In-Depth Review

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How Does Continuous Renal Replacement Therapy Affect Septic Acute Kidney Injury?

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Abstract
Sepsis is the leading cause of acute kidney injury (AKI) in the intensive care unit. As the most common treatment of septic AKI, it is believed that continuous renal replacement therapy (CRRT) can not only maintain the water balance and excrete the metabolic products but also regulate the inflammation and promote kidney recovery. CRRT can remove the inflammatory cytokines to regulate the metabolic adaption in kidney and restore the kidney recovery to protect the kidney in septic AKI. Second, CRRT can provide extra energy supply in septic AKI to improve the kidney energy balance in septic AKI. Third, the anticoagulant used in CRRT also regulates the inflammation in septic AKI. CRRT is not only a treatment to deal with the water balance and metabolic products, but also a method to regulate the inflammation in septic AKI.
Video Journal Club 'Cappuccino with Claudio Ronco' at https://www.karger.com/Journal/ArticleNews/223997?sponsor=52.

Introduction

Acute kidney injury (AKI) is a serious complication in critically ill patients because of high mortality, morbidity, and economic conditions [1, 2]. Sepsis is the leading cause of AKI in the intensive care unit (ICU), and 45–70% of all AKI is associated with sepsis [3–7]. Dialysis requiring AKI is a severe condition with a high mortality rate of 40–50%. When associated with a distant organ dysfunction such as cardiac or respiratory failure, the mortality increases to 60–80% [8–11]. Continuous renal replacement therapy (CRRT) is the most common therapy for septic AKI [12–16]. The main reason for CRRT being widely used in critically ill patients is less hemodynamic instability. CRRT is a complex treatment and many confounders can affect the body directly. As the hemodynamically tolerant in remove of the water and metabolic products during CRRT has been well discussed for many times [17], the present article focuses on other effects of CRRT in septic AKI. Clinicians should pay attention not only to the well-known aspects of CRRT in septic AKI [18, 19] but also to other effects such as clearance of cytokines, anticoagulant, and intervention of nutrition. In this review, we will discuss the clear-

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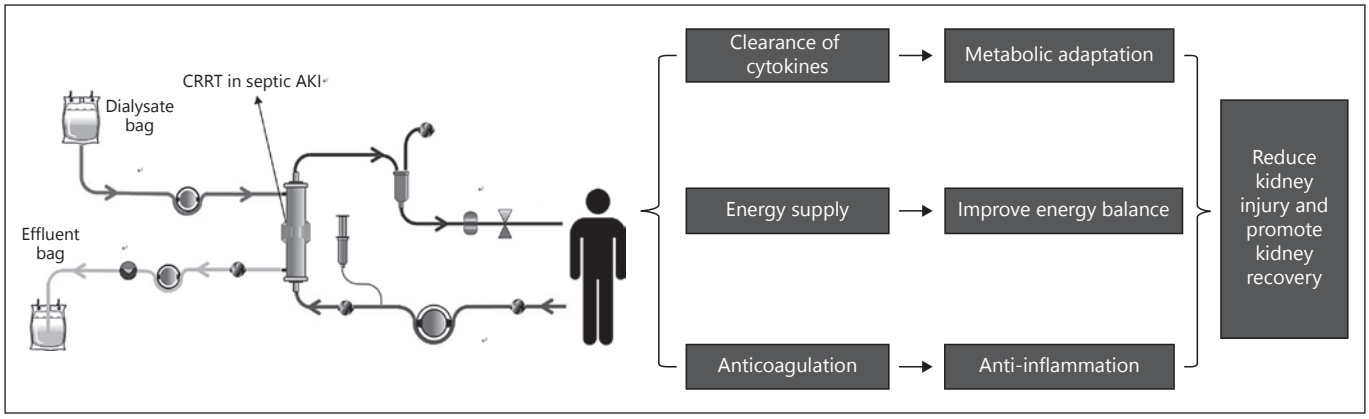

Fig. 1. The mechanism of CRRT affects septic AKI.

ance of inflammation cytokines, anticoagulation, and intervention of energy balance during CRRT in septic AKI (Fig. 1).

The Role of CRRT in Inflammation and Metabolic Adaptation in Septic AKI

It has been well confirmed that high cytokine concentration is associated with slow renal recovery and increased mortality in septic AKI [20]. Cytokines are water-soluble, middle molecules (molecular weight 0.5–60 kDa), which exist in free form in the circulation [21]. During the last decade, the extracorporeal removal of cytokines has been proposed as one of the therapeutic options to reduce these overexpressed molecules [22]. With the improvement in extracorporeal blood purification (EBP) techniques and membrane materials, CRRT is widely used in critically ill patients. It is well known that the efficiency of cytokine removal depends on the molecular weight of cytokines, EBP techniques, and membrane pore sizes. The smaller the molecular weight of cytokines is the more cytokines will be removed in CRRT. The cutoff value of standard CRRT is 30–40 kDa [21], and the molecular weight of common cytokines such as interleukin (IL) 1 beta is 17 kDa, IL-1RA is 15–20 kDa, IL-2 is 15 kDa, IL-6 is 26 kDa, IL-8 is 8 kDa, macrophage migration inhibitory factor (MIF) is 12.5 kDa, IL-10 is 35–40 kDa and tumor necrosis factor (TNF) α is 51kDa. So among the most included cytokines, only IL-10 and TNF-α are outside the cutoff value of standard CRRT; all other cytokines can be slowly removed in standard CRRT [21, 23–25]. However, certain clinical research declared that the concentration of plasma cytokines makes no difference during CRRT, though some cytokines can be detected in the filtrate fluid [24]. Therapies such as high-volume hemofiltration or high cut-off membrane may increase the clearance of inflammatory cytokines, but whether this will benefit the patients is still unknown [22, 26]. Furthermore, no consensus has been performed about which kind of EBP techniques or membrane is able to most benefit the critically ill patients. The clearance of cytokines and ligands may affect the immune pathology and reduce the metabolic adaptation in septic AKI [27]. By now, a few benefits have been confirmed in clearance of inflammatory cytokines in septic AKI [28]. More efficient and special EBPs are emerging with the aim of modulating inflammation in septic AKI.

AKI is a growing global health concern [1, 29]. However, no treatment is currently available to prevent it or to promote kidney repair after injury. How the clearance of inflammatory cytokines affects the pathophysiology of septic AKI is still unknown, but some research in cancer may point to some suggestions. Macrophages play an important role in the immune monitor or progression of inflammatory diseases. Macrophages migrate and infiltrate to the infection site to clear mutated cells or the pathogen. Animal models demonstrate that macrophages represent a major contributor to the inflammatory response to AKI [30]. Emerging data from human biopsies also corroborate the presence of macrophages in AKI and their persistence in progressive chronic kidney disease; we highlight our current understanding of the mechanisms by which macrophages contribute to injury and repair after AKI. Recent analysis of macrophage populations carefully isolated by differential expressions of Ly6C in $CD11b^+$ cells in the kidney injury [31, 32] confirmed that results of previous studies have shown that macro-

phages (predominantly CD11b^{+}/Ly6C^{high} cells) [30, 31] in the kidney early expressed proinflammatory genes, whereas macrophages within the kidney during the tubular repair phase (CD11b^{+}/Ly6C^{intermediate} cells) expressed more wound-healing markers [30]. It has been proved that decreased MIF concentration in cancer can induce macrophage polarization from proinflammatory macrophages (predominantly CD11b^{+}/Ly6C^{high} cells) to pro-wound healing macrophages (CD11b^{+}/Ly6C^{intermediate} cells) [33]. The MIF level decreases obviously during CRRT or hemodialysis and can improve the prognosis [23, 34]; however, how it works is still unknown and the MIF plasma pool is reconstituted early after the termination of hemodialysis from unknown sources. Probably the same thing happens during CRRT of septic AKI patients. The decreased MIF level potentiates the macrophage of kidney polarization from proinflammatory macrophages to pro-wound-healing macrophages [35]. The role of other cytokines removed during CRRT in septic AKI is still unknown.

Sepsis and inflammation at the tissue and cellular levels are associated with decreased levels of intracellular adenosine triphosphate (ATP) and mitochondrial injury in the kidney [36]. This has been considered a result of metabolic adaptation [37]. Metabolic adaptation is like a protective response to inflammation. It increases the circulating levels of glucose by stimulating glycogenolysis and gluconeogenesis [38] and switches metabolism from regulatory energy pathways toward aerobic glycolysis, similar to the Warburg effect in cancer cells [37]. The elevated glucose enables the elevation of aerobic glycolysis in immune cells, which provide metabolic intermediates necessary for the expansion of biomass in immune cells and promotion of tissue repair [39]. Metabolic adaptation participates in triggering inflammation and preparing the kidney cell to withstand the state of hyper-inflammation for clearance of pathogen. But the excessive metabolic adaptation causes uncontrolled hyperglycemia and exhaustion of immune cells, and this plays a key role in immunosuppression and secondary infection. Stimulating regulatory energy pathways can mitigate the kidney injury in sepsis [40, 41]. CRRT can neutralize the hyperglycemia and inflammatory cytokines and mitigate the excessive metabolic adaptation. It has been approved that the increased inflammatory cytokines IL-1β, IL-6 and other cytokines constitute the main cause of insulin resistance [42, 43]. During the CRRT in septic AKI, the clearance of IL-1β, IL-6 may improve the metabolism by increasing the insulin sensitivity. CRRT can also remove the glucagon (molecular weight is 3.4 kDa) and switch metabolism from gluconeogenesis to biogenesis, and promote kidney recovery. But in sepsis, we always focus on the concentration of high molecular weight cytokines. The clearance of small molecular weight cytokines and ligands can also mitigate the activity of cytokines in inflammation, and may play a great role in metabolic adaptation in septic AKI.

CRRT Can Improve the Energy Balance in Septic AKI

Mitochondrial injury and decrease in intracellular ATP are the main characteristics of septic AKI [36], which determines the fate of tissue repair and promote recovery of organ function. A 7-year observational study in 880 units from 46 countries demonstrated that the majority of ICU patients do not receive the recommended amount of calories and proteins [44]. This makes the poor energy balance of the septic AKI patients more serious, thereby leading to the glucose deficiency in the acute stage of shock, which increases gluconeogenesis, due to which there is a rapid depletion of the substrate stored as glycogen in the liver and muscles.

CRRT affects the metabolism of the body by regulating the metabolic adaptation and also can directly or indirectly affect the energy supply in septic AKI. The main reason for CRRT being widely used in critical ill patients is less hemodynamic instability, but the continuous treatment can also induce continuous extra nutrition supply and lose. A prospective study of 10 critically ill adult patients undergoing continuous vein-venous hemofiltration, through detecting the glucose and citrate concentration of pre-filter and post-filter, calculated the extra glucose and citrate intake during CRRT. In this study, substantial uptake of both glucose and citrate delivered exogenous energy and provided 0–512 kcal/day [45], if the replacement fluid contains a high level of lactates, the values exceeding 1,300 kcal during 24 h of treatment [46]. Glucose, citrate, or lactates added to the replacement fluid are absorbed into the body during CRRT, which can provide extra energy by tricarboxylic acid cycle.

Other than providing energy to the body directly, CRRT can also reduce the formation of intestinal wall edema significantly, mainly associated with massive fluid resuscitation in the initial period of treatment of septic shock or during intensified systemic inflammatory response syndrome. The effects of CRRT on fluid balance described above can help in the early initiation (up to 48 h) of enteral nutrition [46], which is recommended in

the guidelines of many scientific societies (i.e., European Society for Nutrition and Metabolism, American Society for Parenteral and Enteral Nutrition, International Symposium on Intensive Care and Emergency Medicine). The initiation of CRRT can reduce the existing edema, thus favoring affective gastrointestinal motility and the ability of absorbing nutrients administered eternally, which is the preferable route in ICU patients.

As CRRT is highly used in ICU patients, clinicians must pay attention not only to positive aspects of this form of extracorporeal therapy but also to its potential adverse effects. The impact of CRRT on the possibility to administer adequate nutritional intervention to critically ill patients is significant due to increased loss of amino acids, L-carnitine, and some vitamins as well as microelements during the procedure [46].

The Role of Anticoagulation During CRRT in Septic AKI

CRRT is commonly used for critically ill patients with AKI. Clotting in the extracorporeal circuit shortens the filter and catheter lifespan, causes blood loss, and decreases solute clearance, consequently reducing the effectiveness of CRRT and increasing treatment cost and workload. Systemic or regional administration of an anticoagulant is the most essential condition of CRRT treatment. We always focus our attention on circuit loss, filter failure, catheter dysfunction, and side effects of bleeding, but ignore the anticoagulation of CRRT, which can regulate inflammation in septic AKI. The activation of coagulation and inflammation are important and intertwined mechanisms in the pathogenesis of serious infection and sepsis [47, 48]. There is extensive cross-talk between these 2 systems, whereby inflammation leads not only to the activation of coagulation, but coagulation also considerably affects inflammatory activity [49]. Inflammatory cytokines can activate the clotting system. This may result in the formation of microvascular thrombosis contributing to multiple organ dysfunctions in patients with sepsis [50]. Conversely, activated coagulation proteases may affect specific cellular receptors on inflammatory cells and endothelial cells and thereby modulate the inflammatory response [51].

It has been proved that anticoagulation promises to protect organ dysfunction and improve clinical prognosis in sepsis. A nation-wide multicenter retrospective registry in 2,663 sepsis patients in Japan indicated that anticoagulant therapy may be associated with a survival benefit in patients with sepsis-induced coagulopathy and very severe disease [52]. In cecal ligation and puncture-induced sepsis rats, unfractionated heparin can attenuate the intestinal injury induced by sepsis [53]. Both unfractionated and low-molecular-weight heparin can decrease the inflammation, lung injury, and mortality in lipopolysaccharide-induced sepsis in rats [54, 55]. In a study of 341 patients with septic shock, it was shown that heparin binding protein (HBP) increased the permeability of vascular endothelial cell in vitro. Unfractionated heparins and low molecular weight heparins that counteracted permeability increased by HBP in vitro were potential inhibitors of HBP-induced permeability [56].

Though anticoagulation with citrate has an unknown effect on the immune function, anticoagulation during CRRT may have an additional benefit to septic AKI. Whether heparin will be more suitable in the CRRT of septic AKI or some subgroup of sepsis is still unknown. Randomized controlled trials are eagerly awaited to determine the use of heparin during septic AKI. The risk of hemorrhage is a major limitation of heparin in patients with severe infection or sepsis who are already vulnerable to this complication due to low levels of platelets and coagulation factors [57]. Given the lower risk of circuit loss, filter failure, bleeding, and HIT, regional citrate is recommended by the recent Kidney Disease: Improving Global Outcomes guideline [58].

Conclusion

Metabolic adaptation in septic AKI results in decreased levels of intracellular ATP and stimulates inflammation in the kidney, but the excessive inflammation is harmful. CRRT as the most common treatment in septic AKI can remove inflammatory cytokines and neutralize the exaggerated inflammation to reduce kidney injury and promote kidney recovery. The clearance of inflammatory cytokines, especially MIF, promises to play an important role in reducing kidney injury and promote recovery. The decreased levels of IL-1β and IL-6 can neutralize the excessive metabolic adaptation and promote kidney recovery. CRRT can provide extra energy supply to improve the kidney energy balance in septic AKI. The anticoagulant used in CRRT can also regulate the inflammation in septic AKI. CRRT is a treatment not only to deal with the water balance and metabolic products, but also to regulate the inflammation of sepsis. Advances in modes and membranes are investigated and promise to be helpful in the treatment of sepsis.

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Ethics Statement

Not applicable.

Disclosure Statement

The authors declare that there are no competing interests to disclose.

Availability of Data and Material

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Author Contribution

J.Z., Y.Y., and C.R. contributed in manuscript writing and editing. All authors read and approved the final manuscript.

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