Review Article

Fluid management in the perioperative setting: mind the kidney

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Abstract: Acute kidney injury (AKI) is one of the most frequent complications in critically ill patients and in the perioperative setting. The anatomical structure and the microvasculature of the kidney makes it highly vulnerable to hypoxia. Although fluid therapy is considered crucial in situations where improvement of cardiac output is needed, it can also contribute to AKI development when administered inappropriately. Hemodilution and anemia during cardio-pulmonary bypass have been demonstrated to be risk factors for AKI and they are likely to be a consequence of fluid administration. In order to assess the perfusion of the kidneys it is necessary to investigate the determinants of delivery of oxygen at the microcirculatory level. Indeed, fluids can decrease the capillary hematocrit and the functional capillary density, affecting the renal oxygenation and increasing the risk of AKI. Monitoring sublingual microcirculation can be a reliable tool to guide fluid administration, aiming to prevent or improve perioperative AKI.

Keywords: Acute kidney injury (AKI); microcirculation; critical care; fluid therapy; surgery

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Introduction

The identification of oliguria as a sign of renal failure and serum creatinine as marker of renal function dates back to nearly two centuries ago. Despite that, the standardization of acute kidney injury (AKI) using serum creatinine and urinary output parameters occurred only with the definition of the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria in 2004. Indeed, in this classification, a urinary output of less than 0.5 mL/kg/hr for more than 6 hours was introduced as an alternative criterion to a rise in serum creatinine by 1.5-fold from baseline. Modifications of this definition took place with the AKI Network (AKIN) classification in 2007 and the Kidney Disease Improving Global Outcomes (KDIGO) classification in 2012. The incidence of AKI varies between one-third to two-thirds of patients admitted to intensive care units (ICUs) when defined by the sensitive RIFLE, AKIN, or KDIGO criteria and it is increasing over time as is the use of renal replacement therapy (RRT) (1).

However, the lack of sensitive and specific diagnostic criteria for metabolic renal impairment hampers the prevention of AKI in critical patients, and the optimization of hemodynamics applying a goal-directed therapy with fluid administration may not be sufficient to improve kidney oxygenation.

AKI is a frequent complication in the perioperative setting and it is associated with major morbidity and mortality (2). The incidence of AKI after surgery ranges from 18% to 47% and it is most common in cardiac surgery patients undergoing open heart surgery with the use of the cardiopulmonary bypass (CPB) (3). The pathophysiology of AKI is usually multifactorial and is associated to both intraoperative events and postoperative complications such as hemodynamic instability, sepsis, and drug toxicity (4). A common mechanism

in the development of AKI is the renal microcirculation impairment affecting tissue oxygenation. Fluid administration is a very common practice in perioperative period setting, which contributes to hemodilution and leads to a decrease of kidney oxygenation and subsequently, AKI. As a consequence, from a pathophysiological point of view, it is of particular importance in perioperative setting to monitor the microcirculation, that is the primary site of oxygen exchange.

The aim of this review is to give an overview of the implications of fluid administration to kidney oxygen consumption and delivery, and to discuss how this may contribute to the risks of AKI in the perioperative setting. Finally, it will be proposed that monitoring of sublingual microcirculation could be used as a hemodynamic monitor to optimize the renal perfusion and oxygenation.

Renal circulation and metabolism

The kidney has the highest blood flow per unit organ weight in the body where it receives 20–25% of the cardiac output which corresponds to 1,000–1,200 mL of blood per minute. Despite this, the oxygen extraction by the kidney is only approximately 10–15% (5). Blood reaches the kidney through the renal artery, proceeds through its branches (the interlobar arteries, the arcuate arteries, and then the interlobular arteries), before entering the afferent arterioles, the glomerular structures and the efferent arterioles. The efferent arterioles of the juxtamedullary glomeruli radiate many peritubular capillaries in the renal cortex, and vasa recta crossing the medulla. The renal microcirculation is intricate and crucial to renal functions and oxygen supply. Renal blood flow has three main regulatory mechanisms that mediate the stability of the organ: the intrinsic autoregulatory mechanism, the renal sympathetic nerve activation and the renin-angiotensin-aldosterone (RAA) system (6). In order to allow the countercurrent exchange and efficient concentration of urine, tubules and vessels form loops in the medulla, causing a oxygen transfer from the arterial to the venous branches of the vasa recta and this is the reason of a lower O_2 tension in the deeper portions of the medulla (7).

Only 5% to 15% of the renal blood flow is directed to the medulla where the partial pressure of oxygen is around 30–40 mmHg in the outer medulla and 15 mmHg in the inner medulla (differently from the cortex where it is 40 to 60 mmHg). The amount of adenosine triphosphate needed for the Na/K pump is the main determinant of renal oxygen requirement (8) and accounts for approximately 90% of the total oxygen consumption in the kidney. The highly complex architecture of the renal microvasculature in combination with high energy demand and the low oxygen pressures make the kidney a highly vulnerable organ to hypoxemic injury.

It is clear that the pathophysiology of AKI does not involve only low cardiac output or hypotension, but rather is more complex and requires further investigation (9). Even in absence of clinically evident renal hypoperfusion or macro-circulatory changes such as low global cardiac output, microcirculatory dysfunction can lead to renal hypoxia (10). For example, this can occur in early phases of sepsis when fluids are being administered during developing or established AKI and the increased cardiac output determines the progression of a "hyperdynamic state".

The risks of fluid therapy on the kidney

It is known that fluid therapy is considered crucial to improve the circulation and in parallel the renal perfusion. In particular, it is well-established in the treatment of sepsis, where prompt fluid resuscitation is needed in order to preserve the intravascular volume and systemic hemodynamics. However, an excess of fluid therapy can also lead to hemodilution which may contribute to AKI (11). In addition, patients with defective cardiac function are prone to fluid overload due to the activation of RAA system and increasing of antidiuretic hormone which may worsen the excess of fluids (12). Fluid administration also increases the workload of the kidneys since an extended need for filtration of electrolytes, such as sodium and chloride, may increase reabsorption and consequently the oxygen consumption of the tubular cells.

Legrand *et al.* found that half of the oliguric ICU patients were not renal responders to fluid challenge although they did show a macrohemodynamic response. This suggests a disassociation between the hemodynamic and the renal response to fluid administration (13). Furthermore, it should be taken into account that fluids are not different from drugs since they carry side effects such as AKI, coagulation disfunctions from both crystalloids and colloids (12), potential nephrotoxicity of the synthetic colloids (14), and electrolytes and acid-basis disorders (15). It should be considered that controversial aspects about the effects of fluids on the glycocalyx have also been reported: different types of fluids could have a different capacity in protecting the glycocalyx (16). In contrast, it has been shown in nontraumatic hemorrhagic shock that fluid administration may not restore the glycocalyx, independent of the fluids composition (17). It has finally been demonstrated that

chloride-restricting intravenous fluid strategy in patients admitted into the ICU was associated with a decrease in AKI incidence and in use of renal replacement therapy (18).

Additionally, several studies demonstrated an increase in mortality associated with fluid overload, and that excess fluid balance may be a negative predictor for the recovery of renal function (1). However, it is hard to account for all potential confounders and to prove whether fluid overload directly causes adverse outcomes or, vice versa where critical illness itself is responsible for fluid overload.

The exact amount and timing of tapering fluid resuscitation is not established and there are also unresponsive subjects within septic patients (19). Furthermore, there are forms of AKI that do not respond to fluid administration, in particular the ones that are not caused by renal hypoperfusion (20). As reported in literature, choosing the correct fluid management in AKI patients is also challenging. There is an increasing focus on the benefits and harms of crystalloids solutions. Saline, one of the most frequently administered fluid has been reported to be detrimental for the kidney and even increases mortality among critically ill patients (21,22). Concerns have been raised in regard to colloids and their use has been strictly limited (23). Consequently, albumin administration has been increasing and its use supported by speculation on its non-oncotic functions, especially in septic patients. However, evidence is sparse and mainly investigating the secondary effects of albumin replacement rather than the use of albumin as a resuscitative fluid. In addition, albumin too has been reported to be able to contribute AKI (24). Finally, there are no general agreement on fluid administration rates and volumes.

A recent meta-analysis including 55 randomized clinical trials reported that crystalloids were less efficient than colloids in stabilizing hemodynamic resuscitation endpoints such as mean arterial pressure, cardiac index, and central venous pressure (25). Moreover, although the primary outcome in the CRISTAL trial showed a not significant lower 30-day mortality in the colloids group in comparison to the crystalloid group (P value =0.26), 90-day mortality was significantly lower (P value =0.03) when colloids (the majority of which were starches) were used for fluid resuscitation (26).

Hemodilution and anemia during surgery increase the risk of AKI

As overall life expectancy continues to increase and technological advances in medical interventions evolve, there is a willingness to offer more complex procedures to patients of advanced age, frailty and comorbidities with the inevitable increase of complications during and after surgery. Among perioperative complications, AKI is one of the most frequent and probably most preventable.

Patients undergoing high-risk surgery (like cardiac surgery, aortic surgery, hepatobiliary surgery) are likely to develop of AKI (27). AKI severity was studied in non-renal recovery setting after major surgery, and among patients with severe postoperative AKI. There was a 5.1% incidence of end stage renal disease during a median follow up of 4.8 years, in contrast with the corresponding incidence of 0.6% in mild AKI patients, and 0.3% in patients without AKI (1).

AKI occurs frequently in heart transplantation, due to anesthesia and surgery related factors, nephrotoxic drugs, and hemodynamic instability (28). Furthermore, right ventricular failure is also associated with AKI due to increased pressure in the venous compartment and therefore affecting renal blood flow (29). Guven *et al.* studied postoperative AKI after heart transplantation and found that preoperative right heart hemodynamic parameters such as pulmonary artery pulsatility index and right atrial pressure were early predictors of AKI (30).

Observational studies have reported inappropriate fluid administration among perioperative risk factors for AKI after surgery (2,31). In addition, preoperative anemia has been associated with increased risk of AKI after cardiac and non-cardiac surgery (32,33).

Intraoperative fluid administration is often used as first line treatment to hypotension due to side effects of anesthetic drugs or bleeding, and is likely to contribute and promote hemodilution. Indeed, hemodilution is associated with anemia and may determine a reduction of renal perfusion decreasing red blood cell flow despite an increase in plasma flow. Studies examining hemodilutional anemia during CPB suggest a decrease in hemoglobin concentration or systemic hematocrit, as possible early sign of anemia-induced renal hypoxia (34,35). In particular, hemodilution increases the cardiac output but is not sufficient to balance the decreased in the oxygen transport capacity. Consequently, a reduction of oxygen delivery in an area normally on the edge of hypoxia such as the renal medulla, promotes renal impairment (36).

At last, has been shown that hemodilution in CPB lowers renal oxygen delivery reducing the vessel density, that indeed improves with a higher hematocrit by blood transfusion (6).

Adverse effects of fluid administration in the microcirculation

In order to study the perfusion and the oxygenation of tissues it is necessary to introduce the determinants of microcirculatory delivery of oxygen: the functional capillary density (FCD), the red blood cell velocity (RBCv), and the capillary hematocrit (cHct).

The FCD is expressed as the sum of the lengths of all vessels containing moving red blood cells, divided per field of view, and it refers to the microcirculatory diffusive capacity of oxygen to the tissue. RBCv is the absolute blood flow velocity and is a measure of convective capacity of the capillaries of microcirculation to transport oxygen, and so is the cHct that is the hematocrit of blood in the capillaries in a moment in time (37,38). These three variables can be useful in assessing the effects of fluid administration and preventing AKI. Fluid administration and priming solutions in cardiac surgery reduce blood viscosity due to hemodilution, affecting the oxygen-carrying capacity and establishing a lack of hemodynamical coherence between macro-circulation and microcirculation (39). This means that in the face of improvement of the cardiac output, it is possible to have an unchanged or even worsening of the microcirculation and oxygenation.

Renal perfusion may benefit from fluid administration that restores an appropriate RBC flow and recruits non-perfused capillaries with limited impact on the cHct when a decrement in the intravascular volume leads to low cardiac output. However, fluid administration may be detrimental because, when leading to a decrease of cHct and FCD, it markedly decreases tissue oxygenation. Hemodilution decreases blood viscosity and promotes intrarenal shunting making some capillaries convey red blood cells while others convey only plasma. As a consequence, hemodilution causes heterogeneity in capillary density and reduction of oxygen diffusion to the renal tissue. Moreover, renal ischemia causes ineffective sodium reabsorption associated with a loss of tubular polarity (40).

Findings by Pranskunas *et al.* partially support the previous hypothesis. They examined changes in sublingual microcirculation before and after fluid administration in patients with clinical signs of impaired organ perfusion, and showed that fluid administration improved microcirculatory flow in patients with an impairment at the baseline, but had no effects on capillary density both in patients with and without microcirculatory flow impairments (41). Accordingly, there was an improvement in signs of impaired organ perfusion only among those patients with microcirculatory dysfunction at baseline but not in those with normal perfusion, regardless of the effects of fluid resuscitation on stroke volume which increased in all subjects. Studies on animal models of sepsis have recently proved that normalization of systemic hemodynamics through fluid resuscitation was unable to improve AKI. This was possible assessing the density, perfusion and heterogeneity characteristics of microcirculation. Despite an improvement of the systemic flow and an increase of mean arterial pressure, it was clear that fluids failed to correct renal microcirculatory dysfunctions, perfusion and oxygenation (42-44).

In contrast, data from other animal experiments suggests that blood transfusion may improve renal microvascular oxygenation and function superior to resuscitation with fluids (44). Similar findings were shown in patients undergoing on pump cardiac surgery who improved microcirculatory perfusion after blood transfusion (45).

Finally, fluid therapy can lead to a microcirculatory dysfunction similarly to what happens in sepsis, which is characterized by heterogeneous abnormalities in renal blood flow and areas of ischemia of tubular cells. This is due to hypoxia, in so far as it contributes to dysfunction of renal oxygen extraction capacity and to production of reactive oxygen species that can further lead to kidney injury (46).

Conclusions

AKI is a frequent complication in critically ill patients and among high-risk patients undergoing surgery. Moreover, its pathophysiology may be iatrogenic and therefore it is necessary to improve patients' management in order to not further harm the patients and worsen their prognosis. Optimization of fluid management in the perioperative setting is fundamental. There is a real need for tools available at the bedside able to define and assess therapeutic targets for fluid management. Monitoring of sublingual microcirculation may be used to prevent renal microcirculatory impairment due to inappropriate fluid administration and, therefore, help with prevention and treatment of AKI (37).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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