The major physiologic function of the lungs is the uptake of oxygen and the elimination of carbon dioxide from pulmonary capillaries. Acute respiratory failure is the inability of the respiratory system to provide adequate oxygenation of the arterial blood, with or without adequate elimination of carbon dioxide, over the course of a few hours to days. Acute respiratory failure can be caused by lesions affecting several parts of the respiratory system, including the airways, lung parenchyma, chest wall and respiratory muscles, and neuromuscular processes involved in breathing.

Definition of Acute Respiratory Failure

ACUTE HYPOXEMIC RESPIRATORY FAILURE

Patients with acute respiratory failure are identified by specific abnormalities in arterial blood gases. Acute hypoxic respiratory failure is defined as a decrease in the delivery of oxygen from the atmosphere to the blood and more specifically as arterial oxygen tension (P_{aO2}) of less than 60 mm Hg. Although somewhat subjective, this value was selected on the basis of the beginning of the descent of the oxygen-hemoglobin dissociation curve at a P_{O2} of 60 mm Hg [see Subsection I].

ACUTE HYPERCAPNIC RESPIRATORY FAILURE

Acute hypercapnic respiratory failure is defined as a partial arterial carbon dioxide pressure (P_{aCO2}) greater than 45 to 50 mm Hg. These changes are associated with an acute respiratory acidosis. The prognostic significance and therapeutic implications of these acute changes in P_{aCO2} are clearly different from chronic hypercapnia that is associated with a renally compensated pH. Therefore, patients with P_{aCO2} levels chronically elevated above 50 mm Hg should not be considered to have acute respiratory failure solely on the basis of an elevated P_{aCO2} level.

Pathogenesis of Acute Respiratory Failure

PATHOGENESIS OF ARTERIAL HYPOXEMIA

The three most important causes of acute hypoxic respiratory failure are alveolar hypoventilation, ventilation-perfusion mismatching, and intrapulmonary shunting. Two less common physiologic causes are the acute hypoxemia caused by a low inspired oxygen tension observed at altitude and the acute hypoxemia caused by diffusion limitation.

Pure alveolar hypoventilation is a relatively rare form of acute respiratory failure that is caused by neuromuscular or central nervous system dysfunction (e.g., opiate overdose). The lung parenchyma is essentially normal. It is characterized by an acute reduction in effective alveolar ventilation and a subsequent decrease in the amount of CO2 that is eliminated by the lungs. Therefore, the P_{aCO2} is always increased in patients with pure alveolar hypoventilation. Hypoxemia occurs as a result of a continuous uptake of O2 and the failure to eliminate CO2.

Calculation of the alveolar-arterial difference in oxygen delivery (A-aDO2) is helpful in determining whether acute hypoxic respiratory failure is purely alveolar hypoventilation. At sea level and without supplemental oxygen, the alveolar PO2 (P_{aO2}) is equal to 150-[P_{aCO2} × 1.25], assuming a respiratory exchange ratio of 0.8. A-aDO2 is measured by subtracting the measured P_{aO2} from the calculated P_{aO2} [see Subsection I]. With pure alveolar hypoventilation, the A-aDO2 is normal. However, when acute hypoxic respiratory failure is caused by V/Q mismatching or an intrapulmonary shunt, the A-aDO2 is always increased.

V/Q mismatching is the most common pathophysiologic cause of acute hypoxemia. It develops when there is a decrease in ventilation to normally perfused regions of the lung, a decrease in perfusion to normally ventilated regions of the lung, or some combination of a decrease in both ventilation and perfusion. Regions of the lung with low V/Q ratios caused by inadequate ventilation result in arterial hypoxemia and hypercapnia. By contrast, regions of the lung with high V/Q ratios caused by inadequate perfusion result in wasted ventilation but do not usually have a direct impact on arterial blood gases. The degree of hypoxemia in patients with pure V/Q mismatching improves in response to an increase in fractional concentration of oxygen in inspired gas (FIO2). This correction occurs because airways to poorly ventilated alveoli remain patent, and the increased partial pressure of inspired oxygen will eventually reach pulmonary capillary blood. Another clinical use for the calculation of the alveolar-arterial difference in oxygen is to identify V/Q mismatching, when the measured P_{aO2} is normalized by hyperventilation. For example, a P_{aO2} level of 90 mm Hg and a P_{aCO2} level of 20 mm Hg when breathing room air would represent significant V/Q mismatching as evidenced by the calculated A-aDO2 level of 35 mm Hg.

Physiologic shunting occurs when venous blood reaches the arterial system and bypasses ventilated alveoli. In the normal lung, a 2% to 3% shunt normally occurs because of the bronchial artery circulation and drainage of some coronary venous blood directly into the left ventricle via the thebesian veins. In patients with severe pneumonia, atelectasis, or pulmonary edema, intrapulmonary shunting occurs when pulmonary capillary blood passes next to alveoli that are completely collapsed or filled with edema fluid or inflammatory cells. Shunting can be differentiated from V/Q mismatching on the basis of the differences in the response to inhalation of 100% oxygen. P_{aO2} levels in patients with shunting who receive 100% oxygen will not improve to normal levels. In fact, the change in the P_{aO2} level that occurs in response to FIO2 values allows the shunt to be estimated as a percentage of cardiac output, assuming normal values for the difference in oxygen content between arterial and mixed venous blood and P_{aCO2} [see Figure 1]. With a shunt of 30% or greater, the P_{aO2} rises little, if at all, with increasing FIO2. By contrast, the rise in P_{aO2} with oxygen therapy is appreciable even with a severe V_{A}/Q mismatch.

PATHOGENESIS OF ACUTE HYPERCAPNIA

Hypercapnia can result from reduced minute ventilation (V_{E}) as a consequence of depression of the central respiratory
Drive or from dysfunction of the neuromuscular system involving the chest wall and diaphragm. Another cause of hypercapnia is an increase in wasted ventilation, defined as the ratio of the dead space volume (V₁₀) to the tidal volume (V₁). An increased V₁₀/V₁ ratio is caused by overventilation of regions of the lung relative to their perfusion. Increased CO₂ production (VCO₂) in hospitalized patients is usually a result of infection, trauma, burns, or other major stresses that lead to hypermetabolism. Agitation, myoclonus, or other causes of muscle activity can increase VCO₂ and contribute to the development of hypercapnic respiratory failure. Lipogenesis during refeeding can increase the metabolic respiratory quotient up to 2.0, which basically doubles VCO₂. In patients with severe lung disease or those on fixed mechanical ventilation, acute hypercapnia may occur.

**Clinical Signs and Symptoms of Acute Respiratory Failure**

**ACUTE HYPOXEMIC RESPIRATORY FAILURE**

When the P\(_{O₂}\) rapidly falls below 40 to 50 mm Hg, harmful effects may be observed in various organ systems. Patients may experience headache, somnolence, confusion, and convulsions. With more severe hypoxemia, permanent encephalopathy may occur. Cardiovascular sequelae from mild hypoxemia, including tachycardia and hypertension, may also develop. With severe hypoxemia, opposite effects may occur, such as bradycardia and hypotension. Disorders associated with hypoxia, defined as decreased delivery of oxygen to the peripheral tissues, without concurrent hypoxemia are also not included as part of the syndrome of acute respiratory failure. Examples of hypoxia without hypoxemia include anemia, decreased cardiac output, and carbon monoxide or cyanide poisoning.

**ACUTE HYPERCAPNIC RESPIRATORY FAILURE**

Signs and symptoms of hypercapnia depend not only on the absolute level of P\(_{CO₂}\) but also on the rate at which the level increases. A P\(_{CO₂}\) level above 100 mm Hg may be well tolerated if the hypercapnia develops slowly and acidemia is minimized by renal compensatory changes. However, acute increases in P\(_{CO₂}\) levels are associated with several neurologic sequelae, including increased cerebral blood flow and elevation in intracranial pressure.

Acute elevation in P\(_{CO₂}\) to 80 to 90 mm Hg may produce many neurologic symptoms, including confusion, headaches, convulsions, and coma. A careful neurologic examination of a patient with acute hypercapnia may reveal agitation, coarse tremor, slurred speech, asterixis, and occasionally papilledema. These effects of hypercapnia on the central nervous system are fully reversible, as opposed to the potentially permanent neurologic sequelae that are associated with acute hypoxemia. An elevated P\(_{CO₂}\) is also associated with myocardial depression, arrhythmias, hyperkalemia, and gastrointestinal bleeding.

**Differential Diagnosis of Acute Respiratory Failure**

The many disorders that cause acute respiratory failure can be classified into two categories on the basis of chest radiography [see Table 1]. The majority of patients with acute respiratory failure have patchy or diffuse infiltrates. Pneumonia, cardiogenic pulmonary edema, noncardiogenic pulmonary edema (acute respiratory distress syndrome, or ARDS), atelectasis, aspiration, progressive interstitial lung disease, pulmonary contusion, and alveolar hemorrhage syndromes (Goodpasture syndrome, Wegener granulomatosis, and systemic lupus erythematosus) are the most common causes of acute respiratory failure in patients whose chest radiographs show infiltrates. Other patients have acute respiratory failure despite a relatively clear chest radiograph. These patients will most likely have one of the following disorders: acute exacerbation of chronic obstructive pulmonary disease, acute exacerbation of asthma, pulmonary embolism, or neuromuscular disease.

**Table 1**  
Radiographic Appearance of Disorders That Cause Acute Respiratory Failure

<table>
<thead>
<tr>
<th>Diffuse or Patchy Pulmonary Infiltrates</th>
<th>Relatively Clear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>Acute exacerbation of chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Asthma</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>Neuromuscular disease</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Respiratory depression secondary to drug overdose</td>
</tr>
<tr>
<td>Progressive interstitial lung disease</td>
<td>—</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>—</td>
</tr>
<tr>
<td>Alveolar hemorrhage syndrome</td>
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</tbody>
</table>
obstructive pulmonary disease (COPD) or asthma, pulmonary emboli, neuromuscular dysfunction, or drug overdose associated with a depressed respiratory drive.

**Management of Acute Respiratory Failure**

The three major steps in the management of acute respiratory failure are to (1) ensure an open airway, (2) restore oxygenation, and (3) maintain or restore ventilation to eliminate CO$_2$.

**Ensurance of Airway Patency**

Airway obstruction may develop in patients with depressed consciousness, dysfunction of the upper airway muscles caused by neuromuscular disease, and an inability to cough and clear secretions. Simple measures such as pushing the mandible forward, laying the patient in a lateral decubitus position, or placing a nasal trumpet or oral airway may alleviate upper airway obstruction caused by relaxed upper airway muscles. However, endotracheal intubation cannot be performed when bronchial secretions are excessive or the patient is at high risk for the aspiration of gastric contents. Emergency cricothyrotomy or tracheostomy is required only if there is glottic or infraglottic anatomic obstruction or if endotracheal intubation cannot be performed for other reasons, such as trauma to the oropharynx.

An endotracheal tube may be passed orally or nasally. The oral route is easier and faster and allows a larger-diameter tube to be placed. The larger tube facilitates suctioning of secretions and fiberoptic bronchoscopy and decreases the risk of sinusitis. Prolonged tracheal intubation may be preferable in awake and unanaesthetized patients, and in patients with ankylosing spondylitis or rheumatoid arthritis that involves the cervical vertebrae and limits mobility.

Complications of endotracheal intubation attempts occur immediately if the tube enters the esophagus. Other early complications of endotracheal intubation include cervical spine injury in patients with trauma or arthritis and injury to the teeth, nose, pharynx, larynx, and tracheobronchial tree. In addition, both prolonged tracheal intubation and tracheostomy can lead to the serious sequelae of tracheal stenosis or tracheomalacia, which can result from ischemic injury of the trachea by the inflatable cuff of the tube. Such difficulties have been reduced since the advent of high-volume and low-pressure cuffs and can be further reduced by not overinflating the cuff. Tracheostomies and endotracheal tubes are associated with the same long-term complications. Tracheostomy may provide greater comfort and more effective secretion removal and should be considered if mechanical ventilation is needed beyond 2 to 3 weeks.

**Restoration of Arterial Oxygen Level**

An increase in the FIO$_2$ may suffice to restore oxygenation. On the basis of the shape of the oxygen-hemoglobin dissociation curve, achieving a P$_{O_2}$ level of 60 mm Hg or higher (> 90% oxygen saturation of hemoglobin) is an optimal goal for most acutely hypoxic patients. In patients with chronic hypoxemia and hypercapnia, a P$_{O_2}$ level of 50 to 55 mm Hg may be needed to prevent respiratory depression and worsening hypercapnia.

A low level of supplemental oxygen may be administered to spontaneously breathing patients with nasal cannulae or loose-fitting Venturi masks that deliver oxygen mixed with various amounts of entrained room air. Nasal cannulae are comfortable and allow the patient to eat, drink, cough, and communicate more easily than when wearing a mask. Loose-fitting masks are less comfortable than nasal cannulae yet allow a more accurate estimation of FIO$_2$. With nasal cannulae, the flow rate can be adjusted upward from 0.5 L/min to achieve a desired oxygen saturation. Flow rates higher than 6 L/min rarely lead to significant improvements in oxygenation and cause significant drying of the upper respiratory tract. Therefore, if an adequate arterial oxygen saturation has not been achieved with a nasal cannula at a flow rate of 6 L/min, a loose-fitting mask should be tried. However, both nasal cannulae and loose-fitting masks seldom provide an FIO$_2$ greater than 0.4 to 0.5. In patients with severe hypoxemia unresponsive to a nasal cannula or a loose-fitting mask, higher levels of inspired oxygen can be supplied through a tighter mask that has a reservoir bag. This system minimizes the entrainment of room air during inspiration by increasing the available supply of oxygen during each breath of the patient.

If the mask or reservoir system fails to correct hypoxemia, continuous positive airway pressure (CPAP) by face mask can be tried. CPAP may improve oxygenation by opening previously closed alveoli and decreasing intrapulmonary shunt. Although the use of CPAP may prevent the need for intubation and mechanical ventilation, its use may be associated with complications such as gastric distention, drying of the eyes from air leaks, and skin breakdown, especially on the bridge of the nose.

**Mechanical Ventilatory Support**

When adequate oxygenation cannot be maintained by noninvasive means or if progressive hypventilation and hypercapnia with respiratory acidosis occur, endotracheal intubation and mechanical ventilatory support should be initiated. Mechanical ventilation can produce positive pressure at the airway opening or create negative pressure around the chest wall. Use of negative pressure ventilators, such as an iron lung, is generally restricted to patients with chronic neuromuscular weakness or chest wall deformity.

**Volume-Cycled and Pressure-Cycled Ventilation**

There are two basic types of positive pressure ventilation. The more commonly used mode in adults is volume-cycled ventilation that supplies a fixed tidal volume, making inflation pressure the dependent variable. When a volume-cycled ventilator is used, changes occurring in pulmonary impedance are associated with alterations in the airway pressures during inflation. A pressure limit can be set using a pop-off valve that prevents further inflation, avoiding excessive overdistention, and functions as an alarm. The second type of positive pressure ventilation is pressure-cycled ventilation, which provides gas flow until a preset pressure is reached so that the tidal volume becomes the dependent variable. With this mode, changes in pulmonary impedance are associated with alterations in tidal volume and therefore minute ventilation.

With volume-cycled ventilation, two primary modes are used: assisted/controlled (A/C) ventilation and synchronized intermittent mandatory ventilation (SIMV) [see Figure 2]. In the A/C mode, the ventilator guarantees a preset number of breaths (backup rate) supplied at a preset tidal volume. If the patient desires to breathe at a respiratory rate higher than the preset rate, the ventilator will deliver the entire preset tidal
way pressure (volume every time the patient generates a small negative air-
respiratory drive. However, a change from A/C ventilation to SIMV does not
continue to perform considerable work during A/C breathing, however, the respiratory muscles may
remain advantages over SIMV: it usually requires less respiratory
supplied at a preset tidal volume. However, the tidal volume
required to overcome flow-resistive and elastic forces and deliver the
preset tidal volume is termed peak airway pressure. The plateau
required to overcome flow-resistive and elastic forces and deliver the
preset tidal volume is termed peak airway pressure. The plateau
is the pressure required to keep the lung and chest wall
inflated with the preset tidal volume during a brief period in which
there is no flow (inspiratory pause). The difference between the peak
and plateau pressures is a reflection of the flow-resistive component of
ventilation and is increased when airway resistance or inspiratory flow
rate is increased. The plateau pressure is a function of lung and chest
wall compliance and is unaffected by airway resistance and inspiratory
flow rate unless auto-PEEP (positive end-expiratory pressure) occurs.
Incomplete emptying is associated with auto-PEEP, the magnitude of
which can be assessed with end-expiratory airway occlusion.

Selecting Appropriate Mechanical Ventilatory Settings
After the patient is intubated, the respiratory rate and tidal volume (in volume-controlled ventilation) should be set to
maintain an adequate minute ventilation that will result in an
appropriate pH level. The tidal volume should be large enough
to prevent microatelectasis and progressive hypoxemia, yet not
so large as to cause barotrauma. For most patients an initial
tidal volume between 6 and 10 ml/kg body weight is appropri-
ate [see Respiratory Failure in Patients with Acute Respiratory Distress Syndrome, below].
Positive end-expiratory pressure (PEEP) is used to improve oxygenation and reduce the possibility of oxygen toxicity for
patients requiring high levels of inspired oxygen. PEEP works
by opening or recruiting previously closed alveoli and redistributing lung water from the alveoli to the interstitial spaces.
CPAP works in a similar manner for patients who are breathing
spontaneously. The benefits of PEEP must be weighed against its deleterious effects, which include decreased cardiac
volume every time the patient generates a small negative air-
way pressure (~1 to ~2 cm H$_2$O). In the SIMV mode, the ventilator also guarantees a preset number of breaths (backup rate)
supplied at a preset tidal volume. However, the tidal volume
for any additional breath above the preset rate is determined
by the effort of the patient. Therefore, the SIMV mode combines a preset number of ventilator-delivered mandatory
breaths with the ability to assist intermittent patient-generated spontaneous breaths. Most patients can be effectively ventilated with either A/C or SIMV, and both modes can be used with pressure-controlled ventilators. The A/C mode has certain advantages over SIMV: it usually requires less respiratory effort, reduces oxygen consumption, and is more likely to rest respiratory muscles. However, the respiratory muscles may continue to perform considerable work during A/C breathing, especially when respiratory drive and minute ventilation are increased. Potential advantages of SIMV include the exercising of respiratory muscles, the prevention of respiratory alkalemia, and possibly improved patient-ventilator coordination. However, a change from A/C ventilation to SIMV does not usually correct respiratory alkalemia caused by an increased respiratory drive.

Pressure-Support Ventilation
Pressure-support ventilation is a pressure-targeted, flow-
cycled mode that requires the patient to initiate every breath [see Figure 2]. During the inspiratory phase, pressures rise rapidly to a preset plateau level. The pressure terminates when
the inspiratory airflow created by the patient falls below a certain
level. Therefore, the total work of breathing for each breath is usually generated by a combination of patient effort and mechanical support. Intubated patients can be ventilated with pressure support alone, as long as they have an adequate ventilatory drive and are strong enough to initiate a sufficient number of breaths to maintain adequate minute ventilation. When used as the primary mode of ventilation, pressure support can be used with certain amounts of CPAP and generally is well tolerated by patients who are being weaned from mechanical ventilation. The pressure support mode of ventilation can also be used in conjunction with SIMV, in which the level of pressure support is applied only to patient-generated breaths.

Selecting Appropriate Mechanical Ventilatory Settings
After the patient is intubated, the respiratory rate and tidal volume (in volume-controlled ventilation) should be set to
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Figure 3 In volume-cycled pressure ventilation, the total pressure required to overcome flow-resistive and elastic forces and deliver the preset tidal volume is termed peak airway pressure. The plateau pressure is the pressure required to keep the lung and chest wall inflated with the preset tidal volume during a brief period in which there is no flow (inspiratory pause). The difference between the peak and plateau pressures is a reflection of the flow-resistive component of ventilation and is increased when airway resistance or inspiratory flow rate is increased. The plateau pressure is a function of lung and chest wall compliance and is unaffected by airway resistance and inspiratory flow rate unless auto-PEEP (positive end-expiratory pressure) occurs. Incomplete emptying is associated with auto-PEEP, the magnitude of which can be assessed with end-expiratory airway occlusion.
output, increased intracranial pressure, and hyperinflation. Selecting the appropriate mode, respiratory rate, tidal volume (or pressure in pressure-controlled ventilation), and amount of PEEP is a dynamic process. No single setting is appropriate for all patients or for a given patient at all stages of acute illness. Optimal ventilatory settings require constant monitoring and numerous readjustments based on acute changes in gas exchange, airway pressures, breathing patterns, and hemodynamics in conjunction with the resolution or progression of the underlying disease process.

During volume-cycled ventilation, peak and plateau airway pressures can be easily seen from most ventilators. Peak airway pressure can be subdivided into three components: (1) flow resistive, (2) elastic distending pressure, and (3) PEEP (either set or intrinsic) [see Figure 3]. The plateau pressure is a close approximation of the alveolar pressure and can be subdivided into only two components: (1) elastic distending pressure and (2) the level of PEEP (either set or intrinsic). Because the pressure required to overcome the flow-resistive properties of the airway and external apparatus is positive, the peak pressure will always be equal to or greater than the plateau pressure. The plateau pressure is measured by interrupting flow or pausing the ventilator at full inspiration. The static compliance of the respiratory system is computed by dividing the tidal volume delivered to the patient by the change in pressure (plateau pressure minus PEEP). A reduction in the normal static compliance is indicative of a stiffer lung or chest wall.

During volume-cycled ventilation, changes in airway pressures can be helpful in determining the cause of an acute deterioration in mechanically ventilated patients. A large increase in peak airway pressure (out of proportion to the increase in plateau pressure) signals a change in the flow-resistive properties. This increase is usually observed in patients with airway problems (e.g., kinking of the endotracheal tube, mucous plug, or bronchospasm). Treatment should be directed at improving airway function, including repositioning the endotracheal tube, suctioning the airways, and administering bronchodilator therapy. When an increase is primarily in plateau pressure, the problem is localized to the lung parenchyma or chest wall rather than the airways. This condition can be seen with worsening of pulmonary edema, tension pneumothorax, a large region of atelectasis, or intubation of the right main stem bronchus.

With both positive and negative pressure ventilators, exhalation is passive and is provided by the elastic recoil of the inflated lungs and chest wall. Exhalation rate depends on the resistance and compliance of the respiratory system. A high resistance is observed in patients who require a prolonged exhalation time, such as those with chronic airway obstruction or asthma. If the subsequent tidal volume is delivered before exhalation is complete, positive airway pressure will be maintained throughout the respiratory cycle, resulting in increases in end-expiratory lung volume and end-expiratory alveolar pressure. PEEP that results from this process of dynamic hyperinflation has been termed auto-PEEP (or intrinsic PEEP). Auto-PEEP increases both peak and plateau pressures and can be measured by briefly occluding the airway at the end of exhalation. When the airflow is interrupted, pressures equilibrate quickly, and the airway-opening pressure rises to the level of the previous alveolar pressure, which is the level of auto-PEEP. The appropriate compliance of the respiratory system can be calculated by dividing the tidal volume by the difference between the plateau pressure and the auto-PEEP.

Management of Respiratory Failure in Specific Clinical Settings

Respiratory failure in patients with airway obstruction

Patients with severe chronic airway obstruction are often hypoxicemic and hypercapnic on a long-term basis and adapt, albeit precariously, to their abnormal state. Acute deterioration is most often triggered by infection, but it may also result from factors such as pneumothorax, congestive heart failure, and increased CO₂ production associated with febrile states. The worsening hypoxemia and hypercapnia that accompany acute deterioration lead to increasing dyspnea, sleep disruption, and occasional alterations in consciousness. Depressed consciousness leads to retention of secretions and further worsening of gas exchange. This cycle can be broken by identifying and rectifying the processes that have precipitated the acute deterioration and by providing support to improve gas exchange while the underlying disorders are being corrected.

Arterial Blood Gas Analysis

Arterial blood gas analysis is crucial to the proper assessment and management of acute exacerbations. The first priority is to achieve a PaO₂ level of 50 to 60 mm Hg but no higher. An elevation in PaCO₂ of 10 to 15 mm Hg is common when oxygen is given to patients with chronic airway obstruction and does not represent a failure of controlled oxygen therapy, provided that there is no critical reduction in blood pH (i.e., ≤ 7.2). Therapy should include promotion of bronchopulmonary drainage by encouragement of cough, administration of inhaled bronchodilators and systemic corticosteroids, and treatment of any underlying infection.

Ventilatory Support

Many patients with severe exacerbations of COPD experience persistent respiratory acidosis and excessive work in breathing even after their initial treatment with bronchodilators. The level for PaCO₂ at which ventilatory assistance becomes necessary cannot be specified, but ventilatory supports should be considered if hypercapnia is severe enough to cause profound acidemia (pH < 7.2) or the patient shows signs of altered mental status or respiratory muscle fatigue. Intubation should be performed if hemodynamic instability or somnolence occurs or if secretions cannot be cleared. However, if the hypercapnic patient remains alert and cooperative, delivery of noninvasive positive pressure ventilation through a facial or nasal mask may reverse or prevent fatigue and thereby eliminate the need for conventional mechanical ventilation through an endotracheal tube. In selected patients with severe exacerbations of COPD, noninvasive ventilation decreases the rate of complications, reduces the need for intubation, shortens hospital stay, and may lower mortality. Patients who do not tolerate the mask or whose acute exacerbation fails to improve should be intubated. The delay in intubation incurred by an unsuccessful trial of noninvasive ventilation should not pose a significant risk to the patient, provided that personnel skilled in airway management and intubation are readily available and the patient does not have hemodynamic instability or sig-

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significant underlying cardiac disease. The success rate for noninvasive ventilation is highly dependent on the skill and commitment of the respiratory therapists and nurses who work with the patient.

**Noninvasive ventilation** The most common method of noninvasive ventilation for patients with airway obstruction is bilevel positive airway pressure (BiPAP). This type of ventilation delivers a specified amount of inspiratory positive airway pressure (IPAP) that supports each spontaneous breath (usually set at 15 to 20 cm H$_2$O) in conjunction with a low level of expiratory positive airway pressure (EPAP) (usually set at 3 to 5 cm H$_2$O). Some patients who have acute hypcapnic respiratory failure tolerate a full face mask better than a nose mask because of large leaks that occur with the nose mask. However, securing the mask too tightly that all leaks are prevented may increase discomfort and decrease the ultimate likelihood of success.

**Invasive ventilation** For exacerbations that require intubation, a reasonable initial ventilator setting is a tidal volume of 8 to 10 ml/kg at 11 to 14 breaths a minute. It is important to remember that $P_{CO_2}$ levels of patients with chronic hypcapnia should not be lowered to the normal range. This procedure could result in alkalemia, which increases the risk of cardiac dysrhythmias and seizures. In addition, overventilation for more than 2 to 3 days may result in renal restoration of the pH to normal. As a consequence, during subsequent trials of spontaneous ventilation, as the $P_{CO_2}$ rises to the baseline hypcapnic level, the patient becomes acidaemic. To prevent this condition, adjustments in respiratory frequency and tidal volume should be aimed at achieving a $P_{CO_2}$ level that allows a normal pH level (obtained from standard nomograms).

Dynamic hyperinflation with auto-PEEP occurs frequently during mechanical ventilation of patients with airflow obstruction [see Mechanical Ventilatory Support, above]. For airflow obstruction, the most critical determinant of the severity of dynamic hyperinflation is the minute ventilation delivered by the mechanical ventilator. Therefore, in addition to the effects on $P_{CO_2}$ and pH levels, excessive ventilation of patients with airflow obstruction increases the risk of pulmonary hyperinflation. The major consequences of excessive auto-PEEP include barotrauma, misinterpretation of central venous and pulmonary arterial wedge pressures, decreased cardiac output secondary to reduced venous return, and increased work in breathing. The effort required to breathe increases because the patient’s inspiratory muscles must generate a negative pressure equal to the auto-PEEP before the proximal airway pressure can be lowered to the −1 to −2 cm H$_2$O required to trigger the ventilator. Auto-PEEP should be suspected in a patient with airflow obstruction when the ventilator does not deliver an assisted breath even though the patient is making obvious inspiratory efforts. Inspiratory effort can be aided by the application of external PEEP at a level equal to or slightly less than the auto-PEEP level. Applying external PEEP causes the ventilator to deliver an assisted breath when the proximal airway pressure is lowered to 1 to 2 cm H$_2$O below the level of applied PEEP rather than to −1 to −2 cm H$_2$O. In effect, the application of external PEEP reduces the inspiratory effort required to trigger the ventilator. In patients with chronic airflow obstruction, applied PEEP does not increase lung volume or airway pressures as long as the level of applied PEEP does not exceed the level of auto-PEEP.\(^{12}\)

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Figure 4 A static pressure-volume curve can be constructed by plotting the tidal volume versus the elastic recoil pressure of the respiratory system for several different tidal volumes. In patients with acute respiratory distress syndrome, the inflation curve demonstrates a lower inflection point, which corresponds to the onset of reopening closed alveoli, and an upper inflection point, which signals the beginning of the overdistention of patent alveoli.

**Respiratory Failure in Patients with Acute Respiratory Distress Syndrome**

Hypoxemic respiratory failure in patients with ARDS results in an unacceptably high mortality (30% to 60%). It may occur in previously healthy patients without preexisting lung disease. The pathophysiology, clinical features, and nonventilatory therapies for ARDS are outlined elsewhere\(^{13}\) [see Subsection X].

**Ventilatory Support**

The initiation of mechanical ventilation for ARDS patients clearly has beneficial effects, yet a growing body of evidence indicates that mechanical ventilation can produce pathologic changes in normal lung tissue that are similar to ARDS. Experimentally, large inflation pressures produce capillary leak and eventually permeability pulmonary edema. Harmful effects of large inflations and subsequent high alveolar pressures have been termed volutrauma.\(^{14}\) Mechanical ventilation strategies for ARDS patients have been supported by studies that examined computed tomography scans and pressure-volume curves. Although the lung appears to be homogeneously involved on chest radiograph, CT scans of ARDS patients reveal a markedly heterogeneous pattern.\(^{15}\) Dependent regions of the lung are consolidated, but more superior regions of the lung appear normal. The inflation portion of the pressure-volume curve of ARDS patients exhibits a lower inflection point, which corresponds to the onset of reopening closed alveoli, and an upper inflection point, which signals the beginning of the overdistention of patent alveoli\(^{16}\) [see Figure 4].

A specific ventilatory strategy that focuses on ventilating patients between the upper and lower inflection points has been proposed for ARDS patients. To limit transpulmonary pressures (plateau pressure of < 30 cm H$_2$O), low tidal volumes should be used. The subsequent decrease in minute ventilation, which is caused by the use of low tidal volumes and may result in hypercapnia and respiratory acidosis, is termed permissive
hypercapnia. This strategy of mechanical ventilation with lower tidal volumes (6 ml/kg) versus traditional ventilation with larger tidal volumes (12 ml/kg) results in decreased mortality and shortens the amount of time that mechanical ventilation is required.  

**Use of PEEP**

PEEP is an effective way to improve oxygenation. However, the optimal amount of PEEP that should be used is controversial. The titration of PEEP to a level above the lower inflection point may decrease the damage to alveoli that would be caused by repetitive reopening and closing of lung units. The application of a level of PEEP, called the open lung approach, was associated with improved mortality when compared with conventional ventilatory strategies. The beneficial effects of PEEP must always be weighed against a possible decrease in cardiac output and increased risk of barotrauma.

**Inverse-Ratio Ventilation**

One strategy for improving oxygenation without increasing FIO2 or PEEP is to prolong inspiratory time by adding an end-inspiratory pause, keeping alveolar pressure briefly at the plateau level. When inspiratory time is prolonged, exceeding expiratory time, the ventilation is termed inverse-ratio ventilation. Inverse-ratio ventilation may improve oxygenation in some ARDS patients; however, prospective studies have found that most patients do not benefit. Caution is required in applying inverse-ratio ventilation because barotrauma and hypotension can result from the development of excessive auto-PEEP as expiratory time is shortened.

**Prone Positioning**

An effective method for improving oxygenation is to place the patient in the prone position. The mechanism by which the prone position improves oxygenation is related to the reduction of shunting and correction of V/Q mismatching. The recruitment of dorsal atelectatic lung is thought to be produced by a more even distribution of pleural pressure. The transmural distending pressure is greater in the dorsal regions but is not significantly reduced in the dependent ventral region. Studies have found that in 60% to 80% of ARDS patients who are placed in the prone position, the P.O2/F.O2 ratio improves (from 80 to 200). However, it is not clear that prone positioning alters mortality for ARDS patients.

**Complications of Mechanical Ventilation**

**PULMONARY COMPLICATIONS**

Serious pulmonary complications of intubation and mechanical ventilation can be divided into three categories: (1) infection related to the presence of an endotracheal tube, (2) alveolar overdistention, and (3) atelectasis.

**Infection**

Mechanically ventilated patients are at high risk (13% to 38%) for nosocomial pneumonia. Early onset pneumonia, occurring 48 to 72 hours after intubation, is usually the result of aspiration during the intubation process. These infections are most often caused by antibiotic-sensitive organisms, including oxacillin-sensitive Staphylococcus aureus, Haemophilus influenzae, and Streptococcus pneumoniae. Ventilator-associated pneumonia that occurs more than 72 hours after intubation is frequently caused by antibiotic-resistant pathogens, including Pseudomonas aeruginosa, oxacillin-resistant S. aureus, Acinetobacter species, and Enterobacter species. The pathogenesis of ventilator-associated pneumonia usually requires two important steps: (1) bacterial colonization of the aerodigestive tract and (2) aspiration of contaminated secretions into the lower airways. The risk of a ventilator-associated pneumonia appears to be higher in trauma or burn patients and as the duration of ventilation increases. Diagnosis of ventilator-associated pneumonia may be difficult because many other processes may cause pulmonary infiltrates and fever. Also, cultures obtained by suctioning secretions through the endotracheal tube do not reliably differentiate between pneumonia and bacterial colonization of the trachea. The use of the fiberoptic bronchoscope to obtain specimens with a protected brush or quantitative cultures of bronchial lavage fluid may be helpful in excluding a pulmonary source of infection in intubated patients who have new clinical signs that may be caused by a noninfectious process.

Nonpharmacologic strategies may decrease the incidence of ventilator-associated pneumonia, including adequate hand washing after contact with each patient. Whenever possible, intubated patients should be kept in a semirecumbent position (45˚ from horizontal), and gastric distention should be avoided to prevent aspiration. In addition, the incidence of ventilator-associated pneumonia can be significantly reduced with the continuous aspiration of subglottic secretions. Several pharmacologic strategies may prevent the development of ventilator-associated pneumonia, such as avoiding the use of unnecessary antibiotics, rotating the class of antibiotics used in the empirical treatment of a suspected bacterial infection, and administering chlorhexidine oral rinse.

Nosocomial sinusitis is strongly related to the nasotracheal route of intubation. CT demonstrated fluid in the maxillary sinus in 95.5% of patients who underwent both nasotracheal and nasogastric intubation for 1 week, compared with only 22.5% of patients in whom endotracheal and feeding tubes were placed via the oral route. Aspiration of the sinus may reveal nonpurulent mucoid material, but in a significant number of cases, sinusitis will be evidenced by positive stains and cultures of aspirated pus. Treatment of nosocomial sinusitis includes administration of antibiotics, replacement of nasal tubes with tubes placed via the oral route, and use of decongestants to facilitate drainage.

**Alveolar Overdistention**

Alveolar overdistention results in two potentially life-threatening problems: hypotension and barotrauma. Ventilator-associated hypotension occurs most often in patients with obstructive airway disease, because the markedly increased lung volume with auto-PEEP impedes venous return. The risk of life-threatening hypotension is greatest at the time of intubation, when preexisting volume depletion and the administration of sedative agents limit the patient’s ability to maintain blood pressure. In addition to receiving rapid infusion of intravenous fluids, hypotensive patients who have underlying airway disease should be allowed to reduce the overdistention themselves by interrupting mechanical inflation, before ventilation is resumed at a reduced frequency [see Figure 5]. Although less common, ventilator-associated hypotension also occurs in ARDS patients who have high levels...
of PEEP and when intrinsic PEEP develops with airway obstruction.

Extra-alveolar air caused by positive pressure ventilation is termed barotrauma. Examples include subcutaneous emphysema, pneumomediastinum, arterial gas embolism, and pneumothorax [see Figure 6]. Extra-alveolar air usually originates from overdistended alveoli that rupture into the surrounding interstitial space. High alveolar (plateau) pressure and infections that produce lung necrosis increase the risk of barotrauma. Tension pneumothorax is the most common life-threatening manifestation of barotrauma. Tension pneumothorax leads to worsening hypoxemia and decreased venous return with hypotension. Hyperresonance and a reduction of breath sounds on the side of the pneumothorax are common, and inflation pressures are increased. In patients with severe airflow obstruction, differentiating a tension pneumothorax from hyperinflation as the cause of hypotension may be difficult at bedside. Therefore, it is advisable to allow a period for deflation to determine whether a reduction of hyperinflation improves the blood and inflation pressure [see Figure 5].

**Atelectasis**

Atelectasis is a common cause of severe hypoxemia that develops during mechanical ventilation. Left lung atelectasis may result from intubation of the right main stem bronchus, a problem that also may lead to overdistention of the right lung signaled by increased inflation pressures [see Figure 7]. A common cause of atelectasis is mucoid impaction of the bronchi. The right lung is more easily suctioned because the right main stem bronchus follows a more direct course. The left lung is more likely to be affected by retained secretions because of the more horizontal course of the left main stem bronchus. With atelectasis of an entire lung, breath sounds are diminished or absent on the affected side, and the trachea is shifted toward that side. A chest radiograph will reveal increased opacity in the affected hemithorax, together with ipsilateral tracheal shift and elevation of the hemidiaphragm. These findings are crucial for radiographic differentiation of whole lung atelectasis from a massive pleural effusion. Massive pleural effusion should cause the trachea to deviate away from the involved lung. A large region of atelectasis may produce a significant intrapulmonary shunt, giving rise to profound hypoxemia caused by shunting that is refractory to an increase in FIO₂.

Atelectasis should be suspected when a sudden onset of severe, refractory hypoxemia occurs in the absence of hemodynamic instability. Other causes of profound hypoxemia, such as massive pulmonary embolism or tension pneumothorax, produce concomitant hypotension. Placing the patient in the lateral decubitus position with the atelectatic lung upright may significantly improve oxygenation, because gravity will redistribute blood flow to the dependent lung. Bronchoscopy should be performed to remove excess mucus if it cannot be easily extracted with endotracheal suctioning after chest percussion.³²

**Nonpulmonary Complications**

Nonpulmonary complications occur in critically ill patients either because of the natural course of the underlying disease or because of iatrogenesis. A major role of the physician is to limit the occurrences of these nonpulmonary complications by anticipating common problems and initiating specific prophylactic measures.

**Venous Thromboembolism**

Venous thromboembolic disease is a significant cause of morbidity and mortality in critically ill patients. On routine clinical screening, 33% of patients in medical intensive care units have deep vein thrombosis (DVT) and 18% of trauma patients have proximal DVT.³³⁻³⁴ Specific independent risk factors associated with the development of venous thromboembolism include trauma, underlying malignancy, immobilization, congestive heart failure, and obesity. Prophylaxis is recommended for all high-risk patients and has been reported to decrease the incidence of DVT by 68%.³⁵ The most commonly used regimen is low-dose unfractionated heparin, 5,000 units administered subcutaneously two or three times daily. Other prophylactic therapies, including intermittent pneumatic compression...
stockings and graded elastic stockings, can be used for patients who cannot tolerate anticoagulation. In patients with major trauma, low-molecular-weight heparin is more effective in preventing the development of proximal DVT than is prophylaxis with standard unfractionated heparin. However, the use of low-molecular-weight heparin as prophylaxis in medical patients has not been shown to provide greater benefit than standard unfractionated heparin.

Gastrointestinal Bleeding

Gastrointestinal bleeding caused by stress ulceration is another important nonpulmonary complication and occurs in 1% to 10% of all critically ill patients. Patients with coagulopathy, burns, head injury, or respiratory failure requiring mechanical ventilation are at increased risk for clinically significant bleeding. Histamine receptor antagonists should be administered to high-risk patients to reduce the possibility of the development of clinically significant bleeding. Other therapeutic options include the cytoprotective agent sucralfate, which does not alter the gastric pH level and may be associated with a lower risk of late-onset pneumonia.

Pressure Ulcers

Critically ill patients are also at an increased risk for pressure ulcers or localized areas of tissue necrosis that develop when soft tissue is compressed between a bony prominence and an external surface. Pressure ulcers occur in 33% to 56% of patients in the ICU and are a source of infection that can result in bacteremia and osteomyelitis. Prevention programs that include regular repositioning of patients, reducing the accumulation of moisture on skin, and adequate nutritional supplementation reduce the incidence of pressure sores. Air-suspension beds that redistribute body weight away from bony prominences also reduce the risk of pressure sores in certain critically ill patients.

Neuromuscular Weakness

Patients who undergo mechanical ventilation may be at risk for neuromuscular weakness that persists long after the cause of respiratory failure has been resolved. A common cause of diffuse weakness is critical illness polyneuropathy, an axonal disorder that occurs with sepsis and multiorgan failure. When present, critical illness polyneuropathy may be an important cause of delayed weaning from mechanical ventilation. Use of neuromuscular paralysis may be associated with weakness that persists after the neuromuscular blocking agents have been discontinued. Prolonged neuromuscular blockade can be diminished by appropriate dosing, adequate monitoring of the degree of neuromuscular blockade, and avoidance of medications that potentiate the action of specific neuromuscular blocking agents. Neuromuscular blocking agents may also contribute to the development of acute myopathy, particularly in patients who receive concomitant corticosteroids. The risk of myopathy is not influenced by the chemical structure of the agent used to induce paralysis but is strongly correlated with the duration of paralysis.

Acute Renal Failure

Acute renal failure is another common nonpulmonary complication of patients in the ICU. Despite considerable advances in the management of critically ill patients and renal replacement therapy, the mortality associated with acute renal failure remains greater than 50%. Although multiple system organ failure and other comorbidities contribute to its high mortality, acute renal failure is independently associated with an increase in morbidity and mortality. In addition, long-term dialysis support is sometimes required for survivors of acute renal failure. Renal dysfunction in ICU patients is usually caused by intrinsic renal disease. Hypotension, sepsis, the use of aminoglycosides, and volume depletion are all risk factors for the development of acute renal failure.
Withdrawal of Mechanical Ventilatory Support

To decrease complications and improve patient comfort, mechanical ventilatory support should be removed as soon as possible. However, premature withdrawal of mechanical ventilation is also associated with adverse events that may further delay appropriate extubation, such as aspiration or severe cardiopulmonary decompensation. Determination of the proper time to extubate a patient is based on several factors, including reversal or improvement of the underlying acute illness, adequate respiratory function, lack of excessive secretions, and ability to protect the airway.

Simple screening criteria have been developed that identify patients who may be ready to be removed from mechanical ventilation. These criteria include a minimal requirement for supplemental oxygenation (FiO2 ≤ 0.40 or PEEP/FiO2 < 200), a PEEP level not exceeding 5 cm H2O, adequate cough during suctioning, and no infusion of vasoactive agents. Measures of adequate respiratory function that are compatible with extubation have also been proposed, including a measure of respiratory function that quantifies the degree of rapid and shallow breathing, determined as a ratio of the respiratory rate divided by the tidal volume during spontaneous breaths. A threshold of 105 breaths per minute per liter, measured after 1 minute of spontaneous breathing, provides an excellent means to predict a successful extubation, with a positive and negative predictive value of 0.78 and 0.95, respectively.48

Most patients can be removed rapidly from mechanical ventilation once the acute illness requiring mechanical ventilation has been reversed, and over 75% of patients who meet these initial screening criteria can be extubated successfully.49 These patients can be quickly identified by a 30-minute to 2-hour trial of spontaneous breathing while they are connected to the ventilator. Patients who appear comfortable after a trial of spontaneous breathing (respiratory rate < 35 breaths/min; heart rate < 140 beats/min; adequate arterial oxygen saturation; and no evidence of anxiety, diaphoresis, or extreme hypotension or hypertension) will likely be successfully removed from mechanical ventilation. Therefore, the concept of weaning, or slowing the removal of the patient from mechanical ventilation, does not apply to the majority of patients who require mechanical ventilation.

The remaining 25% of patients who require mechanical ventilation for acute respiratory failure cannot be removed rapidly from the ventilator. There are several options for this group of patients. The three most commonly used modes of weaning are the following:

1. SIMV, which allows spontaneous breathing and diminishing numbers of mandatory breaths per minute until the patient is breathing unassisted.
2. The use of a T-piece circuit, which allows intermittent trials with total removal of mechanical support.
3. Use of decreasing levels of pressure-support ventilation.

Two large studies compared these three methods of weaning. The first one found that a gradual decrease in the level of pressure support was the most effective.49 The second study found that a daily T-piece trial was associated with the shortest duration of mechanical ventilation.48 The disparate conclusions of these two studies may in part be the result of differing criteria for extubation. Currently, there does not appear to be any clear advantage to the gradual reduction in the level of pressure support or the use of intermittent T-piece trials as methods for weaning. Gradual reduction in the number of machine-supported breaths by use of SIMV appears to be the least effective method of weaning.

Several nonpulmonary factors clearly alter the effectiveness and timeliness of successful removal from mechanical ventilation. The daily screening of the respiratory function of patients receiving mechanical ventilation, followed by trials of spontaneous breathing initiated by a respiratory therapist, can reduce the duration of mechanical ventilation.19,20 Daily interruption of sedative infusions has also been associated with decreased duration of mechanical ventilation and length of stay in the ICU.21 In addition, it has been shown that fewer diagnostic tests to assess change in mental status are performed in patients assigned to daily interruption of sedative agents. Finally, noninvasive ventilation has been used as a technique to expedite weaning for patients with COPD.24 Extubation and the application of noninvasive ventilation by face mask attempted after 48 hours has been associated with a significantly shorter mean duration of mechanical ventilation.

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References