

Lung injury following acute kidney injury: kidney–lung crosstalk

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Abstract The mortality of acute kidney injury (AKI) remains unacceptably high, especially associated with acute respiratory failure. Lung injury complicated with AKI was previously considered as “uremic lung”, which is characterized by volume overload and increased vascular permeability. New experimental data using rodent models of renal ischemia–reperfusion and bilateral nephrectomy have emerged recently focusing on kidney–lung crosstalk in AKI, and have highlighted the pathophysiological significance of increased cytokine concentration, enhanced inflammatory responses, and neutrophil activation. In this review, we outline the history of uremic lung and acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), the epidemiological data on the synergistic effect of AKI and lung injury on mortality, and recent basic research which has identified possible pathways in AKI-induced lung injury. These findings will enable us to develop new therapeutic strategies against lung injury associated with AKI and improve the outcomes of critically ill patients in intensive care units.

Keywords Acute kidney injury · Acute lung injury · Ischemia reperfusion · Bilateral nephrectomy · Neutrophil elastase

Introduction

Acute kidney injury (AKI) is a severe complication for critically ill patients in intensive care units (ICUs). It has been reported that AKI markedly increases their mortality [1–4], although renal dysfunction in AKI can be adequately treated by renal replacement therapy (RRT). This indicates the necessity of new AKI therapeutic strategies to improve the outcomes of AKI patients, targeting not only renal dysfunction alone but also multiple organ failure. Remote organ injury induced by AKI has recently been suggested [5]; for instance, AKI induces cardiac cell apoptosis and interleukin (IL)-1 and tumor necrosis factor (TNF)- α production in a rat renal ischemia–reperfusion model [6]. AKI increases proinflammatory cytokines in the cerebral cortex and hippocampus, activates microglia, and influences locomotor activity in mice [7].

Acute respiratory failure is another life-threatening condition in ICU patients. The mortality of acute respiratory failure is higher than 50% and increases with the development of other organ failure including AKI [8]. One report described a mortality rate above 80% for patients with AKI complicated with acute respiratory failure [1]. Therefore, understanding the pathophysiology of lung injury associated with AKI (kidney–lung crosstalk) and development of a new treatment for AKI complicated with acute lung injury will be crucial to improving the outcomes of AKI. In this review, we outline pulmonary complications in AKI, clinical epidemiological data on acute respiratory failure complicated with AKI, and recent basic

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research which has identified possible pathways in AKI-induced lung injury.

Uremic lung in AKI

“Uremic lung” is a term that describes pulmonary complication observed in uremic patients. Lange described this condition in the literature for the first time and the chest X-ray findings that are characterized by hilar opacities with a clear periphery were reported subsequently in the 1930s (Table 1) [9, 10]. The pathophysiology of uremic lung was assumed to be due to volume overload and increased capillary leakage, possibly caused by uremic substances. However, some groups observed inflammatory changes in the pulmonary lesions in uremic patients. Hopps and Wissler [11] examined lung pathology in autopsy samples from 107 uremic patients and 429 non-uremic patients. They found hyaline membrane formation and inflammatory cell exudates in the alveoli and described these pathological changes as uremic pneumonitis. Rackow and Fein [12] examined pulmonary capillary wedge pressure and bronchoalveolar lavage (BAL) fluid in two AKI patients. They found no volume overload and increased BAL fluid protein concentration, indicating that fluid overload is not necessary to cause pulmonary lesions in uremic patients. Bleyl et al. [13] examined 66 autopsy cases and reported that hyaline membrane formation was found not just in chronic renal failure but in all AKI patients. Physicians now recognize that the pulmonary edema found in end-stage renal disease (ESRD) patients can be rapidly resolved by dialysis induction, while patients with acute respiratory failure complicated with AKI show markedly higher mortality even if treated by dialysis [14, 15]. Taken together, not only fluid overload and increased vascular permeability but also inflammatory changes contribute to the pathogenesis of uremic lung, especially in AKI.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) was first described in 1967 by Ashbaugh et al. [16]. Twelve patients showed acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse pulmonary infiltrates on chest X-ray. Historically, this disorder was frequently observed in the victims of war and recognized as post-traumatic lung (DaNang Lung) [17]. In 1994 a new definition was recommended by the American–European Consensus Conference Committee [18]. ALI/ARDS is defined by the four criteria listed in Table 2. Although formally considered different from ARDS, ALI is now recognized as the less severe form, which is defined by the same parameters except for a $\text{PaO}_2/\text{FiO}_2$ ratio between 201 and 300. There are two stages in ALI/ARDS: the acute phase is characterized by disruption of the alveolar capillary and epithelial barrier, leakage of protein-rich fluid into the interstitium and alveolar space (hyaline membrane formation), and extensive release of cytokines and neutrophil infiltration. The later phase is characterized by fibrosis formation and permanent lung scarring [19, 20].

A number of conditions can cause ALI/ARDS directly (pulmonary injury) and indirectly (systemic injury) (Table 3). The most frequent direct causes are pneumonia and aspiration of gastric contents, whereas the most common causes of indirect injury are sepsis and trauma. Although AKI is not widely considered as a cause of ALI/ARDS, AKI shares common indirect factors such as sepsis, trauma, hemorrhage, and acute pancreatitis with ALI/ARDS. Recent basic researches using the rodent AKI models described below suggest that AKI could be another indirect cause of ALI/ARDS. Further investigation is necessary to demonstrate the kidney–lung crosstalk in the clinical setting of ALI complicated with AKI.

Table 1 History of “uremic lung”

Author	Year	Topics	References
Lange	1901	First description on pulmonary edema in renal failure	[9]
Roubier and Plauchu	1933	Diagnosis of uremic edema by chest X-ray	[10]
Alwall et al.	1953	Description of volume overload (“fluid lung”)	[61]
Bass and Singer	1950	Description of various factors other than volume overload	[62]
Hopps and Wissler	1955	Suggestion of “uremic pneumonitis” by evaluating 536 autopsy cases	[11]
Gibson	1966	Case report of lung edema in renal failure with no increased pulmonary arterial pressure	[63]
Rackow and Fein	1978	Simultaneous measurement of pulmonary arterial pressure and BAL fluid in non-cardiogenic pulmonary edema	[12]
Bleyl et al.	1981	Uremic pneumonitis is a specific characteristic for AKI	[13]

Table 2 Definition of ARDS/ALI

	ARDS	ALI
Pattern of onset		Acute
Image findings	Bilateral pulmonary infiltrates on chest X-ray	
PaO ₂ /FiO ₂	<200	<300
Cardiac function	Normal (pulmonary capillary wedge pressure < 18 mmHg)	

Table 3 Causes of ALI/ARDS

Direct injury	Indirect injury
Pneumonia	Sepsis
Aspiration (stomach content)	Burn/trauma
Pulmonary contusion	AKI/renal dysfunction (?)
Near-drowning	Massive transfusion
Fat embolism	Drug toxicity (e.g., paraquat)
Inhalation injury (smoke/chlorine)	Acute pancreatitis
Reperfusion (lung transplantation/pulmonary embolism)	DIC

Mortality of ALI/ARDS and AKI

ALI/ARDS and AKI will synergistically worsen the outcome of ICU patients. Russell et al. [21] reported that pulmonary dysfunction is common in sepsis syndrome, but not associated with an increased mortality rate. However, they found an increase in mortality with a pattern characterized by worsening renal dysfunction over the first 3 days; development of AKI in respiratory failure patients indicated poor outcomes. Chertow et al. [1] analyzed a clinical cohort of severe AKI patients who required dialysis and observed a markedly higher mortality rate in mechanically ventilated patients (81%) compared with the rest (29%). In an observational cohort study of AKI patients in ICUs at five academic medical centers (the Program to Improve Care in Acute Renal Disease; PICARD study), complications of respiratory failure significantly increased the mortality of AKI patients with an odds ratio of 2.62 (95% confidence interval [CI] 1.70–4.04) [22]. Liu et al. [23] analyzed 876 ARDS patients enrolled in the National Heart, Lung, and Blood Institute ARDS Clinical Network trial. Thirty-five percent of ARDS patients developed AKI and the mortality rate significantly increased with AKI complications (odds ratio 3.36, 95% CI 2.35–4.81). Vieira et al. examined 140 cancer patients who needed mechanical ventilation for acute respiratory failure. They found that AKI had a significant impact on not only the mortality but also the duration of mechanical ventilation and weaning from mechanical ventilation [24]. These clinical data strongly indicate that mortality will be unacceptably high when ICU patients have complications of AKI and ALI/ARDS.

Basic research on AKI-induced lung injury

Recently, it has been suggested that AKI influences other remote organs including the lungs [5, 15, 25]. Experimental evidence indicates that AKI-induced lung injury occurs not only by volume overload but also through deleterious kidney–lung interactions. It is of note that the alveolar epithelium has common features with the renal tubular epithelium in terms of polarization (apical and basolateral sites), localization of channels and transporters, and existence of tight junctional complexes (Fig. 1). Mechanisms of AKI-induced lung injury are assumed to include dysregulation of water clearance, inflammatory reaction,

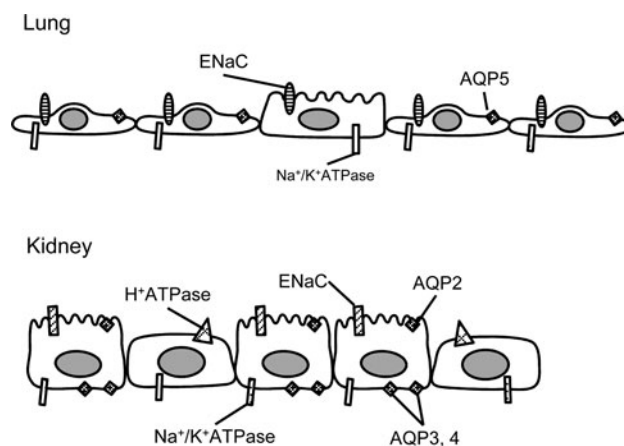


Fig. 1 Similarity of the alveolar and renal tubular epithelium. Localization of water channels and ion transporters are shown. The alveolar epithelium shares many features with the renal tubular epithelium

innate immune response, oxidative stress, apoptosis, and soluble mediator metabolism [26].

Rabb and colleagues [27, 28] reported that ischemic AKI engenders increased pulmonary vascular permeability accompanied by down-regulation of the pulmonary epithelial sodium channel (ENaC), Na,K-ATPase, and aquaporin-5. Interestingly, these changes were found, not in unilateral ischemia with an intact contralateral kidney, but in bilateral nephrectomy (BNx). They concluded that down-regulation of water clearance molecules in the lung might be mediated by unknown uremic toxins rather than reperfusion products. Ischemic AKI induces inflammatory reactions in the lung. Star and colleagues demonstrated activation of inflammatory transcription factors such as nuclear factor- κ B and p38 mitogen-activated protein kinase in the lung. They also showed the protective effect of α -melanocyte stimulating hormone (α -MSH) on AKI-induced lung injury [29]. α -MSH is a potent anti-inflammatory cytokine that decreases inflammatory cytokines, nitric oxide production, and expression of a neutrophil adhesion molecule [30, 31]. α -MSH inhibits multiple forms of inflammation and shows protective effects on AKI induced by ischemia–reperfusion and cisplatin injection [32–35].

Faubel and colleagues reported that AKI after ischemia and BNx induced increases in multiple serum cytokines, including IL-6 and IL-1 β , and lung injury characterized by neutrophil infiltration. The anti-inflammatory cytokine IL-10 attenuated pulmonary neutrophil infiltration and BAL fluid protein levels [36]. They further demonstrated the role of IL-6 in lung injury associated with AKI using IL-6-deficient mice and neutralizing antibody against IL-6 [37]. Rabb and colleagues [38, 39] recently performed a comprehensive gene expression analysis to clarify the response of the lung to AKI. Gene chip analysis identified 266 lung genes with increased expression and 615 with decreased expression at 6 h after surgery of renal ischemia reperfusion. Interestingly, the influence of BNx on pulmonary gene transcription was undetectable at 6 h. Gene ontology analysis demonstrated activation of several proinflammatory and proapoptotic biological processes. They also found that inflammatory transcriptome changes in the kidney and the lung were similar and included the innate immunity genes such as *Cd14*, *Socs3*, *Saa3*, and *Lcn2* (lipocalin 2).

Neutrophil infiltration into the lung is a key event, especially in the early phase of lung injury associated with AKI. Okusa and colleagues reported an increase in lung neutrophil content following ischemic AKI in mouse [40]. They showed a significant increase in marginal neutrophils after ischemic AKI but no significant change in the lung interstitial neutrophil content. These data suggest that transmigration of neutrophils to the alveolar space is not necessary for inducing lung injury in AKI. Activated

neutrophils contribute to the pathogenesis of lung injury by releasing several proteases and reactive oxygen species [41]. Neutrophil elastase (NE) is a serine protease secreted by neutrophils during inflammation and destroys not only bacteria but also host tissue [42, 43]. Recently, we evaluated the possible therapeutic effects of a specific NE inhibitor, sivelestat sodium hydrate (ONO-5046, ElaspolTM), on lung injury associated with AKI using a mouse BNx model [44]. BNx showed neutrophil infiltration into the lung (Fig. 2), increased pulmonary inflammatory cytokine expression (IL-6, neutrophil chemokine keratinocyte-derived chemokine [KC] and TNF- α), and protein leakage accompanied by early increase of systemic and pulmonary NE activity. The sivelestat sodium hydrate treatment reduced systemic NE activity and improved these pulmonary inflammatory responses. Although one randomized controlled trial including 492 patients demonstrated no improvement in ALI/ARDS by sivelestat sodium hydrate [45], several small trials showed beneficial effects of sivelestat sodium hydrate on ALI/ARDS in critically ill patients [46, 47]. No clinical trial evaluating sivelestat sodium hydrate on ALI/ARDS complicated with AKI has

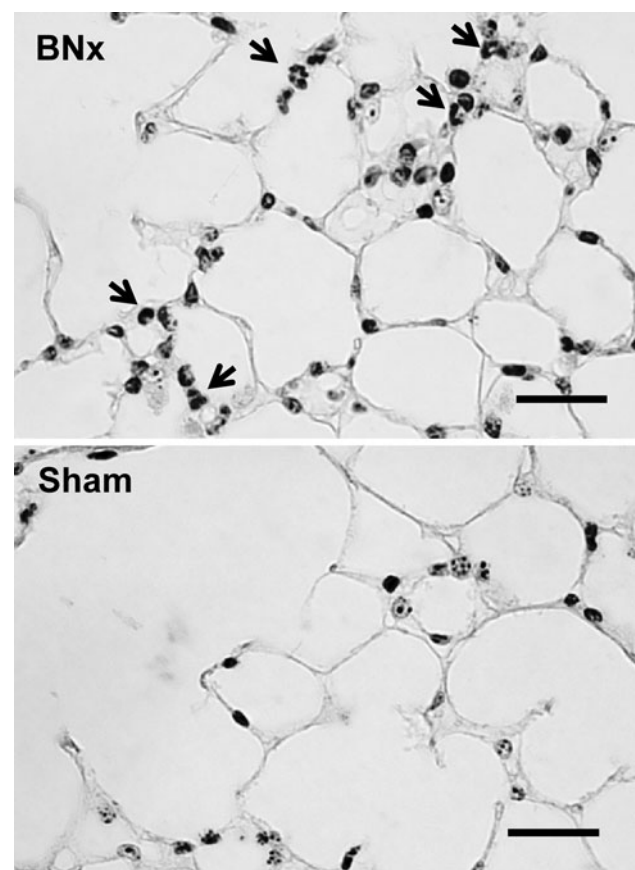


Fig. 2 Neutrophil infiltration in lung injury induced by bilateral nephrectomy (BNx). Neutrophil infiltration at 6 h after the surgery was observed by Giemsa stain (arrows). $\times 400$. Bar 50 μ m

been reported in the relevant literature. This study suggests that blockade of NE activity may be a useful therapeutic strategy for lung injury complication in AKI patients. On the contrary, one study employing a murine two-hit model consisted of AKI (ischemia–reperfusion or BNx) and subsequent ALI (intratracheal HCl instillation), demonstrated that acute renal dysfunction was protective for subsequent lung injury [48]. Reconstitution experiments, in which uremic neutrophils were injected into non-uremic mice and vice versa, identified uremic neutrophils as the primary mediators. Further investigations are necessary to clarify the role of neutrophils in the pathogenesis of lung injury associated with AKI.

Although investigations of AKI-induced lung injury have been conducted by several different groups as described above, there are few animal studies that have examined ALI-induced AKI. Considering the high frequency of AKI complications in ARDS patients [23], there is assumed to be AKI induction by ALI. Slutsky and colleagues [49] reported a rabbit model of acid-aspiration lung injury followed by mechanical ventilation with injurious ventilatory strategies (high tidal volume + high PEEP) which showed increased rates of epithelial cell apoptosis in the kidney. On the other hand, Simon and colleagues found no renal structural and functional alterations in a canine acid-aspiration model of ALI when hemodynamics and arterial blood gas tensions are carefully controlled [50]. It is of note that only aseptic ALI models were used for these studies.

Limitation of animal models

Because failure to translate benefits observed in animal models to the clinical setting is a huge problem, development of clinically relevant animal models is essential [51]. As described above, rodent models of BNx and renal ischemia–reperfusion have been employed to investigate the role of AKI in the pathogenesis of lung injury [27, 29, 36, 37]. Both animal models have some disadvantages. As with renal ischemia, ischemia–reperfusion models of other organs such as the liver, gut, and hind limb also cause lung injury [52–54]. Intestinal ischemia–reperfusion injury induced marked lung injury, as characterized by lung edema, hemorrhage, and infiltration of inflammatory cells, and proinflammatory cytokine (IL-6 and TNF- α) levels in the lung [55]. Similarly, pulmonary edema has been observed within hours of liver transplantation [56, 57], which has been attributed to hepatic ischemia–reperfusion injury via the activation of the hepatic Kupffer cells resulting in the production of oxygen radicals and the modulation of proinflammatory and anti-inflammatory cytokines [58–60]. The secondary organ damage after ischemia–reperfusion in different organ is caused by

systemic induction of oxygen radicals and proinflammatory cytokines rather than the loss of organ function. Therefore, it would be difficult to distinguish the contribution of renal dysfunction itself in lung injury from the effects derived from increased systemic oxidative stress. Because the BNx model induces abrupt and complete decline of renal function, it ideally enables us to investigate the direct relation of renal dysfunction with lung injury without considering the additional issues described above. However, the BNx model is not perfectly relevant to clinical settings because sudden and complete loss of renal function will not be seen so frequently. Kidney cancer patients who have already lost one kidney for some reason and have total nephrectomy, or victims of traumatic accidents, may suffer from this condition.

Reportedly, a mouse model of AKI-induced lung injury using BNx showed no volume overload or pulmonary edema [36, 44]. No significant difference was found between bilaterally nephrectomized and sham-operated animals in terms of total body weight change or the lung wet/dry weight ratio. Severely ill patients with AKI-induced lung injury frequently show lung edema, possibly because they need fluid resuscitation to maintain their hemodynamics. However, these studies administered no fluid to the animals after the surgery. Although marked inflammatory responses including neutrophil infiltration, increased vascular permeability, and inflammatory cytokine expression were demonstrated in the BNx model, adding fluid as resuscitation will produce an AKI-induced lung injury model closer to the clinical settings.

Perspective

ALI/ARDS and AKI synergistically worsen the outcome of critically ill patients, and development of novel therapeutic strategies against these severe conditions will certainly make marked progress in the field of critical care. Basic research has recently demonstrated that lung injury can be induced by AKI and has indicated the possible existence of kidney–lung crosstalk. Several different pathways have been identified that contribute to the lung injury following AKI: dysfunction in water clearance, neutrophil activation, increase in cytokine concentration, activation of inflammatory transcription factors, and induction of inflammatory gene expressions. Although we are accustomed to having a single fixed therapeutic target (e.g., HMG-CoA reductase for hypercholesterolemia), the therapeutic targets in lung injury following AKI will vary and may need new biomarkers to identify which biological targets are active at any given time in the patients.

Lung injury is induced not only by renal ischemia–reperfusion but by BNx in rodent models, indicating that an unknown “uremic toxin” which is eliminated by the

kidney may cause lung injury. This raises questions whether chronic kidney disease and ESRD are the risks for acute lung injury, and whether RRT can ameliorate AKI-induced lung injury by removing unknown substances. Can AKI or renal dysfunction itself be recognized as a cause of ALI/ARDS (Table 3)? Can we improve the ventilator-free days by starting RRT earlier or conducting high-flow, high-volume continuous RRT? Clinical research focused on these issues will further our understanding of kidney–lung crosstalk.

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Conflict of interest All the authors have declared no competing interest.

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