**INTRODUCTION**

Chronic obstructive pulmonary diseases (COPDs) are a group of disorders characterized by airflow limitation that is not fully reversible (1). Being the fourth leading cause of death worldwide (and projected to be the first in 2030), COPD is responsible for a remarkable public health burden. There are several diseases under this designation (Table 113.1), the most common of which are chronic bronchitis and emphysema. These two disorders represent the extremes of the COPD spectrum and usually coexist in COPD patients. Bronchitis is predominantly a disease of the airways and presents as a chronic productive cough for at least 3 months during 2 consecutive years, while emphysema is a disease of the parenchyma and consists of permanent airspace enlargement associated with rupture of the alveolar septa.

The common final pathway leading to COPD is an increased inflammatory response to inhaled particles or gases, of which the most common is cigarette smoke. Occupational exposure to fumes and dusts and use of indoor biomass cooking also account for a significant proportion of cases, especially among nonsmokers in whom they represent roughly a third of cases. The inflammatory process involves the airways and the lung parenchyma, leading to mucosal gland hypertrophy and disruption of alveolar septa with loss of elastic recoil. These alterations ultimately lead to the obstructive ventilatory defect that defines COPD (2,3). Some patients develop pulmonary hyperinflation caused by the loss of elastic recoil and increased airway resistance. During exacerbations, there might be a secondary dynamic pulmonary hyperinflation (2,4) caused by the increased ventilatory requirement and shortened expiratory time (5). The capacity of the respiratory muscles to generate inspiratory pressure is limited by their shortened operating length and impaired geometric arrangement (6). Long-term steroid use and/or malnutrition also contribute to strength impairment in many patients with severe chronic disease (7).

Only about 15% of all smokers will develop the full-blown syndrome with overt clinical symptoms, although a half of elderly smokers fulfill the criteria for COPD (8). The degree of obstruction correlates best with the smoking load, traditionally measured in pack-years. Rarely, the disease results from an inborn imbalance between the proteases and antiproteases present in the lung, as occurs in the autosomal recessive α1-antitrypsin deficiency (9).

**CLINICAL FINDINGS**

The clinical manifestations of COPD appear late in the course of the disease. There is initially a slow decline in lung function that goes unnoticed over the years (10). Cough is the first finding, usually after the patient has been a smoker for many years. After about 20 years of smoking, some patients begin to notice shortness of breath on exertion, reflecting the progressive airflow limitation that is characteristic of the disease. The dyspnea worsens slowly over time, although sometimes patients deny the deterioration of lung function because they slowly adapt their level of activity to their exercise capacity. The decrease in lung function might become steeper during exacerbations, with a slow recovery to baseline levels (at most) after resolution of the decompensation. It can be useful to assess COPD-related symptoms in a systematic manner. One widely used scale to gauge breathlessness is the modified British Medical Research Council Questionnaire or mMRC (Table 113.2). For a more comprehensive assessment of the health status, the COPD assessment test (CAT; Table 113.3) can be used. Either the mMRC or the CAT can be used in the combined COPD assessment (see Spirometry section below).

### Spirometry

Spirometry is the most important functional test for the diagnosis and the classification of severity of the disease. It consists of a forced exhalation after a deep inspiration while the patient is connected to a pneumotachograph. The ratio of the forced expiratory volume in the first second of the exhalation (FEV1) to the forced vital capacity is diagnostic of an obstructive ventilatory defect if below 0.7 (1). The FEV1 is a useful marker of the disease severity (Table 113.4) and is well suited as a longitudinal monitor of lung function (10). The degree of airflow limitation is also associated with the prevalence of exacerbations. However, because of the weak correlation between the patients’ health status and the severity of airflow obstruction, we recommend a combined assessment, which considers not only the severity of the airflow limitation but also symptoms (CAT; see Table 113.3) or the degree of breathlessness (mMRC; see Table 113.2). In this combined assessment, the history of previous exacerbations can substitute the degree of airflow limitation (Table 113.5).

**TABLE 113.1 Diseases Associated with Chronic Obstructive Pulmonary Disease**

<table>
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<tr>
<th>Disease</th>
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<tr>
<td>Chronic bronchitis</td>
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<td>Emphysema</td>
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<td>Bronchiolitis</td>
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<td>Bronchiectasis</td>
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<td>Tuberculosis</td>
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<td>α1-Trypsin deficiency</td>
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Lung Volume and Diffusing Capacity

Lung volumes can be measured using whole-body plethysmography or gas dilution (helium or nitrogen washout) techniques. In emphysema, both total lung capacity and residual volume may be increased because of loss of lung elastic recoil. The carbon monoxide diffusing capacity may be diminished with the progression of the disease, reflecting the impaired gas exchange due to loss of the functional parenchyma. Although not required for the diagnosis of COPD, both lung volumes and diffusing capacity can be used to characterize its severity. Both measurements are part of the COPD workup especially when techniques such as volume reduction surgery or placement of endobronchial valves are being considered.

Chest Radiographic Findings

Chest radiographic alterations usually occur late in the course of the disease, and there is no alteration pathognomonic of COPD. The radiograph is usually normal in mild disease; changes reflecting airway disease and hyperinflation may appear with disease progression. Sometimes it is possible to see enlarged bronchial walls reflected as an increase in bronchovascular markings. Emphysema is manifested by an increased lucency of the lungs. In smokers, these changes are more prominent in the upper lobes, while in α1-antitrypsin deficiency, they are more likely in basal zones. With hyperinflation, the chest becomes vertically elongated with low, flatttened diaphragmatic domes. The heart shadow is also vertical and narrow. The retrosternal airspace is increased on the lateral view, and the sternal-diaphragmatic angle exceeds 90 degrees. Radiographic computerized tomography is more sensitive and specific for the presence of emphysema, but it is rarely required. It is most useful in the preoperative evaluation for lung volume reduction surgery or to plan the placement of endobronchial valves (11,12).

Arterial Blood Gases

Both pulse oximetry and arterial blood gases can be used to determine the need of home oxygen therapy. If oxygen saturation is below 92% on pulse oximetry while breathing room air, an arterial blood sample should be obtained. If PaO2 is below 55 mmHg, long-term oxygen therapy is indicated. When between 55 and 59 mmHg, home oxygen is recommended only if there is polycythemia or signs of right heart failure.

EXACERBATION

COPD exacerbation can be defined as an acute event characterized by an increase in dyspnea, cough, or sputum production that requires therapy (13). The two most commonly identified precipitating factors are infection—viral, such as Rhinovirus spp or influenza, and bacterial, such as Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis, Enterobacteriaceae spp, or Pseudomonas spp—as well as environmental exposure to air pollutants. However, in about one-third of cases, no underlying cause is identified. Infectious agents can also be recovered from some patients with stable COPD, indicating that in some instances, their presence in decompensated COPD represents an epiphenomenon. On the other hand, the acquisition of a new strain of a bacterial
species colonized with a pathogenic bacteria might lead to an exacerbation in stable COPD patients (14). All things considered, the best predictor of future exacerbations is having treated an exacerbation in the past, suggesting the existence of a frequent exacerbation phenotype (15). Other predictors of exacerbation include decreasing lung function, worsening quality of life, a history of gastroesophageal reflux, and an increased white-cell count (14). All exacerbations should be evaluated carefully for their potential to require hospitalization as a result of respiratory failure, which is associated with poor prognosis and increased risk of death. In the following section, we discuss the hospital treatment of COPD exacerbations.

Assessment and Treatment of Exacerbations

The goals of the treatment of COPD exacerbations are to eliminate or control the cause of the exacerbation, provide optimum bronchodilator therapy, assure adequate oxygenation, and correct respiratory acidemia, all the while avoiding tracheal intubation when possible. Most patients with mild exacerbations can be treated at home, but those with a more severe presentation require hospitalization. Signs of severity include use of accessory muscles, paradoxical breathing pattern, hemodynamic instability, and decreased level of consciousness (1). In-hospital mortality in those with severe exacerbations is approximately 10% to 24% and can reach 59% at 1 year (16,17).

Admission criteria according to the American Thoracic Society/European Respiratory Society guidelines (18) include:

- High-risk comorbidities including pneumonia, cardiac arrhythmia, congestive heart failure, diabetes mellitus, renal failure, or liver failure
- Inadequate response of symptoms to outpatient management
- Marked increase in dyspnea
- Inability to eat or sleep because of symptoms
- Worsening hypoxemia
- Worsening hypercapnia
- Changes in mental status
- Inability to care for oneself (i.e., lack of home support)
- Uncertain diagnosis

Pharmacologic Treatment

The mainstay of pharmacologic treatment is the use of bronchodilators, corticosteroids, and antibiotics, all of which are discussed below.

### Bronchodilators

1. β₂-Agonists: The bronchodilators most commonly used are the inhaled short-acting β₂-agonists because of their rapid onset of action. They can be administered via a nebulizer or through metered dose inhalers (MDIs). Typically, two puffs of albuterol or salbutamol are given every 4 hours, or an equivalent dose via nebulizer. During mechanical ventilation, the use of a spacer interposed in the circuit between the tube and the Y-piece is recommended. An unresolved issue relates to dosage when MDIs are used with intubated patients. Fernandez et al. (19) used two puffs, Gay et al. (20) used three puffs, and Fuller et al. (21) used four puffs in their studies. Because the MDI dose deposited in the lungs of intubated patients is, at best, half of the dose deposited in the lungs of ambulatory patients, it seems reasonable to at least double the number of MDI puffs in intubated patients (i.e., at least four puffs). In some patients, this dose will be inadequate, and a greater number of puffs (e.g., 10–20) can be safely and effectively used. In such circumstances, tachycardia—a common and dose-dependent side effect of bronchodilators—should be monitored to avoid β₂-agonists overdose. Other potential side effects should be closely followed, such as agitation, tremulousness, hyperlactatemia, hypokalemia, and hyperglycemia.

   Long-acting β₂-agonists can also be considered. Subcutaneous or intravenous administration should not be used unless there is contraindication for the inhaled route because of their increased systemic effects.

2. Anticholinergics: Ipratropium bromide can be used in association with the β₂-agonists as needed. It is available both via nebulization (500 μg) or MDI (two puffs every 2–4 hours). There are no clinical studies that have evaluated the use of the long-acting anticholinergic tiotropium bromide during COPD exacerbations.

3. Methylxanthines: Methylxanthines are currently not indicated in the treatment of exacerbations of COPD.

### Corticosteroids

Steroids are usually recommended for exacerbations of COPD. If feasible, prednisone can be given orally at a dose of 30 to 40 mg/day for 5 days (22). If the oral route is not an option, hydrocortisone or methylprednisolone can be substituted in equivalent doses. Some investigators advocate the use of much higher doses (methylprednisolone, 125 mg intravenously four times daily) (23), but as no studies have been designed to find the optimal dose, we favor the lower...
dose. The inhaled route can be an option (24,25). The combination of salmeterol, 50 μg, and fluticasone, 500 μg, given twice daily, has been compared with placebo and resulted in a reduction in mortality of 3 years ($p = 0.052$), fewer exacerbations, and improved health status and lung function. Nebulized budesonide, 1,500 μg four times daily, was compared with prednisolone 40 mg and demonstrated equal efficacy and potentially fewer side effects, especially less hyperglycemia.

**Antibiotics.** Antibiotics decrease mortality during exacerbations. These agents are indicated when there is increased production or change in the color of the sputum. For mild exacerbations, amoxicillin, sulfamethoxazole-trimethoprim, or doxycycline for 7 to 10 days is usually adequate. Patients requiring hospitalization should receive penicillin/penicillinase (e.g., amoxicillin/clavulanate), a respiratory quinolone (levofloxacin, moxifloxacin), or a third-generation cephalosporin together with a macrolide (e.g., ceftriaxone plus clarithromycin). In addition to their antimicrobial activity, macrolides possess anti-inflammatory and mucoregulatory properties that may confer beneficial effects to patients with COPD (26).

**Respiratory Support**

The goal of respiratory support in patients with exacerbations of COPD is to correct hypoxemia/acidemia and reduce the respiratory work, thus avoiding respiratory muscle fatigue (27,28). In the acute setting, oxygen therapy alone is able to resolve hypoxemia, but not acidemia and respiratory distress. For this reason, invasive or noninvasive mechanical ventilation is frequently needed (2,28).

**Oxygen Therapy.** To improve the hypoxemia commonly present in exacerbations of COPD, controlled oxygen therapy is the cornerstone of hospital treatment (2). Long-term oxygen therapy is established as the standard of care for selected patients with advanced chronic stable hypoxemia due to COPD (29,30). However, in the acute setting, some patients have an impaired response to hypercapnia when treated with supplementary oxygen, leading to worsening of CO$_2$ retention (31,32). The precise mechanism of this impairment is not well understood, but ventilation/perfusion (33–37) and respiratory drive (34,38) disturbances have been implicated. Some evidence suggests that blunting of the hypoxic vasoconstriction response due to the higher oxygen content in poorly ventilated areas may be the culprit of the acute CO$_2$ retention. The increased perfusion of such poorly ventilated, previously hypoxic areas might suddenly increase the shunt effect, transferring a great part of the venous CO$_2$ content directly to the arterial compartment, causing some worsening of hypercapnia and sometimes deterioration of mental status.

There is no individual risk factor that identifies patients with COPD who will evolve to hypercapnia after oxygen exposure (2,31,32); therefore, the National Heart, Lung, Blood Institute/World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary has recommended controlled oxygen therapy for the exacerbations, where adequate levels of oxygenation—PaO$_2$ of at least 60 mmHg or SaO$_2$ of at least 90%—are easy to achieve in uncomplicated exacerbations. Notwithstanding, CO$_2$ retention can occur insidiously with little change in symptoms; hence, measuring arterial blood gases 30 minutes after the start of oxygen therapy is recommended. Venturi masks are more accurate sources of oxygen than are nasal prongs, but are more likely to be removed by the patient (2). Controlled oxygen therapy must be started at a low inspiratory oxygen fraction—0.24 to 0.28—and titrated upward to reach a PaO$_2$ of at least 60 mmHg or SaO$_2$ of at least 90% without significant retention of CO$_2$. A clinically significant increase in PaCO$_2$ has been arbitrarily defined as a raise in CO$_2$ of 6.5 mmHg, especially if mental status deteriorates (32).

One must always remember that most of these patients have some degree of chronic vascular disease associated with their smoking history, and cardiovascular complications may be frequent during prolonged hypoxic episodes; for example, acute coronary syndromes, atrial fibrillation, cerebral ischemia, and pulmonary congestion. Therefore, the quick reversal of severe hypoxemia is frequently a priority.

**Noninvasive Mechanical Ventilation.** Patients with COPD prone to acute hypercapnic respiratory failure, often resulting in emergency admission to the hospital. Between 20% and 30% of patients admitted with hypercapnic respiratory failure secondary to acute exacerbation of COPD will die in the hospital (39–42). Traditionally, patients who do not respond to conventional treatment are given invasive mechanical ventilation despite its well-known risks. Tracheal intubation and assisted ventilation have been associated with high morbidity and mortality rates, in addition to the difficulties during the weaning process from the ventilator (43,44). Many clinical complications seem to arise from the intubation procedure itself, or during the course of mechanical ventilation. The most common complications have been nosocomial infections, aspiration, pulmonary embolism, muscle atrophy, polyneuropathies, electrolyte imbalances, and gastrointestinal bleeding, as well as prolonging the stay in the intensive care unit (45,46).

In view of such difficulties, noninvasive positive pressure ventilation is an alternative treatment for patients admitted to the hospital with hypercapnic respiratory failure secondary to acute exacerbations of COPD. With this ventilatory modality, the patient receives air, or a mixture of air and oxygen, from a flow generator or a special ventilator through a facial/nasal mask, thus avoiding the need for tracheal intubation (40–42,47–49). Many studies have shown that noninvasive positive pressure ventilation increases pH, reduces PaCO$_2$, reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay (40–42). More importantly, mortality and the intubation rate are consistently reduced by this intervention (40–42). Some studies suggest that the use of proper noninvasive ventilation can reduce the chances of an eventual endotracheal intubation to less than half (0.42, 95% confidence interval [CI] of 0.31 to 0.59) when compared with the conventional treatment with oxygen mask. This alternative has been also associated to a reduced mortality rate (0.41, 95% CI 0.26 to 0.64). In clinical-physiological terms, the expected elevation of pH after 1 hour of treatment should be around 0.03 (95% CI 0.02 to 0.04) and the expected reduction in PaCO$_2$ in the same interval around –3.0 mmHg (95% CI –5.1 to –0.2) (50).

Unfortunately, noninvasive ventilation is not appropriate for all patients (2). Failure rates between 9% and 50% have been reported (51,52). One important signal that this procedure is not working for a patient is the progression—even if slight—of hypercapnia or acidosis 30 to 60 minutes after the procedure, and deterioration of the mental status.
The classic indications for noninvasive mechanical ventilation in exacerbated COPD patients are (1) respiratory distress with respiratory rate above 35 breaths/min; (2) respiratory acidosis with a pH below 7.35, and with normal or high standard base excess; and (3) a PaO₂ below 45 mmHg. These measurements are made after the patient has been breathing room air for at least 10 minutes (40,41,53). Noninvasive mechanical ventilation is contraindicated for patients with profound bradypnea, defined as a respiratory rate below 12 breaths/min, severe hypercapnic encephalopathy with Glasgow Coma Scale score below 10, cardiac and/or respiratory arrest, and hemodynamic instability (40,41,53). Some authors, however, have successfully applied noninvasive mechanical ventilation in comatose COPD patients with a Glasgow Coma Scale score below 8, with other causes of coma being ruled out (54). This latter use of noninvasive mechanical ventilation is not a consensus (53), but could be applied during a short-term trial (typically of 30–60 minutes) under continuous surveillance at the bedside. If the respiratory drive is blunted due to narcosis, the addition of mandatory breaths can be helpful.

Recommended settings of noninvasive ventilation vary among the studies. Few authors used an exclusive inspiratory pressure support (41) or inspiratory volume support (40). However, most physicians would recommend the use of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP). This recommendation is based on the rationale that the use of PEEP/CPAP further reduces the inspiratory work in patients with COPD exacerbation, especially the extra load generated by high levels of intrinsic PEEP (55–57).

There are many approaches to set the noninvasive ventilation. An easy way is to set the expiratory pressure at 5 cm H₂O, the inspiratory pressure at 10 cm H₂O—resulting in a “delta P” of 5 cm H₂O—and to increase the delta P in increments of 5 cm H₂O, up to 20 to 25 cm H₂O or the maximum tolerated, over 1 hour (49). An alternative approach is to adjust the inspiratory pressure in order to obtain a tidal volume of 6 to 8 mL/kg and a respiratory rate of 25 to 30 breaths/min, setting the end-expiratory pressure to 5 cm H₂O to offset the inspiratory threshold induced by intrinsic PEEP. Close observation of inspiratory time is very important for the success of this strategy, whatever the mode of ventilation. Too short, but especially too long inspiratory time causes great discomfort. Typically, inspiratory time should be set in the range of 0.7 to 1 second. In pressure support mode (PSV), inspiratory time can be optimized by adjusting the cycling-off criterion (automatically adjusted in some mechanical ventilators). Typical settings of this parameter lie within the range of 30% to 50% of peak inspiratory flow.

If inspiratory comfort is not achieved, asynchrony with the ventilator is often observed, with the patient often not able to trigger the assisted breath. Trials of 2 cm H₂O elevations in the PEEP/CPAP levels should be performed in order to further reduce the extra load imposed by the intrinsic PEEP. During these trials of augmentation of external PEEP, the minimum inspiratory pressure should be provided to maintain a stable tidal volume (58). Oxygen should be offered to keep oxygen saturation above 85% to 90% (2,49,58).

Theoretically, pure CPAP support in these patients might be of some help, offsetting part of the inspiratory threshold load imposed on COPD patients, caused by intrinsic PEEP. The appeal of such a strategy is the possibility of using low-cost CPAP systems. This approach, however, has not been tested systematically and should be reserved for very special conditions under close supervision. Whenever possible, some level of inspiratory support should always be added to a CPAP strategy, unloading also part of the resistive workload.

Success rates of noninvasive mechanical ventilation for COPD exacerbations can be in the order of 80% to 85% (53). Close monitoring after the start of noninvasive ventilation is very important to recognize early the minority of patients who will fail. Confalonieri et al. (59) evaluated the risk of failure of noninvasive ventilation in 1,033 consecutive patients with exacerbation of COPD admitted to experienced hospital units. In that study, some factors found on admission were associated with a failed attempt at noninvasive ventilation. These risk factors included a Glasgow Coma Scale score <11, an Acute Physiology and Chronic Health Evaluation (APACHE) II score >28, respiratory rate >30 breaths/min, and arterial pH <7.25. The presence of all these risk factors resulted in a predicted risk of failure greater than 70%. An arterial pH below 7.25 after 2 hours of ventilation greatly increased the risk of failure to over 90%. All these numbers and thresholds should be taken as relative reference points, because the success of noninvasive mechanical ventilation depends on a learning curve of the whole staff. The less experienced the staff, the more conservative they should be with these limits, not waiting for further deterioration of the patient before deciding to intubate.

After hospital admission, the correct timing for starting noninvasive ventilatory support is either immediately or at any time the patient shows worsening of the respiratory distress, a fall in PaO₂, or an increase in PaCO₂ (49,58). Noninvasive ventilatory support can be applied in any area of the hospital where close monitoring of the patient by trained personnel is available, such as intensive care units, emergency departments, high-dependency units, and respiratory wards. The duration of the noninvasive ventilation and the number of possible interruptions for oral and facial cleaning varies according to the patient need. Ventilatory periods lasting at least 40 minutes are warranted (41), and some patients will require uninterrupted use (49,58).

The choice for an appropriate mask is an important aspect of noninvasive mechanical ventilation. In general, patients benefit from a facial mask that covers the mouth and the nose; this is more efficient than the nasal type to deliver effective inspiratory pressures. Leaks directed at the eyes, sores in the nasal area, and dry mouth are frequent causes of extreme discomfort to patients. The total face mask may be better tolerated by some patients, but not all, and greatly reduces skin sores. However, one has to be aware that the anatomic dead space increases with this type of mask, which also imposes some challenges to the mechanical ventilator in terms of synchrony and PEEP maintenance.

**High-Flow Oxygen Therapy.** By delivering a high flow (typically 20 to 60 L/min) of heated and humidified air through a special nasal prong, at controlled inspiratory fractions (typically from 30% to 80% oxygen), recent studies in patients with acute lung injury (60) have shown benefits that may exceed the benefits of conventional oxygen therapy, or even the benefits of noninvasive ventilation. Studies are under way to prove the specific benefits of this strategy in patients with hypercapnic respiratory failure, and there is a good rationale to expect future benefits also extended to this population of patients with COPD exacerbation. Among the proven physiologic effects of this strategy, which forces some fresh air to flow from the nasal cavity toward the mouth, passing through
the pharynx, studies demonstrated: (a) a decrease in the dead space, due to the washout of CO₂, accumulated in the nasal cavity, retropharyngeal cavity, pharynx, and mouth; (b) a CPAP effect that amounts to 3 to 7 cm H₂O depending on the flow settings, anatomy of airways, and the maintenance (or not) of a closed mouth; (c) a decrease in minute ventilation demands, which may be related to central effects or just to a decrease in dead space; and (d) an improvement in patient comfort (when compared to pure oxygen or to mask ventilation). Although promising, future trials will provide us with more information about safety and benefits of this new strategy, when compared to the traditional noninvasive ventilation, as described above.

Invasive Mechanical Ventilation. Invasive mechanical ventilation can be either the initial choice in patients with COPD exacerbation or the strategy to be applied after failure of a trial of noninvasive ventilation (2). Mechanical ventilation can reduce or eliminate the work of breathing and improve gas exchange, while allowing the respiratory function to return to baseline through the treatment of the precipitating causes of the acute decompensation (4).

Assuming that all appropriate measures to improve airflow obstruction have already been taken, minimization of dynamic hyperinflation is a key objective of the ventilatory support of these COPD patients. At the bedside, dynamic hyperinflation is typically detected by the presence of nonzero end-expiratory flow in the flow-time curve, or by effectively measuring the end-expiratory pressure (auto-PEEP) after an expiratory pause. Precise quantification of the auto-PEEP, however, is problematic in patients with spontaneous breathing efforts (61).

In some patients, especially in those with predominant emphysema, the airway obstruction in the expiratory phase is disproportionally higher than in the inspiration. In these patients, the measured auto-PEEP is higher than expected when considering the calculated inspiratory airway resistance. This situation can be anticipated by looking at the flow–volume curve available on most ventilators. During pressure-controlled ventilation, the slopes of the inspiratory and expiratory curves are proportional to the time constant of the respiratory system (a higher slope meaning lower resistance), and the differences between inspiratory and expiratory airway resistances can thus be determined (Fig. 113.1) (62).

To reduce the hyperinflation, several concepts should be employed alone or in combination (4,63). The most effective strategy is controlled hypoventilation (64), which decreases dynamic hyperinflation through the reduction of the minute volume. Hypoventilation, with a fixed inspiratory time, decreases the expiratory flow requirement and consequently reduces air trapping and plateau pressures (64–66). An appropriate clinical goal at present is to keep the plateau pressures no higher than 30 cm H₂O, a strategy associated with lower rates (4%) of barotrauma (67,68). Adequate sedation and analgesia help by lowering the production of CO₂ and allowing further reduction of the minute volume (4). At the bedside, the general rules to minimize hyperinflation are to keep the minute volume 8 L/min or less and to keep the expiratory time at at least 4 seconds; low respiratory rates should be used, for example, 8 or 10 breaths/ min, with 5 to 8 mL/kg of tidal volume. Once these goals have been achieved, there is probably little gain from further adjusting the ventilator. For example, Leatherman et al. (69) showed that halving minute ventilation from 7.4 to 3.7 L/min, and more than doubling expiratory time from 4.5 to 9.5 seconds had no significant effect on auto-PEEP and plateau pressure (63). Although controlled hypoventilation is the most effective measure to decrease hyperinflation, this ventilatory strategy frequently worsens CO₂ retention. The hypercapnia and acidosis are generally well tolerated and considered acceptable by most clinicians (4,63,64), provided that such levels of hypoventilation are essential to keep plateau pressures below 30 cm H₂O.

Metabolic acidosis may also accompany the respiratory acidosis seen in COPD exacerbations, resulting in amplification of the acidemia (70). The underlying mechanism of such acidosis is not clear (70), but its buffering may accentuate coexistent pulmonary injury in hypoxemic patients (71). The treatment of metabolic acidosis in these hypercapnic patients should be directed to the etiology of the process and not to the metabolic acidosis per se.

There is no optimal ventilation modality to support exacerbated COPD patients (63). The peak airway pressure may reach high values in the volume-controlled mode (69), but this is of limited clinical relevance because most of this pressure is dissipated in the orotracheal tube and large airways. Consequently, alveolar pressure is usually considerably lower than peak airway pressure (68). Caution is needed when monitoring the plateau pressure during this mode, as the use of an inspiratory pause every breath may worsen dynamic hyperinflation, by shortening expiratory time. On the other hand, in the pressure-controlled mode, conditions of fluctuating airway resistance and auto-PEEP entail the risk of variable tidal volumes, with sometimes unacceptably low alveolar ventilation. Furthermore, with this latter mode, severe respiratory alkalosis may develop if airway obstruction subsides rapidly (63).

Although there is no clear advantage of one over the other, volume-controlled ventilation is currently the preferred mode by most investigators (63,64,66,68,69). When using volume-controlled ventilation, the flow waveform should also be adjusted. The square waveform usually results in higher peak pressures, frequently triggering the high-pressure alarm, which
should not be of much concern, as previously discussed (68,71). On the other hand, the decelerating flow waveform usually minimizes peak pressure, allowing full delivery of the tidal volume, with less interruption by opening of the pop-off safety valve (63). By forcing a slower flow at the end of inspiration, this flow waveform could result in two theoretical benefits: (1) less overdistension of alveoli distal to the least obstructed airways, and (2) slightly better CO₂ exchange. Whenever possible, and provided that peak pressures are effectively reduced (this must be tested), this flow pattern thus should be preferred. During controlled mechanical ventilation with volume-controlled ventilation, the inspiratory pause should be used with extreme caution. If applied continuously, a pause time between 0.25 and 0.5 second is advisable, not enough for full equilibration of pressures (due to marked pendelluft in those patients), but enough for monitoring purposes (to check whether hyperinflation is improving) and to enhance CO₂ removal. During the inspiratory pause, CO₂ diffuses into the larger airways thus lowering the anatomical dead space (72). It should be remembered that the efficacy of the inspiratory pause for CO₂ removal is mild, in the order of 10% at most, and the risks should always be balanced if used for this purpose: a quick test of its effects on hyperinflation should be performed.

When initiating mechanical ventilation in the pressure-controlled mode, one must keep in mind that the inspiratory time should be set in proportion to the inspiratory time constant in order to deliver the desired tidal volume with the lowest possible plateau pressure (73). Thus, patients with increased inspiratory resistance will need a longer inspiratory time. For a fixed respiratory rate, the increase in inspiratory time always occurs at the expense of a shortening of the expiratory time, which might aggravate pulmonary hyperinflation. Therefore, the ideal inspiratory time would optimize delivery of tidal volume without increasing air trapping. That will occur if, when looking at the flow–volume curve, both end-inspiratory and end-expiratory flows are equal or close to zero (4,63,68).

After choosing the best respiratory rate and inspiratory and expiratory times, the physician has to decide on how much PEEP to apply. During controlled mechanical ventilation, PEEP can be detrimental to paralyzed patients with severe airflow obstruction, raising the functional residual capacity (74). Based on this information, some authors have advocated the use of zero PEEP or no more than 5 cm H₂O (63,74). Another study showed that there are three typical responses to PEEP in those patients, suggesting that an individual approach is necessary. Some patients show a paradoxical response to an increase in PEEP, with relief of the air trapping (Fig. 113.2); in these patients, PEEP is generally advantageous. Some other patients may show no worsening of hyperinflation up to moderate PEEP levels (75), presenting the so-called water-fall response.

**Figure 113.2** Three of the possible responses observed in plateau pressure (P_{PLAT}), total intrinsic positive end-expiratory pressure (PEEP), and functional residual capacity (FRC) with the application of external-PEEP (represented as percentage of PEEP measured at zero external-PEEP). The FRC measured at zero external-PEEP was considered as the reference. A: Paradoxical response (patient 4), observed with a tidal volume (Vₜ) of 6 ml/kg and respiratory rate (RR) of 9 breaths/min. B: Biphasic response (patient 7), observed with Vₜ of 9 ml/kg and RR of 6 breaths/min. C: Classic overinflation response (patient 5), observed with a Vₜ of 9 ml/kg and RR of 9 breaths/min. (Adapted from Caramez MP, Borges JB, Tucci MR, et al. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. Crit Care Med. 2005;33:1519–1528, with permission.)
This second group may still present some mild improvement in gas exchange or in hemodynamics after external PEEP application, but, in fact, they will actually benefit during the transition to assisted ventilation, improving their synchrony with the ventilator. And finally there is a third group, probably those with more fixed obstruction, in which every increment in external PEEP causes marked hyperinflation. For this third group, maybe ZEEP would be the best option, or some minimum PEEP just to maintain ventilator performance (2–4 cm H2O).

We propose two alternative bedside procedures to characterize the typical patient response, according to the three possible types described above:

1. Using volume-control mode, with an inspiratory pause of 0.5 to 0.8 second, tidal volume of 5 to 8 mL/kg, and a respiratory rate of 10 breaths/min (with the lowest inspiratory:expiratory ratio possible, e.g., <1:4), increase the external PEEP in steps of 1–2 cm H2O every 10 to 20 respiratory cycles, starting from ZEEP (baseline). In patients with paradoxical response, some PEEP level above ZEEP will cause plateau pressures to drop below baseline. The PEEP causing the lowest plateau should be used. In those with typical water-fall behavior, there will be a few PEEP levels above ZEEP in which plateau pressures will stay equal to baseline. In this latter case, we should choose the highest PEEP in which plateau is equal to baseline. And finally, the third group of patients will present marked elevation of plateau pressures (above baseline), right after the first increments in external PEEP. Probably ZEEP should be used for them.

2. If in pressure-control mode, start with ZEEP, driving pressure, and inspiratory time to achieve a tidal volume of 5 to 8 mL/kg. Raise the external PEEP in steps of 1 to 2 cm H2O every 10 to 20 respiratory cycles, keeping the plateau pressure constant (thus delta-P above PEEP will decrease). If there is an increase in tidal volume during the upward PEEP titration, it means there was recruitment of airways. PEEP should be kept at the level generating the highest tidal volume (in those with paradoxical response) or at the highest level before the tidal volume begins to fall (in those with typical water-fall behavior). Finally, if tidal volume drops markedly after each increment in external PEEP, this patient is not going to benefit from external PEEP.

There are no objective indicators of the best moment to start assisted ventilation; therefore, at least daily trials of assisted ventilation should be made, with close monitoring of patient comfort and plateau pressure (4,63). Adding external PEEP during assisted ventilation can reduce the inspiratory work by means of eliminating the offset of inspiratory pressure threshold induced by auto-PEEP (4). Appendini et al. (76) demonstrated that 41% of the inspiratory muscle effort was expended to overcome auto-PEEP in patients with COPD during spontaneous breathing. Adding external PEEP at an average of 80% of the measured auto-PEEP is well tolerated, with no increase of total PEEP or plateau pressure (77), improving synchrony between patient and ventilator (55–57). However, this is only true for those patients presenting the water-fall or the paradoxical response. Frequent reassessments are essential to ensure that the patient is not presenting a hyperinflation response, or that the level of external PEEP is still adequate to patient’s mechanics and ventilatory requirements.

Many physicians prefer to change to PSV at this stage, trying to improve patient comfort and synchrony with the ventilator, assuming that the transition to weaning is going to be long. By increasing the patient’s freedom to choose different ventilation patterns, the PSV typically provides an inspiratory flow and tidal volume better matching the patient’s demands, providing also greater freedom for the patient to choose his inspiratory time. When pressure support is not properly adjusted it tend to overassist the patients, resulting in higher tidal volume than needed and increasing lung overinflation and intrinsic PEEP and asynchrony. General principles and targets when using this mode in COPD patients should be as follows: (a) inspiratory pressures just enough to achieve a tidal volume of 5.5 to 6.5 mL/kg (PBW) (78); (b) inspiratory rates around 25 to 30 breaths/min (never below 20); and (c) inspiratory time between 0.6 and 1 second (thus changing cycling-off criteria from 25% of peak flow to around 30%–45%) (78). Alternative modes like proportional assisted ventilation (PAV) have been used with success in this population during this transition phase until weaning. In difficult cases, comfort and synchrony during mechanical ventilation can be improved by this mode, especially in weak and distressed patients, consumed by disease. Thus, a trial of PAV is advisable in cases in which the optimization of pressure support as described above did not work, particularly in those patients presenting clear signs of distress and discomfort during mechanical ventilation.

Humidification should be achieved with a heated humidifier, not with heat and moisture exchangers. The latter devices are undesirable for three reasons: (1) they increase expiratory airway resistance, which would hardly be of any help to reduce hyperinflation (79); (2) placed between the tracheal tube and the Y-piece of ventilator tubing, they increase dead space and therefore contribute unnecessarily to hypercapnia (80,81); and (3) the efficacy of any inhalational medication will be blunted by the heat and moisture exchanger (63).

Weaning from the ventilator should be initiated as soon as possible in order to avoid mechanical ventilator-associated complications (82). Roughly one-fifth of patients with COPD exacerbations remain partially dependent on the ventilator (83,84). In one study, the classic rapid shallow breathing criterion (<80 breaths/min/L) was met by 56% of COPD patients who failed the weaning trial (85). General patient condition and subjective dyspnea seemed to be more effective predictors of success of extubation than quantifiable indexes (86). Using spontaneous breathing trials or progressive reduction in pressure support is equally effective to wean the patient from the ventilator (87). Automatic algorithms for pressure support reduction are available today, which resulted in a faster, or at least equivalent, weaning process when compared with the physician-driven approach (88,89). Especially for centers with a low ratio between caregivers and patients, the automatic systems may present some advantage.

If the spontaneous breathing trial is chosen, it can be applied for at least 30 minutes, up to 2 hours, once a day (44). After tracheal decannulation, the use of intermittent or continuous support with noninvasive mechanical ventilation for at least 24 hours is strongly recommended, using settings similar to those used during conventional ventilation weaning.

The last technique is associated with higher rates of extubation success, lower length of stay in the intensive care unit and/or hospital, and a lower mortality at 60 days (90,91). Nava et al. (92) have described a strategy in which patients are ventilated and sedated for 6 to 8 hours after intubation; an assisted mode is subsequently started using pressure support.
After 48 hours of conventional mechanical ventilation, in the absence of hypersecretion or hemodynamically instability, the patient is extubated and supported with noninvasive mechanical ventilation using the same ventilatory settings as before tracheal decannulation. This approach is associated with less ventilator-associated pneumonia, a shorter length of stay in the intensive care unit, and a lower mortality rate.

SEDATION AND NEUROMUSCULAR BLOCKADE

Benzodiazepines, often given with narcotics, are widely accepted (4,6,3,68). Benzodiazepines, especially when associated with opiates, are effective in facilitating the controlled hypventilation in hypercapnic patients without the need of high doses (93). Propofol may also be used because of its bronchodilating action (63), but generally requires high infusion rates (93). Especially for patients presenting moderate airway resistance (≤25 cm H2O/L/sec) during invasive mechanical ventilation, short-acting agents like propofol are preferable, since such numbers suggest that the cause of respiratory failure was acute and reversible, and that the weaning can be started soon.

When patient–ventilator asynchrony cannot be suppressed by increasing the opioid dose, neuromuscular blocking agents should be given as intermittent intravenous boluses rather than as a continuous infusion in order to reduce the dose and duration of administration (4,6,3,68). Long muscle resting is not currently recommended (94); however, muscle unloading for a short time—about 12 hours—has been advocated for muscular recuperation after the fatigue of acute stress (63). Ideally, if the short time—about 12 hours—has been advocated for muscular recuperation after the fatigue of acute stress (63). Ideally, if the patient is going to stay for a long time during assisted mechanical ventilation, the level of muscle effort should be kept at low levels, preferably with pressure swings in between 4 and 8 cm H2O (driving muscle pressure), enough to prevent muscle atrophy, but providing adequate comfort for the patient.

SUMMARY

Respiratory failure in COPD is an exceptionally difficult disorder to manage. Better management during invasive mechanical ventilation and especially new possibilities to avoid invasive mechanical ventilation are already a reality and have contributed to a decreased mortality. Promising future developments include: new noninvasive ventilation techniques, high-flow oxygen systems, and new techniques for low-flow external removal of CO2. All those techniques will make it possible to decrease the extra load to the respiratory muscles during the acute phase of the disease, without causing additional clinical problems as observed in the past.

Key Points

- COPD exacerbation is defined as acute worsening of dyspnea, cough, or sputum that requires therapy.
- Pharmacologic treatment is based on bronchodilators, corticosteroids, and antibiotics.
- Oxygen therapy should target low-normal levels (SpO2 88%–92%) to avoid the risk of worsening hypercapnia.
- Noninvasive ventilation plays an important role and is associated with reduced endotracheal intubations and reduced mortality.
- Tidal volumes should be kept low (6–8 mL/kg) to avoid worsening of intrinsic PEEP and to minimize missed efforts.
- Close monitoring after the initiation of noninvasive ventilation is important to identify early those patients who will require endotracheal intubation.
- The goals of invasive ventilation are to reduce the work of breathing, restore pH levels to normal, and avoid intrinsic PEEP.
- As soon as possible, assisted modes should be employed to avoid ventilator-induced diaphragmatic dysfunction.
- When the patient condition is stable, spontaneous breathing trials should be applied daily to shorten the duration of invasive mechanical ventilation.
- After extubation, noninvasive ventilation should be used for at least 24 hours.

References

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