Edema Caused by Microvascular (Alveolar) Injury

Non-cardiogenic pulmonary edema is caused by injury of the alveolar septa. Primary injury to the vascular endothelium or damage to alveolar epithelial cells (with secondary microvascular injury) produces an inflammatory exudate that leaks into the interstitial space and, in more severe cases, into the alveoli. Injury-related alveolar edema is an important feature of a serious and often fatal condition, *acute respiratory distress syndrome* (discussed below).

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME (DIFFUSE ALVEOLAR DAMAGE)

Acute lung injury (ALI) is characterized by the abrupt onset of hypoxemia and bilateral pulmonary edema in the absence of cardiac failure (non-cardiogenic pulmonary edema). Acute respiratory distress syndrome (ARDS) is a manifestation of severe ALI. Both ARDS and ALI are associated with inflammation-associated increases in pulmonary vascular permeability, edema, and epithelial cell death. The histologic manifestation of these diseases is *diffuse alveolar damage*.

ALI is a well-recognized complication of diverse conditions including both pulmonary and systemic disorders (Table 15.2). In many cases, several predisposing conditions are present (e.g., shock, oxygen therapy, and sepsis). In other uncommon instances, ALI appears acutely in the absence of known triggers and follows a rapidly progressive clinical course, a condition known as *acute interstitial pneumonia*.

Pathogenesis

ALI/ARDS is initiated by injury of pneumocytes and pulmonary endothelium, setting in motion a vicious cycle of increasing inflammation and pulmonary damage (Fig. 15.3).

- *Endothelial activation* is an important early event. In some instances, endothelial activation is secondary to pneumocyte injury, which is sensed by resident alveolar macrophages. In response, these immune sentinels secrete mediators such as tumor necrosis factor (TNF) that act on the neighboring endothelium. Alternatively, circulating inflammatory mediators may activate pulmonary endothelium directly in the setting of severe tissue injury or sepsis. Some of these mediators injure endothelial cells, while others (notably cytokines) induce endothelial cells to express increased levels of adhesion molecules, procoagulant proteins, and chemokines.
- *Adhesion and extravasation of neutrophils.* Neutrophils adhere to the activated endothelium and migrate into the interstitium and the alveoli, where they degranulate and release inflammatory mediators including proteases, reactive oxygen species, and cytokines. Experimental evidence suggest that neutrophil extracellular traps (NETs) are released and also contribute directly to lung damage. These injuries and associated proinflammatory factors set in motion a vicious cycle of inflammation and endothelial damage that lies at the heart of ALI/ARDS.

Table 15.2 Conditions Associated With Development of Acute Respiratory Distress Syndrome

Infection
Sepsis[a]
Diffuse pulmonary infections[a]
Viral, *Mycoplasma*, and *Pneumocystis* pneumonia; miliary tuberculosis
Gastric aspiration[a]
Physical/Injury
Mechanical trauma including head injuries[a]
Pulmonary contusions
Near-drowning
Fractures with fat embolism
Burns
Ionizing radiation
Inhaled Irritants
Oxygen toxicity
Smoke
Irritant gases and chemicals
Chemical Injury
Heroin or methadone overdose
Acetylsalicylic acid
Barbiturate overdose
Paraquat
Hematologic Conditions
Transfusion-associated lung injury (TRALI)
Disseminated intravascular coagulation
Pancreatitis
Uremia
Cardiopulmonary Bypass
Hypersensitivity Reactions
Organic solvents
Drugs

[a]More than 50% of cases of acute respiratory distress syndrome are associated with these four conditions.

- *Accumulation of intra-alveolar fluid and formation of hyaline membranes.* Endothelial activation and injury make pulmonary capillaries leaky, allowing interstitial and intra-alveolar edema fluid to form. Damage and necrosis of type II alveolar pneumocytes lead to surfactant abnormalities, further compromising alveolar gas exchange. Ultimately the inspissated protein-rich edema fluid and debris from dead alveolar epithelial cells organize into hyaline membranes, a characteristic feature of ALI/ARDS.
- *Resolution of injury* is impeded in ALI/ARDS due to epithelial necrosis and inflammatory damage that impairs the ability of remaining cells to assist with edema resorption. Eventually, however, if the inflammatory stimulus lessens, macrophages remove intra-alveolar debris and release fibrogenic cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor. These factors stimulate fibroblast growth and collagen deposition, leading to fibrosis of alveolar walls. Residual type II pneumocytes proliferate to replace type I pneumocytes, reconstituting the alveolar lining. Endothelial restoration occurs through proliferation of uninjured capillary endothelium.

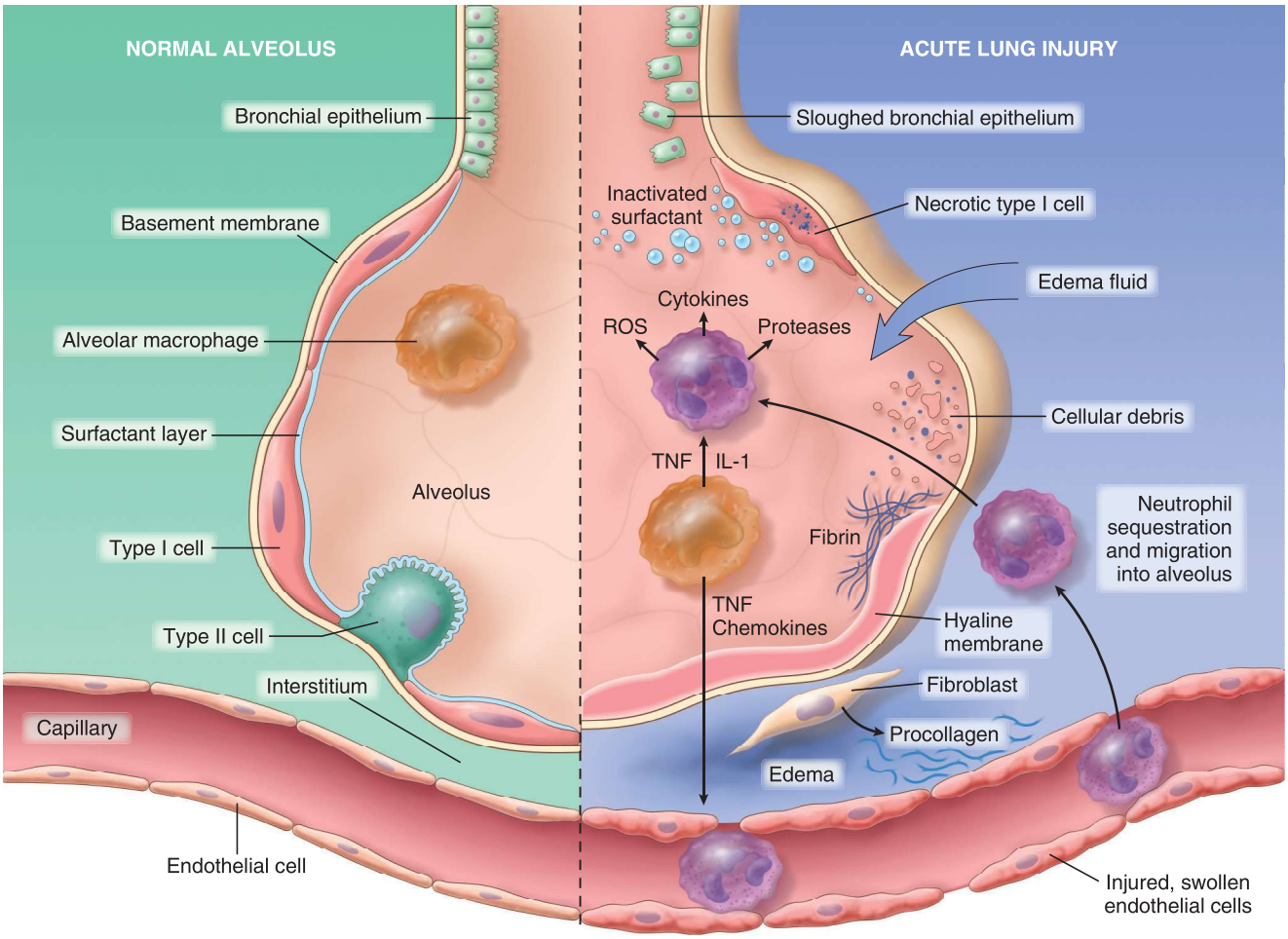

Figure 15.3 The normal alveolus *(left side)* compared with the injured alveolus in the early phase of acute lung injury and acute respiratory distress syndrome. *IL-1*, Interleukin-1; *ROS*, reactive oxygen species; *TNF*, tumor necrosis factor. (Modified with permission from Matthay MA, Ware LB, Zimmerman GA: The acute respiratory distress syndrome, *J Clin Invest* 122:2731, 2012.)

The lesions in ARDS are not evenly distributed, and as a result there are typically areas that are stiff and poorly aerated and regions that have nearly normal levels of compliance and ventilation. Because poorly aerated regions continue to be perfused, there is a mismatch of ventilation and perfusion, a phenomenon that exacerbates the hypoxemia and cyanosis.

Epidemiologic studies have shown that ALI/ARDS is more common and has a worse prognosis in chronic alcoholics and in smokers. Genome-wide association studies have identified a number of genetic variants that increase the risk of ARDS, some of which map to genes linked to inflammation and coagulation.

MORPHOLOGY

In the acute exudative stage, the lungs are heavy, firm, red, and boggy. They exhibit congestion, interstitial and intra-alveolar edema, inflammation, fibrin deposition, and **diffuse alveolar damage.** The alveolar walls become lined with waxy **hyaline membranes** (Fig. 15.4) that are morphologically similar to those seen in hyaline membrane disease of neonates (Chapter 10). Alveolar hyaline membranes consist of fibrin-rich edema fluid mixed with the remnants of necrotic epithelial cells. In the proliferative or organizing stage, type II pneumocytes proliferate, and granulation tissue forms in the alveolar walls and spaces. In most cases the granulation tissue resolves, leaving minimal functional impairment. Sometimes, however, fibrotic thickening (scarring) of the alveolar septa ensues (late fibrotic stage).

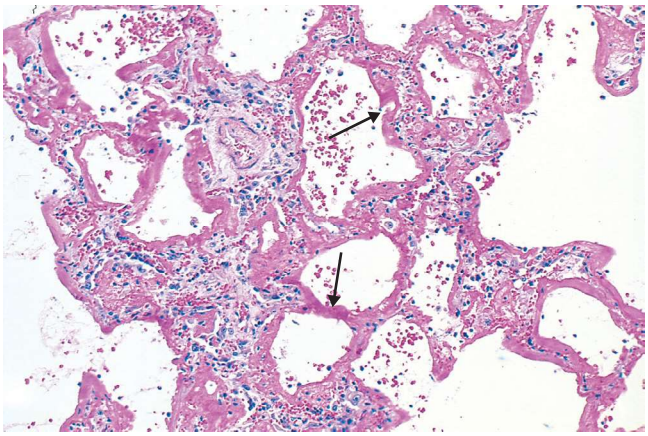

Figure 15.4 Diffuse alveolar damage (acute respiratory distress syndrome). Some of the alveoli are collapsed, while others are distended. Many are lined by hyaline membranes *(arrows)*.

Clinical Features

Profound dyspnea and tachypnea herald ALI/ARDS, followed by increasing respiratory failure, hypoxemia, cyanosis, and the appearance of diffuse bilateral infiltrates on radiographic examination. Hypoxemia may be refractory to oxygen therapy due to ventilation-perfusion mismatch, and respiratory acidosis can develop. Early in the course, the lungs become stiff due to loss of functional surfactant, leading to the need for intubation and high ventilatory pressures to maintain adequate gas exchange.

There are no proven specific treatments for ARDS, which is common in acutely ill patients and continues to take a high toll, even in patients receiving state-of-the-art supportive care. In a 2016 study of intensive care units in 50 countries, the incidence of ARDS was 10.4%, and mortality rates were 35% for mild, 40% for moderate, and 46% for severe ARDS. The majority of deaths are attributable to sepsis, multiorgan failure, or severe lung injury. Most survivors recover pulmonary function, but in a minority of patients, the lung damage results in interstitial fibrosis and chronic pulmonary disease.

KEY CONCEPTS

ACUTE RESPIRATORY DISTRESS SYNDROME

- ARDS is a clinical syndrome of progressive respiratory insufficiency caused by diffuse alveolar damage in the setting of sepsis, severe trauma, or diffuse pulmonary infection.
- Damage to endothelial and alveolar epithelial cells and secondary inflammation are the key initiating events and the basis of lung damage.
- The characteristic histologic finding is hyaline membranes lining alveolar walls, accompanied by edema, scattered neutrophils and macrophages, and epithelial necrosis.

OBSTRUCTIVE AND RESTRICTIVE LUNG DISEASES

Obstructive lung diseases are characterized by an increase in resistance to airflow due to diffuse airway disease, which may affect any level of the respiratory tract. These are contrasted with restrictive diseases, which are characterized by reduced expansion of lung parenchyma and decreased total lung capacity. The clinical distinction between these diseases is based primarily on pulmonary function tests. In individuals with diffuse obstructive disorders, pulmonary function tests show decreased maximal airflow rates during forced expiration, usually expressed as forced expiratory volume at 1 second (FEV_1) over forced ventilatory capacity (FVC). An FEV_1/FVC ratio of less than 0.7 generally indicates obstructive disease. Expiratory airflow obstruction may be caused by a variety of conditions (Table 15.3), each with characteristic pathologic changes and different mechanisms of airflow obstruction. As discussed later, however, the divisions between these entities are not "clean," and many patients have diseases with overlapping features. By contrast, restrictive diseases are associated with proportionate decreases in both total lung capacity and FEV_1, such that the FEV_1/FVC ratio remains normal. Restrictive defects occur in two broad kinds of conditions: (1) *chest wall disorders* (e.g., severe obesity, pleural diseases, kyphoscoliosis, and neuromuscular diseases such as poliomyelitis) and (2) *chronic interstitial and infiltrative diseases,* such as pneumoconioses and interstitial fibrosis.

OBSTRUCTIVE LUNG DISEASES

Common obstructive lung diseases include chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis (Table 15.3). COPD has two major clinicopathologic manifestations, emphysema and chronic bronchitis, which are often found together in the same patient, almost certainly because they share the same major etiologic factor—cigarette smoking. While asthma is distinguished from chronic bronchitis and emphysema by the presence of reversible bronchospasm, some patients with otherwise typical asthma also develop an irreversible component (Fig. 15.5). Conversely, some patients with otherwise typical COPD have a reversible component. Clinicians commonly label such patients as having COPD/asthma.

Chronic Obstructive Pulmonary Disease

COPD, a major public health problem, is defined by the World Health Organization (WHO) as "a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities caused by exposure to noxious particles or gases." It is currently the fourth

Table 15.3 Disorders Associated With Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Term	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hyperplasia, excess mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Airspace enlargement; wall destruction	Tobacco smoke	Dyspnea
Small airways disease, bronchiolitis[a]	Bronchiole	Inflammatory scarring/obliteration	Tobacco smoke, air pollutants, miscellaneous	Cough, dyspnea

[a]Can be seen with any form of obstructive lung disease or as an isolated finding.