Chronic hypercapnic respiratory failure and non-invasive ventilation in people with chronic obstructive pulmonary disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) should no longer be seen as a condition for which little can be done. Novel pharmacotherapeutic interventions, surgical and procedural advances, and respiratory assist devices have provided numerous ways to help patients with COPD and treatable traits. For nearly 30 years, non-invasive ventilation, the application of positive pressure through a mask interface placed outside of the airway, has been the cornerstone for treatment of acute hypercapnic respiratory failure due to COPD exacerbation. Clinical trials indicate that this intervention could benefit patients with COPD and chronic hypercapnic respiratory failure in a stable state. This narrative review aims to provide the necessary background for internists to consider this therapeutic option for their COPD patients. We discuss the mechanism of action and implementation, and provide a glimpse into the future of this promising intervention.

Introduction

Personalised treatments are interventions with a substantial impact on meaningful clinical outcomes, such as decreased dyspnea, reduced healthcare use, and reduced mortality for well defined subgroups of patients with a particular disorder. For example, provision of oxygen to patients with severe hypoxemia, lung volume reduction surgery for patients with heterogeneous emphysema and low exercise capacity, and possibly the use of bronchodilators and inhaled corticosteroids for symptomatic patients with frequent exacerbations could improve survival for well defined subgroups of patients with chronic obstructive pulmonary disease (COPD).

Emerging data suggest that non-invasive ventilation in patients with COPD and chronic hypercapnic respiratory failure could provide a similar clinical benefit to patients. The objective of this narrative review is to describe the current state of the practice of non-invasive ventilation for this patient population, provide a framework for understanding the benefits, and discuss potential future directions in its implementation.

Epidemiology

COPD prevalence estimates vary widely depending on the applied diagnostic criteria and ascertainment method. One study estimates that 174.5 million individuals worldwide had moderate to severe COPD in 2015. The global prevalence of COPD has increased from 10.7% in 1990, to 11.7% in 2010, and further to 13.1% in a report from 2019. These findings are in sharp contrast to the marked decline in global smoking prevalence by 27.2% in men and 37.9% in women since 1990 and highlight the prolonged course of COPD as well as the potential increasing role of other exposures and host factors to its development. In the US, 28.9 million individuals (13.5% of adults aged 20-79 years) are estimated to have been diagnosed with COPD by spirometry. Approximately one in 10 of these individuals has severe COPD characterised by a forced expiratory volume in 1 s (FEV₁) result of <50% of predicted.

By contrast, data are scant for the prevalence of chronic hypercapnic respiratory failure and COPD. In a study from Germany, the prevalence of arterial partial pressure of carbon dioxide (PaCO₂) of ≥50 mm Hg (roughly the threshold for considering non-invasive ventilation for domiciliary use) was found to be 9% in a group of 231 consecutive patients with severe COPD (FEV₁ <50%). Using the aforementioned prevalence estimates of severe COPD and elevated concentrations of arterial carbon dioxide, we estimate that approximately 260,000 patients with COPD may be considered for domiciliary non-invasive ventilation in the US.

Sources and selection criteria

We searched PubMed and Medline from database inception up to 20 May 2022 using two groups of the keywords "COPD and noninvasive ventilation and chronic ventilatory failure" and "COPD and domiciliary noninvasive ventilation" and retrieved a total of 1099 citations. We reviewed the abstracts of these citations and included them if they provided insight into non-invasive ventilation mechanisms of benefit, impact on clinical endpoints, economic and societal impact, patient selection, or future directions. We prioritized meta-analyses, systematic reviews, and large clinical trials but also included narrative

QUESTIONS FOR FUTURE RESEARCH

⇒ How should clinicians screen for suitable candidates for chronic hypercapnic respiratory failure and non-invasive ventilation among patients with chronic obstructive pulmonary disease? Does targeted screening help to improve outcomes?

⇒ What is the best method (protocol, location, and logistics) to titrate non-invasive ventilation settings?

⇒ Can high intensity ventilation be provided via devices without a backup rate?

⇒ How can information from device downloads be used to refine initial settings either directly or by telemedicine?
reviews, case series, and retrospective studies as appropriate. We used references from selected papers that were not in the initial search results if they provided additional insight.

Mechanisms of benefit and rationale of non-invasive ventilation

Respiratory symptoms of COPD originate from hyperinflation of the lungs due to emphysematous loss of elastic recoil and increased airflow resistance in small airways from inflammatory changes of chronic bronchitis. These parenchymal and airway changes result in mismatching of the lung ventilation and perfusion and in consequent gas exchange abnormalities. Hyperinflation, in turn, means that respiratory muscles have to operate at a shorter than optimal resting length. Consequently, respiratory muscles have chronic adaptations that include atrophy and a tendency for more slow twitch, high endurance fibre types. A disequilibrium between the elastic (hyperinflation) and resistive (narrowed, collapsible airways) loads and capacity to counteract these loads (respiratory pump function) result in respiratory failure.

Non-invasive ventilation involves the provision of positive airway pressure to augment inspiration. The positive airway pressure from the ventilator is provided via a mask interface placed on a patient’s face (figure 1). Although the exact mechanism of benefit is unknown in the setting of chronic hypercapnic respiratory failure, non-invasive ventilation can favorably impact several of these pathophysiological mechanisms. After the first night of non-invasive ventilation, patients with COPD have higher average tidal volumes (the amount of inspired and expired air with each respiratory cycle) compared with matched controls without non-invasive ventilation, despite cessation of assisted ventilation, throughout the day.\(^\text{17}\) This favorable breathing pattern of higher tidal volume and unchanged respiratory rate is maintained over six months. One explanation might be that ventilatory response to carbon dioxide inhalation after non-invasive ventilation is improved.\(^\text{18}\) Indeed, a strong correlation has been shown between the decrease in nocturnal PaCO\(_2\) during non-invasive ventilation and a heightened ventilatory response to carbon dioxide rebreathing.\(^\text{19}\) Windisch and colleagues showed persistent improvements in diurnal PaCO\(_2\) concentrations after non-invasive ventilation was applied with the goal of normocapnia.\(^\text{20}\) Normocapnia while on non-invasive ventilation was accompanied by sustained improvement in PaCO\(_2\) and bicarbonate concentrations while the patient was awake and off non-invasive ventilation. Functional respiratory imaging data suggest the recruitment of collapsed small airway units and improved ventilation or perfusion matching.\(^\text{21}\) Application of positive airway pressure at the airway opening could serve as a splint that abrogates a premature small airway closure, thereby improving exhalation. As such, several studies have shown non-invasive ventilation results in modest decreases in total lung capacity, residual volume\(^\text{19,22}\) and higher FEV\(_1\).\(^\text{22}\) Although these studies did not aim to determine exact onset and duration of the salutary changes in lung volumes, these effects seem to be evident as early as day five and persist through six to 12 months.\(^\text{19,22}\) Furthermore, non-invasive ventilation might improve lung edema, reduce a pro-inflammatory state, and enhance innate immunity,
most likely by facilitating the elimination of carbon dioxide, a signalling molecule that mediates adverse effects in the lung.\textsuperscript{23} The improvement in hyperinflation seems to correlate with the reduction in PaCO\textsubscript{2} concentrations.\textsuperscript{21} Non-invasive ventilation could allow respiratory muscle rest and reversal of muscle fatigue. Nonetheless, respiratory muscle strength appears unchanged when measured directly via electromagnetic phrenic nerve stimulation,\textsuperscript{18} in contrast to some studies that showed an improved performance in volitional indices, presumably due to motivational factors.\textsuperscript{17,24} A study from 2022 of 30 patients with COPD on non-invasive ventilation for a year showed an improvement in the thickening fraction of the diaphragm with a statistically significant change in hyperinflation indices, perhaps indicating improved function of the diaphragm.\textsuperscript{25} Figure 2 briefly summarises the pathophysiology of hyperinflation and potential salutary effects of non-invasive ventilation.

Benefits of non-invasive ventilation for hypercapnic respiratory failure

\textit{Individual perspective}

Randomized clinical trials that explore the usefulness of non-invasive ventilation for patients with COPD and chronic hypercapnic respiratory failure have been conducted and published since the early 90s. More recently, two meta-analyses,\textsuperscript{26,27} that used different methods for aggregation of data, arrived at similar conclusions regarding clinical benefits.

The first meta-analysis identified 21 randomized controlled trials and 12 observational studies that enrolled 51,085 patients with COPD and hypercapnia who used domiciliary non-invasive ventilation for more than a month.\textsuperscript{26} That study distinguished between bi-level positive airway pressure machines, with and without a backup rate, which typically deliver pressure targeted ventilation, and non-invasive home mechanical ventilators, which have pressure and volume targeting in addition to greater monitoring, alarm, and backup features. When the data for the two types of devices were aggregated and compared with no respiratory support, non-invasive ventilation was associated with lower risk of mortality (risk difference −5.53\% (95\% confidence interval −10.29\% to −0.76\%)), reduced all cause hospital admissions (−35.26\% (−49.39\% to −21.12\%)) and lower need for intubation risk difference −8.02\% (−14.77\% to −1.28\%). Of note, when the analysis was done with randomized controlled trials only, no difference was reported in clinical outcomes. This discordance might be caused by insufficient power or little heterogeneity of the populations studied in the individual randomized controlled trials. Only two observational studies compared non-invasive home mechanical ventilators with no device. Use of home mechanical ventilators was associated with fewer all cause

Figure 2 | Pathophysiology of hyperinflation and benefits of non-invasive ventilation. Hyperinflation diminishes the force output of the respiratory muscles by shortening muscle fibres and decreasing the zone of apposition of the diaphragm. Increased chest wall recoil at high lung volume adds to the increased work of breathing. Non-invasive ventilation provides inspiratory positive pressure to reduce the effort needed to breathe. Positive pressure can also help to splint narrowed, collapsible airways to improve lung emptying during exhalation reducing hyperinflation. Improved tidal volume, respiratory muscle rest, and improved muscle fibre dynamics could contribute to improved carbon dioxide elimination. These effects are sustained when off non-invasive ventilation presumably due to improved ventilatory response to carbon dioxide.
hospital admissions compared with no respiratory support, but no difference in mortality. In the 19 studies that enrolled patients with stable COPD, non-invasive ventilation was associated with a lower risk of mortality regardless of the device used (odds ratio 0.62 (95% confidence interval 0.42 to 0.92); P=0.02). No significant difference was reported for all cause hospital admissions, intubations, or quality of life. By contrast, when non-invasive ventilation was initiated in patients who had experienced a recent (within one month) COPD exacerbation, no mortality benefit or improvement in quality of life was reported compared with no device use, though a lower need for intubation and fewer all cause hospital admissions were noted.

In the second meta-analysis, 21 randomised controlled trials, encompassing 1142 patients, that investigated non-invasive ventilation for at least 5 h per night for three consecutive weeks or more were included and compared with standard care.27 The investigators obtained individual patient data from most of the clinical trials and conducted linear and cox regression mixed effect modeling as well as meta-analysis on aggregated clinical trial data. Among patients with stable COPD, non-invasive ventilation reduced PaCO₂ concentrations at three months and 12 months. Non-invasive ventilation was associated with low risk for all-cause mortality (adjusted hazard ratio 0.75 (95% confidence interval 0.58 to 0.97)). Among patients who received non-invasive ventilation in the setting of a recent (within 3 months) exacerbation, similar reductions in PaCO₂ concentrations were noted without any improvement in all-cause mortality. However, survival without admission to the hospital seemed to improve with non-invasive ventilation (adjusted hazard ratio 0.71 (95% confidence interval 0.54 to 0.94)).

The findings of these two meta-analyses should be interpreted with some caution. Most of the studies were unblinded. Implementation of non-invasive ventilation varied from study to study by different modes and intensity of ventilation, PaCO₂ thresholds for inclusion, duration of follow-up, relation to exacerbated disease state, and timing of initiation of non-invasive ventilation (in hospital v ambulatory).

From an individual patient’s perspective, non-invasive ventilation is well tolerated and adherence is high. In the three randomized controlled trials with one year follow-up, patients used the non-invasive ventilation device on the average 5.9, 28 6.3, 29 and 7.6 h/night.30 In a large observational cohort study of patients with chronic respiratory failure on non-invasive ventilation, researchers reported an average use of 6.5 h/night use among 334 patients with obstructive lung disease.31 Adherence ≥4 h/night was associated with a lower mortality. Perhaps counter-intuitively, adherence might be better when higher versus lower pressure settings are used.32 This could, in part, owe to patient perception of superior clinical benefits with higher pressure settings. Severe complications from domiciliary non-invasive ventilation have not been reported in clinical trials28–30 33 or real world studies.34–36 Non-invasive ventilation side effects included aerophagia, mask related pressure ulcers, mask intolerance, dry mouth, and shortness of breath on discontinuation of non-invasive ventilation. Overall, the side effects led to discontinuation in a minority of patients (<15%) in clinical trials. Various mask interfaces have been used to facilitate non-invasive ventilation in patients with COPD chronic hypercapnic respiratory failure. Although oronasal masks are more commonly used,37 one randomized crossover trial showed successful non-invasive ventilation delivery with both oronasal and nasal masks and heterogeneity of individual responses to mask type.38

While the meta-analyses concluded no effect of non-invasive ventilation on quality of life measures in the context of chronic hypercapnic respiratory failure and COPD, this conclusion could stem from the use of tools that have not been specifically validated for use in this particular patient population.39 Using the Severe Respiratory Insufficiency questionnaire, a tool validated for this patient group receiving non-invasive ventilation, significant28 30 or a strong trend29 toward improvements in quality of life have been shown in randomized controlled trials with one year follow-up.

**Economic and societal perspective**

Chronic hypercapnic respiratory failure and COPD carries a poor prognosis. In a query of electronic medical records, among 491 patients with compensated hypercapnia of various causes, with 170 (35%) having COPD, each 5 mm Hg increase in PaCO₂ was associated with an increased all cause mortality (hazard ratio 1.09; 95% confidence interval 1.03 to 1.16).40 Over the course of a year, these patients accounted for 1030 hospital admissions and 218 (44.4%) had ≥two hospital admissions. Therefore, implementing non-invasive ventilation in this context could reduce healthcare use and costs. In a retrospective study of the Medicare Limited Data Set (2012–18), patients with COPD and chronic hypercapnic respiratory failure who received non-invasive ventilation treatment experienced reduced risk of mortality (relative risk reduction 39%) and reduced hospital admissions (17%) compared with a matched cohort who did not have reductions.41 Furthermore, a cost effectiveness analysis, based on the results of a randomized controlled trial,30 showed a favorable incremental cost per quality adjusted life year of $50 856 (£42 406, €49 818) in the USA.42

Clearly, the burden of the evidence suggests a salutary effect for non-invasive ventilation in the setting of chronic hypercapnic respiratory failure and COPD. In the following sections, we provide the reader with general recommendations for some of the unresolved.
issues that surround non-invasive ventilation implementation.

Which patients with COPD would benefit from non-invasive ventilation?

Early data for the efficacy of non-invasive ventilation in patients with COPD and stable, chronic hypercapnia were not very encouraging. In 2013, a meta-analysis of seven randomized controlled trials encompassing 245 patients suggested benefits for patients who had higher PaCO₂ concentrations at baseline (≥55 mm Hg), who used nocturnal non-invasive ventilation ≥5 h per night and with high inspiratory positive airway pressure (≥18 cm H₂O). This general notion of patient selection for optimal outcomes guided the design of three randomized controlled trials of one year duration, which inform contemporary practice. The details of these clinical trials are summarized in Table 1.

In 2014, a randomized controlled trial by Köhnlein and colleagues recruited 195 patients who were stable but had severe COPD and a PaCO₂ concentration of ≥5.9 mm Hg without any other conditions that could cause hypercapnia. These individuals were randomly assigned to receive non-invasive ventilation, titrated during an elective hospital admission, and targeted to reduce baseline PaCO₂ concentration by 20% or more, or to reduce concentrations to ≥8.1 mm Hg versus standard of care. At the end of one-year follow-up, the group with patients who received non-invasive ventilation had lower mortality (12 of 102 (12%) vs 31 of 93 (33%)). In the same year, another randomized controlled study (RESCUE study) investigated a similar question among 201 patients with severe COPD but recruited patients during the hospital admission for acute respiratory failure. These patients had PaCO₂ concentrations of >52.5 mm Hg and received non-invasive ventilation using the highest tolerable inspiratory positive airway pressure with the goal of achieving normocapnia. In contrast to the Köhnlein study and despite achieving reduction in PaCO₂, the investigators found no improvement in time to readmission or death at one year. Interestingly, 26% of the patients in the control group had achieved normocapnia after three months, presumably due to resolution of acute disease. Finally, another randomized controlled trials reported the effect of non-invasive ventilation in a study (UK HOT-HMV trial) of 116 patients who had hypoxemia requiring home oxygen and persistent hypercapnia (PaCO₂ >5.1 mm Hg) as documented between two to four weeks after hospital admission for COPD related acute respiratory failure. After one year of follow-up, time to readmission or death within 12 months was significantly improved in the intervention group (63.4% vs 80.4%). The common thread between the three studies has been the recruitment of patients with severe COPD and with hypercapnia and non-invasive ventilation

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**Table 1 | Contemporary randomized controlled trials using high intensity non-invasive ventilation and one year follow-up**

| Clinical trial        | Participants | Baseline PaCO₂, pH | Ventilation target | Non-invasive ventilation settings | Primary outcome | Results | Comments |
|-----------------------|--------------|--------------------|--------------------|-----------------------------------|-----------------|---------|----------|
| Köhnlein et al 2014   | Stable GOLD stage IV COPD; n=195 | ≥5.1 mm Hg, pH<7.35 | Reduce baseline PaCO₂ by at least 20% or PaCO₂ ≥8.1 mm Hg | Mean IPAP 21.6 (SD 4.7) cm H₂O; EPAP 4.8 (SD 1.6) cm H₂O, backup rate 16.1 (SD 3.6) / min | Mortality at 1 year | Patients randomly assigned to non-invasive ventilation had lower mortality at 1 year (12% vs 33%); PaCO₂ reduced by 5.1% from baseline; overall improved quality of life indices | In-hospital titration for an average of 5.6 days; 14% facial rash due to mask |
| Struk et al 2014 (RESCUE) | Patients admitted to hospital for acute respiratory failure with COPD GOLD stage 3 or 4, recruited 48 h after stopping non-invasive ventilation; n=201 | ≥5.5 mm Hg | Normocapnia | Mean IPAP 19.2 (SD 3.4) cm H₂O; EPAP 4.8 (SD 1.0) cm H₂O, backup rate 15 (SD 3) / min | Hospital readmission and death at 1 year | No difference between non-invasive ventilation and standard of care (65% vs 64% readmitted or died); PaCO₂ reduced by 0.5 kPa (3.75 mm Hg); quality of life indices tended to improve with non-invasive ventilation (not significant) | 26% of 100 patients in the standard treatment group had normal PaCO₂ after 3 months |
| Murphy et al 2017 (HOT-HMV) | Patients with COPD admitted with acute decompensated hypercapnic exacerbation requiring non-invasive ventilation, 24 weeks after resolution of acute respiratory failure; n=116 | ≥5.5 mm Hg, pH<7.3 | High intensity non-invasive ventilation aiming for IPAP ≥25 cm H₂O | Mean IPAP 24 cm H₂O (IQR 22-26); EPAP 4 cm H₂O (IQR 4-5), backup rate 14/min (IQR 14-16) | Time to readmission or death | Median time to readmission or death was 4.3 months in non-invasive ventilation plus oxygen group v 1.4 months in the home oxygen alone group (adjusted HR 0.49, 95% CI 0.31 to 0.77), risk of readmission or death was lower in the non-invasive ventilation group (63.4% vs 80.4% absolute risk reduction 17.0%, 95% CI 0.1% to 34.0%) | — |
titrated to high inspiratory positive airway pressure to achieve near or complete normocapnia, the so-called high intensity non-invasive ventilation strategy. The other important insight was the potential advantage of starting non-invasive ventilation in the context of hypercapnia while in a stable state or persisting two to four weeks after resolution of an acute exacerbation.

An important subgroup to consider in the discussion of non-invasive ventilation is the obstructive sleep apnea and COPD overlap syndrome. These patients have been systematically excluded from most randomly controlled trials of non-invasive ventilation in the setting of chronic hypercapnic respiratory failure and COPD, although they might benefit particularly well from the intervention. Another important consideration is whether one should modify the positive airway pressure modality strategy to continuous positive airway pressure rather than non-invasive ventilation when obstructive sleep apnea is the predominant pathology in the overlap syndrome, akin to the recommendation in the obesity hypoventilation syndrome with severe sleep apnea, where continuous positive airway pressure rather than non-invasive ventilation is the first line option. Patients with the overlap syndrome have lower 5-year survival rates than those obstructive sleep apnea even when treated with continuous positive airway pressure. However, in a prospective cohort, continuous positive airway pressure treatment in patients with the overlap syndrome improved survival and decreased hospital admissions. Whether adding high intensity non-invasive ventilation strategy to adequate end-expiratory pressure to maintain airway patency would serve to improve outcomes in this group of patients is not known. When confronted with patients with obesity hypoventilation syndrome and COPD overlap, it might be challenging to determine the primary factor responsible for hypercapnic respiratory failure. Nonetheless, pragmatic goals relating to positive airway pressure treatment for obesity hypoventilation syndrome are similar to chronic hypercapnic respiratory failure and COPD and include correction of sleep hypoxemia, obstructive events and hypercapnia. In the absence of robust clinical trials in this population, the authors tend to use high intensity non-invasive ventilation when clinical evaluation points toward COPD as the biological cause for chronic hypercapnic respiratory failure, and positive airway pressure treatment when obesity hypoventilation syndrome or obstructive sleep apnea predominate.

How and when to implement non-invasive ventilation

High intensity non-invasive ventilation is a strategy that incorporates high inspiratory positive airway pressure with backup rate during nocturnal ventilation with the goal of achieving near or complete normocapnia. High intensity non-invasive ventilation affords greater reduction in PaCO₂ and surprisingly superior patient adherence than low intensity non-invasive ventilation. The non-invasive ventilation settings for achieving high intensity non-invasive ventilation for the three studies discussed above is summarized in Table 1. In all studies, inspiratory positive airway pressure was titrated higher as tolerated starting at 15-18 cm H₂O in pressure-limited modes and expiratory positive airway pressure titrated to abolish signs of upper airway obstruction or snoring. A backup rate was provided at 14-16/min or as tolerated. The need for a backup rate has been questioned in a small randomized study that found no significant difference in reduction of PaCO₂ between high intensity non-invasive ventilation with and without high back up rate.

While the clinical trials suggest accrued benefits when non-invasive ventilation is begun in a stable state or within two to four weeks of discharge from the hospital, practical factors typically force initiation while in the hospital in real life. In large surveys of practicing physicians, inability to wean in hospital non-invasive ventilation is a frequent reason for initiation at home and nearly half of all patients begin non-invasive ventilation during or immediately after an exacerbation. Similar concerns have prompted the Optimal Non-invasive Ventilation Medicare Access Promotion (ONMAP) panel in the US to recommend leaving the timing of initiation to the physician’s discretion. However, titration in hospital can be associated with increased length of stay and costs. For instance, in one randomised controlled trial, an average of 5.6 (standard deviation 1.1) days were needed for successful non-invasive ventilation titration. Acknowledging the complexities of initiation of non-invasive ventilation during outpatient clinics, the ONMAP panel advocated for frequent home visits by respiratory therapists or clinicians to make appropriate device adjustments. With improving telemedicine capabilities, initiation and titration are highly feasible in the ambulatory setting. To that end, a randomised study of home versus in hospital initiation and titration among 67 patients with COPD and stable hypercapnia reported non-inferiority in PaCO₂ concentration reduction and quality of life metrics. In this study, patients at home were closely monitored with transcutaneous PCO₂ measurements and ventilator settings were changed remotely. A nurse visit was required to install the equipment and educate the patient regarding the equipment. In the control group, in hospital non-invasive ventilation titration took seven days, considerably less than the 14.5 days required for at home initiation, nonetheless accounting for the significant cost difference between the groups.

Guidelines

Table 2 lists recent guideline documents that provide a useful perspective for clinicians. These documents are largely concordant with some nuances. All documents recommend the use of...
non-invasive ventilation for patients with COPD and chronic stable hypercapnia; two guidelines suggest the use of high intensity non-invasive ventilation (ie, near or complete normalization of PaCO₂). The ONMAP document endorses a specific threshold of PaCO₂ (≥52 mm Hg) to provide guidance for Medicare coverage determination. Although the European Respiratory Society and the ONMAP documents allow for clinician discretion for the initiation of non-invasive ventilation treatment around the time of the exacerbation (with a recommendation to reassess hypercapnia after two to four weeks), the American Thoracic Society endorses reassessment in two to four weeks (ie, near or complete normalization of PaCO₂). The ONMAP document endorses a specific threshold of PaCO₂.

**Table 2 | Clinical guidelines and recommendations on key issues relating to non-invasive ventilation for chronic obstructive pulmonary disease**

| Key issue                                                                 | European Respiratory Society guidelines | American Thoracic Society clinical practice guidelines | Optimal Non-Invasive ventilation Medicare Access Promotion guidelines |
|---------------------------------------------------------------------------|-----------------------------------------|--------------------------------------------------------|---------------------------------------------------------------------|
| Should patients with COPD and chronic hypercapnic respiratory failure receive non-invasive ventilation? | Yes; conditional, low certainty recommendation | Yes; conditional, moderate certainty recommendation | Yes |
| What is the threshold of PaCO₂, to determine candidacy for non-invasive ventilation in this population? | Not specified | Not specified | PaCO₂ ≥52 mm Hg on arterial blood gas while on prescribed oxygen |
| Should high intensity non-invasive ventilation be preferred over low intensity? | Yes; conditional, low certainty recommendation | Yes; conditional, low certainty recommendation | Not specified |
| Should non-invasive ventilation be started in-hospital during a COPD exacerbation with acute respiratory failure? | Possibly, consider reassessing after 2-4 weeks; conditional, low certainty evidence | No, reassess 2-4 weeks after initial episode; conditional, low certainty evidence | Timing should be left to clinician’s discretion |
| Should sleep apnea be evaluated prior to positive airway pressure initiation? | Not specified | Screening for sleep apnea recommended; conditional, very low certainty | Consider sleep apnea but formal testing not required |
| Should clinicians obtain a sleep study for titrating non-invasive ventilation? | Not specified | No; conditional recommendation, very low certainty | No |

COPD=chronic obstructive pulmonary disease. PaCO₂=arterial partial pressure of carbon dioxide.

**Future directions**

After three decades of research and accumulated real world data, non-invasive ventilation has established itself as an efficacious intervention for chronic hypercapnic respiratory failure and COPD. Notwithstanding, many aspects of the practice need further study. First, although high intensity ventilation is now an accepted goal, whether high pressure and a set respiratory rate combination is the only method to achieve this outcome is still unknown. Second, the value of mechanical ventilation modes with advanced targeting schemes need to be explored further. For instance, compared with bi-level positive airway pressure, a pressure limited and volume targeted mode was associated with similar physiological benefits but led to a faster in-hospital titration by nearly two days. Third, we need to expand and adjust out-of-hospital implementation of non-invasive ventilation. Best practice guidelines for titration of hyperventilation in the sleep center setting have excluded patients with COPD. Sleep laboratories and outpatient clinics could develop and test effective algorithms for non-invasive ventilation titration for patients with chronic hypercapnic respiratory failure and COPD. To this end, specially trained nurses and respiratory therapists will be highly instrumental in implementing domiciliary non-invasive ventilation programs. The so-called internet of things, a network of devices with sensors and interconnectivity, promises to provide real-time availability of data, monitoring of patient and device interaction, analysis, and bidirectional feedback between patients and providers. Smooth flow of information, including increasingly available device download data, should augur better algorithms that facilitate safe and faster ambulatory titration of treatment, as well as ongoing refinement of settings. Finally, non-invasive ventilation devices vary in features and such differences could potentially affect efficacy of the intervention. How the device handles leaks, triggering, pressurization of the circuit, cycling the breath, and alarm algorithms all contribute to optimal delivery of treatment and patient comfort.

**Conclusions**

Treatment of patients with COPD and chronic stable hypercapnia with non-invasive ventilation is associated with improvements in several clinical outcomes, including mortality. Clinicians should note that the intervention has only been shown to be beneficial when initiated in chronic stable state or during recuperation from a severe exacerbation. Patient selection, ideal device and ventilator mode to deliver treatment, and implementation of ambulatory non-invasive ventilation remain important areas of research. Meanwhile, internists should consider
screening patients with COPD for referral to specialized centers that provide this service. Although recurrent acute hypercapnic respiratory failure is the most frequent reason for referral, we should be reminded that this intervention might offer benefits to some patients with COPD who have stable chronic hypercapnic respiratory failure. Early consideration and implementation of non-invasive ventilation in these patients could potentially improve quality of life and reduce healthcare use.

**PATIENT INVOLVEMENT**

No patients were asked for input in the creation of this article.

**Contributors**

UH contributed to the conception and design of the work, drafted and critically revised for critically important intellectual content. LSA contributed to the conception and design of the work, drafted and revised for important intellectual content. UH and LSA (the guarantors) gave final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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