The Big and the Breathless
Sleep Related Hypoventilation

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Objectives

• Respiratory physiology during sleep
• Definition and Physiology of Obesity hypoventilation
• Morbidity of the disease
• Treatment: benefits and options
• HealthPartners experience
Carbon Dioxide
Atmospheric Concentrations of CO$_2$
Carbon Dioxide Emissions

TOTAL GREENHOUSE GAS EMISSIONS
(Metric Tons Carbon Dioxide Equivalent)

- Green: < 500,000
- Light Green: 500,000 - 1,000,000
- Orange: 1,500,000 - 2,000,000
- Red: 3,649,827
- Dark Red: 6,027,181

Source: New Scientist (2009 data)
Respiratory Physiology during Sleep
Some Generalizations

• Sleep is entered through NREM
• NREM and REM alternate with approximately 90 minute periods
• REM sleep predominates in the latter third of the night
• Wakefulness within sleep usually accounts for less than 5% of total sleep time.
Brain Res 1974;82 Montplasir et al
Compliance associated with AHI reduction even when used < 20 hours/week

<table>
<thead>
<tr>
<th>Hours/week</th>
<th>% of patients</th>
<th>Initial AHI</th>
<th>At Home</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>11%</td>
<td>40.4</td>
<td>3.4</td>
</tr>
<tr>
<td>40-50</td>
<td>18%</td>
<td>37.3</td>
<td>4.0</td>
</tr>
<tr>
<td>30-40</td>
<td>17%</td>
<td>33.6</td>
<td>4.7</td>
</tr>
<tr>
<td>20-30</td>
<td>14%</td>
<td>31.4</td>
<td>4.3</td>
</tr>
<tr>
<td>&lt;20</td>
<td>39%</td>
<td>26.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Effects of Sleep on Ventilatory Function

- Minute ventilation is decreases by 6-11% in NREM and 5-15% in REM sleep
- CO2 rises between 2 and 6.5 mm Hg
- Decrease in oxygen saturation occurs NREM 96.5, REM 96.2 (wakefulness 97.3)
- The upper airway lumen is reduced during sleep, this is more pronounced in snorers
Unique Effects of REM Sleep on Ventilation

• The respiratory rate is increased and irregular especially in phasic REM

• The diaphragm: dominant muscle maintaining ventilation

• The upper airway is more susceptible to closure via negative pressure

• Apneas are longer and there is reduced susceptibility to recovery central apneas
Hypoventilation mechanisms

\[ PC02 = \frac{0.863 \times VC02}{VE \times (1 - VD/VT)} \]
Hypoventilation mechanisms

Increasing VD/VT VC02

PC02

P02

PC02

VE
Causes of Hypercapnic Resp. Failure

Neural & Neuromuscular
- Brain
  - Drugs
- Motor neurons
- Neuromuscular junction
- Respiratory muscles

Chest Wall
- Kyphoscoliosis
- Ankylosing spondylitis
- Flail chest

“Medical” Diseases
- COPD
- Severe asthma
- Late stage interstitial lung disease
- Pulmonary edema
- Sleep apnea / obesity-hypoventilation
- Hypothyroidism

Iatrogenic - Drugs, Ventilators
Clinical Categories of Hypoventilation

• *Can’t breathe:*
dyspnea due to mechanical restraint, weakness, or excessive ventilation.

• *Won’t breathe:*
no dyspnea. Depressed drive due to congenital or acquired controller error.
Can’t breathe

-Airway Obstruction
  • COPD, asthma, cystic fibrosis

-Restrictive
  • Obesity
  • Kyphoscoliosis

-Weakness
  • ALS/myopathies
Can’t Breathe

Kyphoscoliosis
Angle > 90°

COPD Fev1 < 30%

Obesity + OSA
Won’t breathe

• *Exogenous:*
narcotics, sedatives.

• *Endogenous:*
  Leptin resistance\(^{1-5}\), alkalosis, myxedema, adaptation, genetic\(^{6-10}\), structural.
Hypercapnic Disorders: Definitions

Hypercapnia: $\text{PaCO}_2 \geq 45 \text{ mm Hg}$

Hypercapnic respiratory failure:
Hypercapnia plus Acidosis
– Acute: no or minimal metabolic compensation
– Chronic: appropriate metabolic compensation
Obesity Hypoventilation Syndrome

• Triad of obesity, daytime hypoventilation and sleep disordered breathing

• Often a diagnosis of exclusion

• Prevalence of OHS amongst patients with a BMI>35 has been reported as 31%

Why some subjects develop OHS whilst others do not at the same BMI is not completely understood
Definitions: BMI

- 25    ideal
- >30   obese
- >40   morbid obesity
- >50   super obese
- >60   super super obese
Obesity in India

Year of survey

1995  2000  2006

Total  Men  Women

23.4  18.7  27.9  29.8  35.4  40.8  50

Obese (%)
HPMG Data

7506 overnight OSA diagnostic studies

→

1844 with CPAP compliance data

Overall AHI reduction 32.1 → 4.6

→

BMI ≥ 40 – 444 patients
AHI reduction 43.2 → 4.9

BMI < 40 – 1399 patients
AHI reduction 28.7 → 4.5
Breathing patterns with Obesity

- Heavy snoring
- Hypoxemia without OSA (hypoventilation)
- OSA
- OHS
OHS

CO2

OSA

Normal CO2

OSA

No OSA

90%

10%

Eucapnic OSA
Obesity Hypoventilation Syndrome (OHS)

• Definition
  – BMI > 30 kg/m²
  – Awake arterial pCO₂ > 45 mm Hg
  – No other causes for hypercapnia
OSA and BMI ≥ 30 kg/m²  
\[ n = 522 \]

Serum \( \text{HCO}_3^- \) < 27 mEq/L  
\[ n = 257 \]  
3% with OHS

Serum \( \text{HCO}_3^- \) ≥ 27 mEq/L  
\[ n = 265 \]  
50% with OHS

Lowest \( S_pO_2 \) during sleep > 60% or AHI < 100 events/h  
\[ n = 186 \]  
36% with OHS

Lowest \( S_pO_2 \) during sleep < 60% or AHI > 100 events/h  
\[ n = 79 \]  
76% with OHS
Pickwickian Syndrome

Little boy who would always fall asleep
OHS: Incidence

• 0.3-0.5% of the general population
• 10-20% in outpatients presenting to sleep clinics
• 50% of hospitalized patients with BMI over 50
Eucapneic OSA versus OHS

- Upper airway resistance
- Distribution of obesity
- Pulmonary mechanics
- Responsiveness to carbon dioxide and oxygen
- Leptin resistance
Eucapnic OSA versus OHS

- Increased healthcare utilization
- Poorer health outcomes
- Greater hypersomnia
- Lower level of social functioning
- More likely to have CHF, angina, cor pulmonale
- Increased severity of pulmonary HTN
Eucapnic OSA versus OHS

- More likely to be hospitalized
- More vulnerable to iatrogenic insults
- Longer ICU stays
- Increased likelihood of LTAC need
- Higher mortality
Hypoxemia + Hypercapnia → Pulmonary Hypertension
Post Hospitalization Mortality

Probability of Survival (%)

Months after Hospital Discharge

Nowbar Am J Med 2004
Obesity

- Leptin resistance
- Increased mechanical load

Blunted ventilatory response

Chronic hypercapnia

OSA

- Acute hypercapnia during sleep

- Decreased compensatory hyperventilation
- Decreased $\text{HCO}_3^-$ excretion rate

Increased serum $\text{HCO}_3^-$
Proposed Mechanisms for OHS

• Ventilatory load

• Sleep Disordered breathing

• Abnormal Ventilatory control mechanisms
## Respiratory Mechanics in OHS

<table>
<thead>
<tr>
<th></th>
<th>OHS</th>
<th>Eucapnic obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>TLC</td>
<td>slightly reduced</td>
<td>normal</td>
</tr>
<tr>
<td>ERV</td>
<td>Markedly reduced</td>
<td>normal/mildly reduced</td>
</tr>
<tr>
<td>Inspiratory muscle</td>
<td>reduced</td>
<td>normal</td>
</tr>
<tr>
<td>strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilatory response to</td>
<td>Normal/reduced</td>
<td>normal/increased</td>
</tr>
<tr>
<td>CO2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCO2</td>
<td>increased</td>
<td>normal</td>
</tr>
</tbody>
</table>
Effects of obesity on upper airway
Proposed Mechanisms for OHS

- Ventilatory load
- Sleep Disordered breathing
- Abnormal ventilatory control mechanism
The bar chart shows the comparison between OSA and OHS in terms of arousal index and percent sleep time with saturation less than 90.
Daytime Hypercapnia in OHS

- Shorter inter-apneic recovery
- Inability to bring pCO2 back to baseline before the onset of the next apnea
- Elevations of bicarbonate
- Abnormality in bicarbonate handling by the renal system
Fig. 3

Diagram showing the relationship between airflow, CO₂ accumulation, and CO₂ elimination during different ventilation cycles. Stable ventilation precedes Cycle 1, which includes hypopnea and interevent periods, followed by apnea and another interevent. Cycle 2 follows with similar patterns.
Proposed Mechanisms for OHS

• Ventilatory load

• Sleep Disordered breathing

• Abnormal Ventilatory Control Mechanisms
Evidence of Abnormal Ventilatory control

• Pts with OHS do not hyperventilate to the same degree when rebreathing CO2

• Pts with OHS do not increase their minute ventilation to the same degree when forced to breath a hypoxic gas mixture
Abnormal Ventilatory Control
Acquired

- The ventilatory responses to hypercapnia are similar between first degree relatives of pts with OHS and controls

- Treatment with PAP therapy improves the responsiveness to hypercapnia and hypoxia
The leptin story
Leptin resistance in OSAH

<table>
<thead>
<tr>
<th></th>
<th>PCO2&lt;45 (106)</th>
<th>PCO2&gt;45 (79)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>32.5 ± 0.3</td>
<td>33.2 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>FEV1/FVC, %</td>
<td>84.2 ± 0.6</td>
<td>85.4 ± 1.7</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>40.9 ± 0.3</td>
<td>46.6 ± 0.4</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>AHI</td>
<td>52.9 ± 2.2</td>
<td>47.4 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Leptin, ng/mL</td>
<td>9.0 ± 0.4</td>
<td>14.3 ± 1.0</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>


Leptin resistance in obesity

leptin CSF/serum ratio is fourfold higher in lean individuals compared to obese subjects

Caro JF. . Lancet 1996; 348:159–161
Treatment of OHS

Address reversible causes
Medications
Oxygen
PAP: CPAP, BIPAP, AVAPS
tracheostomy
Treatment of OHS

Weight loss
Weight loss and OHS

Zavosky: Review of 14 studies 288 patients, mean period of follow up 18 months (12% of patients had OHS) PaO2 increased by 10, PaCO2 decreased by 3

Torchia: Surgical Rx of 95 patients with BMI of >60 OSA/OHS 39% 12 months follow up 30 of 35 had resolution with improvement in the remaining 5

(Surgical series of 34 pts with BMI >70, 58% had OSA 32% had OHS)
No Δ in BMI after Dx (7505 patient database)
Non-PAP Therapy
Stimulants for Hypoventilation

- Progesterone- modestly lowers $\text{PCO}_2^1$; improves hypoventilation$^2$ but not OSA$^3$

- Acetazolamide- may worsen OSA, less effective than progesterone in hypoventilation$^1$

- Thyroid replacement in myxedema

$^1$Skatrud JB. Progress in Clinical & Biological Research. 136:87-95, 1983
$^3$Cook W. Chest 1989;96(2):262-6
Effect of supplemental oxygen on hypercapnia in OHS

76 obese patients screened:
55 from sleep clinic
11 from obesity clinic
6 prior to bariatric surgery
4 from community

Excluded
PtCO₂ <45mmHg
n=51

25 subjects invited to participate in study

Declined
n=1

24 subjects randomized

Did not complete study
n=1

23 subjects completed study
The Effect of Supplemental Oxygen on Hypercapnia in Subjects With Obesity-Associated Hypoventilation
Positive airway pressure treatment

- CPAP
- BIPAP
- BIPAP with Backup rate
- AVAPS
% Probability of Survival

Months after diagnosis of OHS

OHS treated with NIV

Eucapnic obesity

Untreated OHS
PAP in restrictive disease

Simonds AK  Thorax 1995;50:604-609
CPAP Effective ~99%
CPAP

- One level of pressure on inspiration and exhalation
- Device may have the option to provide pressure relief in early exhalation
CPAP for Obesity
Hypoventilation

• Often successful when the predominant physiology is one of airway obstruction
• May result in lowering of pCO2 and increase in pO2
CPAP for OHS

Current Evidence Supports:

- Improvement in awake blood gases
- Ventilatory responsiveness to hypoxemia and hypercapnia
- Improved V/Q mismatch
- Reduced diaphragmatic effort
- Improved quality of life
Greater HTN reduction if BMI > 40?

HPMG data
If BMI >40, compliance matters if initial SBP > 150.
Daytime Hypercapnia in Obstructive Sleep Apnea Syndrome
Naoko Kawata, MD  Chest 2007
Bi-level therapy

• One level of pressure on inspiration and lower level of pressure on expiration. PS the same every breath
BIPAP for Hypoventilation

• OSA often coexists and this component is addressed by EPAP

• Tidal volume support is provided by the difference between EPAP and IPAP

• Oxygen may be needed if hypoxemia is not adequately corrected with BIPAP alone
BIPAP and OHS

• Current Evidence supports:
  • Reduction in need for hospitalization
  • Improvements in secondary polysythemia
  • Improved sleep quality
  • Reduced inspiratory muscle loading
Sleep-disordered breathing

Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation

A J Piper; D Wang; B J Yee; D J Barnes; R R Grunstein
Conclusions

- Similar reductions in PCO2
- Similar compliance
- No difference in daytime sleepiness

- BIPAP group had increased psychomotor vigilance and subjective sleep quality
AVAPs for Hypoventilation

- The treatment is targeted to provide a specified tidal volume support

- The amount of support provided by the machine can constantly adjust to the patients' needs over time.

- May result in lower mean pressures compared to BIPAP
AVAPS

< 1 cmH₂O / min
Average Volume-Assured Pressure Support in Obesity Hypoventilation*: A Randomized Crossover Trial

CHEST. 2006;130(3):815-821. doi:10.1378/chest.130.3.815

Figure Legend:

Ptco2 during the night at baseline, and during therapy with CPAP, BPV-S/T, and BPV-S/T-AVAPS.
Figure Legend:

Summary scale of the SRI at baseline, and following therapy with BPV-S/T and BPV-S/T-AVAPS.
Conclusion

• BPV-S/T substantially improved oxygenation and sleep quality in patients with OHS.

• AVAPS provided additional benefits on ventilation quality, However, this did not provide further clinical benefits regarding sleep quality and HRQL.
Screened = 62

Excluded = 12
Unable to read & write = 6
Declined = 4
Deteriorated and intubated = 1
Unable to provide informed consent = 1

Baseline assessment = 50

Randomised AVAPS = 25
Withdrawn = 1
Did not attend follow-up = 1
3 month assessment = 23

Randomised PS = 25
Withdrawn = 1
Did not attend follow-up = 1
3 month assessment = 23
Pearls

• OHS is becoming more common with the obesity epidemic and has significant adverse consequences when not recognized
• An understanding of the underlying mechanisms is evolving
• Treatment is effective and improves outcomes
• Weight loss and PAP are the mainstays of treatment
• Multimodality approaches likely to be needed