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RENAL BLOOD SUPPLY AND FLUID THERAPY

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Summary
There are different underlying mechanisms of acute kidney injury (AKI) in various type of shock, but restoration of renal blood flow (RBF) is crucial in prevention of AKI. The first 24-48 hours of shock seem to be critical. Monitoring of global RBF and its intrarenal distribution is not possible in current clinical practice. The only way for optimization of renal blood supply is optimization of macrohemodynamics. In volume-responsive AKI, fluid therapy restores kidney function. Many clinical signs and parameters can be of use in determining the volume status. The accuracy of the assessment may be improved with the help of tools quantifying the clinical parameters (e.g. hypovolemic index – HVI). The basis of intravenous fluid therapy are crystalloids, and their effect is reported to be shorter than 120 min. Every form of hydroxyethyl starch has been shown to be harmful for patients at risk of impaired renal function. In sepsis, the boundary between volume-responsive and volume-unresponsive AKI is blurred. Fluid responsiveness can be lost in the course of AKI as early as on the first day of sepsis. According to the results of the ARDS Network study, the conservative approach in fluid therapy resulted in a shorter time of mechanical ventilation and did not affect the renal function, except for a slight increase of the serum creatinine level. Fluid overload is to be avoided, as renal venous and lymphatic congestion can limit the urine filtration rate, further worsening edema.

Keywords: acute kidney injury, blood flow, fluid therapy, septic shock

INTRODUCTION

Despite the development of renal replacement techniques, acute kidney injury (AKI) remains a poor prognostic factor in critically ill patients. AKI is diagnosed based on serum creatinine and urine output (table 1) (1). The optimization of renal blood supply can improve the outcome in patients suffering from AKI (2). The role of venous and lymphatic flow has been underlined in multiple studies on animal and human subjects concerning the pathophysiology of sepsis and cardiovascular disorders (3-8). Despite the availability of an increasing number of biomarkers for the early diagnosis of acute kidney injury, serum creatinine remains the widely available gold standard. In clinical setting, avoiding hypo- and hypervolemia and preserving renal blood flow remain the best preventive measures against AKI (9). The aim of this paper was to review the diagnostic and therapeutic options for AKI.

PATHOPHYSIOLOGY OF AKI

The renal blood flow (RBF) depends on cardiac output and renal vascular resistance. The underlying mechanism of AKI in different types of shock varies. The available data is based primarily on animal studies, as the continuous measurement of RBF in human is difficult to perform. In animal models, glomerular filtration rate (GFR) remains constant until RBF has decreased to 1-10% of the baseline, and the near-total occlusion of the renal artery for 2 hours results in a transient decline of renal function after the restoration of blood circulation (9-12). AKI is very rare in human survivors of cardiac arrest without shock, therefore, the coexistence of another disorder is necessary for the development of renal dysfunction (12).

Septic AKI can develop even in a hyperdynamic circulatory pattern, but low systemic blood flow aggravates

Tab. 1. Definition of acute kidney injury

Class	Serum creatinine	Urine output
I	Increased to ≥ 0.3 mg/dl (≥ 26.4 μmol/l) or 1.5-2 times baseline	< 0.5 ml/kg/hour in > 6 hours
II	Increased to 2-3 times baseline	< 0.5 ml/kg/hour in > 12 hours
III	Increased to > 3 times baseline, or serum creatinine ≥ 4.0 mg/dl (≥ 354 μmol/l), or an acute rise ≥ 0.5 mg/dl (44 μmol/l)	< 0.3 ml/kg/hour over 24 hours or anuria lasting > 12 hours

this condition (13). A decrease in GFR in sepsis can develop as a result of the constriction of afferent arterioles, which lowers the filtration pressure, however, as recent studies underline, it is mainly caused by the dilation of efferent arterioles. Studies suggest that the first 24-48 hours of shock are critical for the renal function (13).

MONITORING AND OPTIMIZATION OF THE RENAL BLOOD FLOW

Arterial blood supply

In an ideal setting, the global and regional RBF of high-risk patients would be continuously monitored, preferably in a noninvasive way. There are several methods for measuring renal blood supply: non-imaging procedures (microsphere deposition, para-aminohippurate clearance, renal vein thermodilution, xenon washout technique, intravascular Doppler), nuclear techniques (scintigraphy, renal extraction of ^{51}chromium-ethylenediaminetetraacetic acid, positron emission tomography), magnetic resonance imaging, and ultrasound imaging (Doppler and contrast-enhanced ultrasound). Unfortunately, these methods are either difficult (para-aminohippurate clearance), risky (renal vein thermodilution), inappropriate for human examination (intravascular Doppler), unavailable in critical care units (nuclear techniques and MRI), or do not provide the possibility of continuous observation of individual patients (15, 16).

Monitoring global RBF and its intrarenal distribution is not possible in current clinical practice. The decreased RBF may be either a cause or a consequence of AKI, e.g. due to venous congestion and elevated interstitial and intracapsular pressure. Dynamic parameters and tests, such as pulse pressure variation (PPV), systolic pressure variation (SPV), stroke volume variation (SVV) and the passive leg raising test are considered the most appropriate for assessing volume responsiveness, and therefore, intravascular hypovolemia (17-20). However, these methods have several limitations. For example, multiple conditions, including arrhythmia, respiratory effort due to an inadequate sedation of a mechanically ventilated patient, and a low tidal volume (< 6 ml/kg) may all result in erroneous results (21, 22).

The risk factors for AKI in surgical patients are listed in table 2. In surgical patients, the optimization of hemodynamic parameters prevents the development of AKI, but targeting for higher than normal values carries no further benefit (2, 9, 23-25).

In all three studies conducted on patients with sepsis, increased RBF was observed (26-28). Nevertheless, due to the dilation of the efferent arterioles and the lack of effective filtration pressure, AKI is the leading cause of death in septical patients (13). However, maintaining mean arterial pressure (MAP) above 65-72 mm Hg, especially between the 6th and 24th hour of sepsis, decreases the incidence of AKI (9, 29-33). The Surviving Sepsis Campaign Guidelines suggest maintaining MAP ≥ 65 mm Hg as one of the hemodynamic targets in septic patients (34).

Fluid therapy

Traditionally, AKI is divided to prerenal, renal, and postrenal in origin, but this classification has little value in clinical practice. Currently, it is more common to refer to prerenal and renal AKI as volume-responsive and volume-unresponsive AKI, respectively. In volume-responsive AKI, fluid therapy restores kidney function and hemodynamic monitoring is not required. In some cases, although kidney function is not improved with fluid therapy, other systemic parameters, such as cardiac output and renal blood flow, improve. In these cases, the term 'volume-responsive AKI' is not appropriate. In other situations, renal function could potentially be volume-responsive, but the patient is not (e.g. due to heart failure with fluid overload) (33).

Estimating the volume status of a patient is often not easy in clinical situations. Many clinical signs (increase in heart rate, decrease in systolic blood pressure, dry mucosa, altered mental status, muscular weakness, impaired speech, and decreased capillary refill time) and parameters (central venous pressure – CVP, global end-diastolic volume index –

Tab. 2. Risk factors for AKI in surgical patients

Patient-related factors	Surgery-related factors
severe cardiac or respiratory condition in patients aged > 70, with moderate functional limitation of one or more organ dysfunction acute massive blood loss (> 2.5 l) severe sepsis shock or severe hypovolemia respiratory failure (low paO_2, SpO_2, or PaO_2/FiO_2 or mechanical ventilation > 48 h) acute intestinal failure acute renal failure	extensive noncardiac surgery (e.g. oncological surgery involving bowel anastomosis, pneumonectomy, etc.) major or combined cardiovascular surgery > 2 h emergency surgery

GEDVI, intrathoracic blood volume index – ITBVI, left and right ventricular end-diastolic area, systolic pressure variation – SPV, pulse pressure variation – PPV, stroke volume variation – SVV, etc.) can be of use in determining the volume status. The accuracy of the assessment may be improved with the help of tools quantifying the clinical parameters (e.g. hypovolemic index – HVI) (35).

The next issue is the amount and type of fluids (crystalloid vs. colloids, type of colloids, restricted vs. liberal fluid strategy) needed for the restoration of euvolemia. The effect of crystalloids is reported to be shorter than 120 min (36). Among colloids, 6% w/v hydroxyethyl starch results in a maximal hemodynamic response reflected in the improvement of several of hemodynamical parameters (MAP, CVP, cardiac index, GEDVI, Oxygen Delivery Index – DO_2I, and Central Venous Oxygen Saturation – $ScvO_2$).

In sepsis, the boundary between volume-responsive and volume-unresponsive AKI is blurred. Achieving the appropriate fluid balance can reverse AKI and normalize renal function. Fluid responsiveness can be lost in the course of AKI as early as on the first day of sepsis (16, 33). According to the results of the ARDS Network study, the conservative approach in fluid therapy (target CVP 9-13 instead of 15-18 mm Hg, and target pulmonary artery occlusion pressure – PAOP – 13-18 instead of 19-24 mm Hg) resulted in a shorter time of mechanical ventilation and did not affect the renal function, except for a slight increase in the serum creatinine level (38, 39). Several papers report that the positive fluid balance and fluid accumulation is a predictor of mortality and AKI (9, 40-44). The Sepsis Occurrence in Acutely Ill Patients trial (SOAP) reported fluid accumulation as an independent predictor of mortality, as well as of the length of ICU stay, duration of mechanical ventilation, and the need for renal replacement therapy (43). In the PICARD study (Program to Improve Care in Acute Renal Disease), increased mortality was observed in patients with a more than 10% increase in body water (9).

Moreover, fluid therapy causes hemodilution. Lower hematocrit results in lower amount of oxygen delivered to kidneys (36). What is more, crystalloid infusions may affect endothelial glycocalyx barrier by diluting the blood, predisposing to edema (45). Isotonic sodium chloride solution can cause renal vasoconstriction (11). This effect has not been observed during the use of balanced solutions (11). Intravenous fluid administration in septic AKI decreases glomerular oncotic pressure and increases chloride concentration on the level of macula densa, activating tubuloglomerular feedback mechanisms (11). Beneficial hemodynamic effects disappear after one hour. Every form of hydroxyethyl starch has been shown to be harmful for patients at risk of impaired renal function (11).

Vasopressors

To achieve the target blood pressure, vasopressors are often administered. In animal models, noradrenaline and phenylephrine increase MAP, as well as RBF and GFR (11,12). In Doppler flowmetry, it has been shown that norepinephrine increases both cortical and medullary renal blood flow (11). Similarly, noradrenaline administration after cardiac surgery seems to be beneficial in the prevention of AKI (12). In animal studies, the prevention of the dilatation of efferent arterioles with vasopressin resulted in a significantly higher urine output (11).

CONCLUSIONS

Nowadays, no clinical signs or measurable parameters are good and practical indicators of the autoregulation of renal vascular bed, therefore, it is clinically difficult to assess whether the autoregulation is still functional. Proper fluid and vasopressor therapy can prevent AKI and reduce costs. Fluid overload is to be avoided, as renal venous and lymphatic congestion can limit the urine filtration rate, further worsening edema. Further study is needed to create guidelines for the amount of fluids necessary to maintain adequate renal blood flow.

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Conflict of interest
None

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