Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets

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Acute kidney injury (AKI) is a common complication in critically ill patients and subsequently worsens outcomes. Although many drugs to prevent and treat AKI have shown benefits in preclinical models, no specific agent has been shown to benefit AKI in humans. Moreover, despite remarkable advances in dialysis techniques that enable management of AKI in hemodynamically unstable patients with shock, dialysis-requiring severe AKI is still associated with an unacceptably high mortality rate. Thus, focusing only on kidney damage and loss of renal function has not been sufficient to improve outcomes of patients with AKI. Recent data from basic and clinical research have begun to elucidate complex organ interactions in AKI between kidney and distant organs, including heart, lung, spleen, brain, liver, and gut. This review serves to update the topic of organ cross talk in AKI and focuses on potential therapeutic targets to improve patient outcomes during AKI-associated multiple organ failure.

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Acute kidney injury (AKI) is 1 of the serious complications in critically ill patients because of high mortality, morbidity, and economic impact.[1–3] The incidence of AKI in hospitalized patients is high,[4] and a recent meta-analysis involving 154 studies with more than 3 million individuals reported that 1 in 5 adults and 1 in 3 children worldwide acquired AKI during a hospitalization.[5] Dialysis-requiring AKI is a severe condition with an unacceptably high mortality rate of 40% to 50%,[6] with mortality increasing to 60% to 80% with associated distant organ dysfunction states such as cardiac and respiratory failure.[7,8] Data from the Nationwide Inpatient Sample showed a major increase in the incidence of dialysis-requiring AKI in the past decade in the United States.[9] AKI is a syndrome that has a broad range of causative factors depending on different clinical settings, such as sepsis, after cardiac surgery, contrast media exposure, hemorrhage, liver failure, and severe heart failure with low output. Sepsis is the leading cause of AKI in intensive care units (ICUs),[10] and 45% to 70% of all AKI is associated with sepsis.[11–13] It is widely recognized that patients with combined sepsis and AKI have an even higher mortality rate than with each occurring individually.[11]

Can we reduce AKI-related mortality through dialysis? There has been remarkable progress in renal replacement therapy in critical care, including in hemodynamically unstable patients in the ICU by continuous renal replacement therapy or sustained low-efficiency dialysis.[14,15] However, complications of AKI significantly increased mortality in critically ill patients in the ICU,[16,17] and dialysis has not appreciably decreased mortality.[6,9,18] Although AKI in the ICU is associated with high mortality, other factors other than loss of kidney function appear to contribute to poor outcomes, because dialysis-requiring patients with AKI still had a considerably higher mortality than patients with end-stage renal disease.[19] These data strongly support the premise that AKI-induced distant organ dysfunction plays a crucial role, especially in critically ill patients (Figure 1).

For the past decade, many basic researchers have started to elucidate the mechanisms of distant organ dysfunction caused by AKI.[20] The most investigated distant organ is the lung, and several studies have demonstrated the interaction of AKI with heart, spleen, brain, liver, and gut. This review updates the recent findings on distant organ effect of AKI in addition to the previous reviews on this topic[20–25] (summarized in Table 1).

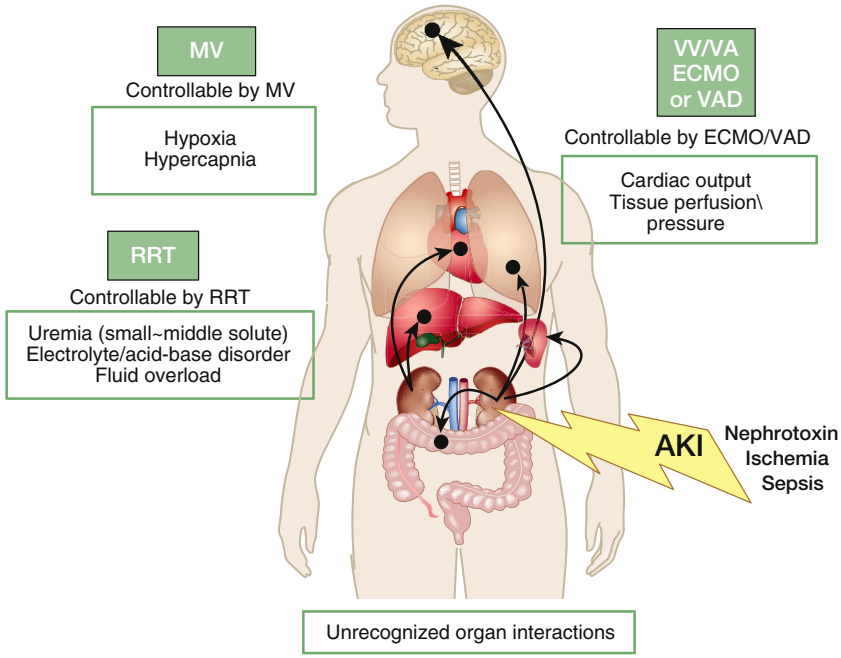

Figure 1 | Unrecognized organ interactions in AKI in the ICU. Mechanical supports including renal replacement therapy (RRT) do not sufficiently improve the outcomes of patients with acute kidney injury (AKI) treated in intensive care units, implicating unrecognized remote organ interactions with the kidney. MV, mechanical ventilation; VAD, ventricular assist device; VV/VA-ECMO, venovenous/venoarterial extracorporeal membrane oxygenation.

Ducts for air and water are connected: kidney–lung interactions in AKI

Significant epidemiologic data link kidney–lung interaction in critically ill patients. First, AKI frequently occurs in acute respiratory distress syndrome (ARDS)/acute lung injury. In a study of the National Heart, Lung, and Blood Institute ARDS Clinical Network trial, 209 (24%) of 876 patients with ARDS acquired AKI for the first 4 study days after enrollment.[26] Of note, AKI that might occur in other patients with ARDS simultaneously with lung injury could not be accounted for because of the study design of this subanalysis. In a recent prospective observational study conducted in 18 French ICUs, 1879 of 8029 enrolled patients experienced ARDS when evaluated by the new definition of Berlin criteria,[27] and AKI occurred more commonly in patients with ARDS (44%) compared with patients without ARDS (27%).[28] Moreover, AKI has a significant impact on pulmonary failure management because increases in serum creatinine levels, oliguria, and the number of antibiotics prescribed predicted a longer duration of weaning from mechanical ventilation.[29] AKI on the day of mechanical ventilation initiation was an independent risk factor for prolonged mechanical ventilation, in addition to longer mechanical ventilation duration before readiness for weaning and a higher rapid shallow breathing index.[30]

Respiratory failure frequently observed in patients with sepsis is presumably caused by systemic arterial vasodilation, vascular leakage, and subsequent pulmonary edema. Volume overload caused by AKI will amplify lung injury, which could be prevented by removing excess extracellular fluid.[31] However, several clinical studies implicate inflammation in the pathogenesis of acute lung injury complicated by AKI. Elevated blood levels of plasminogen activator inhibitor-1, interleukin-6 (IL-6), and soluble tumor necrosis factor receptors are found in patients with ARDS complicated by AKI compared with patients without AKI.[26] Recently, a high incidence of AKI was reported in a cohort of 1836 hospitalized patients with community-acquired severe and nonsevere pneumonia. Six hundred thirty-one patients (34%) experienced AKI (329 with severe sepsis and 302 with nonsevere sepsis), with higher blood IL-6 and tumor necrosis factor-α (TNF-α) levels even in nonsevere sepsis.[32]

Experimental studies using renal ischemia reperfusion injury (IRI) and bilateral nephrectomy (BNx) identified several different mechanisms by which AKI causes lung injury, including increased neutrophil infiltration, vascular permeability, dysregulation of salt and water transporters, and inflammatory cytokine and chemokine expression.[20,33–36] Some lung inflammatory reactions, such as pulmonary myeloperoxidase activity and neutrophil infiltration, were observed even 7 days after operation.[37] Although IL-6 knockout mice were resistant to lung injury induced by renal IRI and BNx,[38] it was unclear whether the protection was caused by inhibition of circulating IL-6 acting at the lung or by inhibition of pulmonary IL-6. Circulating IL-6 was found to be a mediator of lung inflammation and injury after AKI by studying effects of recombinant murine IL-6 administration to IL-6–deficient mice. Moreover, increased pulmonary chemokine (C-X-C motif) ligand 1 (CXCL1) expression induced by IL-6 was observed in AKI, and