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CHAPTER 4

Acute Lung Injury: Acute Respiratory Distress Syndrome

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The acute respiratory distress syndrome (ARDS), first described in the medical literature in 1967,[1] consists of the symptom constellation of acute respiratory distress, cyanosis refractory to oxygen administration, decreased lung compliance, and diffuse opacities on the chest radiograph not explained by hydrostatic causes. Although initially called the adult respiratory distress syndrome because of clinical experience with adult patients,[2] it is now termed the *acute respiratory distress syndrome* and is recognized in the pediatric population.

Confusion over the natural history, incidence, and outcome of this syndrome secondary, in part, to lack of a uniform definition was addressed in 1994 by the American-European Consensus Conference (AECC), which provided operational definitions.[3] The Committee recognized apparent variation in the severity of this disorder and recommended criteria for acute lung injury (ALI) and for ARDS as a more severe subset of ALI. Both ALI and ARDS were recognized as belonging to the same clinical spectrum, with acute onset, bilateral infiltrates on the chest radiograph, and absence of evidence of elevated left atrial pressure. However, the term ALI was used to describe disease in which the Pa_{O_2}/Fi_{O_2} ratio (partial pressure of arterial oxygen/fraction of inspired oxygen) is 300 mm Hg or less, whereas ARDS was considered to be present if this ratio was 200 Hg mm or less. Although these criteria are simple to use and are recommended for description of patient groups, they have several weaknesses. They do not specify the cause of the disorder; the description of bilateral pulmonary infiltrates is nonspecific and difficult to implement reproducibly,[4] and response to positive end-expiratory pressure (PEEP) is not considered. Finally, it has become apparent that mortality outcome is not different between patients with only ALI and patients with ARDS.[5]

ETIOLOGY

Predispositions

Critical care physicians frequently observe that patients respond differently to similar predisposing causes of ALI/ARDS and also respond differently to similar treatments. These observations suggest the presence of underlying genetic predispositions to the development of ALI. Two different approaches, namely, candidate gene and genome-wide analysis, may provide new insight. Leikauf and colleagues, studying gene-environment interactions in inbred mouse strains, examined the relative susceptibility to ALI induced by a variety of environmental agents.[6,7] These investigators found a varied response among different strains and concluded that susceptibility to ALI is heritable. Using complementary DNA (cDNA) microarray analysis to identify clusters of coregulated genes, they found altered expression of relatively few genes that control the complex responses of lung injury and repair. These findings suggest candidate genes that

may contribute to individual susceptibility to the development of ARDS.

Several genetic polymorphisms may predispose patients to the clinical development of ALI. Asp299Gly and Thr399Ile mutations affecting the extracellular domain of the toll-like receptor 4 (TLR-4) are associated with a blunted response to inhaled lipopolysaccharide in humans.[8] The Asp299Gly mutation occurred in 5.5% of patients with septic shock (a recognized predisposition to development of ALI), as opposed to 0% of 73 healthy blood donors. For patients in whom exposure to lipopolysaccharide is a critical determinant of the development of ALI, the presence of the Asp299Gly mutation may be a predisposing factor.

The human angiotensin-converting enzyme (ACE) gene contains a restriction fragment length polymorphism consisting of the presence (insertion, I) or absence (deletion, D) of a 287 base pair alu repeat sequence in intron 16.[9] This (I/D) polymorphism, in a healthy population, accounted for 47% of the variance in observed plasma ACE levels, and it was highest in those with the DD genotype.[10] The ACE DD genotype is reported to be present with markedly increased frequency in patients with ARDS compared with patients in intensive care units (ICUs), patients undergoing coronary artery bypass grafting, or healthy populations.[11] Further, the DD genotype is significantly associated with mortality in the ARDS group. These data suggest a role for the renin-angiotensin systems in the pathogenesis of ARDS and further implicate the DD genotype as a predisposing genetic factor.

Additional genetic predispositions for ALI may be presence of polymorphisms in the SP-B gene. Lin and associates described the C/T (1580) polymorphism that results in an amino acid change (Thr131Ile) that may affect protein glycosylation, and they reported increased frequency of the C allele in patients with idiopathic ARDS compared with patients with ARDS secondary to systemic disease or compared with healthy persons.[12] In addition, the frequency of an I/D variant in SP-B intron 4 was reported to be 46.6% among 15 patients with ARDS in contrast to 4.3% among control subjects. Gong and colleagues attempted to reproduce this latter observation and found a significant association between the variant polymorphism and ARDS only in women.[13]

ARDS was described in four children with a functional defect in a mitochondrial enzyme involved in β-oxidation of long-chain fatty acids.[14] Three of the patients shared a common mutation in the enzyme. The authors theorized that accumulating fatty acid metabolites in patients with 3-hydroxylacyl-coenzyme A dehydrogenase and mitochondrial trifunctional protein defects may alter the phospholipid component of surfactant and may impair its function.

These genetic studies are still in their infancy and require confirmation in larger populations with ARDS. Identification of genes associated with increased susceptibility to ALI should lead to greater understanding of relevant disease mechanisms and to the development of targeted therapy.

Clinical Associations

ALI/ARDS is thought to be the uniform expression of a diffuse and overwhelming inflammatory reaction of the pulmonary parenchyma to either a direct injury to the lung (pulmonary ALI/ARDS) or an indirect lung injury related to a systemic process (extrapulmonary ALI/ARDS) (Table 4.1).[15–18] The most frequent causes include sepsis, severe pneumonia, peritonitis, and multiple trauma.[15,19] However, among these, sepsis is associated with the highest risk, because approximately 40% of septic patients develop ALI or ARDS.[17,20] The presence of multiple predisposing disorders substantially increases the risk of developing ARDS,[20] as does the presence of chronic alcohol abuse.[21] Moss and colleagues showed that the incidence of ARDS in patients with chronic alcohol abuse was 70% compared with 31% in individuals without this history,[22] and using a multivariable logistic regression, these investigators concluded that chronic alcohol abuse is an independent risk factor in this disorder.[23] Using animal models of chronic ethanol ingestion, investigators identified alcohol-mediated

Table 4-1 Examples of Causes and Clinical Disorders Associated with Acute Lung Injury/Acute Respiratory Distress Syndrome

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis and septic shock
Aspiration of acid/gastric contents	Multiple trauma
Air or fat emboli	Acute pancreatitis
Inhalational injury	Cardiopulmonary bypass
Near drowning	Transfusion-related acute lung injury (TRALI)
Pulmonary contusion	Drugs
Reperfusion pulmonary edema (post-thrombectomy, post-transplantation)	Neurogenic pulmonary edema
Severe acute respiratory syndrome (SARS)	

alterations in epithelial and endothelial function, surfactant synthesis and secretion, and alveolar-capillary barrier function.[24]

Severe acute respiratory syndrome (SARS) deserves special mention. This disease, thought to be caused by a novel coronavirus (SARS CoV), appeared in November of 2002 and was first described in March of 2003.[25] In a retrospective study of a cohort of patients with SARS who were admitted to ICUs in Asia, there was a 25% incidence of progression to ALI/ARDS, 37% mortality at 28 days, and 52.5% overall ICU mortality after 13 weeks.[26] One third of the patients with SARS and ALI/ARDS recovered within 14 days of illness; however, most patients underwent a protracted course, with high mortality despite maximum supportive therapy. ARDS has been described as the most common complication of this disease.[27]

Ventilator-Induced Lung Injury

ALI that is directly induced by mechanical ventilation is recognized both in animal models and clinically and is designated ventilator-induced lung injury (VILI).[28–30] VILI is indistinguishable morphologically, physiologically, and radiologically from diffuse alveolar damage resulting from other causes of ALI.[31] The contributions of increased pressure and volume to the development of ALI were first studied systematically by Webb and Tierney,[28] who found that increases in rat lung volume were predominantly responsible for development of acute high permeability lung injury or VILI. Subsequently, Dreyfuss and colleagues were able to dissociate the influence of pressure and volume and confirmed, in animal studies, both the central role of volume in the pathogenesis of VILI and the protective effect of PEEP.[30]

Mechanical factors can lead to lung injury through a variety of mechanisms.[32] Tremblay and associates found a three- to sixfold increase in lung cytokines in ex vivo isolated rat lungs ventilated with high tidal volumes with no PEEP or PEEP of 10 cm H_2O, respectively.[33] The increase in lung cytokines was also associated with an increase in c-fos messenger RNA, an early response gene. Alveolar overdistention coupled with the repeated collapse and reopening of alveoli has also been shown to initiate a cascade of proinflammatory cytokines.[34] Additional mechanisms by which repetitive opening and closing of lung units may result in damage to alveolar cells may include activation of complex intracellular signaling pathways, stimulation of paracrine stimulation of pathways, and disruption of alveolar cell plasma membranes.[35] However, the concept of repetitive opening and closing of distal lung units has been called into question, and the alternative concept of the filling of dependent lung regions with edema fluid and foam has been proposed.[36] The mechanisms associated with development of VILI are reviewed in depth in Chapter 5.

A large body of evidence indicates that ventilation at low lung volumes may also contribute to lung injury. In 1984, Robertson proposed that repeated opening and closing of lung units during tidal breathing of infants with respiratory distress syndrome could result in lung injury.[37] Robertson suggested that in an atelectatic lung, the air-liquid interface may be found proximally in the terminal conducting airways, rather than in the alveoli. Opening of these airways would require relatively higher forces, and the shear stresses produced could cause epithelial disruption. Other investigators have shown evidence for lung injury from low lung volume ventilation using various species, lung injury models, PEEP strategies, and modes of ventilation.[38–42]

In patients with ALI/ARDS, ventilation at traditional tidal volumes (10 to 15 mL/kg of predicted body weight) may overdistend uninjured alveoli, promote further lung injury, and contribute to multiorgan failure.[34] Clinical trials have examined the benefit of protective ventilatory strategies that reduce alveolar overdistention and increase the recruitment of atelectatic alveoli. A National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI) trial showed that the use of a tidal volume of 6 mL/kg ideal body weight resulted in a 22% decrease in mortality compared with ventilation with 12 mL/kg ideal body weight in patients with ALI/ARDS.[43] The excess mortality associated with large tidal volume ventilation may be related to cytokine response and the development of multisystem organ failure.[34,44,45] Ranieri and colleagues found that both the pulmonary and the systemic cytokine responses were reduced in patients with ARDS who were treated with low tidal volume ventilation.[44]

PATHOPHYSIOLOGY

The acute or exudative phase of ALI/ARDS is characterized by increased permeability of the alveolar-capillary barrier leading to the influx of protein-rich edema fluid and inflammatory cells into distal airways and alveoli.[46] The alveolar-capillary barrier is formed of two separate barriers, the alveolar epithelium and the vascular endothelium. The importance of endothelial injury leading to increased vascular permeability and formation of pulmonary edema is well established, and a critical role of epithelial injury in ALI/ARDS has also been recognized.[47] The alveolar epithelium is composed of type I and type II cells, occupying 90% and 10% of the alveolar surface area, respectively. The loss of epithelial integrity and injury to type II cells disrupt normal epithelial fluid transport and impair the removal of edema fluid from

the alveolar space in animal models of ALI,[48,49] as well as in the majority of patients with ARDS/ALI.[50] Injury to type II cells also reduces the production and turnover of surfactant.[51]

The pathogenesis and mechanisms of lung injury have been extensively reviewed.[51–53] In response to an inciting event, the pulmonary macrophages and endothelium become activated; surface expression of adhesion molecules is increased, and this leads to neutrophil migration to the alveoli. Activated neutrophils produce a variety of inflammatory mediators, including reactive oxygen species, nitric oxide (NO), leukotrienes, cytokines, chemokines, proteases, platelet-activating factor, and cationic proteins. Other cells, including pulmonary macrophages and alveolar endothelial and epithelial cells, also produce inflammatory mediators. Alveolar macrophages are able to secrete cytokines including interleukin (IL)-1, IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF-α). Apart from these proinflammatory mediators, a host of endogenous anti-inflammatory mediators can simultaneously be present, including IL-1 receptor antagonist, soluble TNF receptor, autoantibodies against IL-8, and anti-inflammatory cytokines such as IL-10 and IL-11.[54] In fact, imbalance between proinflammatory and anti-inflammatory mediators may play an important role in the pathogenesis of lung injury. The end result of this vicious cycle is alveoli filled with protein-rich edema fluid, cells, cellular debris, red blood cells, and fibrin-rich hyaline membranes on the denuded basement membrane.

Extravascular fibrin deposition, and the abnormalities in the coagulation and fibrinolytic pathways that promote it, may be important in the pathogenesis of ALI.[55] Procoagulant activity is increased in bronchoalveolar lavage (BAL) samples from patients with ALI/ARDS, whereas fibrinolytic activity is markedly decreased or undetectable. This procoagulant response is mainly attributable to tissue factor associated with factor VII,[55] whereas the decrement in fibrinolytic response is attributable to inhibition of urokinase plasminogen activator by plasminogen activators or inhibition of plasmin by antiplasmins.[55,56] The concurrent changes in procoagulant and fibrinolytic activity would be expected to promote pulmonary fibrin deposition and are likely to account for the persistence of alveolar fibrin in ALI.

The acute exudative phase of ALI/ARDS may lead either to rapid resolution of the disorder[57,58] or to progression to a late fibroproliferative phase that may start as early as 5 to 7 days after the onset of injury.[59] At this latter stage, the alveolar space becomes filled with mesenchymal cells, and there is extensive proliferation of myofibroblasts in the lung interstitium.[60] Patients who die during this stage have increased fibronectin and collagen in lung autopsy specimens.[61] This stage of ALI/ARDS may be promoted by early proinflammatory mediators, including IL-1, that stimulate production by fibroblasts of extracellular matrix components including procollagen III peptide.[62–64] The findings of alveolar fibrosis and the appearance of procollagen III in the alveolar space correlate with an increased risk of death.[65,66]

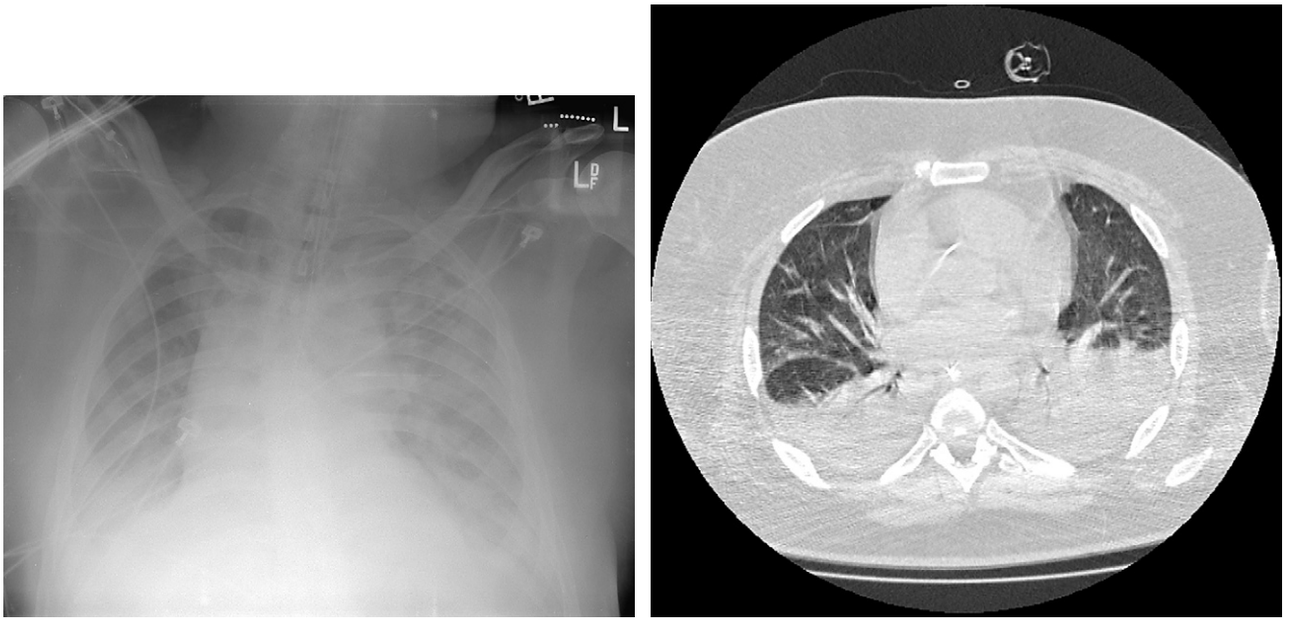
CLINICAL PRESENTATION AND DIAGNOSIS

Symptoms of ALI/ARDS can be nonspecific and consist of dyspnea and dry cough. After the inciting event, tachypnea and tachycardia usually develop within the first 12 to 24 hours, followed by a dramatic increase in work of breathing and a rapid decrease in oxygenation, manifested as cyanosis. Lung examination may reveal bilateral, high-pitched, end-expiratory crackles, although often only bronchial breath sounds are heard, and lung compliance is decreased. The patient may initially be agitated; however, lethargy and obtundation may ensue, with worsening respiratory failure. Clinical and chest radiographic findings may lag behind hypoxemia, and therefore early measurement of arterial blood gases in patients at risk of developing this syndrome is warranted.

Early laboratory abnormalities include hypoxemia, widening of the alveolar-arterial oxygen gradient, and respiratory alkalosis. The hypoxia is attributable to ventilation-perfusion mismatch, intrapulmonary shunting, oxygen diffusion impairment, and hypoventilation.[67,68] As the disease progresses, sometimes rapidly, the patient develops severe hypoxemia unresponsive to oxygen (secondary to increased intrapulmonary shunting) and respiratory acidosis resulting from respiratory muscle failure and increased pulmonary dead space. The clinical, radiographic, and laboratory findings can be indistinguishable from those of cardiogenic pulmonary edema, and therefore measurement of pulmonary arterial wedge pressure is sometimes considered necessary to differentiate between the two conditions.

Chest Radiography

In the first 12 to 24 hours after lung injury, the chest radiograph is often normal; however, when ARDS has followed direct lung injury such as massive aspiration of gastric contents or pneumonia, the chest radiograph is likely to be abnormal at the outset. In the next 36 hours, with greater exudation of fluid in alveolar spaces, a characteristic bilateral diffuse interstitial infiltrate may progress to ground-glass opacification and frank consolidation, as illustrated in Figure 4.1*A*.[69] As shown in Figure 4.2, the patient may also develop pleural effusions, and their presence should not sway the physician from making the diagnosis of ARDS. This progression is typical but not pathognomonic of ARDS.



A B

Figure 4.1 *A,* The chest radiograph of a 54-year-old man with acute respiratory distress syndrome of unknown cause demonstrates diffuse opacification of all quadrants. *B,* A computed tomography scan demonstrates marked heterogeneity of parenchymal involvement, with dense consolidation posteriorly, and with air bronchograms evident. The anterior lung areas are relatively spared.

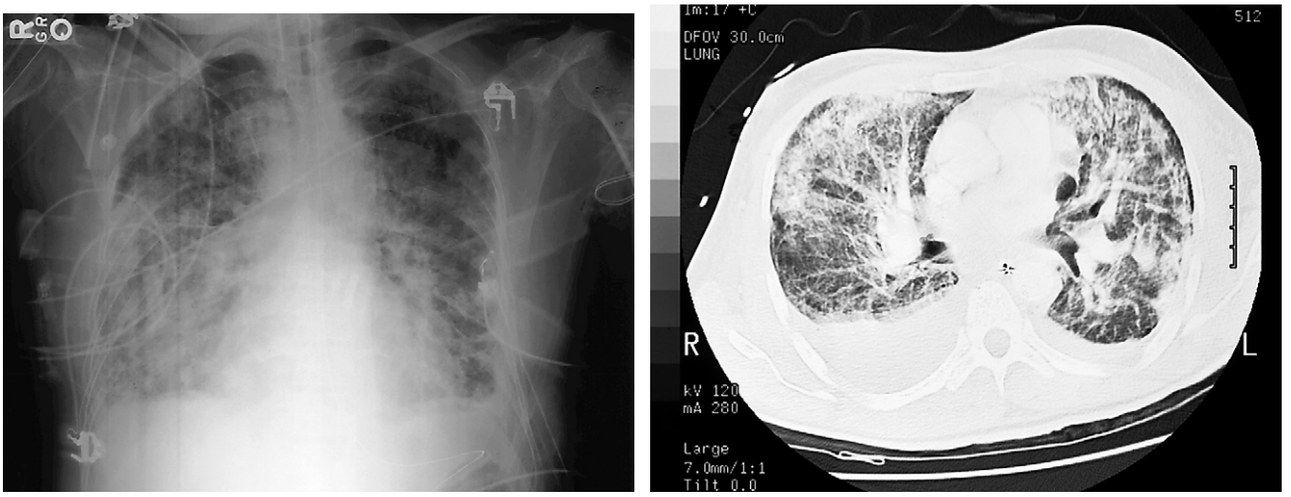
Radiographic findings may resolve rapidly in patients with near drowning, opiate-related ALI/ARDS, or uncomplicated viral pneumonia. However, in most cases, the radiographic findings resolve over weeks. During this time, the development of new focal areas of air space opacities may indicate the development of nosocomial pneumonia.[70] In addition, ARDS may be complicated by pneumothorax and pneumomediastinum secondary to the disease itself or as a complication of mechanical ventilation. With the complete resolution of the disease, the chest radiograph may either revert to normal or reveal coarse reticular opacities, diffuse interstitial fibrosis, and cysts, likely as a consequence of the effects of both lung repair and barotrauma.[71–74] The radiographic criterion of bilateral diffuse infiltrates in the AECC definition of ALI/ARDS shows high interobserver variability when applied by investigators expert in the fields of mechanical ventilation and ARDS.[4]

Computed Tomography Patterns

Computed tomography (CT) scans in patients with ALI/ARDS have revealed that lung disease in ALI/ARDS is not a homogeneous process and that the scan pattern may vary with cause, time, mechanical ventilation, and prone positioning. The most striking CT finding in the early phase of disease is the heterogeneous nature of detectable lung injury (see Figs. 4.1 and 4.2). Three areas of lung are easily recognized: (1) normal or almost normal lung regions, most frequently located in nondependent lung; (2) ground-glass opacification, defined as a hazy increase in lung attenuation, with preservation of bronchial and vascular margins, in the midlung area; and (3) consolidation in the most dependent lung.[75,76] During the late or fibroproliferative phase of the disease, fluid is reabsorbed, leading to a decrease in CT density of the lung. There is also an increase in subpleural cysts or bullae.[77] In patients who survive ALI/ARDS, a reticular pattern is described in the nondependent normal lung regions; this pattern has been correlated with the length of mechanical ventilation and the use of inverse ratio ventilation.[78]

Differences in CT findings in patients with direct as opposed to indirect ALI/ARDS were described by Goodman and colleagues. Abnormalities in patients with direct ARDS tended to be a mixture of consolidation and ground-glass opacification, whereas patients with indirect ARDS had predominantly symmetric ground-glass opacification. In both groups, pleural effusions and air bronchograms were common.[79]

Puybasset and associates found differences between these groups to be less distinct.[80] These investigators showed that in patients with ARDS, the cardiorespiratory effects of PEEP were affected predominantly by lung morphology rather than by the presence of a direct or



A B

Figure 4.2 *A,* The chest radiograph of a 64-year-old man with acute respiratory distress syndrome secondary to bacterial pneumonia demonstrates patchy involvement of all quadrants. B, A computed tomography scan demonstrates diffuse heterogeneous involvement of all lung fields and the presence of bilateral pleural effusions.

indirect ARDS. In their study, PEEP induced marked alveolar recruitment without overdistention in patients with diffuse CT attenuations, whereas in patients with lobar attenuation, PEEP induced mild alveolar recruitment associated with overdistention of previously aerated lung regions.

Study of the relationship between CT data and lung mechanics in patients with ALI/ARDS showed that respiratory compliance was not related to the amount of nonaerated or poorly aerated tissue, but rather was closely related to the amount of normally aerated tissue. Thus, the respiratory compliance in early ALI/ARDS appears to be a direct measure of normally aerated tissue, a finding suggesting that in ALI/ARDS the aerated lung is not stiff, but rather small.[81] The value of the information gained from CT scans must be balanced against the potential risk of transporting critically ill patients, the additional costs, and the additional radiation dose. Therefore, CT scanning of the lungs of patients with ALI/ARDS is most clearly indicated for solving clinical dilemmas, such as detecting occult complications in patients who are deteriorating or not improving at the expected rate, or for formal research protocols.

Respiratory Mechanics

Patients with ALI/ARDS are frequently found to have smaller tidal volumes and higher peak airway and plateau pressures than physiologically normal subjects. Gattinoni and colleagues found a markedly higher static lung elastance in patients with pulmonary ARDS and a high static elastance of the chest wall in patients with extrapulmonary ARDS.[82] Increasing PEEP to 15 cm H_2O caused an increase in static elastance of the total respiratory system in patients with pulmonary ARDS. These investigators proposed that this difference in respiratory mechanics and response to PEEP is consistent with a prevalence of consolidation in pulmonary ARDS, as opposed to the presence of predominantly edema and alveolar collapse in extrapulmonary ARDS. Patients with ARDS also have increased resistance to airflow,[83] and this is substantially reduced by inhalation of a β-agonist.[84]

TREATMENT

Hypoxic and hypercapnic respiratory failure is a common component of ALI/ARDS, and it requires mechanical ventilation to reduce the work of breathing and to ensure adequate gas exchange. The support provided by mechanical ventilation allows time for antibiotics (in infected patients), innate immunity, and endogenous reparative processes to overcome the acute inflammatory state. As a result, approximately 60% or more of patients with ALI survive to hospital discharge.[52]

Lung Protective Ventilation Strategies

Historically, there was a great disparity in physicians' approach to mechanical ventilation of patients with

ALI/ARDS, largely because of a lack of clear guidance from clinical studies and the absence of standards for initiating, monitoring, and adjusting ventilator settings. For example, in a survey of ventilation practices, critical care physicians reported using a broad range of tidal volumes (5 to 17 mL/kg) in patients with ALI.[85] In the 1990s, several clinical trials were conducted to guide clinicians in the choice of tidal volumes.[43,86–89] Amato and colleagues evaluated the effects of a lung protective ventilation strategy on pulmonary complications and mortality at 28 days in patients with ARDS.[86] Patients were randomized to either a conventional study group or a lung protective ventilation group. Patients in the conventional group received tidal volumes of approximately 12 mL/kg of body weight and a mean PEEP of approximately 8 cm H_2O during the first 7 days of treatment, whereas those in the lung protective strategy group received tidal volumes of approximately 6 mL/kg and a mean PEEP level of 16.4 cm H_2O during the first 36 hours of treatment. The tidal volumes in this latter group were further decreased if inspiratory airway pressures exceeded 40 cm H_2O. The results showed that patient survival, frequency of barotrauma, and rate of weaning from mechanical ventilation were all improved in the group receiving lower tidal volumes and higher PEEP. In this small study, it was unclear whether the improvement in outcome was attributable to the lower tidal volumes, the inspiratory pressure limits, or the higher PEEP. There have been four subsequent randomized clinical trials to investigate the role of different tidal volume ventilation strategies in patients with ALI or at risk of developing ALI.[43,87–89] In three of these trials, the volume- and pressure-limited approach was not associated with improved clinical outcome.[87–89] However, a trial[43] by the NHLBI's Acute Respiratory Distress Syndrome Network (ARDS Network) was stopped after enrollment of 861 patients because the mortality was significantly lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31% versus 39.8%). Further, the lower tidal volume group had more ventilator-free and end-organ failure–free days during the first 28 days and a greater reduction in plasma IL-6 levels compared with patients treated with larger tidal volumes and higher pressures. Results of the ARDS Network ALVEOLI study showed no survival benefit when a low tidal volume ventilation strategy was used in conjunction with a higher, as opposed to lower, PEEP value.[90]

Application of a lung protective strategy is associated with reduction in BAL concentrations of polymorphonuclear cells, TNF-α, IL-1β, soluble TNF-α receptor 55, and IL-8. In both plasma and BAL, concentrations of IL-6, soluble TNF-α receptor 75, and IL-1 receptor antagonist are reduced.[44] Reduction in the circulating levels of proinflammatory mediators is associated with reduction in the development of multiorgan failure, the major cause of mortality in patients with ARDS.[91]

Open Lung Approach

The low tidal volume ventilation strategy endorsed by the NHLBI study results in a modest decrement in gas exchange over the first several days of treatment, as compared with the higher tidal volume ventilation strategy. A contrasting "open lung" strategy is to adjust tidal volume and PEEP based on gas exchange and airway pressure measurements (see Chapter 25). Although use of the open lung strategy is effective in animal models of ALI,[92,93] the effect was short-lived in patients with ALI/ARDS who were treated with a low tidal volume strategy and 30-second applications of continuous positive airway pressure of 35 to 40 cm H_2O.[94,95]

High-Frequency Oscillatory Ventilation

During high-frequency oscillatory ventilation (HFOV) use in adults, tidal volumes approaching 150 to 260 mL can be delivered when respiratory rates are set between 3 and 5 cps, mean distending airway pressures are set between 25 and 45 cm H_2O, and pressure amplitudes are set between 60 and 90 cm H_2O. Frequent small breaths augment diffusive exchange of respiratory gases. Use of HFOV theoretically avoids the high peak airway pressure common with conventional ventilation, prevents alveolar overdistention, and maintains a higher peak end-expiratory pressure, thus possibly avoiding lung injury resulting from repetitive recruitment and derecruitment of alveoli. Derdak and associates reported on a multicenter, randomized, controlled trial of oscillatory ventilation for ARDS.[96] Although this trial was not powered to evaluate mortality differences, a trend toward overall improved mortality was observed in the HFOV-treated group (37%) versus the group treated with conventional mechanical ventilation (52%). However, the group treated with conventional mechanical ventilation was not ventilated with a lung protective ventilation approach, because the tidal volumes in this group were approximately 10 mL/kg.

In summary, HFOV is an alternative method of mechanical ventilation for patients with severe adult ARDS, and it may be considered in those who require high mean airway pressures (≥20 cm H_2O) with conventional ventilation, especially if the Fio_2 requirement exceeds 0.60 and the inspiratory plateau pressure cannot be maintained at less than 30 cm H_2O.

Avoidance of Oxygen Toxicity

Both laboratory data and clinical experience suggest that exposure of humans to elevated levels of inspired oxygen

results in lung injury.[97,98] This injury, which may occur as a result of increased generation in the lung of reactive oxygen species, may be mitigated by the presence of antioxidants. Levels of critical components of the antioxidant defense system are induced during exposure to modest levels of inspired oxygen, and thus the patient who requires high levels of inspired oxygen may be at somewhat less risk of lung injury than the patient with a sudden requirement for sustained high levels of inspired oxygen. Thus, a high Fio_2 may be used for brief periods as a temporizing measure; however, it is recommended that aggressive steps be taken to reduce the Fio_2 whenever it exceeds 0.65. These measures include increasing mean airway pressure, improving cardiovascular function, inducing diuresis, or accepting somewhat lower values for hemoglobin oxygen saturation.

Use of Sedation and Paralysis

Deep sedation is frequently used in severely affected patients who are undergoing mechanical ventilation when oxygen consumption demands must be minimized to relieve hypoxemia. Sedation may occasionally be supplemented by nondepolarizing muscle relaxants when an uncomfortable or poorly tolerated ventilatory pattern, such as inverse ratio ventilation, is needed. Any use of a paralytic agent should be brief, with frequent reassessment of depth and continued need, because such use may be associated with the development of neuromuscular dysfunction.[99]

Prone Positioning

Use of the prone position may improve oxygenation in patients with ARDS. Mechanisms that may account for this effect include an increase in end-expiratory lung volume, better ventilation-perfusion matching, and regional changes in ventilation associated with alterations in chest wall mechanics.[100–103] In addition, this modality has also been shown in animal models to lessen VILI.[104] Gattinoni and colleagues conducted a multicenter randomized trial to evaluate use of the prone position for 7 hours per day for up to 10 days in the treatment of ventilated patients with ALI or ARDS.[105] The study showed a significant improvement in oxygenation with prone positioning, no effect on complication rate and no effect on mortality. Post hoc analysis suggested a survival benefit when prone positioning was used for patients with the most severe disease.

Glucocorticoids

Glucocorticoids exert their effects through binding to cytoplasmic glucocorticoid receptors. These receptors, in turn, modulate the transcription rates of many inflammatory response elements, including augmenting synthesis of I-κB that binds and thus limits the proinflammatory action of nuclear factor-κB.[106] Glucocorticoids thus act as natural inhibitors of proinflammatory cytokine production.[107] Glucocorticoids also inhibit fibroblast proliferation and collagen deposition, stimulate T-cell, eosinophil, and monocyte apoptosis, and inhibit neutrophil activation. Glucocorticoid treatment in ARDS/ALI is controversial. Short courses of high-dose glucocorticoids were shown to be ineffective, and possibly harmful, in clinical trials of ARDS prevention in patients with severe sepsis and in patients with established ARDS.[108–111] A small randomized placebo-controlled trial suggested a beneficial effect of prolonged use of glucocorticoids in late ARDS.[112] However, the NIH ARDS Network conducted a larger study of methylprednisolone for patients with ARDS of 7 to 28 days' duration that suggests no outcome benefit.[113] Though use of glucocorticoids improved the cardiopulmonary physiology and increased the number of ventilator-free days, ICU-free days, and shock-free days during the first 28 days, it failed to reduce hospital stay or improve the in-hospital mortality and was associated with an increased incidence of neuromyopathy. In fact, initiation of glucocorticoids two or more weeks after the onset of ARDS was associated with an increased mortality rate when compared with the placebo group. The ARDS Network investigators concluded that their results did "not provide support for the routine use of methylprednisolone in patients with persistent ARDS and suggest that methylprednisolone therapy may be harmful when initiated more than two weeks after the onset of ARDS."[113]

Catheter and Fluid Management

ARDS Network investigators have also shown that the routine use of a pulmonary artery catheter (PAC) to guide fluid therapy in ARDS/ALI patients neither decreases mortality nor reduces the incidence or the duration of organ failure. Such use is associated with higher complications such as atrial and ventricular arrhythmias when compared with central venous catheter (CVC)-guided therapy in patients with ARDS.[114]

The optimal fluid management of ALI and ARDS has long been controversial. The ARDS Network has reported results of a large clinical trial comparing a conservative and liberal fluid management strategy in patients with ALI. Although, there was no difference in mortality between the two groups, those in the conservative strategy group had significantly improved lung function and central nervous system function, and a decreased need for sedation, mechanical ventilation, and intensive care, without an increase in nonpulmonary organ failures or shock.

Surfactant Therapy

Pulmonary surfactant is found at the air-liquid interface of the alveoli and functions to reduce the surface tension, particularly at low lung volumes. It is composed of approximately 90% lipids and 10% surfactant proteins (SP-A, SP-B, SP-C, and SP-D). Analysis of BAL fluid samples obtained from patients with ARDS and from various animal models of lung injury demonstrated changes in the endogenous surfactant system. Specifically, decreased amounts of dipalmitoylphosphatidylcholine and phosphatidylglycerol and decreased amounts of the surfactant-associated proteins were documented in patients with ARDS compared with control subjects.[116]

Several randomized controlled clinical trials have evaluated exogenous surfactant treatment in patients with ARDS. Anzueto and colleagues showed no difference between patients receiving very small doses of the exogenous synthetic surfactant Exosurf by aerosol and control subjects with respect to physiology, ventilator-free days, and mortality rates.[117] A trial in which the modified natural surfactant Survanta was instilled directly into the airways of patients with ARDS evaluated eight doses of 50 mg/kg, four doses of 100 mg/kg, and eight doses of 100 mg/kg over a 28-day period. The middle-dose group had the best outcome, with a mortality of 18.8% compared with 43.8% in the control group.[118] Spragg and colleagues performed a phase I/II randomized clinical trial of a short course of a recombinant surfactant protein C–based surfactant (Venticute) as treatment for ARDS.[119] The results showed no benefit, but they established safety of the intervention. In subsequent phase III studies, treatment with the same surfactant was associated with improvement in oxygenation and with a suggestion of benefit in the subgroup of patients with direct lung injury.[120]

Liquid Ventilation

Tidal liquid ventilation is a technique of respiratory support during which gaseous functional residual capacity (FRC) and tidal volume are replaced with a perfluorocarbon (PFC) liquid.[121] Liquid ventilation has been shown to improve lung mechanics and ventilation-perfusion matching effectively, decrease intrapulmonary shunt, and thereby support pulmonary gas exchange and cardiovascular stability in animal models of ALI/ARDS.[122–124] Moreover, studies have demonstrated that partial liquid ventilation (during which the lung FRC is partially or completely filled with PFC, and gaseous tidal breaths are delivered) and tidal liquid ventilation are associated with a decrease in oxidative lung damage in animal models of ARDS/ALI.[125,126] A prospective randomized controlled trial of partial liquid ventilation compared with conventional mechanical ventilation in adult patients with ARDS/ALI failed to show a significant improvement in the number of ventilator-free days or in mortality in patients treated with partial liquid ventilation.[127] In addition, transient and self-limited episodes of bradycardia, hypoxia, and respiratory acidosis occurred more frequently in the group treated with partial liquid ventilation. In summary, although liquid ventilation may be more effective than conventional mechanical ventilation in selected laboratory models, this advantage has not been shown in clinical studies.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is a technique of providing life support in the treatment of failing lungs that are unable to maintain blood oxygenation. Several terms have been used to describe the variety of techniques that have been designed to oxygenate blood and remove carbon dioxide extracorporeally. These include ECMO, extracorporeal carbon dioxide removal (ECCO2-R) and extracorporeal life support (ECLS). In the typical ECMO setting, a femoral-jugular venovenous bypass is established with oxygenation of the circulating blood by the membrane oxygenator. ECMO was introduced into the treatment of ARDS in the 1970s. In adults with ARDS, two randomized controlled trials failed to show an advantage of ECMO over conventional ventilation.[128,129] However, both these trials were performed before the development of modern heparinized tubings and membrane oxygenators, which may reduce the complications of this modality.

ECMO may be a useful adjunct to the lung protective ventilation strategy in severe ARDS. In profoundly ill patients, use of low tidal volumes and airway pressures may not result in sufficient levels of hemoglobin saturation to sustain life. In such settings, ECMO is able to support gas exchange to the extent that ventilator settings (tidal volume, PEEP, respiratory rate, peak inspiratory pressure, fractional inspired oxygen) may be adjusted to avoid inducing VILI.[130]

Treatment of Pulmonary Hypertension by Inhaled Nitric Oxide

Early in the evolution of ARDS, pulmonary vasoconstriction, thromboembolism, and interstitial edema contribute to the development of pulmonary hypertension. Inhaled NO (iNO) selectively vasodilates the pulmonary vasculature with few systemic effects. Randomized controlled trials comparing iNO treatment with conventional therapy in adult patients with ARDS showed acute improvement in oxygenation and hemodynamics.[131,132] However, because no reduction in mortality has been demonstrated, iNO has an unproven role in the treatment of patients with ALI/ARDS.

OUTCOME

Numerous factors influence the risk of death for a patient with established ARDS. Since publication of the 1992 AECC criteria, most clinical series have reported mortality rates for patients with ARDS that range from 25% to 70%. Differences in the application of ALI/ARDS definitions, associated risk factors and comorbidities, and the time period during which mortality is recorded are likely to contribute to this variation. The mortality rate from ARDS appears to have decreased since the mid- to late 1990s.[5,133131,132 136]

Although the annual age-adjusted mortality, as observed by Moss and colleagues, may have increased from 1979 (5.0 deaths per 100,000 individuals) to 1993 (8.1 deaths per 100,000 individuals), a decrease in mortality was observed from 1993 to 1996 (7.4 deaths per 100,000 individuals). Reasons for the decline in ARDS-associated mortality are varied. In a 9-year retrospective review of surgical and trauma patients, Rocco and colleagues found, predominantly in trauma patients, a declining death rate from ARDS largely resulting from the use of lung protective ventilation strategies.[137] The predictors of death in this study at the onset of ARDS were advanced age, a Multiple Organ Dysfunction Score of 8 or more, and a Lung Injury Score of 2.76 or more. In a similar study, the decrease in mortality of patients with ARDS was attributed mostly to a decreased incidence of nonpulmonary organ failure.[138] Consistent with this view, Page and associates found that, for patients with ARDS who were managed with a lung protective ventilation strategy, the strongest predictor of death was not the degree of pulmonary failure, but rather the presence and severity of circulatory failure.[139] The dominant influence on mortality of comorbidities was noted by Estenssoro and associates, who prospectively studied all patients who developed ARDS in four ICUs for 1 year.[140] Hospital mortality was reported to be 58%, and the main causes of mortality were multiple organ dysfunction syndrome, sepsis, and septic shock. In this study, independent predictors of death included organ dysfunction and Pao_2/Fio_2. A decrease in pulmonary dead space fraction has also been identified as a separate risk factor.[141] The influence of comorbidities was also observed by Davidson and colleagues, who, in a prospective cohort study of 127 patients with ARDS associated with trauma or sepsis, found no difference in the long-term mortality rate for the patients with ARDS compared with 127 control subjects matched for age, risk factors for ARDS, comorbidity, and severity of illness.[142]

It is unclear whether patients with mild ALI (those with Pao_2 between 200 and 300 mm Hg) have a mortality that differs from that of patients with ARDS. In a study of patients in Scandinavian ICUs, Luhr and associates found a similar mortality of approximately 40% in both groups.[5] However, in a study of patients in 78 ICUs in Europe, Brun-Buisson and colleagues found ICU and hospital mortality to be 49.4% and 57.9%, respectively, for patients who developed ARDS and 22.6% and 32.7%, respectively, for patients with ALI.[143] Mortality was associated with age, immunocompetence, physiologic measures of injury, organ dysfunction, and early air leak.

The long-term health consequences in ARDS survivors are significant. Herridge and associates studied 1-year outcomes in 109 survivors of the ARDS.[144] Muscle weakness and fatigue were the major reasons for the functional limitation observed after 1 year, whereas normalization of lung volumes and spirometric measurements were seen by 6 months. Other studies found residual obstructive or restrictive defects to persist for a year or more in a subset of patients.[145,146] All three of the foregoing studies, however, found diffusing capacity to remain low on long-term follow-up. Orme and colleagues found no significant differences in pulmonary function between surviving patients treated with a low or high tidal volume strategy.[146]

Direct measures of the quality of life in patients who survive ARDS indicate impairment in general physical health, mental health, and neuropsychological function.[147,148] Hopkins and associates stressed the significant cognitive impairments in memory, attention, concentration, or mental processing speed exhibited by 78% of the 55 ARDS survivors they evaluated at 1 year after the onset of ARDS.[149] Decrements in quality of life and functional status appear to stabilize by 6 months. An unresolved issue is the extent to which the decrement in quality of life is the result of ARDS or of other factors such as prior health status or other elements of the acute illness. Further research is needed to characterize patients' recovery from ARDS and ALI and the extent to which recovery may be influenced by treatment in the ICU and during rehabilitation.

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