

# NIV in stable hypercapnic COPD

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Patients with end-stage COPD frequently develop chronic hypercapnic respiratory failure (CHRF) associated with end-of-life. In this stage of disease, patients experience extremely disabling symptoms of dyspnea, leading to severely impaired health-related quality of life.

While there is no doubt that applying chronic nocturnal NIV improves outcomes in patients with restrictive and neuromuscular diseases, there has been conflicting evidence for its benefits in COPD patients for a long period.

However, with the introduction of high-intensity NIV (HI-NIV), important benefits have been shown and the discussion about NIV in COPD has changed.

## **The history of high-intensity noninvasive ventilation**

**The first reports of NIV in stable severe COPD date from the 1980s. During this period, negative pressure ventilation using a cuirass or poncho wrap ventilator was the most widely used ventilatory mode.**

**These first studies on negative pressure ventilation in stable severe COPD showed variable results, with some smaller trials showing a positive effect on gas exchange, respiratory muscle strength, hospitalization rates, or dyspnea**

**But a large RCT, showing no benefit at all. Furthermore, almost all studies concluded that there was poor patient tolerance for long-term use of negative pressure ventilation.**

**In the mid-1980s, positive pressure ventilation became more widely available.**

**It was expected that this mode would improve tolerance and outcomes.**

**The benefits of this more easily tolerable mode of ventilation were still not demonstrated unambiguously in COPD.**

## **Noninvasive ventilation after severe exacerbations**

Patients who become respiratory insufficient due to a COPD exacerbation and need invasive or noninvasive mechanical ventilation for the acute event have a very poor prognosis after hospital discharge.

More than 60% of these patients are readmitted and more than 25% die within the first year after discharge.

Therefore, the thought that continuation of NIV at home after discharge might be helpful is quite attractive.

It is well established that the use of NIV in acute COPD exacerbations improves mortality, reduces the need for endotracheal intubation, and decreases hospital ICU length of stay.

The question whether NIV is beneficial in patients with severe COPD outside of exacerbations was the focus of several studies in the late 1990s and early to mid-2000s.

## Patient selection and outcomes

**NIV is most convincingly of benefit in COPD patients with CHRF in a stable condition. Patients with very severe hypercapnia seem to benefit more, at least with respect to gas exchange benefits.**

**In patients that exacerbate frequently the benefits of NIV are less certain. Despite MURPHY *et al.* showing that NIV might increase the time to readmission**

Table 1. Pathophysiologic targets uniquely targeted through application of noninvasive ventilation in patients with chronic obstructive pulmonary disease

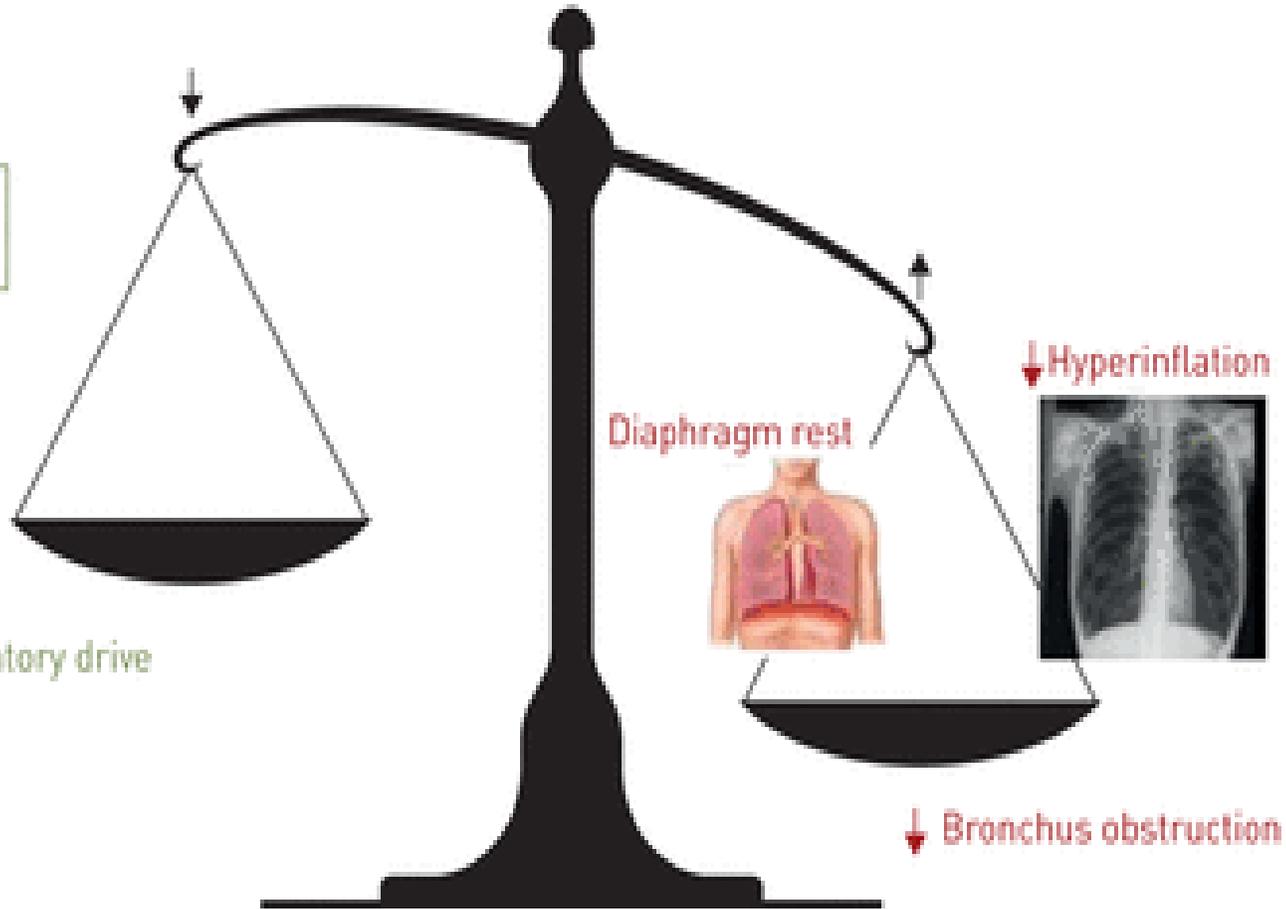
	Abnormalities in Severe COPD	Benefit Conferred by Noninvasive Ventilation
Obstructive airway disease	Increase in inflammatory cells producing mucus, increased smooth muscle contributing to airway constriction (6)	Positive pressure stents open airways
Alveolar destruction	Destruction of alveoli secondary to emphysema, loss of elastic recoil contributing to hyperinflation (7)	EPAP adjusted to overcome intrinsic PEEP to decrease respiratory muscle load
Diaphragmatic dysfunction	Atrophy from hyperinflation, limited excursion to support ventilation, increased respiratory muscle load secondary to increased airway resistance and	High-intensity pressure support ventilation with backup rate reduces diaphragm effort and controls mechanism of breathing, resting diaphragm muscle

Better sleep

Improved breathing patterns

Improvement in gas exchange

Better sputum clearance



## **In two case series examining the effects of nocturnal NIV:**

- **Improvement in daytime gas exchange was noted**
  - **A reduction in daytime PaCO<sub>2</sub>**
  - **A decrease in hyperinflation.**
- decreases RV/TLC, a measure of air trapping at 6 and 12month**
- inspiratory capacity (IC), vital capacity (VC), and forced expiratory volume in one second (FEV<sub>1</sub>) also improved**

Table 2. Summary of clinical trials investigating role of noninvasive ventilation in chronic obstructive pulmonary disease with chronic respiratory failure

	Low-Intensity Noninvasive Ventilation			High-Intensity Noninvasive Ventilation		
	Casanova et al. (10)	Clini et al. (11)	McEvoy et al. (12)	Struik et al. (21)	Kothenlein et al. (20)	Murphy et al. (22)
Design	RCT	RCT	RCT	RCT	RCT	RCT
N	44 24 vs. 20	86 47 vs. 39	144 72 vs. 72	201 100 vs. 101	195 93 vs. 102	116 59 vs. 57
Age, yr	68 vs. 64	66 vs. 64	69 vs. 67	63.5 vs. 63.9	64.4 vs. 62.2	67.1 vs. 66.4
BMI, kg/m <sup>2</sup>	25 vs. 25	25 vs. 26	25.4 vs. 25.5	24.8 vs. 24.6	24.5 vs. 24.8	22.2 vs. 21.5
FEV <sub>1</sub> , % predicted	31 vs. 29	31 vs. 27	23.1 vs. 25	26 vs. 26	27 vs. 26	22.9 vs. 24
Pa <sub>O<sub>2</sub></sub> , mm Hg	57.5 vs. 55.7	49.5 vs. 50	52.5 vs. 54.8			48 vs 48
Pa <sub>CO<sub>2</sub></sub> , mm Hg	53 vs. 50	55.5 vs. 54	54.4 vs. 52.6	57.8 vs 59.3	57.8 vs. 58.5	59 vs. 59
Mode	Bilevel-S	Bilevel-S/T	Bilevel-S	Bilevel-S/T	Bilevel-S/T	Bilevel-S/T
PAP/EPAP, cm H <sub>2</sub> O	12/4	14/2	13/5	19.2/4.8	21.6/4.8	24/4
Adherence, (h/day)	5.9	9.2	4.5	6.3	5.9	4.7
Acclimatization	2 d	10 d	3–4 d	3–4 d	5–6 d	5–6 d
Outcome	No improvement in acute COPD exacerbations, hospital admissions, intubations, or mortality	No improvement in hospitalizations and readmissions overnight	Improved sleep quality and or hypercapnia, decrease in QoL	No change in exacerbations, improvement in daytime Pa <sub>CO<sub>2</sub></sub>	Improvement in mortality, Pa <sub>CO<sub>2</sub></sub> , Sa <sub>O<sub>2</sub></sub> , and FEV <sub>1</sub>	Decrease COPD readmissions

Definition of abbreviations: Bilevel-S = no backup rate; Bilevel-S/T = backup rate; BMI = body mass index; COPD = chronic obstructive pulmonary disease; EPAP = expiratory positive airway pressure; FEV<sub>1</sub> = forced expiratory volume in 1 second; IPAP = inspiratory positive airway pressure; Pa<sub>CO<sub>2</sub></sub> = carbon dioxide tension; Pa<sub>O<sub>2</sub></sub> = arterial oxygen tension; QoL = quality of life; RCT = randomized controlled trial; Sa<sub>O<sub>2</sub></sub> = arterial oxygen saturation

**Windisch and Dreher studies. These findings support the concept that unloading of the ventilatory muscles with high mean IPAP and mandatory high respiratory rates can improve alveolar ventilation and thereby reduce chronic hypercapnia.**

**(IPAP) used was 18 cm H<sub>2</sub>O. Participants at higher inspiratory pressures were demonstrated to have a reduction in diaphragm fatigue.**

**Higher inspiratory pressures were associated with larger tidal volumes and decreased respiratory rates.**

**The study documented improvements in both Pa<sub>O<sub>2</sub></sub> and Pa<sub>CO<sub>2</sub></sub> during spontaneous breathing and improvement in FEV<sub>1</sub>**

**MURPHY *et al.*** recently showed that when you initiate NIV in patients that remain severely hypercapnic after an exacerbation, hospital readmissions are delayed and reduced.

**The RESCUE trial by STRUIK *et al.*** In the latter, 201 patients were included that were moderately hypercapnic 48 h after weaning from NIV or invasive mechanical ventilation and randomised to NIV or standard care to be continued for a year. This study did not show any benefit at all despite the use of HI-NIV (mean IPAP 19 cmH<sub>2</sub>O, mean BURR 5 breaths/min)

## **Noninvasive ventilation in COPD**

**Four larger well-designed RCTs have been performed using HI-NIV in patients with severe COPD. In stable chronic hypercapnic patients, two studies showed quite convincing benefits although a survival benefit was only shown in one study (level B evidence)**

## **Conclusions**<sub>(UpToDate)</sub>:

**Several good quality RCTs have shown that if adequate ventilatory settings are applied, aimed at a substantial reduction in  $P_{aCO_2}$ , then chronic NIV improves outcomes in patients with severe CHRF.**

**An impressive survival benefit was shown;**

**outcomes can be further improved once we increase our knowledge about patient selection**

## Clinical Practice Guidelines (CHEST 2024)

The European Respiratory Society, American Thoracic Society (ATS), and the Canadian Thoracic Society recently published guidelines that agree that a role exists for LTNIIV in chronic stable hypercapnic COPD, but recommendations are weak, with very low- to moderate-certainty evidence.

**LTNIV is suggested after acute hypercapnic respiratory failure requiring acute NIV, provided that the patient remains hypercapnic after resolution of the acute episode.**

**The ATS and Canadian Thoracic Society recommend re-evaluation after 2 to 4 weeks.**

**All three guidelines specify that NIV should aim to normalize or at least significantly reduce hypercapnia.**

**The European Respiratory Society and Canadian Thoracic Society found no evidence to support auto-adjusting modes preferentially and recommend fixed pressure modes.**

**The ATS suggests evaluating patients for OSA at a minimum with a questionnaire (very low-certainty evidence)**

# Chronic stable hypercapnia

While guidelines vary, the most common COPD patients for whom nocturnal NIV is used are those with:

- daytime hypercapnia (eg, arterial carbon dioxide tension [ $\text{PaCO}_2$ ]  $\geq 52$  mmHg),
- oxygen desaturation during sleep (eg, pulse oxygen saturation [ $\text{SpO}_2$ ]  $\leq 88$  percent for  $\geq 5$  minutes of  $\geq 2$  hours of nocturnal sleep oximetry) despite the use of supplemental oxygen at  $\geq 2$  L/min

# **NIV initiated during exacerbation**

**Patients with severe, hypercapnic COPD who have a favorable experience with NIV during a hospitalization for an acute-on-chronic hypercapnic COPD exacerbation may be candidates for long-term nocturnal NIV after discharge.**

**The ATS guidelines advise deferring the decision until after resolution of the acute event (approximately two to four weeks), as approximately 20 percent of patients who required NIV in the hospital were no longer hypercapnic two to four weeks after**

## Evaluation for other causes of chronic respiratory failure

For stable patients who have persistent hypercapnia when awake with or without oxygen desaturation during sleep, we obtain polysomnography and an echocardiogram before initiating nocturnal NIV.

## ● **Polysomnography to exclude sleep apnea**

Nocturnal hypoxemia or hypercapnia may be caused by superimposed or predominant obstructive sleep apnea (OSA), or less commonly central sleep apnea (CSA). For patients with hypercapnic COPD, screening for sleep-related breathing disorders is advisable prior to NIV

● **Echocardiogram** – Heart failure (right and left) and pulmonary hypertension can contribute to nocturnal gas transfer abnormalities and should be evaluated by echocardiogram.

## **Potential negative factors**

**Even the volume-assured settings promoted for comfort did not provide better comfort and tolerance, nor did they provide physiological benefits.**

**On the other hand, the time patients need to get used to the high-intensity setting is increased as compared to the “old” low-intensity setting**

**Some caregivers are worried that with HI-NIV the diaphragm is insufficiently unloaded and that diaphragm atrophy will result.**

**It is known that HI-NIV might reduce cardiac output**

**proportion of COPD patients on HI-NIV experience deventilation dyspnoea, a feeling of severe dyspnoea after being disconnected from the ventilator**

## **Interface :**

- Careful sizing is necessary to ensure absence of leak without creating pressure points on the face.
- A full face mask is used if the patient is a habitual mouth breather.

## PAP selection

- For patients whose hypoventilation is due to severe COPD, bilevel PAP (BPAP) is preferred over continuous PAP (CPAP) . In contrast, for those whose symptoms and hypercapnia are largely due to OSA, CPAP may be sufficient.
- There are no specific data that support the use of a volume-targeted ventilator over a pressure-targeted one in COPD.

## **Protocol for initiation in stable patient:**

**The optimal approach for initiation of BPAP for nocturnal NIV has not been determined. We typically start with an expiratory positive airway pressure (EPAP) level of 5 cm H<sub>2</sub>O and an inspiratory positive airway pressure (IPAP) of 10 cm H<sub>2</sub>O and gradually increase.**

**The final IPAP level is urged to be >15 cm H<sub>2</sub>O guided by patient tolerance (range, 12 to 20 cm H<sub>2</sub>O) with the EPAP level at least 5 cm H<sub>2</sub>O lower than the IPAP pressure.**

- **High intensity NIV aims to decrease arterial carbon dioxide tension ( $\text{PaCO}_2$ ) to normal or near-normal levels, through increases in breathing frequency and airway pressures.**
- **In a series of 73 patients with hypercapnic COPD, high-intensity NIV with breathing frequencies of  $21 \pm 3$  breaths/min and mean inspiratory/expiratory positive airway pressures of  $28 \pm 5/5 \pm 1$  cm  $\text{H}_2\text{O}$  were used. After one year,  $\text{PaCO}_2$  decreased 7 mmHg, on average. The two and five year survival rates were 82 percent and 58 percent, respectively.**
- **Further study is needed to determine the optimal pressures for BPAP in COPD and to assess outcomes such as compliance and quality of life.**

**When NIV is initiated electively, the patient should be familiarized with interface and other equipment during the day.**

**It is often helpful to see how the patient tolerates PAP at the proposed settings several hours before sleep.**

## **Monitoring:**

**During initiation, monitoring should focus on the:**

- **patient's acceptance of the device,**
- **level of dyspnea,**
- **oxygenation,**
- **and stability of vital signs**
- **For more severely ill patients, continuous cardiac, blood pressure, and oximetry**

Arterial blood gases (ABG) are generally not useful while titrating the initial settings in the more stable patients.

However, an ABG obtained in the morning after patients return to their spontaneous breathing state may be useful to guide further titration

A reasonable goal is for the  $\text{PaCO}_2$  to decrease by approximately 5 to 10 mmHg, although the optimal target is not known.

## **Ongoing evaluation after discharge includes:**

- assessment of hours of use per night,
- quality of sleep,
- daytime dyspnea,
- a periodic overnight oximetry
- daytime arterial blood gases
- It has become more common to see the patient within the first month after discharge to avoid the costly penalties of the 30 day readmission.

## Treatment failure :

- Patient intolerance, as indicated by patient request to discontinue nocturnal assisted ventilation.
- Worsening dyspnea, hemodynamic instability, or unresponsive hypoxemia.
- Signs of respiratory failure. Criteria for respiratory failure include tachypnea (respiratory rate  $>24/\text{min}$ ) and respiratory acidosis (eg,  $\text{pH} < 7.35$ ).

## Humidification:

- Nasal saline and/or heated humidification may enhance comfort by decreasing dryness in the upper airway.
- It is important to avoid excess heating that may lead to water condensation, also called "rainout,"

## **Adherence:**

patients using nocturnal NIV, tolerance and adherence are important issues. A comprehensive education program for the patient and appropriate family members when NIV is initiated may help improve adherence.

## **Effects on hospitalization and mortality**

Data regarding the effect of nocturnal NIV on survival and the rate of hospital admissions in patients with COPD and chronic hypercapnia are conflicting, possibly due to differences in the inspiratory pressures used for NIV

**In a meta-analysis of eight trials (837 patients) described in the ATS guideline, mortality risk decreased by 14 percent in the NIV group compared with usual care (RR 0.86; 95% CI 0.58-1.27)**

**In a randomized trial of 116 patients with COPD and hypercapnia (arterial carbon dioxide tension [PaCO<sub>2</sub>] >53 mmHg), continuing nocturnal NIV after hospitalization for a COPD exacerbation prolonged the time to readmission or death compared with supplemental oxygen alone.**

**In a randomized trial of 195 patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) IV COPD and a baseline PaCO<sub>2</sub> ≥52 mmHg (7 kPa), nocturnal NIV resulted in a one-year mortality of 12 percent, while the control group mortality was 33 percent**

**Trials that did not show a benefit to nocturnal NIV generally used lower NIV pressures include the following:**

- **A randomized trial examined the quality of life, mortality rate, hospital stay, and intensive care unit (ICU) admissions in 122 stable hypercapnic COPD patients who were assigned to NIV plus LTOT or LTOT alone. After two years, there was no difference in mortality or hospital admissions between the groups. Health-related quality of life was improved in the NIV group. The only significant difference in outcome was that ICU stay was decreased by 75 percent in the NIV patients and 20 percent in those on LTOT alone.**
- **In a third trial, no benefit was found from domiciliary NIV on the rate of subsequent hospitalizations and mortality in 52 patients with advanced COPD treated for one year**