemia
- Sleep apnea / Periodic Breathing /Cheyne-Stokes-Respiration
- ….

Nocturnal hypoxemia in PH

- Rafanan Chest 2001: 13 IPAH-Pts (12♀)
  - Desaturators = pts with >10% of TST with SpO_2 <90%
  - 10 Patients (77%)
  - not associated with sleep apnea

Sleep Variable	Nondesaturators (n = 3)	Desaturators (n = 10)	p Value
TST, min	278.0 ± 50.6	302.7 ± 48.6	0.46
Sleep efficiency, %	74.3 ± 14.2	76.1 ± 7.2	0.77
REM sleep, %	14.0 ± 7.0	12.7 ± 5.2	0.73
Apnea index, apneas/h	0.08 ± 0.13	1.04 ± 1.93	0.15
Hypopnea index, hypopneas/h	1.67 ± 2.08	4.45 ± 4.59	0.18
Apnea-hypopnea index, apneas and hypopneas/h	1.75 ± 6.7	5.49 ± 9.2	0.28

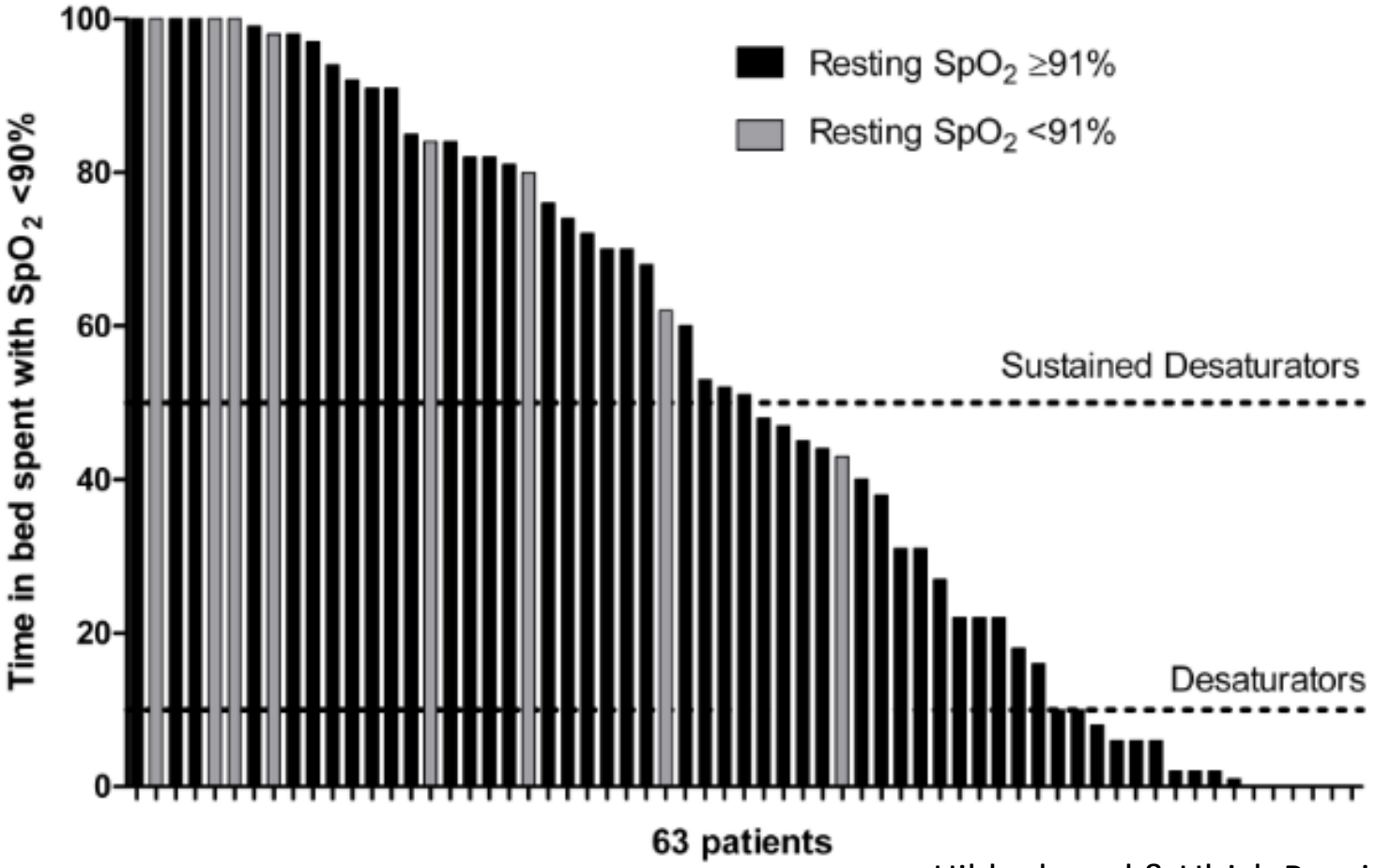
*Values given as mean ± SD, unless otherwise indicated.

Nocturnal hypoxemia in PH

- Minai Chest 2007: 43 Patients (36♀), 88% IPAH, 12% APAH
  - desaturators = pts with >10% of TST with SpO_2 <90%
  - 30 desaturators (69.7%), only 1 sleep apnea
    - older
    - higher BNP, higher Hb
    - lower cardiac index on last RHC
  - desaturation in 6MWT: not good predictor of nocturnal hypoxemia
  - Resting daytime SpO_2 95±3.4

Nocturnal Hypoxemia in PH- very common even in preserved daytime SpO_2

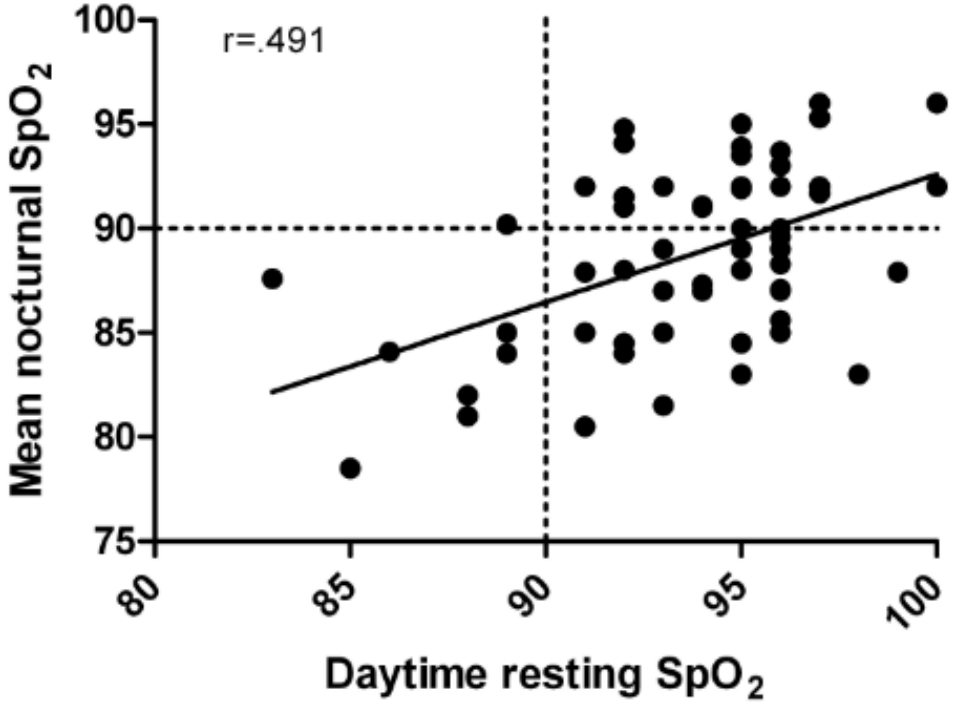
63 patients (68% female), 54% idiopathic, 30% CTEPH, 16% APAH

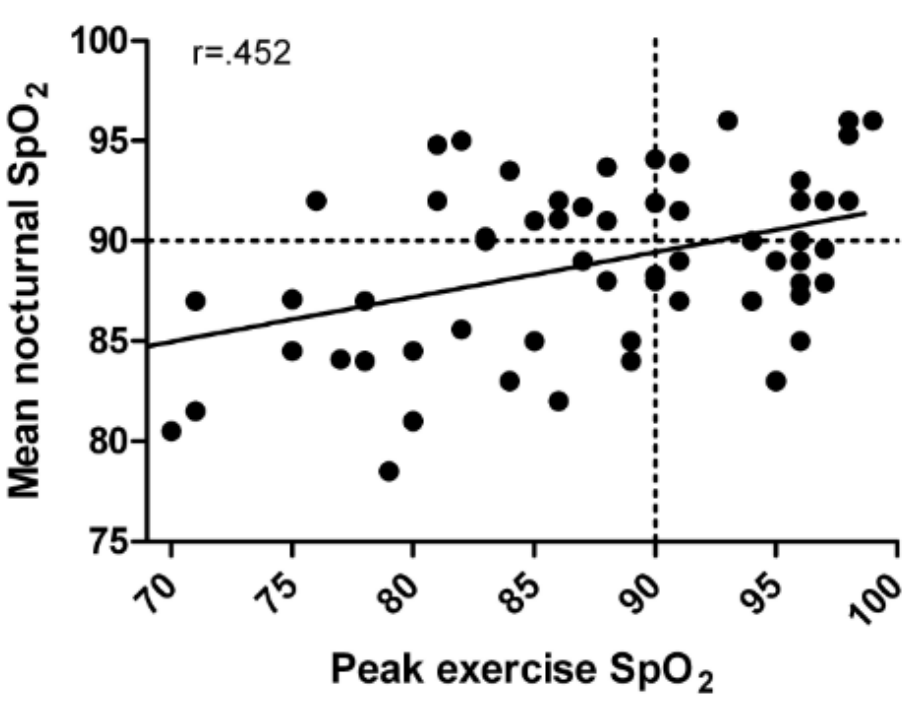


Hildenbrand & Ulrich Respiration 2012

Data given in Numbers (%)	Non-Desaturators	Desaturators	Sustained Desaturators
Total number of patients (%)	14 (22)	49 (76)	33 (52)
Females	9 (56)	34 (71)	21 (66)
Age (years)	65 (40;72)	61 (53;71)	61 (54;71)
WHO functional class II / III / IV	6 / 8 / 0	18 / 23 / 8	12 / 17 / 4
	(43 / 57 / 7)	(37 / 47 / 16)	(38 / 53 / 12)
BMI (kg/m^2)	28 (26;29)	26 (22;29)	26 (23;28)
Tricuspid pressure gradient (mmHg)	43 (38;55)	66 (66;50;83)*	75 (58;89)# §
NT-pro-BNP (ng/l, < 130)	563 (240;1716)	718 (206;1371)	1048 (206;1689)
6 minute walking test (m)	529 (385;568)	450 (363;506)	450 (367;516)
Daytime resting SpO_2 (%)	96 (95;97)	94 (92;96)	93 (91;96)#
Exercise SpO_2 (%, end of 6MWT))	95 (89;97)	87 (80;91)**	86 (78;91)# §
Mean desaturation during exercise (%)	-2 (-7;0)	-6 (-11;-2)*	-6 (-15;-2)
Exercise Desaturators (≥ 4% & absolute <90%)	5 (33)	28 (58)	19 (59)
Mean nocturnal SpO_2 (%)	94 (93;95)	88 (85;90)**	86 (84;88)## §
Oxygen desaturation index (ODI, events/h)	2 (1;4)	3 (1;9)	3 (1;9)
ODI >10 events/h	0	10 (21) *	6 (20)
Apnea/hypopnea index (AHI, events/h)†	9 (5;18)	10 (6;19)	10 (6;19)
AHI >10 events/h†	3 (38)	13 (54)	8 (50)
Periodic breathing (PB, % time in bed)†	5 (4;9)	11 (4;13)	12 (5;15)
Patients with PB ≥10 % of time in bed†	3 (38)	12 (50)	9 (56)

Nocturnal Hypoxemia in PH- very common even in preserved daytime SpO_2





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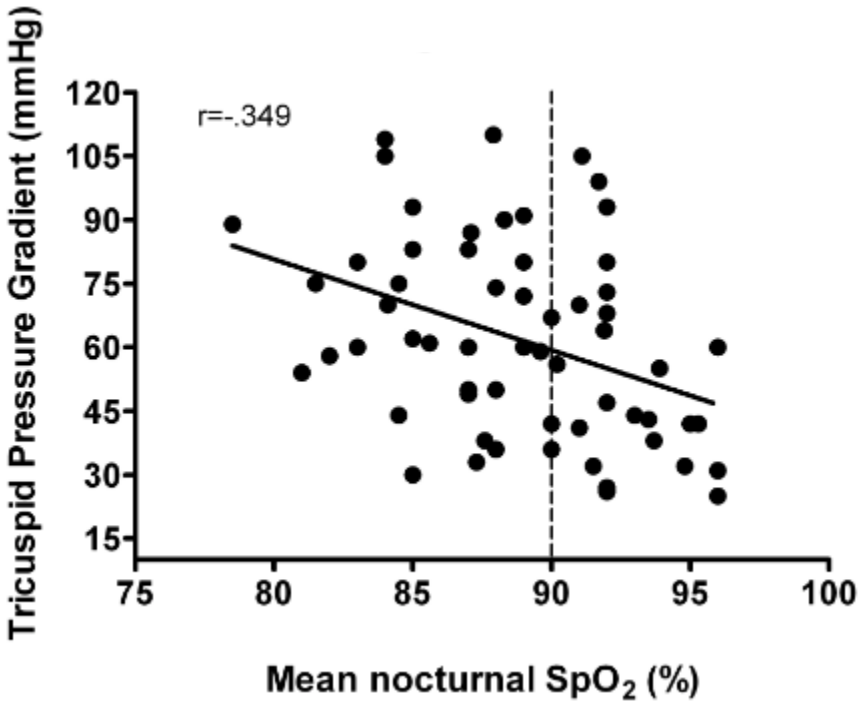
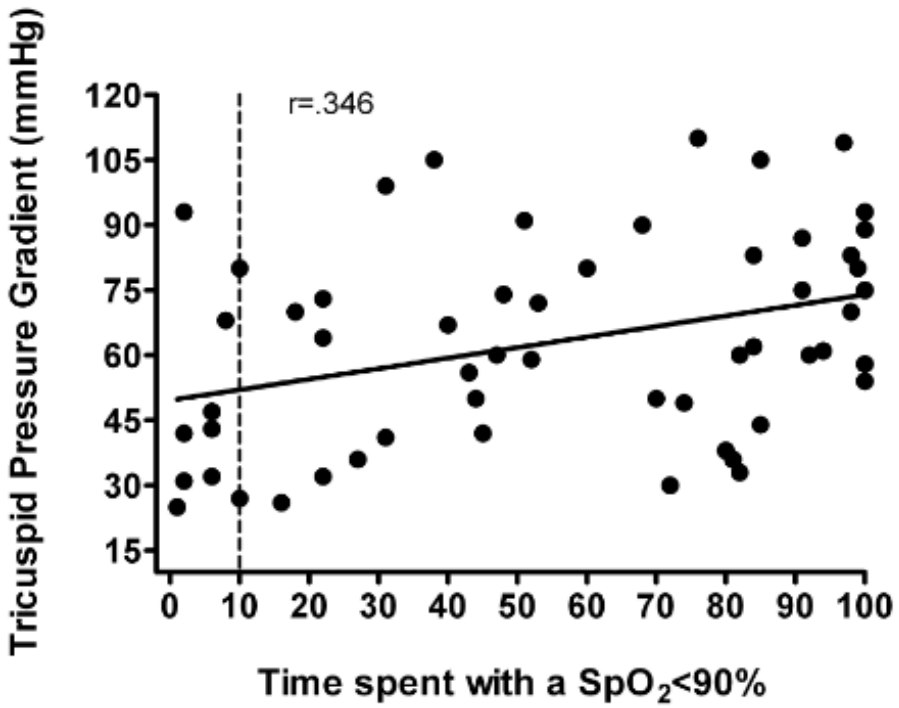
Nocturnal Hypoxemia in PH- correlation to tricuspid pressure gradient





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Nocturnal hypoxemia in PH - Summary

- Very common
- Daytime SpO_2 underestimates nocturnal hypoxemia
- Nocturnal hypoxemia is correlated to hemodynamic disease severity
- Nocturnal hypoxemia is common even in the absence of sleep disordered breathing

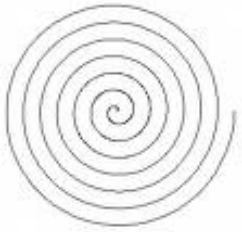
Treatment of nocturnal hypoxemia in PH?????

Sleep disordered breathing in left heart disease

- CSR/CSA is very common in patients with left heart failure (33-45%, Javaheri 1995, Lofaso 1994)
- CSR more prevalent if ejection fraction and VO_2 max are low
- CSR/CSA in left heart failure associated with:
  - arrhythmias↑
  - deterioration of LHF
  - worse prognosis
  - Quality of life ↓

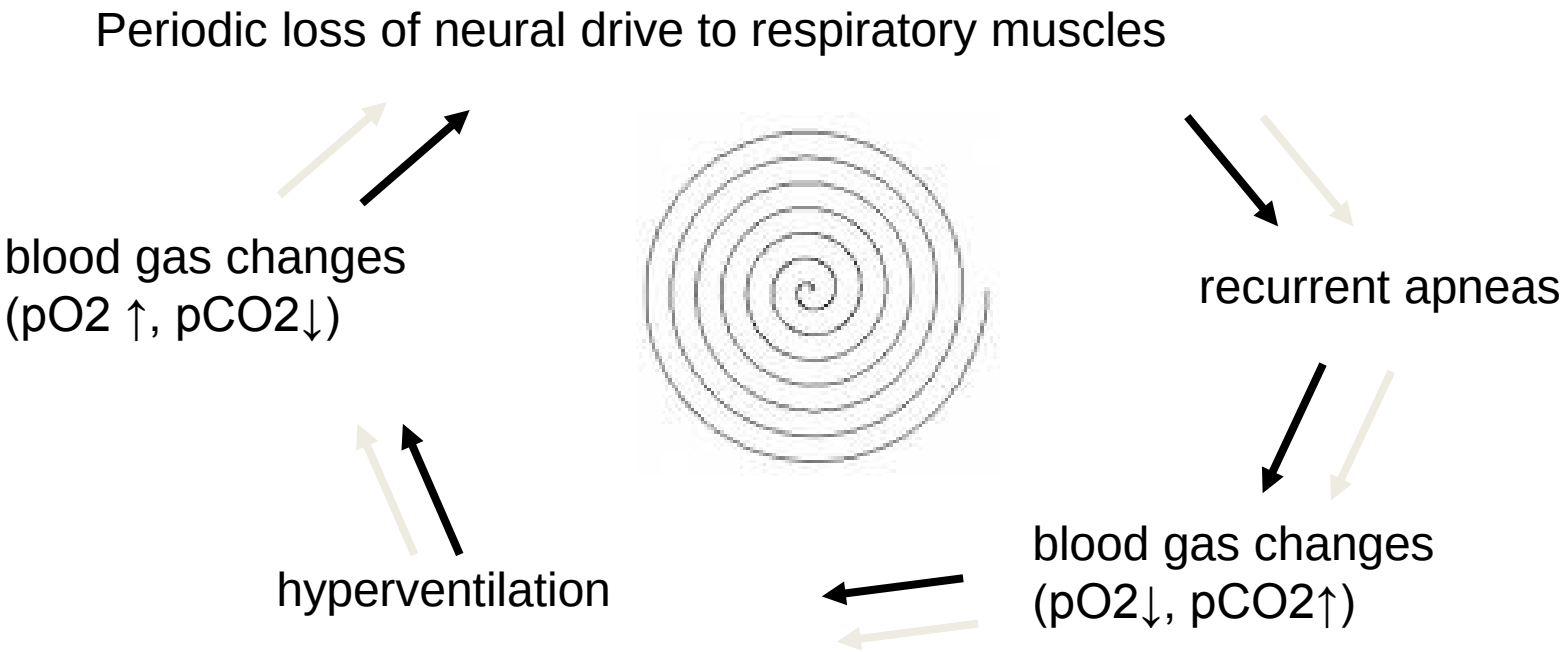
CSR marker of severity in left heart disease

Pathogenesis of CSR/CSA

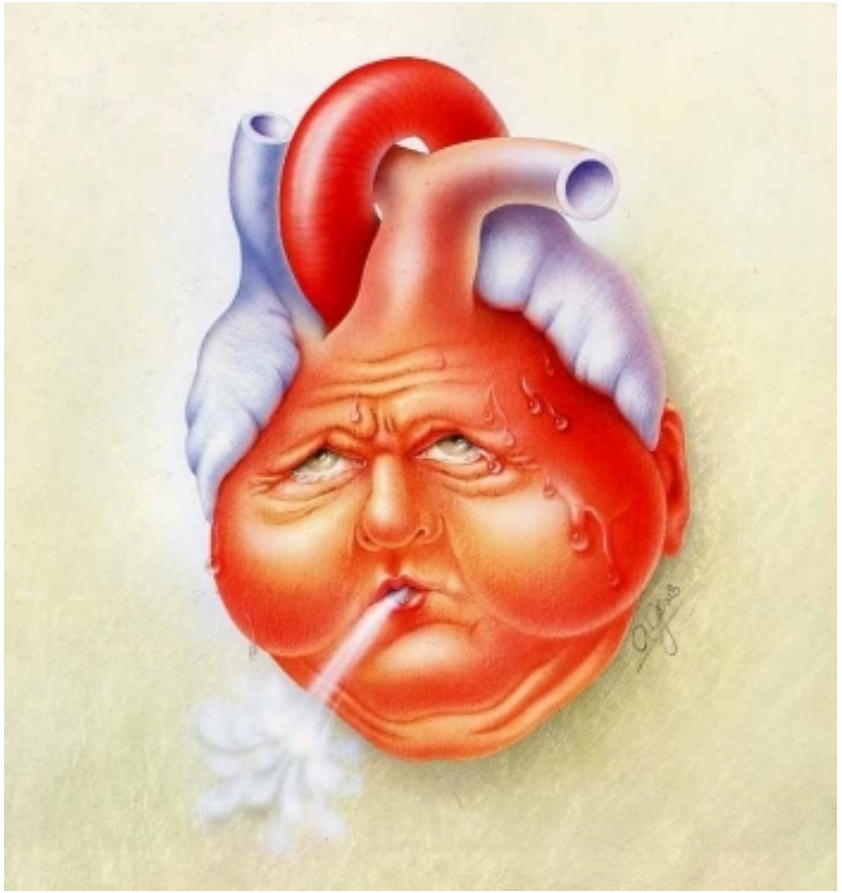


- Stimulation of sympathetic nerve activity → increase in blood pressure & catecholamines
- Low cardiac output → prolonged blood circulation time → delayed sensing of blood gas changes → oscillatory behavior ↑
- Other potentially contributing factors:
  - impaired cardiac afferents
  - water salt balance
  - hormones involved in body fluids
  - increased left atrial pressure

The vicious cycle of CSR/CSA



What about right heart failure in PH?



Sleep disordered breathing in right heart disease due to PH

- Schulz ERJ 2002: 6 out of 20 (30%) patients with PH had nocturnal CSR (PSG)

Table 4. – Anthropometric data, lung function and haemodynamic parameters of the patients with (+) and without (-) periodic breathing (PB)

	PB +	PB -	p-value
Patients n	6	14	
Sex M:F n	3:3	0:14	<0.01
Age yrs	43±3.6	45±2.6	NS
BMI kg·m^{-2}	21.5±0.7	24.4±1.4	NS
P_{a,O_2} kPa	6.6±0.9	9.1±0.7	<0.05
P_{a,CO_2} kPa	3.9±0.2	3.9±0.1	NS
FEV_1 % pred	91.5±6.8	86.5±3.7	NS
VC % pred	90.8±8.1	92.0±3.4	NS
$D_{L,CO}$ % pred	57.1±4.5	69.6±3.5	<0.05
PAP mmHg	63±2.4	53±3.7	<0.05
PVR dyn·s·cm^{-5}	1951±149	1119±134	<0.05
PCWP mmHg	6±0.4	5±0.7	NS
CO L·min^{-1}	2.39±0.1	3.71±0.3	<0.01
CI L·min·m^{-2}	1.38±0.1	2.21±0.2	<0.01
RVEF %	7±0.8	20±2.4	<0.01

CSR associated with:
-worse hemodynamic
-lower DLCO
-lower PaO_2

Sleep disordered breathing in right heart disease due to PH

- Schulz ERJ 2002:
- 5 patients agreed to be re-examined under oxygen therapy (2l via nasal cannula):
- 4 responded with almost complete resolution

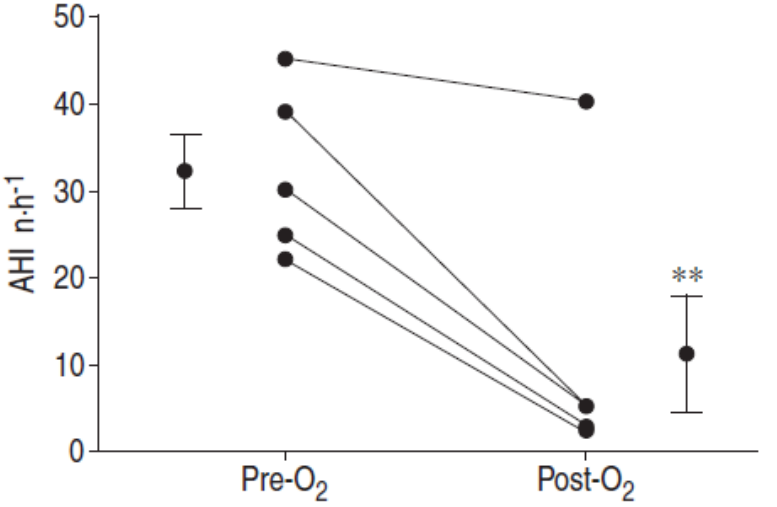


Fig. 2. – Effects of nasal oxygen administration on the apnoea/hypopnoea index (AHI) in five patients with primary pulmonary hypertension and periodic breathing. Data are presented as individual values and as mean±SEM before and after nasal oxygen (O_2). **: $p < 0.01$.

- Schulz Chest 2004: case-report of reversal of CSR after LTPL in a 56y old woman

Sleep related breathing disorders in Zürich PH collective

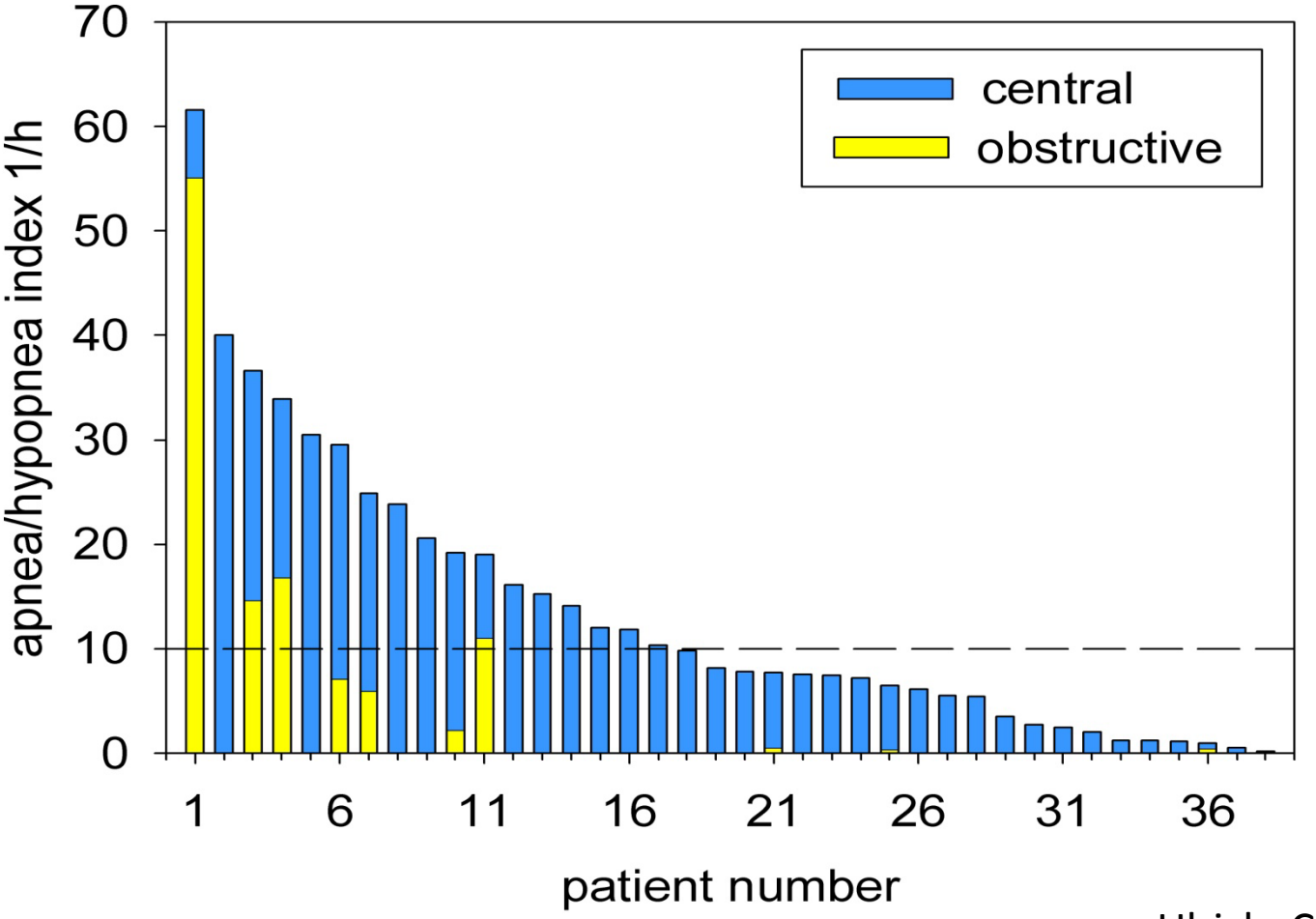
38 patients with PH	Numbers or median (quartiles)
Females	27 (71%)
Age (years)	61 (51-72)
Mean pulmonary arterial pressure (mmHg)*	43 (33-51)
WHO functional class II / III / IV	14 / 16 / 8
6 minute walking distance (m)	481 (429-550)

Sleep studies

Apnea/hypopnea index (AHI, events/h) - obstructive - central	8 (4-19) 0 (0-0.03) 8 (4-16)
Time spent with CSR (% time in bed)	8 (4-13)
SpO_2 (%)	90 (87-92)
Time spent with SpO_2 < 90% (% time in bed)	34 (3-78)
Patients with AHI > 10 /h (%) - obstructive AHI > 10/h (%) - central AHI > 10/h (%)	45 10 40
Patients with time spent with CSR > 10 % of time in bed (%)	42
Patients with time spent with SpO_2 < 90% > 10% time in bed (%)	68

Ulrich Chest 2008

Sleep related breathing disorders in Zürich PH collective



Ulrich, Chest 2008

Potential mechanisms of CSR/CSA in PH – in analogy to left heart failure (?)

- Circulation time: delay in transport of blood to brain resp. carotid sensors (lung to ear time)
  - Crowell Am J Physiol 1956: large prolongation of circulation time necessary to receive CSR in only 30%

Circulation time influences time of breathing cycle and length of hyperpneic episodes

Pepin Sleep Medicine 2006

Potential mechanisms of CSR/CSA in PH – in analogy to left heart failure (?)

- Hyperventilation with low $PaCO_2$ (below apneic threshold)
  - breathing with low CO_2 (2-3%) during sleep increases CSR
  - But: $PaCO_2$ alone is not crucial, e.g. liver cirrhosis patients with the same $PaCO_2$ do not have CSR

Δ PaCO2 may be more important and the combination with other factors

  - increased ventilatory response to CO_2 during exercise (VE/VCO_2) best correlation to CSR

Pepin Sleep Medicine 2006

Potential mechanisms of CSR/CSA in PH – in analogy to left heart failure (?)

- Hypoxemia: may promote instability due to a stimulating effect on carotid chemoreceptors
  - High altitude induces CSR
  - However, hypoxemia not mandatory to develop CSR in HF and oxygen therapy attenuates but not completely suppresses CSR
- Arousal response: magnitude determines lengths of subsequent interruption of ventilation
- Catecholamine hypersecretion:
  - Noradrenalin infusion increases ventilation
  - Important for self-perpetuating effect of CSR-CSA

Pepin Sleep Medicine 2006

Treatment options for CSR in patients with PH

- The indication, type and benefits of potential treatments for CSR/CSA in PH are currently not known

In lack of treatment strategies, it is not know whether screening PH for CSR is sensible

- Extrapolating from left heart failure-associated CSR/CSA
  - nocturnal oxygen therapy (NOT)
  - Acetazolamide
  - non-invasive positive pressure ventilation via a mask

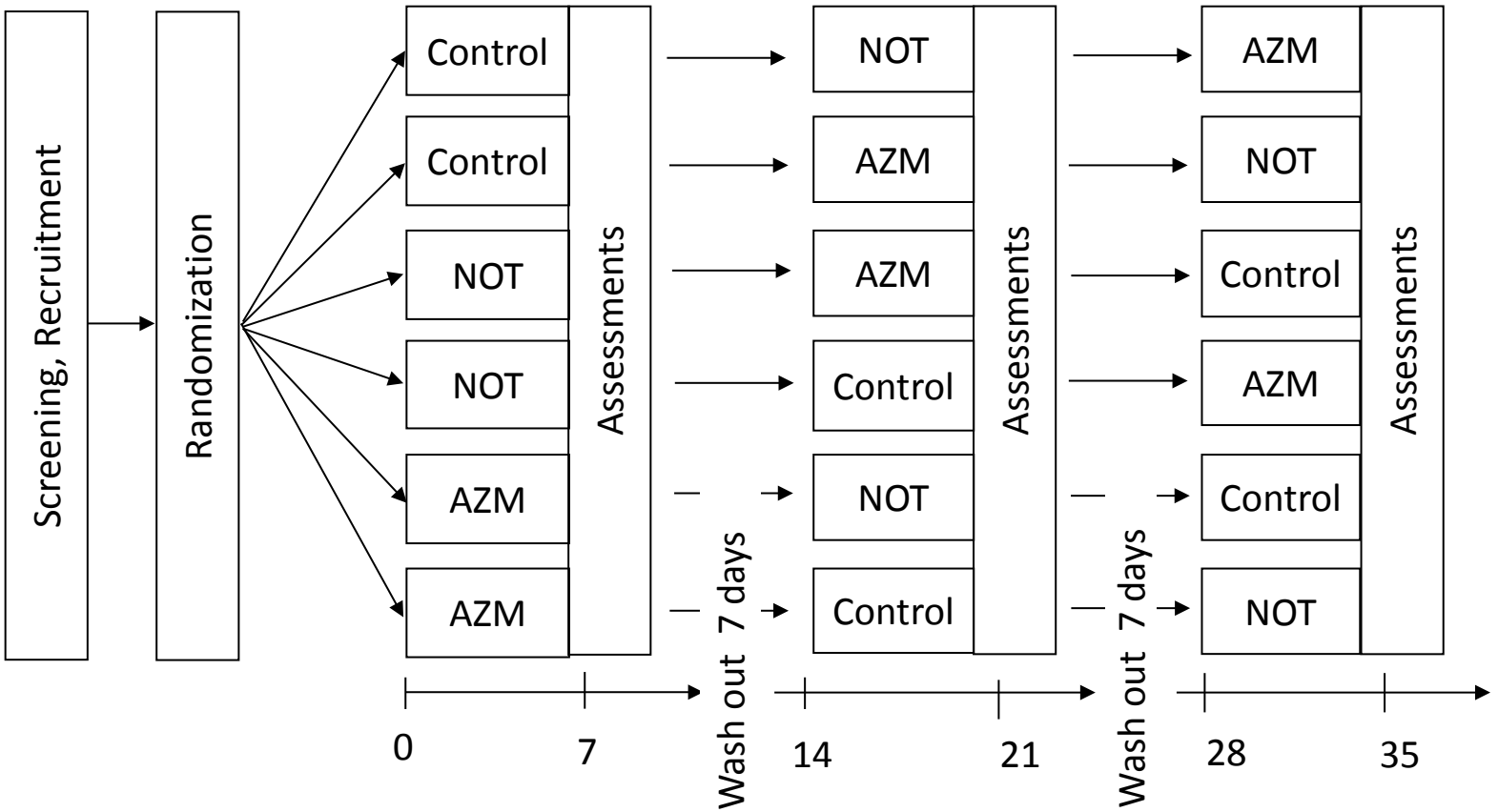
may all be potentially effective

Treatment of and sleep disordered breathing in PH

- Main inclusion criteria: Patients with precapillary PH and sleep disordered breathing defined as: SpO2 < 90% and/or oxygen desaturation index > 10/h during ambulatory pulse oximetry
- Main exclusion criteria: Wedge ≥15mmHg, significant lung disease, co-morbidities, not able to walk, ….
- Actually: > 60 PH-patients screened, 23 patients actually includes

Ulrich NF Study 2011-13

Treatment of and sleep disordered breathing in PH



Ulrich NF Study 2011-13

Treatment of and sleep disordered breathing in PH

- Primary Outcomes:
  - 6 minute walk distance
  - SF36 (1-week recall form) physical component
- Secondary Outcomes:
  - vigilance, sleepiness, QoL (SF-36, MLHF, Camphor)
  - prevalence and severity of sleep disordered breathing
  - hemodynamics by echocardiography
  - changes in arterial and venous blood parameters
  - actimetry

Results awaited soon

Ulrich NF Study 2011-13

Take Home Messages

- OSA may lead to mild PH, significant PH only with concomitant diseases (which are not seldom!)
- Nocturnal hypoxemia is very common in PH, underestimated by daytime measurements and associated with hemodynamic severity
- SDB is common in severe PH, but not the only reason for nocturnal hypoxemia
- Treatment strategies widely unknown