Introduction

James A. Russell and Keith R. Walley

Acute respiratory distress syndrome (ARDS) is a very important problem in critical care medicine. First, ARDS occurs commonly in young, previously well individuals who have major insults such as multiple trauma, sepsis, and aspiration of gastric contents. Second, the mortality of ARDS remains relatively high at 40% to 60% despite improvements in drug therapy, mechanical ventilation, hemodynamic management, more potent antibiotics, better prevention of complications (e.g., stress ulceration), better supportive care (e.g., nutrition), and more effective methods of weaning from ventilation. Encouragingly, there are some indications that the mortality of ARDS may be decreasing. Third, the health care costs of ARDS are considerable because patients are almost exclusively managed in an expensive ICU setting. There is considerable pressure to contain costs and to improve the cost effectiveness of ARDS. Finally, ARDS is important because the quality of life for survivors of ARDS is good with generally very good to excellent return of pulmonary function, good return to quality of life in many, and even preliminary reports of excellent return of quality of life in most.

ARDS has been defined more precisely by an American-European Consensus Conference. Acute lung injury preceding ARDS is defined by presence of bilateral infiltrates on chest roentgenogram, no evidence of congestive heart failure (or pulmonary artery occlusion pressure less than 19 mmHg if a pulmonary artery catheter is in place), need for mechanical ventilation, and PaO_2/FiO_2 less than 200. Severe ARDS is similarly defined, except the PaO_2/FiO_2 ratio must be less than 100.

This textbook provides a comprehensive approach to the clinical management of patients who have ARDS. Our approach focuses heavily on underlying pathophysiology and provides recommendations for cost-effective investigation and management of ARDS, information regarding controversial areas in ARDS, and updates

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regarding the results of clinical trials of new therapy in ARDS. We have recruited an outstanding group of contributors who are internationally acknowledged experts in fundamental and clinical issues in ARDS.

Chapter 1 offers an overview of ARDS, an approach to clinical evaluation, and a review of radiologic assessment of ARDS. The overview component provides a stand-alone summary of some of the topics discussed in much greater detail later in the text in order to provide a general context for subsequent discussions. We also present an approach to the initial clinical evaluation of the patient with ARDS. Then radiologic examination, which is fundamental to the evaluation and management of patients with ARDS, is reviewed.

The clinical causes and epidemiology of ARDS are reviewed in Chapter 2 by Drs. Garber and Hébert. These authors present an approach to reviewing the literature that can be used to critically evaluate clinical studies in any field. Here they apply this approach to studies regarding the epidemiology of ARDS. Important risk factors for ARDS are identified using an evidence-based medicine approach. Finally, Drs. Garber and Hébert review studies regarding the morbidity and mortality of ARDS that suggest the mortality of ARDS may be decreasing for reasons that are as yet unclear.

In Chapter 3, Dr. Wright presents a concise review of the pathology of ARDS. The particular pathologic findings from early to late-phase ARDS are illustrated in detail. Dr. Wright identifies clinically important changes that have an impact on measures of pulmonary physiology.

In Chapter 4, Dr. Kunkel and colleagues review the molecular mechanisms of acute lung injury and ARDS. The key roles of early pro-inflammatory cytokines in initiating a pattern of recognition, recruitment, resolution, and repair are described. These authors point out the importance of the balance of pro- and anti-inflammatory mediators in determining the outcome of the inflammatory response characteristic of ARDS. Futhermore, Dr. Kunkel and colleagues discuss the concept of complex networks of signaling molecules and inflammatory effector cells that make up the pulmonary inflammatory response of ARDS. Finally, they present the changes over time in the inflammatory response in the lung in ARDS.

In Chapter 5, Drs. Walley and Russell discuss pulmonary physiology and approaches to monitoring clinically relevant aspects of the respiratory system of patients who have ARDS. Abnormal gas exchange is fundamental to the pathophysiology of ARDS, and appropriate monitoring using arterial blood gas analysis, transmission and reflectance oximetry, and metabolic cart measures of oxygen consumption and carbon dioxide production are discussed. Lung and airway mechanics are significantly impaired in ARDS. Dynamic and static pressure-volume relationships of ARDS, auto-PEEP, the importance of respiratory muscles, and control of respiratory drive are explained together with clinical approaches to evaluating and therapeutically altering these parameters.

Drs. Walley and Russell then discuss cardiovascular physiology and management in Chapter 6. Using basic concepts from cardiovascular physiology, the authors discuss the sepsis-like circulation of ARDS. Derangements in microvascular control and

how these relate to the impaired peripheral oxygen extraction that occurs in sepsis, and may occur in ARDS, are discussed. Drs. Walley and Russell describe the oxygen delivery/consumption controversy as it relates to patients who have ARDS. They review the role of supranormal oxygen delivery in management of ARDS, the role of the pulmonary artery catheter, and the usefulness of gastric tonometery.

Mechanical ventilation of patients who have ARDS is probably the most complex form of ventilation in critical care. The fundamental issues in mechanical ventilation of patients who have ARDS are discussed by Dr. Schmidt in Chapter 7. These include the mechanics of mechanical ventilation, the effects of mechanical ventilation on normal and abnormal pulmonary and cardiovascular physiology, and the effects of mechanical ventilation on the peripheral vascular system. This review of physiology is used as a basis for understanding conventional and newer modes of ventilation. After discussing conventional modes of ventilation, Dr. Schmidt discusses new methods of mechanical ventilation in severe ARDS with very impaired gas exchange and decreased respiratory compliance including the use of pressure control ventilation, inverse ratio ventilation, and permissive hypercapnia ventilation. One major issue in mechanical ventilation of patients who have ARDS is the controversy surrounding ventilator-induced lung injury.

There have been many changes in techniques for weaning a patient from mechanical ventilation and those that are relevant to management of ARDS are reviewed by Drs. Dhand and Tobin in Chapter 8. They first examine the pathophysiologic determinants of weaning outcome including pulmonary gas exchange, respiratory muscle pump failure, decreased neuromuscular capacity, respiratory muscle dysfunction, increased respiratory muscle pump load, increased work of breathing, and psychological problems. Next, they consider how to predict which patients will be weaned successfully. Drs. Dhand and Tobin then discuss clinical approaches to weaning from mechanical ventilation. The discussion includes simple trials of spontaneous breathing through a T-tube system that were employed at the onset of mechanical ventilation; intermittent mandatory ventilation (IMV), which is the most popular weaning technique in North America; and pressure support ventilation (PSV). A once-daily trial of spontaneous breathing may be the most expeditious approach.

The cornerstones of therapy of patients who have ARDS are (1) reversal of the underlying cause(s) of ARDS (e.g., sepsis) and (2) excellent total patient care to keep the patient alive and free of complication while the patient's inflammatory response runs its course to resolution and repair. Aspects of total patient care are reviewed in Chapter 9 by Drs. Russell, Dhingra, and Walley. Complications occurring during the course of ARDS are reviewed. Prevention or rapid correction of these complications is fundamental in avoiding "second hits" that too frequently lead to multiple organ failure and death.

At present no proven therapy exists that either resolves or shortens the duration of established ARDS. In Chapter 10, Dr. Bernard discusses innovative therapies that are potentially useful and are under investigation in basic science and clinical studies of ARDS. Based on the molecular mechanisms of ARDS (Chapter 4), Dr. Bernard discusses a rationale for use of therapies designed to interrupt pro-inflammatory

mediators. Futhermore, Dr. Bernard discusses therapies specific for management of ARDS such as surfactant replacement, inhaled nitric oxide, use of steroids in early ARDS, use of steroids in the late stage of ARDS, and other novel therapies currently being tested in trials of sepsis and ARDS.

Nosocomial pneumonia, discussed in Chapter 11 by Drs. Bahammaman and Light, is a major complication of patients who have ARDS. The microbiology of nosocomial pneumonia is important to understand from both a pathophysiologic and therapeutic perspective. They discuss the pathogenesis of nosocomial pneumonia including the role of microbial colonization such as oropharyngeal colonization, gastric colonization, and contamination of respiratory therapy equipment. Drs. Bahammaman and Light examine the host factors predisposing to respiratory infection including the roles of endotracheal intubation and aspiration, pulmonary changes that predispose to infection in ARDS, and systemic alterations in the patient who has ARDS that led to infection. The diagnosis of nosocomial infection in ARDS can be problematic, and they discuss issues such as the roles of chest roentgenogram, clinical evaluation, microbiological evaluation, and more sophisticated techniques such as bronchial alveolar lavage. In particularly, they review nonbronchoscopic techniques. The role of fibroptic bronchoscopy combined with protected specimen brushing or bronchial alveolar lavage is discussed. Then they review the pharmacologic considerations as a background to antimicrobial therapy for ARDS. Pending culture results report, empiric therapy is most often necessary when the diagnosis of pneumonia is suspected, and they make suggestions for initial empiric therapy. Prevention of pneumonia is preferable to treatment of established pneumonia because of the very high mortality, approaching 60%, of nosocomial pneumonia in general and of the even higher mortality, 60% to 80%, of nosocomial pneumonia in patients who have ARDS. Preventive measurements include body position, airway care, nutrition, and infection control and resistance.

In Chapter 12, Drs. Bowler, Garat, and Matthay review resolution and repair of acute lung injury. They discuss how excess alveolar fluid and protein are normally removed and how changes in alveolar removal may have prognostic implications. They then discuss fibrosing alveolitis in acute lung injury including the role of fibrin and fibrinogen, fibronectin, collagens, and cellular changes in the pathophysiology of fibrosis. They discuss growth factors relevant to acute lung injury such as platelet-derived growth factor, epidermal growth factor, transforming growth factor-alpha, transforming growth factor-beta, hepatocyte growth factor, and keratinocyte growth factor. They then discuss cytokines important in resolution of lung injury including tumor necrosis factor, IL-1, and IL-10.

Most patients who die of ARDS do not die of hypoxia but rather die of progressive multiple system organ failure (MSOF). In Chapter 13, Drs. Uusaro and Russell review aspects of multiple system organ failure that are relevant to patients who have ARDS. After defining and reviewing the epidemiology of MSOF, they review the evidence that multiple system organ failure is caused by overt or covert tissue hypoxia in patients who have ARDS. The oxygen delivery/consumption relationship as it relates to evidence for occult tissue hypoxia as a cause of MSOF is discussed. They suggest

that the pathologic dependence of oxygen consumption on oxygen delivery has not been established in ARDS and very little evidence supports this as a cause of multiple system organ failure. They then review other mechanisms for multiple system organ failure such as ischemia-reperfusion injury and the role of reactive oxygen metabolites, leukocyte-mediated injury and leukocyte adherence and injury to endothelial cells, cytokine injury mechanisms, and other potential pathways.

Finally, in Chapter 14, Dr. Albert reviews the outcome and long-term care of patients who have ARDS. Dr. Albert again reviews the evidence that mortality of ARDs may be decreasing and discusses potential explanations. He then discusses the symptoms and limitations in survivors of ARDS, the roentgenographic changes in survivors of ARDS, and then reviews pulmonary function test abnormalities in survivors of ARDS. In general, there are mild to moderate reductions in spirometry, increased airway reactivity, modestly reduced lung volumes, somewhat increased dead space and, most commonly, decreased diffusing capacity in survivors of ARDS. Furthermore, survivors of ARDS have abnormal gas exchange that becomes more evident during exercise. Dr. Albert concludes that in the first year after ARDS most physiologic abnormalities will improve, with most of the improvement occurring in the first three months. Deficits persisting beyond one year are unlikely to improve any further. He also discusses the quality of life of survivors of ARDS and studies with somewhat divergent results. One study suggested moderately impaired quality of life, whereas another more recent study suggested relatively good quality of life in survivors or ARDS.

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Overview, Clinical Evaluation, and Chest Radiology of ARDS

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Introduction

The acute respiratory distress syndrome is a relatively new disease that emerged as intensive care units developed. Before mechanical ventilation and ICUs existed, most patients with moderate or severe ARDS would have died. In this chapter we present an overview of ARDS and introduce other concepts dealt with in detail in subsequent chapters. For example, epidemiology is touched on here but is presented in much greater detail in Chapter 2. This overview chapter is also intended to be a stand-alone review of ARDS from a clinically oriented perspective. That is, we have tried to include the most important clinical concepts, present an approach to evaluating and managing the patient, and focus on chest radiology as an integral component of this process.

Definition

Acute lung injury associated with increased capillary–alveolar permeability has been termed the acute respiratory distress syndrome (ARDS). ARDS has many causes. The onset of ARDS is acute, and the duration is usually days to weeks.[1,2] The clinical hallmarks of ARDS are hypoxemia, reduced lung compliance, diffuse bilateral pulmonary infiltrates on chest radiograph, and need for mechanical ventilation.[3–6] Since its initial description in 1967, the criteria for defining ARDS have changed. Normal left ventricular (LV) filling pressures (i.e., PCWP < 18 mmHg)[7–12] and the presence of a risk factor were added as inclusion criteria after introduction of pulmonary artery catheters and after better understanding of the epidemiology of ARDS, respectively.[3–5]

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Table 1.1. Lung injury score

Component	Score
1. Chest roentgenogram	
Alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation confined to 4 quadrants	4
2. PaO_2/FiO_2	
≥ 300	0
225–299	1
175–224	2
100–174	3
<100	4
3. PEEP (cm H_2O) (when ventilated)	
≤ 5	0
6–8	1
9–11	2
12–14	3
≥ 15	4
4. Respiratory compliance (mL/cm H_2O) (when available)	
≥ 80	0
60–79	1
40–59	2
20–39	3
≤ 19	4

The final lung injury score is the average score of the components that were used.

	Lung injury score
No lung injury	0
Mild-to-moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	> 2.5

Source: Adapted from Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720–723.

The criteria for the diagnosis of ARDS have evolved further since the original description.[1] In 1988 Murray and colleagues published the "acute lung injury score" in patients who have a risk factor for ARDS.[3] The score consists of two to four components, and each component is a score from 0 to 4 (Table 1.1). The components are added to yield the total score. This lung injury score has been used in a number of

clinical trials to define ARDS. A meeting in 1992 of the American Thoracic Society and the European Society of Intensive Care Medicine produced a consensus statement for the diagnosis of acute lung injury (ALI) and of ARDS. Both ALI and ARDS require the onset to be acute with bilateral infiltrates on chest radiograph and a pulmonary capillary wedge pressure less than 19 mmHg or no clinical evidence of left atrial hypertension. The ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) needs to be less than or equal to 300 mmHg for ALI and less than 200 mmHg for ARDS.[5] The ATS/ESICM definition of ARDS was recommended for clinical research such as epidemiology and clinical trials of new therapy for ARDS. There is still controversy regarding the current diagnostic criteria.[6,13]

History

Although clinical and pathologic descriptions of ARDS date back to the time of Osler and World War I,[14–19] Ashbaugh and colleagues are credited with the first descriptive study of ARDS in 1967. They described 12 patients who had acute onset of tachypnea, hypoxemia, decreased respiratory compliance, and diffuse infiltrates on chest radiograph.[1] Four years later this constellation of features was termed the adult respiratory distress syndrome. In 1992 the term *acute respiratory distress syndrome* replaced adult respiratory distress syndrome because the syndrome can occur in children, although it is much less common in children than adults.

Epidemiology and Risk Factors

In 1972 the National Institutes of Health estimated the incidence of ARDS at 60 cases per 100,000 population per year.[20] Since then, several methodologically sound studies of the incidence of ARDS have yielded a surprisingly wide range of incidence rates of 1.5 to 8.3 cases per 100,000 per year.[11,21,22] The range in incidence of ARDS in these studies is explained in part by variability in definition of ARDS used in the studies, by the methods used to identify cases, and by the reference sample population.

ARDS can be caused by a variety of risk factors that may be direct or indirect pulmonary insults. Garber and colleagues did an evidence-based literature review of the risk factors of ARDS. The epidemiologic literature indicates that the major risk factors of ARDS are sepsis, aspiration of gastric contents, multiple trauma, multiple transfusions, pulmonary contusion, pneumonia, and near-drowning.[1,2,7–12,22–24] DIC, fat embolism, and cardiopulmonary bypass had the lowest causation scores, indicating weak evidence as risk factors of ARDS. The presence of more than one risk factor further increases the risk of developing ARDS.

The mortality rate of ARDS is reported as 36% to 70%.[22,25–27] Several recent reports[28–30] suggest the mortality rate of ARDS may be decreasing.[28] In a study from the University of Washington,[28] the decreased mortality rate was accounted for by a decreased mortality rate of ARDS secondary to trauma. In contrast, there was no change over 10 years (1983–1993) in the mortality rate of ARDS associated with sepsis. The mortality rate of sepsis-induced ARDS is higher (40%) than for other causes of multitrauma. Using the American-European Consensus Conference definition,

Doyle and colleagues[31] found a mortality rate of ARDS of 59% in San Francisco. The mortality rate of severe ARDS may also be decreasing. The first North American multicenter trial of extracorporeal membrane oxygenation (ECMO) found a mortality rate of approximately 90% in both ECMO and conventionally treated patients who had severe acute hypoxemic respiratory failure. A later randomized controlled trial in North America of extracorporeal CO_2 removal (ECCOR) used very similar entry criteria to define patients who had severe acute hypoxemic respiratory failure.[29] There was no difference in mortality rate between patients treated with ECCOR and patients treated by a clinical algorithm of usual ventilatory care. More importantly, the mortality rate of the control group was only 65% – much lower than the expected 90% mortality rate of the original ECMO trial. The authors concluded that either mortality rate of severe acute hypoxemic resporatory failure has decreased over 30 years or the rigorous algorithms used to make clinical decisions decreased variance of care and also decreased mortality.

The major causes of death of patients who have ARDS are multiple system organ failure and refractory (irreversible) respiratory failure followed by cardiac, neurologic, hematologic, and other causes of death related to the underlying cause(s) of ARDS. Montgomery and colleagues[32] found that in the first three days after onset of ARDS most deaths were caused by the underlying condition that led to ARDS. Deaths more than three days after onset of ARDS were most often caused by multiple system organ failure (84%). Irreversible respiratory failure accounted for only 16% of deaths.

Pathology

The pathology of ARDS is diffuse alveolar damage (DAD). DAD is a nonspecific pattern of lung injury that can occur from many primary insults. Hemorrhage and protein-rich edema fluid accumulate in the alveoli. The pathologic changes can be divided into three phases. The acute or exudative phase (up to 6 days) is characterized by lung tissue edema and eosinophilic hyaline membranes along the walls of the alveolar ducts.[33,34] The proliferative phase (4 to 10 days) has less edema and a decrease in hyaline membranes but the start of interstitial fibrosis seen as proliferation of fibroblasts.[34,35] The final fibrotic phase (from 8 days onward) displays prominent fibrosis, which may obliterate the alveolar and bronchiolar spaces. Emphysematous changes as well as changes in the pulmonary circulation may also be seen in the fibrotic phase.[33–36]

Pathophysiology

The injury sustained by the lung produces progressive damage to the alveolar-capillary membrane and leads to increased vascular permeability, lung inflammation, and pulmonary edema.[37,38] In ARDS there is an increase in hydraulic conductivity for water and a decrease in the reflection coefficient for protein of the alveolar-capillary membrane, both of which lead to an increase in vascular permeability.[13,37,38] When vascular permeability increases, unopposed hydrostatic pressure effects dominate. As a result, small increases in hydrostatic pressure produce large increases in extravascular lung water, as shown in Figure 1.1. Thus excessive fluid resuscitation in patients

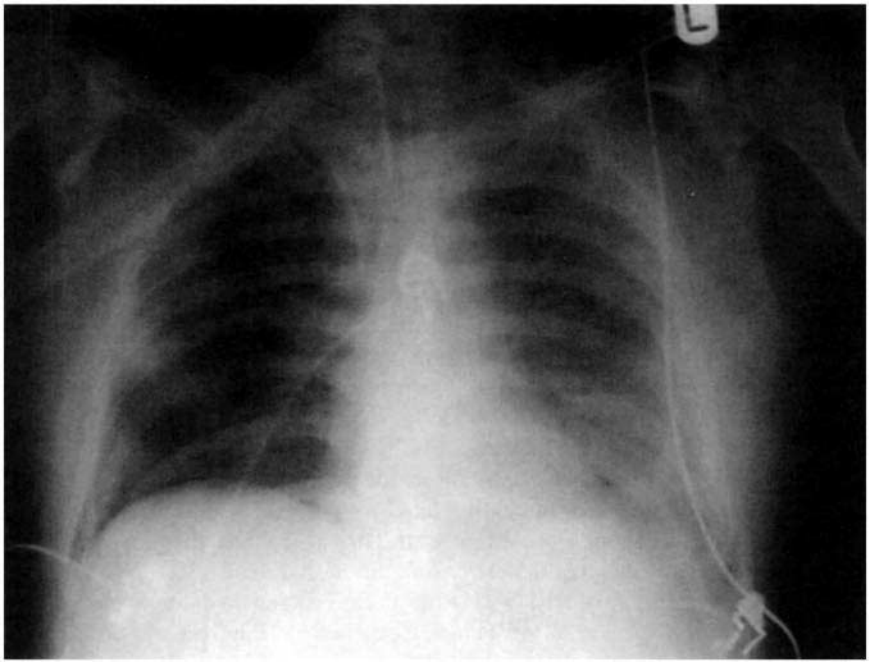

Figure 1.1. Typical chest radiograph of a patient with ARDS.

at risk of ARDS and patients who have ARDS will increase lung water more than normal patients because lung water increases even at normal left atrial pressures.[13] These effects culminate in alveolar flooding and pulmonary edema that is often rapid, progressive, and rich in protein.[37–39]

The pulmonary physiologic consequence of these changes is a decrease in lung compliance.[40] The decrease of lung compliance is a result of loss of aeratable lung volume and not due to changes in the intrinsic elastic properties of the lung.[41,42] Therefore, in early ARDS, the loss of pulmonary compliance reflects the degree of pulmonary edema and atelectasis – not lung injury per se.

The hypoxemia of ARDS is secondary to increased right to left intrapulmonary shunting of blood associated with alveolar flooding and loss of hypoxemic pulmonary vasoconstriction. Ventilation perfusion mismatching plays a much smaller role as a cause of hypoxemia.[13,43] Because of intrapulmonary shunting, hypoxemia is relatively resistant to increased FiO_2. The clinical consequences of high intrapulmonary shunt are that high FiO_2, mask BiPAP, or mechanical ventilation with positive airway pressure are required to correct hypoxemia.

Cardiovascular physiology and cardiopulmonary interaction are important in ARDS because of the effects of ARDS, the underlying cause(s) of ARDS (e.g., sep-