Ventilation of patients with asthma and chronic obstructive pulmonary disease

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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. Curr Opin Crit Care 2002, 8:70–76 © 2002 Lippincott Williams & Wilkins, Inc.

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Abbreviations

COPD	chronic obstructive pulmonary disease
IPMV	invasive positive mechanical ventilation
NPPV	noninvasive positive pressure ventilation
PAV	proportional assist ventilation
PEEP	positive end-expiratory pressure
PEEP$_e$	extrinsic PEEP
PEEP$_i$	intrinsic PEEP
PSV	pressure support ventilation

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 CO_2 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: PEEP$_i$), 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 CO_2 retention. It is hypothesized that nocturnal NPPV alleviates sleep-disordered breathing and thereby improves daytime functioning and the overall sense of well-being [3•].

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

Symptoms such as fatigue, dyspnea, morning headache
Physiologic criteria (one of the following)
  $PaCO_2$ ≥55 mm Hg
  $PaCO_2$ of 50 to 54 mm Hg and nocturnal desaturation (oximeter ≤88% for 5 continuous minutes while receiving oxygen therapy ≥2 L/min)
  $PaCO_2$ of 50 to 54 mm Hg and hospitalization related to recurrent episodes of hypercapnic respiratory failure (≥2 in a year)

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 dyspneic 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 SaO_2 [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 of 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

Cardiac or respiratory arrest
Blunted consciousness or agitation
Overt pneumonia
Obstructed upper airway
Copious sputum or cough reflex disturbance
Concomitant disorders
Severe encephalopathy
Severe upper gastrointestinal hemorrhage
Hemodynamic instability or cardiac arrhythmia

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 airway 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 CO_2. 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 CO_2. 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 H_2O.

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 ($PEEP_i$) is found universally in exacerbated asthma/COPD [15]. Appendini et al. [38] demonstrated that 41% of inspiratory muscle effort was expended to overcome $PEEP_i$ in patients with COPD during spontaneous breathing. In this specific setting, adding PEEP (extrinsic PEEP: $PEEP_e$) 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. $PEEP_e$ must be titrated individually, with an average of 80% of the measured $PEEP_i$ 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 $PEEP_e$ is set higher than $PEEP_i$, 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 β-2 agonists, to administer systematic 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 β-2 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 been recommended as a supplementary 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, $PaCO_2$, 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, $PEEP_i$, 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, PaO_2/FiO_2, congestive heart failure, serum albumin, and presence of cor pulmonale. Surprisingly, pH and PCO_2 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 hypoventilation, 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

1   Roche N, Huchon GJ: Current issues in the management of chronic obstructive pulmonary disease. Respirology 1997, 2:215–229.

2   McCrory MD, Brown C, Gelfand SE, et al.: Management of acute exacerba-
•   tion of COPD: a summary and appraisal of published evidence. Chest 2001, 119:1190–1209.
A compendium of recommended treatments for COPD patients with acute respiratory failure, based on major clinical research from the past three decades.

3   Hill NS: Noninvasive ventilation in chronic obstructive lung disease. Clin
•   Chest Med 2000, 21:783–797.
This article provides a thorough review of the rationale and application of NPPV in patients with severe but stable COPD.

4   Djukanovic R, Roche WR, Wilson JW, et al.: Mucosal inflammation in asthma. Am Rev Respir Dis 1989, 139:242–246.

5   Rossi A, Ganassini A, Polese G et al.: Pulmonary hyperinflation and ventilator-dependent patients. Eur Respir J 1997, 10:1663–1674.

6   Evan TW: International Consensus Conferences in Intensive Care Medicine:
•   noninvasive positive pressure ventilation in acute respiratory failure. Organized jointly by the American Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Societe de Reanimation de Langue Francaise and approved by the ATS Board of Directors, December 2000. Intensive Care Med 2001, 27:166–178.
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.

7   Marchand E, Decramer M: Respiratory muscle function and drive in chronic
•   obstructive pulmonary disease. Clin Chest Med 2000, 21:679–692.

A review focused on dysfunction of inspiratory muscles in patients with COPD and on therapeutic methods in clinical practice.

8   Decramer M, Derom E, Gosselink R: Respiratory muscle mechanics in chronic obstructive pulmonary disease and acute respiratory failure. In Acute Respiratory Failure in Chronic Obstructive Pulmonary Disease. Edited by Derenne JP, Whitelaw WA, Similowski T. New York: Marcel Dekker; 1996:92:47–64

9   Decramer M, Macklem PT: Pressures developed by the respiratory muscles. In The Thorax. Edited by Roussos C. New York: Marcel Dekker; 1995:1099–1126.

10   Perez TLA, Becquart B, Stach B, et al.: Inspiratory muscle strength and endurance in steroid-dependent asthma. Am Rev Respir Dis 1996;153:610–615.

11   Kikuchi Y, Okabe S, Tamura G, et al.: Chemosensivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994, 330:1329–1334.

12   in't Veen JCCM, Smith HH, Ravensberg AJJ, et al.: Impaired perception of dyspnea in patients with severe asthma: relation to sputum eosinophils. Am J Respir Crit Care Med 1998, 158:1134–1141.

13   Hida W: Role of ventilatory drive in asthma and chronic obstructive pulmonary disease. Curr Opin Pulm Med 1999, 5:339–343.

14   Gladwin MT, Pierson DJ: Mechanical ventilation of the patient with severe chronic obstructive pulmonary disease. Intensive Care Med 1998, 24:898–910.

15   Jain S, Hanania NA, Guntupally KK: Ventilation of patients with asthma and obstructive lung disease. Crit Care Clin 1998, 14:685–705.

16   Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation: a consensus conference report. Chest 1999, 116:521–534.

17   Kyroussis D, Polkey MI, Hamnegard CH, et al.: Respiratory muscle activity in patient with COPD walking to exhaustion with and without pressure support. Eur Respir J 2000, 15:649–655.

18   Krachman SL, Quaranta AJ, Berger TJ, et al.: Effects of noninvasive positive pressure ventilation on gas exchange and sleep in COPD patients. Chest 1997, 112:623–628.

19   Lien TC. Wang JH, Huang SH, et al.: Comparison of bilevel positive airway pressure and volume ventilation via nasal or facial masks in patients with severe, stable COPD. Chin Med J (Taipei) 2000, 63:542–551.

20   Perrin C, Ei Far Y, Vandenbos, F et al.: Domiciliary nasal intermittent positive pressure ventilation in severe COPD: effects on lung function and quality of life. Eur Respir J 1997, 10:2835–2839.

21   Dolmage TE, Goldstein RS: Proportional assist ventilation and exercise tolerance in subjects with COPD. Chest 1997, 111:948–954.

22   Ambrosino N, Vitacca M, Polese G, et al.: Short-term effects of nasal proportional assist ventilation in patients with chronic hypercapnic respiratory insufficiency. Eur Respir J 1997, 10:2829–2834.

23   Naralesi P, Fanlulla F, Frigerio P, et al.: Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of mask in patients with chronic hypercapnic respiratory failure. Crit Care Med 2000, 28:1785–1790.

24   Vitacca M, Nava S, Confalonieri M, et al.: The appropriate setting of noninva-
•   sive pressure support ventilation in stable COPD patients. Chest 2000, 118:1286–1293.
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$_e$ may decrease ineffective inspiratory efforts.

25   Lin CC: Comparison between nocturnal nasal positive pressure ventilation combined with oxygen therapy and oxygen monotherapy in patients with severe COPD. Am J Respir Crit Care Med 1996, 154:353–358.

26   Casanova C, Celli BR, Tost L, et al.: Long-term controlled trial of nocturnal
•   nasal positive pressure ventilation in patients with sever COPD. Chest 2000, 118:1582–1590.
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.

27   Levy BD, Kitch B, Fanta CH: Medical and ventilatory management of status asthmaticus. Intensive Care Med 1998, 24:105–117.

28   Fernandez MM, Villagra A, Blanch L, et al.: Non-invasive mechanical ventilation in status asthmaticus. Intensive Care Med 2001, 27:486–492.

29   Plant PK, Owen JL: Early use of non-invasive ventilation for acute exacerba-

tions of chronic obstructive pulmonary disease on general respiratory wards: a multicenter randomized controlled trial. Lancet 2000, 355:1931–1935.

30   Keenan SO, Gregor J, Sibbbald WJ, et al.: Noninvasive positive pressure ventilation in the setting of severe, acute exacerbation of chronic obstructive pulmonary disease: more effective and less expensive. Crit Care Med 2000, 28:2094–2102.

31   Meduri GU, Cook TR, Turner RE, et al.: Noninvasive positive pressure ventilation in status asthmaticus. Chest 1996, 110:767–774.

32   Keenan SP, Kernerman PD, Cook DJ, et al.: Effects of noninvasive positive pressure ventilation on mortality in patient admitted with acute respiratory failure: a meta-analysis. Crit Care Med 1997, 25:1685–1692.

33   Moretti M, Cilione C, Tampiery A, et al.: Incidence and causes of non-invasive mechanical ventilation failure after initial success. Thorax 2000, 55:819–825.

34   Antonelli M, Conti G: Noninvasive positive pressure ventilation as treatment for acute respiratory failure in critically ill patients. Crit Care 2000, 4:15–22.

35   Zuege DJ, Whitelaw WA: Management of acute respiratory failure in chronic obstructive pulmonary disease. Curr Opin Pulm Med 1997, 3:190–197.

36   Hananel JI: Critical care management of the asthmatic patient. Curr Opin Pulm Med 1998, 4:4–8.

37   Leatherman JW: Mechanical ventilation in obstructive lung disease. Clin Chest Med 1996, 17:577–590.

38   Appendini L, Purro A, Patessio A, et al.: Partitioning of inspiratory muscle workload and pressure assistance in ventilator-dependent COPD patients. Am J Respir Crit Care Med 1996, 154:1301–1309.

39   Guerin C, Milic-Emili J, Fournier G: Effect of PEEP on work of breathing in
•   mechanically ventilated COPD patients. Intensive Care Med 2000, 26:1207–1214.
This clinical trial demonstrated that when PEEP$_e$ gradually increased from 0 to 15 cm H_2O in 10 COPD patients with invasive mechanical ventilation, work of breathing decreased from 15.1 ± 5.7 cm H_2O to 10.4 ± 2.8 cm H_2O × 1. End-expiratory lung volume did not change.

40   Tuxen DV: Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis 1989, 140:5–9.

41   Leatherman JW, Ravenscraft SA: Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. Crit Care Med 1996, 24:541–546.

42   Puntillo K, Casella V, Reid M: Opioid and benzodiazepine tolerance and dependence: application of theory to critical care practice. Heart Lung 1997, 26:317–324.

43   Leatherman JW, Fluegel WL, David WS, et al.: Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 1996, 153:1686–1690.

44   Behbehani NA, Al-Mane F, D'yachkova Y, et al.: Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. Chest 1999, 115:1627–1631.

45   Snow V, Lascher S, Mottur-Pilson C, et al.: The evidence base for management of acute exacerbation of COPD: clinical practice guideline, Part I. Chest 2001, 119:1185–1189.

46   Gluckman TJ, Corbridge T: Management of respiratory failure in patients with
•   asthma. Curr Opin Pulm Med 2000, 6:79–85.
A recent review of administration and strategies, including medical therapies and mechanical ventilation, for asthmatic patients with respiratory failure.

47   Nathan RA, Kemp JP: Efficacy of antileukotriene agents in asthma management. Ann Allergy Asthma Immunol 2001, 86(5suppl1:9–17.

48   Kass JE, Terregino CA: The effect of heliox in acute severe asthma: a randomized controlled trial. Chest 1999, 116:296–300.

49   Carter LER, Webb CCR, Moffitt CER, et al.: Evaluation of heliox in children hospitalized with acute severe asthma: a randomized crossover trial. Chest 1996, 109:1256–1261.

50   Henderson SO, Acharya P, Kilaghbia T, et al.: Use of heliox-driven nebulizer therapy in the treatment of acute asthma. Ann Emerg Med 1999, 33:141–146.

51   Jolliet P, Tassaux D, Thouret JM, et al.: Beneficial effects of helium:oxygen versus air:oxygen noninvasive pressure support in patients with decompensated chronic obstructive pulmonary disease. Crit Care Med 1999, 27:2422–2429.

52   Tassaux D, Jolliet P, Roseler J, et al.: Effects of helium-oxygen on intrinsic
•   positive end-expiratory pressure in intubated and mechanically ventilated pa-

tients with severe chronic obstructive pulmonary disease. Crit Care Med 2000, 28:2721–2728.
A prospective study of 23 paralysed intubated patients with COPD showed that heliox (70:30) could dramatically relieved PEEP$_i$, end-expiratory lung volume, and airway pressure but did not affect hemodynamics or arterial blood gases.

53 Marini JJ: Heliox in chronic obstructive pulmonary disease: time to lighten up? Crit Care Med 2000, 28:3086–3087.

54 Appendini L, Gudjonsdottir M , Rossi A, et al.: Therapeutic strategies in weaning failure. Monaldi Arch Chest Dis 1998, 53:372–376.

55 Purro A, Appendini L, Gaetano AD, et al.: Physiologic determinants of ventilator dependence in long-term mechanically ventilated patients. Am J Respir Crit Care Med 2000, 161(4Pt1):1115–1123.

56 Rumbak MJ, Walsh FW, Anderson et al.: Significant tracheal obstruction causing failure to wean in patients requiring prolonged mechanical ventilation: a forgotten complication of long-term mechanical ventilation. Chest 1999, 115:1092–1095.

57 Dasgupta A, Rice R, Mascha E, et al.: Four-year experience with a unit for long-term ventilation (respiratory special care unit) at the Cleveland Clinic Foundation. Chest 1999, 116:447–455.

58 Bagley PH, Cooney E: A community-based regional ventilator weaning unit: development and outcome. Chest 1997, 111:1024–1029.

59 Afessa B, Hogans L, Murphy R, et al.: Predicting 3-day and 7-day outcomes of weaning from mechanical ventilation. Chest 1999, 116:456–461.

60 Vitacca M, Vianello A, Colombo DM, et al.: Comparison of two methods for
• weaning patients with chronic obstructive pulmonary disease requiring mechanical ventilation for more than 15 days. Am J Respir Crit Care Med 2001, 164:225–230.
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.

61 Esteban A, Alia I, Tobin MJ, et al.: Effect of spontaneous breathing trial dura-tion on outcome of attempts to discontinue mechanical ventilation. Am J Respir Crit Care Med 1999, 159:512–518.

62 Nava S: Noninvasive techniques of weaning from mechanical ventilation. Monaldi Arch Chest Dis 1998, 53:355–357.

63 Nava S, Ambrosino N, Clini E, et al.: Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: a randomized, controlled trial. Ann Intern Med 1998, 128:721–728.

64 Morehead RS, Pinto SJ: Ventilator-associated pneumonia. Arch Intern Med 2000, 160:1926–1936.

65 Beejay U, Wolfe MM: Acute gastrointestinal bleeding in the intensive care unit: the gastroenterologist's perspective. Gastroenterol Clin North Am 2000, 29:309–336.

66 Mutlu GM, Mutlu EA, Factor P: GI complications in patients receiving mechanical ventilation. Chest 2001, 119:1222–1241.

67 Yamada S, Nishimiya J, Kurokawa K, et al.: Bilevel nasal positive airway pressure and ballooning of the stomach. Chest 2001, 119:1965–1966.

68 Sethi JM, Siegel MD: Mechanical ventilation in chronic obstructive lung dis-
• ease. Clin Chest Med 2000, 21:799–818.
A comprehensive and incisive review of ventilatory support in COPD.

69 Connors AF, Dawson NV, Thomus C, et al.: Outcomes following acute exacerbation of severe chronic obstructive lung disease. Am J Respir Crit Care Med 1996, 154:959–960.

70 Clini E, Sturani C, Porta R, et al.: Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation. Respir Med 1998, 92:1215–1222.

71 Mran JL, Green JV, Homan SD, et al.: Acute exacerbations of chronic obstructive pulmonary disease and mechanical ventilation: a reevaluation. Crit Care Med 1998, 26:71–78.

72 Tan WC, Lim KP, Ng TP, et al.: Long-term outcome and disease control in near-fatal asthma. Ann Acad Med Singapore 1999, 28:384–388.