REVIEW ARTICLE

The anesthesiologists have a role in preventing perioperative renal failure

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SUMMARY

Acute renal failure faced in perioperative period is associated with increased morbidity and mortality. It is of great import for anesthesiologists to understand the type of the surgery or the patients, in which a risk of precipitation of perioperative renal failure is increased. The risks for renal failure have been classified as surgery-related (e.g. vascular surgery) or patient-related (e.g. preexisting renal disorder, diabetes mellitus etc). A meticulous evaluation of perioperative risks, a careful intraoperative management, and finally realizing renal protection, can guarantee a better outcome. This review is intended to describe the risks of renal injury, the mechanisms of injury and suggest interventions to prevent perioperative renal failure.

Key Words: Perioperative acute renal failure; Acute Dialysis Quality Initiative

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EPIDEMIOLOGY, MORBIDITY & MORTALITY

Perioperative acute renal failure (PARF) faced on the course of surgery or ICU stay is often considered as a complication associated with increased morbidity and mortality. PARF accounts for 20–25% of cases of hospital-acquired renal failure [1]. The incidence varies between 1 and 25% depending on the type of surgery and on the definition of renal failure. PARF can cause several disorders on the other organs or being part of the multiple organ failure syndrome, so increasing the mortality of up to 60% [1]. The patients with PARF are often prone of high rates of infections, cardiac arrhythmias, need of mechanical ventilation, various types of renal replacement therapies, and prolonged hospital stay. Recently has been reported that only approximately 15% of the patients with PARF, can have a full recovery. Kheterpal et al[2] recently reported that in a large national database 1% of all patients undergoing general surgery developed postoperative acute renal injury, increasing 3 times higher risk of postoperative morbidity and a fivefold increase in mortality. PARF occurring during cardiac surgery is often associated with 60 % mortality [3, 4].

DEFINITION

The hallmarks of PARF are decreased glomerular filtration rate (GFR), decreased elimination of nitrogenous wastes, and inability to maintain hydro-electrolytic balance [5]. Commonly used definitions of acute renal failure (ARF) include an increase in serum creatinine of _ 0.5 mg/dL over the baseline value, a reduction in the calculated creatinine clearance rate by 50%; or a decrease in renal function needing renal replacement therapies.

The Acute Dialysis Quality Initiative (ADQI) has classified PARF as a grading system [6] using the acronym RIFLE. This acronym is composed by three grades of increasing severity of illness (R, risk; I, injury; F, failure) and two outcome parameters (L, loss; E, end-stage), basing on the serum creatinine or urine output (Table 1).

Table 1: The RIFLE classification of renal failure

Grade	Glomerular filtration rate	Urine output
R, Risk	Serum creatinine increase: 1.5-fold; GFR decrease:.25%	0.5 ml/ kg/h for 6 h
I, Injury	Serum creatinine increase: 2-fold; GFR decrease: .50%	0.5 ml/ kg/h for12 h
F, Failure	Serum creatinine increase: 3-fold; GFR decrease: .75%; serum creatinine decrease: .350 mmol litre21 (4 mg dl21) with acute increase .44 mmol litre21 (0.5 mg dl21)	0.3 ml/ kg/h for 24 h or anuria for 12 h
L, Loss	Persistent ARF¼complete loss of renal function for 4 weeks	
E, End-stage	ESRD¼complete loss of renal function for 3 months	

Another recently used definition is acute kidney injury (AKI) [7]. Table 2 summarizes three stages of AKI. Serum creatinine and urine output are not the ideal markers for AKI. Nowadays several new biomarkers of AKI include cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and interleukin-18.

Table 2: AKI stages

Stage	Serum creatinine	Urine output
1	Increased 1,5-2 fold from baseline	<0.5ml/kg/h for more than 6 h
2	Increased 2-3 fold from baseline	<0.5ml/kg/h for more than 12 h
3	Increased 4 fold from baseline, or more than 4 mg.dl	<0.3ml/kg/h for more than 24 h or anuria for more than 12h

ETIOLOGY AND RISK FACTORS

PARF is multifactorial. Several situations, surgeries, or current patient's diseases are risk factors to exacerbate PARF.

Cardiac surgery and renal failure

The incidence of PARF after cardiac surgery is estimated 1% -30%,[8] with the mortality rates ranged from 28% to 63%.[9, 10] The abnormal baseline creatinine, older patients, diabetes, prolonged cardiopulmonary bypass, peripherial systemic vascular diseases, and decreased ejection fraction, are generally considered as risk factors. Another study[11] has identified the cardiac catheterization performed within 5 days before operation, baseline glomerular filtration rate less than 60 mL/min, and prolonged cardiopulmonary bypass as risk factors for acute renal failure after cardiac surgery.

Vascular surgery and renal dysfunction

The rate of renal complications associated with thoracic aorta cross-clamping is estimated up to 50% and often presented as acute tubular necrosis.[12] Ischemia-reperfusion injury is generally the pathogenesis mechanism.

Renal failure and sepsis

Sepsis is often complicated with renal failure, increasing mortality to 70 %, as compared with a 45 % mortality among patients with acute renal failure alone.[13] Approximately 19 % of patients with moderate sepsis, 23 % with severe sepsis, and 51 % with septic shock are complicated with renal failure.[14]

Liver failure/transplantation and renal dysfunction

Acute or chronic liver disease is often associated with renal failure. The mechanisms include hepatorenal syndrome, decreased systemic resistance, decreased perfusion pressure, infection induced hypotension.[15, 16]

Ortotopic liver transplantation (OLT) offers great challenges to the anesthesiologist. It is often with several degrees of renal dysfunction or failure. Renal dysfunction pre-OLT has been defined as a serum creatinine > 1.5 mg/dL, while PARF post-OLT has been defined as a requirement for renal replacement therapies or a doubling of serum creatinine.[17, 18] Several predictive models are proposed. Several authors[19, 20] showed that an elevated pre-OLT serum creatinine or blood urea nitrogen predicted PARF requiring renal replacement therapies post-OLT.

Intrabdominal hypertension and kidney

Increased intrabdominal pressure can contribute to the development of perioperative renal failure. The abdominal compartment syndrome reduces significantly venous return, increases afterload, and decreased renal perfusion.[21] All the clinical situations (acute pancreatitis, abdominal trauma, mesenteric ischemia etc) that raise intrabdominal pressure can cause different grades renal dysfunction.

Nephrotoxic drugs induced renal failure

Drug toxicity is a rare complication. Aminoglycosides are well known to cause renal toxicity in 10-20% of the treated patients. The accumulation of aminoglycosides

in proximal tubules may induce several intracellular processes as vacuolization, myeloid bodies, and loss of brush border. These processes damage tubular function. PARF usually develops 7- 10 days after the aminoglycosides administration. Their toxicity is usually potentiated by several situations like advance age, preexisting renal disease, sepsis, liver disease, hypovolemia, metabolic acidosis, and other drugs (loop diuretics, vancomycin, tacrolimus etc).

Non steroid antiinflamatory drugs are usually non toxic if single dose is used in healthy people. The toxicity induced by non steroid antiinflamatory drugs occur mainly when associated with other renal toxic drugs.

Radiocontrast dyes can also induce renal toxicity especially in the patients with preexisting dysfunction, hypovolemia, severe congestive heart failure, multiple myeloma, high contrast dose, and diabetes. PARF occurs mainly within 24-48 hours to intravenous contrast administration and usually recovered at 3-5 days.[22]

Diabetes Mellitus and renal failure

Approximately 30% of insulin-dependent diabetics and 5-10% of non insulin-dependent diabetics may develop renal disease. Hyperglycemia forces the kidney to increase filtration process. This leads to leakage of proteins in the urine. This process is known as microalbuminuria. Within 5 years of microalbuminuria, the diabetic patient progress to renal failure. Hypertension, hyperglycemia, aging, cholesterol, and smoking are considered as risk factors for development of diabetic nephropathy.[23] Hypertension is the most important precipitating factor.

Table 3.summarizes the risk factors, classified as patients and surgery related, and different conditions.

Table 3: Risk factors of PARF

Patients related	Surgery related	Different conditions
Old people	Vascular surgery	Sepsis
Diabetes mellitus	Aortic cross-clamping	Hypotension, bleeding
Female gender	Cardiac surgery	Jaundice
Chronic renal disorders	Cardiopulmonary bypass	Hypoxia
Systemic vascular diseases	Non-renal transplantation	Multi-organ failure
Advance liver disease	Emergency surgery	Rhabdomyolysis
Drug nephrotoxicity	Contrast administration	Intra-abdominal hypertension

PATHOPHYSIOLOGY

Ischemic or toxic acute tubular necrosis (ATN) is the predominant cause of PARF in hospitalized patients and in the ICU, respectively accounting for 38% and 76% of cases of ARF. Prerenal azotemia accounts for 70% of the community-acquired causes of ARF, and for 40% of hospital-acquired causes. Acute tubular necrosis is caused by toxic or ischemic mediated mechanisms. The epithelial apoptosis and necrosis, tubular obstruction, and transtubular leak of glomerular filtrate, are the possible mechanisms of tubular cell damage. Inflammatory responses induced by renal ischaemia–reperfusion injury also play a significant role in the development of ATN

The hemodynamic hallmark of sepsis[24] is generalized arterial vasodilatation with a decreased systemic vascular resistance (endotoxins, inflammatory response, and nitric oxide). Arterial underfilling activates the neurohumoral axis and an increase in cardiac output secondary to the decreased cardiac afterload. Activation of the sympathetic nervous system, the renin–angiotensin–aldosterone axis, vasopressin, and an increase in cardiac output are essential in maintaining normal hemodynamic but may lead to acute renal failure if exaggerated. It is well known that glomerular filtration is determined by the difference in arterial pressure between the afferent and efferent arterioles across. During sepsis PARF can be caused not only by hypotension, but by several other mechanisms. These mechanisms include intrarenal vasoconstriction (due to imbalance between vasodilatory and vasoconstrictory substances, results in a decline in renal blood flow), release of cytokines and oxygen radicals, and finally disorders of coagulation and fibrinolysis (causing intraglomerular thrombosis).

A great number of patients awaiting OLT may have reversible renal dysfunction due to renal hypoperfusion.[25,26] While awaiting OLT, patients often develop varying degrees of renal impairment, ranging from prerenal azotemia to hepatorenal syndrome and acute tubular necrosis. These changes, which are attributable to events and/or interventions such as large-volume paracentesis, diuretic therapy, sepsis, or gastrointestinal bleeding, Intraoperatively sharp hemodynamic changes often induce renal hypoperfusion. Bleeding, great vessel clamping, anhepatic phase, lactic acidosis, and finally need for vasopressors can explain the fragile intraoperative hemodynamic of these patients.

Radiocontrast dyes can induce renal toxicity by causing hyperosmolarity and renal cell damage. Non steroid antiiflamatory drugs impair the balance between intrarenal vasodilators and vasoconstrictors, so inducing intrarenal ischemia.

GENERAL PREVENTIVE MEASURES

General preventive measures include optimizing oxygen and blood supply, decreasing the demands, and minimizing the renal perioperative insult.

Optimizing oxygen and blood supply:

Optimizing oxygen and blood supply is realized by good control of hemodynamic, cardiac output, and oxygen delivery.

Maintaining euvolemia and renal perfusion is the hallmark of care.[27] The negative effect of hypotension can also be potentiated or caused by volume depletion, dialysis, sepsis, cardiac dysfunction, anesthesia, mechanical ventilation, spinal induced vasodilatation, and excessive using of antihypertensive medications. Several studies[28] confirmed that the loss of autoregulation of renal blood flow usually occurs when the mean arterial pressure drops below of 75 to 80 mm Hg. Although it has been recommended that MAP should not be increased over 65 to 70 mm Hg, whereas maintaining a MAP of 65 mm Hg may be inadequate in order to prevent renal damage in elderly patients, or in patients suffering from diabetes.[29] So it is of great importance to avoid both hypovolemia and overfilling the patient. There are several clinical parameters helping us to judge the adequacy of liquid therapy such as mean arterial pressure, capillary return, heart rate, urinary output, varialbility of pulse pressure. More invasive technique include pressure measurement in left atrium (Swan Ganz), PICCO, Vigileo, mix venous saturation etc.

The blood supply generally maintained by euvolemia and vasodilatation (if necessary) of afferent arterioles. Fenoldopam, natriuretic peptide, and dopamine can induce vasodilatation of afferent arterioles, increasing renal blood flow as well. Dopamine has a dose related effect. At lower dose (2 mcg/kg/min) it acts on dopamine-receptor increasing renal blood flow, glomerular filtration, and sodium excretion. Dopamine can increase urine output, but seems not efficient to prevent the perioperative renal damage.[30] Another study [31] confirmed that dopamine did not decrease the rate of renal injury and hospital stay length. Fenoldopam acts on DA-1 receptors, inducing dilatation of renal vessels and maintaining the renal perfusion.[31,32] Fenoldopam also increases urine output and natriuresis. Several studies[33-35] found fenoldopam a suitable agent to prevent renal failure during cardiovascular surgery and radio-contrast examination.

Atrial natriuretic peptide is secreted after the right atrium is dilated as a consequence of increased filling and pressure. Its mainly pharmacological actions are vasodilatation of afferent arterioles, vasoconstriction of efferent arterioles, increasing glomerular filtration rate, and increasing urine output. The studies[36] failed to prove its efficacy in prevention of PARF.

Finally increasing hemoglobin level up to 10 g/dl is essential to prevent perioperative renal ischemia and PARF. Table 4 summarizes the physiological hemodynamic goals in order to prevent PARF.

Table 4: Hemodynamic goals to prevent PARF

Parameter	Target
Cardiac Output	⩾4,5 L/min
Pression of Wedge	⩾15-⩽18 mmHg
Central Venous Pressure	⩾5 mmHg
Hematocrit	⩾30%
Mean Arterial Pressure	⩾70-⩽100 mmHg
Delivery O_2	⩾500 ml/min/m2
Partial arterial pressure O_2	⩾ 60 mmHg, FiO_2⩽ 0,5

Decreasing demands:

Good sedation and aggressive treatment usually are effective measures in order to decrease the metabolic rate and demands. Loop diuretics and mannitol are both proposed for decreasing renal oxygen consume. Decreased renal oxygen consume make the renal cortex less fragile in the course of ischemia. Mannitol seems to have several pharmacologic properties like increasing renal blood flow and free radical scanvenger,[37] but its use for PARF prevention is not justified by large trials.[37] Loop diuretics can reduce oxygen demands because of their effect on Na/K- ATP. It is well known that this pump in order to be fully functional consumes energy, so blocking the pump can reduce the energy consume and can save energy very useful to the ischemic kidney. Conflicting results are available from studies, but the non anuric patients can benefit more than those with anuria.[37, 38]

Minimizing perioperative renal insult:

Minimizing perioperative renal insult is realized by using new agents (free radical scanvenger) and avoiding drug induced nephrotoxicity. Superoxide dismutase, a free-radical scavenger, has been shown to preserve renal function[39] in animal models of radiocontrast-induced nephropathy. N-acetylcysteine acts as an antioxidant and has been reported to prevent a reduction in

renal function in patients with contrast agents' nephrotoxicity.[40,41] Nevertheless adequate hydration is a crucial step to prevent renal failure after contrast agent administration. Avoiding non steroidal antiiflamatory drugs, aminoglycosides, convertase inhibitors are effective measures to prevent PARF.

CONCLUSIONS

Perioperative renal failure is a major complication that can dramatically increase morbidity and mortality. Indentifying the patients on risk, current diseases, and surgical procedures that can induce PARF, are important steps to prevent this complication. Adequate hydration, maintaining good blood pressure, and avoiding nephrotoxic drugs can ameliorate the prognosis.

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