Obesity hypoventilation Syndrome

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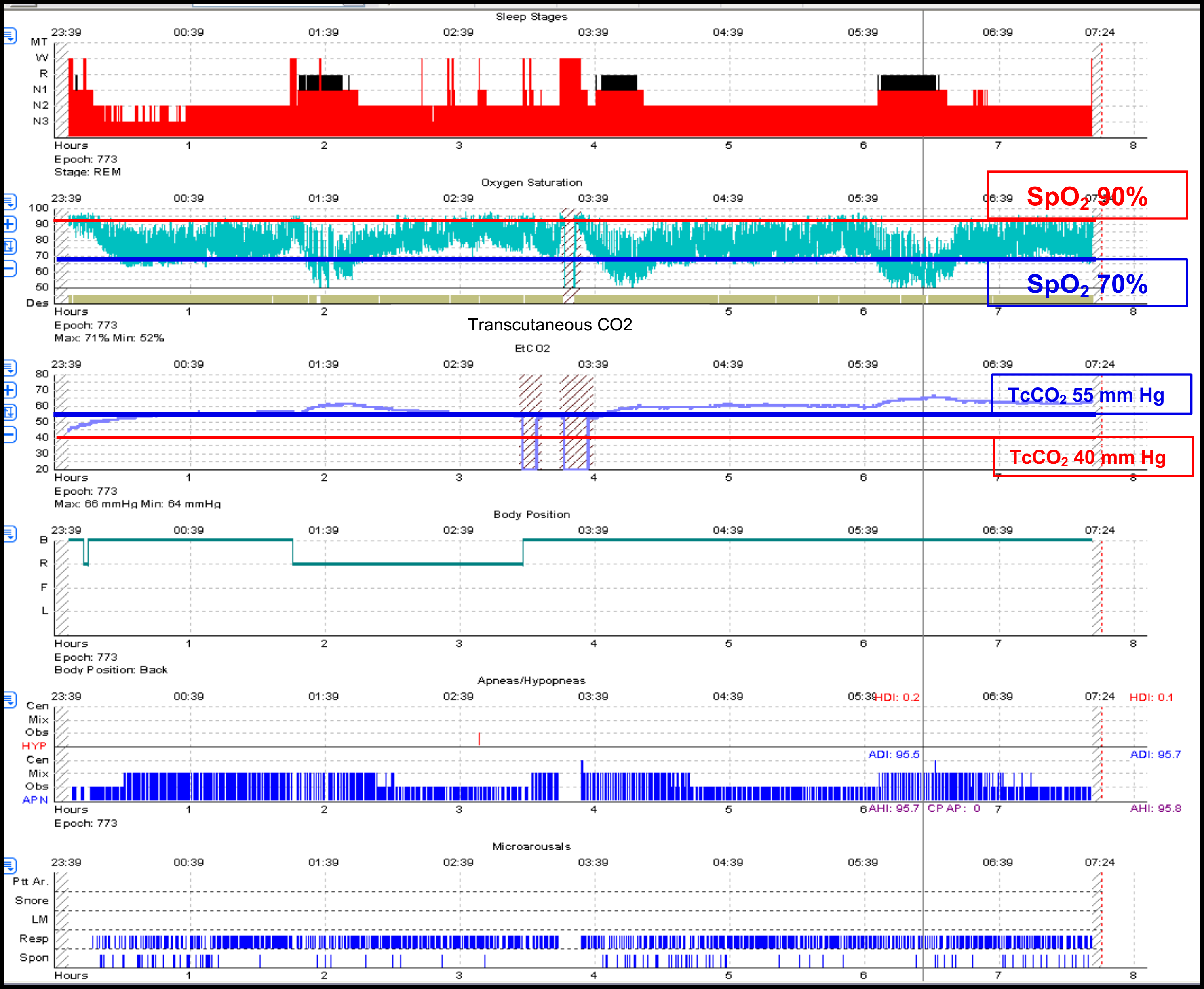
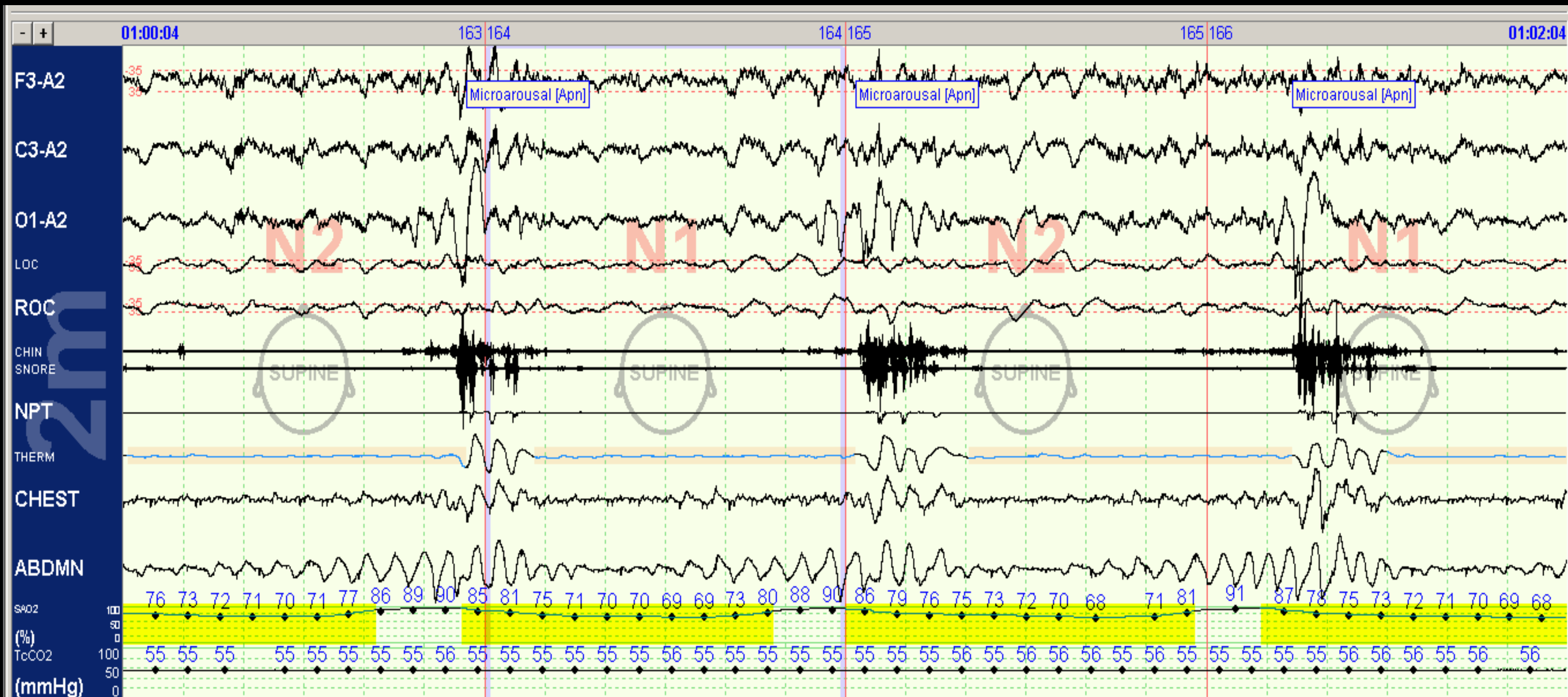
Objectives

- Review the definition and epidemiology of OHS
- Understand the clinical presentation and diagnosis and when to suspect OHS
- Recognize the high morbidity and mortality associated with undiagnosed and untreated OHS
  - Postoperative risk of OHS
- Discuss treatment strategies

An example of a patient with OHS

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Definition and epidemiology

Definition of OHS

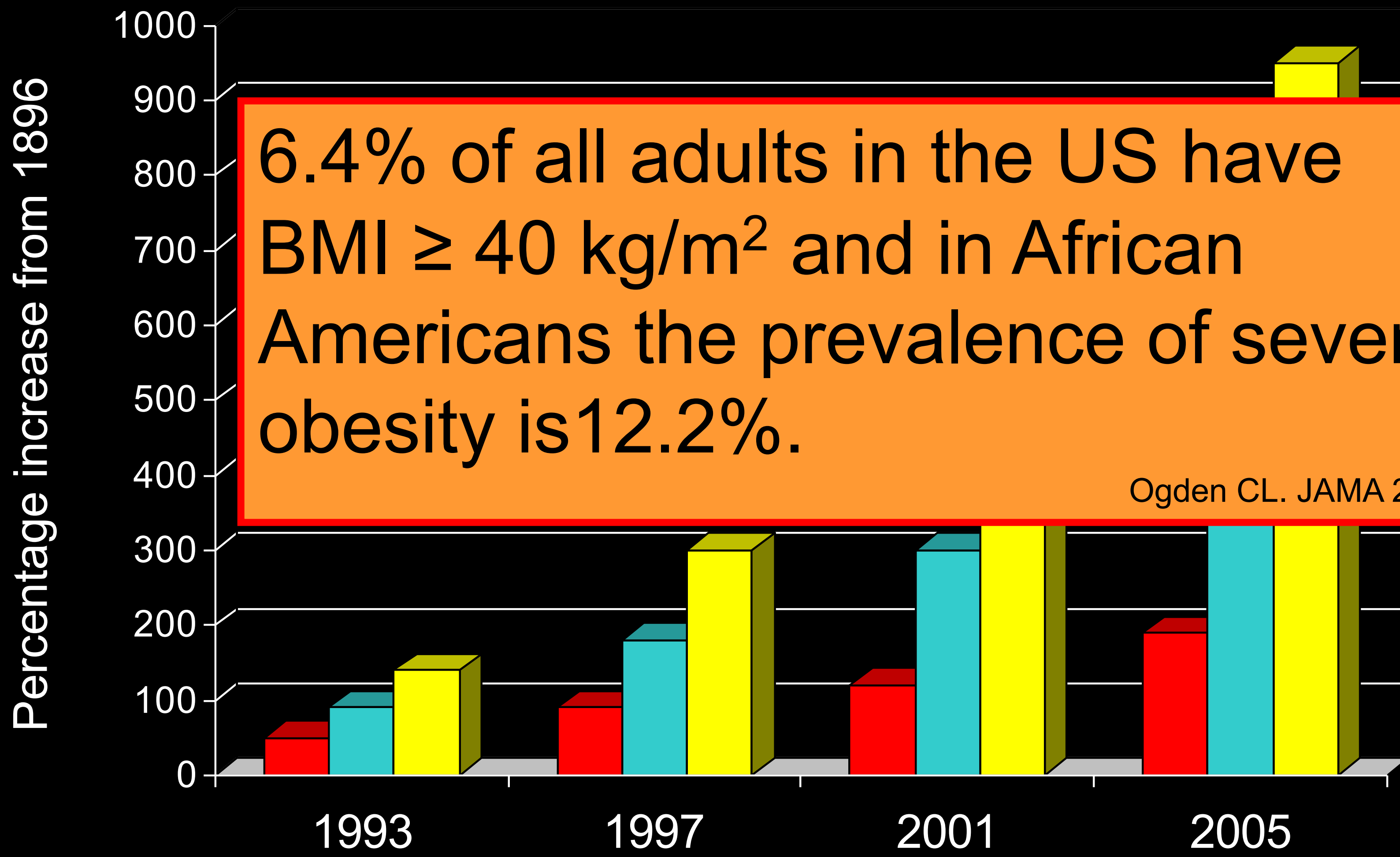
Required conditions	
Obesity	• Body mass index ≥ 30 kg/m^2
Chronic Hypoventilation	• Awake daytime hypercapnia ($PaCO_2$ ≥ 45 mm Hg)
Sleep-disordered breathing	• OSA (AHI ≥ 5) present in 90% of cases • Sleep hypoventilation (AHI < 5) present in 10%
Exclude other causes of hypercapnia	• Significant obstructive airways disease • Significant interstitial lung disease • Severe chest wall disorders (e.g., kyphoscoliosis) • Severe hypothyroidism • Neuromuscular disease

Mokhlesi B, Tulaimat A. Chest 2007; 132:1322-1336

Obesity Hypoventilation Syndrome

Diagnosis of Exclusion!

Highest Increases in Clinically Severe Obesity, U.S. 1986-2005



6.4% of all adults in the US have BMI ≥ 40 kg/m^2 and in African Americans the prevalence of severe obesity is12.2%.

Ogden CL. JAMA 2014

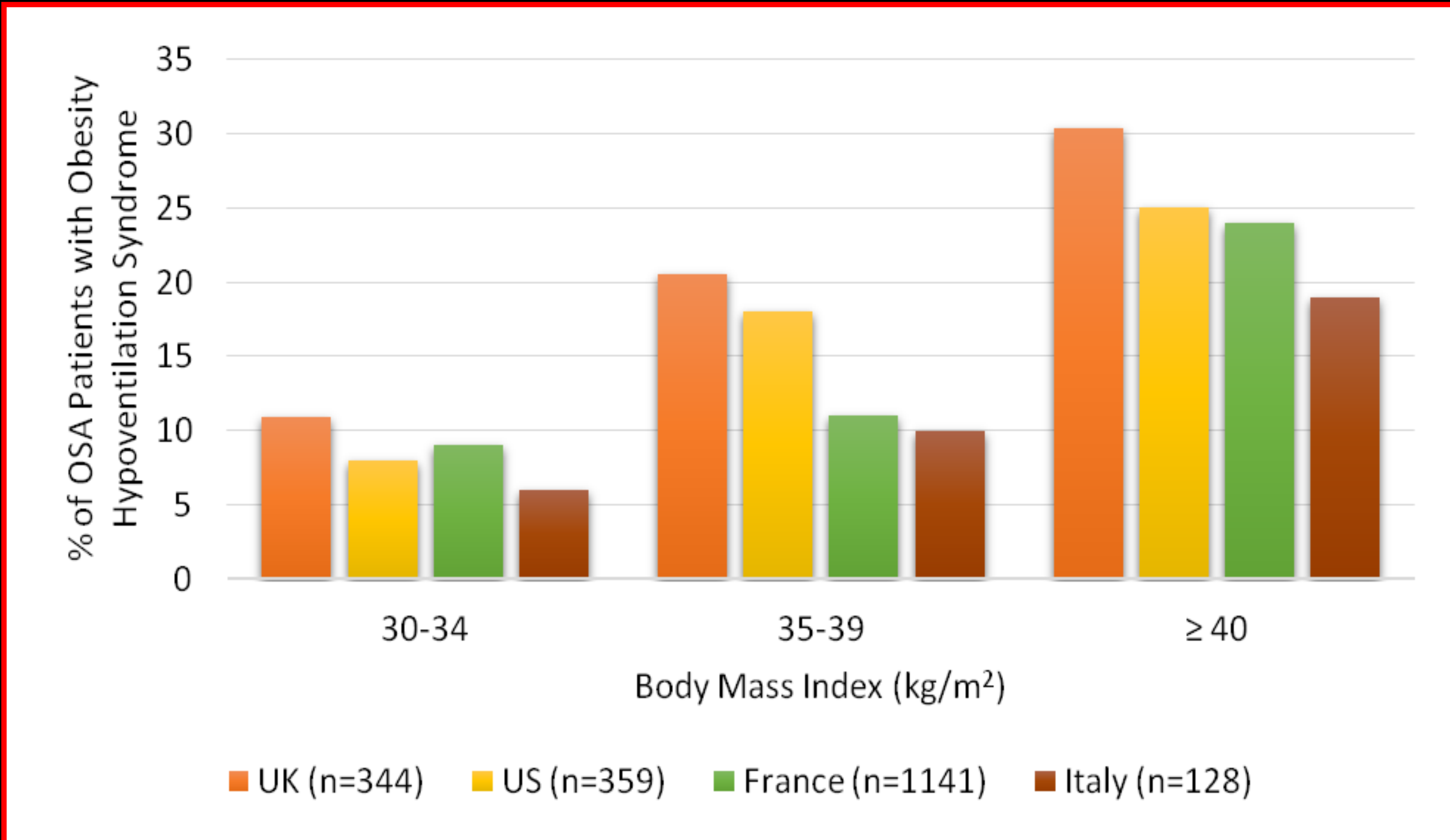
Sturm R. Public Health 2007; 121:492

Prevalence of OHS in obese patients being evaluated for OSA

Author, Country	Year	Patients (No.)	Male (%)	Age (yrs)	BMI (kg/m2)	AHI	OHS (%)
Leech, US[x]	1987	111	68%	47	NR	58	37%
Resta, Italy[x]	2000	219	64%	50	40	45	17%
Verin, France[x]	2001	218	92%	55	34	51	10%
Akashiba, Japan	2002	143	100%	48	30	55	38%
Laaban, France	2005	1141	83%	56	34	55	11%
Mokhlesi, US[x]	2007	522	56%	48	44	59	24%
Kawata, Japan[x]	2007	1227	89%	50	29	42	14%
Banerjee, Australia[ǂ]	2007	74	54%	43	59	62	31%
Macavei, UK[x]	2013	344	64%	52	39	25	21%
Aggregate or mean		**3999**	**74%**	**50**	**38**	**50**	**17%**

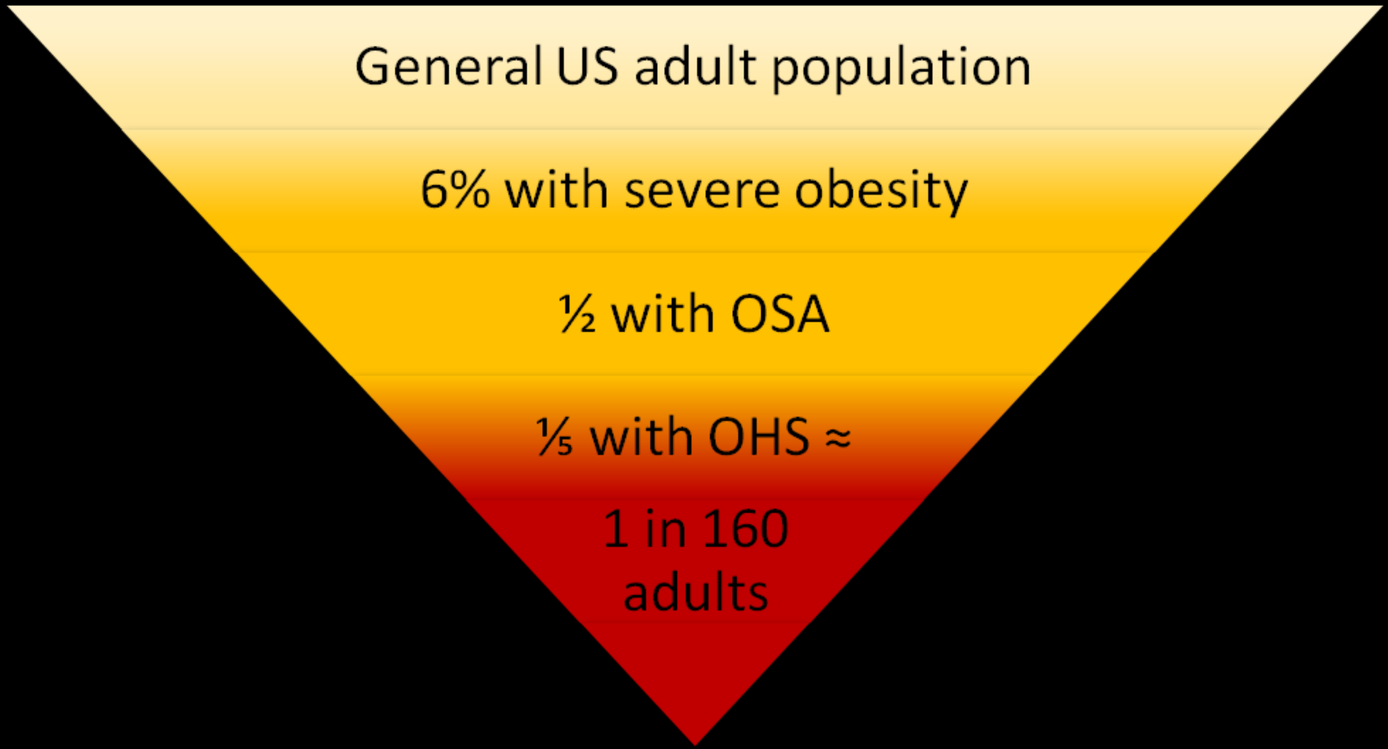
Balachandran JS, Masa JF, Mokhlesi B. Sleep Med Clin 2014

Prevalence of Obesity Hypoventilation Syndrome in patients with OSA



Balachandran JS, Masa JF, Mokhlesi B. Sleep Med Clin 2014

Estimated prevalence of OHS in the general population



Balachandran JS, Masa JF, Mokhlesi B. Sleep Med Clin 2014

Diagnosis and Presentation

Clinical features of OHS from 16 studies and a total of 757 patients

Variables	Mean (range)
Age, *year*	52 (42-61)
Men, *%*	60 (49-90)
Body mass index, *kg/m²*	44 (35-56)
Neck circumference, *cm*	46.5 (45-47)
pH	7.38 (7.34-7.40)
$PaCO_2$, *mm Hg*	53 (47-61)
PaO_2, *mm Hg*	56 (46-74)
Serum bicarbonate, *mEq/L*	32 (31-33)
Hemoglobin, *g/dL*	15
MRC dyspnea class 3 and 4, *%*	69
Epworth sleepiness scale	14 (12-16)

Mokhlesi B et al. Proc Amer Thorac Soc. 2008:5;221

PSG and PFT features of OHS from 16 studies and a total of 757 patients

Variables	Mean (range)
Apnea-hypopnea index	66 (20-100)
SpO_2 nadir during sleep, %	65 (59-76)
Percent time SpO_2 < 90%, %	50 (46-56)
FVC, *% of predicted*	68 (57-102)
FEV_1, *% of predicted*	64 (53-92)
FEV_1/FVC	77 (74-88)

Mokhlesi B et al. Proc Amer Thorac Soc. 2008:5;221

Two Patterns of Presentation

- Acute on chronic respiratory failure
  - 8% of all admissions to ICU had a diagnosis consistent with OHS
  - 75% were misdiagnosed as COPD with no evidence of obstruction on PFT

Marik PE, Desai H. J Intensive Care Med 2012; 28:124

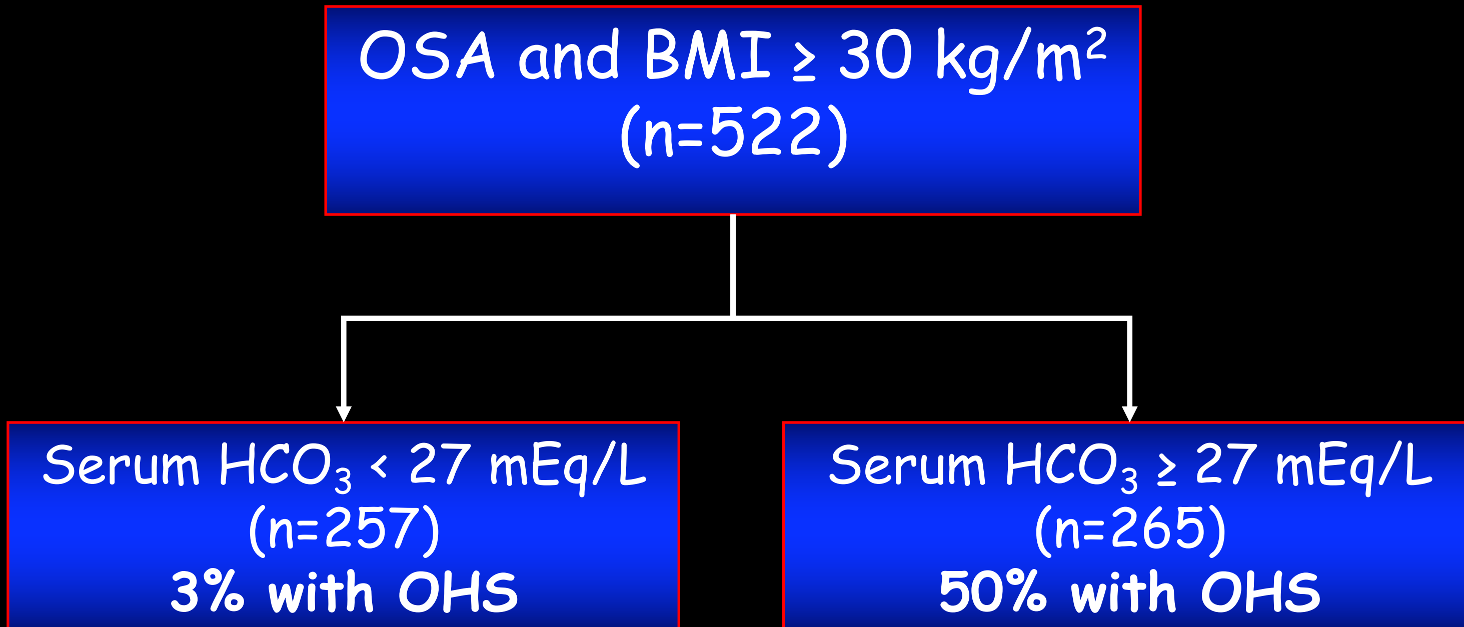
- As part of routine evaluation of OSA
- Frequently missed and diagnosed at late stage by pulmonologists or sleep specialists

Quint et al, Thorax 2007

When to suspect OHS

- Severely obese (BMI ≥ 40)
- Elevated venous bicarbonate levels from recent basic metabolic panels
- Room air hypoxemia by finger pulse oximetry
- Significant and persistent hypoxemia during PSG
- Spirometry/PFT with mild restrictive defect due to body habitus

Bicarbonate as a screening tool



Mokhlesi B et al. Sleep Breath 2007; 11:117

Macavei VM, et al. JCSM 2013; 9:879-84

A one unit increase in serum HCO_3 was associated with a 14% increase in the probability of having OHS

BaHammam AS. Saudi Med J 2015; 36:181-189

Does the current definition need revisiting?

- The current definition is based on a single one-time measurement of $PaCO_2$
- Calculated arterial or measured venous bicarbonate is a longer term guide to 24-h ventilation
- Proposed new definition:
  - Obesity
  - $PaCO_2 \geq 45$ mm Hg OR an arterial base excess >3 mmol/L OR a standard HCO_3 >27 mmol/L
  - absence of another cause for a metabolic alkalosis

Hart N, Mandal S, Manuel A, Mokhlesi B, Pépin JL, Piper A, Stradling JR. Thorax 2014.

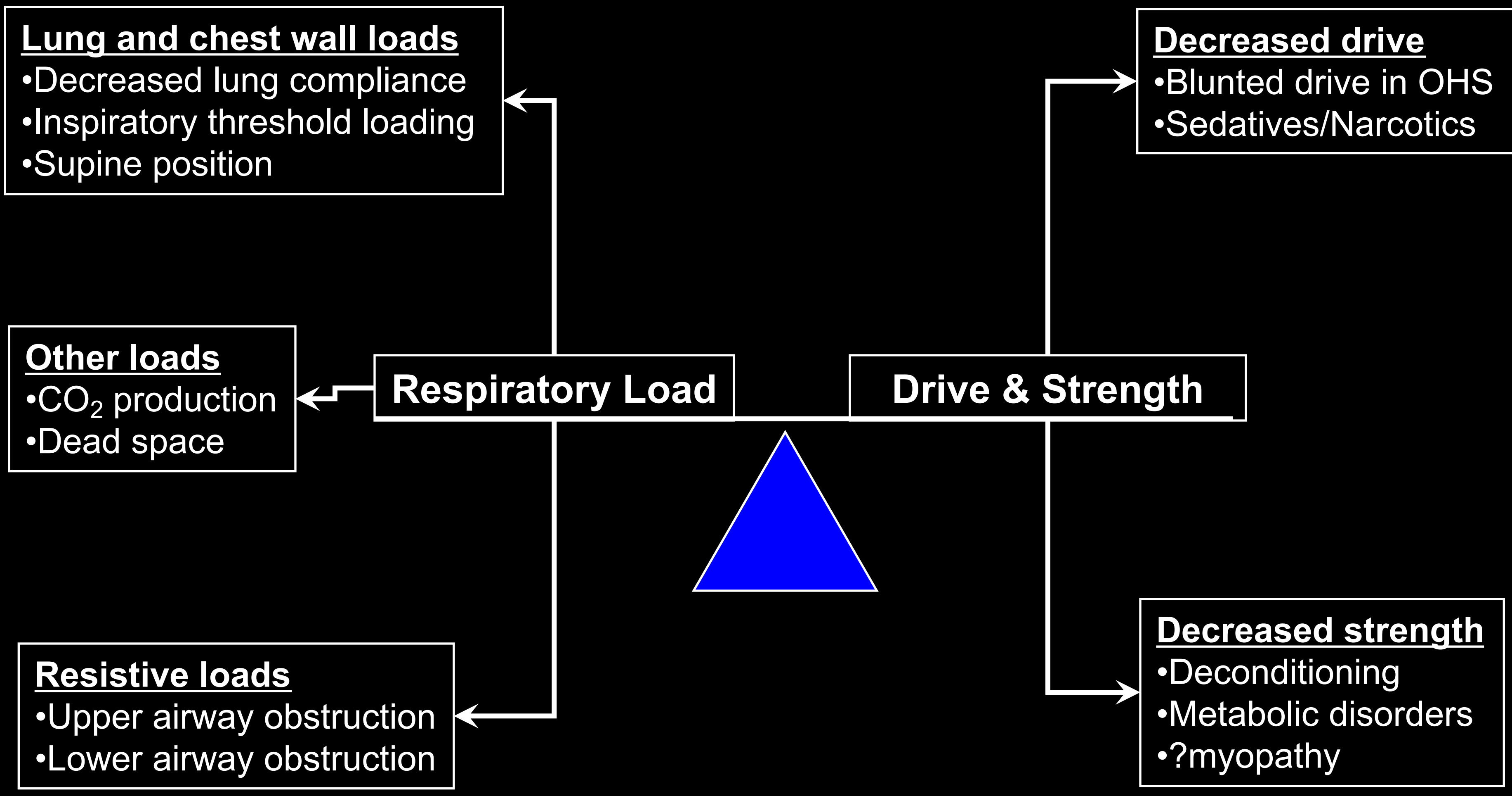
Is a raised bicarbonate level without hypercapnia part of the spectrum of OHS?

	Eucapnic normal BE n=33	Eucapnic Elevated BE n=22	Hypercapnic Elevated BE n=16	P value
Age	53.6	48.7	53.7	0.09
BMI	45.2 (9.1)	46.5 (7.9)	51.6 (11.7)	0.056
Base Excess, mEq/L	**0.12 (1.38)**	**3.01 (0.98)**	**4.78 (2.10)**	**<0.001**
HCO_3, mEq/L	24.4 (1.18)	27.0 (0.87)	28.5 (2.11)	<0.001
pH	7.41	7.44	7.41	<0.001
$PaCO_2$, mm Hg	38.6	40.6	49.6	<0.001
SpO_2	96	96.3	92.4	0.007
VE, L/min	8.05	8.33	7.54	0.47
VE hypercapnic test, L/min	**14.6**	**11.96**	**11.76**	**0.035**

Manuel AR, Hart N, Stradling JR. Chest 2015

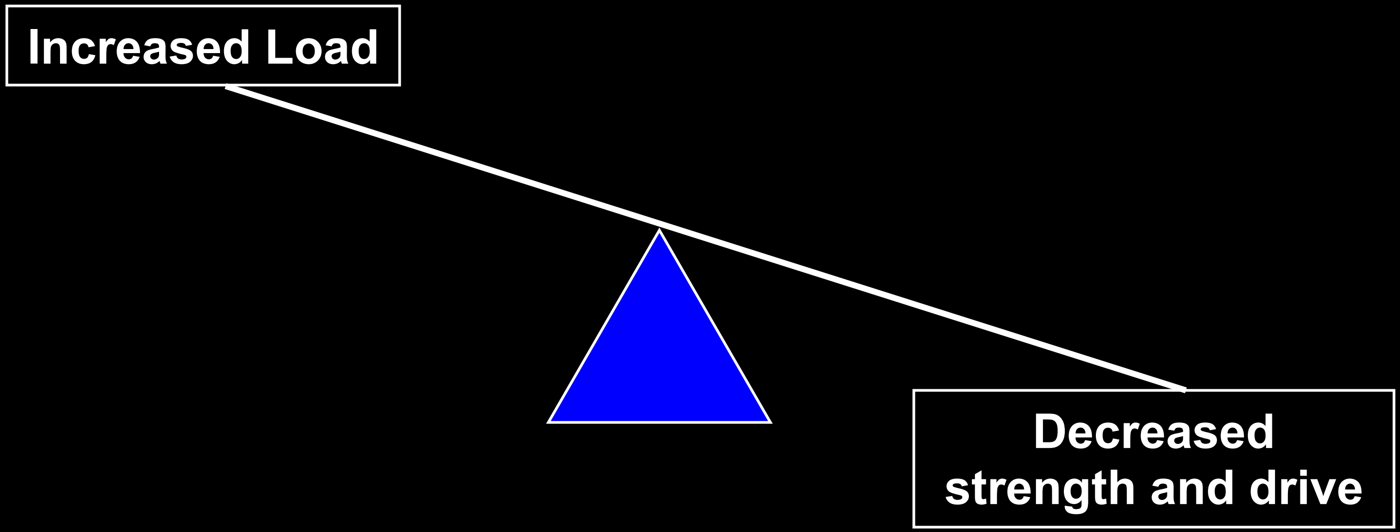
Pathophysiology of respiratory failure in OHS

Pathophysiology of respiratory failure

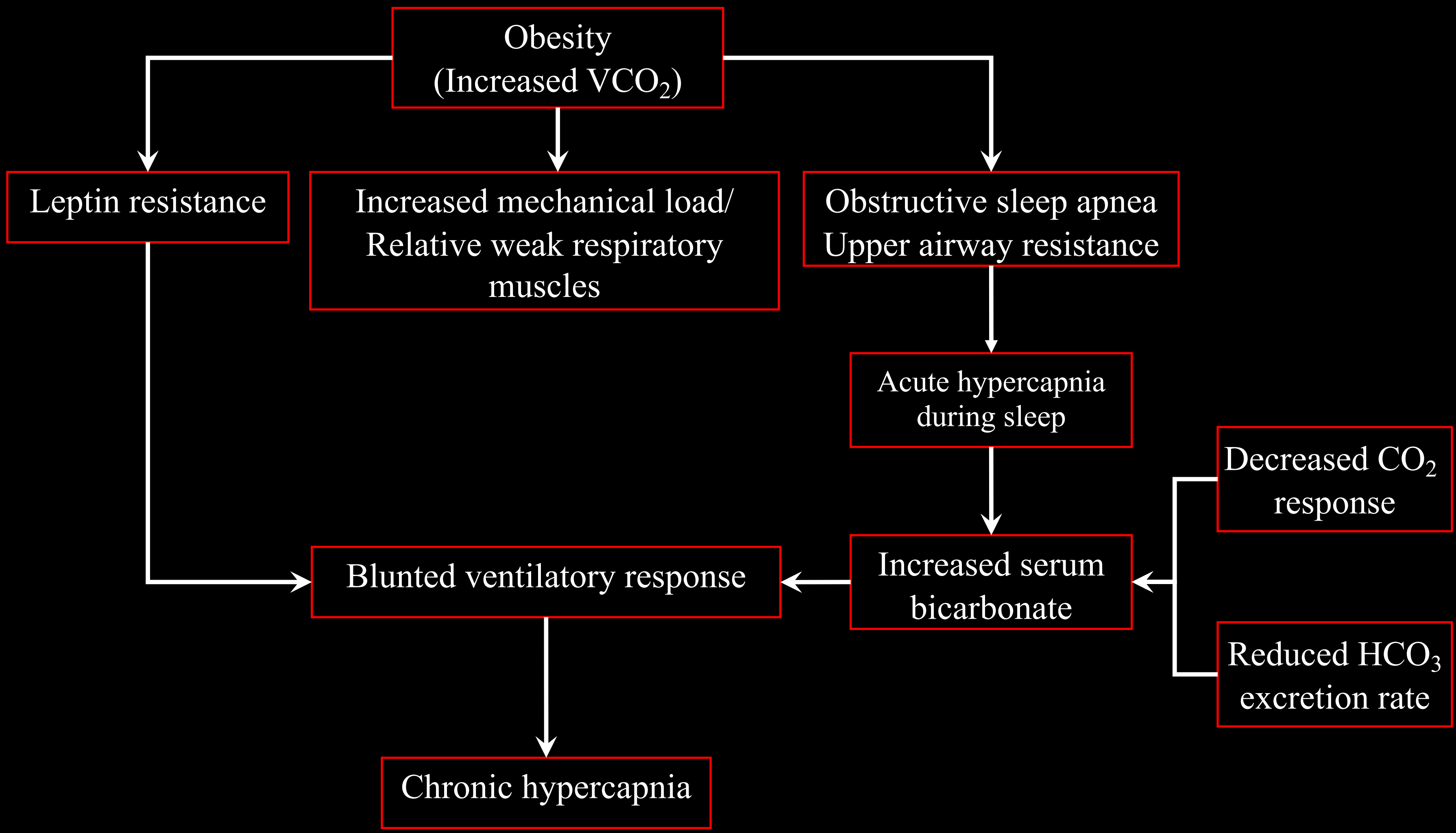


Carr GE, Mokhlesi B, Gehlbach BK. Chest 2012 141:798

Pathophysiology of respiratory failure



How does sleep hypoventilation lead to wake hypoventilation



Morbidity and Mortality

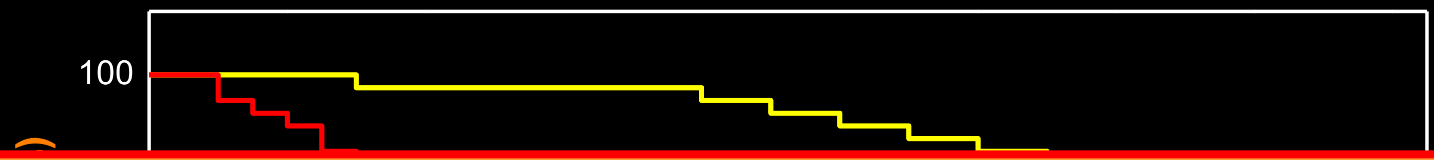
Clinical Implications of OHS

- Compared to simple eucapnic OSA, patients with OHS have:
  - Lower quality of life
  - Greater healthcare expenses
  - Higher risk of pulmonary hypertension
  - Higher risk of death attributed to:
    - severe obesity
    - severe OSA
    - chronic respiratory failure

Berg G. Chest 2001; 120:377-83
Hida W. Sleep Breath. 2003; 7:1

OHS in hospitalized patients

Outcome of patients admitted to medicine wards found to have OHS



31% of obese patients admitted to the wards were found to have undiagnosed OHS (BMI 45±9) NO HOSPITAL DEATHS but more ICU transfers and intubations

- Mortality at 18 months was 23% vs. 9% (HR=4.0; 95% CI: 1.5 to 10.4)
- Adjusted for age, BMI, electrolytes, renal and thyroid function

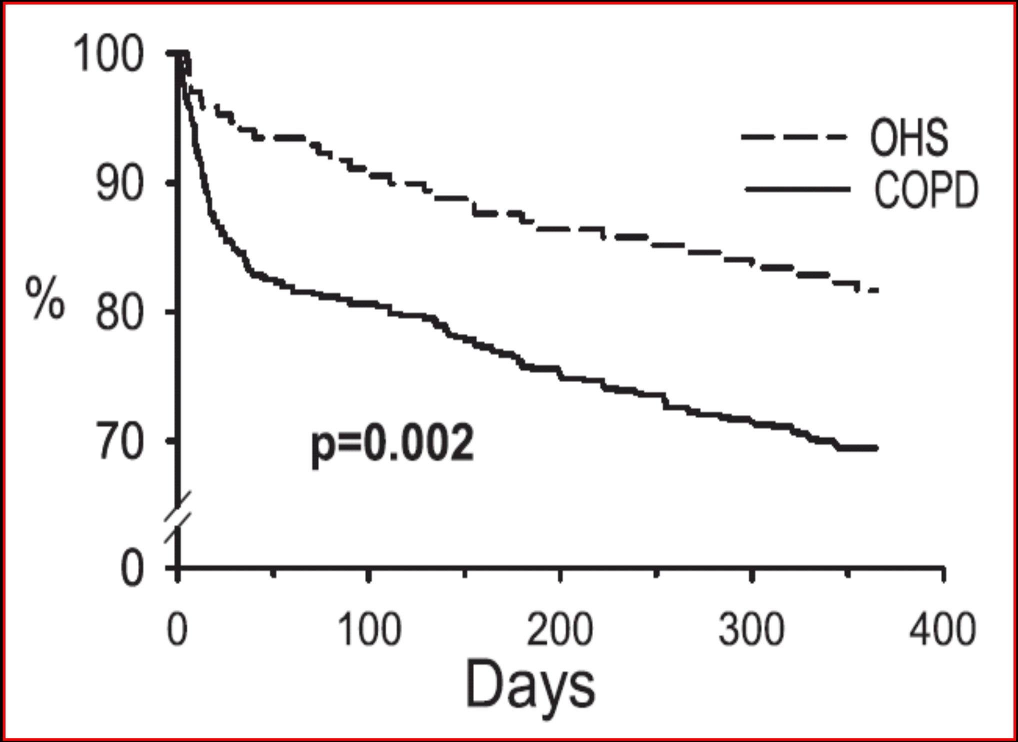
Nowbar S, Zwillich CW. *Am J Med* 2004; 116:1-7

Causes of acute on chronic hypercapnic respiratory failure in OHS

- Prospective study over 13 years in Spain
- 173 OHS patients with acute exacerbation
- BMI 42, age 74
- Only 9% of OHS were on home NIV but 39% on oxygen
- Causes of exacerbation:
  - Respiratory infection: 68%
  - Cardiac: 13%
  - Depressant drugs: 5%
  - Trauma: 3%
  - Surgery: 3%

Carrillo A, et al. AJRCCM 2012; 186:1279

Outcomes in OHS after acute hypercapnic respiratory failure treated with NIV



- OHS n=173, BMI 42, age 74
- COPD n=543, BMI 30, age 71
- Only 9% of OHS were on home NIV but 39% on oxygen
- 4% in each group required ET-T intubation
- OHS had lower ICU and hospital mortality (6% vs. 18%)
- Adjusted survival was not significantly different (p=0.11)
- At one year 45% were on CPAP and 10% on NIV

Carrillo A, et al. AJRCCM 2012; 186:1279

Long-term survival compared to OSA

- Retrospective study of 110 OHS vs 220 matched OSA patients
  - Similar age, sex, AHI, Epworth
  - PAP adherence ~ 6 h/night in both groups
  - Mean NIV 18/8 cm H_2O in OHS, mean CPAP 9 cm H_2O in OSA
  - Mean follow-up time of 7±4 years
- Five year mortality rates:
  - OHS: 15.5%
  - OSA: 4.5%
  - Risk of mortality: OR 2 (95% CI: 1.11–3.60)
  - Risk of CV event: OR 1.86 (95% CI: 1.14–3.04)
  - Strongest predictor of mortality was adherence to NIV < 4 hours

Castro-Añón O, et al. PLoS One 2015; Feb 11;10(2):e0117808

Treatment

Therapeutic options

- Positive airway pressure therapy
- Surgery
  - Tracheostomy
  - Bariatric surgery
- Pharmacological therapy
  - Medroxyprogesterone
  - Acetazolamide
  - Oxygen

PAP Therapeutic options

- Positive airway pressure therapy
  - CPAP
  - Bi-level PAP (spontaneous mode or S/T)
  - Volume-targeted pressure support
    - AVAPS (Respironics)
    - iVAPS (ResMed)

CPAP or bilevel PAP S mode in OHS

- CPAP titration failure rate can be as high as 43% in patients with OHS due to persistent hypoxemia

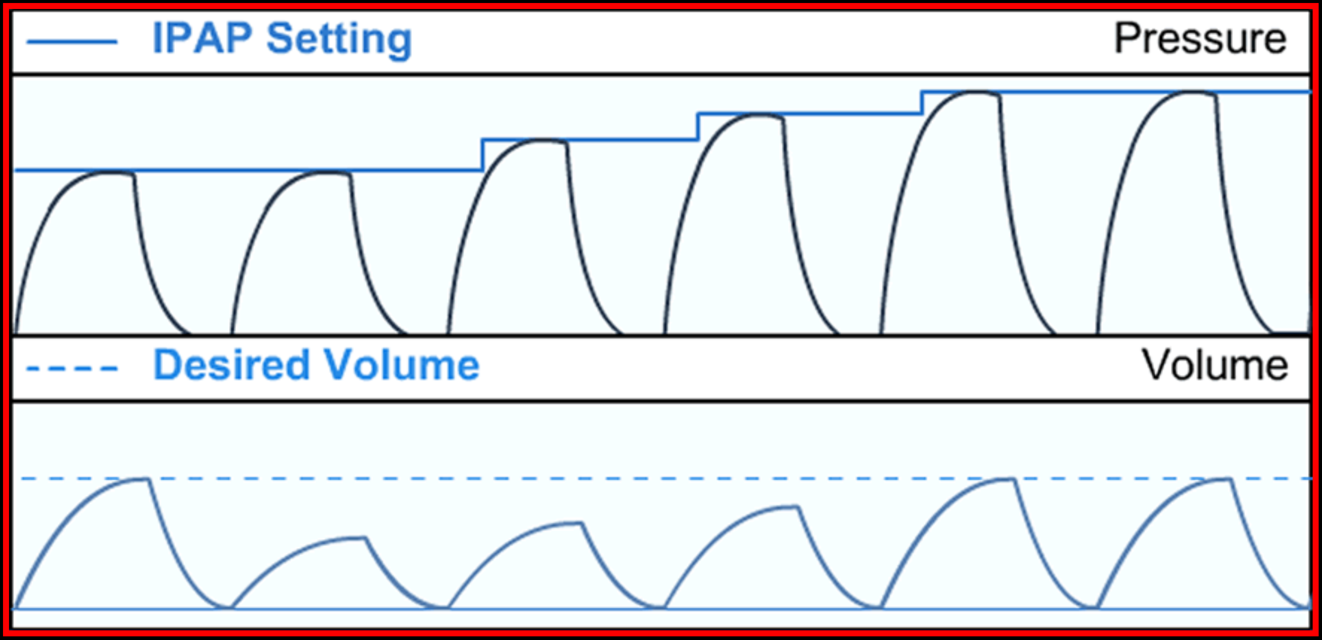
Banerjee D, et al. Chest 2007; 131:1678

- In an RCT, 36 patients were randomized to CPAP (n=18) vs. bi-level PAP in spontaneous mode (n=18) for 3 months
  - CPAP failures were excluded
  - Change in $PaCO_2$ was 5.8 mm Hg with CPAP and 6.9 in bilevel PAP S mode

Piper AJ et al. Thorax 2008; 63:395

Volume-Targeted Pressure Support

- Automatically adjusts IPAP to guarantee a target tidal volume



Murphy PB et al. Thorax 2012;67(8):727-34

Masa JF et al. AJRCCM 2015; 192: 86

AVAPS vs. bilevel PAP/ST in OHS

- RCT of 50 OHS patients to bilevel PAP/ST vs. AVAPS
  - 34% enrolled during an acute-on-chronic respiratory failure
- At three months there was no group differences in:
  - $PaCO_2$ and PaO_2
  - Epworth and QOL
  - Decrease in BMI
  - Improvement in FVC

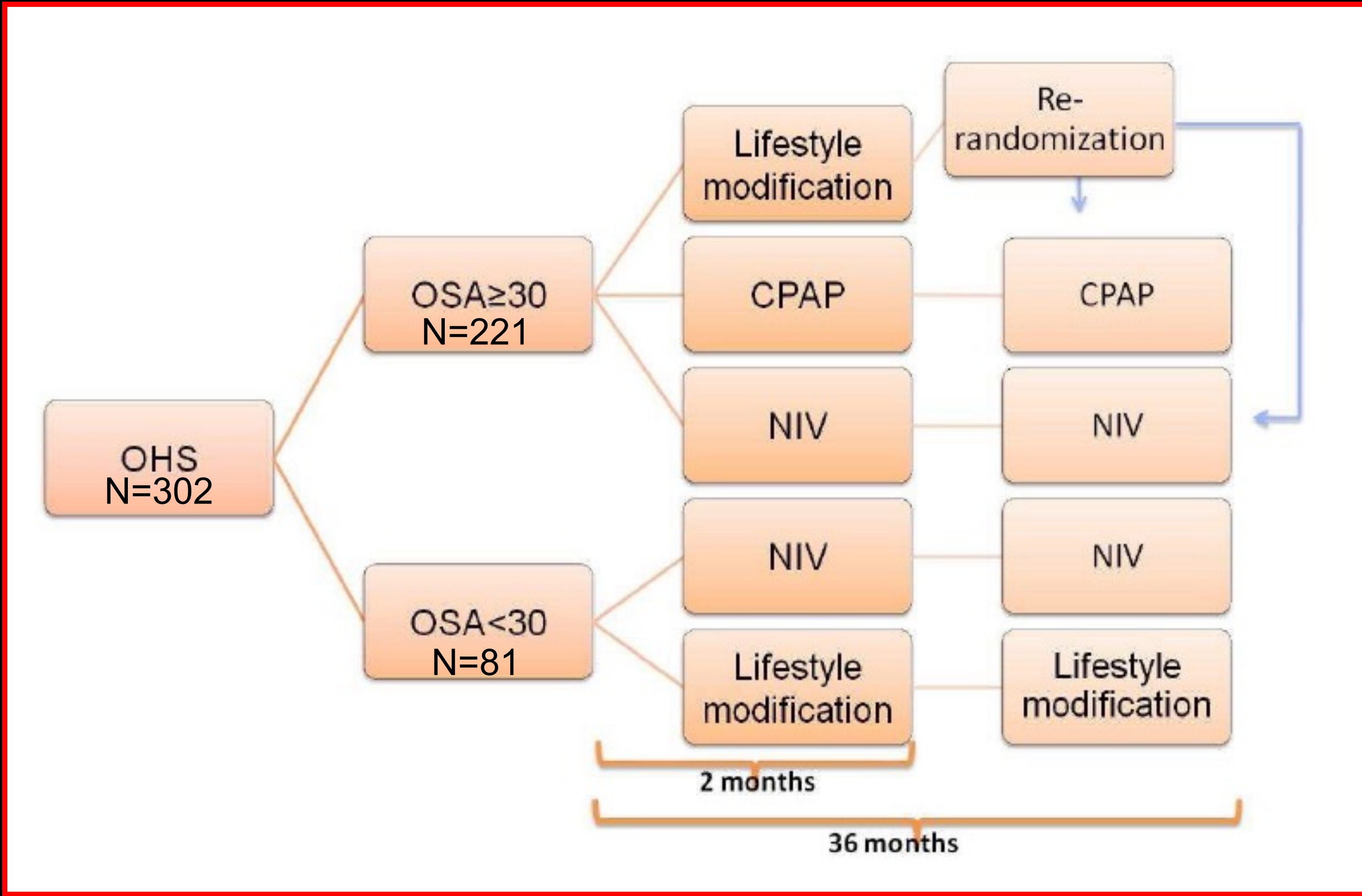
Murphy PB et al. Thorax 2012;67(8):727-34

No differences in ventilator parameters

Parameters	AVAPS (n=25)	Bi-level PAP/ST (n=25)
Delivered IPAP, cm H_2O	22±5	23±4
Set EPAP, cm H_2O	9±1	10±2
Leak, L/min	53±13	53±19
Patient triggered breaths, %	43±27	45±27
Mean adherence, h:min	4:11±2:53	5:08±2:22
Delta $PaCO_2$, mm Hg	- 4.5±7.5	- 4.5±8.2

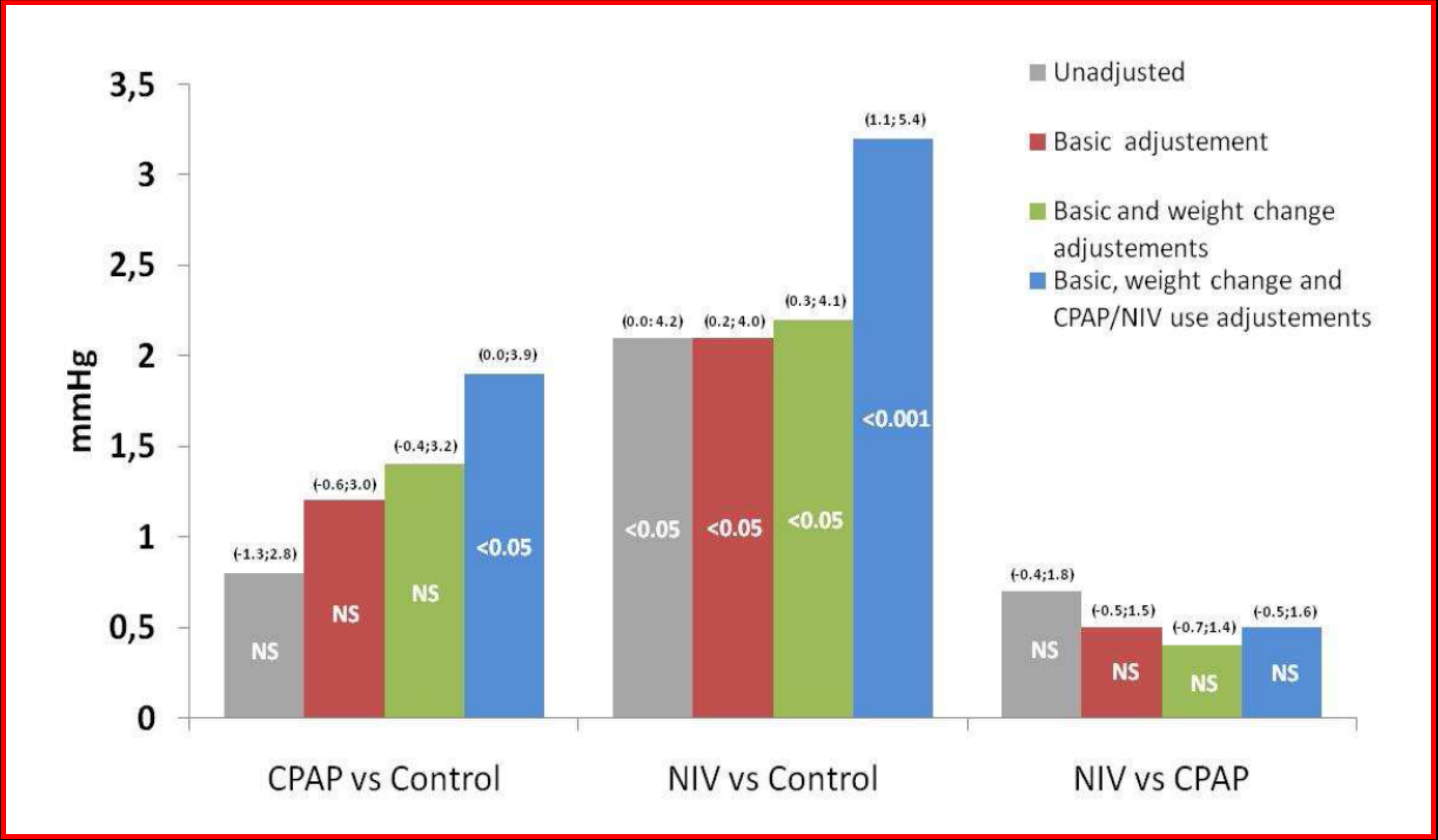
AVAPS set in pressure control mode, tidal volume of 8-10 ml/kg IBW

Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome: Pickwick Study

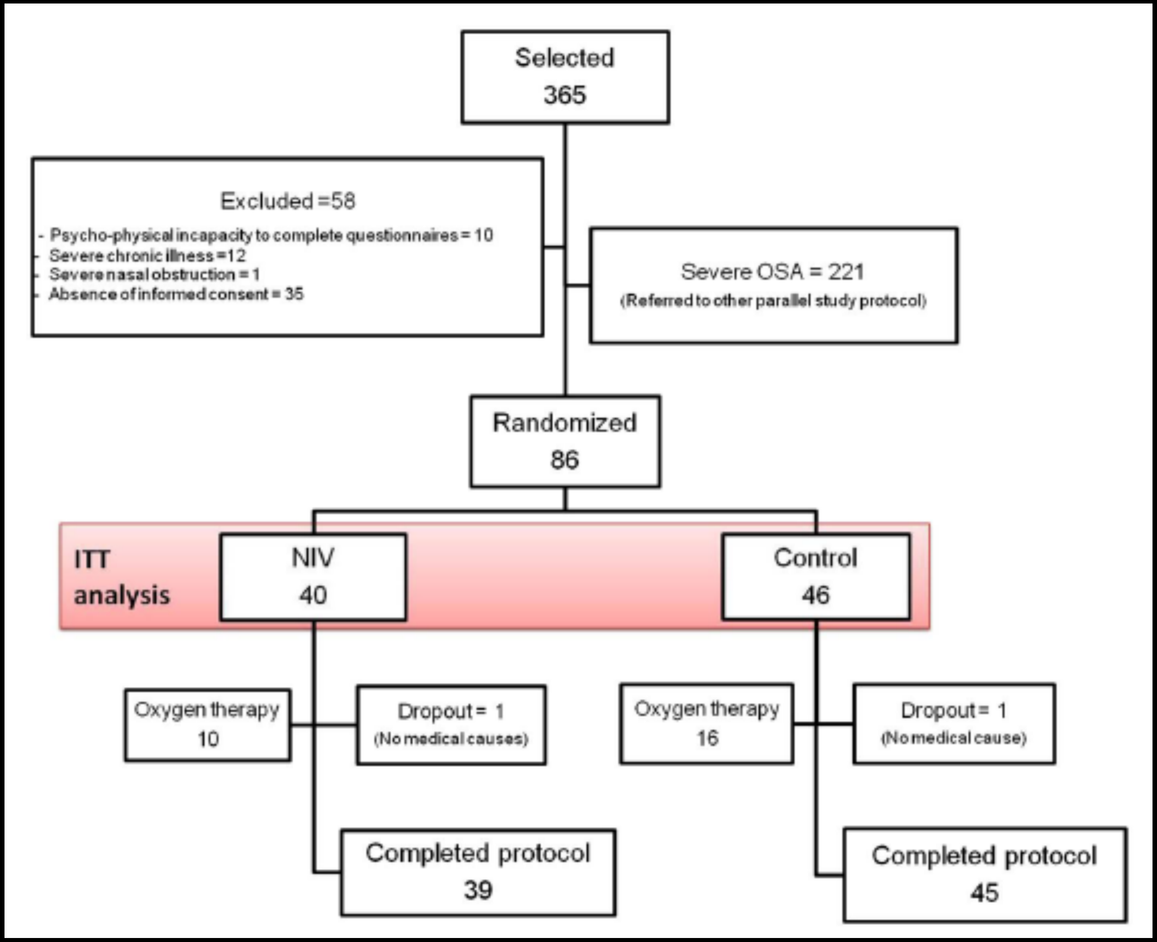


Masa JF et al. AJRCCM 2015; 192: 86

Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome: Pickwick Study



NIV in patients with OHS without severe OSA



Masa JF, et al. Thorax 2016; 71(10):899

NIV in patients with OHS without severe OSA

- NIV was more effective in improving PSG parameters, ESS and QoL

	Baseline, mean (SD)/median (IQR)		Intra-group differences, mean (95% CI)		p Value of inter-group differences§	
	NIV	Control	NIV	Control	Unadjusted	Adjusted
$PaCO_2$, mm Hg	*49 (4.0)*	*49 (3.5)*	**−6 (−7.7 to −4.2)‡**	**−2.8 (−4.3 to −1.3)‡**	0.006	0.019
Serum bicarbonate, mmol/L	*30 (4.1)*	*29 (3.8)*	**−3.4 (−4.5 to −2.3)‡**	**−1 (−1.7 to −0.2)***	0.000	0.004
pH	7.400 (0.040)	7.400 (0.030)	0.005 (−0.005 to 0.157)	0.031 (−0.008 to 0.147)	NS	–
PaO_2, mm Hg	64 (10)	67 (10)	**4.6 (0.5 to 8.8)***	1.4 (−2.6 to 5.5)	NS	–
FEV_1, %	72 (16)	80 (20)	1.8 (−2.7 to 6.4)	1.9 (−1.2 to 5.1)	NS	–
FVC, %	75 (21)	82 (20)	4.7 (−4.2 to 14)	2.9 (−0.5 to 6.3)	NS	–
6-MWD, m	309 (105)	349 (105)	29 (−16 to 74)	−7.2 (−25 to 11)	NS	–
Systolic BP, mm Hg	136 (18)	136 (15)	−4.2 (−11 to 2.5)	−4.3 (−10 to 1.7)	NS	–
Diastolic BP, mm Hg	*80 (16)*	*80 (18)*	0.5 (−5.3 to 6.2)	−1.2 (−5.4 to 2.9)	NS	–

Masa JF, et al. Thorax 2016; 71(10):899

Impact of PAP Adherence on hypercapnia/hypoxemia in OHS

Subgroup	N (%)	Change in $PaCO_2$	Change in PaO_2
		Mean ± SD	
Adherence with therapy			
Average PAP use > 4.5 h/day	34 (45%)	**8±5**	**9±11**
Average PAP use < 4.5 h/day	41 (55%)	2±4	2±9

Mokhlesi, B et al. J Clin Sleep Med 2006; 2:57

Non PAP treatment modalities

- Oxygen: no role as single therapy
  - At high concentrations it can increase $PaCO_2$ because of reduction in minute ventilation
    - Wijesinghe M, et al. Chest 2011; 139:1018
    - Mokhlesi B, et al. Chest. 2011 ;139:975
- Recent study revealed that 20 minutes of FiO2 at 50% increased PavCO2 from 53 mm Hg to 58 mm Hg with a drop in tidal volume by 89 ml.
    - Hollier CA et al. Thorax. 2014; 69(4):346-53

Need for oxygen during PAP titration

- During CPAP titration 43% required supplemental oxygen (average CPAP pressures of 14 cm H_2O).

Banerjee D, Chest. 2007; 131:1678

Mokhlesi B, J Clin Sleep Med. 2006; 2:57

- Other studies of similar patients undergoing aggressive NIV titration (IPAP of ~ 13 cm H_2O above an average EPAP of 10), or volume targeted pressure support only 12%-23% required oxygen supplementation

Murphy PB et al. Thorax 2012;67:727

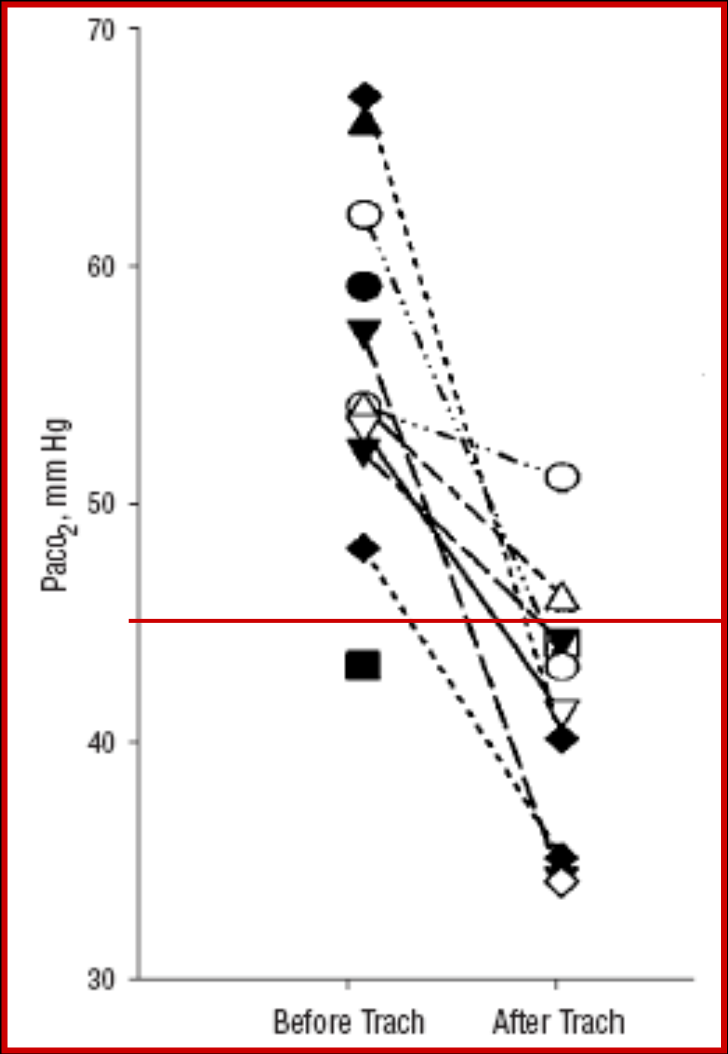
Masa JF et al. AJRCCM 2015; 192:86

The effect of supplemental oxygen in OHS in the Pickwick study

- Post-hoc analysis of a previous RCT
- 302 sequentially screened OHS patients who were randomly assigned to NIV, CPAP, or lifestyle modification.
  - 78 out of 302 (26%) were prescribed home oxygen therapy
- Oxygen therapy (1-2 L/min) was not associated with an increase in worsening ABG or hospital resource utilization in any of the groups at two months.
- Long-term studies are necessary.

Masa JF, et al. JCSM 2016; 12 (10):1379

Tracheostomy



- Retrospective study
- 13 patients with OSA plus OHS
- Tracheostomy improved but did not fully resolve SDB in patients with OSA plus OHS
  - NREM AHI 64 to 31
  - REM AHI 46 to 39
  - 7/13 had AHI > 20
  - Persistent SDB due orifice obstruction b/o chin or neck adiposity or central sleep apnea
- Hypercapnia resolved in most patients

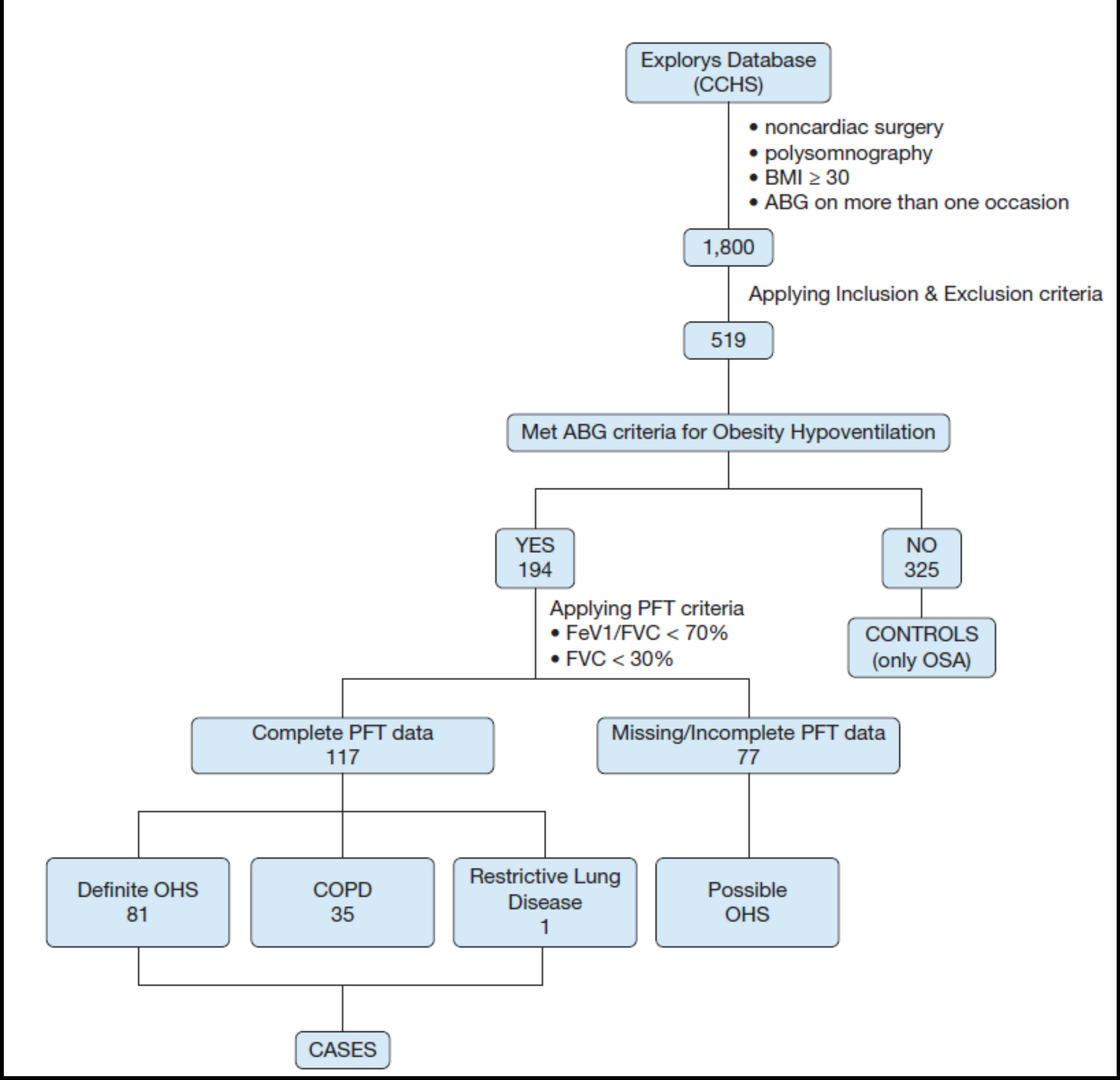
Kim SH, et al. Arch Otolaryngol Head Neck Surg. 1998;*124*:*996*

Impact of Bariatric Surgery on Respiratory Insufficiency

- 29 patients with OHS or OSA+OHS
- Mean weight loss of 50±29 kg (110±65 pounds)
- PaO_2 increased from 53±9 to 68±11 mm Hg
- $PaCO_2$ decreased from 51±7 to 41±4 mm Hg
- Hb decreased from 16.9 to 14.9 g/dl
- Significant improvements in ERV, FRC, FVC

Sugerman HJ. Chest 1986; 90:81

Postoperative complications in patients with unrecognized OHS: A retrospective study



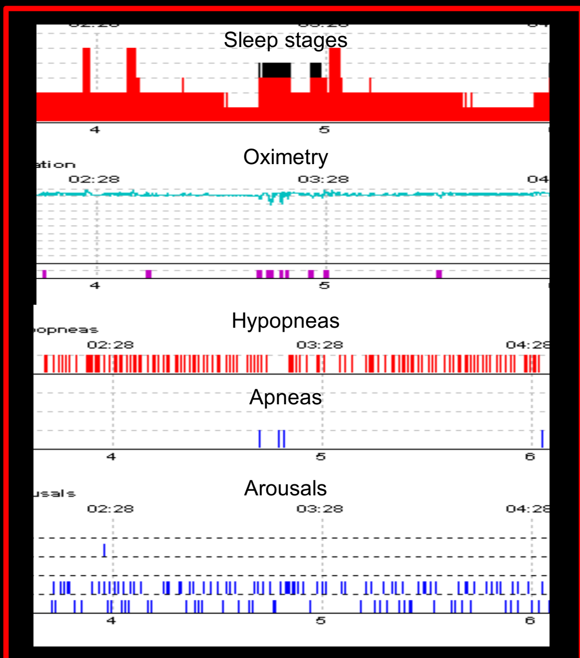
Kaw R, et al. Chest 2016; 149: 84

Adjusted postoperative complications in patients with unrecognized OHS

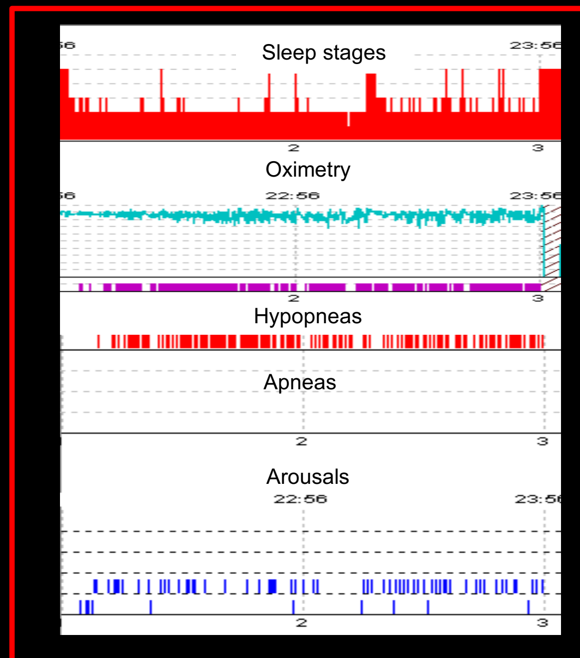
Postoperative Outcome	Hypercapnic OSA (n = 194)	OSA (n = 325)	OR (95% CI)	*P* Value
Respiratory failure	39 (21)	8 (2)	10.9 (3.7-32.3)	< .0001
Heart failure	15 (8)	0	5.4 (1.9-15.7)	.002
Prolonged intubation	24 (13)	12 (4)	3.1 (0.6-15.3)	.2
Reintubation	12 (6)	5 (2)	1.7 (0.2-13.4)	.6
Tracheostomy	4 (2)	3 (1)	3.8 (1.7-8.6)	.002
ICU transfer	41 (21)	19 (6)	10.9 (3.7-32.3)	< .0001
Death at 30 d	2 (1)	0	...[a]	...
Death at 1 y	10 (5)	2 (0.6)	0.9 (0.1-7.5)	.9

Variables	Hypercapnic OSA (n = 194)	OSA (n = 325)	$\beta \pm$ SE	*P*
ICU length of stay, d			0.86 ± 0.32	.009
Median (IQR)	0 (0-0)	0 (0-0)		
Mean ± SD	0.12 (0.93)	1.04 (3.8)		
Hospital length of stay, d			2.94 ± 0.87	.0008
Median (IQR)	5 (3-9)	0 (0-4)		
Mean ± SD	7.3 (8.2)	2.8 (5.1)		

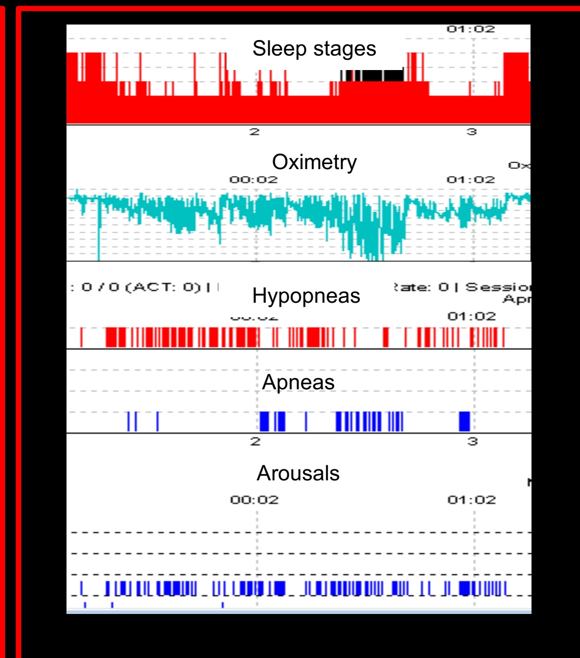
Postoperative complications in patients with OSA: hypercapnia may be more relevant than AHI!



AHI 45
3% ODI 2
T90 0 min
Arousal index 50



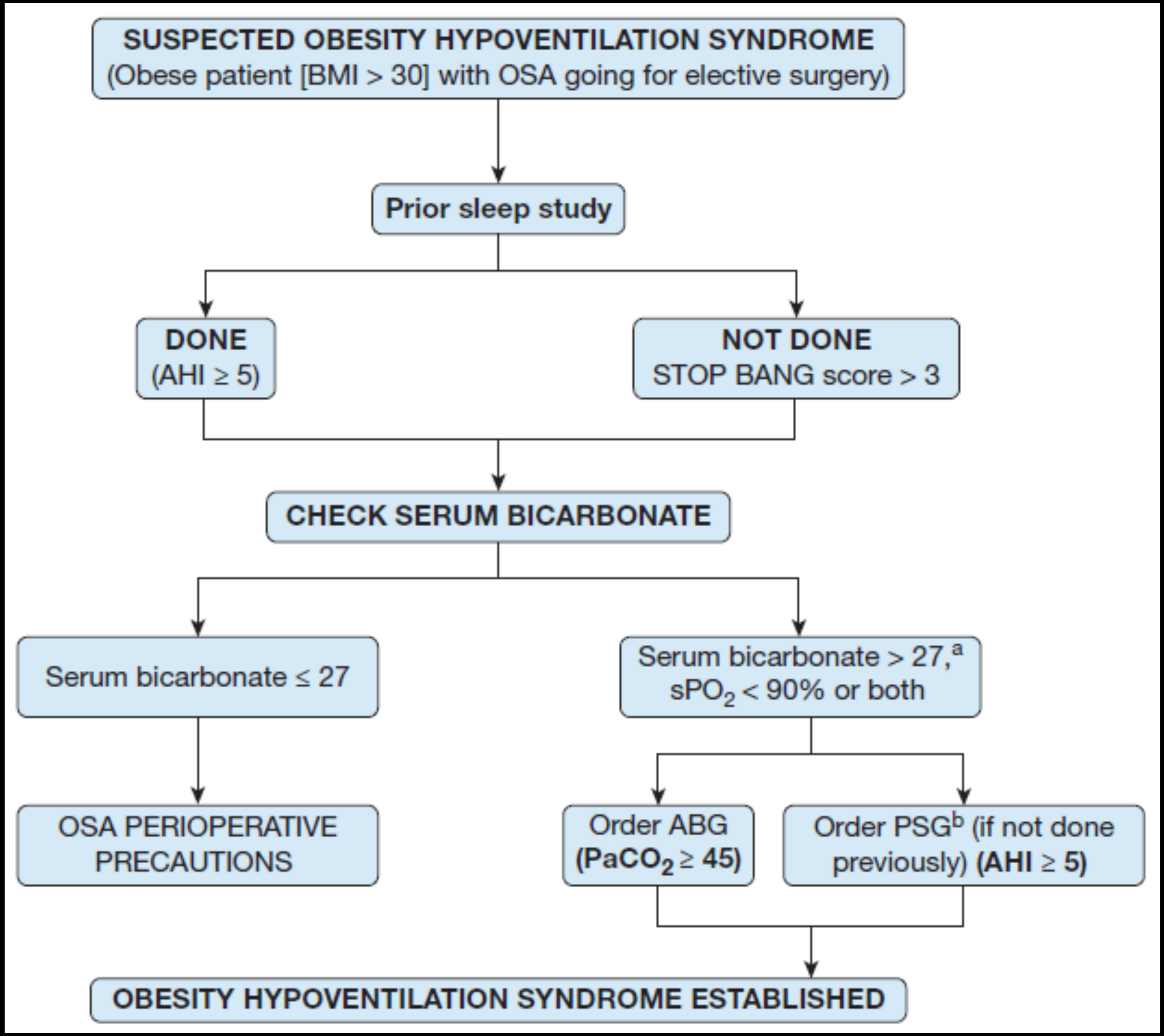
AHI 45
3% ODI 43
T90 9 min
Arousal index 36



AHI 45
3% ODI 47
T90 77 min
Arousal index 43

Cooksey J, Mokhlesi B. Chest 2016; 149: 11

One possible preoperative approach to OHS



Kaw R, et al. Chest 2016; 149: 84

Research questions

- How to best screen preoperative patients for unrecognized OHS
- How to approach patients with OHS who are nonadherent to PAP therapy
- How safe is postop supplemental oxygen
- Best monitoring strategies for patients with hypercapnia
  - Oxygenation
  - Ventilation
- Avoiding management pitfalls:
  - Over diuresis
  - Excessive oxygen supplementation

Conclusions

- OHS is prevalent in patients with severe obesity and OSA
- It is frequently unrecognized and undertreated
- Untreated OHS significantly increases the risk of morbidity and mortality
- Comprehensive treatment strategies should focus on:
  - Nocturnal resolution of sleep disordered breathing
  - Weight loss
  - Increasing physical activity