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SECTION 19

Interaction of the Lung and Kidney

CHAPTER 121

Lung-Kidney Cross-Talk

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OBJECTIVES

This chapter will:

1. Review the pathophysiology of acute lung injury.
2. Summarize the emerging understanding of lung-kidney cross-talk in the critically ill patient.
3. Identify the mechanisms by which acute kidney injury may potentiate acute lung injury.

Growing evidence points to harmful interactions between lung and kidney dysfunctions, which suggests a partial explanation for the natural history of multiorgan failure. This is important because typically the cause of death in patients with acute respiratory failure is sepsis and/or multiorgan failure rather than refractory hypoxemia.[1] Critically ill patients with acute respiratory failure have an estimated incidence of acute kidney injury (AKI) of 35% and face a mortality rate as high as 80% when their illness is combined with AKI, with the rate rising with AKI severity.[2,3] Observational data indicate that 75% of all patients with respiratory failure require some form of renal replacement therapy.[2,4]

ALVEOLAR-CAPILLARY BARRIER AS A FUNCTIONAL UNIT

The alveolus represents the actual site of gas exchange with a total surface area of approximately 50 to 100 m^2. An extensive capillary network occupies most of the area surrounding the alveoli, which makes the thin alveolar-capillary membrane (0.5–2 μm) highly efficient but also susceptible to injury. Under resting conditions, 25% to 33% of the diffusion area is sufficient to ensure gas exchange, and the high diffusion reserve is used only under conditions of increased cardiac output and/or impaired diffusion (e.g., prolonged diffusion abnormality in pulmonary edema or pneumonia, and capillary rarefaction in emphysema or lung fibrosis). Because the diffusion coefficient for CO_2 is 20 times higher than that for oxygen, any disturbance in alveolar diffusion primarily manifests as hypoxemia without influencing CO_2 elimination. This is in contrast to hypercapnia, which is mainly a result of alveolar hypoventilation (e.g., respiratory muscle weakness and hyperinflation).

To ensure adequate function of the alveolar-capillary barrier, it is important that the alveoli and interstitium remain not overloaded with fluid. This is maintained by a complex interplay of alveolar hydrostatic and capillary protein osmotic pressures, which leads to passive fluid transport to the capillary bed and lymphatic drainage of fluid accumulated in the interstitium. Importantly, type 1 and 2 pneumocytes express apical sodium channels (ENaCs) and basolateral sodium-potassium transporting adenosine-5′-triphosphatases (Na^+-K^+-ATPases) that actively pump sodium into the interstitium with secondary chloride adsorption via apical cystic fibrosis transmembrane conductance regulators (CFTRs). This promotes passive fluid clearance across the alveolar epithelium, which potentially is facilitated by aquaporin 5 water channels (Fig. 121.1). Notably, the lung and the kidney appear to have similar electrolyte and water channels, and this issue is addressed below. In the setting of an imbalance in any of these components (e.g., increasing capillary hydrostatic pressure in pulmonary congestion resulting from left heart failure or fluid overload), interstitial pulmonary edema can be the consequence, followed by alveolar pulmonary edema.

Acute Lung Injury

Acute lung injury (ALI) describes the classic response to different inciting inflammatory insults, which result in diffuse pulmonary epithelial and endothelial cellular damage, leading to increased alveolar-capillary permeability and the development of protein-rich inflammatory pulmonary edema. The primary molecular and cellular determinants of ALI are poorly understood and are likely to be

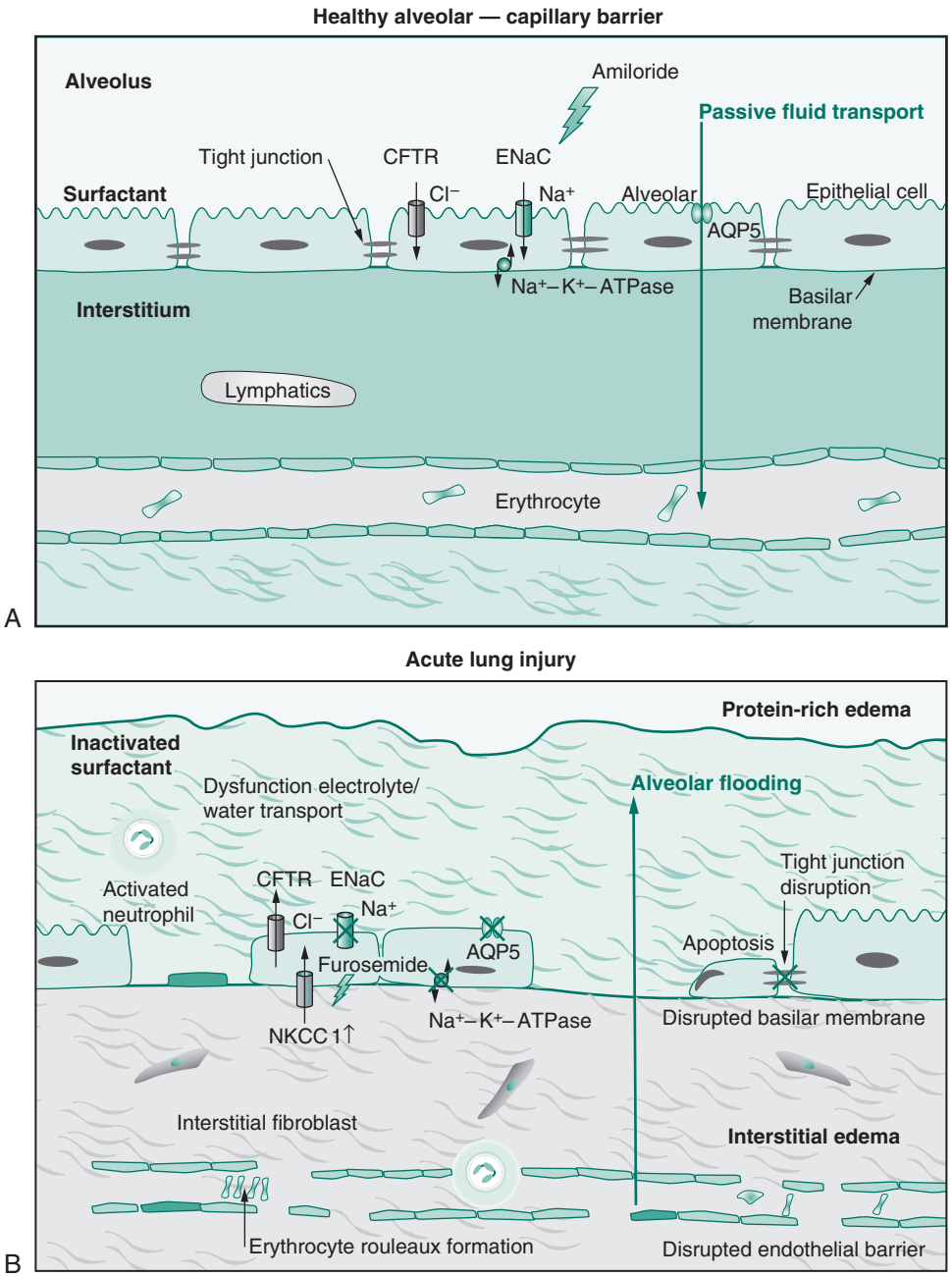

FIGURE 121.1 Alveolar-capillary barrier in normal conditions and acute lung injury. A, Schematic representation of the intact alveolar-capillary barrier. B, Schematic representation of the disrupted alveolar-capillary barrier with dysfunctional epithelial electrolyte/water transport and resultant alveolar flooding in acute respiratory distress syndrome. *AQP,* Aquaporin; *CFTR,* cystic fibrosis transmembrane conductance regulator; *ENaC,* epithelial sodium channel; *NKCC1,* Na^+-K^+-$2Cl^-$ cotransporter 1.

heterogeneous. There is considerable evidence that an increase in lung vascular permeability occurs primarily at the level of the lung microcirculation and leads to interstitial and alveolar fluid accumulation. This fluid is characterized by high concentrations of proteins and cytokines (e.g., interleukin-1, interleukin-6, and tumor necrosis factor-alpha), which activate secondary neutrophil- and platelet-dependent pathways that augment lung injury and vascular thrombi.[5–7]

Acute respiratory distress syndrome (ARDS) is the clinical manifestation of ALI with an incidence of 10.4% of intensive care unit admissions.[8] Among the most common clinical disorders associated with ARDS development are pneumonia and extrapulmonary sepsis (40% to 50%), aspiration, and noncardiogenic shock.[8] Recently, a new consensus definition of ARDS, the Berlin definition, was published. This definition introduces three levels of severity, according to the PaO_2/FiO_2 ratio and a minimum positive end-expiratory pressure, that should reflect the underlying lung injury.[9] Because hydrostatic edema as a result of left ventricular failure and/or fluid overload may superimpose ARDS, the Berlin definition has removed the pulmonary artery wedge pressure criterion for ARDS diagnosis. Patients would have ARDS if they meet the following diagnostic criteria: (1) acute hypoxemic respiratory failure; (2) onset within 1 week

of a known clinical insult, or new worsening respiratory symptoms; (3) bilateral airspace disease on chest x-ray or computed tomography not fully explained by effusions, lobar or lung collapse, or nodules; and (4) cardiac failure not the primary cause. The term ALI as a clinical categorization no longer exists. Under the Berlin definition, patients with a PaO_2/FiO_2 ratio of 200 to 300 mmHg will now be diagnosed with "mild ARDS."

Conceptually, ARDS requires increased lung fluid in the absence of underlying heart failure *(noncardiogenic pulmonary edema)*, which leads to noncompliant and nonaerated lungs with the consistency of a "wet heavy sponge" and an increase in extravascular lung fluid from 5 mL/kg to 15 mL/kg (Fig. 121.2). The increased lung weight can produce compression atelectasis with further impairment of lung mechanics and gas exchange. Additional microvascular thrombi promote ventilation/perfusion mismatching and the development of pulmonary hypertension (PH), all of which result in severe hypoxemia and hypercapnia resulting from increased alveolar dead space.

In cardiogenic pulmonary edema, alveolar fluid theoretically can be absorbed across the intact alveolar epithelium and lead to edema resolution once the elevated pulmonary microvascular pressure normalizes.[10] This is in contrast to ARDS, in which the impaired alveolar fluid clearance is a result of (1) an injury to the alveolar-capillary barrier[5] and (2) inflammation/oxidant-mediated injury and/or downregulation of the epithelial active ion transport system.[11] Experimental studies have attempted to restore and/or potentiate electrolyte movement across the alveolar epithelial barrier. They have found that the activation of various transcriptional and translational pathways, and hormonal (e.g., dopamine, corticosteroids, and thyroid hormone) and cAMP-induced stimulation of sodium conductance can reduce bronchoalveolar lavage protein levels and improve alveolar fluid clearance and respiratory mechanics.[12] However, no pharmacologic treatment addressing impaired vectorial fluid transport across the alveolar epithelium has as yet resulted in an improvement in survival,[13,14] most likely because of the lack of functional alveolar epithelium and microvascular endothelium.

In summary, ARDS is characterized by the disruption of the endothelial-epithelial barrier and alveolar damage that lead to acute, diffuse, noncardiogenic, inflammatory, and protein-rich pulmonary edema with increased lung weight, loss of lung aeration, and respiratory failure. Airspace infiltration with neutrophils amplifies and sustains the lung injury. Impaired alveolar fluid clearance is mediated by several mechanisms, including dysfunction of the transepithelial ion transport system.

Acute Lung Injury and the Kidney

In respiratory failure, AKI may be initiated and/or aggravated through different mechanisms, including (1) blood gas disturbances that may compromise renal blood flow and renal compensatory mechanisms, (2) PH and venous congestion that may lead to renal tissue edema, and (3) mechanical ventilation-induced hemodynamic and neurohormonal alterations, and systemic release of mediators (especially under conditions of increased alveolar-capillary permeability), which promote end-organ cell injury (biotrauma) (Fig. 121.3). The last point is of great significance, and the implementation of lung-protective ventilatory strategies has disclosed the role of a variety of mediators and specifically ventilator-induced lung injury in the pathogenesis of AKI.[15–17]

Blood Gas Disturbances and Acid-Base Disorders

Blood gas disturbances can affect adversely renal hemodynamics and function. Hypoxemia and hypercapnia are associated with reduction of renal blood flow and glomerular filtration rate in a dose-dependent manner, their effects being synergistic.[18–21] Possible mechanisms underlying hypoxemia-induced renal effects include alterations of vasoactive factors, such as nitric oxide, angiotensin II, endothelin, and bradykinin, and stimulation of adrenergic nerves.[15] Hypercapnia can directly induce renal vasoconstriction and stimulate the sympathetic nervous system or lead to peripheral vasodilation with secondary neurohormonal vasoconstriction (via noradrenaline and the renin-angiotensin-aldosterone system).[15] Importantly, the decrease in renal blood flow in response to hypercapnia also occurs in the presence of normal oxygen levels or even hyperoxemia, suggesting its dominance in the regulation of renovascular responses to changes in arterial blood gases.[19] It has been demonstrated that combined hypoxemia and hypercapnia may induce apoptosis of renal tubular cells in vitro.[22] However, permissive hypercapnia as a result of lung-protective ventilatory strategies in ARDS in the absence of hypoxemia appears to be beneficial in diminishing lung inflammation and lung/kidney cell apoptosis, and this remains an area of active study.[23]

Respiratory acidosis (arterial pH, 7.25–7.15) frequently is associated with lung-protective ventilatory strategies and generally is well tolerated. Here, treatment with intravenous bicarbonate may not beneficial, because bicarbonate is converted to CO_2 and may exacerbate respiratory acidosis further. Under this condition, tromethamine is the preferable buffer because it does not increase CO_2 but may accumulate to above safe plasma levels in conditions of inadequate renal function. Therefore, in patients with acute or chronic renal impairment and concomitant metabolic acidosis, early treatment with renal replacement therapy seems to be beneficial to prevent complications of severe, combined respiratory/metabolic acidosis (including arrhythmias and hemodynamic instability).[24]

The ARDS Net trials recommend a large range of SaO_2, down to 88%, because the maintenance of normal gas exchange may require ventilator settings that further injure the lungs.[25] No adverse effects of mild hypoxemia have been reported (e.g., no increased rate of organ dysfunction, including AKI).[26] However, mild hypoxemia may affect renal compensatory mechanisms via loss of the renal vasodilatory response and adversely affect long-term renal function. It has been shown that short-term mild hypoxemia (SaO_2 around 88%) in mechanically ventilated ARDS patients without evidence of renal failure is associated with substantial modification of renal function, including increased creatinine clearance, increased diuresis, and increased renal resistance.[27]

Pulmonary Hypertension, Venous Congestion, and Fluid Overload

In ARDS, hypoxemia is a potent pulmonary vasoconstrictor, whereas increased intrathoracic pressures associated with mechanical ventilation and positive end-expiratory pressure, vascular compression by edema and fibrosis, mediator-induced vasoconstriction, and in situ thrombosis and thromboembolism are additional factors that contribute to increased pulmonary vascular resistance.[28] PH is a characteristic feature of ARDS and is an independent predictor of mortality.[29] Several observations have demonstrated that

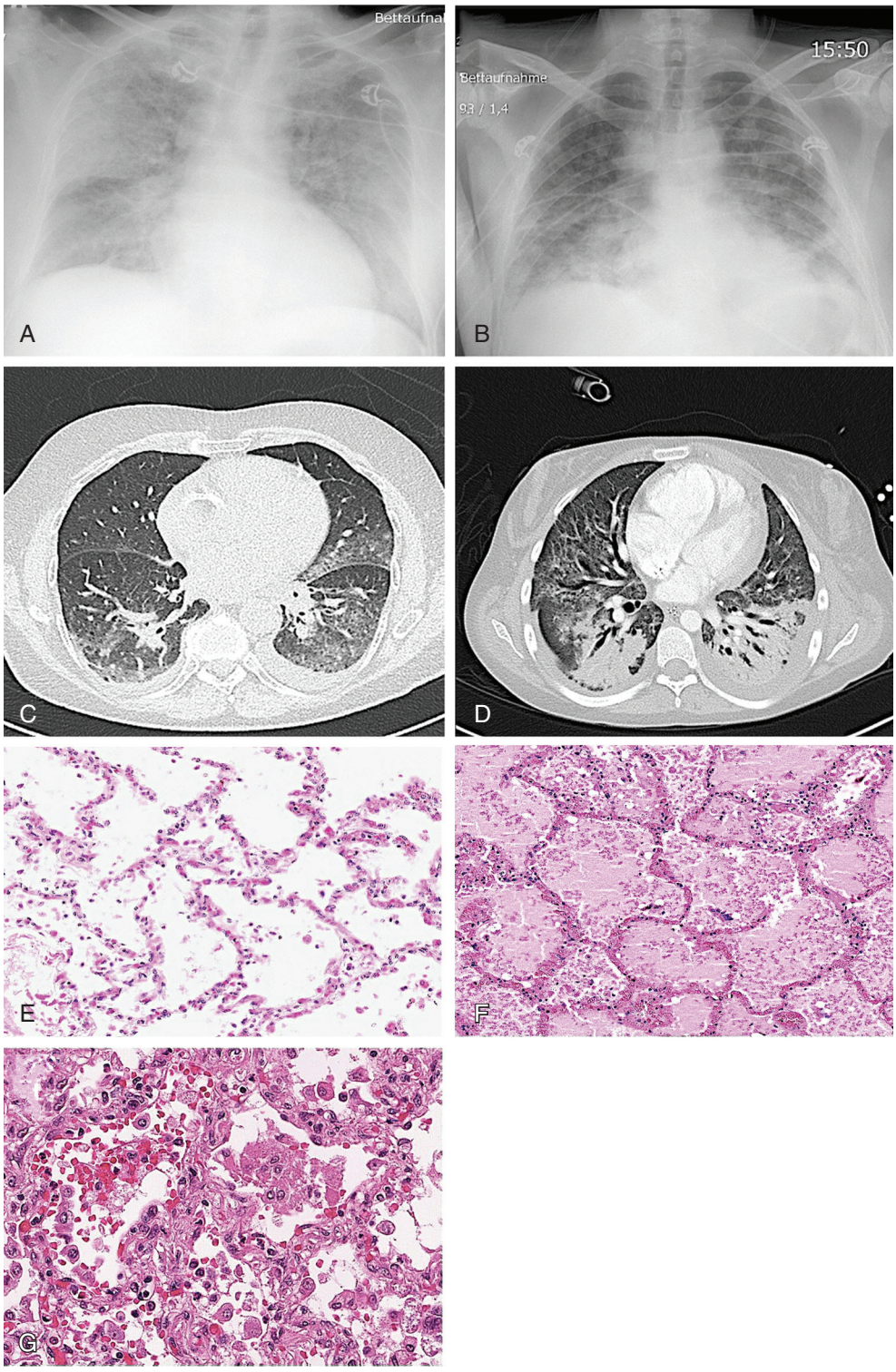

FIGURE 121.2 See also color plates. Cardiogenic pulmonary edema and acute respiratory distress syndrome. (A) Cardiogenic pulmonary edema and (B) acute respiratory distress syndrome share similar radiographic findings of bilateral opacification. (C) Cardiogenic pulmonary edema is characterized by perihilar ground-glass opacity (alveolar filling), an enlarged heart (note the aortic valve calcification), septal thickening with basal predominance (Kerley lines), and pleural effusion. Usually these patients are not imaged using CT, because the diagnosis is made readily based on anamnesis, clinical response to treatment (e.g., fluid removal) and radiographic findings. (D) Acute respiratory distress syndrome is characterized by a more asymmetric finding with a mix of normal lung tissue in the nondependent region, ground-glass opacities and consolidation, and a normal-sized heart. CT-scan. (E) Normal lung histology. (F) Histologic image showing cardiogenic pulmonary edema with intraalveolar transudate (pale-eosinophilic, finely granular), and thickened alveolar walls resulting from interstitial edema and capillary distension. H&E staining. (G) Histologic image of acute respiratory distress syndrome. The alveolar spaces are filled with mononuclear/neutrophilic infiltrates, proteinaceous edema, and hyaline membranes (resulting from fibrin, debris, erythrocytes), with occasional areas of alveolar hemorrhage. H&E staining. (A-D, From radiologic images courtesy of the Department of Diagnostic and Interventional Radiology, University Hospital Giessen, Justus-Liebig University Giessen, Giessen, Germany; images contributed by Fritz Roller, MD and Gabriele A. Krombach, MD. E-F, From virtual microscope slides courtesy of the Department of Pathology and the Duke University School of Medicine, Durham, North Carolina, USA; curated by J. Matthew Velkey, PhD. G, Iowa Virtual Slidebox: http://www.mbfbioscience.com/iowavirtualslidebox (slide contributed by Rakesh Kumar, MD, UNSW).)

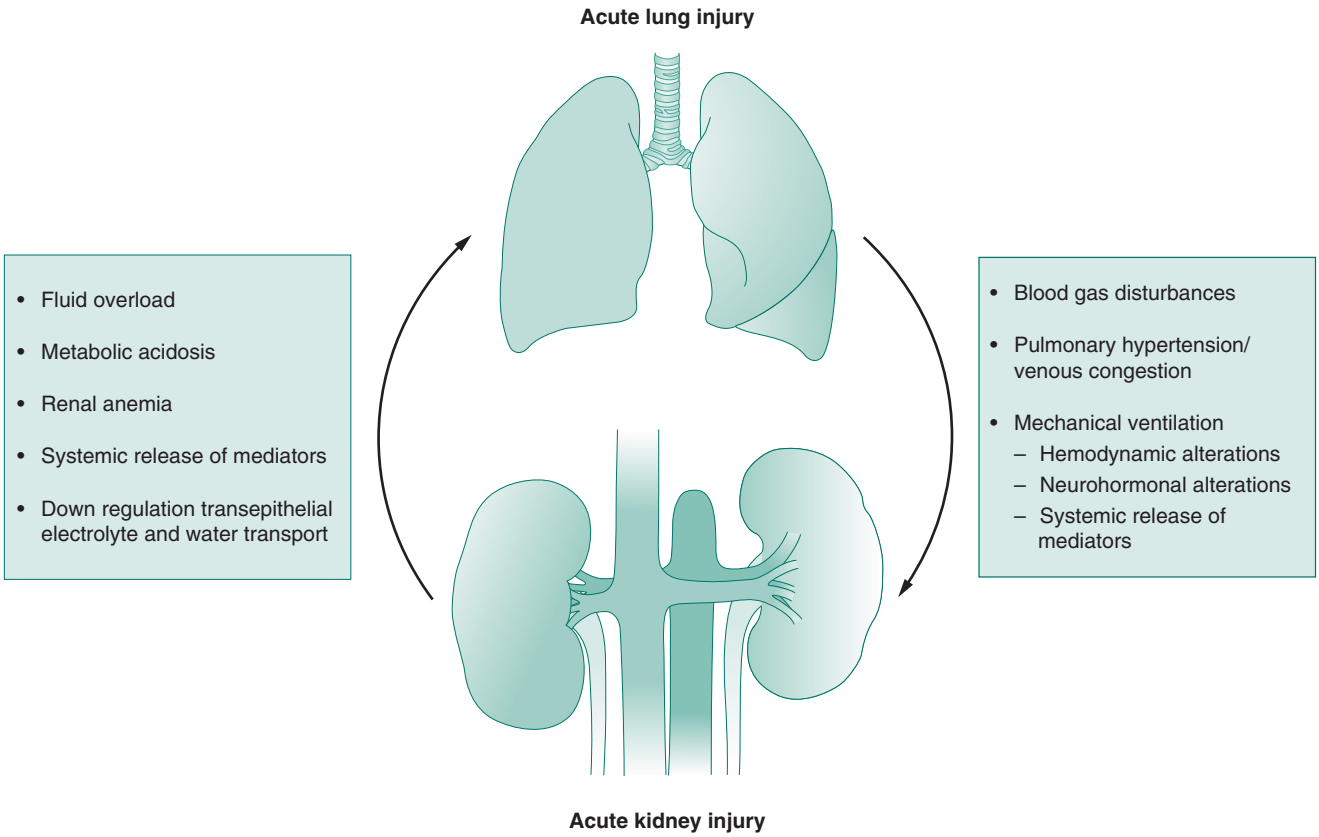

FIGURE 121.3 Lung kidney cross-talk in critical care.

venous congestion, which is a surrogate for PH and right ventricular impairment, is one of the predominant mechanisms underlying AKI in different critically ill populations.[30–32] Venous congestion can increase renal venous pressure directly, which experimentally has been associated with elevated interstitial and intratubular pressures.[33] The resultant renal tissue edema can decrease renal perfusion pressure (arterial minus venous pressure), which contributes to ongoing organ dysfunction. A similar mechanism is assumed in fluid overload, because it may result in increased venous congestion without a substantial benefit in renal perfusion, leading to a positive feedback loop with predisposition to renal failure and further fluid overload.

In the case of the lungs, a higher hydrostatic pressure as a consequence of fluid overload is likely to worsen alveolar edema formation. A conservative fluid strategy aiming to maintain a net even daily fluid balance rather than a positive fluid balance is associated with improved oxygenation and more ventilator-free days.[34] Excess fluid administration during a critical episode cannot prevent organ dysfunction, including AKI, or alter the severity of AKI, but potentially can lead to increased rates of renal replacement therapy resulting from fluid overload.[35]

ACUTE KIDNEY INJURY AND THE LUNG

Noncardiogenic pulmonary edema is a hallmark of ALI. AKI can aggravate fluid overload and acid-base disorders, which in turn may exacerbate alveolar flooding, impair pulmonary gas exchange, and increase respiratory work resulting from metabolic acidosis (Fig. 121.3). It is well known that fluid overload and/or AKI affect the duration of mechanical ventilation and weaning from mechanical ventilation.[15,34] However, lung injury and edema during AKI can occur even in the absence of fluid overload. In 1951 Bass et al. were the first to describe the uremic lung by its butterfly appearance on x-ray and associated it with advanced kidney failure and left ventricular failure.[36] With the introduction of dialysis, the classic presentation of bilateral perihilar lung edema in the absence of fluid overload became rare, suggesting a possible dialysable capillary toxic factor. However, the pathophysiologic principles of this condition are illustrative of the complex interactive effects of lung and kidney dysfunctions.

Experimental evidence has shown that AKI likely contributes to the development and exacerbation of lung injury and dysfunction, whereas renal transplantation can improve this.[37,38] In rodent models, ischemic/reperfusion injury of the kidneys results in an increase in pulmonary vascular permeability with consequent leukocyte trafficking, alveolar hemorrhage, and interstitial edema as well as the activation of proinflammatory and transcriptional pathways that lead to lung inflammation and apoptosis.[39,40] Interleukin-6 is probably the best described mediator that drives lung inflammatory cascades after AKI, with supporting data from human and animal studies.[41,42] Recent experimental studies have demonstrated that the systemic release of damage-associated molecular patterns originating from necrotic renal cells[43] and tumor necrosis factor receptor 1–dependent caspase activation[44] mediate lung apoptosis and pulmonary microvascular barrier dysfunction. Perhaps the strongest evidence of lung-kidney cross-talk is that renal ischemia/reperfusion injury and bilateral nephrectomy lead to the downregulation of ENaC, Na^+-K^+-ATPase, and aquaporin 5

channels in the lung, independent of fluid status.[40] The clinical relevance of decreased membrane transporters in the lung is supported by the observation of augmented pulmonary edema in response to ENaC inhibition (e.g., with the diuretic amiloride) in experimental pulmonary ischemia/reperfusion injury[45] and cardiogenic pulmonary edema.[46] Notably, ENaC inhibition promotes reversed transepithelial chloride transport mediated by CFTR and Na^+-K^+-$2Cl^-$ cotransporter-1 (NKCC1) with secondary fluid flux into the alveolar space (see Fig. 121.1).[46] In contrast, NKCC1 inhibition (e.g., with furosemide) can prevent active alveolar fluid secretion, which is a possible explanation for the rapid and diuresis-independent action of furosemide in pulmonary edema in addition to its venous vasodilating properties.[46]

Accumulating data suggest that the kidney plays a causal and modulatory role in acute respiratory failure, via not only the production but also decreased clearance of mediators. Continuous hemofiltration with a negative or even fluid balance has a hypothesized therapeutic benefit in patients with ARDS because of its ability to remove inflammatory mediators and cytokines related to AKI and/or ARDS. This field remains an area of active study.[46a] Additional therapeutic benefits may include a decrease in pulmonary and renal congestion. The impact of nonbiologic polymers found in the dialysis circuit has long been known, and proinflammatory effects have been found, although less markedly, of the biocompatible membranes in use today.[24] However, it is likely that continuous dialysis provides more physiologic support for the critically ill patient with renal dysfunction, and thus is more likely to be useful in multiorgan failure.

Clinical Strategies in the Care of Patients With Combined Acute Lung Injury and Acute Kidney Injury

Lung-protective mechanical ventilation with the use of a low tidal volume (6 mL/kg of ideal body weight) and a plateau pressure limit (less than 30 cm of water) is the standard of care and is associated with a 9% absolute decrease in mortality, including markedly less organ system failure (and renal failure).[25] A lung-protection strategy leads to less pulmonary and systemic inflammation, which provides a plausible link between ventilatory strategy, biotrauma, circulating mediators, and renal dysfunction.[47] Besides, having the patient maintain a prone position rather than a supine position for a minimum of 16 hr/day improves oxygenation in mechanically ventilated ARDS patients and has been shown to reduce mortality, likely by further preventing ventilator-induced lung injury.[48] High levels of positive end-expiratory pressure are often necessary to maintain arterial oxygen tensions because of alveolar flooding and collapse in ARDS; however, they also may exacerbate hemodynamic instability in certain situations (e.g., fluid depletion). Clinical studies have endorsed the importance of fluid resuscitation in maintaining venous return, cardiac output, and renal blood flow in this context.[49,50] Early fluid administration is beneficial to manage shock; however, fluid overload should be avoided, particularly in patients with lung injury, because it is associated with fewer ventilator-free days, prolonged intensive care unit stay, and increased use of renal replacement therapy. In addition, fluid overload may aggravate renal impairment by causing renal congestion and tissue edema. In patients with renal impairment and concomitant metabolic acidosis, early treatment with renal replacement therapy should be considered to prevent complications of severe, combined respiratory/metabolic acidosis.

Chronic Kidney Disease and the Lung

Chronic pulmonary congestion can initiate lung structural remodeling via fibroblast proliferation, fibrosis, and extracellular matrix deposition, which result in thickening of the alveolar wall.[51] Although the resultant reduction in vascular permeability is initially protective against pulmonary edema and can be seen as a restorative mechanism, the process can cause a restrictive, poorly compliant lung with impaired gas exchange. It is assumed that similar mechanisms are operative in chronic kidney disease, in addition to the above-mentioned uremia-related dysfunction of the pulmonary microcirculation. One of the most common pulmonary abnormalities in patients with chronic kidney disease is a marked decrease in diffusion capacity for carbon monoxide that correlates with the severity of renal impairment after correcting the effects of renal anemia, and leads to decreased cardiopulmonary exercise capacity.[52] Pulmonary hypertension is prevalent among 21% to 36% of chronic kidney disease patients, with higher rates among those with declining renal function.[53,54] In general, patients with chronic kidney disease develop pulmonary venous hypertension (class II PH) rather than pulmonary arterial hypertension (class I PH) because of the higher prevalence of left heart disease resulting from coronary artery disease, arterial hypertension, and/or diastolic dysfunction.[29] However, according to our current understanding, renal dysfunction may have an adverse effect on pulmonary vascular remodeling, and this has led to its recognition as an independent risk factor (class V PH). Possible pathophysiologic factors include endothelial dysfunction, decreased availability of nitric oxide, increased levels of endothelin-1, fluid overload, and shunting via arteriovenous fistulae. This is an emerging field of clinical research. In patients with end-stage chronic kidney disease, the prevalence of pulmonary arterial hypertension is 13%, whereas that of pulmonary venous hypertension is 65%.[55]

Key Points

1. Cardiogenic and noncardiogenic pulmonary edema represent the two entities of pulmonary edema and differ significantly in terms of alveolar fluid clearance.
2. After acute lung injury, acute kidney injury may develop as a result of (1) blood gas disturbances that may compromise renal blood flow and renal compensatory mechanisms, (2) pulmonary hypertension and venous congestion that may lead to renal tissue edema, and (3) mechanical ventilation-induced hemodynamic and neurohormonal alterations, and systemic release of mediators, which promote end-organ cell injury.
3. After acute kidney injury, acute lung injury may develop as a result of fluid overload and the systemic release of mediators that promote increased pulmonary vascular permeability, lung inflammation and apoptosis, and breakdown of the transepithelial electrolyte and water transport, ultimately leading to respiratory failure.
4. Lung-kidney crosstalk has clinical relevance, and may suggest novel mechanisms of multiorgan dysfunction and conceivably lead to new therapies.

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