

# Acute Respiratory Distress Syndrome

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The acute respiratory distress syndrome (ARDS) is a devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. More than 30 years ago, Ashbaugh and colleagues<sup>1</sup> described a unique set of physiologic, radiographic, and pathologic characteristics among patients who had cyanosis refractory to oxygen therapy, severe dyspnea, and tachypnea. These patients had decreased respiratory compliance with radiographic evidence of diffuse alveolar infiltrates. Pathologic examination of lung tissue from these patients showed atelectasis, hyaline membranes, and pulmonary edema. Petty<sup>2</sup> called this set of findings the *adult respiratory distress syndrome*, distinguishing it from the respiratory distress syndrome seen in newborns. The name was later changed to *acute* respiratory distress syndrome to recognize that it may occur in patients of any age. This article provides an overview of ARDS and its management.

## DEFINITIONS

Because ARDS can occur in a wide range of clinical settings and is primarily a clinical diagnosis, clinicians and researchers have used a number of definitions. This heterogeneity and lack of consensus in defining ARDS has led to difficulty in effectively comparing studies related to the various epidemiologic, clinical, and management issues surrounding ARDS. In 1994, the American-European Consensus Conference Committee recommended new definitions of ARDS and acute lung injury (Table 1), which are based on the presence of pulmonary infiltrates and impaired oxygenation in the setting of acute onset of respiratory failure. To exclude patients with cardiogenic pulmonary edema, the pulmonary artery occlusion (wedge) pressure must be assessed. The term *acute lung injury* describes the early phase of ARDS, in which hypoxemia is less severe.

The consensus definition of ARDS has 2 advantages. First, the definition recognizes the importance of the severity of clinical lung injury. Second, the definition is

simple to apply in the clinical setting. However, this simplicity may also be a disadvantage because some factors that influence outcomes (eg, underlying cause, whether other organ systems are affected) do not need to be assessed in order to arrive at the diagnosis. Some studies have used relatively more strict criteria for the diagnosis of ARDS, requiring that patients with ARDS meet the following 5 criteria simultaneously: (1) acute respiratory failure from a known at-risk diagnosis, (2) low static compliance of the respiratory system, (3) pulmonary artery wedge pressure that is not increased, (4) bilateral radiographic infiltrates, and (5) decreased ratio of alveolar to arterial partial pressure of oxygen ( $PAO_2/PaO_2$ ).<sup>3,4</sup>

## EPIDEMIOLOGY

An accurate estimation of the incidence of acute lung injury and ARDS has been hindered by the lack of a uniform definition. An early estimate by the National Institutes of Health suggested that the annual incidence in the United States was 75 per 100,000.<sup>5</sup> More recent studies reported incidences of 1.5 to 8.3 per 100,000.<sup>6</sup> To clarify the incidence of ARDS, a prospective epidemiologic study using the 1994 consensus definition is currently underway in Seattle.

## CLINICAL DISORDERS ASSOCIATED WITH ARDS

The clinical disorders most commonly associated with ARDS (Table 2) can be divided into those associated with direct injury to the lung (eg, pneumonia, aspiration of gastric contents, pulmonary contusion, fat emboli) and those that cause indirect lung injury (eg, sepsis, severe trauma, cardiopulmonary bypass, drug overdose). Overall, sepsis is associated with the highest risk of progression to acute lung injury or ARDS

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**Table 1.** Definitions for the Diagnosis of Acute Lung Injury and Acute Respiratory Distress Syndrome

Parameter	Acute Lung Injury	Acute Respiratory Distress Syndrome
Oxygenation status	Pao <sub>2</sub> /Fio <sub>2</sub> ratio < 300	Pao <sub>2</sub> /Fio <sub>2</sub> ratio < 200
Respiratory status	Acute onset of respiratory failure	Acute onset of respiratory failure
Chest radiograph	Bilateral pulmonary infiltrates	Bilateral pulmonary infiltrates
Fluid status	Pulmonary artery occlusion pressure (wedge pressure) < 18 mm Hg or no clinical findings suggestive of increased left atrial pressure	Pulmonary artery occlusion pressure (wedge pressure) < 18 mm Hg or no clinical findings suggestive of increased left atrial pressure

Pao<sub>2</sub> = partial pressure of arterial oxygen; Fio<sub>2</sub> = fraction of inspired oxygen.

Adapted from The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994;149:818–24.

**Table 2.** Conditions Associated With Acute Respiratory Distress Syndrome

**Shock**

Any type, especially septic shock

**Infection**

Any pneumonia or sepsis from any cause, especially viral pneumonia, *Pneumocystis carinii* pneumonia, or gram-negative pneumonia/sepsis

**Trauma**

Burns, fat emboli, lung contusion, head trauma

**Toxic gas inhalation**

Prolonged hyperoxia, smoke, nitrogen dioxide, ammonia, chlorine, cadmium, phosgene

**Aspiration**

Gastric contents, near-drowning

**Drug ingestion**

Barbiturates, chlordiazepoxide, colchicine, dextran 40, ethchlorvynol, fluorescein, heroin, methadone, salicylates, thiazides

**Miscellaneous**

Pancreatitis, post-cardiopulmonary bypass, multiple blood transfusions, leucoagglutinin reaction, eclampsia, air emboli, amniotic fluid emboli, bowel infarction, carcinomatosis, high altitude, neurogenic causes other than head trauma, radiologic contrast media, protamine, diffuse alveolar hemorrhage

Adapted with permission from Campbell GD Jr, Payne DK. Bone's atlas of pulmonary and critical care medicine. Philadelphia: Lippincott Williams & Wilkins; 2001.

(approximately 40%).<sup>7</sup> The presence of multiple predisposing disorders substantially increases the risk of ARDS,<sup>7</sup> as does the presence of secondary factors, in-

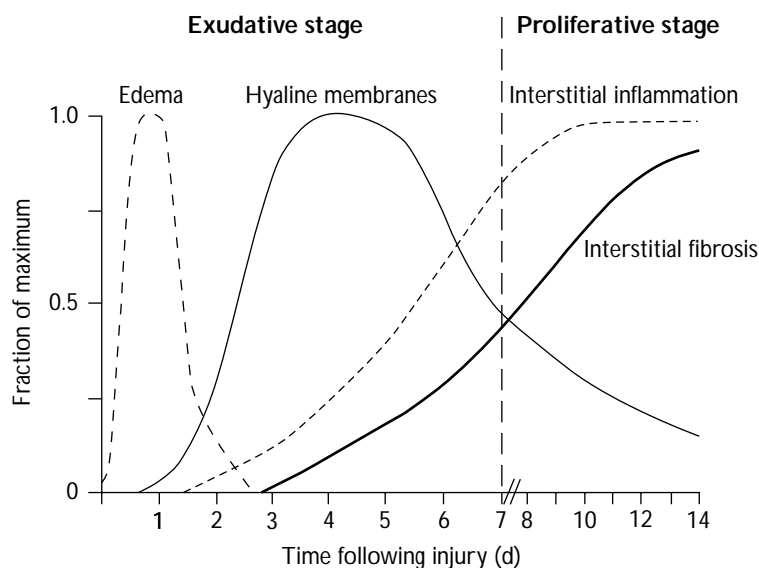
cluding chronic alcohol abuse,<sup>7</sup> chronic lung diseases,<sup>8</sup> and aspiration of very low pH gastric fluid. Diffuse alveolar damage has not been documented for all of the conditions most commonly associated with ARDS; therefore, some may simply represent a noncardiogenic pulmonary edema (eg, a near-drowning).

**PATHOPHYSIOLOGY**

Irrespective of the specific primary etiology, it appears that it is the nonspecific host response that results in the development of ARDS. This nonspecific host response may be mediated via a number of unique mechanisms involving leukocytes, platelets, and endothelium. It has been shown that neutropenic patients can develop ARDS,<sup>9</sup> suggesting the role of other mechanisms as the source for potentially harmful mediators (eg, cytokines, complement, arachidonic acid products, oxygen free radicals). Injury of the pulmonary endothelium results in activation of chemical mediators, which leads to increased vascular permeability during the initial exudative phase of ARDS (first 7 days) and to the development of fibrosis in the fibroproliferative phase.

**CLINICAL, PATHOLOGIC, AND RADIOGRAPHIC FEATURES**

ARDS is a progressive syndrome that can be divided into 2 phases with differing clinical, histopathologic, and radiographic manifestations (**Figure 1**). The exudative phase (days 1–7) is characterized by pulmonary capillary congestion, endothelial swelling, and microatelectasis, and is associated with fluid leakage from capillaries, fibrin deposition, and formation of hyaline membranes. Clinically, this phase is manifested by the rapid onset of hypoxemic respiratory failure that is refractory to treatment with supplemental oxygen. Patients may progress to requiring positive pressure ventilator support with worsening of the respiratory status. Patients



**Figure 1.** Schematic representation of the time course of the acute respiratory distress syndrome. Adapted from Katzenstein AA, Askin FB. Surgical pathology of non-neoplastic lung disease. Philadelphia: Saunders; 1982, with permission from Elsevier Science.

are usually tachypneic and tachycardic and may also be hypotensive. The chest radiographic findings in this stage include interstitial edema and increasing parenchymal opacification, which may appear patchy but rapidly coalesces to a uniform pattern. Bilateral infiltrates may be patchy or asymmetric and may include pleural effusions.<sup>10</sup> Involvement is usually bilateral and symmetrical, but marked asymmetry has been reported. Chest radiograph findings during the exudative stage are indistinguishable from those of cardiogenic pulmonary edema.<sup>11</sup>

The fibroproliferative phase (after day 7) comprises the healing process. Radiographically, it appears as a developing interstitial fibrotic pattern; the end result of this fibroproliferation may be honeycomb lung. Computed tomographic scanning shows a more heterogeneous distribution of disease at any stage than does chest radiography. Clinically, the patient will have progressive hypercarbia with stiff lungs. Pathologic findings during the fibroproliferative stage (Figure 2) include diffuse alveolar damage characterized by increased numbers of neutrophils, macrophages, and erythrocytes; and the presence of hyaline membranes, protein-rich edema fluid in the alveolar spaces,<sup>12</sup> capillary injury, and disruption of the alveolar epithelium.<sup>13</sup>

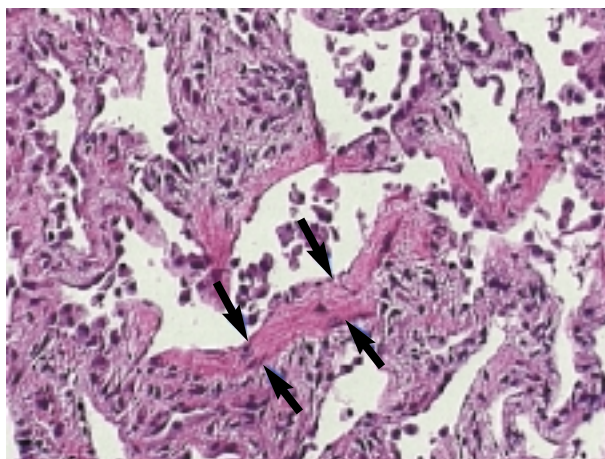
#### DIFFERENTIAL DIAGNOSIS

Diagnosis of ARDS is primarily clinical in nature (Table 1). It requires a constellation of historical and physical findings, as well as exclusion of specific processes that mimic ARDS. If the predisposing factor (or factors) is obvious, very little is generally required to

make a clinical diagnosis. When the presentation is less clear, however, a more thoughtful process is required to establish the diagnosis.

In the setting of the intensive care unit, congestive heart failure (CHF) is the most common alternative diagnosis for ARDS. A chest radiograph by itself often cannot distinguish cardiogenic from noncardiogenic pulmonary edema. A pulmonary artery occlusion pressure of 18 mm Hg or greater argues for a cardiogenic pulmonary edema, although lung injury can coexist with intravascular volume overload. Clinical evaluation suggesting CHF may include the presence of elevated neck veins, a displaced apical pulse, lower-extremity edema, bibasilar rales, an enlarged cardiac silhouette, and/or prior myocardial infarction evidenced on an electrocardiogram.<sup>14</sup> When the possibility of CHF exists, and if the patient appears clinically capable of tolerating a reduction in circulating blood volume, it is reasonable to attempt diuresis and observe its impact on oxygenation and on radiographic results. Alternatively—or in combination with the clinical evaluation—an echocardiogram can be used to diagnose CHF by evaluation of cardiac chamber enlargement and reduced stroke volume.<sup>15</sup>

Even more challenging is the patient for whom no immediate or obvious cause of a pulmonary process can be identified. In this situation, a thorough clinical evaluation must be carried out, keeping in mind that the most probable cause of the ARDS is likely to be infection. Complete history, physical examination, and laboratory evaluation should be performed. Bronchoalveolar lavage (BAL) may be helpful in evaluating



**Figure 2.** Photomicrograph of lung tissue showing diffuse alveolar damage (original magnification  $\times 20$ ). The alveolar septa are markedly thickened by loose connective tissue and edema and contain increased numbers of lymphocytes and macrophages. The alveoli contain scattered macrophages. Hyaline membranes are seen (arrows). Image reproduced with permission from T.V. Rajan, MD, PhD, and the Pathology Department of the University of Connecticut Health Center. Available at <http://pathweb.uchc.edu>. Accessed 26 Sept 2002.

for viral pneumonia, pneumocystic pneumonia, tuberculosis, legionella disease, fungal infection, and other unusual infectious diseases.

A subgroup of patients with the conditions listed in [Table 2](#) present with a noncardiogenic pulmonary edema does not meet the definition of either ARDS or acute lung injury. It can be difficult to differentiate between cardiogenic and noncardiogenic pulmonary edema in patients with suspected ARDS. Noncardiogenic pulmonary edema can be secondary to overdose of opioid agents, ethchlorvynol, or other toxins, or to hypersensitivity or neurogenic processes. The precise pathogenesis of noncardiogenic pulmonary edema is unknown but most likely involves hypoxia. Hypoxia causes severe pulmonary vasoconstriction, and the high pressures may cause direct pulmonary capillary damage and leakage, which would explain the high protein content of the alveolar fluid found in patients with noncardiogenic pulmonary edema. The edema usually clears rapidly within 24 to 36 hours with simple oxygen therapy and supportive care.

Absence of cardiac dysfunction by echocardiogram, low central venous pressures, low pulmonary wedge pressures, and a high cardiac output have been demonstrated in patients with noncardiogenic pulmonary edema. The radiologic findings in these patients are

extremely variable, ranging from a classic butterfly pattern of pulmonary edema to unilateral patchy infiltrates resembling pneumonia. The size of the heart is normal. Infiltrates caused by pulmonary edema clear within 24 to 48 hours, and those lasting longer should be considered highly suggestive of other processes.

Bronchoscopy with BAL is an important part of the evaluation of ARDS patients with immunosuppression or patients whose ARDS is of unclear origin. Although the results of BAL are not specific for ARDS, they can serve to rule out certain acute processes. The presence of high number of eosinophils (more than 15% to 20% of the total cell count) suggests acute eosinophilic pneumonia. A high lymphocyte count suggests hypersensitivity pneumonitis, sarcoidosis, bronchiolitis obliterans-organizing pneumonia, or other acute forms of interstitial lung disease. The presence of many erythrocytes, especially in the presence of hemosiderin-laden macrophages, suggests pulmonary hemorrhage. Cytologic examination should be considered to evaluate for the presence of pneumocystic pneumonia, malignancy, and viral inclusion bodies. Transbronchial lung biopsies are generally contraindicated in mechanically ventilated patients. Open lung biopsy is rarely of help.

## MANAGEMENT

Treatment of ARDS is supportive and consists primarily of oxygenation and ventilatory support. Improvement in the supportive care of patients with acute lung injury and ARDS may have contributed to the recent decline in the mortality rate.<sup>16</sup> Search for the underlying cause should be made promptly, with particular attention to the possibility of treatable conditions such as sepsis, pneumonia, and abdominal infection. Prevention or early treatment of nosocomial infections is critical, because uncontrolled infection is a frequent cause of death in patients with ARDS.<sup>3</sup> Adequate nutrition through the use of enteral feeding is preferred to parenteral nutrition to avoid the serious risk for catheter-induced infections<sup>17</sup> and reduce the risk for multi-system organ failure. Prevention of gastrointestinal bleeding and thromboembolism is also important.<sup>18</sup>

### Monitoring Thoracic Compliance

In addition to monitoring laboratory and radiographic results and other usual clinical parameters (eg, pulse oximetry, arterial blood gases) the physician should closely monitor thoracic compliance as part of the ongoing assessment of patients with ARDS. A decrease in thoracic compliance is observed with disorders of the thoracic cage or a reduction in the number

of functioning lung units (as in conditions of resection, bronchial intubation, pneumothorax, pneumonia, atelectasis, pulmonary edema, or ARDS).

In patients receiving mechanical ventilation and making no respiratory effort, it is possible to obtain a rough measure of total thoracic compliance by noting the tidal volume ( $V_T$ ) being delivered and the airway pressure displayed on the ventilator gauge. Conditions of zero gas flow are necessary and can be achieved by employing the “inspiratory-hold” option on the ventilator, during which period airway pressure falls to a plateau. If the patient is receiving positive end-expiratory pressure (PEEP), this amount of pressure first must be subtracted from the plateau pressure before calculating total thoracic compliance, thus:

$$\text{Static compliance (mL/cm H}_2\text{O)} = \frac{\text{delivered } V_T \text{ (mL)}}{\text{plateau pressure} - \text{PEEP (cm H}_2\text{O)}}$$

The normal range is generally considered to be 60 to 100 mL/cm H<sub>2</sub>O. Because the level of PEEP must be taken into account when calculating total thoracic compliance, it is important to check for the presence of patient-generated PEEP (ie, auto- or intrinsic-PEEP).

Dynamic compliance is often confused with static compliance, and it is important to differentiate the two measures. Dynamic compliance takes into account the peak airway pressure rather than the plateau pressure. It is calculated using the following equation:

$$\text{Dynamic compliance (mL/cm H}_2\text{O)} = \frac{\text{delivered } V_T \text{ (mL)}}{\text{peak airway pressure} - \text{PEEP (cm H}_2\text{O)}}$$

Dynamic compliance is not a measure of true thoracic compliance because peak airway pressure also includes the resistive pressure component of the applied pressure. Dynamic compliance may be decreased by disorders of the airways, lung parenchyma, or chest wall, and if it falls to a greater extent than does the total thoracic compliance, an increase in airway resistance (eg, from bronchospasm, mucus, plugging, kinking of the endotracheal tube) or an excessive flow rate may be present. Normal dynamic compliance is about 50 to 80 mL/cm H<sub>2</sub>O at normal flow rates (50 to 80 L/min).

#### NOVEL TREATMENT STRATEGIES

An improved understanding of the pathogenesis of acute lung injury and ARDS has led to the assessment of several novel treatment strategies.

#### Low Tidal Volume Mechanical Ventilation

It has been shown that large  $V_T$ s and high peak inspiratory pressures contribute to secondary lung injury (volutrauma). Patients with ARDS may need a much smaller  $V_T$  in comparison with individuals with healthy lungs. The ARDS Network Trial provided convincing evidence that ventilation with reduced  $V_T$ s significantly lowered mortality in patients with ARDS. The trial compared a traditional  $V_T$  (12 mL/kg of predicted body weight) with a lower  $V_T$  (6 mL/kg of predicted body weight) in 861 patients.<sup>19</sup> In the group receiving lower  $V_T$ s, a detailed protocol was used to adjust the  $F_{IO_2}$  and PEEP such that the plateau pressure (airway pressure measured after a 0.5-second pause at the end of inspiration) could not exceed 30 cm H<sub>2</sub>O. The in-hospital mortality rate was 39.8% in the group treated with traditional  $V_T$ s and 31.0% in the group treated with lower  $V_T$ s ( $P = 0.007$ ). Thus, mortality was reduced by 22% in the group treated with lower  $V_T$ s, a finding of major importance.

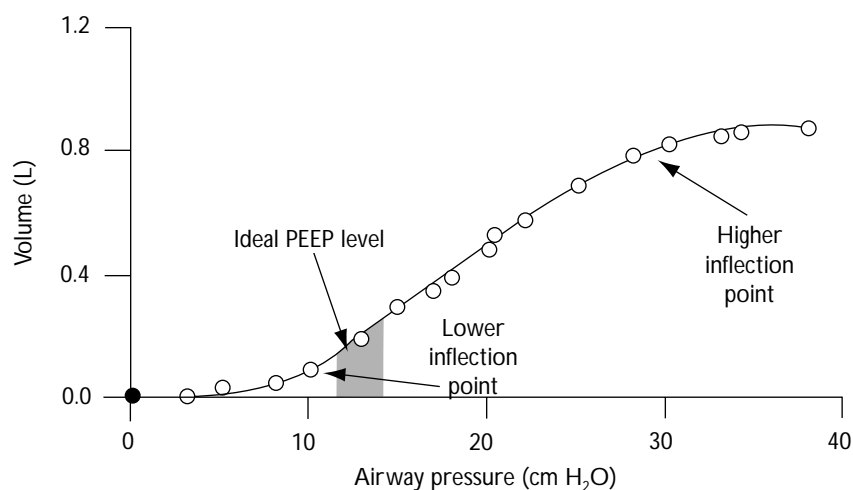
#### Permissive Hypercapnia

Use of low  $V_T$ s in mechanical ventilation typically results in hypoventilation with an associated rise in  $P_{aCO_2}$  that can result in acidosis. When permissive hypercapnia is employed,  $P_{aCO_2}$  is allowed to increase slowly (but generally is kept < 100 mm Hg), and acid-base status is optimized using chemical alkalization techniques.<sup>20</sup> In general, pH is maintained at a level of 7.20 or higher (preferably 7.25), which is achieved by using sodium bicarbonate, acetate, or tromethamine. The level of chemical alkalization may be limited by the development of hypernatremia and/or hypoventilation. Hence, it may become necessary to increase minute ventilation in order to reduce  $P_{aCO_2}$  to maintain an acceptable acid-base status.

Ventilation can also be improved by increasing the expiratory cycle (ie, increasing the expiratory time relative to the inspiratory time) and the  $V_T$ . It is crucial while increasing respiratory (ventilator) rates and  $V_T$ , however, that the patient is carefully observed for auto-PEEP that could cause significant air trapping, worsen ventilation-perfusion mismatch, and increase risks of barotrauma. In a small number of studies, permissive hypercapnia has been shown to improve survival in patients with ARDS.<sup>20</sup>

#### Use of PEEP in ARDS

PEEP has been used for several years in the management of patients with ARDS. By restoring functional residual capacity to more than closing capacity, PEEP decreases the risk of atelectasis and improves



**Figure 3.** Pressure-volume (compliance) curve for determination of optimal positive end-expiratory pressure in patients with acute respiratory distress syndrome.

recruitment. Amato et al<sup>21</sup> used lower VTs and raised the level of PEEP to keep it above the lower inflection point on a pressure-volume curve (Figure 3) generated for each patient in an attempt to ensure adequate recruitment of atelectatic lung. With this approach, mortality was reduced. This approach is currently being tested in a new ARDS Network ventilation trial. In the protocol used in this trial, a VT of 5 to 7 mL/kg is utilized. PEEP is rapidly increased in increments of 2 to 3 cm H<sub>2</sub>O in order to achieve F<sub>IO<sub>2</sub></sub> levels lower than 0.6. When applying PEEP in the mechanical ventilation of adults with ARDS, most centers use increasing amounts of sedation (eg, propofol) to the point of unconsciousness; neuromuscular blockade is no longer used routinely owing to concerns regarding prolonged paralysis.

When weaning a patient from PEEP, a conservative approach is employed with the aim of minimizing alveolar derecruitment. This is in contrast to the rapid increment used to encourage alveolar recruitment when applying PEEP. Thus, PEEP is weaned slowly in small decrements every few hours. Once PEEP has been weaned to a range of about 5 to 7 cm H<sub>2</sub>O, the F<sub>IO<sub>2</sub></sub> is decreased to lower levels to maintain adequate oxygenation.

### Prone Positioning

Prone positioning usually results in immediate but transitory improvement in oxygenation. Prone positioning requires greater nursing effort and vigilance, and a recent study did not demonstrate improved survival in patients with acute respiratory failure who underwent prone positioning.<sup>22</sup>

### Inverse Ratio Ventilation

The rationale for adopting an inverse ratio ventila-

tor mode (inspiratory phase longer than expiratory phase) rests in the ability of this mode to allow minimal time for recruited unstable alveoli to collapse during exhalation. Inverse ratio ventilation provides less time for exhalation, which may result in stacking of breaths, creating auto-PEEP, which may increase functional residual capacity and oxygenation. Inverse ratio ventilation is usually accompanied by decreases in peak pressure and plateau pressure and an increase in mean airway pressure with improvement in oxygenation. Until large studies aimed at evaluating this approach are completed, it remains unclear whether this mode of ventilation is associated with improved outcomes in patients with ARDS.

It is important to be vigilant for any deleterious consequences of auto-PEEP when using inverse ratio ventilation. Because this mode of ventilation is very uncomfortable, most patients will require heavy sedation. Reduction in oxygen demand should be achieved first with sedation and analgesia. Neuromuscular blocking agents are occasionally useful when sedation and analgesia are ineffective at reducing excessive muscular activity. However, use of neuromuscular blocking agents in critically ill patients may contribute to neuromuscular complications such as myopathy and neuropathy. Judicious and sparing use of these drugs is recommended.

### Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a mode of ventilation that provides 2 levels of continuous positive airway pressure (CPAP) and allows spontaneous ventilation at both levels. APRV is different from other modes of ventilation in that it is based on an intermittent decrease in airway pressure, rather than an increase to provide ventilation. This minimizes mean

airway pressure and reduces the likelihood of over-distending the lungs. Each level of CPAP is time-cycled and time-triggered.

APRV is indicated for patients with acute lung injury or ARDS with stiff lungs and oxygenation problems. The advantages of APRV include sustained oxygenation in spontaneously breathing patients, a decreased need for sedation and/or paralysis, an improvement in respiratory muscle tone by maintaining spontaneous respirations, improved ventilation-perfusion matching, reduced incidence of barotrauma (owing to the reduced main airway pressure), and reduced incidence of hemodynamic compromise (owing to decreased intrathoracic pressure).<sup>23-25</sup> A survival benefit of APRV use in patients with ARDS has not yet been shown.

### Glucocorticoids and Other Anti-inflammatory Agents

Recognition of the inflammatory nature of the lung injury in acute lung injury and ARDS prompted interest in anti-inflammatory treatments, particularly glucocorticoids. However, glucocorticoids had no benefit when they were given before the onset of the disease or early in its course.<sup>4</sup> More recently, glucocorticoids have been used to treat the later, fibrosing/alveolitis phase of the disease. Encouraging results were reported in a small randomized trial of 24 patients.<sup>26</sup> A larger randomized, multicenter trial of treatment with high-dose methylprednisolone for at least 7 days is underway in the United States. Because treatment with high-dose methylprednisolone may increase the incidence of infection, the routine use of this drug in patients with established acute lung injury and ARDS cannot be recommended until results of a large multicenter trial become available.

### Unproven Therapies

**Ventilatory strategies.** High frequency ventilation, extracorporeal membrane oxygenation, intravenous oxygenation, and liquid ventilation have not been shown to improve outcome in ARDS in adults.

**Vasodilation therapy.** Randomized, prospective, placebo-controlled trials investigating the use of nitric oxide inhalation in adult patients with ARDS are currently underway. Treatment with several less selective vasodilators, including sodium nitroprusside,<sup>27</sup> hydralazine,<sup>28</sup> alprostadil (prostaglandin E<sub>1</sub>),<sup>29</sup> and epoprostenol (prostacyclin)<sup>30</sup> have not been shown to be beneficial.

**Surfactant use.** Surfactant is currently not recommended for use in adults with ARDS. Newer preparations of surfactant that contain recombinant surfactant proteins, and new approaches to their instillation (in-

cluding tracheal instillation and BAL), are being evaluated in clinical trials.

### CONCLUSIONS

Substantial progress has been made in the understanding of acute lung injury and ARDS. More information regarding epidemiology and pathogenesis has become available, and the importance of the resolution phase of the illness has been recognized, opening up new avenues for therapeutic intervention. Large, prospective, randomized trials of new ventilatory and pharmacologic strategies may further reduce mortality from this common clinical syndrome. **HP**

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