2023 수면호흡장애연구회 심포지움

Sleep disordered Breathing (SDB) and Airway diseases

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Can you tell me professionally about the relationship between sleep-disordered breathing and airway diseases such as COPD and asthma?

1. ****COPD and Sleep-Disordered Breathing:****

COPD is a chronic inflammatory lung disease that causes obstructed airflow from the lungs. Patients with COPD often suffer from a variety of sleep-related problems due to the disease itself and the hypoxemia that can occur during sleep.

Also, ***COPD is an independent risk factor for OSA, and the coexistence of the two conditions, termed the overlap syndrome, is associated with worse symptoms and outcomes than either condition alone***. ***The overlap syndrome often leads to severe nocturnal hypoxemia, frequent exacerbations, poor quality of life, and increased mortality.***

Hence, it's critical to screen COPD patients for OSA, particularly those with significant daytime sleepiness.

2. ****Asthma and Sleep-Disordered Breathing:****

Asthma is a condition in which your airways narrow and swell and produce extra mucus. There is also a strong association between asthma and SDB. Poorly controlled asthma can lead to disrupted sleep due to nocturnal asthma symptoms. On the other hand, sleep apnea can exacerbate asthma by promoting airway inflammation, increasing bronchial hyperresponsiveness, and impairing lung function.

Recent studies suggest that the prevalence of OSA is significantly higher in patients with asthma, and that OSA may contribute to poor asthma control. ***The relationship between asthma and OSA appears to be bidirectional, with each condition potentially exacerbating the other.***

In summary, sleep-disordered breathing, COPD, and asthma are closely interrelated, and their interaction can lead to significant morbidity.

The interplay between these conditions involves complex mechanisms, including systemic inflammation, increased airway resistance, and alterations in lung volumes.

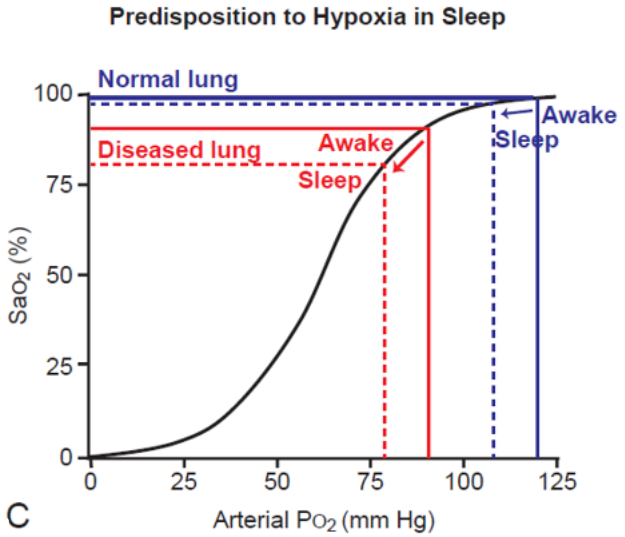
Therefore, a comprehensive and integrative approach is needed in diagnosing and managing patients with these conditions.

Sleep & COPD

- Sleep disturbance is common in COPD (without primary sleep disorders)
  - 40% : problems with their sleep (Survey in North America & Europe)
  - 27.3% : insomnia (Budhiraja et al.)
  - 78.1% : some degree of nighttime symptoms (European survey)
    - Dyspnea, cough, sputum, wheezing, difficulty with the maintenance of sleep
- Prevalence of nighttime symptoms
  - Positively correlated with the severity of airflow obstruction
- PSG
  - Problems initiating or maintaining sleep, ↓REM sleep, ↑microarousals

Sleep-related breathing disorders in COPD

- **Sleep-related hypoxemia**
  - Prevalence : ↑ with the severity of COPD
  - Often associated with daytime hypoxemia (but not always)
- **Coexisting obstructive sleep apnea**
- **Hypoventilation during sleep**
- **Respiratory effort related arousals** (RERA)



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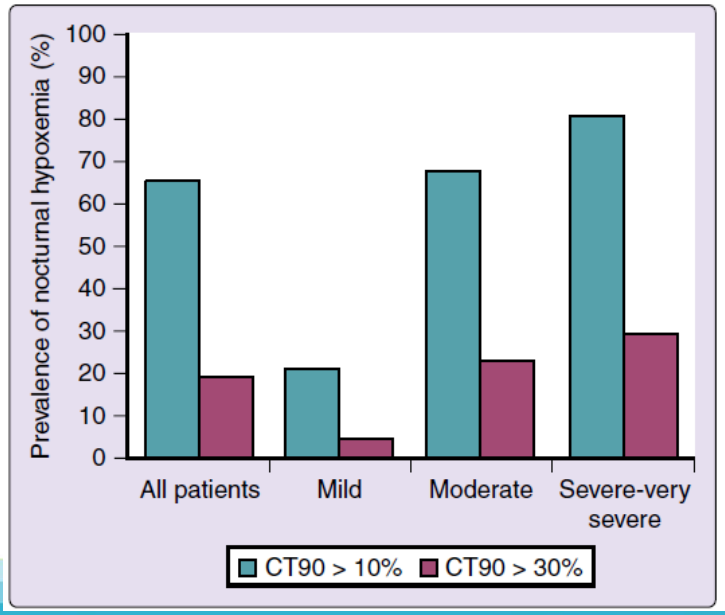
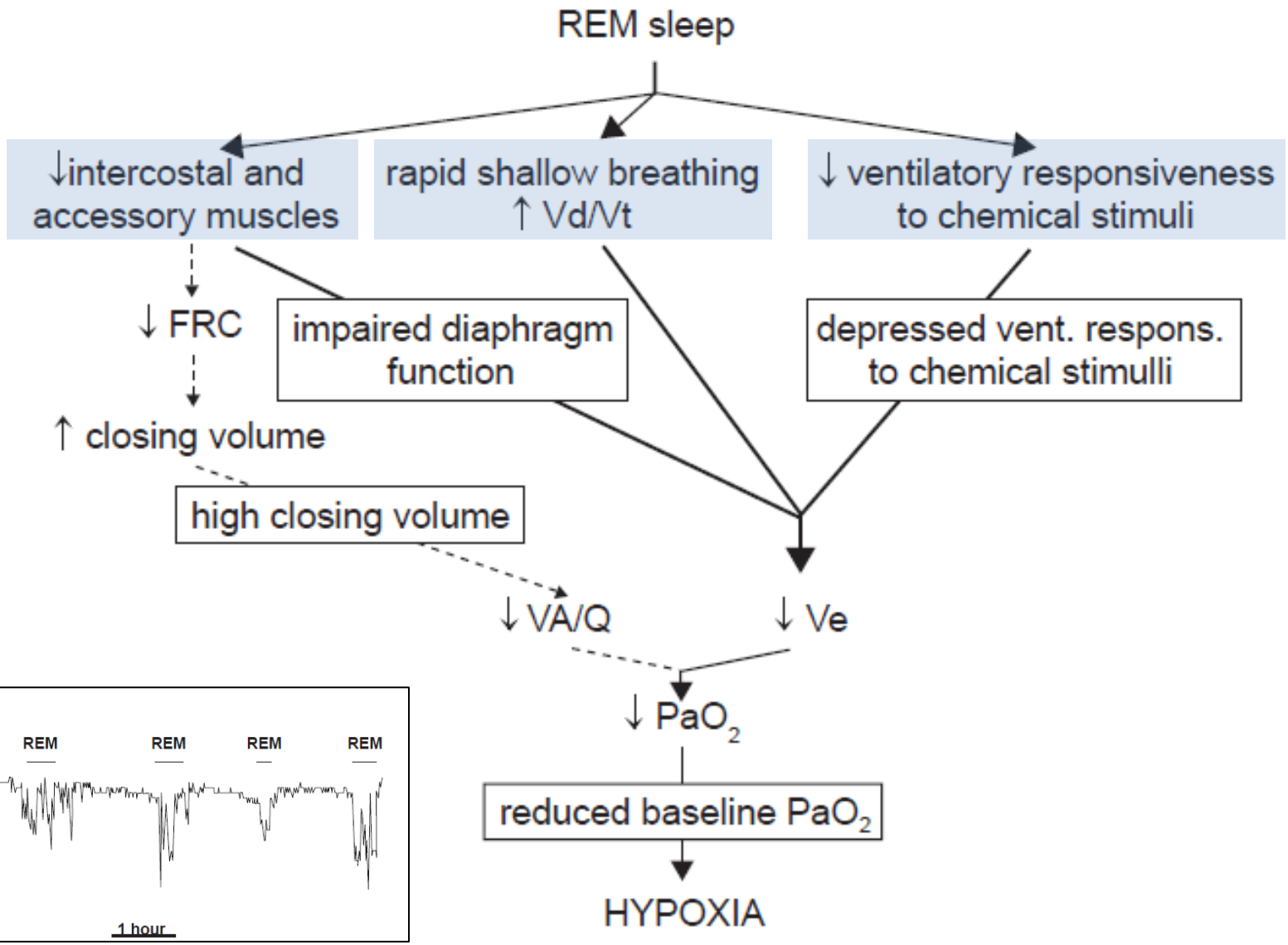
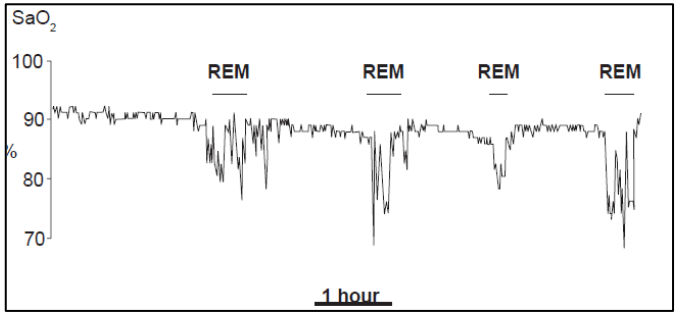






International Journal of COPD 2006:1(4) 363–372

Sleep-related HVS & COPD

- Result of an accentuated physiologic hypoventilation

- To define HVS, sleep $PaCO_2$ or $etCO_2$ must be measured
  - $PaCO_2$ or $etCO_2$ during sleep > 50 mmHg for more than 10 mins

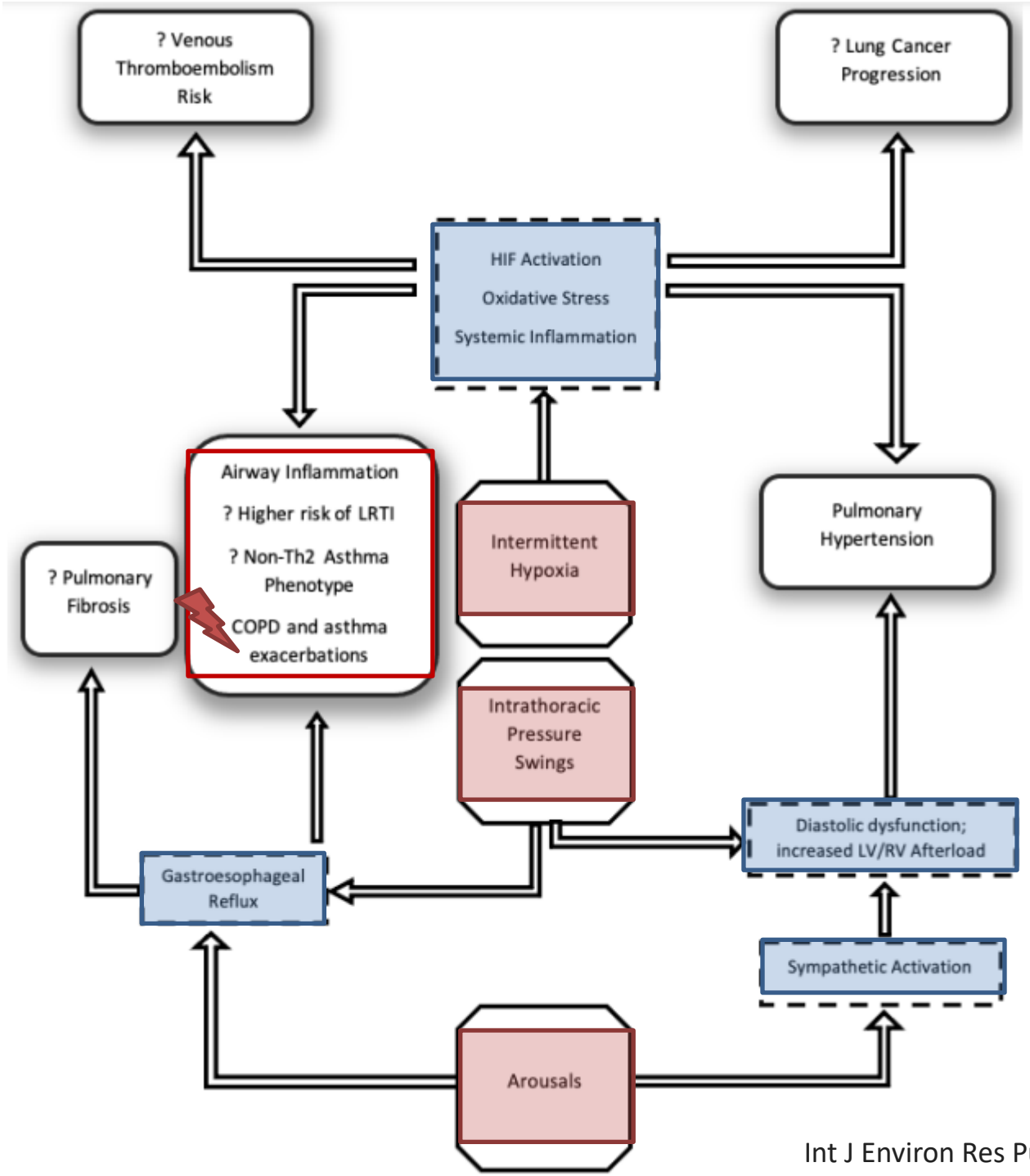
- Most hypercapnic patients with COPD also develop HVS during sleep
  - However, in normocapnic patients, HVS may occur in REM sleep

HVS : Hyperventilation syndrome

RERA & COPD

- Prevalence of RERAs in COPD : unclear
- COPD → can contribute to RERAs
- Need more studies
  - Evaluate the clinical significance of COPD-RERAs overlap

COPD & OSA Overlap Syndrome



Int J Environ Res Public Health. 2022 Apr 30;19(9):5473.

COPD & OSA Overlap Syndrome
Prevalence

- Wide variation in results
  - Differences : definitions, study populations
  - Ranging from 10-65% depending on the study design & geographical location

- Shawon et al. (2017)
  - Systematic review
  - Overall prevalence was low in the general population (1-3.6%)

- Highly prevalent when individual populations of either COPD (2.9-65.9%) or OSA (7.6-55.7%)

- Korea (Choi KM et al., 2017)
  - 10.8% of OSA patients had an overlap syndrome with COPD

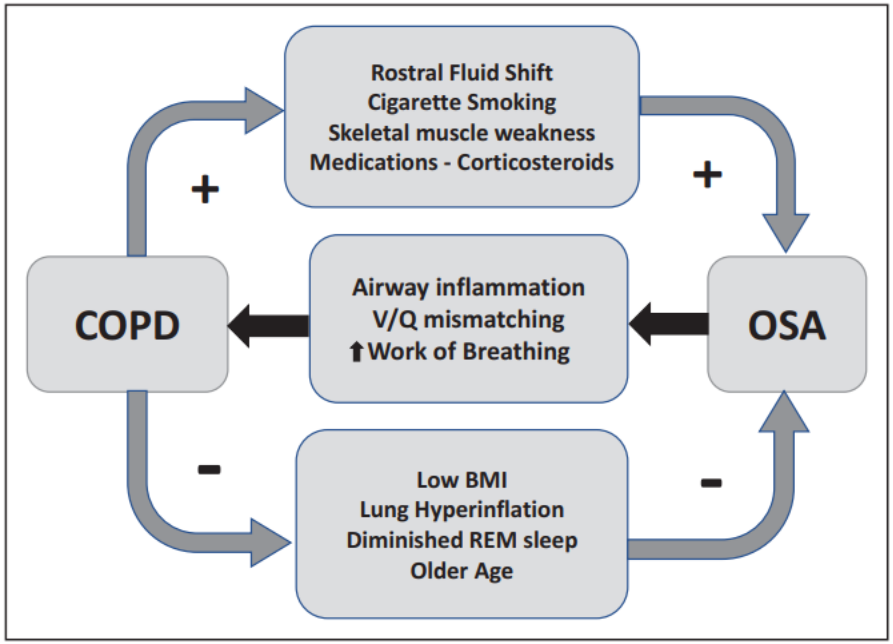
COPD & OSA Overlap Syndrome

Risk Factors

- Typical patient with COPD, **overweight-obese and sleepy ("blue bloater") has a high probability** of suffering from overlap syndrome

- **Emphysematous phenotype ("pink puffer") : much lower risk** of suffering from OSA
  - Lung hyperinflation : ↓ critical closing pressure

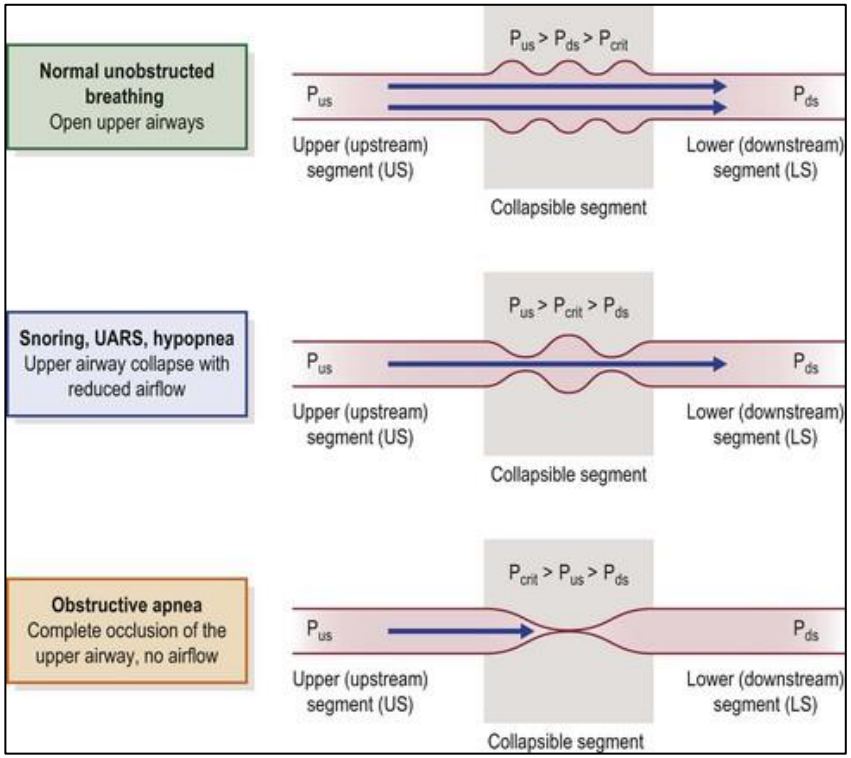
- COPDGene project
  - Inverse relationship between AHI & emphysema
  - Chronic bronchitis phenotype : higher prevalence of OSA even in the absence of differences in BMI & lung function



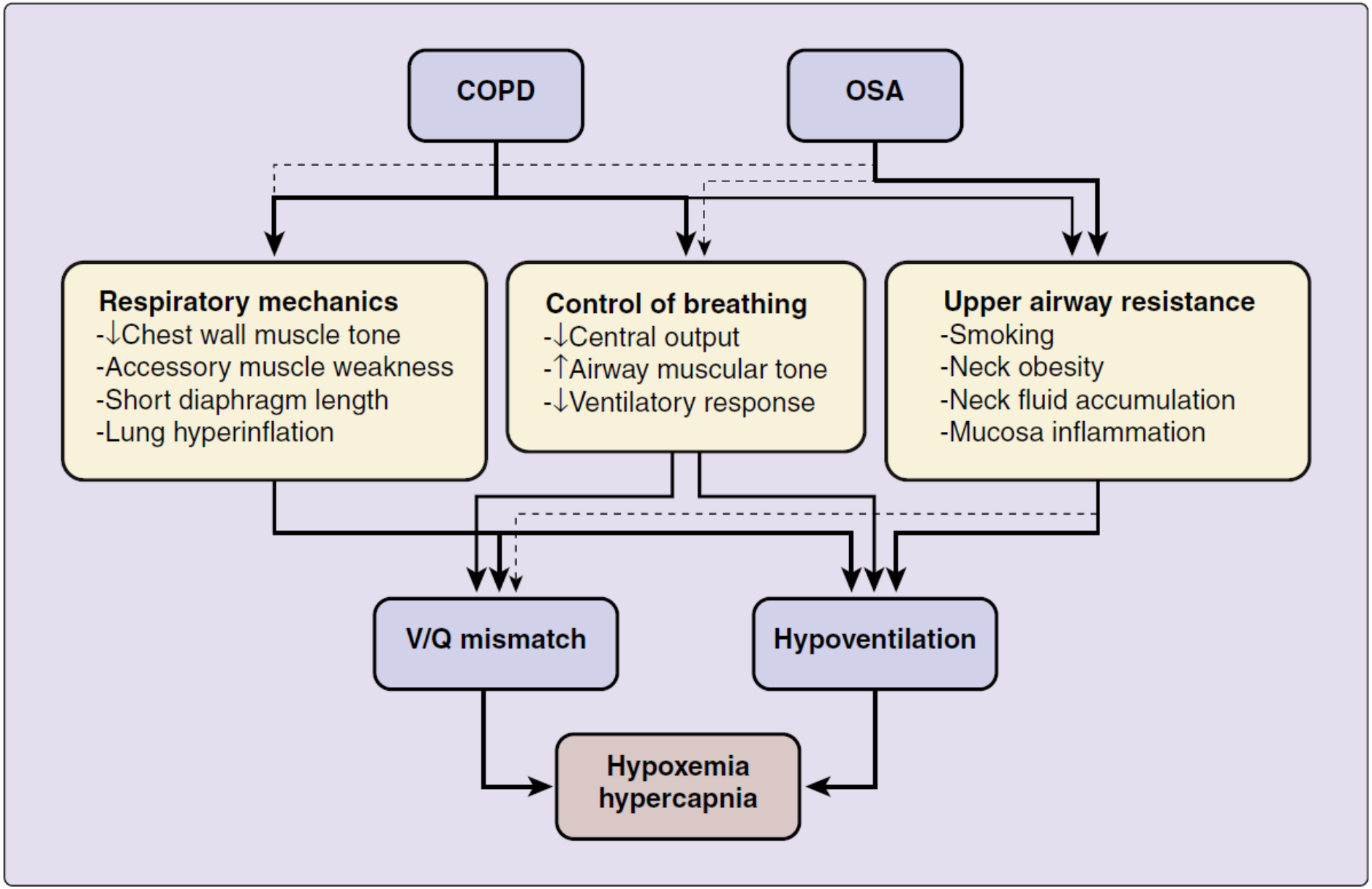
Curr Opin Pulm Med. 2022 Nov 1;28(6):543-551.

Lung volume & Pcrit

- **Critical closing pressure (Pcrit)**
  - Gold standard measure of pharyngeal collapsibility
- Change in Pcrit with lung volume
  - Tracheal traction → caudal force on the trachea causes improvements in pharyngeal mechanics
  - May unfold the airway, stiffen airway walls, remove redundant tissue, or combine with other forces to create a net ventral force vector that opens the upper airway
- ↑500ml lung volume : substantially improves Pcrit (↓3–4 cmH_2O)



Sleep Apnea: Current Diagnosis and Treatment
(Progress in Respiratory Research, Vol. 35) 1st Edition



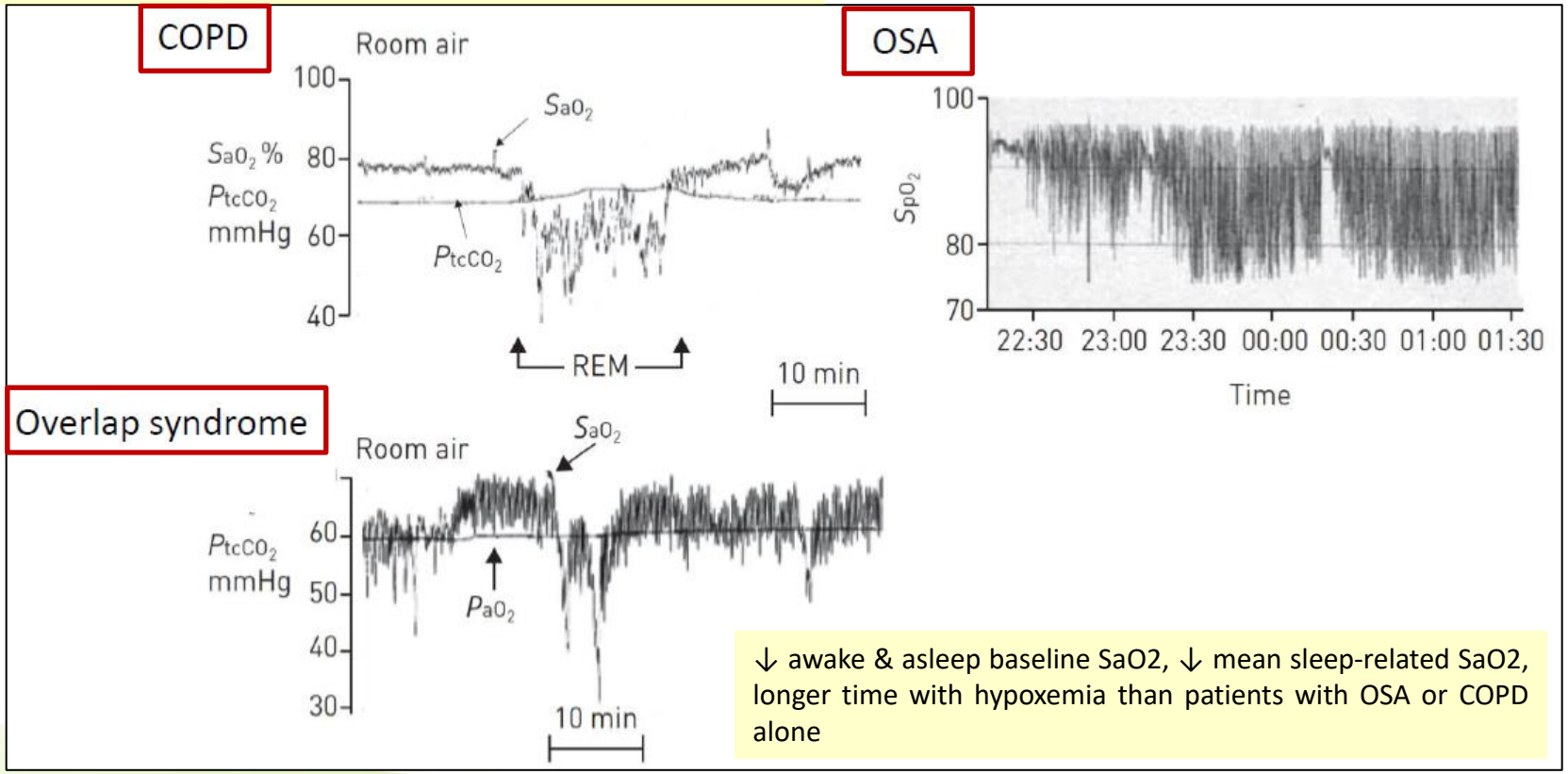
Principles and Practice of Sleep Medicine, 7th Edition

COPD & OSA Overlap Syndrome

Different patterns of oxygen desaturation during sleep

- Nocturnal O2 saturation characteristically decreases more evenly throughout sleep
- Termination of an apnea or hypopnea episode tends not to return to the initial baseline level

Return to a normal SaO2 in sleep between obstructive events

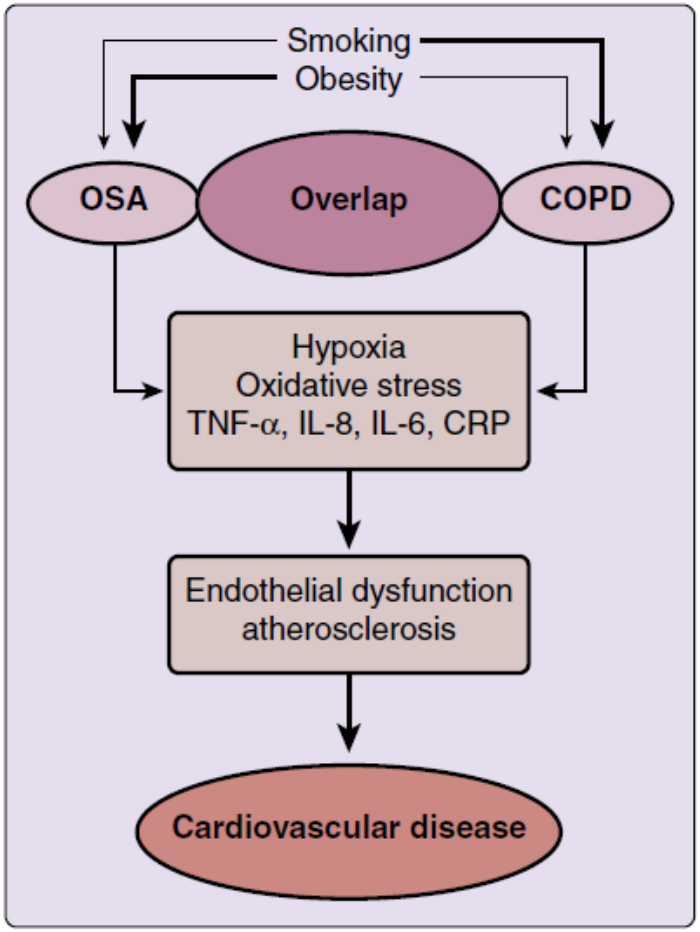


↓ awake & asleep baseline SaO2, ↓ mean sleep-related SaO2, longer time with hypoxemia than patients with OSA or COPD alone

COPD & OSA Overlap Syndrome

Clinical Features : CV diseases

- Prevalence of **hypertension**
  - COPD alone = general population, Overlap = OSA alone
- New-onset **atrial fibrillation**
  - Overlap > OSA or COPD alone (retrospective cohort)
- Incidence of **CAD, stroke, and HF**
  - ↑ OSA & COPD
  - No incidence data are available for COPD/OSA overlap
- ↑ Daytime **pulmonary vascular resistance**
  - Overlap > OSA alone (Chaouat et al.)
- ↑ **RV mass and remodeling** indices
  - Overlap > COPD alone (Sharma et al.)
- ↑ **Arterial stiffness**
  - Overlap > OSA alone



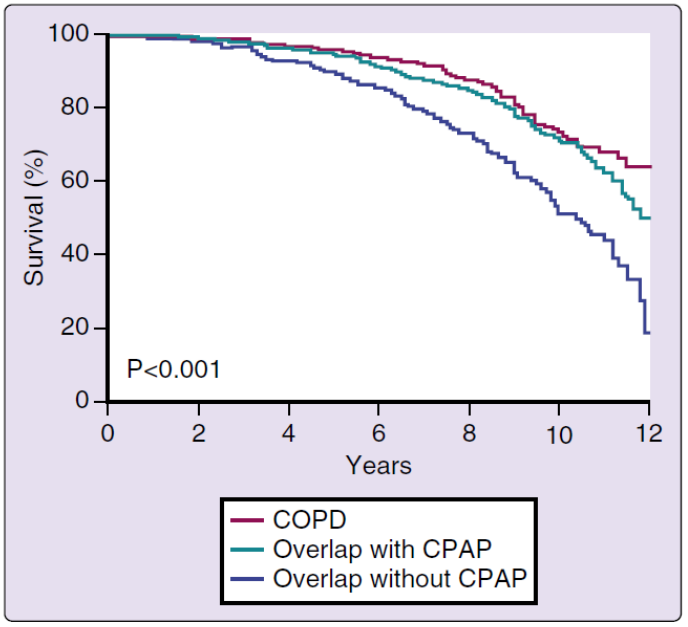
Principles and Practice of Sleep Medicine, 7th Edition

COPD & OSA Overlap Syndrome

Clinical Features : mortality

- ↑ Mortality : COPD/OSA overlap

- Marin JM et al. (*Am J Respir Crit Care Med*. 2010;182:325–331)
  - Large cohort, referred with suspected SDB
  - All-cause mortality
    - Overlap, untreated for OSA (42.2%) > COPD-only group (24.2%)
  - Comorbid untreated OSA
    - Remained a risk factor for death even after adjustment for FEV1 % in the patients with COPD



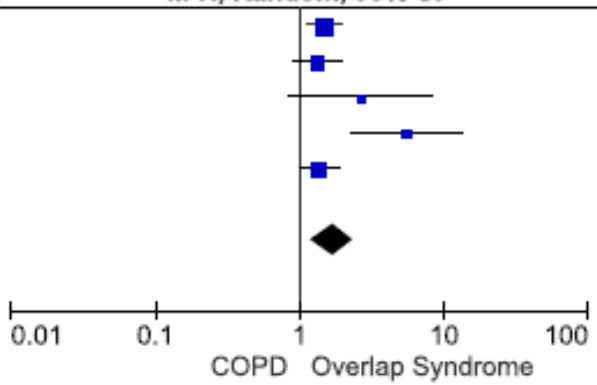
Cardiovascular outcomes in patients with COPD-OSA overlap syndrome: A systematic review and meta-analysis

Shah AJ et al.,
Sleep Med Rev. 2022 Mar 22;63:101627.

- 18 retrospective, observational studies
- Meta-analysis
  - Challenging d/t the significant heterogeneity amongst studies, many of which used differing AHI cut-offs
- Complex interplay between COPD, OSA and CVD?
  - Still not known whether overlap increases the occurrence of CVD and whether this increase is greater than with either condition alone

Study or Subgroup	Overlap Syndrome Events	Total	COPD Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Hu et al. 2020 [17]	270	660	98	308	29.6%	1.48 [1.11, 1.97]
Marin et al. 2010 [29]	85	213	70	210	24.6%	1.33 [0.89, 1.98]
Wang et al. 2019 [22]	15	25	9	25	7.0%	2.67 [0.85, 8.37]
Zhou et al. 2020 [33]	16	28	24	123	10.6%	5.50 [2.30, 13.14]
Zhu et al. 2020 [34]	219	520	86	246	28.3%	1.35 [0.99, 1.85]
Total (95% CI)		**1446**		**912**	**100.0%**	**1.68 [1.21, 2.35]**
Total events	605		287			

Heterogeneity: Tau² = 0.08; Chi² = 10.29, df = 4 (P = 0.04); I² = 61%
Test for overall effect: Z = 3.05 (P = 0.002)



- **Overlap syndrome**
  - Associated with a significantly higher risk of HTN compared to patients with COPD alone (OR = 1.68, 95% CI 1.21-2.35)
  - Associated with an increased risk of peripheral vascular disease compared to OSA alone (OR = 3.30 95%CI 2.66-4.10)
    - Subset of studies also suggesting an increased risk of ischemic heart disease, heart failure, and cerebrovascular disease
  - Increasing severity of OSA in the overlap population results in a greater prevalence of HTN (demonstrated in 2 studies)

Screening patients for OSA-COPD overlap

Symptoms or findings indicative for sleep disordered breathing in patients with COPD
Sleep-related symptoms such as snoring, gasping and choking, as well as nocturia or morning headache
Increased daytime sleepiness
Signs of obesity including BMI >30 $kg \cdot m^{-2}$ in men and >35 $kg \cdot m^{-2}$ in women, neck circumference >43 cm in men and >41 cm in women
Reduced daytime pulse oxygen saturation (<93%) at rest or during exercise
Daytime hypercapnia
Signs of pulmonary hypertension or right heart failure, such as peripheral oedema
Polycythaemia
Patients who use opioids and/or hypnotic medications
Comorbidities such as atrial fibrillation, end-stage renal disease, type 2 diabetes, heart failure, difficult to treat hypertension and stroke

Eur Respir Rev 2019; 28: 190064

Screening patients for OSA-COPD overlap

- Sleep Apnoea Clinical Scale (SACS)
- Berlin Questionnaire (BQ)
- Epworth Sleepiness Scale (ESS)

COPD & OSA Overlap Syndrome
Diagnosis and Management

- **PAP delivery** with a nasal or face mask : most effective Tx. for OSA

- **Overlap syndrome patients not treated with CPAP**
  - ↑ risk of death & ↑ risk of hospitalization for COPD AE (vs overlap patients who were treated with and adhered to CPAP)
  - Use of CPAP added to LTOT : improved survival among overlap patients with chronic respiratory failure
  - COPD/OSA overlap syndrome treated with CPAP : greater time on CPAP was associated with a reduced risk of death after controlling for common risk factors

COPD & OSA Overlap Syndrome
Diagnosis and Management

- **CPAP (preferred for OSA) vs bilevel PAP (possibly preferred for hypoventilation)**
  - **<u>PAP titration needed</u>**
  - Reduced mortality and less hospital readmissions
  - Dose-response with patients who had higher usage of CPAP having better outcomes
  - No specific evidence : CPAP vs bilevel PAP (long-term outcomes)

- **Supplemental oxygen**
  - Should be added if optimal-appearing PAP regimen alone fails to provide satisfactory oxygenation
  - Ideal setting in the sleep laboratory, TcCO2 tracking during titration is ideal
  - Risk of inducing hypercapnia in these patients, oxygen alone

Impact of PAP Therapy Adherence on Outcomes in Patients with OSA and COPD

Sterling KL et al.,
Am J Respir Crit Care Med. 2022 Jul 15.

- Retrospective observational study
  - US claims data linked to PAP user data

- Effects of PAP adherence on health outcomes, resource utilization & costs in overlap syndrome
  - Adherent : PAP usage ≥4 h/night on ≥70% of 30-day period within a 90-day timeframe Ⅹ 8 consecutive 90-day timeframes
  - Non-adherent : none of the eight consecutive 90-day timeframes

Resource use	Adherent (n=712)	Non-adherent (n=712)	p-value
Year before PAP			
Doctor visits	15.80	17.65	0.01
ER visits	1.75	1.89	0.59
Hospitalizations	0.51	0.50	0.67
PAP Year 1			
Doctor visits	16.71	17.37	0.33
ER visits	1.25	1.83	<0.001
Hospitalizations	0.24	0.46	<0.001
PAP Year 2			
Doctor visits	15.43	15.71	0.37
ER visits	1.16	1.70	<0.001
Hospitalizations	0.21	0.42	<0.001

- *PAP usage was associated with reduced all-cause hospitalizations and ER visits, severe acute exacerbations and health care costs*.

Nocturnal nasal high-flow oxygen therapy in elderly patients with concomitant COPD and OSA

Spicuzza L et. al.,
Sleep Breath. 2022 Sep 3.

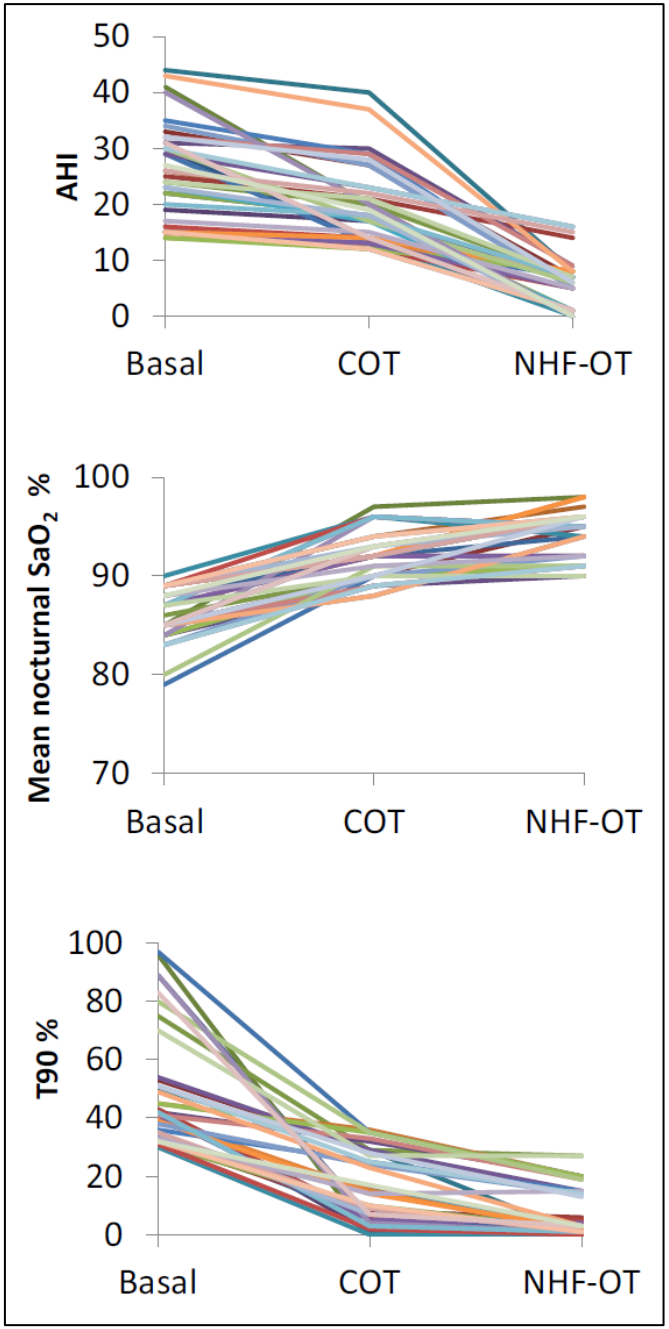
- **Overlap syndrome**
  - Usually older than pts with OSA alone
  - Suffer from more profound oxygen desaturation during the obstructive events often accompanied by sustained nocturnal hypoventilation

- **Tx. of choice**
  - Oxygen-enriched PAP: often poorly tolerated particularly by the elderly

- HFNC flow set : highest tolerated, starting from 30 up to 60 L/min

	Patients ($n=40$)
Males (%)	22 (55)
Age, yrs	75.6 ± 7.0
Body mass index, kg/m^2	29.3 ± 5.2
Current smokers (%)	14 (35)
PaO_2, mmHg	67.4 ± 6.2
$PaCO_2$, mmHg	43.7 ± 4.6
PH	7.40 ± 0.02
Awake SaO_2, %	93.3 ± 2.5
FEV_1, % predicted	58.4 ± 13.4
FVC, % predicted	75.8 ± 10.4
Severity of COPD	
GOLD 1, *n* (%)	0
GOLD 2, *n* (%)	27 (65.5)
GOLD 3, *n* (%)	10 (25)
GOLD 4, *n* (%)	3 (7.5)
Severity of OSA	
Mild, *n* (%)	4 (10)
Moderate, *n* (%)	25 (62.5)
Severe, *n* (%)	11 (27.5)
ESS	11.6 ± 4.6

	Baseline	COT	NHF-OT	*P* value
AHI (events/h)	25.4 ± 8.6	19.4 ± 7.0	5.4 ± 4.6	< 0.001
CAI (events/h)	0.3 ± 0.01	0.4 ± 0.01	0.4 ± 0.01	0.9
HI (events/h)	15.2 ± 4.1	9.4 ± 3.0	1.4 ± 0.6	< 0.05
Mean nocturnal SaO_2, %	86.2 ± 2.6	91.8 ± 2.4	93.9 ± 2.5	< 0.001
T90, %	48.7 ± 20.1	16.8 ± 11.7	8.8 ± 8.0	< 0.001
ΔSaO_2, %	4.9 ± 0.8	3.7 ± 1.14	2.4 ± 1.0	< 0.001
Minimal nocturnal SaO_2, %	75.8 ± 7.9	81.5 ± 7.4	84.1 ± 7.7	< 0.05
PaO_2, mmHg	67.4 ± 6.2	67.8 ± 5.6	68.1 ± 4.8	0.9
$PaCO_2$, mmHg	43.7 ± 4.6	44.2 ± 4.5	42.1 ± 5.8	0.3
PH	7.40 ± 0.02	7.39 ± 0.02	7.41 ± 0.02	0.8

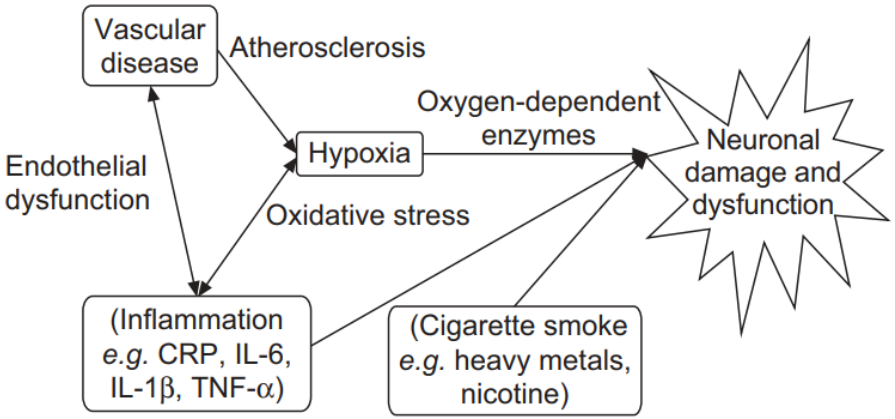


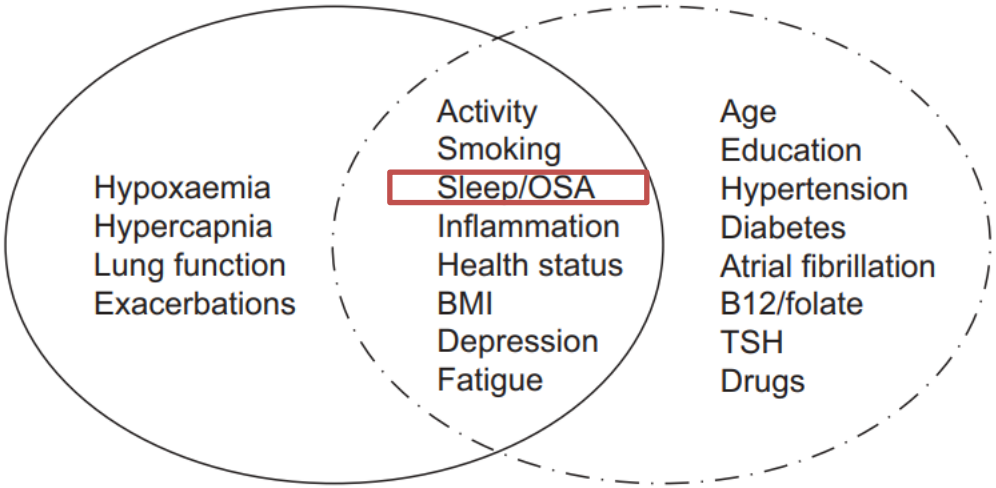
Spicuzza L et. al., Sleep Breath. 2022 Sep 3.

- ***Patients with both COPD and OSA have a worse prognosis compared with either condition alone.*** During sleep, patients with both COPD and OSA suffer more frequent episodes of oxygen desaturation and have more total sleep time with hypoxemia and hypercapnia than OSA patients without COPD.
- ***The apneic events in patients with combined OSA and COPD have more profound hypoxemia and more cardiac arrhythmias.*** Additionally, patients with combined COPD and OSA are more likely to develop daytime pulmonary hypertension than patients with just OSA or COPD alone.
- ***The use of positive pressure ventilation in patients with COPD and OSA has been reported to reduce all- cause hospitalizations, emergency room visits, moderate and severe exacerbations and associated healthcare costs.***

COPD & OSA Overlap Syndrome

Cognitive impairment?





- Severe obstructive sleep apnea in patients with chronic obstructive pulmonary disease is associated with an increased prevalence of mild cognitive impairment.
  - Sleep Med. 2020 Nov;75:522-530.
- Moderate-to-Severe Obstructive Sleep Apnea and Cognitive Function Impairment in Patients with COPD.
  - Int J Chron Obstruct Pulmon Dis. 2020 Jul 27;15:1813-1822.
- Cognitive performance is lower among individuals with overlap syndrome than in individuals with COPD or obstructive sleep apnea alone: association with carotid artery stiffness.
  - J Appl Physiol (1985). 2021 Jul 1;131(1):131-141.

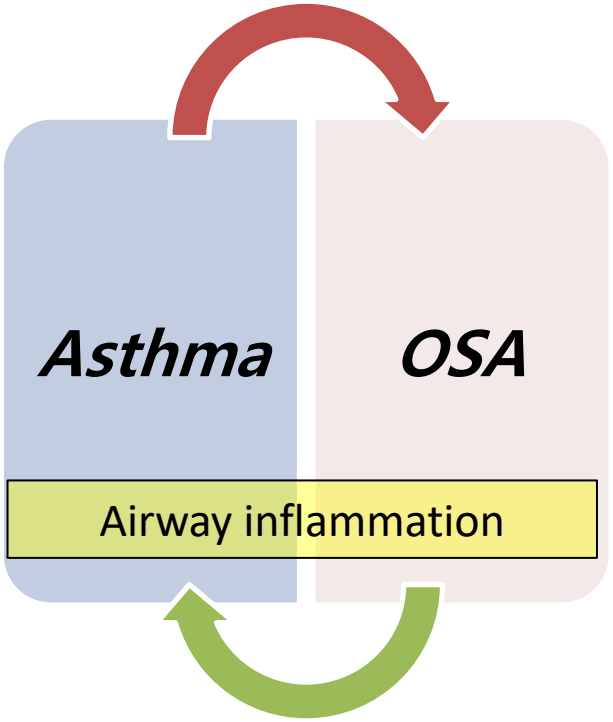
Eur Respir J 2010; 35: 913–922

Asthma

- **Nocturnal asthma**
  - Coughing, wheezing, or dyspnea → interrupts & disturbs sleep
    - Frequent arousals & poor sleep quality
  - Indicate poor asthma control & need to modify overall asthmatic Tx.
  - Impaired cognitive performance
    - Circadian peak expiratory flow variation ≥ 20%
      - Poorer daytime cognitive performance compared with healthy control
    - Effective asthma Tx. → recovery of cognitive impairment

As asthma worsens, patients are at greater risk of OSA

: PSG-diagnosed OSA is present in most patients with severe asthma



OSA increases asthma burden & associated with poor asthma control

: OSA aggravates asthma through non-eosinophilic inflammatory pathways independent of obesity & other confounders

: OSA may be a contributor to neutrophilic asthma & PSG should be considered in this asthma phenotype

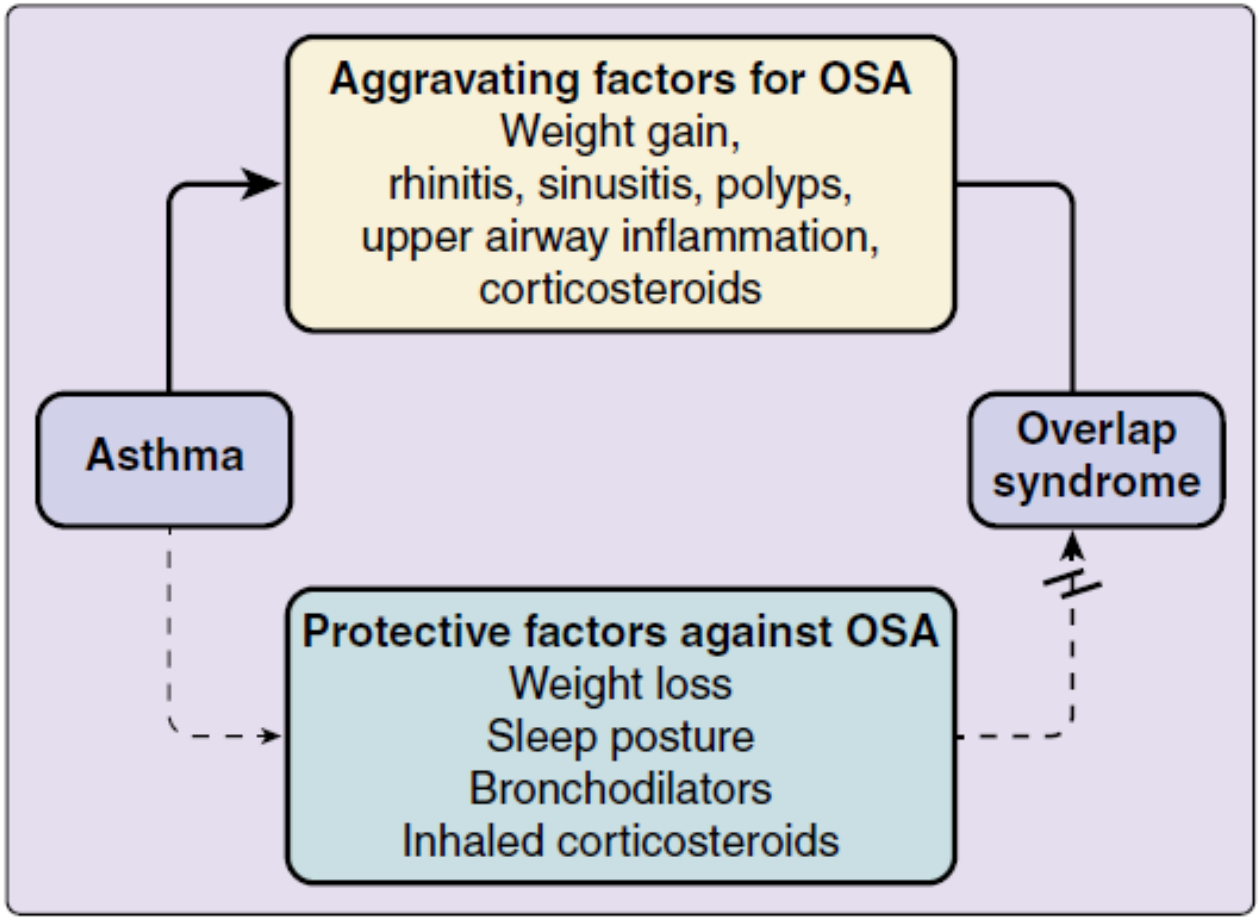
Asthma & OSA Overlap Syndrome
Epidemiology

- Occurrence of OSA in patients with asthma
  - Shows a prevalence of OSA 2~3 times higher than patients without asthma
    - Studies using sleep questionnaires & PSG

- **GINA recommended investigation for the coexistence of OSA in all patients with asthma**
  - Severe asthma
  - Difficult to control asthma
  - Asthma with associated obesity

Asthma & OSA Overlap Syndrome
Pathophysiology and Risk Factors

- **Obesity**
  - Risk factor for both asthma & OSA & asthma/OSA overlap syndrome
- **Nasal obstruction from rhinitis & chronic sinusitis**
  - ↓ airway caliber → ↑intrathoracic & pharyngeal negative pressure → upper airway collapse during inspiration, snoring, obstructive apnea
- **Patients with chronic asthma**
  - Persistent mucosal inflammation affects the upper airway by decreasing the cross-sectional area of the pharynx, promoting upper airway collapse
- **ICS**
  - Long-term effects on the collapsibility of the pharynx remain unknown
- **OCS on the upper airway : generally adverse**
  - Myopathy of the pharynx, fatty infiltration of the pharyngeal wall, accumulation of liquid in the neck



Principles and Practice of Sleep Medicine, 7th Edition

Potential mechanisms : OSA may worsen asthma

- Multifactorial

- OA episodes
  - Repetitive arousals from sleep, perturbations in autonomic activity & IH
  - ↑vagal tone
    - Can contribute to nocturnal asthma through stimulation of muscarinic receptors of the central & upper airways
  - Negative intrathoracic pressure
    - Intermittent loss of lower esophageal sphincter tone (associated GE reflux) is associated with bronchial microaspiration of gastric acid, potentially promoting nocturnal asthma
  - By stimulation of carotid body receptors, IH can enhance bronchial responsiveness through vagal pathways

- CIH in OSA → may also induce a low-grade systemic inflammation

Asthma & OSA Overlap Syndrome
Clinical Outcomes and Treatment

- No long-term studies of comorbid OSA & asthma
  - No current specific guidelines
- OSA treatment with CPAP
  - Important potential pathophysiologic beneficial effects for patients with asthma
  - Improves asthma symptoms, ↓ use of rescue medication, improves asthma-specific QOL
- 2nd-line treatments for OSA, such as MAD & upper airway surgery
  - Have not been prospectively evaluated in patients with asthma/OSA overlap
- Bariatric surgery for patients with OSA and morbid obesity
  - Effective not only for OSA resolution but also for improving asthma

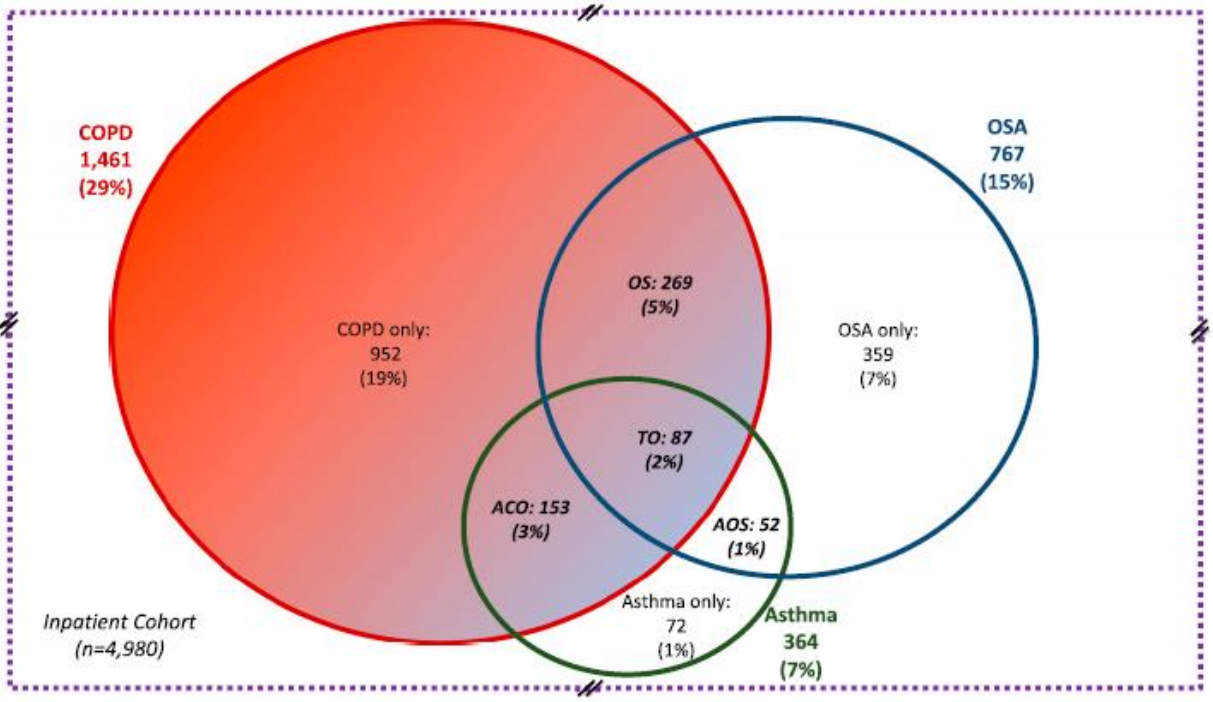
JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Obstructive Lung Disease and Obstructive Sleep Apnea (OLDOSA) cohort study: 10-year assessment

Octavian C. Ioachimescu, MD, PhD[1,2]; Nicholas J. Janocko, MD[1]; Mary-Margaret Ciavatta, PAC[2]; Marjorie Howard, MS[1]; Megan V. Warnock, MS[1]

[1]Emory University, Atlanta, Georgia; [2]Atlanta Veterans Affairs Medical Center Atlanta, Georgia



- 4,980 veterans with an acute hospitalization

- 10yr all-cause cumulative mortality
  - : asthma 54.2%
  - : OSA 60.4%
  - : COPD 63.0%
  - : COPD-OSA 53.2%
  - : asthma-COPD 62.1%
  - : asthma-OSA 63.5%
  - : asthma-COPD-OSA 67.8%

- PAP therapy & adherence : related with mortality in patients with OSA (after adjustment)

Summary

- **COPD/OSA overlap syndrome**
  - Hypoxia, ↓sleep quality & QOL, ↑ Pulmonary artery pressure, ↑ respiratory failure & death, Cardiovascular outcomes
  - Effective identification and Tx of the comorbid OSA, and the other features of SDB improve overall clinical outcomes
  - Chronic bronchitis phenotype : higher prevalence of OSA (vs Emphysema)

- **Asthma and OSA**
  - By common risk factors & mutually exacerbating pathophysiologic and clinical features
  - Effective Tx. of the comorbid OSA : improves asthma-related & overall pathophysiologic and clinical outcomes of the asthma/OSA overlap syndrome

- **Sleep study should be considered in any patient with COPD or asthma with signs and symptoms of SRBD**