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Review Article

Nephrogenic acute respiratory distress syndrome: A narrative review on pathophysiology and treatment

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ABSTRACT

The kidneys have a close functional relationship with other organs especially the lungs. This connection makes the kidney and the lungs as the most organs involved in the multi-organ failure syndrome. The combination of acute lung injury (ALI) and renal failure results a great clinical significance of 80% mortality rate. Acute kidney injury (AKI) leads to an increase in circulating cytokines, chemokines, activated innate immune cells and diffuse of these agents to other organs such as the lungs. These factors initiate pathological cascade that ultimately leads to ALI and acute respiratory distress syndrome (ARDS). We comprehensively searched the English medical literature focusing on AKI, ALI, organs cross talk, renal failure, multi organ failure and ARDS using the databases of PubMed, Embase, Scopus and directory of open access journals. In this narrative review, we summarized the pathophysiology and treatment of respiratory distress syndrome following AKI. This review promotes knowledge of the link between kidney and lung with mechanisms, diagnostic biomarkers, and treatment involved ARDS induced by AKI.

Introduction

The kidneys receive more cardiac output on a per-gram basis than some other organs such as the liver (approximately 25% of cardiac output). Therefore, kidneys are constantly exposed to small peptides and immune regulatory molecules, which can reabsorb these substances from circulation and excrete them. It is clear that in kidney injury situations, accumulation of these molecules and peptides leads to increased concentration of substances in blood and initiates immune responses with deleterious effects in distant organs. In addition, epithelial tubular cells are active to producing a variety of inflammatory mediators with presenting circulatory antigens and promoting the activation of leukocytes that passing through the kidney via this rich circulation.[1] Now it is known that renal epithelial cells up regulate and secrete some chemokines and cytokines such as nuclear factor-κB (NF-κB) in injured situations, which can initiate the inflammatory cascade in other organs.[2,3]

Acute kidney injury (AKI), also known as acute renal failure, is a common clinical disorder resulting from some conditions such as renal ischemia reperfusion injury with an abrupt loss of kidney function and decline in renal filtration fraction.[4–6] The incidence of AKI varies about 5%–7% in hospitalized patients and it seems that this ratio is rising every year.[7] Despite recent advances in the treatment of AKI, this disorder still has a high mortality and morbidity rates in approximately 50% hospitalized patients, presumably due to the unchanged dysfunction of other organs.[8] Recent studies have found an association between kidney and remote organs dysfunction.[9,10] In most cases kidney disease directly or indirectly affects pulmonary functions and causes the lungs to be recognized as one of the most affected distant organs of kidney injury.[11] Respiratory complications are mostly associated with renal failure, and conversely AKI is a common incidence in mechanically ventilated patients.[12]

This crosstalk involves a complex interaction between many of biochemical, cellular and tissue specific factors that excite remote pro-inflammatory and pro-apoptotic signaling.[13,14] The innate immune pathways were mostly mediated through production of oxygen free radicals, secretion of inflammatory cytokines and recruitment of polymorphonuclear cells.[13,15] Impaired renal filtration leads to elevated trans-capillary filtration pressure gradient

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and promotes tissue edema.[16] Edema especially has serious consequences in the lungs because pulmonary edema impairs gas exchange and can lead to potentially life-threatening condition.[17] Pulmonary failure can develop to acute lung injury (ALI) and eventually respiratory distress syndrome with a high mortality rate. The mortality rate of ALI alone is 30%–40%, but the rate rises to 80% in combination with AKI.[11,18,19] Therefore, at least partial causes of the high morbidity and mortality rate of AKI derive from extrarenal complications, usually related to pulmonary dysfunction,[20] which shows particular importance of extrarenal organs complications and requires knowledge of link between lung and kidney in determining therapeutic strategies to decrease the mortality rate in critically ill patients. Unfortunately, little is known about the potential interactions between these tissues in critically ill patients. In this review we summarize some potential mechanisms, diagnostic biomarkers and treatments involved in the acute respiratory distress syndrome (ARDS) after renal failure.

Pathophysiological interactions of kidney injury and ARDS

Edema

One of the most effects of AKI on pulmonary system is through the water imbalance. Pulmonary fluid and electrolyte transporters change after AKI. Sodium ATPase pump and epithelial sodium channel (ENaC) promote sodium absorption from the alveolar cavity into the alveolar epithelium cells. Then, water passively follows sodium out of the alveoli. Studies have shown that renal failure can down regulate the epithelial salt-water transporters such as ENaC, sodium-potassium ATPase and aquaporin-5 in the lung, which all contribute to high pulmonary vascular permeability and low alveolar fluid clearance.[21–24] This type of edema is a consequences of following disorders: water-sodium retention induced by renal injury; increased hydrostatic pulmonary capillary pressures and changed Starling's forces; loss of membrane integrity in capillary endothelial and alveoli epithelial; leakage of plasma protein and alveolar fluid accumulation.[25] Because the lung contains many blood vessels, it is the most vulnerable organ to injury.[26] Pulmonary edema patients have prolonged hospital stays, mechanical ventilation, and higher rates of pneumonia. Renal injury-induced water retention results in decreased pulmonary compliance and increased respiratory work in patients.[27] These conditions lead to impaired gas exchange, which can be severe refractory arterial hypoxemia and life-threatening.[28] Any intervention to reduce pulmonary edema can have a significant effect in improving patients' health.

Pulmonary edema has many plasma proteins including proteolytic enzymes, proteins, fibrinogen and fibrin in its contents, which can lead to destruction of the surfactant proteins. The damage of alveolar epithelial cells caused by inflammatory mediators can have additional effects in the destruction and decrease of surfactant. Although over-load volume of renal failure has an important role in the onset of ALI but evidence indicates that lung damage may occur even in absence of positive fluid balance.[24] On the other hand, it seems that the uremia is responsible for effects of renal injury on the lung's salt and water transporters.[29,30]

Cytokines

The harmful effects of AKI on the lung function could relate to the loss of normal balance of immune, inflammatory and soluble mediator metabolism.[31] The kidney plays a key role in cytokines metabolism and clearance. Impaired kidney function is associated with cytokine imbalance (both production and elimination) in the circulation. It revealed that an important pathway of lung injury subsequent kidney injury could arise from cytokine dysregulation in the kidney, with further activation of the lung's indigenous immune cells and respiratory complications.[12] Additionally there is a massive system of vessels in the lungs that accelerate lung deposition of multiple inflammatory mediators. The up-regulation of pro-inflammatory genes and inflammatory cytokines after AKI have important effects on the onset and progression of ALI.[32] Animal experiments have shown that AKI causes the activation of proinflammatory and anti-inflammatory mediator's gene in the lung.[29] The products of these proinflammatory genes such as Cd14, lipocalin-2, chemokine ligand-2 (CXCL2), and IL-6 can be released into circulation and initiate inflammation cascade in pulmonary.[33]

In addition, inflammatory cytokines especially interleukins (IL-6, IL-8, IL-1β), tumor necrosis factor α (TNF-α), macrophage inflammatory protein 2, amyloid protein A are the main mediators involved in the progress of distant organs injury including lung failure after AKI.[12,29,33] NF-κB is a pro-inflammatory transcription factor that leads to gene expression of inflammatory proteins, including cytokines, chemokines and adhesion molecules.[34]

The systematic inflammatory reactions, accumulated toxic metabolites after AKI, and the decrease of omission and inactivation of the inflammatory mediators through kidneys, cause increase of mediators in the plasma.[26] These mediators can change pulmonary vascular permeability which exacerbates edema, leukocyte infiltration and respiratory disorders.[35–40] IL-6 seems to be a patient mortality factor in AKI due to its particular role in the initiation and extension of the inflammatory process.[12,39] Recently, Klein et al[12] demonstrated that IL-6 knockout mice models have less neutrophil infiltration, myeloperoxidase activity and capillary permeation resulting in lower pulmonary edema. TNF-α also is a vital cytokine in mediating ALI. It persuades the pulmonary endothelial cells activation, white blood cells migration, granulocyte degranulation, reactive oxygen species stimulation and capillary leakage.[41] Furthermore, TNF-α interacts with multiple cytokines which can induce extensive effects. For example TNF-α increases the genesis of IL-6.[42] We can classify the release of different cytokines in AKI-induced ARDS as diagnostic biomarkers in time variant occurrence phases (Fig. 1).

Neutrophil trafficking

Neutrophils are the first immune cells to arrive at the site of injury or inflammation. After activation, neutrophils inflow from the vascular endothelial cells to the interstitium and into the alveolar space. Recruitment of neutrophils into the lung is one of the key events in the development of ARDS.[43] Alveolar capillaries are the main site of sequestration and margination of neutrophils.[44] Lung capillary network consist of large number of segments with about 40% equal to, or smaller diameter than the neutrophils.[45] Almost 50% of the circulating leukocyte population can be segregated within the pulmonary vasculature.[46–48] Pulmonary neutrophil sequestration is an early event that occurs in pathologic lung inflammation.[49] Apoptotic events and inflammatory mediators especially the cytokines IL-6 and IL-8 are responsible of the leukocyte recruitment during the inflammatory response of AKI.[50] Moreover, cytokines and chemokines cause integrins activation leading to adhesion of neutrophils on the endothelium.[51] It appears that β2-integrins have particular role in neutrophil recruitment.[52]

Neutrophils margination to vascular endothelium participates in microvascular plug, vascular congestion and damaging by releasing reactive oxygen species and potent proteolytic enzymes.[51] Neutrophils can also release a variety of cytokines including interferon (IFN)-γ,[53] IL-4,[54] IL-6,[55] IL-10,[56] and TNF-α.[57]

It appears that neutrophils and neutrophil elastase, a serine protease which is available in the granules of the neutrophil, have important roles in endothelial injury and increased vascular permeability in ARDS.[58]

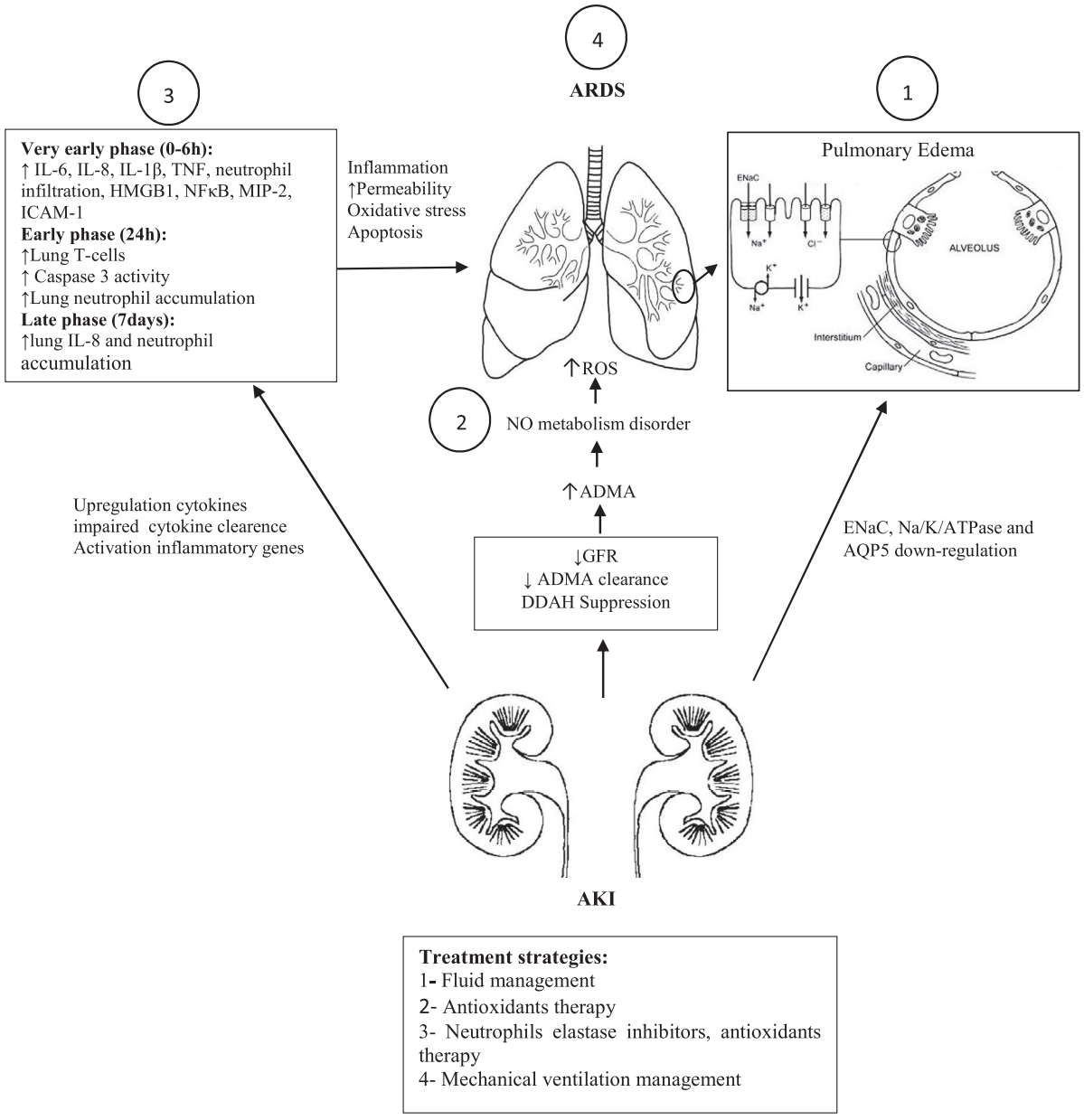

Fig. 1. The effects of AKI on lung dysfunction. AKI caused lung inflammatory responses and apoptosis through releasing many inflammatory mediators and cytokines. These mediators can be used as diagnostic markers in three time phases: very early (within 0–6 h), early (24 h) and late (7 d). Neutrophil accumulation and trafficking occurs following inflammation, cytokines and integrins activation such as IL-6 and ICAM-1. On the other hand, renal dysfunction after AKI leading to decreased GFR and ADMA clearance with NO metabolism disorder and reactive oxygen production. Pulmonary edema is often caused by down-regulation of ENaC, Na/K/ATPase and AQP5. As a result, all events lead to increased permeability and edema, oxidative stress and apoptosis in the lung that finally caused ARDS.
Abbreviations: GFR, glomerular filtration rate; AKI, acute kidney injury; ICAM-1, intercellular adhesion molecule 1; ADMA, asymmetric dimethyl arginine; ENaC, epithelial sodium channel; AQP5, aquaporin 5; HMGB1, high-mobility group protein B1; MIP-2, macrophage inflammatory protein 2; NFkB, nuclear factor kB; TNF, tumor necrosis factor.

Oxidative stress

Oxidative stress and its systemic consequences likely play a significant role in AKI-induced lung injury. The increased lung tissue levels of malondialdehyde (MDA) (a marker of lipid peroxidation) have been observed in rats with AKI.[26,59]

There are three main sources of oxidative stress: 1) Activation of neutrophils in the pulmonary circulation causes the release of large amounts free radicals and reactive oxygen species[60]; 2) Accumulation of activated macrophages to injured tissue can induce cell death by releasing reactive oxygen species; 3) Last source of oxidative stress in ARDS patients is availability of high levels of oxygen employed during ventilator therapy. It seems that antioxidant activity and potency also decreased in these patients.[61] Glutathione is an important antioxidant in the lung that decreases in patients with ARDS.[62] Metnitz and colleagues[63] showed that plasma levels of alpha-tocopherol, vitamin C, beta-carotene, and selenium were reduced in ARDS patients. These events lead to the increased production of oxidants, creating an imbalance between antioxidants and oxidants which will lead to the pathways of cell death. Inflammation condition in lung injury is a suitable opportunity for free radicals to overwhelm the endogenous antioxidants.

Inflammatory factors following AKI activate oxidative stress and reactive oxygen species production that can lead to ALI by several mechanisms including: lipid peroxidation, direct oxidative damage and mutations in DNA, changes in cellular protein activity by proteins and enzymes oxidation, alteration in genomic transcription and direct surfactant damage.[64] Cellular DNA damage inhibits protein syntheses that are involved in cell growth, genes encoding antioxidant enzymes and cell repair.[65]

Apoptosis

AKI activates variants lung apoptosis-related genes including tumor necrosis factor receptor 1 (TNFR1) and programmed cell death.

Tumor necrosis factor receptor 1 (TNFR1)-mediated programmed cell death[66] and lung microvascular barrier dysfunction[67] have been identified prominent factors in mediating lung dysfunction through endothelial cell apoptosis. Endothelial cell apoptosis has deleterious effects on solute transport across the vascular membrane. Impaired endothelial barrier function has a key role in increased vascular permeability and inflammation.[68] There was increased lung vascular permeability at 24 and 48 h post ischemia in a rat model of bilateral renal ischemia reperfusion injury, quantified by leakage of labeled albumin outside the vascular space.[23,69] Pulmonary cellular apoptosis may also contribute to ARDS.

AKI also leads to an increase in lung caspases. Administration of caspase inhibitors reduces lung injury following acute renal failure.[15]

Asymmetric dimethyl arginine

NO metabolism disorder due to renal failure makes the lungs more sensitive to injury. The mechanism underlying NO dysregulation is not completely clear, but it appears that asymmetric dimethyl arginine (ADMA), an inhibitor of endothelial NO synthase (eNOS), plays a significant role. ADMA shifts NO metabolism toward the production of free radicals and lung damage.[70] ADMA is in part excreted by renal excretion.[71] Reduced glomerular filtration fraction of ADMA in renal failure is associated with slight increases of ADMA plasma levels and impaired pulmonary vascular vasodilation.[72] The high-level clearance process of ADMA is carried out by dimethylarginine dimethylaminohydrolase (DDAH), enzyme involved in the degradation of the ADMA. It seems that DDAH is suppressed in acute renal injury, leading to accumulation of ADMA in plasma and tissues.[73]

Diagnostic biomarkers

Some mediators and indicators indicate that lung injury after AKI can be classified into 3 phases according to the time of occurrence, as follows:

1) Very early phase (0–6 h): Pulmonary edema and lung neutrophil accumulation occur very early with increased serum proinflammatory cytokines. Increased serum IL-6 (not in local lung), within 2 h in patients with AKI leads to increased lung chemokine (C-X-C motif) ligand 1 (CXCL1) such as IL-8 production and neutrophil infiltration.[36,74] Therefore, increased serum and lung IL-8 at 2 h after AKI can predict lung injury.[36] Tumor necrosis factor (TNF) is another marker that induces TNFR1-mediated pulmonary apoptosis within 2 h after ischemic AKI.[66] Increased serum high-mobility group protein B1 (HMGB1), an agonist of TLR-4, within 6 h after AKI[75] and lung markers such as nuclear factor κB (NFκB),[76] macrophage inflammatory protein 2 (MIP-2),[29] intercellular adhesion molecule 1 (ICAM-1)[77] and IL-1β[75] are associated with lung injury after AKI.
2) Early phase (24 h): lung T-cell accumulation via increased lung endothelial apoptosis with caspase 3 activity and lung TUNEL staining is responsible of continuing pulmonary edema and lung neutrophil accumulation within 24 h after AKI onset.[14,67]
3) Late phase (7 days): increased lung IL-8 and lung neutrophil accumulation indicate lung injury occurrence in AKI patients.[78]

Treatment strategies

Mechanical ventilation management

Protective ventilation term means sufficient oxygenation of the blood and carbon dioxide elimination to avoid from over distension, barotrauma, atelectasis, hemodynamic impairment, and patient-ventilator asynchrony. The choice of proper ventilation strategy is capable of preventing the progression of the lung disease and its outcomes. Incorrect mechanical ventilation methods can be associated with more damaging effects and increased mortality that named ventilator-associated lung injury. The use of adequate levels of tidal volume 6 ml/kg predicted body weight (PBW), plateau pressure kept below 30 cm H_2O, inspiratory oxygen concentration (FiO_2) as low as possible, and a permissive hypercapnia to a pH level of 7.2 are more successful strategies in protective ventilation to ARDS therapy.[79,80]

This protective ventilation has important consequences in AKI and ARDS patients. It can prevent the development of AKI by creating mild hypercapnic that is well tolerated. Mild hypercapnic acidosis has shown anti-inflammatory and cytoprotective effects.[81,82] Inactivation of calcium channels and vasodilation of vessels, decrease in NF-kappaB production and cytokines releasing are involved in protective effects of hypercapnic acidosis.[83–85]

Fluid management

Fluid accumulation has an adverse effect on recognition of AKI due to dilution of creatinine in body compartments. Therefore, an increase of 0.3 mg/dl or change more than 50% within 48 h in creatinine concentration must be considered as a diagnostic criterion of AKI.[86] Fluid management in ARDS with AKI is complicated because of two aspects: first, liberal fluid therapy is required for kidney perfusion and second, restriction of fluids with a diuretic drug can limit the amount of lung edema, reduce pulmonary capillary pressure, central venous pressure and eventually decrease mortality.[87,88] But according to a study that compared two fluid protocol therapies (liberal and conservative) with 1000 patients in 2006, showed the conservative fluid therapy using diuretics has better outcomes, including shorter duration of mechanical ventilation and ICU stays.[89]

Neutrophils elastase inhibitors

Neutrophil elastase is a serine protease secreted from neutrophils in inflammation and has a significant role in pathogenesis of AKI-induced ALI.[90] It seems that neutrophils elastase inhibitors such as Sivelestat are able to inhibit the progression of ARDS and AKI.[91,92] Sivelestat decreases neutrophil infiltration and cytokines expression in the lung[92] and has improve outcome in multiple organ failure.[93]

Antioxidants therapy

Administration of antioxidants has beneficial effects in ARDS patients with AKI. Antioxidant vitamins and trace elements such as vitamins A, C, and E, selenium and zinc have radical scavengers and antioxidant activities.[94] However, the use of high doses of

antioxidant vitamins and trace elements is not recommended in patients with nephrogenic ARDS due to renal impairment.

Vitamin C reacts directly with free radicals and can restore antioxidant property of oxidized vitamin E.[95] Zinc does not interact directly with free radicals but it can increase the activity of antioxidant enzymes such as superoxide dismutase (SOD).[96] In addition, zinc inhibits pro-oxidant enzymes such as the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, inducible NOS (iNOS).[97]

Selenium is a potent antioxidant because it can bind to hydroperoxides (H_2O_2) with more affinity than catalase.[98] SOD or synzyme mimics are catalytic drugs with potent anti-inflammatory and ROS detoxification properties.[99] It seems that SOD mimics inhibit neutrophil-mediated injuries.[99]

Diseases affecting both lungs and kidneys

There are several “pulmonary renal syndromes” that affect both the kidneys and the lungs.[100,101] These disorders are often associated with hemoptysis from diffuse alveolar hemorrhage along with renal insufficiency from either acute glomerulonephritis or other vasculitis.[57,58] Three of these most familiar diseases are Wegener's granulomatosis, systemic lupus erythematosus, and Goodpasture's syndrome.[102] Some of the known diseases with both pulmonary and renal manifestations were listed as follows:

Wegener's granulomatosis;
Microscopic polyangiitis;
Mixed cryoglobulinemia;
Henoch-Schonlein purpura;
Immune complex glomerulonephritis;
Pauci-immune glomerulonephritis;
Systemic lupus erythematosus;
Goodpasture syndrome;
Thrombotic thrombocytopenic purpura;
Allergic granulomatous angiitis (Churg–Strauss syndrome).

Conclusion

Pulmonary dysfunction is a common complication in patients with AKI that contributes to increasing the mortality rate. The kidney-lung crosstalk in AKI and ARDS is a consequence of complex biological process which leads to dysregulation of cytokines/mediators and apoptotic signaling pathways. This review summarized the most important various aspects of pathophysiology, diagnostic and treatment involved in lung injury associated with AKI. Better understanding this relation can be a gateway to novel therapeutic strategies against AKI and decrease high mortality rate during AKI-related pulmonary failure.

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