Pulmonary edema is defined as an increase in extravascular lung water, which collects in two principal compartments, the interstitium and the alveoli; when water accumulates in the latter, gas exchange is severely compromised, with life-threatening consequences. Pulmonary edema is generally divided into two main pathogenetic types: (1) hydrostatic (commonly cardiogenic), also termed hemodynamic or high pressure, and (2) permeability edema, also termed “normal pressure” or noncardiogenic, encompassing predominantly acute respiratory distress syndrome (ARDS) and acute lung injury (ALI). Hydrostatic edema results from alterations in the “pressure” parameters in the Starling equation (below), most commonly microvascular pressure. The principal etiologies are shown in Table 19-1. In contrast, permeability edema, characterized by the elevation of microvascular permeability, is currently synonymous with ARDS and ALI. Each, as proposed by the American–European Consensus Conference (AECC), is defined as “a syndrome of inflammation and increasing permeability that is associated with a constellation of clinical, radiographic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension.” ALI and ARDS differ only in severity, and their defining criteria are given in Table 19-2; all patients with ARDS have ALI, but not all patients with ALI have ARDS. The classification of ARDS (Table 19-3) separates it into direct and indirect etiologies. Some investigators have used the terms pulmonary and extrapulmonary, based on differences in respiratory mechanics and response to positive end-expiratory pressure (PEEP), with predominant consolidation (implying a pneumonia process) in pulmonary ARDS versus prevalent edema and hyaline membranes, that is, diffuse alveolar damage (DAD) (see below), in extrapulmonary ARDS. The time frame for the “acute” in ALI/ARDS is “less than 7 days from the onset of the critical illness.”

This chapter presents the authors’ personal view of pulmonary edema in the adult. We focus on the definitions and classification, the basic pathogenetic mechanisms, including molecular, that result in pulmonary edema, the pathways of fluid movement in the lung, the imaging and pathologic appearances, and the pathophysiologic consequences for lung function and gas exchange. We open small windows on therapeutic vistas and their complications. Animal models are used as appropriate to explain mechanisms.

**STARLING EQUATION AND NORMAL FLUID BALANCE**

To understand pulmonary edema, it is important to consider the “Starling equation.” Although Starling enunciated the concepts of fluid exchange across vascular walls over a century ago, he provided no actual equation in his publication; rather, succeeding authors and investigators designed and refined several variants. One oft-quoted version is \( J_v = L_s [(P_{mv} - P_{pmv}) - \sigma (\Pi_{mv} - \Pi_{pmv})] \), in which (with approximately normal values for the lung in parentheses) \( J_v \) is net transvascular fluid flow (mL/min); \( L_s \) is specific vascular hydraulic conductance or permeability, dependent on endothelial pore size; \( S \) is the vascular surface area of those vessels participating in fluid exchange; \( L_s \) is \( K_f \) fluid filtration coefficient, a measure of permeability to fluid and vascular surface area (=0.2 mL/min/100 g/mm Hg); \( P_{mv} \) is microvascular (=capillary) hydrostatic pressure (=5 to 10 mm Hg); \( P_{pmv} \) is perimicrovascular or interstitial hydrostatic pressure (=−5 to −7 mm Hg); \( \sigma \) is the osmotic reflection coefficient, determining the relative contribution of the oncotic pressure gradient across the vasculature to the net driving pressure—expressly a measure of the permeability of a specified membrane (eg, endothelial) to a particular solute (eg, albumin), varying between 0 when the membrane is totally impermeable, to 1 when it is totally permeable; in the lung, \( \sigma \) is 0.75 to 0.80; \( \Pi_{mv} \) is the oncotic pressure of the blood in the microvasculature of the lung (=24 mm Hg); and \( \Pi_{pmv} \) is the oncotic pressure in the perimicrovascular interstitium (=14 mm Hg).

Of the parameters of the Starling equation, \( P_{mv} \) and \( \Pi_{mv} \) are those most easily measured or calculated as detailed below: both are measurable in experimental animals but not in humans, except for estimates of \( \Pi_{pmv} \) calculated from the protein level in alveolar fluid from patients with fulminant pulmonary edema. Similarly, \( J_v \), \( L_s \), and \( \sigma \) must be determined in animals or calculated from the other parameters (see Granger and colleagues for a comprehensive discussion). Under normal circumstances, the lung and, in particular, the alveoli are kept optimally hydrated or “dry” and...
Ventilation, Pulmonary Circulation and Gas Exchange

protected against edema by several physiologic safety factors, including the following:

1. Low pulmonary $P_{mv}$ compared to systemic capillaries ($\approx 25$ mm Hg).

2. Low $P_{pmv}$ compared to $P_{alv}$ (alveolar pressure $\approx 0$ mm Hg), so that filtered fluid preferentially enters the interstitium (negative $P_{pmv}$) rather than alveoli. As fluid builds up in the interstitium, $P_{pmv}$ rises, acting as negative feedback in the Starling equation.

3. A normally low $\Pi_{pmv}$, approximately 50% of $\Pi_{mv}$, estimated from protein concentrations in pulmonary edema.

4. The interstitium, able to accommodate a $\approx 50$% increase in extravascular lung water, largely proportional to glycosaminoglycans.

5. Lymphatics that drain the interstitial space and whose flow can increase 10 to 15 times acutely or 20 times chronically.

6. As $J_v$ rises, as long as $LS$ and $\sigma$ are normal, the $\Pi_{pmv}/\Pi_{mv}$ ratio drops because the endothelium sieves proteins.

7. An epithelial barrier substantially less permeable than the endothelial barrier because of tighter interepithelial junctions forming a more effective barrier to the passage of solutes and proteins (effective pore radii of 0.5 to 0.9 nm in epithelium vs 6.5 to 7.5 nm in capillary endothelium), affording protection against alveolar flooding.

In general, edema results when the filtered fluid $J_v$ rises beyond the capacity of the lymphatics and other mechanisms to remove it.

**Microvascular Pressure**

An understanding of the measurement and factors affecting $P_{mv}$ remains critical in the investigation of hydrostatic and

<table>
<thead>
<tr>
<th>Table 19-1</th>
<th>Classification of Hydrostatic Edema</th>
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<tbody>
<tr>
<td>Cardiogenic</td>
<td>High cardiac output</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Shunts (cardiac, pulmonary, peripheral)</td>
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<tr>
<td></td>
<td>Beriberi</td>
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<tr>
<td></td>
<td>Hyperthyroidism</td>
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<tr>
<td>Systolic dysfunction (low cardiac output)</td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Idiopathic (cardiomyopathy)</td>
</tr>
<tr>
<td></td>
<td>Tachycardia-induced</td>
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<tr>
<td></td>
<td>Peripartum</td>
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<tr>
<td></td>
<td>Toxin</td>
</tr>
<tr>
<td></td>
<td>Viral</td>
</tr>
<tr>
<td>Diastolic dysfunction (normal-to-high cardiac output)</td>
<td>Ischemia</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Noncardiogenic</td>
<td>Volume overload, eg, renal failure</td>
</tr>
<tr>
<td></td>
<td>Low oncotic pressure, eg, hypalbuminemia, dilutional from crystalloid overinfusion</td>
</tr>
<tr>
<td></td>
<td>Pulmonary venous diseases</td>
</tr>
<tr>
<td></td>
<td>Pulmonary venoocclusive disease</td>
</tr>
<tr>
<td></td>
<td>Mediastinal fibrosis</td>
</tr>
</tbody>
</table>

Inspired in part by Poppas and Rounds.

<table>
<thead>
<tr>
<th>Table 19-2</th>
<th>Definition of ARDS According to the American–European Consensus Conference, 1994¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute onset</td>
<td>Hypoxemia ($P_{aO_2}$ in mm Hg/FiO$_2$ ≤ 200) regardless of PEEP</td>
</tr>
<tr>
<td></td>
<td>Bilateral infiltrates on frontal chest radiograph</td>
</tr>
<tr>
<td></td>
<td>Pulmonary capillary wedge pressure ≤ 18 mm Hg or no evidence of left atrial hypertension</td>
</tr>
</tbody>
</table>

Acute lung injury differs only in having a $P_{aO_2}$/FiO$_2$ ≤ 300.

<table>
<thead>
<tr>
<th>Table 19-3</th>
<th>Classification of Permeability Pulmonary Edema (Acute Respiratory Distress Syndrome and Acute Lung Injury)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct lung injury</td>
<td>Infections (pneumonia)</td>
</tr>
<tr>
<td></td>
<td>Bacterial</td>
</tr>
<tr>
<td></td>
<td>Viral (eg, cytomegalovirus, adenovirus, herpes, SARS-associated coronavirus)</td>
</tr>
<tr>
<td></td>
<td>Fungal (eg, Aspergillus, Pneumocystis carinii)</td>
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<tr>
<td></td>
<td>Inhalation</td>
</tr>
<tr>
<td></td>
<td>Aspiration of gastric contents</td>
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<tr>
<td></td>
<td>Toxic gases and chemicals (eg, smoke, Cl$_2$, NH$_4$, NO$_2$, O$_2$, SO$_2$)</td>
</tr>
<tr>
<td></td>
<td>Near-drowning</td>
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<tr>
<td></td>
<td>Injury, traumatic (pulmonary contusion)</td>
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<tr>
<td></td>
<td>Intravascular</td>
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<tr>
<td></td>
<td>Embolism (air, amniotic fluid, fat)</td>
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<tr>
<td></td>
<td>Iatrogenic</td>
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<tr>
<td></td>
<td>Drugs</td>
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<td></td>
<td>Anticancer drugs (eg, bleomycin, busulfan, all-trans retinoic acid)</td>
</tr>
<tr>
<td></td>
<td>Antibiotics</td>
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<tr>
<td></td>
<td>Antiarrhythmics (eg, amiodarone)</td>
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<tr>
<td></td>
<td>Irradiation</td>
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<tr>
<td></td>
<td>Idiopathic</td>
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<tr>
<td></td>
<td>Acute eosinophilic pneumonia</td>
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<tr>
<td></td>
<td>Acute interstitial pneumonia</td>
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<tr>
<td>Immunologic</td>
<td>Acute lupus pneumonitis</td>
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<tr>
<td></td>
<td>Goodpasture’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Cryptogenic organizing pneumonia/bronchiolitis obliterans organizing pneumonia</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity pneumonitis</td>
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<tr>
<td></td>
<td>Idiopathic pulmonary hemosiderosis</td>
</tr>
<tr>
<td></td>
<td>Ischemia–reperfusion-mediated edema (eg, after embolectomy or lung transplantation)</td>
</tr>
<tr>
<td></td>
<td>Infiltration by malignancy</td>
</tr>
<tr>
<td></td>
<td>Lymphangitic carcinomatosis</td>
</tr>
<tr>
<td></td>
<td>Leukemic or lymphomatous infiltration</td>
</tr>
</tbody>
</table>

Indirect lung injury

|                | Sepsis                                                                                                         |
|                | Multiple fractures, severe trauma with shock                                                                   |
|                | Cardiopulmonary bypass                                                                                        |
|                | Major burns                                                                                                    |
|                | Drug overdose                                                                                                  |
|                | Acute pancreatitis                                                                                            |
|                | Multiple transfusions of blood products                                                                       |
|                | Disseminated intravascular coagulation                                                                         |
|                | High altitude*                                                                                                |

*With a hydrostatic component. Inspired in part by Lesur and colleagues, Murray and colleagues, Steinberg and Hudson, and Ware and Matthay.

[^262]: Murray and colleagues, 198
[^82]: Steinberg and Hudson, 82
[^264]: Ware and Matthay.
permeability forms of edema. Unlike its counterpart in the systemic circulation, \( P_{mv} \) is difficult to measure in the lung; its value depends directly on the distribution of pulmonary vascular resistance (PVR). In experimental animals, \( P_{mv} \) has been measured indirectly and, more recently, directly; in the clinical setting, only indirect measurements are possible. In normal lungs, \( P_{mv} \) has generally been measured or assumed to be close to the midpoint between pulmonary arterial and venous pressure (or left atrial pressure, \( P_{la} \)). Gaar and colleagues\(^8\) determined in isolated perfused canine lobes, using the isogravimetric method, that 56% of total PVR was in arteries and 44% in veins. This led to a widely quoted equation for the calculation of \( P_{mv} \), using the assumption that 40% of resistance was in the veins, such that 

\[
P_{mv} = P_w + 0.4(P_{pa} - P_w)
\]

where \( P_{pa} \) is pulmonary arterial pressure and \( P_w \) pulmonary arterial wedge pressure. The principal methods used for the estimation of \( P_{mv} \) have included (1) wedge catheters; (2) the isogravimetric method; (3) arterial, venous, or double occlusion; and (4) micropuncture.

Wedge catheters, introduced in 1948 (reviewed by Levy\(^12\)), are employed extensively in clinical practice to measure \( P_w \), an indirect measure of left ventricular end-diastolic pressure, although recently their benefits have been seriously questioned.\(^13\) The principle guiding the measurement of \( P_w \) is occlusion of a small-to-medium pulmonary arterial branch, approximately 1.5 to 3.0 mm,\(^14\) by inflation of the catheter’s balloon, thereby “wedge”-ing it; as flow distal to the balloon stops, the pressure measured at the tip of the catheter equals the pressure along the vascular tree supplied by that artery until a vein of about the same size is reached, wherein bloodflow resumes. The pressure measured at the tip of the catheter approximates left atrial and ventricular end-diastolic pressures, provided that (1) there is a continuous column of blood into the left atrium and, at end-diastole, into the left ventricle (ie, the lung is in zone 3), and (2) resistance of the large pulmonary veins is low.

In abnormal lungs, particularly in ARDS, with hypoxia or activation of the inflammatory cascade, release of mediators such as histamine, leukotrienes, platelet-activating factor (PAF), and thromboxanes may alter pulmonary arterial and venous resistances, and the relationship between \( P_{mv} \) and \( P_w \) and reduce the validity of \( P_w \) measurements in the estimation of \( P_{mv} \). These considerations impact directly on the management of patients with ARDS, in whom a delicate balance must be maintained between an adequate filling pressure and minimizing pressure-related fluid filtration, and they prompted detailed studies on the distribution of PVR.

In 1979, Hakim and colleagues\(^15\) first used the venous occlusion technique in isolated canine lung lobes to examine the distribution of resistance across the pulmonary vascular bed. The technique, extended to arterial and venous occlusion (AVO) in sequence, generated a simple model in which PVR was partitioned into relatively inelastic arterial and venous segments, each contributing 40% to 45% of the total, separated by a more compliant middle segment contributing 10 to 15%.\(^16\) These segmental resistances and the \( P_{mv} \) values dependent on them vary with the physiologic environment, pharmacologic stimuli, and pathologic conditions. For example: (1) the relative proportion of arterial and venous resistance rises with bloodflow and venous pressure; (2) middle segmental resistance increases with airway pressure and hypoxia\(^17,18\); (3) arterial segmental resistance increases with serotonin level; (4) venous segmental resistance rises with levels of histamine, leukotrienes,\(^19\) PAF\(^20\) and thromboxane\(^21\); (4) systemic-to-pulmonary shunts raise mainly the arterial segmental resistance,\(^22\) and fibrosis increases middle segmental resistance.\(^23\)

Nearly simultaneously with the introduction of the occlusion technique, Bhattacharya and Staub\(^24\) measured for the first time pressures by micropuncture in subpleural pulmonary arteries and veins, 10 to 50 \( \mu \)m in diameter, of isolated canine lobes and found that 45% of total resistance was in alveolar wall vessels, with most of the balance of resistance being in small arteries. A dozen years later, similar data were obtained by Negrini and colleagues\(^25\) in intact animals by puncturing the pleura. These and subsequent findings, recently reviewed,\(^26\) reveal that one-third to one-half of the total pressure drop from pulmonary artery to left atrium takes place in alveolar capillaries.

The findings of the micropuncture studies are difficult to reconcile with the occlusion data. Explanations for the discrepancies include (1) technical considerations related to the vascular and alveolar pressures under which micropuncture measurements are made\(^27\) and (2) the notion that subpleural vessels differ morphologically and may not be representative of the entire lung because of their relatively low density and reduced bloodflows.\(^28,29\) In a study in which both techniques were compared,\(^30\) a pressure gradient of only 0.5 mm Hg between 30 and 50 \( \mu \)m arteries and veins, and a large pressure gradient in arteries and veins > 0.9 mm, were found. Nagasaka and colleagues\(^31,32\) reported that, in feline lungs, there was a substantial gradient in arterial and venous vessels and that their relative contributions to the total gradient were flow dependent, consistent with the notion that at low flows, or in vessels with intrinsically lower flow rates, such as in the subpleural region, the contribution of the middle capillary segment to total PVR may be unduly high. One criticism leveled against the occlusion data is the uncertainty concerning the anatomic size limits of each of the segments: Hakim and Kelly\(^33\) addressed this point and concluded that AVO measured pressures in vessels 50 to 900 \( \mu \)m in diameter, probably in the vicinity of 100 \( \mu \)m; a similar size estimate was obtained in a structure–function study of a model of chronic unilateral pulmonary artery ligation.\(^33\) Although the discrepancies between the micropuncture and occlusion data are incompletely resolved, the evidence appears to favor the notion that, for the lung in its entirety, the majority of the resistance lies in the larger arterial and venous vessels, ensuring protection from both arterial overperfusion and elevations in venous pressure. Moreover, a distinct advantage of occlusion is that it offers an experimental model and theoretical framework for the measurement of \( P_{mv} \), in patients at the bedside.
Indeed, the AVO techniques have been adapted for use in intact animals and humans, under conditions of pulsatile flow. In animals, pressure transients recorded immediately after occlusion have been caused by inflation of the Swan-Ganz catheter's balloon are analyzed to obtain estimates of $P_{mv}$, yielding values linearly related to those obtained by the isogravimetric method and by double occlusion over a range of pressures. In patients, the methods of analysis and results of the occlusion technique vary with the clinical situation, as discussed elsewhere.

To summarize, the clinical measurement of $P_{mv}$ remains difficult, particularly in ARDS, because of (1) regional disparities in severity of disease; (2) difficulties in interpretation of occlusion pressure measurements because of respiratory movements; (3) high levels of PEEP, so that arterial pressure tracings reflect alveolar rather than vascular pressure (ie, zone 1); (4) subjectivity of measurements; and (5) the relatively long time needed for the occlusion to appear on the tracings. In both hydrostatic and permeability edema, the key message is that the fluid filtration pressure $P_{mv}$ is substantially higher than the frequently measured $P_w$. In particular, the AECC criterion for $P_w$ of 18 mm Hg (see Table 19-2) is relatively high since the corresponding $P_{mv}$ in normal lungs is 23 to 24 mm Hg, above which lung water rises in linear fashion even in normal lungs (see below). Perturbations in the distribution of PVR in ARDS caused by cytokines and mediators, as indicated above, increase the likelihood of an even greater differential between $P_{mv}$ and $P_w$.

**OTHER PRESSURES IN THE STARLING EQUATION**

The intravascular oncotic pressure $\Pi_{mv}$, counterbalancing $P_{mv}$, can be measured directly with an osmometer, calculated from equations originally described by Landis and Pappenheimer, with knowledge of the plasma concentrations of albumin and globulins, or read directly from a nomogram. The $\Pi_{mv}$ is also subject to change, for example, in disease states associated with hypoproteinemia: when the protein concentration falls by about half, patients are at risk of developing pulmonary edema because of the reduced threshold for $P_{mv}$. In hydrostatic edema, the normal $\Pi_{pmv}/\Pi_{mv}$ ratio of about 50% may fall to 30% under conditions of high filtration as long as the sieving properties of the microvascular barrier are maintained.

The $P_{pmv}$ varies with location in the pulmonary parenchyma. Bhattacharya and colleagues found, in normal lungs, that $P_{pmv} = -3$ cm H$_2$O at interalveolar junctions, to which is added the gradient between the perimicrovascular space in the subpleural and parenchymal areas and the hilar interstitial tissues ($=5$ cm H$_2$O), driving fluid toward the hilum. Alterations in $P_{pmv}$ with hydrostatic edema are discussed below.

**EDEMA: SOURCES AND PATHWAYS OF LEAKAGE, SEQUENCE AND SITES OF ACCUMULATION, AND CLEARANCE**

**Sources and Pathways of Fluid Leakage**

In the systemic circulation, particularly under conditions of increased permeability, it is accepted that venules are the most leaky vessels. However, in the lung, demonstration of a gradient of vascular permeability between capillaries, small arteries and veins has been difficult, prompting Staub to advocate the term “microvascular” over “capillary” to describe sites of fluid filtration. Morphologic studies with tracers have shown that much of the leakage occurs from capillaries, with lesser amounts from small nonmuscular arteries and veins. Physiologic data show edema leaks from extraalveolar as well as alveolar vessels: alveolar vessels, that is, those subject to alveolar pressure, include the majority of alveolar capillaries but also some small arteries and veins vessels in the extraalveolar compartment, in contrast, are those whose liquid pressure is influenced by pleural pressure and anatomically are composed of most of the arteries and veins and of capillaries at alveolar corners.

An important variable in the ascertainment of sources and relative amounts of fluid filtered is vascular surface area. As summarized by Staub, morphometric studies of the pulmonary vasculature in humans have shown that 90 to 95% of the vascular surface area is provided by capillaries, with the small balance being provided by arteries and veins. These data suggest that at high alveolar pressure (zone 1 conditions), there should be 10 to 20 times less fluid filtered than under zone 3 conditions; in fact, there is only a two-fold difference, reflecting continued filtration in zone 1 by extraalveolar vessels, particularly capillaries in alveolar corners. This reasoning is true if we assume that filtration is directly proportional to surface area, but this has not been demonstrated in pathologic states of permeability edema or even in hydrostatic edema.

Where does the fluid move after its filtration? From capillaries, it enters the thick part of the alveolar–capillary septum and tracks to the “juxtaalveolar region” (junction between alveolar and extraalveolar interstitial spaces), where it enters the initial lymphatics, the movement being driven by passive interstitial hydrostatic pressure gradients facilitated by respiration. As referred to above, the pressure gradient from the alveolar–capillary septum to the interalveolar junctions of $-3$ cm H$_2$O is added to a further 1.5 cm H$_2$O to the initial lymphatics, for a total interstitial pressure gradient from capillaries to lymphatics of 4 to 5 cm H$_2$O. From there, fluid moves to the hilar interstitial tissues and lymphatics within them.

**Sequence and Sites of Edema Fluid Accumulation**

When the lymphatics are unable to cope with the demands of filtration, fluid accumulates first in the interstitium around arteries, veins, and airways and in interlobular septa (Figures 19-1 and 19-2), protecting the lung against the final stage, alveolar edema. Studies in which quantitative morphologic was used to investigate the distribution of interstitial fluid in hydrostatic and in permeability edema induced...
Pulmonary Edema

by α-naphthylthiourea (ANTU) have shown preferential fluid accumulation around arteries over veins and around larger vessels; in bronchovascular bundles, more fluid collects around arteries than around airways (see Figure 19-1), with none around bronchioles. These preferred sites of fluid collection result from differences in compliance of the interstitial spaces and their hydrostatic pressures. Several authors have shown (reviewed by Lai-Fook) that the distribution of edema in the lung depends on gradients of interstitial pressures, resistance and compliance. Peribronchial pressures are less negative than perivascular pressures and rise relative to pleural pressure with inflation because peribronchial pressure follows intrabronchial pressure, which rises with alveolar pressure; in contrast, perivascular pressures are more negative than pleural and peribronchial pressures and reflect the mechanical stress exerted on the vessels by the pulmonary parenchyma. Movement of fluid in the peribronchovascular interstitium also depends on tissue resistance, determined by hyaluronan and the extent of hydration: resistance to fluid flow drops with increasing edema or when hyaluronidase is added.

Interstitial fluid cuffs protect against alveolar flooding by acting as reservoirs. Their volume can rise to 2 to 3 mL/g dry lung weight and in proportion to lung volume. Consequently, the lung can augment its wet weight by 50% prior to the onset of alveolar flooding, with the proviso that the alveolar epithelium remains intact. In permeability edema, this reservoir function appears to be much less effective since alveolar flooding may occur early and in some instances bypass altogether the interstitial edema phase.

In interesting morphologic and physiologic studies, primarily in the 1980s, the relationships between the fluid in large peribronchovascular interstitial cuffs and lymphatic drainage were examined; it was found that lymph flow is more closely related to fluid filtration rate from pulmonary microvessels (ie, predominantly to $P_{mv}$) than to the amount of lung water. It has been demonstrated in morphologic studies that tracers injected intravenously emerge in lymphatic vessels within minutes, whereas their appearance in perivascular interstitial cuffs is delayed in proportion to their distance from the site of filtration. In a physiologic model of hydrostatic lung edema, lymph flow was proportional to vascular pressure; when the latter was normalized, lymph flow returned to control values, despite the presence of considerable edema in the lung, consistent with a two-compartment model of the pulmonary interstitium: a perimicrovascular compartment, in direct contact with the filtering vessels, and a second compartment, consisting of “sequestered” spaces around larger bronchovascular bundles and in interlobular septa. This relationship may not hold true in permeability edema, as shown in ANTU-induced edema by Pine and colleagues, who found abundant alveolar edema with little interstitial edema and low lymphatic flow rates.

In hydrostatic edema, the question of precisely how fluid enters alveoli from a filled interstitium remains unanswered. Staub suggested an “overflowing bathtub theory,” but the exact site of passage is not clear: morphologic evidence points to the epithelia of alveoli, alveolar ducts, and respiratory

![Figure 19-1](image1.png)

**Figure 19-1** Part of a frozen canine lung slice after induction of hydrostatic edema: note artery (A) and vein (V) surrounded by fluid cuffs (arrows); B = airway.

![Figure 19-2](image2.png)

**Figure 19-2** Light photomicrograph of lung from a patient with cardiogenic pulmonary edema. A, Low-power view, showing fluid in the interlobular septum (arrows) and adjacent alveoli. Hematoxylin-eosin stain; ×50 original magnification. B, Higher-power view, showing dilated lymphatic (Lymph) with its valve (arrow) and edema in some alveoli (Alv). Hematoxylin-eosin stain; ×250 original magnification.
bronchioles as sites of passage, possibly via normally tight interepithelial junctions forced open by the pressure. The terminal respiratory airway epithelium is particularly susceptible to damage, and it is thought that the pores between the interstitium and the alveoli must be fairly large, that is, about 10 to 12 nm, because the protein concentration in alveolar liquid approaches that in the interstitium.

**Clearance of Alveolar Edema**
The important and clinically relevant topic of the resolution of alveolar edema came to the forefront of research about 20 years ago, when studies provided evidence that alveolar fluid balance in the lung was regulated through active ion transport mechanisms by pulmonary alveolar and distal airway epithelium. The current model for the mechanism of the clearance of water and ions is that active transepithelial transport of salt drives water movement and supplants the passive forces of the Starling equation. Although the alveolar epithelium, with its large surface area (99% of respiratory epithelial area), is the favored site of fluid reabsorption, the precise contribution of each segment of pulmonary epithelium remains undefined. Clara cells and nonciliated cuboidal cells in airways <200 μm in diameter are capable of transporting Na⁺ and Cl⁻ ions and, despite their relatively small numbers, may contribute to alveolar fluid clearance; new evidence suggests that some fluid may be removed by convective surface active forces that propel it into the distal airways, with absorption occurring across respiratory bronchiolar epithelial cells. These cells, along with type II and possibly type I pneumocytes, have their ion transporters distributed asymmetrically on the apical and basal surfaces, enabling unidirectional transport of Na⁺ ions. The specific mechanisms involve Na⁺ uptake on the alveolar side of epithelial cells via amiloride-sensitive and amiloride-insensitive channels and active pumping from the basolateral surface into the pulmonary interstitium by Na⁺/K⁺-ATPase.

Supporting the importance of active clearance of alveolar edema are demonstrations that (1) in uninjured lungs, variations in transpulmonary airway pressure resulting from ventilation play a relatively small role in fluid clearance—for example, elimination of ventilation to one lung did not change the rate of fluid clearance in sheep, and similar results in dogs obtained with the use of computed tomography (CT) of frozen lungs and light microscopy showed that ventilation had little effect on the clearance of alveolar edema and acted primarily by aerating alveoli, and (2) clearance is inhibited by hypothermia in several models in different species, including humans.

In contrast, the clearance of alveolar protein across the alveolar–epithelial barrier, which is much slower than that of water and solutes, is mediated chiefly by restricted diffusion, with added contributions from endocytosis and transthyretin; in nonanesthetized spontaneously breathing sheep, Matthy and colleagues found that albumin cleared at a slow constant rate of 1%/h; in contrast, in the first 4 hours, water was removed at 8.3%/h, gradually slowing to 1.4%/h at 24 hours, due to the increasing osmotic pressure of the residual alveolar protein.

Clearance of fluid differs in hydrostatic and in permeability edema. In clinical studies of hydrostatic edema due to left heart failure, in which the epithelium remains intact, fluid was cleared in most patients within 4 hours of intubation and positive pressure ventilation. In one study, 75% of patients had intact fluid clearance, and the inability to clear fluid in the remaining patients was unrelated to the elevated vascular pressures. In permeability edema, clearance of alveolar fluid is impaired and associated with prolonged respiratory failure and elevated mortality; only those patients who clear fluid quickly have a higher survival rate, consistent with the notion that an intact distal pulmonary epithelium is coupled to a better prognosis in patients with ALI. The subject of the clearance of pulmonary edema is discussed in greater detail elsewhere in this book (see Chapter 38, “Epithelial Function in Lung Injury”).

**Hydrostatic Pulmonary Edema**

**Epidemiology**
The epidemiology of hydrostatic pulmonary edema is intimately related to that of congestive heart failure (CHF). The American Heart Association reports about 550,000 new cases each year in the United States, and CHF contributed to approximately 287,200 deaths in 1999. Recent data from the Framingham Heart Study on 3,757 male and 4,472 female subjects free of CHF at baseline, from 1971 to 1996, revealed that, at age 40 years, the lifetime risk for CHF was 21.0% for men and 20.3% for women, remaining at this level with advancing index age because of rapidly increasing CHF incidence rates; the lifetime risk for CHF doubled for subjects with blood pressure >160/100 versus <140/90 mmHg, and in those subjects without antecedent myocardial infarction, the lifetime risk for CHF at age 40 years was 11.4% for men and 15.4% for women. Therefore, hypertension and myocardial infarction are the major antecedents of heart failure, including hydrostatic pulmonary edema. In another recent study of 10,311 eligible Framingham Heart Study subjects, Levy and colleagues reported CHF in 1,075 (10.4%) subjects between 1950 and 1999; over those 50 years, the incidence of heart failure declined among women but not among men, and survival after onset of CHF has improved in both sexes. It remains the case that hydrostatic edema as part of CHF is a formidable health problem and that the prognosis after development of CHF is poor, with a median survival of 1.7 years in men and 3.2 years in women.

**Pathogenesis**
The major causes of hydrostatic pulmonary edema are cardiac, generally left ventricular failure. The customary initiating event is a fall in ventricular ejection fraction, elevating end-diastolic volume and then pressure; this raises PՎla to maintain output, with passive transmission to the pulmonary venous and microvascular network. According to the Starling equation, this rise in P vant increases Jw directly and vascular surface area S indirectly by recruitment. As first shown in the seminal study of Guyton and Lindsey, raising PՎla above 24 mm Hg produces a linear rise in lung water as...
determined by wet/dry weight ratios; similar findings have
been reported in humans.\textsuperscript{69} It is noteworthy that in the def-
nition of ARDS (see Table 19-2), the threshold value for
$P_{mv}$, as estimated from $P_w$, is generally set at a lower level,
that is, approximately 18 mm Hg. This relatively high pres-
sure threshold reflects the action of the two principal safety
factors: (1) lymph flow (an indirect measure of $J_v$), which
increases to clear fluid in direct proportion to $P_{la}$ and $P_{mv}$,
up to approximately double normal $P_{mv}$, and (2) an osmotic
feedback mechanism, with a proportionate reduction in pro-
tein osmotic pressure of the interstitium ($\Pi_{pmv}$) and lymph
due to sieving of proteins at the endothelial barrier, which,
at pressures under $\approx 40$ mm Hg (cf. West and colleagues—
later in this chapter), remains intact and reduces fluid filtra-
tion by approximately 50%.

Notably, when the right heart also fails, the elevation of
systemic venous pressure abrogates part of the safety factor
provided by the lymphatics: these enter the neck veins, so
that their downstream pressure is increased, reducing their
flow rate and accentuating the edema.\textsuperscript{40,70} Drake and col-
leagues\textsuperscript{71} found that increases in systemic venous pressure
$>11$ mm Hg produced by heart failure in sheep interfered
more with lymph flow from the caudal mediastinal lymph
node (which drains predominantly pulmonary lymph) than
with lymph flow with zero outflow pressure. Similarly,
$20$ mm Hg PEEP, which increases central venous pressure,
impedes pulmonary lymph flow, and facilitates the forma-
tion of hydrostatic pulmonary edema, was reversed by an
external thoracic duct fistula, isolating this important source
of pulmonary drainage from the elevated venous pressure.\textsuperscript{72}

**Pathology and Imaging**

In the acute stage, the first alteration as $P_{mv}$ rises is pul-
monary vascular congestion with distention and recruit-
ment, increasing surface area; as it increases further and the
lymphatics are overwhelmed, fluid accumulates, first in the
interstitium (interlobular septa and peribronchovascular
spaces, and interalveolar septa) and then in alveoli (Figures
19-1 to 19-4). On hematoxylin and eosin (H&E)-stained
histologic sections, the interstitial and alveolar spaces are
distended by thin eosinophilic fluid (reflecting a lower pro-
tein content) that may contain small amounts of blood.

The findings of imaging studies mirror the pathologic
alterations (Figure 19-5). The sequential alterations on
chest radiographs are (1) vascular “redistribution” to and
distention of upper pulmonary veins; (2) enlargement and
loss of definition of hilar structures; (3) septal lines in the
lower lung, termed Kerley A and B lines; (4) peribronchial

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image1.jpg}
\caption{Part of a lung slice from a patient with hydrostatic
edema, showing dilated interlobular septa (one at arrow), some
extending to pleura (corresponding to Kerley B lines on a chest
radiograph).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2.jpg}
\caption{Chest radiograph showing hydrostatic edema resulting
from heart failure after recent myocardial infarct superimposed
on long-standing aortic stenosis in a 74-year-old male. Note dis-
tended upper zone vessels, prominent interstitial markings, and
fluffy airspace edema in lower lung fields.}
\end{figure}
and perivascular cuffing with widening and blurring of the margins; and (5) thickening of interlobar fissures with subpleural fluid accumulation. Cardiomegaly and pleural effusions are frequent. There are gradients of distribution of edema, both gravity dependent and gravity independent. Several studies have confirmed that, because of the balance of forces favoring fluid filtration, there is more interstitial edema, both gravity dependent and gravity independent. Effusions are frequent. There are gradients of distribution of

Chronic or repeated episodes of elevated pulmonary venous pressures may lead to characteristic vascular and parenchymal alterations that include “brown induration of the lung” with abundant hemosiderin-laden alveolar macrophages (see Figure 19-4), mild interstitial and alveolar fibrosis, “arterialization” of veins, and arterial medial thickening, the last of these leading to secondary pulmonary hypertension. At the ultrastructural level, in isolated perfused canine lobes, descriptive and morphometric studies of acute hydrostatic edema have revealed (1) widening of the air–blood barrier at the thick part of the alveolar–capillary septum, leaving intact its thin part, where endothelial and epithelial basement membranes are fused (and where gas exchange occurs), and (2) increased density of pinocytotic vesicles in capillary endothelium and in alveolar type I pneumocytes and more open interendothelial junctions; in intact dogs, however, endothelial vesicular densities are normal, and edema fluid is seen only in the extraalveolar connective tissue spaces, probably as a result of differences in $P_{pmv}$, $\Pi_{pmv}$, or lymph flow rates. More recent studies in excised and perfused rabbit lungs have shown blebs or frank disruptions of epithelium with rare endothelial lesions, distributed in an apical–basal gradient and present in fluid-filled alveoli.

In chronic heart failure or mitral stenosis, electron microscopy of lungs from experimental animals or patients shows (1) edema, degeneration, and even reduplication of endothelial cells (ECs); (2) edema of epithelial cells and of the thick part of the alveolar–capillary septum; (3) proliferation of dense connective tissue around capillaries and of type II pneumocytes; and (4) increased numbers of intraalveolar macrophages. This remodeling has been associated with an elevation of PVR, a fall in vascular compliance, and, as dictated by the Laplace equation, a reduction in stress on capillaries with an increased threshold for high vascular pressure–induced injury. Mechanisms for the remodeling, reviewed by West and Mathieu-Costello, involve increased expression of genes for extracellular matrix proteins, such as various procollagens and fibronectin, and for growth factors, for example, fibroblast growth factor-2 (FGF-2) and transforming growth factor-$\beta_1$ (TGF-$\beta_1$).

**PERMEABILITY PULMONARY EDEMA**

**Epidemiology**

Although the exact yearly incidence of ALI/ARDS has not been established, estimates in the United States have ranged from highs of 75 in 100,000 to lows of 1.5 to 8.4 in 100,000. More recent data from the ARDS Network study of low-tidal-volume ventilation have suggested rates ranging from 16 to 96 cases of ALI/ARDS per 100,000 population. This wide range reflects both the difficulties in conducting such epidemiologic studies and the absence of a specific diagnostic test. The mortality associated with ALI/ARDS, despite over three decades of intensive investigation into causes and treatment, remains disturbingly high, at approximately 50%, and although beneficial effects of low-volume ventilatory management have been reported, numerous pharmacologic agents tested have failed to significantly improve this outcome.

Much of the early literature regarding ALI reported discrepant defining criteria, making comparisons between studies difficult. Although designed to address this lack of uniformity, the AECC criteria for ALI/ARDS (see Table 19-2) were rendered suspect by a recent report of poor interobserver agreement in the radiographic interpretation of ARDS. There are similar concerns about the other criteria for ARDS since hypoxemia and oxygenation are altered by PEEP or alveolar recruitment maneuvers, and measurements of $P_w$ to exclude hydrostatic edema are complicated by concurrent heart failure, application of PEEP, and other variables. Furthermore, the classification of ARDS is hampered by the lack of unique defining criteria: the pathologic characteristics of ARDS are encompassed by DAD as detailed below, but attempts to correlate DAD with the clinical presentation of ARDS have led to frustration. Indeed, in a retrospective study, Patel and colleagues reported that in 57 patients meeting AECC criteria, a specific histologic diagnosis other than DAD was revealed by open-lung biopsy in 60%, underscoring the severe limitations of the AECC definition, and any clinical studies examining pathophysiology and treatment of ALI/ARDS.

Adding to this confusion, data fromGattinoni and colleagues identified two distinct subgroups of ALI: among their 21 patients, 12 were deemed to have suffered a direct pulmonary injury, and in 9 an extrapulmonary cause was thought to be responsible. Although overall respiratory system elastance was similar in both subgroups, differences emerged after its partition into different categories: (1) lung elastance was significantly higher in the pulmonary group, whereas chest wall elastance and abdominal pressure were higher in the extrapulmonary group, and (2) PEEP increased respiratory system elastance in the pulmonary group but failed to recruit any additional lung volume when set to 15 cm H$_2$O, whereas PEEP decreased elastance in the extrapulmonary group and recruited additional lung volume. The authors explained these results by the consolidation in pulmonary ALI and by the edema and collapse in extrapulmonary ALI.

Given this lack of specificity and of readily available histologic confirmation, plasma markers would be useful to identify the syndrome, similar to troponin in acute coronary syndromes. To date, this search has been unsuccessful. Von Willebrand factor antigen, produced primarily by endothelial cells and, to a lesser extent, by platelets, has been variably identified as a diagnostic and prognostic indicator of

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ALI: Ware and colleagues\(^87\) reported that very high levels (>450%) have a greater than 80% positive predictive value for death in ALI, although they stressed that its high plasma-to-pulmonary edema ratio strongly supports the notion that its release reflects a generalized systemic endothelial activation/injury rather than specific lung injury.

More particular to the lung, and perhaps more promising as a diagnostic aid, is the bedside assessment of the activity of pulmonary endothelium-bound angiotensin-converting enzyme (ACE): Orfanos and colleagues\(^88\) found reduced activity of the enzyme early in the course of ALI and an inverse relationship between its activity and the severity of lung injury as characterized by the Murray score. If this assay is to gain clinical credibility, it will have to be assessed both in conditions characterized by systemic endothelial injury, such as sepsis, and in those where lung disease other than ALI plays a prominent role, for example, pneumonia.

To quantify the risk of developing ALI following the onset of specific predisposing conditions, three large prospective studies were conducted, with similar qualifying criteria being used in each, although prior to the AECC definition. Pepe and colleagues\(^89\) followed prospectively 136 patients with sepsis, aspiration of gastric contents, pulmonary contusion, multiple red cell transfusions, multiple major fractures, near-drowning, pancreatitis, and prolonged hypotension: 38% of patients with sepsis and 30% with aspiration developed ALI. Fowler and colleagues\(^90\) similarly followed 993 patients with eight prospectively defined risk factors and identified 68 patients who developed ALI: aspiration carried the greatest risk (36%), and only 4% of the 239 patients with established bacteremia developed ALI. These findings contrast sharply with those of Pepe and colleagues\(^89\); this could be partly explained, perhaps, by the fact that their definition of sepsis included both infection (but not necessarily bacteremia) and a systemic response to that infection. More recently, Hudson and colleagues\(^91\) prospectively followed patients with eight predefined conditions: 41% of patients with sepsis, 36% of patients following multiple blood transfusions, and 22% of patients with pulmonary contusion or gastric aspiration developed ALI. Together, these three studies also revealed that multiple risk factors markedly increased the incidence of ALI, and that =85% of patients who develop ALI do so within 72 hours of the onset of the risk factor, with those patients with aspiration tending to do so earlier than those with sepsis or trauma.

The mortality of ARDS in the three aforementioned studies\(^89,90,91\) and a later review\(^92\) ranged from 41 to >60%, and in two of the studies mortality was two- to threefold higher in those patients who developed the syndrome than in those patients at risk who failed to do so.\(^90,91\) Although median survival has been reported to be \(=13\) days from onset of ARDS,\(^90\) most studies have shown no relationship between respiratory failure and death. In their retrospective analyses, Montgomery and colleagues\(^93\) reported that only 16% of patients with ALI who died did so because of irreversible respiratory failure; most deaths after 72 hours were due to multiple organ failure and sepsis (interestingly, principally of pulmonary origin). Moreover, even those deaths attributed to respiratory failure had sepsis as a major contributing factor, and cardiac dysfunction, deemed the second leading cause of death, was also complicated by sepsis in 80% of cases. Even the more recent studies have been able to link only a minority of deaths with respiratory failure,\(^94\) a finding with critical implications for any lung-directed pharmacotherapy.

A recent interesting prospective study from Argentina conducted over 15 months identified 235 patients who met AECC criteria for ARDS\(^95,96\): sepsis was the main risk factor in 44% (particularly secondary to pneumonia) and aspiration in 10%. Although the arterial partial pressure of oxygen (\(P_aO_2\)/fraction of inspired oxygen (\(FiO_2\)) on day 1 did not differentiate survivors from nonsurvivors, by day 2 survivors exhibited significantly improved oxygenation compared to nonsurvivors; additionally, increased mortality was significantly associated with (1) sequential organ failure assessment score at 72 hours; (2) the degree of hypoxemia at 72 hours; and (3) the presence of severe comorbidities. In this study, despite the suggestion from several recent controlled interventional trials of improved survival, a very high mortality rate of 58% was found. It also reinforced the concept that patients with ARDS die with, not from, the disease, in that only 15% of patients died of refractory hypoxemia, whereas multiple organ dysfunction syndrome (MODS) and sepsis were deemed to be responsible for death in 69% and 66% of patients, respectively.

Other investigators identified additional factors predictive of increased mortality in ALI/ARDS. Monchi and colleagues\(^97\) found in 259 patients that the following factors were associated with an elevated risk of death that overall reached 65%: (1) the SAPS II and McCabe scores; (2) the prior duration of mechanical ventilation and the oxygenation index; (3) the presence of direct (over indirect) lung injury; (4) right ventricular dysfunction; and especially (5) cirrhotic liver disease. Nuckton and colleagues\(^98\) confirmed the importance of the SAPS II score and found that an elevated dead space measured during the first several hours of ARDS was the most sensitive prognostic indicator of death. Two recent preliminary reports have linked an increased hematocrit\(^98\) and numerous red blood cell transfusions\(^99\) to an increased risk of death in patients with ALI, findings all the more intriguing given the recent controversy over transfusion requirements in the critically ill patient.\(^100\)

**Pathogenesis**

The final common pathway of permeability edema is endothelial and epithelial injury resulting from a variety of insults, causing predominant alveolar flooding that contrasts with the orderly sequence of edema accumulation in hydrostatic edema.\(^55,101\) Filtration occurs independently of \(P_{mv}\), although it is aggravated by its elevation, and the fluid has a high protein concentration, \(\approx70\)% of plasma.

Sepsis frequently predisposes to ARDS, and there has been considerable recent interest in a “two-hit hypothesis” for pulmonary (and other organ) injury in sepsis leading to ARDS: the first hit, for example, sepsis, damages the gut–blood barrier; gram-negative bacteria move through the epithelium and enter the bloodstream, and cytokines such...
as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α) are released, initiating the systemic inflammatory response syndrome (SIRS). This first hit renders the lung susceptible to a second more direct hit (eg, thoracic trauma, ischemia, pulmonary infection, ventilator-induced injury), producing ARDS.

**Role of Cells in ARDS**

**Endothelial Cells** ECs have always occupied a central role in the pathogenesis of pulmonary edema, either through their simple function as a barrier in hydrostatic edema or through their injury in ARDS and other forms of permeability edema. ECs can be injured directly and indirectly by endotoxin via polymorphonuclear neutrophils (PMNs), as shown by Meyrick and Brigham; in vivo, a single infusion of *Escherichia coli* endotoxin into sheep causes margination of PMNs and B and T lymphocytes, with pulmonary hypertension at 15 minutes, migration of leukocytes into the interstitium by 30 minutes, and interstitial edema and focal EC damage by 60 minutes. In vitro, endotoxin causes direct dose-dependent damage to bovine pulmonary endothelial monolayers, with retraction, pyknosis, and sloughing, increased prostacyclin production, lactic dehydrogenase release, and heightened permeability to small solutes; electron microscopy shows widened intercellular junctions and cellular contraction at 30 and 60 minutes and cell death beyond 2 hours. More recently, cultured human pulmonary artery ECs were also found to be injured by low concentrations of endotoxin. It is noteworthy that pulmonary ECs from large arteries are more sensitive to endotoxin than are microvascular cells, indicating endothelial phenotypic heterogeneity within the lung. Therefore, endotoxin can injure pulmonary endothelium directly, and this injury is enhanced by complement and granulocyte activation.

Other mediators injurious to ECs and found in increased amounts in bronchoalveolar lavage fluid (BALF) from ARDS patients include TNF-α and angiotatin, a cleavage product of plasminogen, and markers of endothelial dysfunction such as ACE, which decreases in level early in ALI and correlates with the clinical severity of lung injury. Endothelial dysfunction is also manifest in its reduced ability to metabolize the potent vasoconstrictor endothelin-1 (ET-1), contributing to pulmonary hypertension complicating ARDS. In patients with ARDS, the arteriovenous ratio for ET-1 is increased, probably because of a combination of increased secretion and reduced clearance by the lung. In an autopsy study of ARDS, tissue immunostaining for ET-1 in vascular ECs, alveolar macrophages, smooth muscle, and airway epithelium was augmented compared with lungs of patients dying without ARDS; immunostaining for both endothelial nitric oxide synthase (NOS) and inducible NOS in the lung was concomitantly reduced.

In addition to their passive role as bystanders or victims, ECs participate actively in the defense against and mediation of lung damage by their activation in response to stimuli such as endotoxin, cytokines, thrombin, and others involved in ARDS. ECs also release and metabolize vasoactive and inflammatory molecules such as serotonin, bradykinin, prostaglandins, ET, NO, and cytokines. Endothelial activation is critical for initiation of the inflammatory response and occurs through the expression of adhesion and signaling molecules and inducible enzymes recognized by different classes of leukocytes, particularly PMNs. For example, when stimulated with lipopolysaccharide (LPS), IL-1, or TNF-α, ECs express E-selectin and IL-8, with adhesion and signaling of PMNs. Other substances expressed by pulmonary ECs in ARDS include epithelial–neutrophil-activating peptide-78 (ENA-78), one of the C-X-C chemokines, the enzyme COX-2, and P-selectin, all implicated in interactions with PMNs. In a recent immunohistochemical study of adhesion molecules in autopsy lungs of patients with ARDS, it was found that intercellular adhesion molecule (ICAM)-1 was up-regulated in all pulmonary vessels (compared with normal subjects), whereas E-selectin and vascular cell adhesion molecule (VCAM) were strongly expressed in larger vessels, with only weak mosaic-like expression in capillary ECs; platelet endothelial adhesion molecule (PECAM/CD31) strongly stained ECs of control and ARDS lungs. It is also of interest that pulmonary microvascular ECs cultured from ARDS patients retain the ability to express increased adhesion molecules such as ICAM-1 and VCAM and secrete more of the cytokines IL-6 and IL-8 compared with cells from control lungs.

In relation to macrophages, as detailed below, macrophage migration inhibitory factor (MIF) is enhanced in ECs in ARDS and causes a modest rise in the expression of aquaporin 1, one of a family of newly discovered water channel proteins, in ECs of lungs from ARDS patients and in cultured ECs, suggesting a role in transcellular fluid movement in this condition.

As detailed below, hyaline membranes and intravascular thrombi are histologic hallmarks of DAD in ARDS, and fibrin is an important component of these, suggesting a dysfunctional coagulation cascade at least locally in the lung: the procoagulant response is increased, related to tissue factor associated with factor VII/VIIa, with concurrent depression of fibrinolytic activity secondary to tissue plasminogen activator and urokinase plasminogen activator (uPA). ECs, as well as epithelial cells and leukocytes, play an important role in these processes: the deposited intra- or extravascular fibrin and its proteolytic fragments and fibrinolytic proteases can independently amplify the inflammatory response, elevate vascular permeability, and activate fibroproliferative processes through complex interactions with cytokines and the kinin and complement systems. Supporting the important role of the coagulation cascade in ARDS, anticoagulant therapy with activated protein C has shown promise in reducing mortality in sepsis. Ware and colleagues very recently reported that in patients with septic and nonseptic ALI/ARDS, levels of protein C in plasma were significantly lower than in normal subjects and similarly critically ill patients with cardiogenic pulmonary edema and that their levels correlated directly with survival and ventilator-free days. The level of protein C was also lower in edema fluid than in simultaneously measured plasma samples, and the lower level was associated with greater respiratory impairment. Moreover, the authors found higher levels of thrombomodulin in the edema fluid of
patients with ALI than in patients with heart failure and consistently higher levels in the edema fluid than in simultaneously measured plasma samples, suggesting local intrapulmonary production; it was demonstrated that alveolar type II cells in vitro, stimulated by various cytokines, released thrombomodulin into the media. Additionally, levels of plasminogen activator inhibitor-1 were found to be higher in plasma and edema fluid from patients with ALI than in patients with heart failure and predicted a poor outcome. These data suggest that in ALI/ARDS the alveolus provides a procoagulant antifibrinolytic environment. The topic of activation of the coagulation system in ALI/ARDS is further covered in recent reviews.

Clinically and pathogenetically important soluble products of EC activation have been measured in plasma from patients with ARDS: Moss and colleagues found that levels of von Willebrand factor antigen, soluble ICAM-1, and soluble E-selectin were higher in patients at risk for or with ARDS who had sepsis rather than trauma as the predisposing factor, consistent with the notion of differential EC activity. A recent review further details the involvement of ECs in sepsis.

Polymorphonuclear Neutrophils An impressive body of literature generated over the past two decades implicates polymorphonuclear neutrophils (PMNs) as pivotal players in the pathogenesis of ALI. Several groups have documented, by histology, increased accumulation of PMNs within capillaries (rather than venules, as in the systemic vascular bed) and in interstitial and alveolar edema fluid of the injured lung compared with either normal volunteers or patients with respiratory failure not due to ALI (approximately 90% of cells recovered) compared with 3 to 10% in normal subjects, and Fowler and

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**FIGURE 19-6** Light photomicrographs of lung biopsy done 12 days after the onset of respiratory failure resulting from sepsis in a 64-year-old female treated with azathioprine for Crohn's disease. A, Low-power view, showing diffuse alveolar damage, with alveoli uniformly filled with exudate, including hyaline membranes. H&E stain; ×50 original magnification. B, Low-power view of another area, showing heterogeneous involvement on either side of the interlobular septum. The alveoli on the left are better aerated, contrasting with the poorly aerated airspaces with early fibroproliferation on the right. H&E stain; ×50 original magnification. C, Medium-power view, showing alveoli (Alv) filled with proteinaceous exudate, hyaline membranes (HM), hemorrhage, and neutrophils (arrow). H&E stain; ×250 original magnification. D, High-power view, showing alveoli with hyaline membrane (HM), with erythrocytes, and lined by hyperplastic type II pneumocytes, one with a mitotic figure (arrow). H&E stain; ×1,000 original magnification.
and CD11/CD18 mediated activation generates transient sequestration whose increasing the formation of cytoskeleton at the cell’s periphery, the assembly of soluble G-actin to F-actin filaments, thereby through interactions between integrins on the surfaces of PMNs and ICAM-1 on the surfaces of ECs and by the integrins, the latter particularly after activation. Adhesion also plays a role in activation and initiates a cascade of events critical in PMN function. Third, PMNs migrate out of the microvessels into the parenchyma, principally via interendothelial junctions on the thick side of the alveolar–capillary barrier. Migration is either mediated by CD11/CD18 (eg, upon endotoxin stimulation) or is independent of it (eg, upon Streptococcus pneumoniae or C5a stimulation), being mediated via undiscovered mechanisms.123

The fourth event, PMN activation, intimately related to adhesion, is mediated principally by the integrins and results in migration, phagocytosis and the respiratory burst, degranulation, and production of oxidants and cytokines. Activation is associated with increased PMN cross-sectional area regardless of location (circulating, marginated, or adherent).130 The mechanisms of activation involve bidirectional signals between the surface and the inside of the PMN, from which signal transduction occurs through kinases such as the Src kinases, mitogen-activated protein (MAP) kinases, MEK (MAP/extracellular signal-regulated kinase [ERK] kinase), and phosphoinositide-3-OH kinase (PI 3-K). It is of interest that different stimuli of PMN activation (eg, endotoxin, PAF, and TNF-α) each trigger different kinases, contributing to the heterogeneity of cellular effects. The importance of activation is confirmed by a report that the degree of PMN activation in patients with ALI correlates with the degree of lung injury and levels of TNF-α, IL-6, and IL-8.131

Once activated, PMNs injure the lung through diverse mechanisms: (1) generation of reactive oxygen species (hydrogen peroxide, hydroxyl radicals, and superoxide anions), via either NADPH oxidase or, as suggested more recently, the NOS pathway; and (2) secretion of proteolytic enzymes such as PMN elastase, cathepsin G, and the matrix metalloproteinases (MMPs) gelatinase A and B (MMP-2 and -9, respectively). Gelatinase B, released in a latent proform from PMNs, is activated principally by PMN elastase and plays a role in the migration of these cells across the basement membrane by degrading collagen IV.132 Both gelatinase B and gelatinase A (a product of epithelial, endothelial, and fibroblastic cells) have been found in the epithelial lining fluid of patients with ARDS, correlating with indices of lung injury.133

The PMN-mediated damage must be regulated if the resolution of the edema is to proceed. One mechanism is through rapid apoptosis (programmed cell death), mediated by pathways involving PI 3-K and ERK, as well as p38 MAP kinase. PMNs undergoing apoptosis lose surface adhesion molecules and the ability to secrete their granular contents and are promptly ingested by macrophages, minimizing their damaging effects. In patients with ARDS, inhibition of apoptosis of PMNs is mediated by the growth factors granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF) and the mediators endotoxin, IL-2, IL-6, interferon (IFN)-γ, and leukotriene B4 (LTB4).134 Delays in the onset of apoptosis could explain the development or persistence of ARDS: a randomized controlled trial showed that patients with pneumonia receiving G-CSF had higher levels of blood PMNs, faster radiographic improvement, and a lower incidence of ARDS.135 Recently, Matute-Bello and colleagues134 found that the antiapoptotic effect of ARDS BALF on normal PMNs was highest in early ARDS and decreased later and that the concentrations of G-CSF and GM-CSF in BALF from patients with ARDS paralleled the antiapoptotic effect of ARDS BALF, supporting the concept that the life span of PMNs in airspaces is modulated during acute inflammation. Also, the presence of GM-CSF in airspaces was associated with improved survival in ARDS, although there was no association between alterations in the antiapoptotic properties of BALF and the clinical outcome of patients with ARDS, suggesting the involvement of more complex processes.136

Notwithstanding the aforementioned evidence, the role of PMNs in ALI/ARDS remains somewhat confusing: for example, ARDS occurs in patients with profound neutropenia137 (Figure 19-7), and some experimental models of ARDS are independent of PMNs.123 Martin and colleagues138 demonstrated that injection of LTB4, a potent PMN chemoattractant, into the lungs of normal volunteers caused significant recruitment of PMNs into the airspaces without increased permeability of the epithelial barrier to protein. Wiener-Kronish and colleagues139 elegantly demonstrated in sheep that although intravenous E. coli endotoxin significantly increased lung vascular permeability, it failed to alter epithelial permeability when administered either intra-venously or intraalveolarly, despite a robust neutrophilic...
response in airspaces. Therefore, even with an apparently similar initial response to a particular insult, the ultimate development of ALI/ARDS must depend on other, as yet unidentified, factors, and it may be that PMNs are essential but not sufficient for its development. Indeed, PMNs may be beneficial in ARDS, providing an adaptive response in host defense and perhaps explaining the lack of success of a number of antiinflammatory therapeutic strategies.

**Macrophages** Although numerically less important than PMNs, macrophages, normally found in the interstitium and alveoli and constituting the majority of cells in BALF, have been implicated in ARDS, and indeed may be responsible for the pulmonary damage in ARDS in neutropenic patients. First, alveolar macrophages constitute the earliest line of defense against direct or indirect injury: in response to endotoxin, they rapidly produce TNF-α and IL-1β, mediated by Toll-like receptors, activation of transcription factors such as nuclear factor kappa B (NF-κB), and downstream events; the cytokines then activate other cells, including ECs, that initiate the recruitment of PMNs. As the acute phase proceeds, the alveolar mononuclear phagocyte population expands, primarily by recruitment of peripheral blood monocytes into the lung rather than by local proliferation; these recruited cells are recognized by the high-level immunophenotypic expression of CD14, CD11b, and 27E10 (identifying inflammatory acute-phase monocytes) and the low-level expression of CD71, HLA-DR, and 25F9 (a marker of mature tissue macrophages). Rosseau and colleagues followed 49 patients with ARDS by performing sequential BALs, and distinguished two groups, one in which monocyte influx fell and recruited cells matured and a second in which there was sustained monocyte recruitment. The latter phenotype correlated with persistent up-regulation of monocyte chemoattractant protein-1, one of the C-C chemokines responsible for recruitment and subsequent activation of monocytes, and with severity of respiratory failure. Macrophages also appear to be

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**FIGURE 19-7** Light photomicrographs of diffuse alveolar damage in lung from a markedly neutropenic 61-year-old female who died from ARDS following chemotherapy for acute myeloid leukemia. A, Low-power view, showing alveoli filled with dense exudate and a thin interlobular septum (arrows) without edema. H&E stain; ×50 original magnification. B, Medium-power view of alveoli with hyaline membrane (HM), and dense edema fluid admixed with erythrocytes (arrows) but entirely devoid of neutrophils. H&E stain; ×250 original magnification. C, Medium-power view, showing hyaline membrane (HM) loosely lining an otherwise denuded alveolus (arrows), and an absence of neutrophils. H&E stain; ×250 original magnification. D, High-power view, showing dense fibrinous edema fluid (left) and proliferating type II pneumocytes lining the alveolus (arrow). There are no PMNs, only erythrocytes at the bottom. H&E stain; ×1,000 original magnification.
involved in proximal activation of the numerous cytokines that are produced simultaneously in ARDS and are associated with adverse outcome, such as IL-1β, TNF-α, IL-6, and IL-8: they do this through activation of nuclear transcriptional regulatory proteins, particularly NF-κB, which binds to enhancer/promoter sequences of the proinflammatory cytokines and increases their expression. DNA binding and transactivation by NF-κB are strongly induced by hydrogen peroxide, superoxide, endotoxin, cytokines such as TNF-α and IL-1β, and ischemia–reperfusion injury.

It has been suggested that MIF, a recently rediscovered cytokine expressed by anterior pituitary cells and monocyte–macrophage cells, counterbalances the antiinflammatory properties of glucocorticoids. MIF has attracted attention as a mediator in ARDS, with enhanced expression in alveolar capillary ECs, infiltrating macrophages in lung tissue from ARDS patients and stimulating the release of proinflammatory cytokines such as TNF-α and IL-8; anti-MIF antibody attenuates this response. In addition, MIF induced significant MIF and TNF-α synthesis in cultured ECs, and treatment with anti-MIF or glucocorticoids attenuated pulmonary pathology and the synthesis of MIF or TNF-α in mice with LPS-induced acute lung injury, data all consistent with the notion that MIF induces TNF-α production via an amplifying proinflammatory loop. As intimated above, in addition to proinflammatory effects, macrophages have a potential role in the resolution of ALI: relative and absolute numbers of macrophages in BALF have been correlated with resolution of lung injury and improved survival.

Second, macrophages have an important role in progression from the acute to the fibroproliferative phase of ARDS. They secrete a variety of mediators and growth factors (FGF-2, TGF-β, platelet-derived growth factor, TNF-α, IL-1, IGF-1, and fibronectin) that lead to mesenchymal cell proliferation and migration and to deposition of extracellular matrix, stimulated by cytokines such as GM-CSF; IL-1β, IFN-γ, TNF-α, and TGF-β1, thereby perpetuating a vicious circle, by paracrine or autocrine action, leading to deposition of connective tissue in several fibrotic lung disorders, including ARDS. In a recent study, it was found that there was increased immunohistochemical staining for insulin-like growth factor-I (IGF-I) and its receptor in alveolar and interstitial macrophages and mesenchymal cells in fibroproliferative ARDS compared with controls that correlated with enhanced immunoreactivity for collagens I and III and proliferating cell nuclear antigen.

Third, in addition to their proinflammatory and profibrotic roles, monocytes and macrophages from patients with SIRS and sepsis can be induced to become tolerant to bacterial endotoxin (LPS), consistent with an immune dysregulation rendering patients with SIRS and MODS more susceptible to infections: this “LPS-tolerant” phenotype is characterized by inhibition of LPS-stimulated TNF production, altered IL-1 and IL-6 release, COX-2 activation, inhibition of MAP kinase activation, and impaired NF-κB translocation. Certain mediators, for example, interleukins-4, -10, -11, and -13, TGF-β, and colony-stimulating factors, profoundly alter monocyte function, including antigen-presenting activity, and inhibit T- and B-lymphocyte activity, resulting in immune suppression manifested clinically as anergy and increased susceptibility to infection. Therefore, as elegantly summarized by Bone, a battle rages between pro- and antiinflammatory mediators: if they achieve a balance to overcome the injurious insult, homeostasis is restored; if not, mediators enter the systemic circulation, producing either the proinflammatory SIRS or a “compensatory anti-inflammatory reaction syndrome” (CARS).


Epithelial Cells Epithelial cells, like ECs, are important targets in ARDS, and damage to them is critical in the development of alveolar edema. Even in early ARDS, type II pneumocytes proliferate; upon resolution, they are removed through extensive apoptosis, as indicated by specific labeling of nuclear DNA fragments. The time frame of the apoptotic response varies with etiology and degree of injury. Apoptosis of type II pneumocytes in DAD is associated with increased expression of p53, WAF1 (p27), and BAX, the latter two induced by p53; the antiapoptotic protein BCL2 is found only in interstitial cells, suggesting that it may play a role in the fibroproliferative stage. Adamson and colleagues found an increased proliferation index in type II pneumocytes and interstitial cells in DAD that correlated with patient survival, with increased expression of c-Myc and cyclin D1, both potentially contributing to dysregulated cellular proliferation and apoptosis in DAD. As summarized above, epithelial cells also play a crucial role in the clearance of pulmonary edema. Further details of the role of epithelial cells in ARDS, including in relation to surfactant and cytokines, are given elsewhere in this book (see Chapter 38, “Epithelial Function in Lung Injury”).

Role of Selected Cytokines and Chemokines in ARDS Cytokines are soluble extracellular peptides produced by inflammatory and other cells that act at very low concentrations (10^{-15} M) by binding to surface receptors, in either an autocrine or a paracrine manner. Chemokines, related to cytokines, activate leukocytes and cause them to alter their shape, follow a chemotactic stimulus, and adhere to ECs. The relationship between levels of cytokines in BALF and the pathophysiology and outcome of ALI is complex, being affected by the animal model studied, the techniques used to measure the cytokines, and the specific clinical condition associated with ALI. Although still controversial, the consensus is that the predominant cytokines and chemokines implicated in ALI are IL-1β, IL-8, and TNF-α and that these are produced locally in the lung.

Suter and colleagues studied BALF and plasma levels of cytokines over time in patients with ALI: they found elevated levels of TNF-α in BALF, rising significantly from those at risk, reaching very high levels during early ALI (12 to 36 h after onset), and falling significantly by day 3, whereas plasma levels rose modestly, suggesting intrapulmonary secretion. Surprisingly, they also noted little biologic activity of these levels of TNF-α, which they attributed to high levels of the TNF-α inhibitors, sTNF-R1 and -R2, found in the same BALF samples. They also found increased production of IL-1β. BALF levels of IFN-α and elastase, both thought to
be released by PMNs, increased with the severity of the lung injury. It is of interest that none of the plasma levels of these cytokines correlated with disease activity.

Several groups have described a relationship between the levels of pulmonary cytokines and outcome. Meduri and colleagues measured significantly and persistently higher levels of TNF-α, IL-1β, IL-6, and IL-8 in patients with ARDS who did not survive than in those who did. One problem in chronicling the role of various cytokines in ALI/ARDS is the difficulty in differentiating between concentration and biologic activity. To address this, several investigators focused on evaluating the overall inflammatory milieu of the lung in ALI by determining not only the levels of the cytokines but also the levels of their specific and nonspecific antagonists. The latter include α2-macroglobulin and IL-10, whereas specific antagonists include IL-1 receptor antagonist (IL-1ra), soluble IL-1 receptor II (sIL-1RII), and soluble TNF receptors I and II (sTNF-RI, sTNF-RII). Park and colleagues showed that although the bioactivity of TNF-α and IL-1β was elevated in patients with ARDS compared with normals, the bioactivity of IL-6, an antiinflammatory cytokine, was also increased, so that an overall antiinflammatory milieu predominated in the lungs of these patients. Furthermore, the level of antiinflammatory activity appeared to confer a degree of protection, in that both lung compliance and the degree of injury improved with an increased antiinflammatory environment. Similarly, Donnelly and colleagues found increased concentrations of IL-10 and IL-1ra in the BALF of patients with ARDS and noted an association between low levels of these antiinflammatory cytokines and mortality. Taken together, these data suggest that the injured lung is capable of limiting a potentially overwhelming proinflammatory response and that the net state of inflammation must be considered if we are to understand the complexity of the response.

The role of IL-8 is similarly complicated. Although IL-8 is a known chemoattractant of PMNs to the lung in ALI, data relating to its role as a marker of disease and of its severity are controversial. One group of investigators reported significantly increased BALF levels of IL-8 in patients at risk and progressing to ARDS compared with those patients failing to progress. Kurdowska and colleagues were unable to find any such correlation, and although they documented a relationship between IL-8 and the number of PMNs in the BALF of patients beyond day 1 in ALI, IL-8 levels failed to distinguish between survivors and nonsurvivors. However, levels of IL-8 complexed with anti-IL-8, the latter attributed to intrapulmonary production by B cells, were significantly increased in those patients at the onset of ARDS compared with those at risk and were initially higher on day 1 of the established syndrome in survivors than in nonsurvivors, falling significantly in survivors. Subsequently, the same group of investigators reported that in patients at risk, those with lower BALF levels of free IL-8 failed to go on to the full-blown syndrome, whereas those patients with elevated levels, only those with elevated levels of IL-8-anti-IL-8 complexes in the BALF went on to develop ARDS, supporting the counterintuitive notion that these antibodies, when complexed, enhance disease activity.

Poly (ADP-ribose-1) polymerase (PARP-1), a nuclear DNA-binding enzyme participating in DNA repair, has been implicated in lung injury following the overwhelming oxidative stress that occurs with endotoxin in ARDS. Activation of PARP-1 occurs by breaks in single-stranded DNA, results in depletion of NAD+ levels, and ultimately leads to cell death. PAPR-1 has also been implicated in the generation of the inflammatory cascade through stimulation of the NFκB pathway. Recently, in a model of LPS-induced lung injury, PMN infiltration, the elaboration of TNF-α, IL-1β, and IL-6 and of the chemokines MIP-1 and MIP-2, the generation of NO, protein leakage, and lipid peroxidation were all significantly diminished by either pharmacologic inhibition of PARP-1 or by its genetic elimination (in PARP-1-deficient mice).

**PATHOLOGY AND IMAGING**

The pathologic abnormalities of ARDS arise from the damage inflicted on the lungs and the subsequent cascade of pathogenetic events, differing substantially from those observed in hydrostatic edema (Table 19-4). The alterations of ARDS have been summarized in several studies and have been divided into those (1) general to ARDS and several forms of permeability edema and (2) reflecting a specific etiology. The general pathologic abnormalities, specifically at the light microscopic level, are encompassed by the term “diffuse alveolar damage” and separated into an acute exudative phase lasting approximately 1 week, a fibroproliferative or organizing phase lasting another 2 weeks, and, beyond 3 to 4 weeks, a fibrotic phase.

In the acute exudative phase, macroscopically the lungs are heavy, at least twice normal and often up to 2,000 g combined weight, dark red and solid, with variably frequent secondary findings such as pneumonia and thromboemboli (Figure 19-8). The cut surface is hemorrhagic and indurated, and close inspection reveals spaces about 1 mm in diameter, corresponding to widened alveolar ducts, surrounded by dense parenchyma.

Light microscopy (see Figures 19-6 and 19-7) initially shows capillary congestion, hemorrhage, and deeply eosinophilic interstitial and alveolar edema, followed by the appearance of characteristic homogeneous, dense, eosinophilic “hyaline membranes” composed of cellular debris, including necrotic epithelial cells (predominantly type I pneumocytes), admixed with fibrin, other plasma proteins, and variable numbers of PMNs. Hyaline membranes typically line alveolar ducts, as well as alveoli and respiratory bronchioles. Interstitial edema is less prominent than in hydrostatic edema (see Figure 19-7A), overshadowed by the alveolar phase secondary to the severe damage to type I pneumocytes, which occupy most of the alveolar surface area.

Several studies, most published between 1965 and 1985, have detailed the ultrastructure of the exudative phase of ARDS. Capillary lumina contain predominantly neutrophils, lower numbers of erythrocytes, and few platelets. The endothelium shows swelling, blebs, widened intercellular junctions with formation of folds or flaps, increased numbers of pinocytotic vesicles, and, rarely,
disruption and necrosis with exposure of the underlying basal lamina and intravascular fibrin accumulation. Neutrophils, erythrocytes, and platelets frequently emigrate with edema fluid between ECs, widening the interalveolar interstitium, primarily on the thick side of the alveolar–capillary septum, although fibrin deposits may be seen beneath ECs even in the thin part of the septum.122 The ultrastructural alterations in ECs are subtle compared with those in epithelial cells, which exhibit prominent sloughing of necrotic type I pneumocytes and become admixed with fibrin to form the hyaline membranes. Although type II pneumocytes may also be damaged, they are tougher than type I pneumocytes and indeed replace them in the proliferative phase of ARDS. Ultrastructural morphometric studies have revealed increased interstitial and epithelial cellular volumes, the latter related to transformation of the alveolar lining from type I to type II pneumocytes, and a reduction in capillary volume.

In the absence of resolution, a fibroproliferative phase ensues. Macroscopically, the lung becomes firmer and less hemorrhagic, with reorganization of the alveoli into large spaces separated by fibrous tissue (Figure 19-9). In the advanced fibrotic phase, a “honeycomb” pattern may be seen, with reorganized airspaces, 3 to 12 mm in diameter, being visible on chest radiographs and high-resolution CT scans (Figure 19-10), and with a cobblestone pattern on the pleura.

By light microscopy, the fibroproliferative phase is characterized by large numbers of cuboidal type II pneumocytes with abundant cytoplasm, large nuclei with mitoses and prominent nucleoli proliferating along the previously denuded alveolar lining, and replacing lost type I pneumocytes and hyaline membranes (Figure 19-11). If disruption of the lung architecture is significant, distal small airway epithelial cells proliferate and enter adjacent alveoli, and type II pneumocytes may undergo squamous metaplasia.167 In concert with epithelial regeneration, hyaline membranes organize, with proliferation of granulation tissue composed of myofibroblasts and abundant acid mucopolysaccharides: these may extend into alveoli and form “fibroblastic foci” (also termed Masson bodies) in alveolar ducts to produce so-called alveolar duct fibrosis165 or less commonly into respiratory bronchioles and bronchioles, to assume the appearance of bronchiolitis obliterans. If repair extends

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**Table 19-4** Contrasting Features of Hydrostatic Pulmonary Edema and Acute Respiratory Distress Syndrome (ARDS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hydrostatic edema</th>
<th>Permeability edema (ARDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology and pathogenesis</td>
<td>Elevated $P_{mv}$, normal endothelium and epithelium</td>
<td>Inflammatory cells and mediators, damage to endothelium and epithelium, elevated permeability</td>
</tr>
<tr>
<td>Protein content of edema fluid</td>
<td>Low versus plasma, due to sieving</td>
<td>High with fibrin</td>
</tr>
<tr>
<td>Sequence of fluid accumulation</td>
<td>Orderly: congestion, then IS edema, alveolar edema</td>
<td>Prominent early alveolar flooding, less IS edema</td>
</tr>
<tr>
<td>Imaging (especially chest radiographs)</td>
<td>Interlobular septal thickening with Kerley A and B lines; edema in perihilar distribution; associated cardiomegaly, vascular redistribution or distention, pleural effusion</td>
<td>Diffuse homogeneous bilateral dense infiltrates; often peripheral</td>
</tr>
<tr>
<td>Macroscopy</td>
<td>Spongy lung, frothy fluid on cut surface; wide interlobular septa</td>
<td>Lungs consolidated, hemorrhagic</td>
</tr>
<tr>
<td>Light microscopy</td>
<td>More prominent congestion, IS edema, less alveolar edema</td>
<td>Alveolar edema, hyaline membranes, inflammatory cells, microemboli</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Generally normal endothelium and epithelium</td>
<td>Endothelium and epithelium with blebs, damage; inflammatory cells</td>
</tr>
<tr>
<td>Chronic effects</td>
<td>“Brown induration,” mild fibrosis</td>
<td>May progress to fibroblastic and type II pneumocyte proliferation, severe fibrosis; increased procollagen peptides in edema fluid</td>
</tr>
<tr>
<td>Long-term prognosis</td>
<td>Resolution if cause treated</td>
<td>Depends on associated organ failure and extent of lung damage, fibrosis</td>
</tr>
</tbody>
</table>

Modified from Lesur O et al.263

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**FIGURE 19-8** Lung slice from a patient who died with ARDS 7 days after the onset of respiratory failure. It is solid, with areas of edema and hemorrhage.
beyond ≈3 weeks, fibroblastic foci mature into dense pauci-cellular fibrous tissue, and destroyed and collapsed alveoli and alveolar ducts are replaced by large simplified spaces lined with hyperplastic type II pneumocytes and separated by thick walls of connective tissue, with collagen, extracellular matrix, and inflammatory cells. In advanced stages, the lung may assume the appearance of usual interstitial pneumonia, with variable parenchymal honeycombing. Immunohistochemical studies have revealed albumin, fibrinogen, immunoglobulins, complement and surfactant apoprotein in hyaline membranes in the exudative phase, and fibronectin in the proliferative phases, with type II pneumocytes expressing TNF-α and surfactant apoprotein.

In addition to the relatively nonspecific, albeit characteristic, pathologic alterations of DAD in ARDS, several forms of permeability edema have specific patterns recognizable with the use of light microscopy. Notable in this respect are the infectious etiologies: bacterial pneumonias associated with ARDS are distinguished on light microscopy (in addition to microbiologic findings) by large numbers of PMNs filling alveoli, usually seen in relatively small numbers in ARDS; in Pneumocystis carinii pneumonia, in BALF or lung biopsies, there is a distinctive intraalveolar foamy exudate containing the organisms, demonstrated by histochemical silver stain; in viral pneumonias, there are inclusions, for example, of cytomegalovirus, herpesvirus, or adenovirus, visible with H&E or immunohistochemical stains. It is of considerable interest that severe acute respiratory syndrome (SARS) caused by SARS-associated coronavirus produces a histologic picture of DAD in both its acute and proliferative phases; no definite viral inclusions have been seen, but multinucleated cells, of either epithelial or macrophage origin, have been described, although their significance is unclear. This syndrome is reviewed in detail elsewhere. In aspiration pneumonia, aspirated material is frequently identified associated with a foreign body giant cell reaction. With fat embolism, lipid globules obstruct capillaries, giving them an empty appearance, devoid of erythrocytes, and there is an associated variable macrophage-rich inflammatory response. Some drugs may also produce relatively specific reactions, for example, amiodarone, which may cause foamy macrophages to fill alveoli.

When DAD is idiopathic, it is considered to be synonymous with acute interstitial pneumonia (AIP), a rapidly progressive form of pulmonary fibrosis whose histologic
features are identical to those of the fibroproliferative phase of DAD and that probably corresponds to the Hamman–Rich syndrome. One noteworthy difference in AIP is that the duration of symptoms prior to the onset of ARDS may be longer than the accepted 7 days; also, the likelihood of progression to end-stage fibrosis is greater and the prognosis is poorer than in other forms of ARDS.

The pulmonary vascular lesions in ARDS, particularly evident on postmortem angiograms and under light microscopy, have been detailed in several elegant studies. In the acute phase, thrombi or thromboemboli, generally macrothrombi, are observed in up to 95% of patients. Microthrombi are also frequent, either the hyaline platelet–fibrin type in capillaries and arterioles or the laminated fibrin type in larger arteries. The overall mean external diameter of partially muscular and muscular arteries is reduced in ARDS, with dilatation of intraacinar muscular arteries. In the early proliferative phase of ARDS, fibrocellular intimal proliferation mainly affects small and medium muscular arteries (an obliterative endarteritis) but also veins and lymphatics, with a concentric or eccentric arrangement of fibrin, myointimal cells, hyperplastic endothelial cells, mucopolysaccharides, and collagen, explaining the reduced vascular luminal area and background filling observed on postmortem arteriograms (see Figure 19-11C,D). In the late stages of ARDS, arteriograms show decreased peripheral arterial filling, extension of smooth muscle into normally nonmuscular pulmonary arteries, and medial thickening of precapacinar arteries, the last-mentioned becoming tortuous and stretched around dilated airspaces; moreover, the pulmonary capillary bed creates a background ground-glass haze, associated with an increased vascular density that probably mirrors the combined effects of crowded and abnormally dilated and tortuous vessels rather than true pulmonary arterial angiogenesis.

FIGURE 19-10 Sequential chest CT scans of a 39-year-old female with ARDS due to acute pneumococcal pneumonia. A, First scan, 6 days after onset. Note the diffuse ground-glass opacification, consolidation with early abscess in the left lower lobe, and subcutaneous emphysema in the left lateral chest soft tissue. B, Three weeks after onset: note increased heterogeneity in opacities, abscesses in the left posterior lung and cystic spaces in the right posterior lung. C, Scan taken just under 4 months after onset, showing residual irregular fibrosis in the right anterior lung field. The patient was then at home, asymptomatic, and had normal pulmonary function test findings.
The pathogenetic mechanisms responsible for the thrombotic vascular lesions include thromboembolism resulting from systemic venous thrombi, in situ thrombosis related to EC injury, and platelet sequestration with localized intrapulmonary or disseminated intravascular coagulation. The chronic vascular remodeling parallels the parenchymal fibrotic process, with similar mechanisms (detailed above), and superimposed hypoxia associated with ARDS and hyperoxia resulting from the therapy. Additionally, the pulmonary hypertension, resulting from vasoconstriction and the aforementioned thrombotic and other vascular lesions, completes the vicious circle of vascular remodeling.

On imaging studies, the evolution of ARDS, detailed elsewhere, has been shown to be more disorderly than that of hydrostatic edema. Although in the early stages the chest radiograph may be normal, it typically progresses rapidly from initial bilateral symmetric hazy opacities, with or without air bronchograms, or occasionally an interstitial pattern as in cardiogenic edema, to dense homogeneous opacities, obscuring pulmonary vessels, cardiac margins, and diaphragm and culminating in the characteristic “white-out” of the lungs (Figure 19-12), with a tendency to peripheral accentuation. Although frequently symmetric, the distribution may be inhomogeneous. In the chronic phase, the chest radiograph shows a more heterogeneous distribution of densities, with linear or reticular patterns (see Figure 19-12). In the latest stage of fibrosis, which develops in 10 to 15% of survivors, radiographs show low lung volumes with irregular round areas of hyperinflation due to reorganized architecture related not only to ARDS but also to complications such as barotrauma, superimposed infections, and vascular events. Complications of therapy as manifested on radiographs are reviewed elsewhere.

The reliability of the chest radiograph in distinguishing hydrostatic from permeability edema with the use of a variety of criteria has been controversial, and although several authors have reported success rates of 70 to 85%, Goodman concludes that the value of the chest radiograph in making this distinction is limited and that clinical...
assessment and ancillary diagnostic tests must be taken into account.

CT scans (see Figure 19-10), which are not used routinely, have nevertheless contributed to our understanding of ARDS by (1) emphasizing the heterogeneity of lung involvement; (2) documenting the effects of prone positioning on the distribution of opacification; (3) revealing complications of ARDS, particularly emphysema and abscesses; and (4) enabling follow-up of long-term survivors of ARDS. Desai and colleagues described a coarse reticular pattern of pulmonary fibrosis anteriorly in 23 of 27 patients, perhaps attributable to alveolar overdistention in the acute stages.

**VENTILATOR-INDUCED LUNG INJURY**

An important advance in the therapy of ARDS (see below) came with the understanding of ventilator-induced lung injury (VILI) and its pathophysiology. We should distinguish at the outset between VILI, a term describing injury induced by ventilation of normal experimental animal lungs, and ventilator-associated lung injury (VALI), an expression used in the clinical or experimental context of application of injurious ventilation to already injured lungs.

Thirty years ago, Webb and Tierney were among the first to demonstrate the damaging effect of positive pressure ventilation on the lungs: they reported that rats ventilated with peak inspiratory pressures of 30 and 45 cm H₂O developed perivascular and alveolar edema, respectively, and that the latter suffered from severe hypoxemia and decreased dynamic compliance and died within 1 hour; animals ventilated at 14 cm H₂O had normal lungs. They were also perhaps the first to report the salutary effect of PEEP, in that animals exposed to both 45 cm H₂O of peak pressure and 10 cm H₂O of PEEP failed to develop alveolar edema and hypoxemia.

Subsequently, Kolobow and colleagues mechanically ventilated normal sheep at tidal volumes of 50 to 70 mL/kg and peak inflating pressures of 50 cm H₂O and observed marked lung injury not seen in controls ventilated at volumes of 10 mL/kg and pressures of 15 to 20 cm H₂O; interestingly, the injury was attenuated by ventilation with higher levels of carbon dioxide. Tsuno and colleagues.
provocatively suggested that mechanical ventilation rather than the underlying disease process could be primarily responsible for the histopathologic changes deemed to be pathognomonic of ALI. Despite these results, the question of whether the parenchymal damage was due to the applied pressure or to the resulting alveolar stretch remained unanswered. In further studies, it was determined that the injury resulted from lung overdistension181 and that similar amounts of edema were induced whether lung volume was increased through application of positive or negative pressure.182 Dreyfuss and Saumon183 suggested that edema in VILI is more a function of end-inspiratory lung volume than either tidal volume or level of PEEP alone because experimentally it could be induced by combining modest increases in both tidal volume and PEEP that, applied independently, did not produce those increases.

Although an emerging consensus favors alveolar stretch in the pathogenesis of VILI, the mechanisms of injury remain unclear. One theory implicates the increased lung volume and its impact on PVR, whereas the second maintains that injurious forms of mechanical ventilation lead to the elaboration of inflammatory mediators indistinguishable from those found in other models of lung injury, such as LPS-induced ALI.

In support of the first theory, Broccard and colleagues184 demonstrated in an isolated perfused rabbit lung model that mean airway pressure rather than tidal volume determines lung injury, through an increase in PVR, particularly of the middle segment, known to accompany rises in lung volume above functional residual capacity. The authors underlined the importance of extraalveolar vessels in the pathogenesis of the increased lung water, given that these are subject to greater increases in transmural vascular pressure at high lung volume than are alveolar vessels. Additionally, they demonstrated that, for a given transpulmonary distending pressure, animals with higher pulmonary blood flow rates suffered more lung injury and that the mitigating effect of PEEP on lung water was due primarily to altered hemodynamics.185 Another effect of high lung volume and increased PVR is the increased capillary wall strain that causes, as discussed below, capillary stress failure with increased permeability.186

Despite these findings, the studies linking PEEP and lung injury are partly contradictory. Notwithstanding the aforementioned observation of worsening pulmonary injury in rats in whom PEEP of 15 cm H2O was applied to a tidal volume not injurious by itself,183 Muscedere and colleagues187 reported that PEEP applied at levels above the inflection point prevented the worsening lung injury seen in those animals exposed to lower levels of PEEP. In this regard, it should be noted that of the initial four studies determining whether or not a protective ventilatory strategy is beneficial,188–191 the only study giving positive results was one that targeted PEEP therapy to the lower inflection point.189

Two additional findings from the study by Muscedere and colleagues187 merit mention: (1) despite a lack of perfusion in this model, hyaline membranes formed, which is surprising in view of the accepted notion that activation of PMNs with release of proteolytic enzymes and oxygen radicals is necessary for their development, and (2) the location of the injury within the lung depended on the level of PEEP. Indeed, at zero PEEP (ZEEP), most of the injury lay in respiratory and membranous bronchioles, whereas at higher levels of PEEP (although still below the inflection point), the injury was mostly distal in alveolar ducts. This topographic distribution supports the hypothesis that repeated closure and opening of small airways and the failure to maintain the lung open beyond its inflection point are responsible for the lung injury.

With regard to the second theory concerning mechanisms of injury in VILI, several groups have shown a relationship between alveolar stretch and the elaboration of inflammatory cytokines. Tremblay and colleagues192,193 in rats lungs ventilated ex vivo with injurious patterns of mechanical ventilation, demonstrated (1) significantly elevated expression of TNF-α and IL-6, originating primarily from the epithelium of airways and alveoli; (2) increased lung lavage levels of protein, inflammatory and antiinflammatory cytokines, and mRNA levels of TNF-α and c-fos, the latter being a representative immediate-early response gene with a stretch-responsive promoter; (3) increased release of TNF-α and macrophage inflammatory protein-2, but not of IL-1β, IL-6, interferon-γ, or IL-10, in LPS-sensitized rats; and (4) the greatest injury, produced by a ventilatory strategy combining high transpulmonary distending pressures and ZEEP.

Pursuing these investigations in patients, Zhang and colleagues194 exposed PMNs of normal volunteers to the supernatant of BALF from patients with ALI after approximately 40 hours of mechanical ventilation with and without a protective ventilatory strategy and found in the latter significant increases in release of elastase, PMN oxidant activity, surface expression of CD18 and CD63, and shed L-selectin.

A recent and intriguing theory is that ventilatory strategies not only induce local pulmonary inflammation but also promote widespread systemic inflammation. Testing this theory in patients with ARDS, Ranieri and colleagues195 compared two ventilatory strategies. A control group was ventilated to maintain normocapnia with PEEP titrated to achieve a saturation of oxygen (SaO2) of ≈90% (3 to 15 cm H2O), and a second group was ventilated with the use of a lung-protective strategy. In the latter group, there were reductions in the levels of PMN, TNF-α, IL-1β, IL-6, and IL-8 in BALF and of the first three mediators in plasma, whereas the levels of these cytokines rose with time in the control group. The authors suggested that, because the majority of ALI patients who die do so secondary to MODS, the systemic inflammatory changes elicited by injurious ventilatory modes may be ultimately responsible for the development of MODS. A further mechanism whereby ventilation could contribute to SIRS is through translocation of bacteria from airspaces to the circulation, as shown experimentally, and analogous to what takes place in the gut.177

Hypercapnia, alluded to above, has been advanced as an additional important factor in the attenuation of injurious ventilatory strategies, over and above mechanical
Because right-to-left shunt is the fundamental oxygenation,
have also lent graphic support to the concept that position-
ventilatory management of these patients
injury. probably accounted for their differential effects on lung
similar extent, so that as yet unidentified mechanisms
probably accounted for their differential effects on lung injury.

**Clinical and Therapeutic Issues**

ALI and ARDS are characterized by severe hypoxemia, due
principally to a large right-to-left shunt, and by stiff, non-
compliant lungs, both resulting from alveolar edema. 
Although the AECC radiographic criteria require only the
presence of bilateral pulmonary infiltrates, Murray and
colleagues had previously proposed a Lung Injury Score to
stratify radiographic findings, in which the disturbance of
respiratory mechanics was offered as a reference against
which radiographs from various clinical trials of ALI could be compared.

**Oxygenation**

ALI and ARDS are characterized by inhomogeneity of parenchymal involvement, which is well visualized on CT scans (see Figure 19-10), so that only limited portions of the diseased lungs actively participate in ventilation.

This concept, in turn, led to (1) the suggestion that a maximum plateau pressure of 35 cm H2O be applied in the ventilatory management of these patients; (2) the positive trial on low-lung-volume ventilation; and (3) an understanding of the heterogeneous impact of PEEP. CT scans have also lent graphic support to the concept that positioning these patients in the prone position could improve oxygenation.

**PEEP**

Because right-to-left shunt is the fundamental pathophysiologic mechanism that impairs oxygenation, the major therapeutic challenge in this syndrome, the efficacy of high levels of exogenous oxygen, is severely limited, and the attendant toxicity may be considerable. To improve oxygenation, various mechanical ventilatory modes and maneuvers have been attempted. PEEP, by far the most commonly used method to diminish shunt, acts by increasing functional residual capacity through the recruitment of lung units for gas exchange and by decreasing perfusion to unventilated parts of the lung. Despite the consensus that PEEP should be applied to mitigate the effects of high levels of inspired oxygen, there is no agreement on what level of oxygen poses a toxic threat or on the level of PEEP to apply. Traditionally, PEEP has been set at a level yielding acceptable arterial and venous oxygen saturations. Recently, convincing experimental data have emerged, discussed more fully below, suggesting that allowing the lung to repeatedly fall below its lower inflection point is harmful, and in at least one clinical trial in which the amount of PEEP was targeted to just above the lower inflection point, improved survival was observed compared with a conventionally managed ventilator group. Detection of that inflection point, however, is labor intensive, its reproducibility and inter-observer variability are controversial, and whether to use the inflation or the deflation portion of the curve is debated.

Furthermore, despite this strong supporting evidence, there are as yet no definitive data on this “open-lung” approach. To date, three trials have addressed this issue: two, one in Canada and the other in France, are ongoing. Although not yet published, the results of the third, with 550 patients in the United States, reviewed recently (R. Brower, personal communication, April 2002), demonstrate that high levels of PEEP are no better than low levels.

It is noteworthy that PEEP may, in fact, increase shunt by the relative overexpansion of previously normal parts of the lung and failure to recruit diseased areas; also, PEEP does not reduce lung water and may even cause it to rise. Despite the apparent beneficial effects of low–lung-volume ventilation, it results in alveolar derecruitment and worsening hypoxemia in many patients, even when PEEP is held near or just above the lower inflection point.

To counter this trend and reverse the derecruitment during suctioning, for example, several investigators have proposed various recruitment maneuvers, including sustained inflation at 30 to 45 cm H2O for 20 seconds and periodic sighs.

Regardless of the apparently improved oxygenation achieved by these maneuvers, however, there are as yet no data on their potential for exacerbating lung injury.

**Inverse Ratio Ventilation**

Unfortunately, there are no randomized trials to support the efficacy of this strategy to enhance gas exchange. The only available data come from small studies in which inverse ratio ventilation (IRV) has been compared with conventional ventilation, and the results vary. Huang and colleagues reported that at constant mean airway pressure, both arterial and venous oxygenation deteriorated on IRV, whereas both oxygen delivery and consumption remained unaltered. In contrast, Abraham and Yoshihara reported that in nine patients with ALI before and after the institution of pressure-controlled IRV, oxygenation improved significantly on IRV, whereas peak airway pressure fell, albeit nonsignificantly, and hemodynamic variables remained unchanged.

**Liquid Ventilation**

Liquid ventilation with perfluorocarbon was introduced because of this compound's unique physical properties, which include low surface tension, high solubility of oxygen and carbon dioxide, and the capacity for lung recruitment (liquid PEEP). Although the results of animal studies and uncontrolled studies in humans suggested physiologic and clinical efficacy, a large randomized study in which partial liquid ventilation at two different doses was compared with conventional mechanical ventilation failed to demonstrate any clinical benefit.

**High-Frequency Oscillatory Ventilation**

The application of high-frequency oscillatory ventilation to adult patients with ALI stemmed from its successful use in the neonatal and pediatric populations and from data implicating...
mechanical ventilation in aggravating lung injury. As in the early studies with NO, preliminary results demonstrated improvements in oxygenation, but results from the one controlled multicenter trial failed to show benefit in duration of mechanical ventilation or survival.

Prone Position The effect of a change in body position on lung volumes has been appreciated since Moreno and Lyons documented an increased functional residual capacity in the prone compared with the supine position. It took another 25 years for the improvement in oxygenation accompanying these position changes to be widely appreciated, but numerous studies have now documented the efficacy of the prone position in improving gas exchange.

Although the literature suggests that 50 to 75% of patients with ALI respond to the change in position, the mechanisms are far from clear. In an experimental study, the transition from the supine to the prone position was accompanied by a fall in right-to-left shunt due to increased dorsal regional ventilation rather than to altered bloodflow. A recent review of the topic concluded that the improved oxygenation stems from a more homogeneous distribution of ventilation and perfusion. Despite the high number of responders, however, two randomized controlled trials failed to demonstrate a significant survival benefit.

Nitric Oxide NO would seem conceptually to be the perfect treatment for ALI because (1) it is delivered by inhalation, so its vasodilator effects on the pulmonary vasculature should be confined to those alveolar units participating in ventilation, and (2) its half-life is measured in seconds, eliminating any effects on the systemic circulation. Although the number of articles chronicling its benefits on gas exchange has increased greatly since the first report in 1993, four controlled trials failed to demonstrate a significant survival benefit compared with controls, despite an initial transient increase in oxygenation. In a post hoc analysis, however, Dellinger and colleagues reported a significant increase in the number of patients alive and off mechanical ventilation by day 28 in the group given 5 ppm NO.

Recently, Gerlach and colleagues confirmed the initial ephemeral improvement in gas exchange but also described a leftward shift in both the oxygenation and pulmonary vascular responses to NO: although all patients had a peak response to 10 ppm initially, the peak response in those receiving continuous treatment with 10 ppm NO fell to 1 ppm by day 4, and gas exchange actually deteriorated in some of these patients; the control group continued to demonstrate a peak response at 10 ppm. The authors suggested that the negative results of randomized trials in which a constant dose of NO was used might have been due, at least in part, to the failure to appreciate this phenomenon.

Surfactant Although surfactant dysfunction is not considered to be the primary abnormality, as in the infant respiratory distress syndrome, it still plays an important role in ARDS. As reviewed by Lewis and Brackenbury, despite several case reports and uncontrolled trials supporting its use, four large randomized controlled trials have yielded variable results. In the first, the synthetic surfactant Exosurf failed to modify ventilator-free days or mortality, but there may have been a design flaw in the study, whereby little surfactant reached distal alveoli. In a smaller trial, a modified natural surfactant, Survanta, was instilled directly into the airways and caused a significant reduction in mortality. Finally, in two larger trials, a recombinant surfactant protein C-based preparation was instilled directly into the airway but failed to change ventilator-free days or mortality, even with significantly improved oxygenation. Post hoc analyses revealed significantly lower mortality rates in those patients with ALI resulting from a direct insult, pneumonia, and aspiration.

Ventilation Given the results of the studies in animals linking large tidal volumes and lung injury, as detailed above, four small clinical studies were undertaken to determine whether a protective ventilatory strategy would yield a measurable clinical benefit in patients with ALI: of these, only one demonstrated a mortality benefit. However, in 2000, the Acute Respiratory Distress Syndrome Network (ARDS Net) published its results on the beneficial effects of a protective ventilatory strategy in 800 patients with ALI. This strategy, which consisted of a maximum plateau pressure of 30 cm H2O and a tidal volume of 6 mL/kg predicted body weight, was compared with a traditional ventilatory strategy of 12 mL/kg predicted body weight and a plateau pressure <50 cm H2O. The trial was terminated prematurely because of efficacy: the authors found that mortality in the protective strategy group fell by approximately 10% (39.8% vs 31%), for a relative decrease of approximately 25%. Furthermore, ventilator-free days at day 28 were significantly greater in the protective strategy group. Although this study has generated much controversy concerning the safety of low–tidal-volume ventilation, it appears that ventilation with large tidal volumes (>10 mL/kg) and high plateau pressures (>32 cm H2O) should be avoided and that permissive hypercapnia up to 90 mm Hg, and perhaps higher, is safe.

Fluid and Pulmonary Vascular Pressure Management Although, as detailed above, microvascular pressures (ie, $P_{mv}$) are thought to remain relatively normal in ALI/ARDS, edema formation is exquisitely sensitive to $P_{mv}$ because of the rise in $K_{f}$ and fall in $\sigma$. Knowing this, several investigators have examined the impact of manipulating $P_{mv}$ and/or $\Pi_{mv}$ on edema formation in various models of lung injury. Ali and colleagues reported that in dogs with oleic acid–induced edema, furosemide improved oxygenation and intrapulmonary shunt without changing $P_{aw}$, plasma oncotic pressure or, indeed, the amount of pulmonary edema; they concluded that furosemide acted by dilating the pulmonary vasculature.

A series of clinical studies that followed appeared to support the conclusion that a strategy of “fluid restriction to seek the lowest $P_{aw}$ consistent with adequate cardiac output” is beneficial in patients with ALI. A retrospective analysis of patients with sepsis identified initial protein levels and
their change over time as the most significant predictors of weight gain, prolonged mechanical ventilation, development of ALI and mortality. 230; Humphrey and colleagues reported a significant survival advantage in those patients with ALI in whom \( P_w \) was aggressively lowered by at least 25%.

In a prospective study of patients with ALI, a fluid strategy in which \( P_w \) was kept at \(<18 \text{ mm Hg} \) was compared with one aimed at maintaining extravascular lung water (EVLW) at \(<7 \text{ mL/kg} \).222; EVLW decreased significantly over time in the EVLW group but not in the \( P_w \) group, and by 24 hours and beyond, cumulative fluid balance was significantly lower in the former group; importantly, the study demonstrated that the EVLW group spent significantly fewer days on mechanical ventilation, with a trend toward a lower mortality. Pursuing this line of inquiry, Martin, in a randomized trial of patients with ALI and hypoproteinemia (\( \leq 5 \text{ g/dL} \)), compared one group receiving thrice-daily infusions of 25 g of albumin and continuous infusion of furosemide with a second group treated conventionally: the treatment group experienced increased diuresis and a decrease in weight, accompanied by significantly improved oxygenation within the first 24 hours, with a clear trend toward a reduced need for mechanical ventilation.

**Other Therapeutic Strategies** With the recognition of the importance of tissue injury and inflammation in ARDS, corticosteroids were studied early on but were found not to be of any benefit in the initial stages. 234 More recently, Meduri and colleagues295 prospectively examined the effects of methylprednisolone (2 mg/kg starting on day 9 for \( =32 \) days) on the fibroproliferative stages of ARDS: treated patients had significant improvements in gas exchange, lung injury score, multiple organ dysfunction scores, and rate of successful extubation and significantly decreased rates of intensive care unit and hospital mortality. Although impressive, the results of the study must be tempered by the very small sample size. This therapeutic approach is presently being addressed in a study sponsored by the National Institutes of Health.

The inflammation of ARDS also severely tips the prooxidant–antioxidant balance in favor of the former. Bernard and colleagues 36 reported that plasma and red blood cell levels of the antioxidant glutathione and its precursor cysteine were low in their subjects with ARDS. They compared the effects of therapy with two antioxidants, N-acetylcysteine and L-2-oxothiazolidine-4-carboxylate (Procysteine), with those of placebo: although they failed to yield any survival benefit, antioxidants nevertheless appeared to provide clinical benefit by significantly reducing the duration of ALI and, although the effect was not quite significant, by decreasing the number of new organ failures. Considering the relatively small number of patients in this trial and the positive results of a previous study, a larger trial may yield more impressive results.

In conclusion, there has been a striking and frustrating lack of efficacy of these many and varied interventions. Possible reasons for this are the diagnostic imprecision in their definition and the heterogeneous groups of patients serving as subjects. Another possible explanation is the lack of power in many of these trials: in this regard, the ARDS Net trial on low–lung-volume ventilation included over 800 patients. 83 Third, when these trials are being designed, end points must be framed with respect to “best practice”: specifically, although overall mortality in ALI still approximates 50% in the uncontrolled setting, it has proven to be considerably less in the context of the randomized trial, in which the control arm is highly structured, raising the question of the impact of highly structured conventional “best practice” therapy alone on mortality. Finally, it must be remembered that, in numerous studies, patients die not from ARDS but rather with ARDS, so that it may be naive to expect a treatment designed to improve oxygenation to give a major survival advantage to those patients dying from MODS and sepsis.

**MIXED AND OTHER FORMS OF PULMONARY EDEMA**

**Pathogenesis** Although it is convenient to distinguish hydrostatic and permeability edema, in practice they may overlap and interact. Generally, etiologies of edema can be determined, and most forms of permeability edema, at least in the early stages, do not involve substantial elevations in pulmonary vascular pressures. Several issues, however, deserve consideration, as follows.

Some models of lung injury and clinical forms of permeability pulmonary edema are associated with transient or sustained pulmonary hypertension. For example, in sepsis, a major causal association of ARDS, there is formation of microemboli and/or release of mediators that raise pulmonary vascular pressures.

The difficulty of correctly estimating \( P_{mv} \) in states of elevated pulmonary vascular permeability is substantial because the distribution of PVR may be altered. As discussed above, mediators and microemboli may preferentially constrict or block arterial, venous, or microvascular segments of the pulmonary circulation, reducing the reliability of measurements of \( P_w \) with the Swan-Ganz catheter.

Hydrostatic pressure is at least additive with permeability in producing edema, in both the experimental and the clinical setting. For example, in perfused canine lungs in situ, Huchon and colleagues 75 found that elevation of \( P_{la} \) to 18 mm Hg for 1 hour did not significantly raise lung water above the normal 2.4 g/kg, that oleic acid with low \( P_{la} \) (0 mm Hg) for 1 hour increased lung water to 6.4 g/kg, and that both oleic acid and high \( P_{la} \) elevated lung water to 10.1 g/kg, consistent with a significant synergistic interaction between increased permeability and hydrostatic pressure.

Over the last 10 to 12 years, the distinction between hydrostatic and permeability edema has become further blurred through the elegant studies of West and colleagues, reviewed recently, who championed the notion that microvascular pressures over \( =40 \text{ mm Hg} \) can raise permeability. The pulmonary blood–gas barrier, composed of endothelial and epithelial cells, basement membrane, and
interstitium, must be both extremely thin (0.2 to 0.3 μm on the thin side of the barrier in humans) for efficient gas exchange and very strong to withstand the enormous stresses in the capillary wall; the latter property has been attributed largely to type IV collagen in the basement membranes. As described by West and colleagues, when the capillary wall stresses and/or intraluminal pressure rise to very high levels, the phenomenon of “stress failure” occurs, characterized by damage demonstrable on ultrastructural examination. Stress failure occurs (1) under physiologic conditions such as strenuous exercise in elite human athletes; (2) in pathologic conditions such as neurogenic pulmonary edema (NPE), high-altitude pulmonary edema (HAPE), severe left heart failure, and mitral stenosis; and (3) in therapeutic maneuvers with overinflation of the lung, for example, in VILI. The stresses to which the capillary (and adjacent epithelium) are subjected may be either circumferential, related to the capillary transmural pressure, or longitudinal, associated with inflation. The characteristic alterations seen in capillary stress failure reported by West and Mathieu-Costello include the following: (1) there are disruptions of ECs, most probably transcellular, some at intercellular junctions, and attachment of platelets to the exposed basement membrane; (2) there are breaks in alveolar type 1 pneumocytes measuring ≈4 by 1 μm, generally not at intercellular junctions, suggesting that these have considerable mechanical strength; (3) the number of endothelial and epithelial disruptions per millimeter of cell boundary increases with intravascular pressure; (4) the breaks are rapidly reversible, with about 70% of both endothelial and epithelial breaks closing within minutes. Of note, the basement membranes remain generally intact, consistent with their superior strength. In keeping with Laplace’s law, stress failure of capillaries occurs at different pressures in different species, for example, 39 mm Hg in the rabbit, 67 mm Hg in the dog, and 96 mm Hg in the horse. The result of capillary stress failure is leakage of proteinaceous fluid and erythrocytes into the interstitium and alveoli, that is, increased permeability edema.

**High-Altitude Pulmonary Edema**

HAPE, also reviewed elsewhere, occurs in susceptible persons who ascend to altitudes >2,500 m, generally rapidly, although it may occur at lower altitudes. Symptoms characteristically develop 2 to 3 days following ascent, often after strenuous activity or exposure to cold, and include dyspnea, cough, weakness and limitation of physical activity, dizziness, and nausea. There are crackles, tachypnea and tachycardia on physical examination, infiltrates on chest radiographs, generally bilateral, either central or peripheral, and hypoxemia. Recovery typically occurs with descent to sea level, and the rare fatalities are usually related to the unavailability of oxygen or the inability to descend to lower altitudes. In 1991, a consensus committee at the Inter-national Hypoxia Symposium defined HAPE, in the setting of a recent gain in altitude, as the presence of at least two symptoms (dyspnea at rest, cough, weakness, decreased exercise performance, chest tightness or congestion) plus two signs (rales or wheezing, central cyanosis, tachycardia or tachypnea). The same committee proposed a functional grading of disability. The incidence of HAPE is about 5% but varies with altitude, gender, and age (more frequent in males and children); subclinical cases are more frequent. Physiologic parameters show elevated Ppa and PVR, normal Pwv, reduced cardiac output, mean systemic arterial pressure, and arterial oxygen saturation. Pathologic findings in 26 cases summarized by Hultgren include lung weights =2.5 times normal, bloody and foamy edema, macro- or microthrombi, hyaline membranes, and infiltration with PMNs consistent with permeability edema. Although incompletely understood, the putative mechanisms for HAPE involve hypoxic vasoconstriction with high altitude as the initiating stimulus, resulting in inhomogeneous obstruction of the pulmonary vascular bed and perhaps thromboses. With increased activity, cardiac output rises, the unobstructed areas of the pulmonary vasculature are subjected to a high Pmv, and, via mechanisms proposed by West and enunciated above, permeability edema with high protein content ensues. Additional proposed contributory factors are endothelial dysfunction, a defect in alveolar transepithelial Na+ transport, increased ET-1 or reduced NO production, and exaggerated sympathetic activation in HAPE-susceptible subjects during acute hypoxia. This susceptibility to HAPE, as recently reported by Droma and colleagues, may be explained by the discovery that two polymorphisms of the endothelial NOS (eNOS) gene were significantly associated with HAPE, underlying impaired synthesis of NO by pulmonary vessels.

**Neurogenic Pulmonary Edema**

NPE shares some pathogenetic similarities with HAPE but also exhibits differences. Its incidence determined from postmortem studies ranges from 33 to 71%, and it develops in various conditions and injuries of the central nervous system that produce increased intracranial pressure or cerebral ischemia. These lead to a massive sympathetic nervous discharge and catecholamine release, which result in severe systemic vascular vasoconstriction and translocation of blood from the systemic to the pulmonary circulation; this raises Ppa and Pw (unlike in HAPE) and produces a variably protein-rich edema. Indeed, the controversy, as in the case of HAPE, has been whether NPE is of the permeability or hydrostatic type: the answer appears to be that when the pressures rise sufficiently, microvascular stress failure and increased permeability follow. Clinical measurements on patients and experimental studies have shown that Ppa and Pw can reach 70 to 80 mm Hg and 40 to 70 mm Hg, respectively, consistent with the presence of an important element of cardiac dysfunction being added to the pulmonary hypertension. Further observations
favoring a primary hydrostatic mechanism (albeit very severe) include the rapidity of onset and reversibility, the variable protein concentrations in the edema fluid, including some within the range of hydrostatic edema, and the absence of endothelial damage as determined with electron microscopy.

**HETERGENEITY IN PULMONARY EDEMA**

Despite a perception of diffuse involvement in pulmonary edema and the aforementioned definition of ARDS and ALI, which includes “diffuse bilateral infiltrates on chest radiographs,” there is substantial heterogeneity in pulmonary edema, which remains largely unexplained. The specifics are as follows:

1. As indicated by the AECC in 1994, the definition of ARDS already entails considerable heterogeneity of etiologies, mechanisms, and associations.1

2. Despite the sizeable population of patients at risk of developing ALI/ARDS, relatively few do so; as detailed above, Hudson and colleagues91 reported an overall incidence of 26% of patients admitted to the intensive care unit, suggesting a role for genetic influences, among others, in differences in susceptibility.251

3. As is particularly well visualized on CT scans, some lung regions in ARDS have densities of solid tissue because of consolidation, edema, or atelectasis, whereas others retain normal air density and are apparently free of disease252; in addition to the systematic dorsal-to-ventral (or other gravity-dependent) gradients explained by hydrostatic forces, there are gravity-independent central-to-peripheral pulmonary heterogeneities whose mechanisms remain incompletely understood.

4. Heterogeneity, both macroscopic and microscopic, is also evident pathologically, in both hydrostatic and permeability edema, since the lung is not affected uniformly by edema; temporal heterogeneity also exists76,253 (see Figures 19-6C, 19-12B, and 19-13C).

5. Heterogeneities at the cellular level could partly explain those observed on a wider scale. For example, significant regional differences in normal EC ultrastructure exist in the different vascular segments (alveolar and extraalveolar): mean EC thickness is significantly greater in the muscular than in other microvessels, whereas vesicular numerical densities are significantly greater in ECs of capillaries than in those of nonmuscular, partially muscular and muscular vessels, and in venules than arterioles.254 Endothelial responses to

**FIGURE 19-13** Ultrastructure of heterogeneity in hydrostatic edema induced in rabbits by fluid infusion (methods detailed elsewhere76). A, Low-power scanning electron micrograph showing alveoli on the left side of the interlobular septum (arrow) with less edema than those on the right, which contain more fluid and are partly collapsed (×130 original magnification). B, Medium-power transmission electron micrograph showing one partly flooded alveolus and two empty ones; capillaries (Cap) are empty because of vascular fixation (×9,300 original magnification). C, High-power electron micrograph showing alveolar (Alv) edema, with different densities and protein contents on either side of the alveolar-capillary septum (×13,300 original magnification). Cap = capillaries.
stimuli such as endotoxin show considerable variation between species, between organs within species, between pulmonary and systemic vessels, and between large and small vascular ECs.  

6. The many mediators, cytokines, growth factors, and transcription factors produced by the varieties of cells in the lung are alternative sources of heterogeneity.  

7. Important inhomogeneities exist in ventilation/perfusion ratios, probably as a result of heterogeneous pulmonary arterial and venous constriction and airway closure, factors that could alter the distribution of edema.  

8. Heterogeneity in lung injury is in part responsible for the amplification of mechanical forces that precipitate VALI: preferential distribution of a positive pressure tidal breath to normally aerated areas renders them vulnerable to overdistention.  

9. The reported rates of recovery from ARDS vary considerably, and there is no clear explanation for this.  

Therefore, one of the goals of future research, both basic and clinical, as aptly pointed out in a recent publication of the AECC, should be to "progress from clinical syndromes, as presently defined, to more specific entities that are delineated by alterations in specific immunologic or biochemical pathways." To this should be added genetic predispositions and pathologic findings. One immensely successful example of this approach, albeit in a totally different domain, is the latest World Health Organization classification of neoplasms of hematopoietic and lymphoid tissues (leukemias and lymphomas), in which combined clinical, pathologic, immunologic, genetic, and molecular approaches have led to clearly defined entities with specific therapeutic approaches and prognostic implications. This is a challenge of major proportions in ALI/ARDS because obtaining tissue for many of these studies is fraught with difficulty. Nevertheless, the ability to biopsy small samples of tissue and to subject them to increasingly complex analyses, both morphologic and molecular, is rapidly improving and is a definite goal for the future. We have come full circle nearly 30 years after Murray's statement that "lumping these disorders together serves no useful purpose and has the disadvantage of detracting from important and distinctive differences in pathogenesis, therapy and prognosis." Perhaps we could start by splitting off those entities that do not correspond to DAD-associated ARDS.  

**SUMMARY AND CONCLUSIONS**  

Although the Starling equation remains a key determinant of our classification and approach to the physiology and management of pulmonary edema, its application and scope have been substantially enlarged and complicated by the acquisition of vast amounts of cellular and molecular biologic data that must be integrated into its basic parameters. The notion that edema can be simply divided into hydrostatic and permeability types has been compromised, for example, by studies showing that markedly elevated hydrostatic pressures induce capillary stress failure and permeability edema. Interactions between the two forms of edema complicate the management of such patients, as does the existence of mixed forms of pulmonary edema. Therefore, a clear understanding of the principles guiding the balance of forces and pressures in the lung circulation, airways, and interstitium is required to integrate the advances made by modern biologic approaches into a coherent whole.  

Still, in most instances, major differences remain between hydrostatic and permeability forms of edema. Hydrostatic edema, caused by an elevation of microvascular pressure, mainly in the setting of heart failure, is characterized by a transudate with a low protein concentration relative to plasma, an intact alveolar–capillary septal barrier, and an orderly sequence of fluid accumulation that starts in the interstitium before flooding alveoli and that is readily reversible, provided that the stimulus responsible for the elevation in pressure is treated. Furthermore, even repeated episodes of this form of edema leave the lung with little more than hemosiderin-laden macrophages in the alveoli, mild interstitial fibrosis, and generally mild vascular remodeling.  

In contrast, the permeability edema of ALI/ARDS is much more problematic. With its varied etiologies and associations, it is characterized by damage to pulmonary endothelium and epithelium with rapid and predominant alveolar flooding by a protein-rich exudate, causing early compromise of gas exchange. Mechanisms of damage involve activation of a variety of parenchymal and inflammatory cells and production or activation of many cytokines, chemokines and other mediators, growth and transcription factors, receptors, and signal transduction molecules, with multifaceted and complex interactions. Unlike in hydrostatic edema, failure to secure prompt resolution by appropriate therapeutic maneuvers results in activation of a fibroproliferative phase that may terminate in pulmonary fibrosis, with potentially devastating or even fatal consequences.  

For these reasons, the major challenges for the future in pulmonary edema lie in the sphere of ALI and ARDS. As mentioned earlier, the definition of ALI/ARDS does not take into account the heterogeneity of disorders and patient populations, so that different diagnostic entities may have to be separated off from the umbrella term, each with specific diagnostic, therapeutic, and prognostic implications. Also, the criteria of the AECC may be difficult to apply consistently. One of the concerns is the lack of a diagnostically accurate biochemical marker and reliable noninvasive measure of alveolar–capillary injury or permeability: specifically, there is a vital need for a marker of lung injury analogous to CPK-MB or troponin in acute myocardial infarction or to serologic tests for the infectious diseases. Furthermore, although considerable progress has been made in our understanding of the mechanisms of injury in ARDS, our knowledge of the interactions and balances between mediators and modulators of inflammation remains incomplete; similarly, the search for reliable markers of severity and mortality has been fraught with obstacles. One area of major progress, as detailed above, is the recognition of VILI and VALI, with the subsequent undertaking of clinical trials demonstrating the value of lung-protective ventilatory strategies in reducing mortality in ALI/ARDS.
Major challenges and directions for future research in ALI are summarized in a recent report from a National Heart, Lung, and Blood Institute Working Group. Some examples of promising avenues for exploration include the following: (1) in epithelial cells, the factors regulating cytokine production in response to injury and mechanisms of protection; (2) in ECs, the molecular mechanisms that regulate responses to injury and interactions with epithelial cells; their diversity also awaits further exploration; (3) mechanisms governing apoptosis and necrosis, responses of fibroblasts and other mesenchymal cells, to shed light on the remodeling of parenchyma and vessels in the fibrolamellar and fibrotic phases of ARDS; (4) in VILI and VALI, the molecular mechanisms of mechanosensing and mechanotransduction during stretching, and how they affect cellular interactions in injured lungs; also the detailed mechanisms whereby injurious ventilatory strategies lead to translocation of mediators, endotoxin and bacteria from the lung to the systemic circulation; and (5) detailed understanding of molecular signaling mechanisms by cells of the immune system and how cells involved in hemostasis and thrombosis are dysregulated in ARDS/ALI; for example, the roles of Toll-like receptors, of NFκB, and of other transcription factors require further scrutiny, as does the role of anticoagulants in the modulation of the injurious effects of ARDS.

With regard to these challenges, a combination of genomic and proteomic approaches and genetic and epidemiologic methods, correlated with traditional physiologic parameters and outcome measures in clinical trials, should substantially advance our knowledge base in this group of complex disorders, supplant the current physiologic and radiographic criteria, and deal with the substantial phenotypic heterogeneity of these disorders.

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