whether the addition of intravenous aminophylline is beneficial and, in view of the difficulties associated with its use (see above), this agent should be reserved for resistant cases and life-threatening situations.

The efficacy of systemic corticosteroids given to reverse the inflammatory component of airways obstruction in asthma is supported by meta-analysis (Rowe et al., 1992). There is also evidence that in asthmatic patients steroids rapidly reverse the bronchodilator desensitization induced by regular treatment with inhaled formoterol (Tan et al., 1997), further emphasizing the importance of early steroid administration in severe asthma. In most patients there appears to be no advantage in the intravenous as opposed to the oral route of administration and, although there is a dose–response relationship, the effect of steroids is maximal at a dose of about 50 mg prednisolone daily. Dispersible tablets can be used for those who have difficulty swallowing, while the intravenous route is reserved for patients who are vomiting or who have the features of life-threatening asthma. Provided that the patient has responded adequately to systemic steroids (PEF > 60% of predicted or best), high-dose inhaled corticosteroids can be substituted after 24–48 hours.

Magnesium sulphate has been shown to be safe and effective in acute severe asthma. A single dose of intravenous magnesium sulphate (1.2–2 g i.v. infusion over 20 minutes) has been recommended for patients with unresponsive acute severe life-threatening or near-fatal asthma (British Thoracic Society; Scottish Intercollegiate Guidelines Network, 2003), although the use of magnesium sulphate in this situation remains controversial. There is also some evidence that nebulized magnesium sulphate can provide additional bronchodilation when used in conjunction with standard measures in patients with severe asthma (Hughes et al., 2003).

Antibiotics should only be given when there is strong evidence of bacterial infection. Correction of any metabolic acidosis with sodium bicarbonate will be associated with a transient increase in carbon dioxide production and should, if possible, be avoided. In general oxygen should be administered in high concentrations because respiratory drive is well maintained and there is little risk of promoting hypercarbia. There is, however, some evidence that in those with severe airways obstruction, high inspired oxygen concentrations may precipitate or worsen hypercarbia and in such cases it may be prudent to initiate oxygen therapy in a controlled fashion, adjusted according to the results of blood gas analysis (Mcfadden, 1991). Humidification is important to avoid cold-induced bronchoconstriction and minimize the risk of inspissated secretions. Administration of sedatives, cough suppressants or β-blockers can cause rapid, and sometimes fatal, deterioration.

MECHANICAL VENTILATION

Although ventilating patients with severe asthma is extremely hazardous, it is equally dangerous to procrastinate when the patient is exhausted. Some characteristic features of those requiring mechanical ventilation include:

- youth;
- a long history of asthma;
- previous hospital admissions in status;
- attacks lasting more than 24 hours before admission.

It can be difficult to assess which patients require ventilation, but some generally accepted criteria are:

- extreme exhaustion;
- ineffective respiratory efforts;
- increasing mental disturbance;
- coma;
- severe hypoxaemia;
- life-threatening respiratory acidosis:
  - a $P_{CO_2}$ that is rising despite aggressive therapy.

Patients who have a respiratory arrest will require immediate intubation and ventilation.

Selecting the pattern of ventilation. There are a number of important considerations when selecting an appropriate pattern of ventilation for an asthmatic patient. Because of the severe airway obstruction, a long expiratory phase is required to avoid overinflation of the lungs. On the other hand, the time constants of most lung units are markedly increased (see Chapter 3) and inspiration may have to be prolonged to allow adequate distribution of inspired gases. Therefore, a slow respiratory rate (e.g. 6–10 breaths/min), with long inspiratory and expiratory phases (e.g. to achieve an I:E ratio of at least 1:2), is usually required. $V_I$ should be limited (e.g. to 6–8 mL/kg) to avoid high inflation pressures and the risk of barotrauma. Peak inspiratory pressures should probably not be allowed to exceed 40 cm H₂O. For a given minute volume, hyperinflation is minimized by using a lower $V_I$ and a higher respiratory rate. The inspiratory flow rate can be increased (e.g. to > 80 L/min) to allow a longer expiratory phase, although this may adversely affect the distribution of ventilation (Tuxen and Lane, 1987). Conversely, reducing the inspiratory flow rate from 100 to 40 L/min reduces peak inspiratory pressures but also decreases expiratory time, which in turn decreases lung emptying (Tuxen, 1994). In severe cases, the minute volume is inevitably inadequate and moderate hypercarbia should be tolerated. The patient should be heavily sedated and may occasionally require muscle relaxants, particularly in the early stages (avoiding agents that might release histamine). The use of neuromuscular-blocking agents under these circumstances seems to be associated with an increased incidence of muscle weakness/myopathy and of ventilator-associated pneumonia (Adnet et al., 2001). Control mode ventilation (volume or pressure) is usually used initially, but as the patient recovers and muscle relaxation is discontinued spontaneous modes (e.g. synchronized intermittent mandatory ventilation with pressure support; see Chapter 7) can be introduced. If pressure-limited ventilation is chosen, expired
tidal volume must be closely monitored to avoid inadvertent underventilation.

The use of PEEP in severe asthma is controversial since an ‘intrinsic PEEP’ associated with airway compression and lung hyperinflation is already present. Nevertheless externally applied PEEP downstream from the compressed distal airways may overcome the obstruction to flow without increasing alveolar pressure (Marini, 1989). Although a few have recommended high levels of PEEP, most would suggest that only low levels (< 5 cm H2O) should be used to avoid overdistension of near-normal or partially obstructed lung units. In general, however, PEEP appears to be detrimental in severe asthma since it further increases lung volume, elevates intrathoracic and airway pressures and depresses the circulation (Tuxen, 1989). Nevertheless, caution application of low-level PEEP may be useful during spontaneous breathing. The role of CPAP and non-invasive ventilation in the management of acute severe asthma is uncertain (see Chapter 7).

Apart from increasing the risk of pneumothorax, over-inflation of the lungs compresses the heart and attenuates the pulmonary vasculature, further increasing pulmonary vascular resistance. Eventually, the right ventricle fails and cardiac output falls. This may be a terminal event. The risk of this complication can be minimized by ensuring that expiration is completed before the next inspiration begins, either by auscultation or by disconnecting the patient from the ventilator and listening at the endotracheal tube. A tape measure placed between two marks drawn on the chest is a useful means of assessing progressive hyperinflation. A rising central venous pressure (CVP) may also indicate hyperinflation. In severe cases it may be necessary to disconnect the patient from the ventilator intermittently to allow lung deflation.

Similar considerations apply when ventilating patients with chronic airflow limitation (see below). Moreover, rapidly lowering the $P_aCO_2$ towards normal in these patients, some of whom have a compensatory metabolic alkalosis, may cause a marked increase in pH with a reduction in ionized calcium levels, cerebral vasoconstriction and a danger of seizures. There may also be a dramatic fall in cardiac output.

**BRONCHIAL LAVAGE**

Obstruction by tenacious mucous plugs is an important component of the increased airway resistance in severe asthma. Some authorities therefore recommend bronchial lavage in patients who require mechanical ventilation. This procedure is almost invariably associated with severe hypoxia and hypercarbia and as a consequence is extremely hazardous. An alternative is to instil small quantities of saline into the endotracheal tube at regular intervals, although the efficacy of this technique is questionable.

**EXTERNAL CHEST COMPRESSION**

In severe cases expiration can be assisted by external chest compression (Fisher et al., 1989).

**DISCONTINUING RESPIRATORY SUPPORT**

The reported duration of mechanical ventilation in acute severe asthma varies from an average of 12 hours up to several days. Weaning and extubation of patients with reversible airway obstruction may precipitate a further episode of severe bronchospasm. In such cases the patient can be sedated with a continuous infusion of propofol or an inhalational agent during the danger period.

**MORTALITY**

Reported mortality rates for patients requiring mechanical ventilation for acute severe asthma vary considerably from 38% to zero, and in part depend on whether patients who have suffered brain injury as a result of cardiorespiratory arrest prior to the institution of ventilatory support are included.

**ACUTE RESPIRATORY FAILURE ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

The prevalence of, and mortality from, COPD continues to increase. COPD is now the fourth leading cause of death in the USA, where approximately 16 million people are thought to suffer from this disease. Moreover, given that chronic lung disease is probably often a contributing factor to death from other common conditions, the importance of COPD as a cause of death is likely to be underestimated. Reasons for the dramatic increase in COPD worldwide include reductions in mortality from other causes (such as cardiovascular disease in industrialized countries and infection in developing countries), together with a marked increase in cigarette smoking and environmental pollution in developing countries. It is likely that there are important interactions between these environmental factors and a genetic predisposition to COPD. Patients with COPD suffer exacerbations at regular intervals, with up to 2 or 3 episodes per annum. Furthermore exacerbations are more frequent in active smokers.

**Pathophysiology**

**Airflow limitation** in patients with COPD is not fully reversible and is due to a combination of mucosal and peribronchial inflammation and fibrosis (obliterative bronchiolitis), bronchial gland hypertrophy, mucus hypersecretion and bronchoconstriction, the latter being caused by stimulation of airway sensory receptors by inhaled irritants and the release of inflammatory mediators. Although chronic inflammation plays an important role in the pathogenesis of COPD, the mechanisms differ markedly from those seen in asthma. Inflammation is most obvious in the peripheral airways and lung parenchyma, which are infiltrated with macrophages and T lymphocytes (mainly type 1 helper T cells or CD8 T cells), whilst secretions contain increased numbers of macrophages and neutrophils. In contrast to asthma, eosinophils are not prominent, except during exacerbations or in patients with concomitant asthma. Inflammatory mediators implicated in COPD include leukotriene B₄, tumour necrosis factor and interleukin-8 (IL-8). Protease—
patients with COPD and to reduce the amount of health care needed (Griffiths et al., 2000).

**CONTROLLED OXYGEN THERAPY**

Relief of life-threatening hypoxia is clearly the first priority; this can usually be achieved by administering supplemental oxygen and optimizing cardiac output. It is important to appreciate, however, that administration of oxygen is nearly always associated with a rise in $P_{a}CO_{2}$ due to:

- a fall in minute ventilation (Calverley, 2000), caused by suppression of the hypoxic drive to breathe which is mediated by the carotid chemoreceptors;
- reversal of hypoxic pulmonary vasoconstriction, with worsening V/Q mismatch and an increased physiological dead space;
- the Haldane effect (i.e. carbon dioxide dissociates from haemoglobin).

In most cases this rise in $P_{a}CO_{2}$ is of no consequence, but in those with severe COPD, long-standing hypercarbia and a ‘hypoxic’ drive to respiration, oxygen therapy may significantly decrease alveolar ventilation and precipitate severe carbon dioxide retention. Because these patients are hypoxic they are operating on the steep portion of their oxyhaemoglobin dissociation curve and small increases in $P_{a}O_{2}$, not sufficient to cause significant carbon dioxide retention, will lead to useful increases in arterial oxygen content ($C_{O_{2}}$). Oxygen saturation values of 90–92% should be targeted. This forms the basis for controlled oxygen therapy (Campbell, 1960a) using fixed-performance masks (Ventimask) delivering 24%, 28% or 34% oxygen. Alternatively nasal cannulae can be used to administer a low flow of oxygen. Careful monitoring is essential with frequent blood gas analysis to achieve the optimal effect. Although small increases in $P_{a}CO_{2}$ can be tolerated, the pH should not be allowed to fall below 7.25. If significant carbon dioxide retention does occur it is important not to deprive the patient of supplemental oxygen since, because of the respiratory depression and the increase in $P_{a}CO_{2}$, $P_{a}O_{2}$ is likely to fall to a level lower than that on admission. Evidence suggests that, provided oxygen therapy is carefully controlled, hypoxaemia can be corrected with a low risk of CO$_2$ retention, indicating that hypercapnic ventilatory drive is preserved in most patients. Generally those who develop clinically important CO$_2$ retention are more severely hypercapnic on presentation (Moloney et al., 2001). Inhalation of nitric oxide (see below) may worsen, rather than improve, gas exchange in COPD (Barberà et al., 1996).

**MECHANICAL VENTILATION**

If the patient continues to deteriorate despite these measures, institution of mechanical ventilation should be considered. This decision is primarily clinical (see above) and intervention is often prompted by deteriorating mental status, ineffective cough or apnoea.

*Selection of patients for mechanical ventilation.* In general it is prudent to be cautious about embarking on mechanical ventilation in those with severe chronic respiratory failure because they are particularly susceptible to complications and in a proportion of cases weaning will prove to be difficult or very occasionally impossible. Selection of suitable patients is based largely on an assessment of the severity and nature of the underlying chronic pulmonary disease. The patient’s previous exercise tolerance and ability to lead an independent existence are perhaps the most important considerations. Those who were severely incapacitated (e.g. able to walk only a few metres on the flat) before the acute episode will be extremely difficult to wean from the ventilator. Conversely, if the patient was previously leading a full and active life an aggressive approach to treatment should be adopted. It is also important to enquire about previous admissions to hospital with respiratory failure and whether the patient has required mechanical ventilation in the past. If possible, the duration of any previous intensive care admissions and details of the weaning process should be ascertained. Polycythaemia and cor pulmonale suggest that the patient has been hypoxic for some time, whereas an elevated bicarbonate concentration indicates that hypercarbia has been present for at least a few days. In general, success is most likely in patients with a clearly reversible component to their lung pathology (e.g. superadded infection and/or reversible airways obstruction), whereas those with end-stage lung disease associated with unresponsive airflow limitation are less likely to benefit from mechanical ventilation. Clearly if there is any doubt, as is frequently the case, the patient should be intubated and ventilated.

The principles underlying the selection of the most appropriate mode and pattern of ventilation for a patient with COPD are similar to those described earlier for patients with severe asthma. There is some evidence that the application of an external PEEP at a level close to that of the intrinsic PEEP can significantly reduce work of breathing in mechanically ventilated COPD patients (Guerin et al., 2000). In one study values for static intrinsic PEEP averaged 13 ± 2.9cm H_{2}O in ventilator-dependent, tracheostomized COPD patients (Purro et al., 1998). Non-invasive mechanical ventilation may be useful as a means of avoiding endotracheal intubation and has been associated with improved outcomes in patients with exacerbations of COPD (see Chapter 7).

**GENERAL MEASURES**

Mechanically ventilated patients with COPD require prophylaxis against thromboembolism and adequate nutritional support (usually via the enteral route). Hypophosphataemia, which can impair respiratory muscle function (Aubier et al., 1985), is extremely common and may be related to an intracellular shift of phosphate secondary to correction of respiratory acidosis (Laaban et al., 1989). Phosphate administration is indicated in those with severe hypophosphataemia, those with symptoms related to low phosphate levels, when there is pre-existing hypophosphataemia and in alcoholics. The benefits of phosphate administration in those with lesser