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Renal Oxygenation and Hemodynamics in Kidney Injury

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Abstract

Acute kidney injury continues to be a major therapeutic challenge. Despite significant advances in cellular and molecular pathophysiology of AKI, major gaps in knowledge exist regarding the changes in renal hemodynamics and oxygenation in the early stages and through the continuum of AKI. Particular features of renal hemodynamics and oxygenation increase the susceptibility of the kidney to sustain injury due to oxygen demand-supply mismatch and also play an important role in the in the recovery and repair from AKI as well as the transition of AKI to CKD. However, lack of well-established physiological biomarkers and non-invasive imaging techniques limit our understanding of the interactions between renal macro and microcirculation and tissue oxygenation in AKI. Advances in our ability to assess these parameters in pre-clinical and clinical AKI will allow the development of targeted therapeutics to improve clinical outcomes.

Introduction

Acute kidney injury (AKI) is a common clinical entity affecting up to 21.6% of hospitalized patients worldwide [1]. It is associated with high mortality and development of chronic kidney disease (CKD), even with apparent renal recovery [2]. Unfortunately, this syndrome continues to be a therapeutic challenge due to the multifactorial etiology, repeated insults, various pre-existing comorbidities and predisposing conditions, and the complicated pathophysiology of AKI. There have been significant advances in our understanding of the cellular and molecular pathways in tubular cell injury in AKI. However, early changes in renal hemodynamics and tissue oxygenation play an important role in the pathophysiology and need to be better studied. In the present article, we review renal oxygenation and hemodynamics in the context of common etiologies of AKI.

Renal Oxygenation and Hemodynamics

Kidney tissue oxygenation is determined by oxygen in arterial blood, oxygen consumed by the cells, and arterial-to-venous oxygen shunting [3]. Particular features of renal oxygenation increase the susceptibility of the kidney to hypoxia and impact the pathophysiology of AKI. As is known, there is regional heterogeneity in renal perfusion, with the medulla being relatively hypoxic compared to the cortex. Importantly, the outer

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medullary region is further impacted due to the high metabolic requirements of the thick ascending limbs in the face of diminished oxygen delivery in this region [4]. Majority of oxygen consumed by the kidney is utilized for sodium transport, while the rest is utilized for other cellular activities referred to as basal metabolism. Changes in the ratio of oxygen consumption and tubular sodium reabsorption have been interpreted to indicate altered transport efficiency. However, this interpretation assumes a fixed basal metabolism unaffected with changes in sodium transport, which is not always true [5]. Maneuvers that change GFR and sodium transport can independently change basal metabolism.

Increase in renal blood flow (RBF) to the kidney simultaneously increases GFR under most physiological conditions, which increases tubular oxygen consumption linked to increased reabsorptive sodium load. In fact, renal oxygen extraction remains stable over a wide range of RBF, indicating the increased oxygen delivery is counteracted by increased oxygen consumption [6]. At the molecular level, several factors have been identified in the regulation of renal oxygenation including nitric oxide and angiotensin II. Another important molecular regulator of renal oxygenation is hypoxia inducible factor-1 alpha (HIF-1α). This transcription factor regulates several downstream proteins in oxygen delivery and consumption and plays an important role in the cellular response to hypoxia [7].

In terms of renal hemodynamics in AKI, changes in RBF at the whole kidney level, glomerular hemodynamics at a single nephron level and peritubular capillary microcirculation need to be considered. The technique of renal micropuncture allows the measurement of several proximate parameters in glomerular filtration. It was elemental in elucidating the pathophysiology of ischemic and nephrotoxic AKI in the past, but limited information in sepsis-AKI is available. Recent publication by the Acute Dialysis Quality Initiative (ADQI) workgroup [8] has urged that a better understanding of the interactions between systemic, total renal, and glomerular hemodynamics, including the role of tubuloglomerular feedback (TGF) in AKI is needed. Better imaging techniques that would allow direct visualization of renal macro and microvasculature and tissue oxygenation are needed to provide new insights into AKI.

Alterations in Renal Hemodynamics and Oxygenation in AKI Sepsis-Associated AKI

AKI is a common and devastating complication in sepsis. Reduction in total RBF as the etiology in sepsis-associated AKI (sAKI) has been called in question by various studies reporting normal or increased RBF. Langenberg et al [9] found increased or unchanged RBF in 38% of animal studies of sepsis. In sAKI in sheep, an increase in RBF corresponding to increase in cardiac output was seen from 24 till 48 hours after E. coli infusion [10]. However, in hyperdynamic sepsis due to fecal peritonitis in sheep, reduction in RBF at 12 hours was observed [11]. In septic mice, early (4 hours) and persistent (18 hours) reductions in RBF have been reported [12,13]. Overall, there is significant variability in RBF in sAKI depending on species and model of sepsis, especially, in the early stages. Human data is limited, but a recent study demonstrated reduced RBF measured by phase-contrast MRI in established sAKI, albeit, with significant intra-group variability [14]. Data on regional

perfusion or glomerular hemodynamics is minimal. In one study using lipopolysaccharide (LPS) bolus in rats, afferent arteriolar vasoconstriction leading to reduced transcapillary hydraulic pressure was observed in hypodynamic sepsis [15]. Glomerular hemodynamics in hyperdynamic sepsis has not been examined.

In sAKI, early changes in renal oxygenation have been examined. Tran et al, examined tissue oxygenation in LPS model in mice at 18 hours using blood oxygen level-dependent (BOLD) MRI and found no difference compared to pre-LPS infusion [13]. However, in mice with cecal ligation and puncture, tissue hypoxia at 4 and 6 hours was demonstrated by immunohistochemical staining with pimonidazole [12]. At 3 hours after E.Coli bacteremia or endotoxemia, renal oxygen consumption, calculated by the product of RBF and renal oxygen extraction, was examined in rats [16]. Renal oxygen delivery was decreased but renal oxygen extraction was increased in both conditions. Sodium transport was decreased in both, hence, renal oxygen consumption factored for sodium reabsorption was increased in both. In another study in pigs with endotoxin infusion for 24 hours, renal oxygen extraction increased at 12 hours and remained persistently elevated at 24 hours [17]. In the above studies, renal oxygen utilization was increased despite a reduction in GFR and the filtered tubular load. This indicates an inefficiency in oxygen utilization for transport and/or changes in basal metabolism of tubular cells as discussed above.

Ischemia-reperfusion

An important cause of AKI with a high degree of mortality is ischemia-reperfusion (IR) injury commonly seen in ICU patients. Early studies utilizing renal micropuncture have examined glomerular hemodynamics in rodent models of IR and found persistent preglomerular vasoconstriction and reduction of regional blood flow to outer medulla [18]. Tubular injury can directly impact GFR by activating TGF. We have previously reviewed and published on the role of TGF in the pathogenesis of AKI [19,20]. Increased sensitivity to vasoconstrictors along with abnormal renal autoregulatory responses have also been observed in IR [18-21].

Recent studies have examined RBF and oxygenation in animal models of IR. In rats with 30 minutes of ischemia, RBF and cortical and medullary oxygenation were persistently reduced at 3 hours after reperfusion [22]. Similarly, in pigs with 45 minutes of aortic cross-clamping, reduced oxygenation and persistent hypoxia at 4 hours of reperfusion was observed [23]. Using MRI in rats before and after 45 minutes of ischemia followed by reperfusion for approximately 100 minutes, global reduction in tissue oxygenation during ischemia was observed [24]. Cortical oxygenation was at baseline after reperfusion, but outer medullary oxygenation remained persistently low. Interestingly, Abdelkader et al [25] did not find any differences in cortical and inner medullary oxygenation from baseline during reperfusion in rats with 60 minutes ischemia and 120 minutes reperfusion. This was likely due to both the oxygen delivery and oxygen consumption being significantly decreased in this time period. Outer medullary oxygenaton was not reported, but they did find evidence of hypoxia, especially in the outer medulla as evidenced by pimonidazole immunohistochemistry. Tissue oxygenation beyond 3-4 hours of reperfusion has not been examined. Late changes in renal

hemodynamics and oxygenation may be important in the recovery/repair from AKI and transition of AKI to CKD.

Studies examining renal hemodynamics and oxygenation in clinical AKI are limited. Redfors et al [26] studied renal hemodynamics and oxygenation in post-cardiac surgery patients with and without AKI. They noted that noted that although GFR, RBF, and sodium resorption were lower in the AKI group, renal oxygen extraction and oxygen consumption factored for sodium reabsorption were nearly 2-fold higher. Sward et al [27] found loop diuretics improved renal oxygenation by reducing tubular-transport related oxygen consumption. However, Lassnigg et al [28] demonstrated that GFR decreased by 12% when furosemide was used in low-risk cardiac surgery patients. Since, theoretically furosemide can lead TGF activation by increasing distal delivery of sodium, further studies on the dose and timing of loop diuretics are needed to determine their utility in AKI. Major limitations in studying renal hemodynamics in clinical AKI are the lack of physiological biomarkers and non-invasive imaging techniques for real-time changes tissue oxygenation and hemodynamics. Recent advances in methodologies to assess such physiological biomarkers was recently reviewed by the ADQI workgroup [29]. They discussed in details the need for physiological biomarkers not only in the early stages of AKI to assess alterations in renal microcirculation and tissue oxygenation that increase the susceptibility to AKI, but throughout the continuum of AKI to allow appropriate therapeutic manipulations.

In summary, renal hemodynamics and oxygenation have a significant role in the pathophysiology of AKI. Both pre-clinical and clinical studies indicate that despite reduced GFR and tubular reabsorptive load, oxygen extraction and consumption by the kidney is higher in AKI. This indicates either an inefficiency of the oxygen utilized for sodium transport or the utilization of oxygen for other non-transport processes. Physiological biomarkers and techniques to study renal hemodynamics and tissue oxygenation and the development of novel therapeutic strategies to preserve their integrity in patients with AKI are essential.

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