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Review

New insights into the mechanisms of acute kidney injury in the intensive care unit☆

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Abstract Acute kidney injury is a frequent complication in the intensive care unit that is associated with increased mortality and morbidity. Traditional models consider reductions of global renal blood flow as the cause of acute kidney injury. However, a complex interplay between ischemia-reperfusion injury and inflammation may lead to intrarenal hypoperfusion and acute kidney injury. The role of changes of global renal blood flow as a cause for acute kidney injury remains controversial, especially in sepsis-induced acute kidney injury.

1. Introduction

Evaluating renal function in the context of systemic hemodynamics is a cornerstone of intensive care medicine. Interventions taken in the intensive care unit (ICU) such as use of fluids or vasoactive and inotropic agents are often instituted with the goal of effectively resuscitating or supporting a failing kidney and preventing acute kidney injury (AKI). The diagnosis of AKI has been hampered by imperfect, insensitive, and slow laboratory tests. The absence of early sensitive markers of AKI is, in part, related to limited understanding of AKI and affects of the ability to intervene early and successfully. The traditional differentiation between prerenal azotemia and AKI is a simplification that has been challenged by recent preclinical and clinical studies.

1.1. Definition and incidence

Acute kidney injury represents an abrupt and sustained decrease in kidney function [1]. It manifests as a decrease in urine output followed by an increase in serum creatinine. Most definitions of AKI are based on these 2 variables, serum creatinine and urine output, and for a long time, there were many different definitions of AKI that complicated the comparison of studies and hampered clinical research. The RIFLE (risk, injury, failure, loss of function and end-stage kidney disease) criteria have emerged as a commonly accepted way to define and grade the severity of AKI in the ICU [2] (Fig. 1). Another commonly used definition was derived from the observation that even smaller changes in serum creatinine, for example, after cardiac surgery, affect outcome [3]. The Acute Kidney Injury Network (AKIN) definition defines AKI as an abrupt (within 48 hours) reduction in kidney function with an absolute increase in serum creatinine ≥ 0.3 mg/dL (≥ 26.4 μmol/L) or $\geq 50\%$ (1.5-fold from baseline), or a reduction in urine output less than 0.5 mL/kg per hour for more than 6 hours [4]. Both definitions have limitations, and a third definition proposed more recently by the Kidney Disease Improving Global

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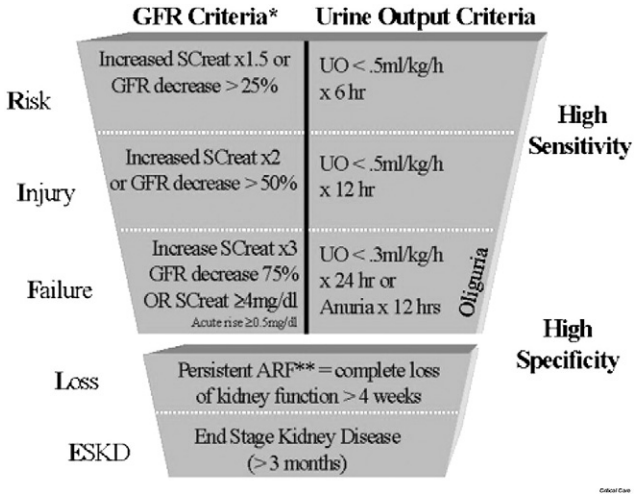

Fig. 1 Levels of acute kidney injury as defined by the Second International Consensus Conference of the Acute Dialysis Quality Initiative Group: the RIFLE (Risk, injury, failure, loss of function and end-stage kidney disease) criteria. UO = urine output; GFR = glomerular filtration rate; SCreat = serum creatinine; ARF = acute renal failure; ESKD = end-stage kidney disease. With open access permission from *Crit Care* 2004;8(4):R204–12.

Outcomes group aims to combine the advantages of RIFLE and AKIN definitions [5]. KIDGO defined AKI as either an increase in serum creatinine by 0.3 mg/dL within 48 hours or an increase of serum creatinine by 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days or a decrease of urine volume to less than 0.5 mL/kg per hour for 6 hours. The group further defined 3 stages of AKI: stage 1 is defined as either an increase of serum creatinine by 1.5 to 1.9 times or by 0.3 mg/dL above baseline or a decrease of urine output to less than 0.5 mL/kg per hour for 6 to 12 hours. Stage 2 is defined as an increase of serum creatinine by 2.0 to 2.9 times baseline or a decrease of urine output to less than 0.5 mL/kg/h for more than 12 hours. Stage 3 is defined by a tripling of serum creatinine or an increase of serum creatinine to more than 4.0 mg/dL or the initiation of renal replacement therapy or anuria for more than 12 hours.

The incidence of AKI in a general surgery population has been reported as 0.8% when AKI was defined as a postoperative estimated creatinine clearance of 50 mL/min or less [6]. After major surgery, however, the incidence of AKI defined by RIFLE criteria can be as high as 36.7% and is associated with an increase of 90-day mortality from 3% without AKI to 11 % with any stage AKI [7]. After elective cardiac surgery, the incidence of AKI defined by AKIN criteria is 27.9% and the 5-year risk of death in patients with AKI was 26.5% compared with 12.1% in patients without AKI [8].

The incidence in ICU patients is significantly higher. Using RIFLE criteria to identify the incidence of AKI, Mandelbaum et al in 2011 [9] found an incidence of AKI of 57% in critically ill patients and the mortality with stage 1 AKI defined by AKIN criteria was 13.9% compared with 6.2% in patients without AKI. Nisula et al [10] described a slightly lower incidence (39.3%) when using the KIDGO definition in 17 Finnish ICUs. The 90-day mortality of patients with AKI was 33.7% compared with 16.6% in patients without AKI. These results emphasize the importance and clinical relevance of AKI in the ICU.

There are some common clinical scenarios that are associated with a high incidence of AKI. For example, patients with preexisting renal insufficiency undergoing major cardiac surgery have a likelihood of developing AKI after surgery. This may, however, not be evident early in the postoperative course because hemodilution with the use of cardiopulmonary bypass also dilutes serum creatinine concentrations. If mannitol was added to the cardiopulmonary bypass circuit, diuresis may actually be brisk early after surgery despite a profound renal insult. The diagnosis of AKI in these patients is frequently delayed. After general surgery, AKI is rare and the cause is often multifactorial: preexisting renal insufficiency, intraoperative hypovolemia, vasopressor use, and nephrotoxic medication may cause sufficient renal injury to progress toward AKI. However, low urine output in the early postoperative period may also be caused by hypovolemia and prerenal azotemia. Early after surgery in the postanesthesia care unit, it may difficult to differentiate prerenal azotemia and intrinsic AKI. Serum creatinine is too slow and insensitive to be useful in this scenario.

2. Renal physiology

The kidney is exquisitely sensitive to hypoxic injury due to the precarious match of renal blood flow (RBF) to oxygen utilization. Tubular cells of the renal medullary thick ascending limb have the highest oxygen extraction ratio (oxygen consumption [VO_2] to oxygen delivery [DO_2] ratio) of any cell in the human body; approximately 80% of delivered oxygen is used [11]. This results in a relatively hypoxic renal medulla with a tissue pO_2 of around 10 to 20 mm Hg [12]. These high O_2 requirements of the medullary thick ascending limb are due to Na reabsorbtion, which is a highly ATP-dependent process. Interestingly, Na reabsorption and therefore O_2 consumption are closely correlated with glomerular filtration rate (GFR); the more ultrafiltrate is delivered to the distal nephron, the more Na is reabsorbed, and consequently, the more oxygen consumed. This "flow dependence" is inherently matched by peritubular perfusion so that VO_2/DO_2 relationship does not reach a critical value under physiologic conditions [11]. In other words, although increased blood flow to the kidney may increase GFR, it will also increase peritubular perfusion, and thus, oxygen consumption and oxygen delivery should be matched.

3. Mechanisms of AKI

3.1. Ischemia/Reperfusion

Renal ischemia secondary to hypoperfusion triggers a cascade of events that results in loss of renal cellular