Ventilation of patients with asthma and chronic obstructive pulmonary disease
Yin Peigang, MD, and John J. Marini, MD

Ventilatory intervention is often life-saving when patients with asthma or chronic obstructive pulmonary disease (COPD) experience acute respiratory compromise. Although both noninvasive and invasive ventilation methods may be viable initial choices, which is better depends upon the severity of illness, the rapidity of response, coexisting disease, and capacity of the medical environment. In addition, noninvasive ventilation often relieves dyspnea and hypoxemia in patients with stable severe COPD. On the basis of current evidence, the general principles of ventilatory management common to patients with acutely exacerbated asthma/COPD are these: noninvasive ventilation is suitable for a relatively simple condition, but invasive ventilation is usually required in patients with more complex or more severe disease. It is crucial to provide controlled hypoventilation, longer expiratory time, and titrated extrinsic positive end-expiratory pressure to avoid dynamic hyperinflation and its attendant consequences. Controlled sedation helps achieve synchrony of triggering, power, and breath timing between patient and ventilator. When feasible, noninvasive ventilation often facilitates the weaning of ventilator-dependent patients with COPD and shortens the patient’s stay in the intensive care unit.

Even though the pathogenesis and clinical course of asthma and chronic obstructive pulmonary disease (COPD) differ, the management of both conditions is similar in many respects, especially with regard to ventilatory support. Medical therapies remain indispensable components in the treatment of asthma and COPD [1,2•], but mechanical ventilation often proves imperative when medical treatment fails to reverse the course of respiratory failure. This update focuses attention on recent progress in understanding rationales for ventilatory management, strategies for ventilation, adjunctive therapies to improve the efficiency of gas exchange, and outcomes of mechanical ventilation in patients with asthma/COPD.

Rationale for ventilatory support of stable but severe chronic obstructive pulmonary disease
Although the evidence is conflicting and far from definitive, noninvasive positive pressure ventilation (NPPV) is now considered for the patient with stable but severe COPD (eg, that characterized by CO₂ retention, nocturnal oxygen desaturation, or superimposed neuromuscular disease). The rationale is based on the following hypotheses:

Muscle resting hypothesis
Patients with severe COPD are usually in a state of chronic respiratory muscle compromise because of flattened diaphragm, accessory muscle recruitment, incomplete alveolar emptying at the end of expiration (dynamic hyperinflation) (intrinsic positive end-expiratory pressure: PEEPi), and inefficient configuration of the chest wall. Intermittent rest provided by NPPV in these patients alleviates overload, thereby improving inspiratory muscle strength, ventilatory capacity, and arterial blood gases [3•].

Sleep hypothesis
Even after patients with frank obstructive sleep apnea are excluded from consideration, patients with severe COPD have a high prevalence of sleep-disordered breathing, characterized by frequent desaturation and episodic hypoventilation. These phenomena are closely linked to nocturnal worsening of CO₂ retention. It is hypothesized that nocturnal NPPV alleviates sleep-disordered breathing and thereby improves daytime functioning and the overall sense of well-being [5•].
Rationale for ventilation of exacerbated asthma and chronic obstructive pulmonary disease

Dynamic pulmonary hyperinflation is a characteristic feature common to patients with acutely exacerbated asthma/COPD. The major causes of dynamic pulmonary hyperinflation are increased ventilatory requirement, a prolonged expiratory time constant (resulting from airway obstruction caused by inflammation, mucus plugging, and bronchospasm, with or without reduced elastic recoil) [4], and shortened expiratory time [5]. The inspiratory threshold load for breath initiation and the work of breathing are remarkably increased in consequence (see Fig. 1 in [6•]). It is important, therefore, to relieve or control dynamic hyperinflation in designing the strategy of mechanical ventilation.

The capacity of the respiratory muscles to generate inspiratory pressure is limited by decreased operating length and impaired geometric arrangement [7•,8,9]. Long-term steroid use and/or malnutrition also contributes to strength impairment in many patients with severe chronic disease [10].

In addition, blunted respiratory drive may decrease responsiveness to hypoxia and hypercapnia in patients who experience near-fatal exacerbations of asthma/COPD [11], encouraging respiratory acidosis. The impaired perception of dyspnea further limits the patient’s capability to respond to the stress of severe asthma [12]. Blunted perception of breathlessness also could delay the search for treatment and precipitate a life-threatening situation [13]. In this setting, mechanical ventilation can assist or support impaired ventilatory function, reduce the work of breathing, allow needed muscle rest, facilitate sleeping, and improve gas exchange, allowing time for restoration of ventilatory function through treatment of either the underlying disease or the precipitating causes of acute decompensation.

At the bedside, dynamic hyperinflation is typically detected by noting end-expiratory flow or measuring end-expiratory pressure. Precise quantitation of the degree of dynamic pulmonary hyperinflation is more problematic, however, especially in patients who make spontaneous breathing efforts. The measurement of hyperinflation, a complex topic within itself, is outside the scope of this overview. The reader is referred to the recent reviews by Gladwin and Pierson [14] and by Jain et al. [15] on this topic.

Ventilatory strategy for patients with severe chronic obstructive pulmonary disease at stable stage

In 1999, a consensus conference convened by the National Association for Medical Direction of Respiratory Care [16] described the indications for NPPV in severe COPD (Table 1).

### Table 1. Indications for noninvasive positive pressure ventilation for stable severe chronic obstructive pulmonary disease

<table>
<thead>
<tr>
<th>Symptom(s)</th>
<th>Physiologic criteria (one of the following)</th>
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<tr>
<td>Symptoms such as fatigue, dyspnea, morning headache</td>
<td>PaCO₂ ≥ 55 mm Hg</td>
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<tr>
<td>PaCO₂ of 50 to 54 mm Hg and nocturnal desaturation (oximeter ≥ 88% for 5 continuous minutes while receiving oxygen therapy ≥ 2 L/min)</td>
<td>PaCO₂ of 50 to 54 mm Hg and hospitalization related to recurrent episodes of hypercapnic respiratory failure (≥ 2 in a year)</td>
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</table>

Data from [16].

NPPV can provide the patient with stable severe COPD with intermittent respiratory muscle rest [17] or improve nocturnal gas exchange [18]. Several ventilation modes are currently used to deliver NPPV through nasal or facial masks: bilevel positive airway pressure [19], pressure support, and volume preset ventilation [20]. Bilevel positive airway pressure, the most popular of these options, has been reported to be more effective than volume preset ventilation in providing inspiratory muscle rest and reducing dyspnea [19].

Proportional assist ventilation (PAV) (also known as proportional pressure support) is a newly available mode proposed for use in the patient with COPD. A recent study by Dolmage and Goldstein [21] showed that PAV combined with continuous positive airway pressure significantly increased the duration of high-intensity exercise among patients with COPD and achieved greater benefit than either PAV or continuous positive airway pressure alone. Ambrosino et al. [22] applied PAV in patients with stable hypercapnic respiratory insufficiency, demonstrating that different settings of nasal PAV are well tolerated and may improve gas exchange and dyspnea.

Although facial masks have more dead space than their nasal counterparts, they are usually preferable for dyspnic patients, who tend to breathe with the mouth open. Ventilation has been shown to be better through the full-face mask than the nasal mask, irrespective of ventilatory modes [23].

Noninvasive ventilator settings are adjusted to provide comfort and maximize gas exchange. Interestingly, recent data suggest that noninvasive pressure support ventilation (PSV) is effective in improving arterial blood gases and in unloading inspiratory muscles, independently of whether it is set on the basis of the patient’s comfort and improved arterial blood gases or tailored to a patient’s respiratory muscle effort and mechanics. However, setting the levels of PSV and PEEP by invasive evaluation of lung mechanics and respiratory muscle function may reduce the number of ineffective inspiratory efforts [23].

The short-term benefits of NPPV are easier to document than the long-term benefits. Indeed, the efficacy of
NPPV in stable COPD has been doubted by some investigators. In a randomized, crossover design study lasting 4 weeks, Lin [25] compared oxygen inhalation alone with oxygen-supplemented NPPV in patients with severe COPD. NPPV plus oxygen and oxygen monotherapy had similar effects on arterial blood gases and heart function, but NPPV tended to disturb sleep to a greater extent. Oxygen monotherapy also appears to be more effective than ventilation assist in improving SaO₂ [24]. Casanova et al. [26•] conducted a prospectively randomized, controlled study lasting 1 year to evaluate the efficacy of NPPV plus long-term oxygen therapy in patients with severe COPD. They did not detect that NPPV had favorable effects on frequency of acute exacerbations, hospital admission, or intubation. However, NPPV did tend to relieve dyspnea, even if it failed to change the natural course of severe COPD.

**Ventilatory strategies for exacerbations of asthma and chronic obstructive pulmonary disease**

When the patient with exacerbated asthma/COPD does not respond to all appropriate medical therapy, mechanical ventilation must be promptly established. There are two ways to do this: NPPV and invasive positive mechanical ventilation (IPMV) [14,27]. Clinical trials demonstrate that early use of NPPV can reduce the need for invasive mechanical ventilation, not only for the patients with exacerbated COPD but also for those with status asthmaticus [28,29]. A theoretical model analysis suggests that NPPV is more cost-effective than standard therapy alone for well-selected patients with acute exacerbation of COPD [30]. Yet, although NPPV now seems to be recognized as a desirable option for many patients with acute respiratory failure caused by asthma or COPD [31,32], early intervention and moderate severity are keys to success [29], and certain patients should be carefully excluded (Table 2). Moreover, even if NPPV is initially successful, it may eventually fail; Moretti et al. [33] reported that approximately 20% of patients with COPD treated with NPPV eventually decompensated after 48 hours of initial success. Such patients have a poor in-hospital prognosis, particularly if NPPV is kept going.

The indications for intubation and invasive mechanical ventilation are given in Table 2.

**Table 2. Indications for intubation and invasive mechanical ventilation**

<table>
<thead>
<tr>
<th>Cardiac or respiratory arrest</th>
<th>Blunted consciousness or agitation</th>
<th>Overt pneumonia</th>
<th>Obstructed upper airway</th>
<th>Copious sputum or cough reflex disturbance</th>
<th>Concomitant disorders</th>
<th>Severe encephalopathy</th>
<th>Severe upper gastrointestinal hemorrhage</th>
<th>Hemodynamic instability or cardiac arrhythmia</th>
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Data from [26•, 33–35].

**Principles of mechanical ventilation in severe airflow obstruction**

As already noted, minimization of dynamic hyperinflation is a key objective of ventilatory support. To this end, several principles have emerged from recently published work in treating patients with asthma/COPD who require mechanical ventilation.

**Provide controlled hypoventilation**

Minute volume, expiratory time fraction, and severity of airflow narrowing are primary determinants of dynamic hyperinflation. Assuming that all appropriate measures to improve airflow obstruction have already been taken, the most effective measure to decrease dynamic hyperinflation is to reduce minute volume, which at a fixed inspiratory time fraction lessens the expiratory flow requirement, allowing the lung to decompress and the peak static lung pressures (plateau pressures) to decline. Adequate sedation and analgesia are the first steps in lowering the production of CO₂. Unless minute volume falls entirely on the basis of reduced ventilatory requirement, however, reducing minute ventilation by machine adjustments of tidal volume, frequency, or set pressure unavoidably leads to further retention of CO₂. The hypercapnia and acidosis are generally well tolerated; maintaining pH above 7.20 is considered acceptable by most researchers [15,36,37] if such levels of hypoventilation are needed to keep plateau pressure below 30 cm H₂O.

**Prolong expiratory time**

Apart from using a lower respiratory rate, expiratory time can be prolonged by using a higher peak inspiratory flow setting (70–100 L/min) or a shorter inspiratory time fraction, and by eliminating inspiratory pause time. Within a broad range, however, lengthening of the expiratory period is only modestly effective if minute ventilation remains the same.

**Unload breathing effort**

As a marker of dynamic hyperinflation, auto-PEEP (PEEP,) is found universally in exacerbated asthma/COPD [15]. Appendini et al. [38] demonstrated that 41% of inspiratory muscle effort was expended to overcome PEEP in patients with COPD during spontaneous breathing. In this specific setting, adding PEEP (extrinsic PEEP: PEEPₐ) helps to negate the expiratory pressure gradient between alveolus and airway, attenuating the inspiratory muscle effort needed to trigger inspiration and improving patient-ventilator interaction. PEEPₐ must be titrated individually, with an average of 80% of the measured PEEP tolerated without an increase of total PEEP or plateau pressure [14,39•]. Although there are many individual exceptions, asthmatic patients tend to be less responsive to this stratagem. As was shown more than 12 years ago by Tuxen et al. [40], PEEP often adds to (rather than replaces) auto-PEEP in patients with asthma. If PEEPₐ is set higher than PEEP, it may...
worsen the dynamic hyperinflation. Moreover, measurement of end-expiratory “port occlusion” pressure may seriously underestimate the alveolar pressures behind airways that are occluded by mucus or otherwise sealed at end expiration [41]. For this reason, plateau pressure during volume-targeted ventilation, or tidal volume during pressure-targeted ventilation, are the preferred monitors of the effect of PEEP on auto-PEEP.

**Promote synchrony between patient and ventilator**

Under the stress of the disease, most patients take shallow quick breaths and become agitated shortly after intubation because of dyspnea and the discomfort of invasive ventilation. There are few objective data to recommend which agents, combinations, or protocols are best. Benzodiazepines (diazepam, lorazepam, midazolam), often given with narcotics, are widely accepted therapy [37]. Over the long term, a clinician must be aware of problems related to tolerance, dependence, and unintended drug accumulation that prolong ventilator dependence [42]. Once-daily interruption of scheduled sedative medications helps to avoid the latter error.

Neuromuscular blocking agents should be used only for short periods and only as absolutely necessary in an attempt to achieve synchrony in patients with asthma. The use of these agents may cause diffuse muscle weakness that persists long after reversal of respiratory failure and discharge from the hospital [43]. The high-dose steroids that are universally used in asthma (and often in COPD) add to the neuromuscular risk. New data provided by Behbehani et al. [44] indicated once again that 30% of patients with near-fatal asthma who were given neuromuscular blocking agents experienced acute myopathy. Furthermore, the duration of the therapy (>24 hours) was the only independent predictor of myopathy. Therefore, if these agents must be used, muscle relaxation time is best limited to 24 hours or less and monitored closely to prevent total blockade.

**Pharmaceutical therapies**

New recommendations from the American College of Chest Physicians and the American College of Physicians–American Society of Internal Medicine propose that it is reasonable and beneficial to administer inhaled anticholinergic bronchodilators and short-acting β2 agonists, to administer systemic corticosteroids for up to 2 weeks, and to give narrow-spectrum antibiotics in moderate or severe acute exacerbations of COPD. Mucolytic medications, chest physiotherapy, and methylxanthine bronchodilators are not advised [1,45]. For severely asthmatic patients with respiratory failure, intensive doses of β2 agonists, systemic corticosteroids, and oxygen are first-line options; anticholinergics, methylxanthines, magnesium sulfate, and heliox have been recognized as second line choices [46•]. In addition, antileukotrienes have been recently recommended as a supplemen-

tary agent in combination with other asthma medications at all levels of disease severity [47], but the definite benefits of antileukotrienes have not been documented in patients with severe asthma.

**Heliox**

Heliox, a blended gas of helium and oxygen (usually in a 70:30 ratio), has a lower density than oxygen-enriched air, permitting higher flow rates through a given airway segment for the same driving pressure. In theory, therefore, heliox may help alleviate dynamic hyperinflation in patients with severe airflow obstruction, and some data suggest that it may do so. Kass et al. [48] reported a rapid reduction of airflow obstruction and dyspnea score in patients receiving heliox therapy by mask. Other investigations, however, showed that short-term inhalation of heliox by mask did not reduce either dyspnea scores in children [49] or peak expiratory flow rates in adults with acute asthma [50].

Jolliet et al. [51] applied heliox to patients with exacerbated COPD by NPPV, reporting significantly decreased dyspnea scores, PaCO₂, and shortened inspiratory time. These results implied that this combination may be able to reduce the need for intubation. Similarly, Tassaux et al. [52•] supplied heliox through an invasive ventilatory system, demonstrating that 70:30 heliox can dramatically reduce trapped lung volume, PEEPi, and peak and mean airway pressures. There were no significant changes in hemodynamics or arterial blood gases. However, because of apparent methodologic errors in the study, such positive results must be considered unverified. Although simple enough when given by mask, heliox is technically challenging to use during mechanical ventilation because it may influence measured flows and tidal volume. Its prospective value for exacerbated air flow obstructive disorders is not only questionable on this basis but is cumbersome to deploy and very costly [53].

**Weaning**

Patients with COPD who require mechanical ventilation generally have greater dependence on ventilators than do those with asthma. In addition to an excessive workload and the weakened pressure-generating capacity of inspiratory muscles [54,55], tracheal obstruction may be an important factor prolonging ventilator dependence [56]. According to reports from two specialized weaning units, only 22 to 35% of patients with COPD could be liberated eventually from the ventilator, and 19% of those remained partially dependent on the ventilator [57,58].

Some commonly used weaning indices, like the rapid shallow breathing index, seem to be only imperfect indicators for clinical decision making in patients with COPD because 56% of the patients with rapid shallow
breathing indexes <80 breaths/min/L failed the weaning trial [55]. In one study, the patient’s estimated overall condition bore a closer relation to successful ventilator removal than did some known and quantifiable indexes [59]. With regard to weaning method, there is general agreement that a single trial of unassisted breathing should be attempted each day, with adequate rest afterward. The T-piece trial during 120 minutes appears to be an unreliable way for weaning patients with COPD who are slow to improve [60•], even though in other situations it is recognized to be effective [61]. In a controlled randomized trial, Vitacca et al. [60•] reported that either a spontaneous breathing trial or a gradual decrease in the level of PSV held similar benefits for the liberation of patients with COPD who required mechanical ventilation for more than 15 days.

Another way to facilitate weaning is to make use of NPPV as a “bridge” to independent breaths [62]. In an important study by Nava et al. [63], patients were first supported in their ventilation for 48 hours and then were treated conservatively or extubated and shifted to NPPV after a failed T-piece trial. A multicenter randomized trial that compared NPPV after extubation against conventional weaning with PSV showed that weaning success was higher in the NPPV group (88% vs 68%). This bridging technique using NPPV appears to shorten weaning time and length of stay in the intensive care unit, to reduce the incidence of concurrent nosocomial pneumonia, and increase the 60-day survival rate.

Complications
Patients with asthma/COPD who undergo positive pressure mechanical ventilation are as likely as other patients receiving the same treatment to experience ventilation-related complications. Nosocomial pneumonia [64], deep venous thrombosis, gastrointestinal bleeding [65,66], and gastric insufflation [67] are distressingly common, especially in patients receiving NPPV [7•]. The severity of dynamic pulmonary hyperinflation correlates with the additional risk of barotrauma and hemodynamic disturbances in the patient with asthma and COPD. This topic has been emphasized in the reviews by Gladwin and Pierson [14] and by Sethi and Siegel [68•].

Outcome
In a prospective cohort study of 1016 adult patients with exacerbations in five hospitals, Connors et al. [69] reported that 38% of inpatients who needed IPMV experienced a decreased survival rate (57%) at 180 days. The patients’ prognosis independently predicted by severity of the disease measured by Acute Physiology and Chronic Health Evaluation (APACHE) III, age, body mass index, previous function status, PaO2/FiO2, congestive heart failure, serum albumin, and presence of cor pulmonale. Surprisingly, pH and PCO2 had no independent relation to survival. Unfortunately, this article did not provide more information about results related to IPMV. Other data showed that nocturnal NPPV or treatment with IPMV did not change the long-term survival of patients with COPD [70,71]. The data from weaning units describe another picture: 42% of the patients with COPD in a weaning unit became partially or completely ventilator dependent, and 23% of them died there [55].

Only a few investigations of the prognosis of asthmatic patients receiving IPMV have appeared in recent years. Tan et al. [72] reported that 19% of 93 patients with near-fatal asthma (defined as severe and unresponsive asthma) who were given IPMV died in the hospital. After discharge from the hospital, another 17% of the patients succumbed to asthma attacks over the long term, even though they received comprehensive medical care.

Conclusions
Mechanical ventilatory support plays a crucial role in the management of severe airflow obstruction, especially when the patients confront life-threatening respiratory failure. Recent evidence suggests that mechanical ventilation applied noninvasively also benefits patients with severe but stable COPD. NPPV also appears to be the best initial choice for most acute obstructive exacerbations of moderate severity, but intubation is preferred for patients with complications, such as those who are obtunded, intolerant of the NPPV interface, or unable to clear their airway secretions. Effective ventilatory strategies minimize dynamic hyperinflation by controlled hyperventilation, prolonged expiratory time, and well-synchronized spontaneous breathing.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
- Of special interest
- Of outstanding interest
A compendium of recommended treatments for COPD patients with acute respiratory failure, based on major clinical research from the past three decades.
This article provides a thorough review of the rationale and application of NPPV in patients with severe but stable COPD.
This article objectively evaluates the effects of NPPV on acute respiratory failure and reaches a broad consensus on how to deliver it in a clinical situation.
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A review focused on dysfunction of inspiratory muscles in patients with COPD and on therapeutic methods in clinical practice.


A randomized controlled trial evaluating two settings (usual and physiologic) of NPPV for the stable but hypercapnic patient with COPD. Both had a similar impact on arterial blood gases and unloading inspiratory muscles, but physiologic setting and PEEP, may decrease ineffective inspiratory efforts.


A prospective randomized study to compare NPPV plus standard therapy and standard therapy alone on patients with severe COPD during 1 year showed that NPPV did not change the natural course of the disease but could relieve dyspnea.


This clinical trial demonstrated that when PEEP gradually increased from 0 to 15 cm H2O in 10 COPD patients with invasive mechanical ventilation, work of breathing decreased from 15.1 ± 5.7 cm H2O to 10.4 ± 2.8 cm H2O x 1. End-expiratory lung volume did not change.


A recent review of administration and strategies, including medical therapies and mechanical ventilation, for asthmatic patients with respiratory failure.


52 Tassaux D, Jollet P, Roseler J, et al.: Effects of heliox-oxygen on intrinsic positive end-expiratory pressure in intubated and mechanically ventilated pa
A prospective study of 23 paralyzed intubated patients with COPD showed that heliox (70:30) could dramatically relieve PEEPi, end-expiratory lung volume, and airway pressure but did not affect hemodynamics or arterial blood gases.


A prospective multicenter randomized controlled study declared that PSV and spontaneous breathing trial had equal effects on weaning a patient with COPD, if guided by a well-designed protocol.


