Pulmonary hypertension in COPD

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Pulmonary hypertension (PH) in COPD: Definition

- **Mean PAP > 25 mmHg**  
  (by right heart catheterization)

- **Severe PH:**  
  mean PAP > 35 mmHg

- **Out-of-proportion PH:**  
  mean PAP > 35–40 mmHg and a mild-to-moderate airflow limitation

# Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. **Pulmonary arterial hypertension (PAH)**
   - 1.1 Idiopathic PAH
   - 1.2 Heritable: BMPR2, ALK1, endoglin, unknown
   - 1.3 Drugs and toxins-induced
   - 1.4 Associated with
     - 1.4.1 Connective tissue diseases
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
     - 1.4.6 Chronic haemolytic anaemia
   - 1.5 Persistent pulmonary hypertension of the newborn

1’ **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)**

2. **Pulmonary hypertension owing to left heart disease**
   - 2.1 Systolic dysfunction
   - 2.2 Diastolic dysfunction
   - 2.3 Valvular disease

3. **Pulmonary hypertension owing to lung diseases and/or hypoxia**
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental abnormalities

4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**

5. **Pulmonary hypertension with unclear multifactorial mechanisms**
   - 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
   - 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: LAM, neurofibromatosis, vasculitis
   - 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoural obstruction, fibrosing mediastinitis, CRF on dialysis

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แนวทางการวินิจฉัยภาวะ PH

แผนภูมิที่ 1 ขั้นตอนการตรวจวินิจฉัย PH

ขั้นตอนที่ 1 (PH diagnosis)
- History taking & PE
- CXR
- EKG
- ECHO
- RHC

ขั้นตอนที่ 2 (PH classification)
- Blood test: anti-HIV, Cr, LFT, CBC, ANA
- O₂ saturation/ABG
- CTA หรือ V/Q scan
- PFT, DLCO ± bronchodilators
- Polysomnography
- RHC

Echo : การตรวจคลื่นเสียงสะท้อนหัวใจ (echocardiography) ตรวจเพื่อคัดกรองและวินิจฉัยผู้ป่วย PH
RHC : right heart catheterization

แนวทางปฏิบัติเพื่อการวินิจฉัยและการดูแลรักษาภาวะความดันโลดดีปอดสูงในประเทศไทย พ.ศ. 2556
Pulmonary hypertension (PH) in COPD

- Exact incidence of clinically significant PH is difficult to estimate, as most reports are in patients with advanced disease
- Up to 90% of COPD patients have exercise-induced PH
- Resting PH is reported less frequently (5 - 30%
- Several recent large epidemiologic studies on severe COPD patients found an incidence of PH
  - up to 91%, with most patients having mild to moderate PH (mean PA pressures 20-35 mm Hg)
  - 1% to 5% had severe elevations of mean PA pressures > 35 mmHg [1]
    or >40 mmHg [2], respectively

FIGURE 1. Mean pulmonary artery pressure ($\bar{P}_{pa}$) in a hospital-based cohort of 998 chronic obstructive pulmonary disease (COPD) patients with a mild to very severe airflow limitation. It can be seen that severe pulmonary hypertension is uncommon in COPD but does exist. Data taken from [6].
Pulmonary hypertension in severe COPD

- FEV1 post BD < 50%pred.
- N = 98
- mPAP : 14-50 mmHg
- Mild: 29%
- Moderate: 2%
- Severe: 1%

Severity of PH was categorised according to ATS criteria

**Figure 1** Frequency distributions of mPAP of patients with severe COPD (n=98).

Mild PH : 25 < mPAP ≤ 35 mmHg
Moderate PH: 35 < mPAP ≤ 45 mmHg
Severe PH: mPAP > 45 mmHg

Figure 2 Exercise capacity, as measured by volume of oxygen consumed.
Table 2  Cardiopulmonary exercise test and six minute walk tests variables between PH and non-PH in patients with severe COPD.

<table>
<thead>
<tr>
<th></th>
<th>non-PH n=67</th>
<th>PH n=31</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak watt (% predicted)</td>
<td>21 ± 15</td>
<td>15 ± 9</td>
<td>0.016*</td>
</tr>
<tr>
<td>Peak VO₂ (% predicted)</td>
<td>36 ± 15</td>
<td>30 ± 9</td>
<td>0.012*</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>11.3 ± 4.1</td>
<td>9.5 ± 2.5</td>
<td>0.007*</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>22 ± 10</td>
<td>18 ± 7</td>
<td>0.030*</td>
</tr>
<tr>
<td>VE/VO₂ at rest</td>
<td>50 ± 9</td>
<td>49 ± 9</td>
<td>0.632</td>
</tr>
<tr>
<td>VE/VO₂ at peak</td>
<td>36 ± 8</td>
<td>36 ± 7</td>
<td>0.969</td>
</tr>
<tr>
<td>PetCO₂ at rest (mmHg)</td>
<td>37.5 ± 7.1</td>
<td>40.3 ± 7.7</td>
<td>0.068</td>
</tr>
<tr>
<td>PetCO₂ at peak (mmHg)</td>
<td>45.2 ± 9.0</td>
<td>47.6 ± 10.1</td>
<td>0.255</td>
</tr>
<tr>
<td>MVV (L)</td>
<td>24 (17-31)</td>
<td>17 (15 - 26)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Breathing Reserve (%)</td>
<td>17 (11 - 25)</td>
<td>13 (-2 - 25)</td>
<td>0.153</td>
</tr>
<tr>
<td>Respiratory exchange ratio (RER)</td>
<td>0.86 ± 0.13</td>
<td>0.85 ± 0.13</td>
<td>0.773</td>
</tr>
<tr>
<td>Oxygen pulse (mL/beat)</td>
<td>5.2 (4.2-7.7)</td>
<td>5.0 (3.9 – 6.9)</td>
<td>0.021*</td>
</tr>
<tr>
<td>Vt at peak (L)</td>
<td>0.8 ± 0.3</td>
<td>0.7 ± 0.2</td>
<td>0.055</td>
</tr>
<tr>
<td>HR at rest (beat/minute)</td>
<td>94 ± 13</td>
<td>92 ± 15</td>
<td>0.572</td>
</tr>
<tr>
<td>HR at peak (beat/minute)</td>
<td>118 ± 15</td>
<td>113 ± 16</td>
<td>0.114</td>
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<tr>
<td>SBP at rest (mmHg)</td>
<td>131 ± 15</td>
<td>135 ± 19</td>
<td>0.280</td>
</tr>
<tr>
<td>SBP at peak (mmHg)</td>
<td>174 ± 26</td>
<td>174 ± 19</td>
<td>0.894</td>
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<tr>
<td>DBP at rest (mmHg)</td>
<td>76 ± 6</td>
<td>78 ± 7</td>
<td>0.161</td>
</tr>
<tr>
<td>DBP at peak (mmHg)</td>
<td>89 ± 9</td>
<td>89 ± 9</td>
<td>0.866</td>
</tr>
<tr>
<td>SpO₂ at rest (%)</td>
<td>98 (96 – 99) %</td>
<td>97 (95 – 99) %</td>
<td>98 (96- 99) %</td>
</tr>
<tr>
<td>SpO₂ at peak (%)</td>
<td>96 (93 – 98) %</td>
<td>96 (93 – 98) %</td>
<td>96 (93 – 98) %</td>
</tr>
<tr>
<td>Six-minute walk distance (ft)</td>
<td>1101 ± 307</td>
<td>980 ± 283</td>
<td>0.082</td>
</tr>
<tr>
<td>Time between RHC and CPET (days)</td>
<td>3 (-3 - 10)</td>
<td>3 (1 - 15)</td>
<td>0.800</td>
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<tr>
<td>Time between CPET and PFT (days)</td>
<td>0 (0 - 7)</td>
<td>1 (0 - 10)</td>
<td>0.921</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. VO₂ = oxygen uptake, VCO₂ = rate of carbon dioxide production, VE = minute ventilation, Vt = tidal volume, PetCO₂ = end tidal carbon dioxide, HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, SpO₂ = pulse oxymeter oxygen saturation.

* = Significantly different between non-PH and PH.
† = Mann-Whitney U tested used.
Mean PAP >25 mmHg had a significantly lower survival rate at 5 yrs compared with patients without PH (33 versus 66%; p<0.001) (Oswald-Mammosser M, et al. CHEST 1995)

# Table 1

Confirmed and suspected factors leading to an increased pulmonary vascular resistance in chronic obstructive pulmonary disease (COPD)

<table>
<thead>
<tr>
<th>Factors of PH in COPD</th>
<th>Consequences on pulmonary vessels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airflow limitation</td>
<td>Pressure swings</td>
</tr>
<tr>
<td>Emphysema</td>
<td>Reduction of the vascular bed</td>
</tr>
<tr>
<td><strong>Alveolar hypoxia</strong></td>
<td>Vasoconstriction, remodelling</td>
</tr>
<tr>
<td>Hypercapnic acidosis</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Polycythaemia</td>
<td>Hyperviscosity</td>
</tr>
<tr>
<td>Lung and systemic inflammation</td>
<td>Remodelling, including fibrosis</td>
</tr>
</tbody>
</table>

PH: pulmonary hypertension.

Alveolar hypoxia is a predominate factor
Pathophysiology of pulmonary hypertension in COPD

- Traditionally, PH in COPD has been considered to be the result of
  - hypoxic pulmonary vasoconstriction
  - polycythemia
  - destruction of the pulmonary vascular bed by emphysema

- Recently, it has been recognized that hyperinflation and endothelial dysfunction also play a role in the pathogenesis of PH

NO, nitric oxide; ET-1, endothelin-1; PVR, pulmonary vascular resistance; PH, pulmonary hypertension

Pathology

- The structural basis of PH in COPD includes three potential mechanisms:
  - remodeling
  - reduction in the total number of pulmonary vessels
  - pulmonary thrombosis

- The only structural basis of PH that is well investigated in pathology is the remodeling of pulmonary arteries and arterioles

http://www.scleroderma.org/medical/r&t_articles/Varga_2004_2.shtm

Chaouat A. Eur Respir J 2008; 32: 1371–85

Diagnosis of PH in COPD

- **Dyspnea on exertion and fatigue**, are generally present in advanced COPD patients with or without PH.
- Out-of-proportion PH in COPD have more severe dyspnea on exertion in comparison with COPD patients, with more-severe airflow limitation but lower PAP.
- **Loud P2, pansystolic murmur (TR)**, are rarely noticed, except during severe exacerbations of the disease. This can be explained by the presence of mild-to moderate PH in most of the patients and by the late occurrence (or no occurrence at all) of right heart failure.
- Peripheral oedema occurs rather late in the course of COPD and is not synonymous with right heart failure.

Chaouat A. Eur Respir J 2008; 32: 1371–85
Pulmonary function tests

- Early studies indicate that, with the exception of low oxygen tensions during exercise and resting hypercapnia, pulmonary function tests are poor predictors of the severity of pulmonary hypertension in COPD (Keller et al 1986)
- However in a selected group of patients undergoing LVRS the level of PAP varies inversely with the FEV1 (Scharf et al 2002; Thabut et al 2005)
- Similarly studies of COPD patients without severe hypoxia (PaO2 > 55 mm Hg) have also shown that mPAP better correlates with the FEV1 than with the resting PaO2 (Oswald-Mammosser et al 1991; Doi et al 2003)
- It is also notable that these studies indicating a closer FEV1 PAP relationship were conducted in patients with severe hyperinflation which itself is likely to predispose to PH

Chest radiography

- An increase in the diameter of the right descending pulmonary artery to more than 16 mm on the PA projection combined with a diameter of the left descending pulmonary artery of more than 18 mm on the left lateral projection can identify PH with 98% sensitivity (Matthay et al. 1981)

The sensitivity for right ventricular hypertrophy is only 25%–40%. Presence of S1S2S3 or right atrial overload pattern ie, P wave axis of +90° or more, implies a poor prognosis (Incalzi et al 1999)
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Right heart catheterization

- is the gold standard to determine the exact PAPs
- The degree of PH in stable COPD is usually mild to moderate (mPAP < 35 mm Hg)
- mPAP > 40 mm Hg is rare in COPD and should initiate a search for an additional cause of PH eg, left heart disease, sleep apnea syndrome, pulmonary embolism
- Rarely a COPD patient may present with severe PH (Chaouat et al 2005; Thabut et al 2005)

<table>
<thead>
<tr>
<th>Methods</th>
<th>References</th>
<th>At least one randomised trial?</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTOT</td>
<td>[112–116]</td>
<td>Yes</td>
</tr>
<tr>
<td>Nocturnal oxygen therapy</td>
<td>[117, 118]</td>
<td>Yes</td>
</tr>
<tr>
<td>Medical treatment dedicated to PAH</td>
<td>[119, 120]</td>
<td>Yes</td>
</tr>
<tr>
<td>Ca$^{2+}$ channel blockers</td>
<td>[121]</td>
<td>No</td>
</tr>
<tr>
<td>Urapidil</td>
<td>[122]</td>
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</tr>
<tr>
<td>Angiotensin inhibitors</td>
<td>[123, 124]</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>[125]</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pulmonary rehabilitation</strong></td>
<td>[126]</td>
<td>No</td>
</tr>
<tr>
<td>LVRS</td>
<td>[127–130]</td>
<td>Yes</td>
</tr>
<tr>
<td>Lung transplantation</td>
<td>[131]</td>
<td>No</td>
</tr>
</tbody>
</table>

LTOT: long-term oxygen therapy; PAH: pulmonary arterial hypertension; LVRS: lung volume reduction surgery.

Chaouat A. Eur Respir J 2008; 32: 1371–85
Exercising PH

Kessler et al. 2001: 131 COPD with FEV1 45 ± 16% pred. and mild hypoxemia (71 ± 13 mmHg), mean time interval 7 ± 3 yrs,
- mean PAP 15 ± 3 mmHg
- 76 had exercising PH (mean PAP > 30 mmHg)
- Patients having exercising PAP at onset were more prone to develop resting PH with time
- Slow progression +0.4 mmHg/yr
- The more PaO2 worsened the more mean PAP increased during follow up

Weitzenblum E, et al. 1984: The slow progression of mean PAP was also demonstrated in more advanced COPD patients with PH at rest

Chaouat A. Eur Respir J 2008; 32: 1371–85
Exercising in advanced COPD

- Resting PH have a marked increase in PAP during steady-state exercise
- Baseline mean PAP is modestly elevated (25–30 mmHg) may exhibit severe PH (50–60 mmHg) during moderate exercise (30–40 W) (PVR does not decrease during exercise)
- This means that daily activities, such as climbing stairs, or even walking, can induce marked PH

Chaouat A. Eur Respir J 2008; 32: 1371–85
Peaks of PH during sleep

- Some COPD patients who are normoxaemic or mildly hypoxaemic during the day develop moderate to severe hypoxaemia during sleep
- These episodes of hypoxaemia are due to alveolar hypoventilation which occurs mainly in rapid eye movement (REM) sleep
- They coincide with transient increase in Ppa
- It has been hypothesised that intermittent episodes of PH during sleep in COPD could lead to permanent PH. However, the investigations performed in this area are rather controversial

Chaouat A. Eur Respir J 2008; 32: 1371–85
“out-of-proportion” PH in COPD

- Retrospective study of 998 patients with COPD who underwent right heart catheterization, only 1% had severe pulmonary hypertension (mean PAP > 40 mm Hg)
- The authors described an unusual pattern of cardiopulmonary abnormalities in the patients with
  - more severe PH
  - mild to moderate airway obstruction
  - severe hypoxemia
  - Hypocapnia
  - very low DLCO

Cor pulmonale

- Classically defined as “hypertrophy of the right ventricle resulting from diseases affecting the function and/or structure of the lungs except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart”

  (WHO expert committee report 1963)

- Cor pulmonale and right heart failure are not synonymous

- Pulmonary hypertension (PH) however is always the underlying pathologic mechanism for right ventricular hypertrophy in cor pulmonale

International Journal of COPD 2007:2(3) 273–82
Diagnosis of cor pulmonale in COPD: Clinical features

- True right heart failure is characterized by
  - raised jugular venous pressures
  - congestive hepatomegaly
  - peripheral edema

- The clinical exam lacks sensitivity and specificity

- Hyperinflation reduces the yield of cardiac auscultation for the classic signs of PH and CP ie, loud P2, S3 gallop, the systolic murmur of tricuspid regurgitation

- Peripheral edema can be present in the absence of right heart failure in COPD and is not diagnostic of cor pulmonale

pathogenesis of edema formation in COPD

- is complex
- Renal blood flow is reduced, the renin-angiotensin system is activated, renal dopamine output is reduced and plasma ANP level is elevated leading to increase in proximal renal tubular sodium reabsorption (Skwarski et al 1998; de Leeuw and Dees 2003)
- Sodium retention is enhanced by hypercapnia and ameliorated by long-term oxygen therapy in hypoxemic patients (Bratel et al 2003)
Summary

- Pulmonary hypertension in COPD is common
- PH is defined by mean PAP > 25 mmHg (right heart catheterization– gold standard) or RVSP ≥ 36 mmHg by echocardiography
- Out-of-proportion PH: mean PAP > 35–40 mmHg and a mild-to-moderate airflow limitation
- Pathophysiology:
  - vasoconstriction and remodeling
  - alveolar hypoxia is a predominate factor (other emphysema)
- Exercise - increased PAP
- Treatment – LTOT
Sleep disorder in COPD
Normal sleep cycle

http://ipemb.org.uk/the-stages-of-sleep/
Respiratory Response to Sa02 During Normal Sleep

Ventilation (L/min) vs Oxygen Saturation (%)

- Awake
- 3/4
- 2
- REM

Respiratory Response to CO₂ During Normal Sleep

- Ventilatory response to CO₂ is depressed during NREM sleep.
- Slope of response line is depressed further in REM sleep.
- Set point for response to CO₂ increases during NREM sleep and further in REM sleep.
  - Requires a higher PaCO₂ to stimulate respiration.

Overall Changes in Breathing During Sleep

- Decrease in minute ventilation 0.5-1.5 L
- Increase in airway resistance
- Decrease in metabolic rate (CO$_2$) production 10-15%
- Decrease in chemosensitivity 20-50%
  - PaO$_2$ 3-10 mmHg
  - SaO$_2$ 2%
  - PaCO$_2$ 2-8 mmHg

Effects of COPD on Sleep

• Cough and wheezing interrupt and delay sleep (Klink M Chest 1987)

• Sleep is more fragmented, with increased arousals and reduced amounts of deep nREM and REM sleep (McSharry DG, Respirology 2012)

• Severity of COPD correlates with severity of subjective sleep complaints (Omachi TI Sleep Med 2012), but not with objectively measured sleep variables (Hynyninen MJ Sleep Med 2013).
Effects of COPD on Sleep

- Daytime sleepiness (by Epworth) and poor quality sleep (by PSQI) compared to that of matched controls (Zohal A Glo J Health Sci 2013).

- Increased prevalence of insomnia complaints

- Increased use of hypnotics

McNicholas WT Sleep Breath 2013
Patients with COPD are most profoundly hypoxemic at night (McNicholas WT, Chest 2000).

COPD patients are more likely to die at night (McNicholas WT Br Med J 1984).

Oxygen desaturation is greater during sleep than during exercise in COPD, and wake SaO₂ predicts nocturnal desaturation better than exercise SaO₂ or wake PaCO₂ (Mulloy E, Chest 1996)
How does sleep impact COPD?

- Reduced chemosensitivity
- Reduced pulmonary function
- Impaired muscle performance
- Systemic inflammation

How does COPD impact sleep?

- Symptoms cause sleep disturbance
- Hypoxemia and hypercarbia disturb sleep
### OSA + COPD= Overlap Syndrome

- Definitions of COPD and OSA vary, so..

- Prevalence estimates of the Overlap Syndrome vary.

| As many as 15% of COPD patients have co-existent OSA (Carratu P ERJ 2008) |
| In patients with OSA, prevalence of COPD is 7.6% (compared to patients without OSA, where prevalence is 3.7%) (Greenberg-Dotan S, Sleep Breath 2013) |
| For patients with GOLD stage 4 COPD, the prevalence of OSA is 43% (Areias V, Rev Prt Pneumol 2014) |
How is the Overlap Syndrome Different than COPD or OSA?

Patients with the Overlap Syndrome have increased risk of complications compared to those with COPD or OSA alone (Gan WQ Thorax, 2004, Greenberg-Dotan S, Sleep Breath 2013)

- Respiratory failure
- Pulmonary hypertension
- Hypoventilation
- More severe hypoxemia
- Diabetes
- Obesity
- Death
Overlap Patients at Greater Risk for A Fib Than OSA or COPD (Ganga HV JACC 2013)
<table>
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<th>Overview</th>
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<td>Effects of sleep on breathing</td>
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<td>The Overlap Syndrome</td>
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<td>Treatment of the Overlap Syndrome</td>
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<td>Potential Treatments for Sleep Disorders in COPD</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<tr>
<td><strong>Medications</strong></td>
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<td>Hypnotics</td>
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<tr>
<td>Cognitive Behavioral Therapy</td>
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<tr>
<td><strong>Pulmonary Rehabilitation</strong></td>
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<tr>
<td>Nocturnal oxygen</td>
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<tr>
<td>Positive airway pressure</td>
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<tr>
<td>CPAP</td>
</tr>
<tr>
<td>Bilevel PAP</td>
</tr>
<tr>
<td>NIPPV</td>
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</tbody>
</table>
### COPD Medications

- Theophylline (a xanthine) has the potential to impair sleep, but data are conflicting.
- Other COPD meds appear to improve symptoms without impairing sleep.
The evidence that chronic use of hypnotics is dangerous is much more compelling than the evidence that hypnotics improve any important objective outcome.

This is probably particularly true in patients with lung disease, including COPD.

Short-term use of BDZ hypnotics only for acute problems is probably the most appropriate way to use sleeping pills in patients with COPD.
Exercise is known to promote and to consolidate sleep. In this study of 64 patients with severe COPD (FEV1% 53), 8 weeks of pulmonary rehab improved Pittsburgh Sleep Quality Index (PSQI) and Health-related Quality of Life (HRQoL).
Nocturnal Oxygen

Nocturnal oxygen for COPD

- The goal is $\text{SaO}_2 > 90\%$
- Titration is useful, but risk of hypercarbia may be overstated (Moloney ED Lancet 2001).
- Benefits of supplemental O2 for those with modest daytime hypoxemia ($\text{PaO}_2$ 55-60) mmHg is still unclear
  - 38% of COPD subjects with a daytime PaO2 of 56–69 mm Hg (mean 65 mm Hg) spent 30% of the night with an oxygen saturation 90%.
    (Lacasse Y Respir Med 2011).
- In the US, nocturnal oxygen is generally covered if nocturnal $\text{SaO}_2$ is <89% for at least 5 minutes.
Effect of nocturnal nasal oxygen on \( \text{SaO}_2 \), systemic and pulmonary artery pressures. (Clement ID Respir Physiol 1992.)
The NOTT and MRC studies demonstrated that patients with PaO\(_2\) < 55 or PaO\(_2\) < 59 with cor pulmonale had better survival if they received nocturnal oxygen, and even better survival if they received continuous oxygen.

NOTT recommended 2 l/min during day, 3 l/min at night (which is largely ignored).

The benefit of nocturnal oxygen for those with only nocturnal hypoxemia has not been demonstrated.
Nocturnal Oxygen for the Overlap Syndrome

Improved oxygenation, but increased apnea duration and PCO$_2$ in 20 patients with the overlap syndrome (Fletcher EC Chest 1986)
CPAP for the Overlap Syndrome

Reduces risk of death and of exacerbations

Improves walking capacity  (Wang T Respiratory Research 2013).
CPAP Reduces Death Rates
Marin JM Am Rev Respir Crit Care Med 2010

![Graph showing survival rates with and without CPAP in COPD and overlap cases.](image-url)

<table>
<thead>
<tr>
<th>Group</th>
<th>No at Risk</th>
<th>Year 0</th>
<th>Year 2</th>
<th>Year 4</th>
<th>Year 6</th>
<th>Year 8</th>
<th>Year 10</th>
<th>Year 12</th>
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<tbody>
<tr>
<td>COPD</td>
<td>210</td>
<td>203</td>
<td>196</td>
<td>184</td>
<td>144</td>
<td>89</td>
<td>10</td>
<td></td>
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<tr>
<td>Overlap with CPAP</td>
<td>228</td>
<td>223</td>
<td>215</td>
<td>201</td>
<td>167</td>
<td>97</td>
<td>8</td>
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<tr>
<td>Overlap without CPAP</td>
<td>213</td>
<td>204</td>
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<td></td>
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</table>

*P < 0.001*
CPAP Reduces Exacerbation Rates
(Marin JM Am Rev Respir Crit Care Med 2010)
CPAP use is associated with reduced mortality in the Overlap Syndrome, and some use (2-4 hours) is better than none. (Stanchina ML, JCSM 2013, N=227)
In patients with the Overlap Syndrome CPAP reverses the increased mortality (above that of COPD alone). (McNicholas WT Eur Respir J 2013)

In patients who chose between LTOT and CPAP+LTOT, 5 year survival was

• 26% for LTOT alone
• 71% for LTOT+ CPAP (Machado MCL Eur Respir J 2010)
<table>
<thead>
<tr>
<th>Summary/Conclusions</th>
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<tbody>
<tr>
<td>Sleep and COPD have adverse effects on each other.</td>
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<tr>
<td>COPD + insomnia treatment probably should not involve hypnotics</td>
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<tr>
<td>COPD + OSA (Overlap Syndrome) is best treated with CPAP</td>
</tr>
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