

The Triple Overlap Syndrome

OSA OHV COPD

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Learning Objectives

- Describe the *Triple Overlap Syndrome* and its significance
- Discuss basic principles of hypoventilation
- Understand the diagnoses of OSA, OHV, and COPD as individual entities and their impact on sleep disordered breathing
- Consider diagnostic and treatment options for patients with Triple Overlap Syndrome

A Word on Language

- **The language that we use regarding weight is sensitive and evolving**
- **I am going to use the terms obesity and BMI for the purposes of this talk**
- **I am also aware that not every person with BMI >40 has the issues that I am speaking about today**
- **I am open to feedback on how to improve my use of language as it pertains to this vulnerable group of patients**

A Case

61 year old male former smoker, with HTN, DMII, COPD on 2L, HFpEF, CAD s/p PCI, presents to clinic for hospital discharge follow up after heart failure exacerbation.

- Compliant with inhalers and diuretic regimen. Limited dietary indiscretions. Former smoker. Hospitalized 2 previous times in past year for COPD exacerbation and heart failure exacerbation.**
- Exam: Normotensive, oxyhemoglobin saturation 93% on 2L, BMI 41, No wheezing, 1+ edema and venous stasis in bilateral LLE**

Laboratory Data

Pulmonary Function Testing:

Spirometry		Units	Pred	Best	%Pred	Best	%Pred	%Change
FVC	Liters		4.75	2.31	49			
FEV1	Liters		3.22	1.50	46			
FEV1/FVC	%		68	65				
FEV6	Liters			2.20				
FEF 25-75	L/Sec		2.88	0.71	25			
FET 100%	Sec			9.39				
FEF 50/FIF 50			< 1.00	0.62				
PEF	L/Sec		8.86	6.40	72			
PIF				2.44				

Diffusion		Units	Pred	Best	%Pred	Best	%Pred	%Change
DL Corr	ml/Min/mmHg		31.66	7.95	25			
DL Corr/VA			3.58	2.64	74			
VA	Liters			3.01				
IVC	Liters			2.06				
BHT	Sec			10.81				

Metabolic Values:

141	93	18	/
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4.3	45	0.9	\

Cardiac Echo:

- LVEF 55%
- Grade 2 DD
- RV mildly dilated
- PASP 45mmHg
- No valvular abnormalities

What else can you do to optimize your patient?

Medication reconciliation

Pulmonary rehab

Referral to weight loss clinic

Inhaler training

Tobacco cessation

Dietary counseling

Home monitoring program

Ensuring up to date on vaccination

Address hypoventilation

Triple Overlap Syndrome

Defining the syndrome and its significance

The Triple Overlap Syndrome

-
- **Disorder of hypoventilation**
 - **Daytime awake hypercapnia PaCO₂ \geq 45 mmHg (pH \geq 7.35)**
 - **OSA with AHI $>$ 5**
 - **Morbid obesity BMI \geq 40 kg/m²**
 - **COPD FEV₁/FVC \leq 0.7**

Sharma, G., & Lastra, A. Chest Physician 2023

What's in a name?

Hypercapnic OSA-COPD

Morbid obesity and OSA-COPD overlap

Hypercapnic morbidly obese COPD

COPD OSA Obesity overlap

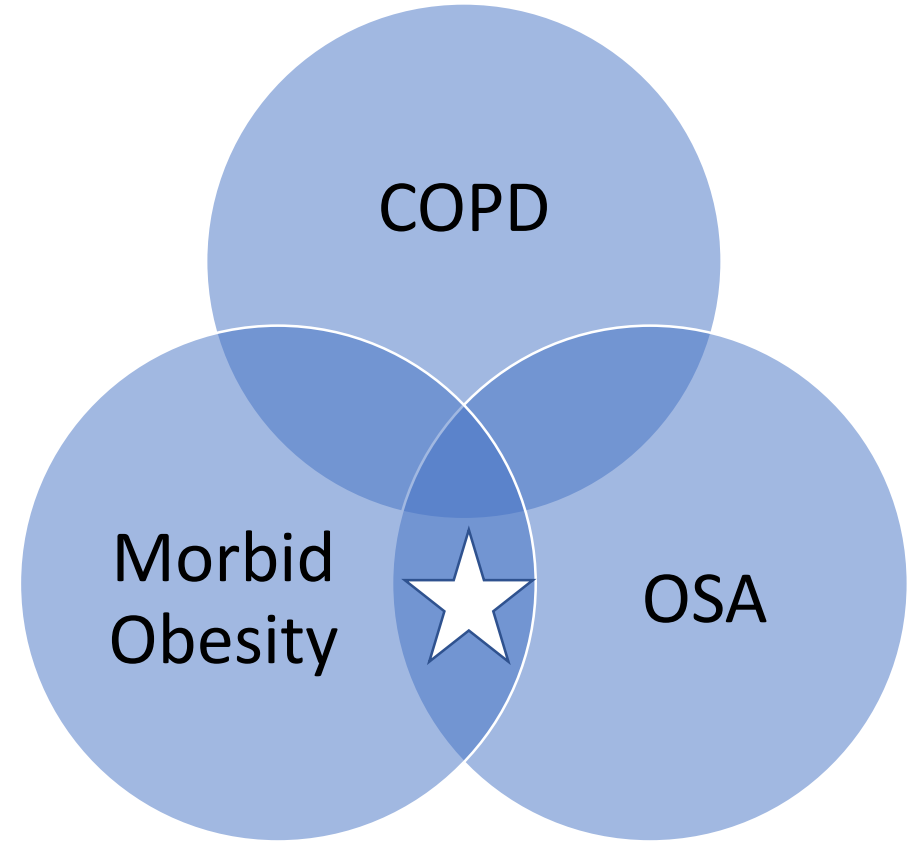
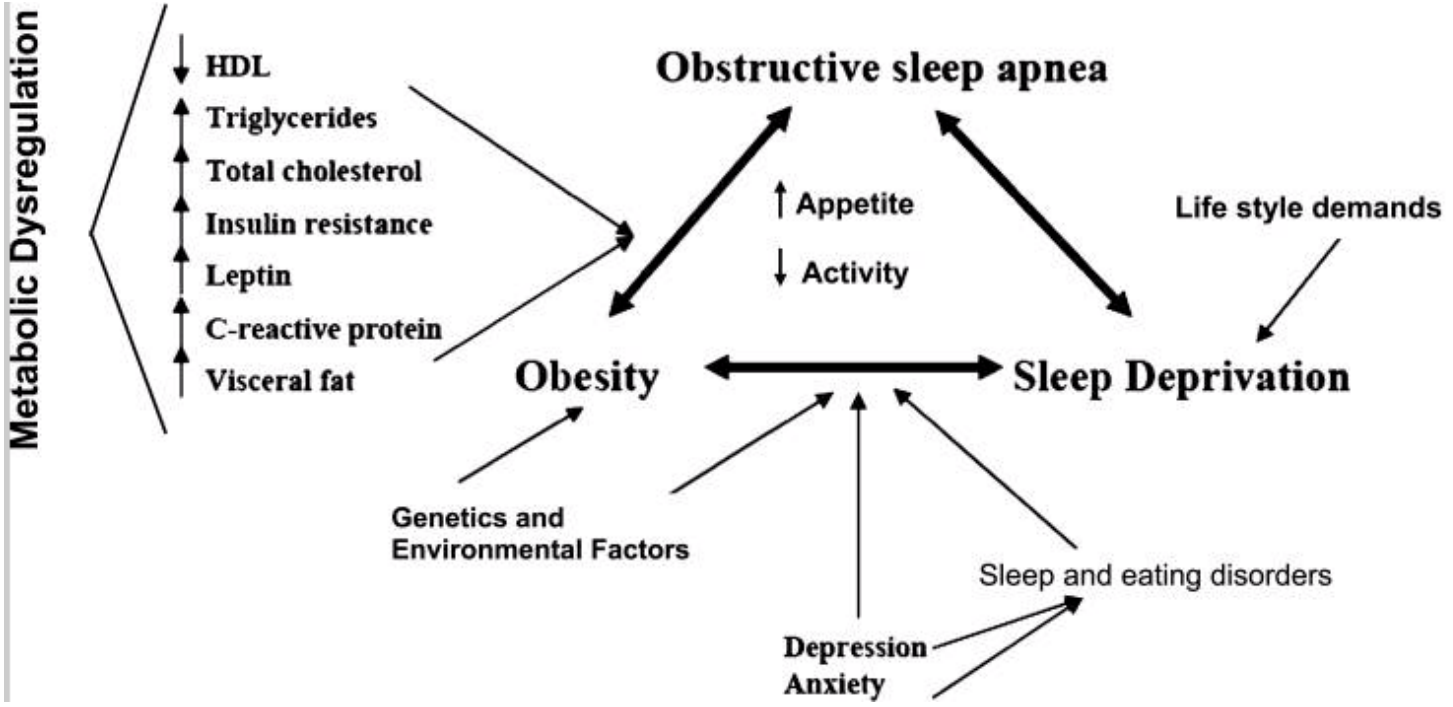
Why Does Triple Overlap Matter?



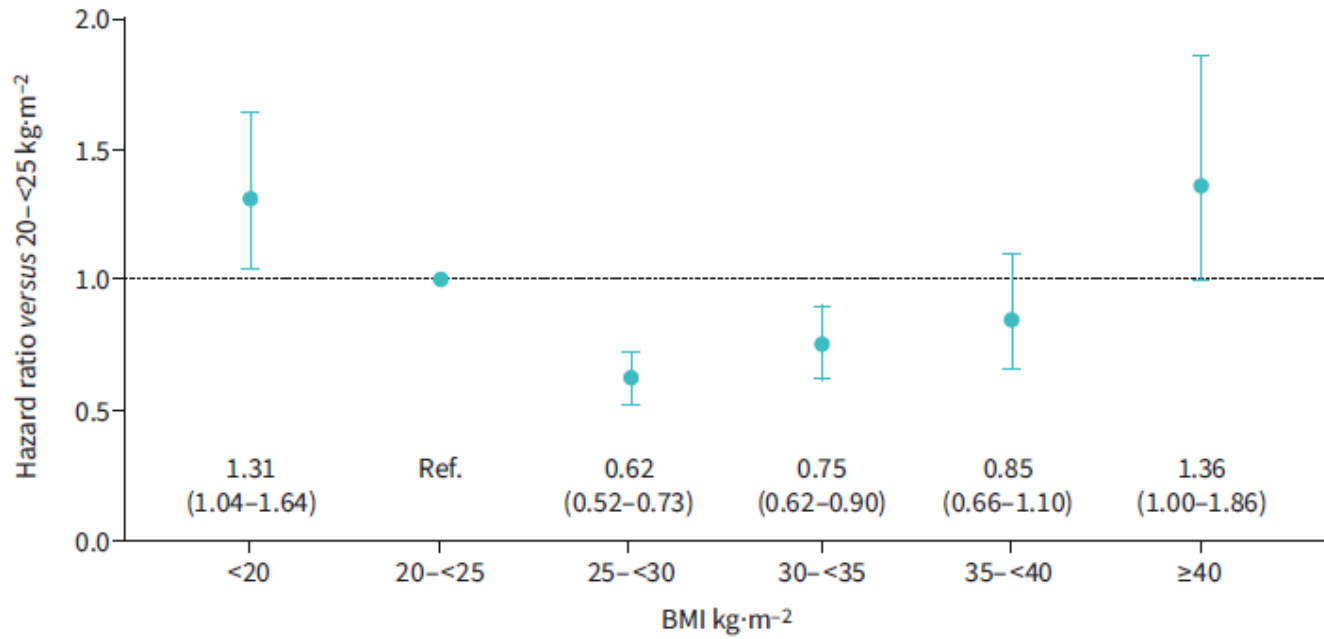
Growing Epidemic of Morbid Obesity and COPD

-
- **Pre-pandemic (2017-2020) estimated percentage of adults with BMI > 40 kg/m₂ is close to 10%**
 - **Age adjusted prevalence of COPD between 2011 – 2020 remained unchanged among US adults**
 - **Patients in your clinic who have recurrent hospital admissions**
 - **Volume overload, Respiratory failure, Cellulitis, Etc.**

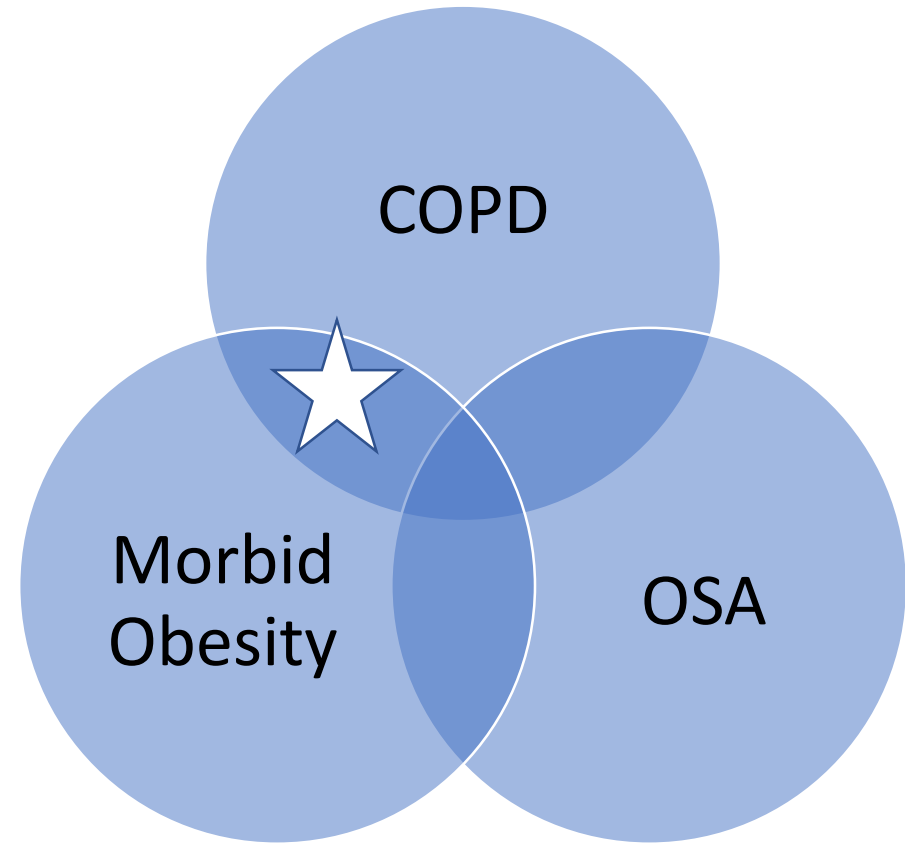
Obstructive sleep apnea and obesity have a complex, reciprocal relationship



All-cause mortality by body mass index (BMI) category in patients with moderate COPD and increased cardiovascular risk



Patients	1111	4306	5662	3452	1367	587
Deaths	105 (9.5%)	332 (7.7%)	274 (4.8%)	201 (5.8%)	76 (5.6%)	49 (8.3%)



Within a large, multinational cohort with moderate COPD and increased cardiovascular risk, the phenomenon of reduced mortality with obesity did not persist at BMI >40 kg·m⁻²

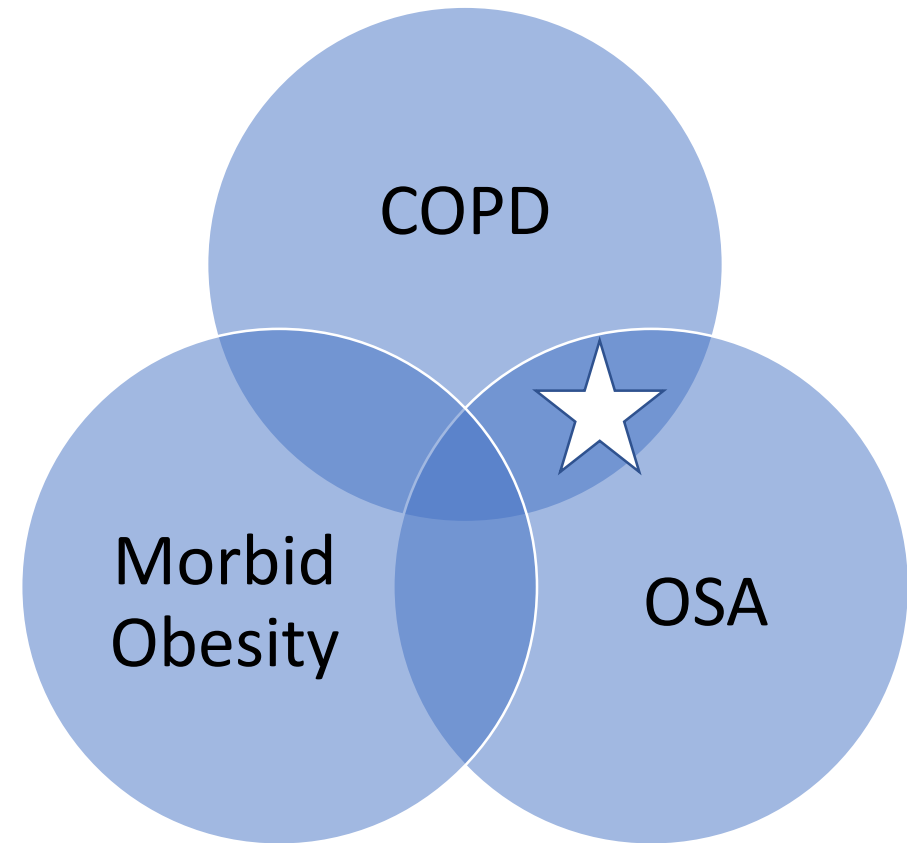
Outcomes in patients with OSA and COPD are worse than patients with either individual diagnosis

When compared to patients with OSA, patients with COPD and OSA have been shown to have:

- Greater nocturnal oxygen desaturation (NOD)
- Increased sleep time spent with SpO₂ < 90%
- Worse sleep quality than patients with only OSA

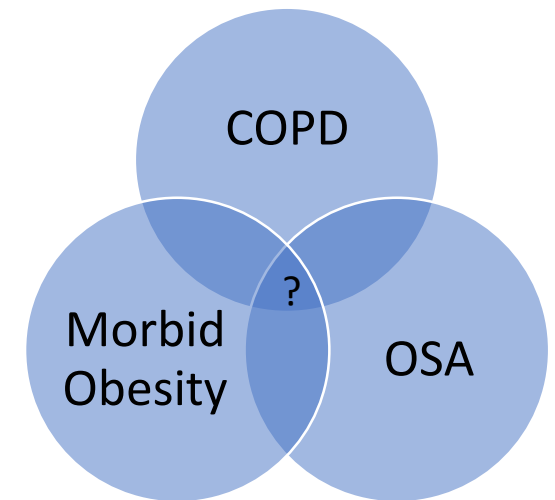
When compared to COPD alone, COPD OSA overlap is associated with:

- More frequent cardiovascular morbidity
- Poorer quality of life scores
- More frequent COPD exacerbation and increased medical costs



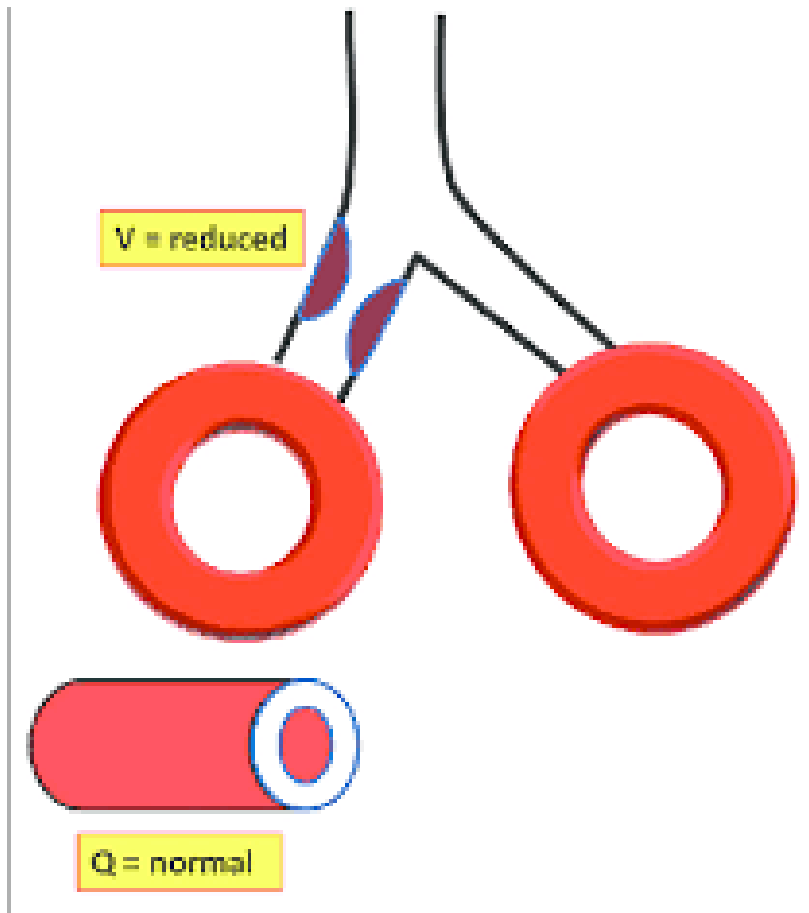
Importance of the Triple Overlap Syndrome

- **This is a small, but growing cohort of patients**
- **When compared to patients with single, or dual comorbid diagnoses, we hypothesize that patients with triple overlap are at**
 - **Increased risk for COPD and heart failure exacerbations**
 - **Increased risk for respiratory failure**
 - **Have higher all cause and cardiovascular mortality**



Hypoventilation Primer

Review basic principles of hypoventilation



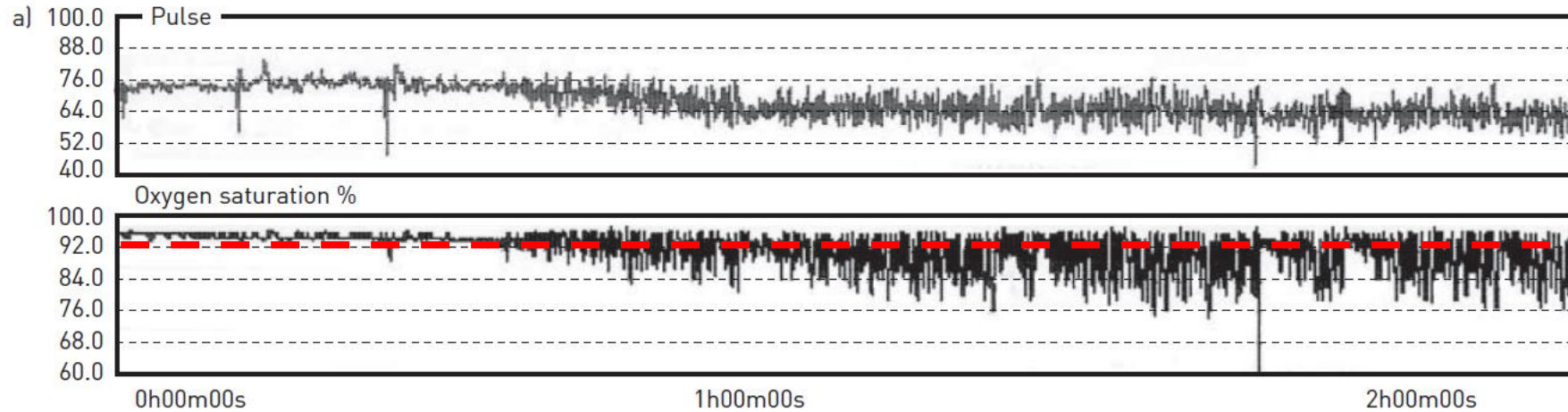
Hypoventilation

- **Hypoventilation syndrome comprises disorders associated with alveolar hypoventilation**
 - Elevation in PaCO_2 to levels >45 mmHg
 - Hypoxemia, particularly during sleep
- **Primarily due to low V/Q**
 - Hypoxemia is more common and a first sign of hypoventilation
 - Hypercapnia is a later finding



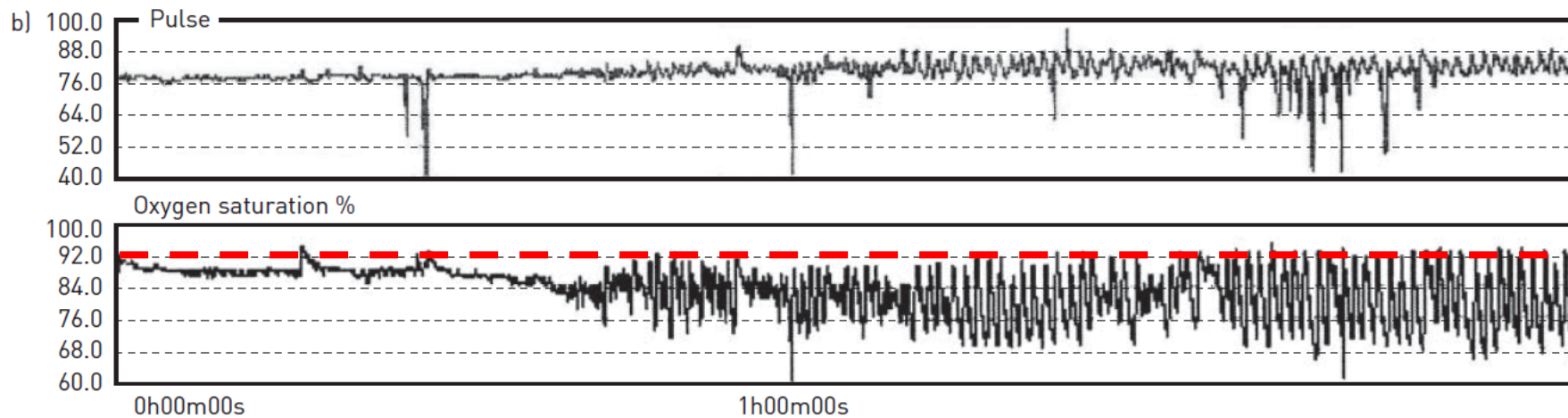
Sleep Oximetry in OSA and Overlap Syndrome

OSA alone



Overlap syndrome demonstrating the persisting pattern of desaturation in the overlap patient whereas the OSA patient returns to normal SaO₂ between apnea events.

Overlap Syndrome



Blood Gas Interpretation

Acute Respiratory Acidosis

pH 7.25*

pCO₂ 74

paO₂ 80

HCO₃: 23

Chronic Respiratory Acidosis

pH 7.40

pCO₂ 74

paO₂ 80

HCO₃: 35*

Serum Bicarbonate: The Poor Man's Blood Gas

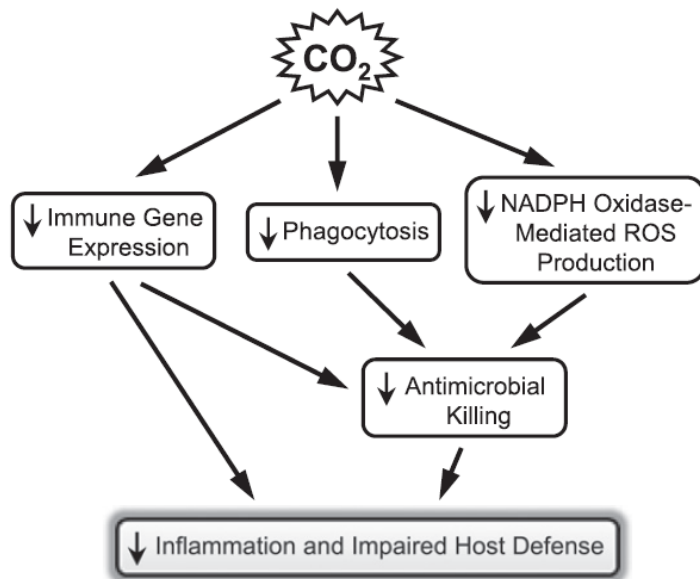
9/7/2023 5:48 AM EDT	136	n 4.6	92	38	11	17
9/6/2023 4:02 PM EDT	139	4.3	91	43	9	20
9/6/2023 3:34 AM EDT	137	3.9	89	42	10	17
9/5/2023 3:17 AM EDT	141	4.5	92	40	14	15
9/4/2023 3:55 AM EDT	141	4.3	93	45	7	18
9/2/2023 2:15 AM EDT	138	4.1	94	40	8	18
9/1/2023 4:47 PM EDT	136	4.0	92	38	10	16
2/22/2023 4:21 AM EST	135	4.4	95	35	9	21
2/21/2023 5:29 AM EST	134	4.1	94	35	9	20
2/20/2023 4:41 AM EST	138	4.6	96	37	10	22
2/19/2023 3:46 AM EST	137	4.7	95	37	10	19
2/18/2023 4:15 AM EST	141	4.4	94	43	8	19
2/17/2023 3:11 AM EST	138	4.5	93	39	11	22

<input type="checkbox"/> pHv	7.34	7.33
<input type="checkbox"/> PvCO2	n 91	n 85
<input type="checkbox"/> PvO2	53	60
<input type="checkbox"/> HCO3v	47	43
Base Deficit, Venous		
<input type="checkbox"/> Base Excess, Venous	18	15

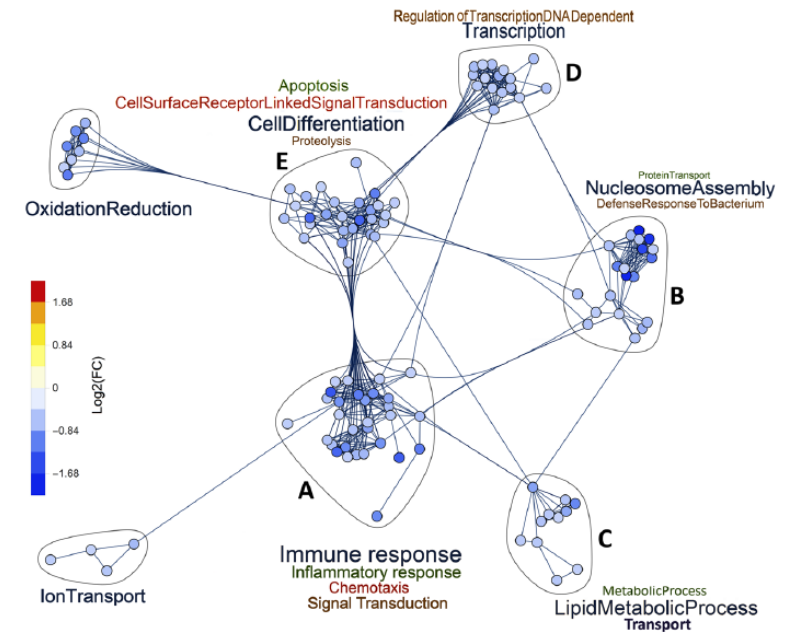
Hypercapnia: “A Nonpermissive Environment for the Lung”



Schematic representation of mechanisms leading to impaired host defense during hypercapnia



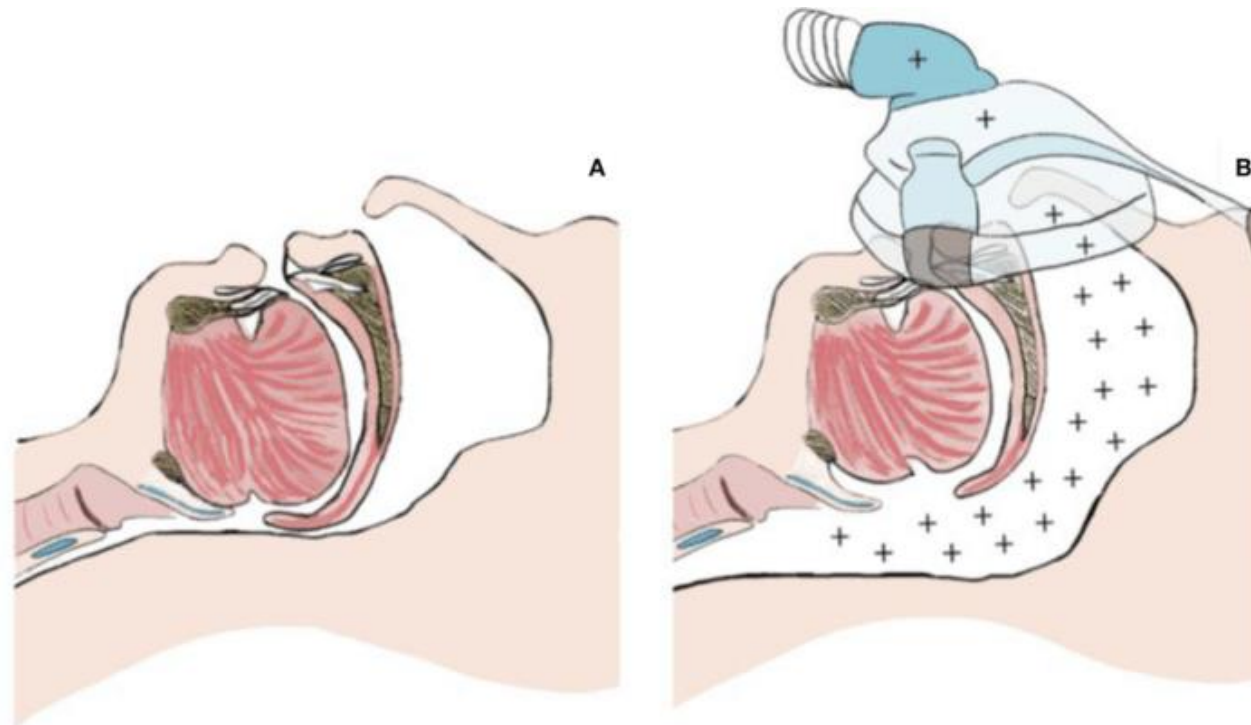
Networks of Gene Ontology biological processes downregulated by hypercapnia



The suppressive effect of elevated CO₂ on immune gene expression in the airway epithelium, along with similar effects on immune cells, suggest a reason why severe COPD and other lung disease associated with hypercapnia all carry a high risk of pulmonary infection.

Continuous Positive Airway Pressure (CPAP)

- CPAP: Delivers one constant pressure throughout inhalation and exhalation
- Goal is to "stent" the upper airway open



Bi-level Positive Airway Pressure (BPAP)

- Delivers higher pressure during inspiration and lower pressure during exhalation
 - Inspiratory positive airway pressure (IPAP)
 - Expiratory positive airway pressure (EPAP)
 - **Pressure support = IPAP – EPAP**
- Can be as a comfort modality to “pneumatically splint” the airway open (usually pressure support ~ 3 cm H₂O)

or
- As a “ventilatory modality” to generate a tidal volume (usually pressure support \geq 10 cm H₂O) sufficient to eliminate retained carbon dioxide

Impact of OSA, OHV, and COPD on Sleep Disordered Breathing

Review diagnosis and treatment of individual diagnoses

Let's Talk About Diagnosis and Treatment of Hypoventilation in....



OSA

OHV

COPD

Obstructive Sleep Apnea

- **Periods of apnea (i.e. complete cessation of airflow) or hypopneas (i.e. partial limitation of airflow) during sleep secondary to instability of the upper airway**
- **Associated with oxyhemoglobin desaturations associated with events**
- **Can result elevation in tCO₂ or pCO₂ during sleep**
- **However no evidence of daytime hypercapnia or hypoxemia**
- **Diagnosed with a sleep study**

Treating OSA with PAP

- **Continuous Positive Airway Pressure (CPAP)**
 - **Auto titrating CPAP**
 - **For example: min CPAP 5cmH2O, max CPAP 18cmH2O**
 - **Fixed CPAP obtained through therapeutic PSG**
- **Bilevel Positive Airway Pressure**
 - **Second line – intolerance to CPAP or CPAP failure**
 - **Goal is not to ventilate, it is still to stabilize the upper airway**
 - **Pressure support no more than 4**

Let's Talk About Diagnosis and Treatment of Hypoventilation in....



OSA



OHV



COPD

Obesity Hypoventilation Syndrome

- **BMI \geq 30 kg M²**
- **Sleep disordered breathing**
 - **OSA**
 - **Hypoventilation**
- **Daytime hypercapnia (PaCO₂ \geq 45 mmHg)**
- **In the absence of an alternative neuromuscular, mechanical or metabolic explanation for hypoventilation**

Making the OHV Diagnosis

1

Suspect
hypoventilation

Look at the serum bicarb,
old blood gases

2

Order
a sleep study

HSAT or In-Lab PSG
Determine degree of OSA
and hypoventilation

3

Confirm
daytime hypercapnia

Arterial blood gas

The Phenotype Informs Treatment in OHV

OSA Predominant

- Moderate to severe OSA
 - Stable outpatient



- Start treatment with CPAP
 - Follow up resolution of hypercapnia
 - Ensure adequate therapy of obstructive events



Hypoventilation Predominant

- Mild OSA
 - Respiratory failure
- Failure to improve with CPAP



- Start treatment with Bilevel Ventilation
 - Focus on generating tidal volumes with sufficient pressure support
 - Preventing atelectasis with prolonged iTime
 - Managing underlying obstructive apneas with individualized EPAP titrations

Let's Talk About Diagnosis and Treatment of Hypoventilation in....



OSA



OHV



COPD

Hypercapnic COPD

ATS Clinical Practice Guideline: 2020

- Recommends the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD
- PaCO₂ > 45 mmHg at least 2 weeks after an exacerbation
- Target is normalization of PaCO₂

GOLD 2023: Non pharmacologic Treatment of Hypercapnia

- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long term noninvasive ventilation may be considered (**Evidence Level B**)



Ventilatory Strategy in Hypercapnic COPD

Bilevel ventilation

- **Pressure support > 20 cm H₂O**
- **EPAP ~ 5 cm H₂O**
- **Often challenging to achieve**

Bilevel settings in non-obese COPD patients

- **Short iTime, allowing for prolonged expiratory time**
- **Accelerate rise time to address air hunger**
- **Ensure that the patient is able to trigger the pressure support (i.e. IPAP)**

Summarized Treatment Basics

OSA

- Pneumatically “splint” the airway
- CPAP or Bilevel with PS < 4 cmH₂O

OHV

- CPAP for OSA phenotypes
- Bilevel with variable PS requirements to ventilate
- Longer Inspiratory Time
- Higher EPAP is sometimes required

Hypercapnic COPD

- Bilevel with PS >20 cmH₂O
- Short inspiratory time
- Fast rise time
- Sensitive trigger
- Lower EPAP

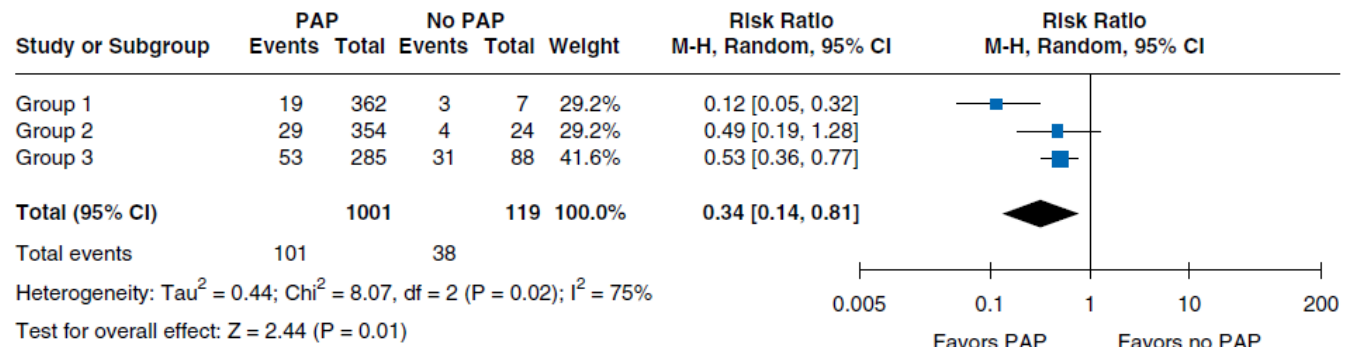
The Effect of Hospital Discharge with Empiric Noninvasive Ventilation on Mortality in Hospitalized Patients with Obesity Hypoventilation Syndrome. An Individual Patient Data Meta-Analysis

Systematic review with individual patient data meta-analyses demonstrated that in patients with OHV and acute on chronic hypercapnic respiratory failure who were discharged with PAP, there was reduced mortality at 3 months (relative risk 0.12, 95% confidence interval 0.05–0.30, risk difference 214.5%) when compared to patients discharged without PAP. This effect was maintained at 1 year.

Conclusions: Hospital discharge with PAP reduces mortality following acute-on-chronic hypercapnic respiratory failure in patients with OHS or suspected of having OHS.

Forest Plot of Mortality

1-year mortality



Making the Triple Overlap Diagnosis

1

Suspect
hypoventilation

Look at the serum
bicarb, old blood
gases

2

Review
Spirometry

Confirm obstruction
with FEV1/FVC ratio
of <0.7

3

Order
a sleep study

HSAT or In-Lab PSG
Determine degree of
OSA

4

Confirm
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Arterial blood gas

A Case

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A case continues...

<input type="checkbox"/> pHa	<input type="checkbox"/> PaCO2	<input type="checkbox"/> PaO2	<input type="checkbox"/> HCO3a
7.42	66	125	42

Indices

AHI:	30.9
RI:	32.1
Apnea Index:	8.0
UAI:	6.0
OAI:	2.0
CAI:	0.0
MAI:	0.0
Hypopnea Index:	22.8
%Flow Lim. Br. without Sn(FL):	15.0
%Flow Lim.Br. with sn(FL):	0.0



O2 Saturation <= 90%:	63.7% : 232 minutes
O2 Saturation <= 89%:	59.3% : 216 minutes
O2 Saturation <= 88%:	54.4% : 198 minutes
O2 Saturation <= 85%:	33.8% : 123 minutes
O2 Saturation <= 80%:	4.9% : 18 minutes

Confirmed Triple Overlap

- Daytime hypercapnia
- FEV1/FVC ratio demonstrating obstruction
- Sleep study demonstrating sleep disordered breathing
- BMI > 40

Therapy Goals

Lifestyle Interventions

- **Weight loss**
- **Low sodium, heart healthy diet**
- **Tobacco cessation**
- **Pulmonary rehabilitation**

Ventilation

- **Reduce hypoxic burden at night**
- **Reduce daytime hypercapnia**
- **Longitudinal, personalized titrations**
- **Adherence**

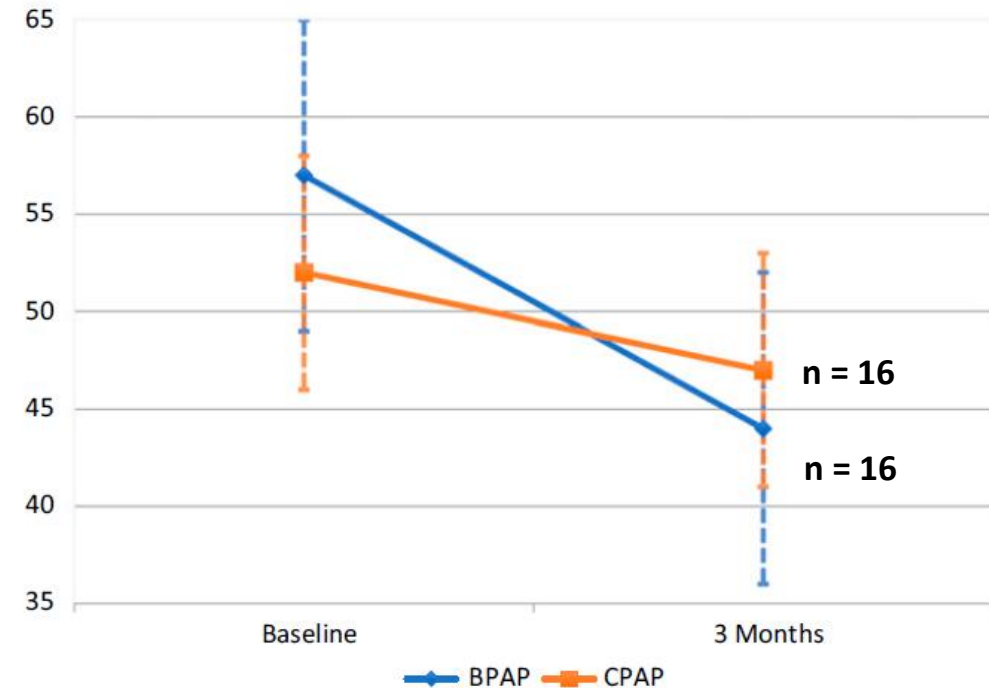
A pilot randomized trial comparing CPAP vs bilevel PAP spontaneous mode in the treatment of hypoventilation disorder in patients with obesity and obstructive airway disease

32 PAP-naïve patients with stable chronic hypercapnic respiratory failure ($\text{PaCO}_2 > 45\text{mmHg}$), obesity (body mass index $> 30\text{ kg/m}^2$), and obstructive airways disease. Participants were randomized to continuous positive airway pressure or bilevel positive airway pressure spontaneous mode treatment for 3 months. Participants were blinded to their PAP allocation.

Bilevel positive airway pressure yielded a greater improvement in PaCO_2 compared to continuous positive airway pressure (9.4 mm Hg, 95% confidence interval, 4.3–15 mm Hg).

Conclusions: Both PAP modalities improved hypercapnic respiratory failure in this group of individuals, bilevel positive airway pressure spontaneous mode showed greater efficacy in reducing PaCO_2 .

Change in mean PaCO_2 (mm Hg) after 3 months of PAP Rx compared to baseline



A case continues...

<input type="checkbox"/> pHa	<input type="checkbox"/> PaCO2	<input type="checkbox"/> PaO2	<input type="checkbox"/> HCO3a
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Indices

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In order to obtain bilevel, we demonstrated intolerance and desaturations on CPAP, and transitioned to a bilevel titration with final settings of Bilevel S IPAP 18cmH2O and EPAP 8cmH2O in order to manage hypoxemia and reverse hypercapnia.

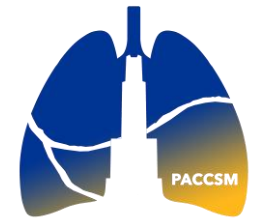
PAP Treatment Takeaways for Triple Overlap

- **Limited data, but can extrapolate from COPD/OSA overlap and OHV patients**
- **If the patient has a predominant obstructive sleep apnea phenotype, it is not unreasonable to first trial CPAP**
- **When might it be time to refer to a pulmonary sleep specialist?**
 - **If there is uncertainty about hypoventilation or if it is unclear which sleep study would be best**
 - **If nocturnal hypoxemia and daytime hypercapnia are not resolving on CPAP**
 - **If the patient is having difficulty tolerating CPAP**
 - **You think a patient needs bilevel, but are having difficulty obtaining a machine due to insurance regulations**
 - **Admissions for acute hypercapnic respiratory failure**

Summary

- **Although data is limited, we know that triple overlap patients exist and this is a growing population**
- **A serum bicarbonate level is often readily available and can help you to identify these patients**
- **Confirm obstruction with spirometry, obtain an ABG, and diagnose sleep disordered breathing with a sleep study**
- **Diagnosing sleep disordered breathing in these patients can most of the time be achieved with an HSAT**
- **Treating patients with triple overlap consists of lifestyle modifications and ventilation**
- **Ventilation may not be a one size fits all CPAP or bilevel setting**
- **Pulmonary sleep specialists can help to manage these complex patients**

PACCSM BREAThE Clinic



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Website coming soon!

www.BREAThE.Pitt.edu

