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# Chronic Obstructive Pulmonary Disease Exacerbation

GUILLERMO DOMÍNGUEZ-CHERIT AND DELIA BORUNDA NAVA

Chronic obstructive pulmonary disease (COPD) is the only leading cause of death with a rising prevalence It is the fourth leading cause of death in the United States and accounts for approximately 500,000 hospitalizations and 110,000 deaths for exacerbations each year. Patients who are admitted to the intensive care unite (ICU) for COPD exacerbations have an in-hospital mortality of 24%.[1–4] It has been estimated that by the year 2020, COPD will be fifth among the conditions that will be the most burden to society.[5]

Morbidity and mortality due to COPD vary dramatically between industrialized countries. These variations have been attributed to different exposures to risk factors such as tobacco, atopy, occupational hazards, genetic factors, and air pollution. Outside the United States, COPD has had a similar impact on health and mortality throughout the developed and underdeveloped world, and many of the important issues surrounding COPD in the United States apply elsewhere.[6]

## Definitions

The term *COPD*, as recommended by the American Thoracic Society, must be applied to patients who have chronic bronchitis and/or emphysema with significant airflow limitation that does not change significantly over a period of several months of observation, thus distinguishing these patients from those with asthma.[5]

New definitions of acute COPD exacerbation (AECOPD) have been suggested, but the one widely accepted is generally considered as the presence of one or more of the following findings: increase in sputum purulence, increase in sputum volume, and worsening of dyspnea. Patients with COPD present acute decompensation one to three times a year, and 3% to 10% require hospitalization.[1,2] Assessment of the magnitude of these three symptoms can determine the severity of an exacerbation. When all three symptoms are present, it is a type I exacerbation. If any two of the three symptoms are present, it is



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type 2. Type 3 occurs when only one symptom is present with any one of the following features: upper respiratory tract infection in the past 5 days, fever without cause, increased wheezing, cough, tachypnea, or heart rate of 20% above baseline.[2]

## *Pathophysiology*

Expiratory flow limitation is the principal physiologic alteration in COPD that results from the following factors: narrowing of the peripheral airways,[7] mucus hypersecretion,[8] impaired ciliary,[9] and mucus plugging. Bronchial mucosal hyperplasia and edema also contribute to anatomic obstruction.[7,8] as well as infection,[10–12] and inflammation[13–17] may compound the airway narrowing through recruitment of neutrophils and local mediator-released bronchoconstriction.[18,19]

In stable COPD patients with severe airflow obstruction, shallow breathing and inspiratory muscle weakness are the main factors associated with $CO_2$ retention.[20] In stable COPD patients the diaphragm is less effective than in normal subjects, and with increasing airflow obstruction and hyperinflation, the contribution to the generation of ventilatory pressure of the rib cage inspiratory muscles increases.[21] Abdominal muscles are recruited during expiration in severe COPD patients and the expiratory rise in gastric pressure is directly related to intrinsic positive end-expiratory (alveolar) pressure (PEEPi).

Emphysematous lungs contribute to functional airway narrowing[22–25] and collapse due to loss of the elastic recoil.

Upper airway obstruction may also contribute to expiratory flow limitation due to functional narrowing of central airways during marked expiratory effort,[26] glottic narrowing,[27] tracheal stenosis from prior intubation,[28] or narrow-bore endotracheal tubes during mechanical ventilation.[29,30]

The airflow obstruction contributes to an incomplete alveolar emptying at the beginning of the next inspiration[31], therefore the preceding tidal volume is not completely exhaled, resulting in air trapping and hyperinflation.[32]

Air trapping, hyperinflation, and development of intrinsic PEEP are most likely to occur with increasing severity and inhomogeneity of airway obstruction,[33,34] during dynamic airway compression,[31,35] and with any change that minimizes expiratory time, such as hyperventilation.[36–38]

Alveolar hypoxia is a potent stimulant to local pulmonary vasoconstriction.[39] It also causes regional bronchoconstriction, further contributing to airflow obstruction.[40,41] Hypoxemia may interfere with respiratory muscle performance and contribute to respiratory muscle fatigue.[42] Arterial desaturation and hypercapnia both may sedate the patient, producing somnolence and inability to cooperate with therapy.[43] With profound tissue hypoxia, lactic acidosis may ensue.

During acute exacerbations in patients with severe COPD there are several factors which together can explain the worsening gas exchange and the deterioration of the arterial blood gas values. These factors are, in no particular

order: respiratory muscle fatigue,[44] increases in dead space ventilation, alveolar hypoventilation, and worsening of impaired ventilation-perfusion matching.[45] Minute ventilation may be normal during the beginning of an exacerbation, but the respiratory rate is generally increased.[46] There is an associated increase in physiologic dead space that impairs carbon dioxide elimination and results in acidemia, which in turn can further reduce respiratory muscle function.[47] The hypoxemia seen during exacerbations results mainly from the combination of two factors, alveolar hypoventilation[48] and an increase in ventilation-perfusion mismatching.[49,50] Increases in ventilation-perfusion heterogeneity are attributed to

- Reduction in the effectiveness of hypoxic vasoconstriction as a hypoxemic protective mechanism, resulting from a raise in pulmonary artery pressure and the release of vasodilating inflammatory mediators,[50]

- Failure to redirect perfusion away from inadequately ventilated regions because of the reduction in the cross-sectional area in the pulmonary vascular bed.

## *Etiology*

The etiology of the exacerbations is mainly infectious (up to 80%).[1,5,24,33] Other conditions, such as heart failure, pulmonary embolism, nonpulmonary infections, and pneumothorax, can mimic an acute exacerbation or possibly act as triggers. Community-acquired pneumonia (CAP) is an infectious disease with a broad spectrum of severity. Among the the seriously ill patients who require hospitalization, COPD is the most common co-morbidity. When COPD patients acquire AECOPD, the latter come together with CAP when it is caused by it The clinical manifestations meet the criteria for the diagnosis of AECOPD, and CAP is determined only in those cases in which a chest radiograph is obtained and a pulmonary infiltrate is found.[51–54.]

Acute exacerbations are caused in approximately 50% of cases by bacterial pathogens, in 30% of cases by viral infections; and in the rest by atypical pathogens and environmental allergen exposures.[2,3]

## Precipitating Factors

The following are some precipitating factors of COPD:

1. Smoking
2. Infections
3. Environmental factors
4. Pulmonary embolism

5. Cardiovascular disease
6. Failure of medications
7. Other causes

## *Smoking-Related Lung Damage*

Cigarette smoking is the most important cause of COPD. It compromises local airway defense mechanisms by damaging ciliated airway epithelium, increasing mucus viscosity, and slowing mucociliary clearance. This promotes bacterial colonization of the lower respiratory tract. *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis* are the most common bacterial pathogens isolated from patients with COPD.

## *Infections*

Infectious agents are the major cause of acute exacerbation on COPD. Several respiratory viruses are associated with 30% of exacerbations with or without a superimposed bacterial infection.[55]

Several studies have been conducted to investigate airway infection as etiologic factors involved in COPD exacerbation. *H. influenzae, S. pneumoniae,* and *Moraxella catarrhalis,*[56] nevertheless, can be isolated frequently in patients during the stable phases of COPD.[57,58] Atypical bacteria, mostly *Chlamydia pneumoniae,* have been implicated in something like 10% of acute exacerbations.[59–61] At present, there appears to be an agreement that the major pathogens isolated from sputum during acute exacerbation are what you have to treat [62,63] Other potential microorganisms that should be considered include other *Streptococcus* species, enteric Gram-negative bacilli, and *Legionella.*[64] The role of bacterial pathogens when they are isolated from the respiratory tract during an acute exacerbation has become better defined by application of several of the newest investigative techniques, such as bronchoscopic protected brush sampling with quantitative or semiquantitative cultures. When properly defined, up to 80% of acute exacerbations are likely to have an infectious origin.[65–67]

The major cause of acute exacerbation is infection. As we have mentioned before, *H. influenzae, S. pneumoniae,* and *M. catarrhalis* are the main pathogenic agents. Nevertheless, all these bacteria can be isolated frequently in patients during the stable phases of COPD. The most likely agent to be found in sputum during exacerbations is *S. pneumoniae.* Atypical bacteria, mostly *C. pneumoniae,* have been implicated in something like 10% of acute exacerbations, even though recent studies reported *Legionella* spp. and *Mycoplasma pneumoniae* but no *C. pneumoniae.*[51] This is probably due to the difficulty in acute setting diagnosis, since these patients have a high prevalence of chronic infection with this pathogen.[2,3,51]

Other potential microorganisms that should be considered include other *Streptococcus* species, enteric Gram-negative bacilli, and *Legionella.*

Fagon et al. reported evidence of bacterial infection in 50% of patients who required mechanical ventilation.[66]

Another cause of COPD exacerbation is associated with viral infection, ranging from 7% to 63%. Several respiratory viruses are associated with 30% of exacerbations with or without a superimposed bacterial infection.[41]

Influenza, parainfluenza, and coronavirus were the most frequent pathogens to be significantly associated with exacerbations.[3,51]

## *Environmental Factors*

Environmental factors should be considered as precipitating causes of COPD.[68,71] Poor air quality may account for slightly more than 5% of episodes of AECOPD. The recent dramatic increase in motor vehicle traffic has produced a relative increase in the levels of newer pollutants, such as ozone and fine-particulate air pollution.[6] Several epidemiologic studies have associated elevated suspended particulate matter less than 10 ìm in diameter produced by vehicle and industrial processes with a wide range of respiratory outcomes, including reduced pulmonary function and increased chronic respiratory symptoms, rate of hospitalization, and mortality. Similar associations exist for other pollutants, notably sulfur dioxide and nitrogen dioxide.

## *Pulmonary Embolism*

Another condition that may trigger AECOPD is pulmonary embolism. This condition either increases pulmonary vascular pressure or impairs lung function. Pulmonary thromboembolic disease (PE) is the primary cause of death every year in the United States. Risk factors for COPD are sedentary lifestyle, right ventricular mural thombi, and secondary polycythemia. Another predisposing factor that has been described is increased platelet aggregation and plasma b-thromboglobulin. The importance of identifying and treating pulmonary thromboembolism as a precipitating factor of AECOPD is underscored by the fact that mortality associated with untreated PE is as high as 30%.

Diagnosis of pulmonary thromboembolic disease is extremely difficult in patients with AECOPD, in whom the evaluation of V-Q scan find that the most quantity of patients have intermediate results between normal perfusion scan and multiple perfusion defects in areas where ventilation and chest radiograph results are normal.[72] Noninvasive testing for deep venous thrombosis of the lower extremity should be conducted for patients with such indeterminate results.[73,74] Anticoagulation therapy must be initiated when positive results for deep venous thrombosis are obtained. It has been proposed that measurement of the D-dimer has a role as a diagnostic tool, with a sensitivity of 98% and a specificity of 39%.[75]

### *Cardiovascular Disease*

Congestive heart failure or cardiac arrhythmia is another cause of descompensation of patients with COPD. Mortality rate, as a result of coronary disease, is approximately 27%.[1,5] In this setting smoking has been considered to play an important role.

### *Failure of Medications*

Lack of compliance of pharmacologic therapy can explain AECOPD. In addition, patients may take extra medication that leads to a toxic drug effect or to cardiac, gastrointestinal, or metabolic dysfunction that results in acute respiratory failure. Also, the physician must consider the pharmacologic drug interactions that can precipitate toxicity or loss of effect of one drug.[5]

### *Other Causes*

Among other causes that must be considered are sleep disorders; vocal cord paralysis; tumor or scarring from prior intubations; and development of spontaneous pneumothorax, even a small pneumothorax; and pleural effusion independent of magnitude.

## Clinical Manifestations

Most of the COPD patients show impairment of their permanent symptoms, such as an increasing cough, worsening of dyspnea, greater production of sputum or marked decrement in a productive cough, and an increase in purulence and viscosity of the sputum. Associated symptoms include an increase in aerophagia, a diminished appetite, orthopnea, and deterioration in sleep length and quality. Frequently, there is a history of upper respiratory tract infection. Patients generally appear in distress. Accessory inspiratory muscle use is seen with increasing severity grades of exacerbation. Patients may also show a paradoxical pattern of breathing. This sign precludes respiratory muscle fatigue, ventilatory failure, and respiratory arrest. Wheezing may be audible even without a stethoscope. Cyanosis is an insensitive manifestation, but when it is seen, it denotes hypoxemia. Patients who have severe acute carbon dioxide retention may present in a coma. Symptoms include malaise, fever, altered mental status, somnolence, sleepiness or insomnia, and depression. Vital signs demonstrate tachycardia and tachypnea, and blood pressure can be reduced in response to the effect of intrinsic positive end-expiratory pressure. Hypertension also occurs as a consequence of respiratory acidemia.

A chest radiograph is not done routinely in the outpatient setting unless pneumonia is suspected or if the patient is being considered for hospital admission based on the severity of initial symptoms. In two retrospective studies, chest radiograph abnormalities were reported in 16% of patients who were admitted to

the hospital for COPD exacerbation. Base line chest radiography and arterial blood gas analysis during an exacerbation are recommended.[1,2,51]

## Management

The main goals for treatment of acute exacerbation of COPD are prompt improvement of symptoms, with reduction in relapse rates. Hospitalization and all available resources must be used. In this chapter we provide an overview of the most common therapeutic choices.

### *Oxygen*

Oxygen remains the mainstay of COPD exacerbations management. Relief of hypoxemia and consequently of hypoxemic pulmonary vasoconstriction decreases pulmonary vascular resistance, with net effects on ventilation/perfusion mismatch.[76,77] Oxygen delivery increases, possibly due to increases in oxygen arterial content. Although previously it was thought that relief of hypoxemia increased cardiac output due to decreased right ventricle afterload, one study could not find hemodynamic modifications in systemic vascular resistances or cardiac output.[78]

Oxygen administration has been feared in chronic hypercapnic patients, since it is known to be related to increases in hypoventilation and more hypercapnia, probably due to changes in physiologic dead space and suppression of the respiratory drive.[79,80] However, hypercapnia is well tolerated, especially when it is chronic.[81–83] A randomized study has shown that, although oxygen administration can worsen hypercarbia and respiratory acidosis, there is no need for ventilatory support due to these two complications, without respiratory acidosis reaching dangerous levels.[84] Indeed, in acutely ill hypoxemic patients oxygen therapy should not be withheld, since tissular hypoxia can lead to metabolic acidosis and possibly to multiple organic dysfunction syndrome. In all hypoxemic patients, oxygen should be administered at the lowest $F_IO_2$ possible, with special attention to oxigenation (maintaining oxygen saturation slightly over 90%), and monitoring carbon dioxide serum levels, pH, and patient's mental status. Nasal cannulae or Venturi masks can be used to attain low $F_IO_2$ when needed. In severe hypoxemic patients with impending respiratory failure, some authors suggest that a trial with 100 % oxygen therapy must be done before use of mechanical ventilation.[85]

### *Drug Treatment*

#### Aerosol Delivery

Classically, aerosolized drugs in acutely ill nonintubated patients have been administered with pressure-driven jet nebulizers. However, recent investigations have shown that inhaled therapy can be safely used with commercial

metered-dose inhalers (MDI) or dry-powder inhalers (DPI) without decrease in pharmacologic effects. Indeed, there is no clinical difference whether aerosol therapy is administered via nebulized wet aerosols, metered-dose inhalers, or dry-powder inhalers.[86–88] However, when using MDI, the addition of a spacing device increases the efficacy of drug delivery, especially in patients who have difficulty using it alone, enhancing lower airway drug deposition.[89] Also, some reports have described a suboptimal dose when MDI are used in patients with extremely impaired airway function. An increase of two- to fourfold in drug dosage has been recommended.[90–92] An exception to this is very tachypneic and dyspneic patients, in which inhalation with MDI and spacing devices or DPI are not feasible; in them nebulizers are still the best option for drug delivery.

In mechanically ventilated patients, a review of published reports did not find differences among drug delivery using MDI or jet nebulizers.[93] Clinical response to inhaled bronchodilators has been observed when metered-dose inhalers are used with mechanically ventilated patients.[94] Nowadays, most modern commercial mechanical ventilators have a built-in nebulization system, so jet nebulization may be preferred over MDI, since it allows a more synchronized administration during mechanical inspirations and avoids manipulation of ventilator circuitry.

## Bronchodilators

As airway obstruction is a physiopathologic hallmark of COPD, bronchodilator therapy is indicated in acute COPD exacerbations, even in patients without clinical wheezing. Although systemic bronchodilators are available (such as beta agonists or methylxantines), inhaled delivery of beta agonists and/or anticholinergics is now the route of administration of choice, since bronchodilators have better local action with less collateral effects. Bronchodilator treatment in acutely ill COPD patients has been shown to decrease inspiratory muscle loading, because of an increase in $FEV_1$ and a decrease in FRC (funcional residual capacity) and dynamic hyperinflation.[95] In mechanically ventilated patients, reduction in expiratory resistance and dynamic hyperinflation (measured as a decrease in intrinsic end-expiratory positive pressure) has been described.[96]

No strong evidence supports use of one beta agonist over another. Any chemical compound (salbutamol, albuterol, pirbuterol, etc.) may be used with similar clinical responses and degree of collateral effects. The widespread use of inhaled beta agonists has been accompanied with clinical concern of cardiac complications in elderly and myocardial ischemic patients. A study performed on clinically stable COPD or asthma and myocardial ischemia outpatients observed no ischemic events, arrhythmias, or tachycardia when commonly used doses of salbutamol were administered.[97] However, in high-risk cardiac patients, anticholinergics may be preferred over beta agonists because of their low rate of cardiac collateral effects.

Although ipratropium bromide is widely used in stable COPD patients, with better improvement of pulmonary mechanics than is obtained with beta

agonists,[98,99] its use as a first-line drug in acute exacerbations is not fully recommended by some authors,[100] and differences in clinical responses when compared with beta agonists have not been observed.[101] Anticholinergic drugs are especially effective in patients who chronically use beta agonists and who present with clinical resistance to beta agonists.

Use of a combination of beta agonists and ipratropium bromide is still controversial, since some reports have shown clinical improvement with combined use over individual use,[102,103] and others have not shown difference.[104–107]

Although theophylline and its derivatives are widely used in severe obstructed chronic patients, at this time parenteral use of methylxanthines has not provided better results than those obtained with inhaled bronchodilators in acutely ill patients.[94] However, in severely ill patients in which mechanical ventilation should be deferred as long as possible, theophylline compounds can be used parenterally as a last-resort treatment once conventional therapy has failed. Magnesium sulfate, although used in few reports with moderate effects on bronchodilation,[108] is not indicated as a regular drug in COPD patients.

## Corticosteroids

Although systemic parenteral corticosteroids have been considered a cornerstone of pharmacologic treatment in acute exacerbations of COPD,[98] a systematic review of the literature does not show strong evidence for their use.[109,110] Indeed, reports advocating the use of corticosteroids are based on chronic stable patients and outpatient acute exacerbations.[111,112] Although some papers showed clinical improvement in $FEV_1$ in acute exacerbation patients,[113,114] a more recent report found no differences when methylprednisolone was compared with a placebo.[115] One report found an improvement in respiratory mechanics in ventilated patients, with a decrease in airway resistance and dynamic air trapping after systemic methylprednisolone, although there is no reference concerning complications or ventilator weaning.[116] In a report that described corticosteroid responders and nonresponders, failure of treatment correlated with no increases in $FEV_1$ during the first two in-hospital measures (a 100-mL increase in nonfailure patients).[112] As more evidence is gathered on this issue, we still use methylprednisolone parenterally for at least the initial 48 hours of intensive management.

In stable patients, experimental evidence suggests an anti-inflammatory effect of inhaled steroids in airway mucosa.[117,118] Although some clinical reports support the use of inhaled steroids in stable patients, since their chronic use increases $FEV_1$ and diminishes exacerbation rate and symptoms,[119] some show no difference.[120] However, at this moment no evidence supports the use of inhaled steroids in acute exacerbations. Further research in this field is needed.

## Antibiotics

As infection is a recognized precipitating factor, antibiotic management in COPD patients seems a good choice. However, this is a controversial issue, since some

authors preclude its use[121] and some recommend it.[122] It is our belief that antibiotic therapy benefits COPD exacerbated patients, since bacteria are frequently found in patients' lower respiratory tract.[65–67] A classic large randomized double-blind study by Anthonisen et al.[123] and a recent meta-analytic report on randomized trials between 1957 and 1992 by Saint et al.[124] have shown a small but clinically important effect on COPD patients who were given antibiotics (defined as more rapid improvement in peak flow, and fewer days in the hospital), when compared with those given a placebo. Also, although several antibiotics have been widely used in daily practice and clinical trials, at this moment evidence does not strongly support the use of one over another. Antibiotics should probably be selected individually foreach patient, based on clinical assessment of severity, precipitating factors, and patient´s status.[122] Some authors have classified antibiotics for exacerbated COPD patients as first-line antibiotics[125] (amoxicillin, trimethoprim/sulfamethoxazole, tetracycline, erythromycin), second-line (cephradine, cefuroxime, cefaclor, cefprozil), and third-line antibiotics (amoxicillin/clavulanate, azithromycin, ciprofloxacin), the latter having been associated with an increased rate of clinical response to treatment when compared with the other two groups.[125] In a retrospective study, Adams et al. found similar results.[126]

Other authors[127] have suggested an easy approach to the use of antibiotics in these patients. (See Table 9.1.)

Although microbial identification is important and noninvasive sputum collection techniques are advisable in all exacerbated COPD patients, invasive techniques (such as transtracheal aspirates,[128,129] bronchoscopic aspirates, and/or protected specimen brushing[65,66,130,131] and lung biopsies) are indicated in only a few patients, ( e.g., when the patient has culture-negative nonresponding community-acquired pneumonia, or ventilator-associated pneumonia[132-135]). Indeed, because some COPD patients have airway colonization by bacteria without clinical signs of infection and/or exacerbation, there is still no clear significance for a positive culture in a COPD patient´s sample.[131]

### Other Drugs

Respiratory stimulants have been used in COPD patients under the rationale that stimulation of central respiratory centers will increase respiratory drive and avoid respiratory acidosis. However, this group of drugs has a very narrow therapeutic threshold, with production of generalized convulsions as the commonest complication.[136] Most drugs used are analeptic (although they have been discarded as therapeutic agents, because of the increased rate of convulsions) and peripheral stimulants (doxapram, almitrine bismesylate). The latter are still under clinical research. At this moment there is no clear indication that they should be used in COPD patients,[137–139] since stimulation of central respiratory centers has not been shown to decrease the rate of mechanical ventilation.[140]

Factors associated with poor treatment outcome include severity of underlying diseases, type of pathogens with their susceptibility, and resistance patterns.[6]

Table 9.1. Risk Stratification in Acute Exacerbation of Acute Bronchitis

| Group | I | II | III | IV |
|---|---|---|---|---|
| **Clinical State** | Acute tracheo-bronchitis | Acute exacerbation of chronic bronchitis | Acute exacerbation of chronic bronchitis with risk factors | Chronic suppurative airway desease |
| **Risk Factors** | None | None | Multiple* | Most have bronchiectasis |
| **Probable Pathogens** | Viral, rarely *M. pneumoniae* *C. pneumoniae* | *H. influenzae* *Haemophilus* spp, *M. catarralis*, *S. pneumoniae* | Same as group II. Also consider Gram negatives, especially in patients with severely impaired lung function | Same as group III plus multiresistant Gram negatives, particularly *P. aeruginosa* |
| **First Choice** | No antibiotics | Amoxicilin, tetracycline, TMP/SMX | Fluoroquinolone | Antipseudo-monal fluoroquin-olone (ciprofloxacin) |
| **Alternatives** | Macrolide or tetracycline (for persistent symptoms) | Second-generation cephalosporin, second-generation macrolide, amoxicilin/ clavulanate, fluoroquinone | Amoxicilin/ clavulanate, oral second- or third-generation cephalosporin, or second-generation macrolide | Consider parenteral therapy with antipseudo-monal agents |

Source: Modified from reference 127.
*FEV1 < 50% predicted, frequent exacerbations, significant co-morbid conditions, malnutrition, chronic steroid use, mucous hypersecretion, duration of COPD > 10 years, previous pneumoniae. TMP/SMX= trimethoprim /sulfamethoxazole.

## *Hemodynamic Support*

### Fluid Management

COPD patients often have chronic pulmonary hypertension, which in turn may worsen with acute increases in pulmonary artery pressure (due among other factors to hypoxic vasoconstriction, dynamic lung hyperinflation, and, in mechanically ventilated patients, extrinsic PEEP), which can lead to right ventricular failure. As with other right ventricular failure patients, hemodynamic stability and cardiac output in COPD patients rely upon mean systemic pressure. Mean systemic pressure can be modified with increased vascular volume or by decreased unstressed volume and compliance of vessels.[141] Since the latter two are not easily modified with pharmacologic treatment, intravenous fluid management remains the initial step in hemodynamic support in

these patients. These patients frequently are peripherally edematized, and fluids are strictly restricted in fear of left ventricular failure. This restriction may lead to decreased venous return, decreased cardiac output, and finally worsening of right ventricular failure, so cautious but aggressive fluid management is a step that must not be overlooked in these patients.

However, since pulmonary hypertension increases right atrial pressure, clinical management of COPD patients is difficult even with monitoring of right atrial pressure. Although a fluid challenge is advised in hemodynamically ill patients, special care must be taken, since fluid overload may complicate patients with stiff ventricles and poor or borderline left ventricular function. Indeed, one study found a prevalence of right ventricular failure in terminal COPD patients of 66%; left ventricular failure was found in only 6%.[142] At this moment, there are no guidelines for invasive pulmonary artery catheterization in this group of patients or consensus on this procedure. However, patients who are severely hypotensive, who require inotropic support, who have severe congestive heart failure, or who have renal failure may benefit from invasive monitoring.

### Inotropics and Vasodilators

In patients whose hemodynamic instability does not respond to fluid management, inotropic support may be advisable. Although right ventricular failure in other nosologic entities has been treated with norepinephrine[143–145] or dobutamine, we could not find controlled trials of inotropic drugs in hemodynamically unstable COPD patients. However, since patients with pulmonary embolism have a clinical hemodynamic derangement similar to that of COPD patients, in-field management has been transpolated, so nitroglycerine or dobutamine may be used, since both have been shown to increase right ventricular function, increase cardiac output, and have a minimal effect on pulmonary or renal vasoconstriction. Nitroglycerine may add further increases in right ventricular performance when associated with dobutamine.[146] Digitalis has no clinical use in right ventricular failure, unless it is associated with left ventricular failure or arrhythmias treated with digitalis.[147–149]

Although several vasodilator drugs have been used in clinical trials,[150–158] there is currently no indication for systemic vasodilator therapy. Inhaled nitric oxide, a local pulmonary vasodilator with a short-term effect and lack of systemic vasodilator properties, is now extensively used in several clinical scenarios. Recent clinical trials show variable results in COPD patients, so no conclusion can et be made about its use.[159–162]

### Physiotherapy

Although mucus hypersecretion has not been linked with mortality,[163] clearance of secretions improves respiratory mechanics, accelerates recovery from acute exacerbations, and improves comfort.

Chest physical therapy has a doubtful place in secretion management; a report did not find clinical differences in sputum volume or arterial gases

when patients with chest physiotherapy (expansion exercises, postural drainage and vibrations) were compared with patients treated conventionally.[164] Postural drainage has not proved efficacious when used alone.[165] Indeed, some studies have shown that postural drainage, percussion, directed cough, and vibrations produced a significant fall in $FEV_1$ not observed with postural drainage and directed cough alone.[166–167] In some guidelines, therefore, they recommended chest physiotherapy in patients with large volumes of airway secretions (>25 mL/d), particularly those with bronchiectasis.[3,98] Bronchoscopy may be used in any patient with abundant central airway secretions and in atelectasis that does not respond to conventional therapy.

Although mucolytic drugs are not currently indicated in COPD patients, recent reports describe a decreased rate of COPD exacerbations with orally administered *N*-acetylcysteine in ambulatory patients.[168–171] However, its use in acutely ill COPD patients remains to be established.

## *Nutritional Support*

Indeed, malnutrition has been recognized as a negative factor that increases mortality.[172–176] Weight gain has been associated with decreased mortality.[177] Nutritional status tends to decline markedly during acute illness in COPD patients,[173,178–179] and patients may not recover to their previous nutritional state during convalescence, leading to a step-wise decline over time.[174] Recent studies have shown that skeletal muscle mass determines muscle dysfunction in COPD patients.[180] Even nutritional status has been associated with successful weaning.[181] Short-term studies of oral supplement feeding or enteral feeding have found increased body weight, immunologic markers, and respiratory muscle function.[182–184] One recent report analyzed nutritional support in hospitalized patients with acute exacerbation, which found favorable results on lung function.[185]

Special care must be taken with carbohydrate administration in hypercarbic spontaneously breathing patients, since carbohydrate-rich diets elevate total oxygen consumption and $CO_2$ production, which in turn may complicate patients with worsening hypercapnia and even respiratory failure.[186–188] Also, in one study of mechanically ventilated patients, in which enteral nutrition with a fixed carbohydrate content was given, an association was found between total caloric intake and production of $CO_2$. The authors recommend that enteral alimentation, when needed, provide total calories of from 1.25 to 1.3 times the resting energy expenditure of the patient.[189] Respiratory quotients must be between 0.7 and 0.8, and carbohydrate in the diet should be about 40%.

## *Noninvasive Mechanical Ventilation*

### Indications

Frequently, patients with COPD, in spite of adequate and aggressive treatment, require mechanical ventilatory support. The frequency of this support varies

enormously between series, being as high as 74% in some.[190] This ventilatory support may be of two types: invasive and noninvasive. During this decade great breakthroughs in this field have happened, and although before intubation was recommended for invasive mechanical ventilation, noninvasive positive pressure mechanical ventilation (NIPPV) techniques have become clinically important. Even if there are several different methods of noninvasive ventilation, such as negative pressure ventilation, clinical results with these modalities have been only occasionally reported.[191,192] However, NIPPV using nasal or facial masks has proved its efficacy in several clinical studies and has been shown to be successful in up to 65% of cases.[193–195]

According to the consensus statement of the American Association of Respiratory Care,[196] initiation of noninvasive ventilation is recommended when at least two of the following criteria are present:

- Ventilatory distress with moderate to severe dyspnea
- pH of less than 7.35 with $PaCO_2$ above 45 mmHg
- Ventilatory rate of 25 breaths per minute or more

Also, an informal indication for noninvasive ventilation is to avoid or decrease complications associated with invasive ventilation, such as those related to placement of the endotracheal tube itself and long-term sequelae, such as increased risk of ventilator-associated pneumonia.

An important issue in patients with COPD is that noninvasive ventilation preserves patients' ability to communicate, which helps decrease their sense of isolation and thereby decreases their level of anxiety, which leads to the administration of fewer analgesics and sedatives.

With all of this we will be easily able to understand that noninvasive ventilation in these patients decreases hospital morbidity, facilitates the weaning process from mechanical ventilation, and decreases both the length of stay in the ICU and costs.

The mechanism of action through which noninvasive ventilation works is the same as that for invasive ventilation. Supraatmospheric pressures are applied intermittently through the airways, thus increasing transpulmonary pressure and insufflating the lungs. Exhalation is a passive process related to the elastic recoil properties of the lung. The major salutary effects of NIPPV appear related to its ability to decrease the work of breathing and thereby improve alveolar ventilation while simultaneously resting ventilatory musculature. Improvement in gas exchange with NIPPV positive airway pressure is due to an increase in alveolar ventilation without any observable change in ventilation-perfusion matching.[197] Transdiaphragmatic pressure, diaphragmatic pressure-time product, and diaphragmatic EMG amplitude are all decreased by the application of mask pressure support ventilation (PSV) to patients with exacerbations of COPD.[198] Externally applied expiratory pressure decreases the work of breathing more than PSV alone by partially overcoming the auto-PEEP that is frequently present in these individuals. The net

result of expiratory positive pressure is to allow triggering of the ventilator with less negative inspiratory force. In this sense, NIPPV may prevent the development of muscle fatigue by providing support during ventilatory crisis and preventing intubation and its related complications.

### Selection of the Patient

Selection of the patient is important, since the patient must cooperate with NIPPV. The patient must in fact decide or participate in the decision of the kind of interface to be used, whether the nose or orofacial mask is chosen, or even the full-face mask. It is also indispensable that the physician and patient be in close communication. This will help decrease the anxiety of being subjected to this type of ventilatory support. One critical item in this ventilatory method is the interface for the application of noninvasive ventilation; this can be accomplished via a facial or nasal mask. The nose mask has less dead space, causes less claustrophobia, minimizes the potential complications in case of vomiting, and allows both expectoration and the intake of fluids orally without the need to remove the mask. However, facial masks are preferable in dyspneic patients, because this kind of breathing through the mouth decreases the resistance implied by the passage the air through the nose. Also, opening the mouth while breathing with the nose mask may cause a leak in the tidal volume and may decrease the effectiveness of this method. However, no study has directly compared the efficacy of one or the other type of masks. We believe that the face mask is the one that is best for patients with ventilatory distress and dyspnea.

The patient should be comfortable, given the fact that this plays an important role in tolerating noninvasive ventilation. Therefore the mask should be adjusted in the most comfortable way, trying to avoid chafing in sites of pressure of the mask, because this might be enough to cause ventilation to fail. It is important to use masks that are soft in pressure points. Although it is very important to have adequate adjustment of the mask, small leaks of air are possible if ventilatory tidal volume is adequate. This adjustment may be difficult in patients with teeth prosthetics and in those who wear a beard. The use of a nasogastric tube is indicated only in those patients who develop gastric distension or in those in whom an enteral portal is essential for feeding.

As to the ventilatory modality, several different techniques have been described and studied, among which are volume-controlled ventilation, pressure-controlled ventilation, and continuing positive pressure in the airways (CPAP). (Even if technically it is not a form of ventilatory assistance, it might prove useful in the case of flare-ups in the patient with COPD.)

Randomized, controlled trials of NIPPV in COPD exacerbations have shown efficacy using assist-control,[193] PSV,[190] bilevel positive airway pressure,[194] and BiPAP[195] modes of NIPPV. Assist-control volume-cycled ventilation delivered by mask reduces the work of breathing to a greater extent than PSV[199] but is no more effective than mask PSV in preventing intubation among COPD patients.[200]

PSV usually is better tolerated by patients than assist-control mask ventilation because of greater patient-ventilator synchrony and the ability of the patient to independently regulate the depth and pattern of breathing.[200] Bilevel positive airway pressure has become the preferred mode of NIPPV administration in COPD patients because it is generally as comfortable as PSV but produces greater improvements in gas exchange and reduces the work of breathing more effectively than PSV alone.[196,201]

Similar rates of success have been shown in patients who have been subjected to noninvasive mechanical ventilation, both pressure-limited and volume-cycled, although patients feel more comfortable with pressure-limited modes of ventilation, with fewer complications.[200] Inspiratory pressure support improves spontaneous ventilation and allows adequate synchronization between the patient's effort and the ventilator. In the same way, pressure support minimizes peak pressures at mask level and decreases the amount of air. However, tidal volume may vary according to the changes in resistance of the airways and compliance, even if this variability does not cause a serious problem in managing these patients.

Physiologic effects of support pressure with a mask include improvement in tidal volume, gas exchange, ventilatory rate, heart rate, oxygenation, and diaphragm activity, all of which involves a reduction in arterial $CO_2$ and a concomitant improvement in pH. All of this can be seen in the first hours after beginning ventilation. The use of CPAP as the only method of support (5 to 10 cm of water) may be beneficial in patients who are having flare-ups of their COPD. The reason for its application lies in the finding that CPAP decreases ventilatory work in patients with COPD, mainly by counteracting the effect of auto-PEEP. Some studies related to acute COPD patients treated with CPAP have found clinically important $CO_2$ and dyspnea score decreases, comparable to those of NIPPV-treated patients; however, further research is needed to establish comparisons.

### Selection of the Ventilator

Several types of ventilators are available today, with pressure-limited and/or volume-cycled modes. Even if some portable ventilators have support pressure, common ventilators for intensive care have been used. These microprocessor-controlled ventilators currently in use in the intensive care unit (ICU) offer a number of advantages over portable units such as the BiPAP ventilator[202,203]:

- Precise and/or high concentrations of oxygen can be delivered.
- Separate inspiratory and expiratory tubing minimizes $CO_2$ rebreathing.
- Large mask leaks or patient disconnection can be more readily detected.
- Monitoring and alarm features are more sophisticated.

However, specific ventilators for this context have the advantage of being compact, portable, and less expensive.

## Initial Approach

We recommend starting with low pressures with the idea of facilitating acceptance by the patient.

A great deal of cooperation is required from the patient so that he/she can synchronize with the ventilator. Therefore patients should not be sedated or paralyzed with the idea of facilitating the coupling with the ventilator, because the patient's airway should allow adequate air flow to the lungs and the patient should be able to maintain respiratory efforts. Even though this may be easily obtained with the patient awake and cooperating, it might be difficult in a patient who is uncooperative or who is confused or somnolent. This does not mean that the patients who are confused may not be candidates for noninvasive ventilation. Recent studies have shown that the opening of the glottis is a key point to allow the passage of tidal volume and that there are both active and passive mechanisms in the soft palate and in the larynx that permit adequate access for the passage of air to the trachea.

Special care must be paid to explaining the procedure to the patient so that he/she cooperates with ventilation. A close-fitting mask must be used. Facial masks are recommended over nasal masks when ventilation is initiated. Close surveillance by all personnel in care of the patient and monitoring in the ICU are strongly advised.

In this way, the initial inspiratory support pressures may go from 4 to 10 cm of water, and expiratory pressures may go from 4 to 5 cm of water [e.g., from 8 to 12 cm of water for inspiratory positive airway pressures (IPAP) and 2 to 4 cm of water for expiratory positive airway pressures (EPAP) If the decision is made to start with the volume-cycled mode, the starting tidal volumes must be from 10 to 15 mL/kg of ideal body weight. Afterward, we must choose between a spontaneous cycle mode or controlled assistance mode so as to allow triggering of the ventilator through the patient's effort. We recommend plugging in an oxygen cannula directly into the entry port located at the mask, titrating oxygen flow according to oxymetric desired values. We can later increase tidal volume gradually according to the patient's tolerance until we reach small reductions in $PaCO_2$ (5 to 10 mmHg). Initial EPAP of 4 to 5 cm of water is selected to minimize the effects of the auto-PEEP in these patients. Some authors recommend increasing EPAP if oxygenation is not adequate. Adequately managed patients normally have rapid synchronization with the ventilator and show a decrease in their respiratory rate, heart rate, and $PaCO_2$ during the first hours of ventilation. In the absence of these improvements, intubation and invasive mechanical ventilation are advisable.

## Weaning from NIPPV

Weaning from NIPPV may be accomplished either by progressively decreasing the levels of positive pressure support or by permitting the patient to be off of the mask for increasing lengths of time; a combination of both strate-

gies can also be used. In general, it is useful to wean patients by progressively lengthening the period of spontaneous breathing without NIPPV. Once the crisis is over, the patients may be weaned relatively quickly from the ventilator. Anyway, noninvasive ventilation may be reinstalled easily and quickly if the patients show signs of fatigue or intolerance to spontaneous breathing. In some cases we recommend nocturnal noninvasive pressure until recovery. Occasionally, some patients may be candidates for ventilation at home.

## Mechanical Ventilation

### *Indications*

In spite of initial aggressive management, the COPD patient may eventually require support by mechanical ventilator. This is usually accomplished by endotracheal intubation and ventilation via a volume-limited ventilator. The indications for mechanical ventilation are ventilatory failure due to extreme fatigue of the respiratory muscles (usually evidenced clinically or by rising $Paco_2$), inadequate oxygenation, or intubation following an emergent event such as cardiac arrest, seizures, or emergency surgery.

Since these patients are frequently hypoxemic and/or acidotic, administration of 100% oxygen via an appropriate delivery system is initiated prior to intubation. As the equipment for intubation and ventilation is being assembled, an anesthesia mask is used with manual assistance via an Ambu bag. Oral endotracheal tubes with the largest diameter possible (greater than 8 mm) are preferred to improve the ability to remove tenacious secretions and lower the added resistance of the artificial system.[204] To minimize the trauma of intubating a spontaneously breathing patient, placing the endotracheal tube over the bronchoscope has benefits if performed by a skilled bronchoscopist. Accurate placement of the tube and immediate removal of thick secretions are among them. Whatever method of intubation is used, close monitoring of vital signs and oxygen saturation during the procedure are important.

### *Maximizing Ventilator Controls*

A wide variety of mechanical ventilators is available, and the specific modes of ventilation may vary somewhat among them. Nevertheless, basic principles exist that should be familiar to all responsible for care of patients with acute respiratory failure (ARF) and COPD.

Frequently, endotracheal intubation and mechanical ventilation for respiratory failure require the patient to be sedated initially and sometimes even paralyzed so that complete control of ventilation is possible while the underlying cause of the respiratory failure is addressed. Sedation of the patient allows delivery of the tidal volume, respiratory rate, and inspiratory airflow without increasing metabolic demands, although prolonged sedation must be balanced against the possibility of developing respiratory muscle weakness or atrophy. Initially,

the preferred mode of ventilation is the assist control (AC) mode, which allows the patient triggered breaths. Even the most closely watched patient may make inspiratory efforts against a closed valve as the sedative wears off, which further increases the stress to the patient. The continuous mandatory ventilation (CMV) mode does not offer this small amount of flexibility and is usually not used.

The use of different modes of ventilation in COPD patients is purely empirical, with no large studies demonstrating the benefits of one mode over the other or even defining precisely which patients benefit most from assisted mechanical ventilation. The following are guidelines based on studies in the medical literature and the combined experience of the authors.

Once the patient is intubated, the first settings to address are the tidal volume, respiratory rate, and inspired oxygen concentration. The tidal volume initially set should be in the range of 10 to 12 mL/kg. For COPD exacerbations, we recommend that the initial ventilatory rate be set to no more than 10, the inspired oxygen concentration be 100%, and inspiratory flow be in the range of 60 to 100 L/min. Following intubation, bedside mechanics should be measured, allowing further adjustments in ventilator settings. The patient may require sedation, and sometimes a paralytic agent is necessary. Bedside mechanics should include measurements of auto-PEEP, expired volume, and peak and static pressures.[205-207] To attempt to control the respiratory rate by setting the ventilator higher than the patient's own desired rate often worsens hyperinflation and auto-PEEP. To minimize auto-PEEP and improve gas exchange, we recommend that adjustments in inspiratory flow, tidal volumes, and respiratory rates be made that favor long expiratory times.[208,209] The higher flow rates favor better gas exchange, controlled lower respiratory rates (8 to 10 per minute) help prevent alkalosis while permitting longer exhalation times, and oxygen relieves hypoxemia. The ventilator is adjusted based on results of the initial measurements of bedside mechanics, by increasing inspiratory flow, decreasing respiratory rate, and adjusting tidal volume to minimize auto-PEEP. It may be necessary to decrease the tidal volume or adjust the inspiratory flow rate to keep the peak airway pressure less than 50 cm $H_2O$, where risk of barotrauma is least.[210]

After the initial ventilator settings have been adjusted to favor optimal ventilatory mechanics and gas exchange, arterial blood gas analysis is obtained, and further adjustment of the inspired oxygen concentration or change to a different mode of ventilation is then made as the clinical situation warrants. Other modes of ventilation require increasing degrees of patient assistance, so paralytic agents should not be used.

## *Auto-PEEP*

Mechanically ventilated patients with severe airflow obstruction, as stated earlier, develop auto-PEEP because the lungs do not have time during exhalation to reach their relaxed volume. As a result, airflow continues until the next breath is initiated, resulting in air trapped within the lung and an elevated airway pressure at end-exhalation. Measurement of auto-PEEP is per-

formed on the mechanical ventilator by occluding the expiratory port of the ventilator at the end of the exhalation period. The pressure equilibrates throughout the system, and the value of the PEEP is measured from the ventilator manometer. Most patients with severe COPD on mechanical ventilators have some degree of auto-PEEP during ARF. This has the potential not only to decrease cardiac output but also to interfere with other hemodynamic measurements, such as blood pressure, central venous pressure, and wedge pressures.[209] It is not known exactly how much auto-PEEP is deleterious. Levels greater than 10 cm $H_2O$ have been associated with adverse hemodynamic effects, although this depends on the patient's fluid status and cardiac function. The amount of auto-PEEP should be subtracted from the pressure measurements during calculations of static lung compliance on the ventilator.[205]

For airflow to begin, the ventilator must generate a pressure greater than the level of auto-PEEP.[205] Similarly, when the patient breathes through the ventilator circuit, he or she must pull a pressure more negative than the auto-PEEP level to trigger the ventilator and begin airflow. This adds to the burden of the respiratory muscles, which are already at a mechanical disadvantage from the associated hyperinflation. Some researchers have indicated that the increased burden from auto-PEEP can be alleviated with the addition of small amounts of exogenous PEEP through the ventilator circuit. Although this does increase the hyperinflation slightly, levels of external PEEP less than the level of auto-PEEP have been reported to prevent some airway collapse and allow more even exhalation,[211,212] much the way patients spontaneously use pursed lip breathing.[213,214] Thus exogenous PEEP is best used when the patient is making spontaneous efforts. Since the addition of exogenous PEEP can lead to deleterious hemodynamic effects, it must be used with extreme caution and close monitoring of circulatory variables.

## *Sedation and Paralytic Agents*

Sedatives and paralytic agents may be needed initially as the patient is placed on the mechanical ventilator long enough to start treatment of the underlying disease states, but they should not be used so long as to promote respiratory muscle atrophy. Prolonged use of sedatives and paralytic agents in ICU patients has been associated with profound muscle weakness and atrophy, which can further prolong the dependence on mechanical ventilation.[215] Mild sedation, however, may be required for longer periods to alleviate anxiety. We favor the use of short-acting benzodiazepam derivatives, since they have the fewest long-term side effects in COPD patients.

## *Ventilator Modes*

Ventilatory modes most commonly used in the care of COPD patients are CMV, synchronized intermittent mandatory ventilation (SIMV), continuous positive airway pressure (CPAP), and PSV. Since the AC mode of ventilation

allows the patient to increase the respiratory rate by making inspiratory efforts that trigger a ventilator breath, the patient does perform some of the work of breathing.[216,217] With auto-PEEP, the effort the patient must make to trigger the ventilator may be much greater than would be estimated by examining the ventilator sensitivity value. Therefore some patients may make a great effort but still be unable to trigger the ventilator.

The other modes of ventilation commonly used in COPD patients—SIMV, CPAP, and PSV—are used when the intention is to give the patient more control of the breathing rhythm. The various combinations of ventilator settings permit a degree of flexibility in tailoring each patient's ventilatory support. When using the SIMV mode with COPD patients, one must remember that higher set respiratory rates suppress the patient's ventilatory drive and risk additional hyperinflation if insufficient time is allowed for exhalation. Also, use of SIMV at significantly lower set rates (4 to 6/min) in these patients increases their ventilatory workload, sometimes to the point of exhaustion.

Since PSV is an aid to spontaneous ventilation, it is often used during weaning. Combined with the SIMV mode, however, it may allow ventilatory support with lower airway and intrapleural pressures in the COPD patient. It is generally accepted that modes of ventilation designed to increase auto-PEEP in order to improve oxygenation, such as high-frequency jet ventilation or inverse-ratio ventilation, are to be avoided in patients with respiratory failure due to severe COPD.

## *Weaning from Mechanical Ventilation*

Patients with COPD who require mechanical ventilation need ventilatory assistance until the precipitating factors and physiologic consequences of the acute episode are corrected so that respiratory work is minimized. Concomitantly, the respiratory muscles need a period of relative rest to overcome muscular fatigue so that function of the ventilatory pump is restored.[218] In general, restoration of respiratory muscle function requires approximately 24 to 48 hours of mechanical ventilation.[218–220] After the precipitating causes of ARF, such as bronchospasm or infections, have been controlled, consideration should be given to removing the patient from the ventilator. Three out of four patients are successfully weaned within the first 72 hours.[221]

The first step in this process is to evaluate the overall balance between the patient's ventilatory needs and ventilatory reserve. This is generally accomplished by combining the physician's clinical assessment of the patient with simple bedside physiologic measures. All such schemes attempt to incorporate simple measurements that give information about the mechanics of breathing, ventilatory requirements, gas exchange, and respiratory drive. In general, these measures are predictive of weaning success. However, it should be remembered that as many as 29% of patients who do not fulfill these criteria can still be readily extubated. Indeed, in patients with COPD who require prolonged mechanical ventilation, initial measures of standard weaning criteria

have a poor correlation with ultimate weaning success.[222–225] Clinical improvement and successful progression to weaning can occur without improvement in these weaning parameters.[226]

A more prolonged and concerted effort may be required to achieve successful weaning in the small group of patients who fail early attempts to extubate. In these patients it is not likely that the choice of a specific mode of weaning is of particular relevance. T-piece trials,[226,227] IMV,[227–230] and PSV[231] have all been used with success. However, no outcome-based study has demonstrated the superiority of one mode over another.[227] The choice should be based upon such factors as the experience and familiarity of staff with a particular mode as well as patient comfort and tolerance.

## *T-Piece Method*

Once the initial support phase of mechanical ventilation has passed, simple weaning variables should be measured. At the same time, the patient should be placed on a brief period (15 to 30 minutes) of spontaneous T-piece breathing for purposes of assessment.[221] The proper conduction of such a trial requires that patients be adequately prepared. They should be seated comfortably in a chair or in Fowler's position if they must be kept in bed. Ideally, the trial should take place early in the day, when the patient is well rested. The patient should be well rid of the effects of sedation or paralytic agents. The process and intent of the trial should be carefully explained to the patient. The airway should be carefully cleared by having the patient attempt to cough and by suctioning. Once the patient is fully prepared, the ventilator is discontinued and the patient is attached to 40% to 50% oxygen, which is warmed, humidified, and attached to the patient's endotracheal tube via a T-piece connector. The flow rate is adjusted so that there is still evidence of the humidified gas escaping from the end of the tube during inspiration. This ensures that the patient is not taking room air. The patient is then coached to breathe comfortably with slow, deep inspiratory efforts and a slow breathing frequency.[232] The trial is continued as long as the patient appears comfortable, maintains an acceptable cardiac rhythm and rate, maintains an acceptable respiratory rate (e.g., less than 25 to 30 breaths/min), and continues to have adequate oxygenation (e.g., saturation more than 90%). At the end of the trial a blood gas sample is obtained and the patient is returned to the ventilator.[221,226] The trial is considered successful if the patient remains comfortable, has stable pulse and respiratory rate, and maintains adequate oxygenation (e.g., $Pao_2$ greater than 60 mmHg and saturation more than 90%), without significant $CO_2$ retention (e.g., less than 5 mmHg $Paco_2$ increase or fall in pH).

Those who demonstrate the ability to sustain unassisted ventilation during such a trial and who have met the standard bedside weaning criteria can be immediately extubated and expected to do well 90% of the time.[223] Those who do not meet the standard weaning criteria but who are able to sustain T-piece breathing without problems should be considered for extubation at this

point. Those who appear to do poorly during the initial trial should undergo a repeat T-piece trial several hours later because patients may demonstrate changes early after first discontinuing mechanical ventilation that are not necessarily reflective of their more sustained performance.[224–226,233–235] Ultimately, the decision to extubate the patient is a clinical judgment that is tempered by the patient's ability to sustain spontaneous breathing and by the resources immediately available to handle clinical deterioration. Extubation may relieve the patient of a significant source of airway resistance, especially if the endotracheal tube is of narrow bore. If adequately trained personnel are readily available, then the risk of reintubation under controlled circumstances should be minimal.[236,237] The potential risks and morbidity of unnecessary continued mechanical ventilation cannot be accurately determined, but mechanical ventilation is clearly not without risk or discomfort.

If the first trial is not successful, the patient is started on short periods of T-piece breathing (e.g., 5 to 10 minutes) interspersed with 2-hour periods of rest on a support mode of mechanical ventilation.[223,228] The duration of T-piece trials is then progressively increased as tolerated until the patient is able to support continuous spontaneous breathing. If the patient is not carefully attended during the T-piece run, there is no back-up mode of ventilatory assistance and there are operative ventilator alarms.

Another approach is to leave the patient connected to the ventilator and using the CPAP mode but with a low level of actual CPAP. This practice should not be used in an attempt to obviate the need for careful direct monitoring of the patient and should be used with caution, since it is not equivalent to T-piece breathing because of the internal resistance of the ventilator circuits, which can be considerable, especially with demand-flow systems.[236,237] The application of CPAP at low levels (5 to 15 cm $H_2O$) has been suggested to overcome this problem and to reduce the inspiratory work of breathing.[238] However, it is not clear if this approach offers any advantage over T-piece.[239]

## *Pressure–Support Method*

PSV allows the patient to breathe spontaneously; the patient determines the overall respiratory pattern, including both the initiation and the termination of inspiration.[240] Since the patient is still connected to the ventilator, the monitoring, alarm, and back-up ventilation functions can be left intact. The work of breathing is partially offset by the ventilator through the administration of additional inspiratory flow adjusted to maintain a preset inspiratory airway pressure. As such, the work of each breath is performed partially by the patient and partially by the ventilator.[240,241] This allows the patient to develop a larger tidal volume (and thus lower breathing frequency) for the same spontaneous effort.[242] PSV is usually started at a level that results in an adequate tidal volume and breathing frequency. This usually requires about 15 to 25 cm $H_2O$ of pressure support[243] to achieve a tidal volume of approximately 10 to 12 mL/kg. The level of pressure support is then gradually decreased as

long as the generated tidal volume is adequate and the respiratory rate is not too rapid. At low levels (5 to 10 cm $H_2O$), the pressure support is probably serving principally to overcome the internal resistances of the ventilator[244] and the patient should be considered for extubation.

## *Intermittent Mandatory Ventilation Method*

Intermittent mandatory ventilation (IMV) has been used to wean such patients. The method has been well described elsewhere.[229,230,245] During IMV there are no prolonged periods of rest, because the mandatory breaths are interspersed with spontaneous breaths. As the IMV rate is lowered significantly, the patient may begin to tire and experience significant respiratory muscle fatigue. If this is allowed to occur or goes unrecognized, then the training effect may be lost and a considerable period (24 to 48 hours) may be required to return the patient to the previous status.[219] Further, the internal resistance of the ventilator circuit through which the patient must breathe can be considerable and may result in an unacceptable superimposed load and work of breathing.[246]

Of greater importance than the mode of weaning are all the other factors that determine the patient's overall condition. Morganroth et al. reported that successful weaning accompanied improvement in what they called an "adverse factor score," which attempted to quantify the patient's overall status.[226] In difficult-to-wean patients this was more predictive than standard measures of ventilatory performance.

Nutritional support should be designed to provide protein and caloric intake adequate to meet needs while avoiding excesses. The patient's cardiovascular and volume status should be optimized. Contraction alkalosis must be avoided because this will suppress respiration. Electrolyte abnormalities that may affect muscle function, such as hypophosphatemia, hypokalemia, hypomagnesemia, and hypocalcemia, must be corrected. Underlying endocrinopathies such as hypothyroidism[247] or adrenal insufficiency should be suspected when appropriate.[221] Adequate pharmacologic therapy must be maintained, including bronchodilators, steroids, and antibiotics as needed. Prophylactic measures against thromboembolism and gastric bleeding should also be considered.[248] With a concerted effort the vast majority of patients should be successfully weaned; only about 2% of all patients should be expected to remain truly ventilator dependent.[249]

Tracheostomy should be considered if the process is anticipated to be lengthy, primarily to enhance patient comfort and mobility.[250] Tracheostomy also may allow the patient to eat.

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