Perioperative renal protection

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Key points

Perioperative acute renal failure is a common complication of major surgery and is associated with increased morbidity and mortality.

Ischaemia- or toxin-mediated acute tubular necrosis is the primary cause of perioperative acute renal failure.

The key non-pharmacological strategies are intravascular volume expansion, maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic agents, careful glycaemic control, and the appropriate management of post-operative complications.

At present, there is no firm evidence to suggest that the use of any specific pharmacological intervention is clinically beneficial.

Dopamine infusion has not been shown to prevent acute renal failure, avert the need for renal replacement therapy, or reduce mortality, and should not be administered solely for renal protection.

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Acute renal failure (ARF) occurring around the time of surgery is a serious complication associated with considerable morbidity and mortality. Appropriate perioperative strategies are required to protect renal function to optimize patient outcome.

Perioperative ARF accounts for 20–25% of cases of hospital-acquired renal failure. The incidence varies between 1 and 25% depending on the type of surgery and on the definition of renal failure. Renal dysfunction after surgery is often associated with multiple organ dysfunction syndrome and may result in a mortality of up to 60%. It is also associated with a high risk of infection, prolonged intensive care unit (ICU) and hospital stay, progression to chronic renal failure (CRF), and dialysis-dependent end-stage renal disease (ESRD). The chance of full recovery from an episode of ARF in the surgical setting is only 15%—many patients progress to develop varying degrees of chronic renal dysfunction.

Patients undergoing cardiac and vascular surgery are at particular risk of developing ARF. ARF related to major surgery in patients with significant co-morbidity commonly results in a poor outcome. A large multi-centre cohort study demonstrated that ARF requiring dialysis occurred in 1.1% of cardiac surgical patients and was associated with an operative mortality of 63.7%.[1] This study confirmed that ARF was an independent predictor of mortality in this group of patients, resulting in a 7.9-fold increase in risk of death. ARF after open abdominal aortic surgery is similarly associated with a high mortality.[2]

Definition of acute renal failure

The term *acute renal failure* is a non-specific description of an acute, sustained decrease in renal function. There is a wide spectrum of severity of acute renal injury ranging from mild reversible impairment to severe dysfunction necessitating renal replacement therapy (RRT). An international interdisciplinary collaborative group, the Acute Dialysis Quality Initiative (ADQI), has recently formulated a standard grading system for acute renal dysfunction.[3] The term *acute renal dysfunction* encompasses the full range of abnormalities of renal function. The acronym *RIFLE* defines three grades of increasing severity of acute renal dysfunction (R, risk; I, injury; F, failure) and two outcome variables (L, loss; E, end-stage) that are based on the change in serum creatinine or urine output (Table 1). The RIFLE criteria have undergone evaluation in cardiac surgical patients and in ICU patients, and have been shown to appropriately define acute renal dysfunction. The term acute kidney injury (AKI) has been recently proposed to define the full spectrum of severity of acute renal dysfunction.[4]

Pathophysiology

The aetiology of ARF is classically divided into pre-renal, renal, and post-renal causes. The majority of cases of ARF in surgical and critically ill patients are because of intrinsic renal causes; acute tubular necrosis (ATN), which is typically caused by ischaemic or toxic processes, is the most common.

Acute tubular necrosis

A combination of microvascular and tubular injury contribute to the development of ATN.[5] Intra-renal vasoconstriction because of local vasoactive mediators, activation of tubuloglomerular feedback, structural endothelial damage, and leucocyte activation all lead to microvascular damage. Mechanisms of tubular injury include epithelial apoptosis and necrosis, tubular obstruction, and transtubular leak of glomerular filtrate. Inflammatory responses induced by renal ischaemia–reperfusion injury also play a significant role in the development of ATN.

Nephrotoxic agents

Nephrotoxic agents commonly used in perioperative patients include non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, aldosterone-receptor

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Table 1 The RIFLE classification of acute renal dysfunction. GFR, glomerular filtration rate; UO, urine output; ARF, acute renal failure; ESRD, end-stage renal disease

Grade	Glomerular filtration rate criteria	Urine output criteria
R, Risk	Serum creatinine increase: 1.5-fold; GFR decrease: >25%	UO <0.5 ml kg^{-1} h^{-1} for 6 h
I, Injury	Serum creatinine increase: 2-fold; GFR decrease: >50%	UO <0.5 ml kg^{-1} h^{-1} for 12 h
F, Failure	Serum creatinine increase: 3-fold; GFR decrease: >75%; serum creatinine decrease: >350 μmol $litre^{-1}$ (4 mg dl^{-1}) with acute increase >44 μmol $litre^{-1}$ (0.5 mg dl^{-1})	UO <0.3 ml kg^{-1} h^{-1} for 24 h or anuria for 12 h
L, Loss	Persistent ARF=complete loss of renal function for >4 weeks	
E, End-stage	ESRD=complete loss of renal function for >3 months	

antagonists, i.v. radio-contrast agents, aminoglycoside and beta-lactam antibiotics, amphotericin B, and cyclosporin.

Cardiac and vascular surgery

Several specific factors are involved in the development of ARF related to cardiac and vascular surgery:

1. Renal hypo-perfusion outside the limits of auto-regulatory reserve, particularly during cardiopulmonary bypass (CPB), is a major determinant of ATN.
2. The systemic inflammatory response syndrome (SIRS) triggered by major surgery results in cell-mediated and cytotoxic injury.
3. ATN may also be exacerbated by renal embolic injury: aortic atheroma disrupted by operative manipulation and thrombus, air, lipid, and tissue may contribute to the embolic load during surgery.
4. Prolonged surgery produces haemolysis: renal excretion of haem derivatives may result in renal tubular injury.
5. Toxic injury from the administration of nephrotoxic drugs may also contribute to post-operative ARF. Patients who present for non-elective cardiac surgery shortly after pre-operative cardiac catheterization are at increased risk related to both the radiocontrast load and surgery itself. Endovascular aortic surgery is also associated with ARF because of the administration of a large dose of contrast.

Risk factors

Evidence from epidemiological studies has established the major risk factors for perioperative ARF (Table 2). Two risk stratification tools for ARF after cardiac surgery have recently been tested and validated.[6, 7] Similar risk scoring systems for ARF after non-cardiac surgery are under development. The incidence is increasing because of the increasing age of the surgical population and the performance of more complex surgery.

Table 2 Risk factors for perioperative acute renal failure. IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass

Pre-operative factors	Intra-operative factors	Post-operative factors
Chronic disease	Type of surgery	Acute conditions
Advanced age	Cardiac	Acute cardiac dysfunction
Female sex	Aortic	Haemorrhage
Chronic renal disease	Peripheral vascular	Hypovolaemia
Diabetes mellitus	Non-renal solid organ transplantation	Sepsis
Chronic cardiac failure	Cardiac surgery	Rhabdomyolysis
Aortic and peripheral vascular disease	Prolonged CPB time	Intra-abdominal hypertension
Chronic liver disease	Combined procedures	Multiple organ dysfunction syndrome
Genetic pre-disposition	Emergency surgery	Drug nephrotoxicity
Acute conditions		
Hypovolaemia	Previous cardiac surgery	
Sepsis	Aortic surgery	
Preoperative IABP	Aortic clamp placement	
Multiple organ dysfunction syndrome	Intra-operative radiocontrast	
Drug nephrotoxicity		

Prevention

The identification of high-risk patients and the implementation of prophylactic measures are the goals of perioperative renal protection. Strategies to reduce the occurrence of renal injury in patients without evidence of acute renal dysfunction are referred to as primary prevention. The avoidance of additional renal injury in the setting of established acute renal dysfunction is termed secondary prevention. Both non-pharmacological and pharmacological interventions may be considered.

Non-pharmacological strategies

These include intravascular volume expansion, maintenance of renal blood flow and renal perfusion pressure, avoidance of nephrotoxic agents, strict glycaemic control, and appropriate management of post-operative complications.

Intravascular volume expansion

Perioperative hypovolaemia should be rapidly corrected by volume expansion with i.v. fluids, whether occurring before, during, or after surgery. The role of crystalloids compared with colloids for intravascular volume expansion remains unclear. Although not a primary outcome measure, a large multi-centre trial of fluid resuscitation in critically ill patients found no difference between albumin and 0.9% sodium chloride in terms of the risk of ARF. The renal effects of different colloids have not yet been fully elucidated. Albumin and gelatin appear to be safe in patients with normal renal function. The safety of hydroxyethyl starch solutions in the setting of established renal impairment has not been clarified. Recent evidence suggests that hydroxyethyl starch is associated with a higher incidence of ARF than Ringer's lactate in critically ill patients with severe sepsis.

The benefit of isotonic i.v. fluid expansion for the prevention of radiocontrast-induced nephropathy has been clearly demonstrated. However, the ideal composition of such fluid and the optimal rate of infusion have not been determined and should be individualized. Surgical patients receiving contrast will benefit from the use of the lowest possible volume of non-ionic, iso-osmolar contrast in conjunction with isotonic i.v. fluids.

Maintenance of renal blood flow and renal perfusion pressure

Maintenance of adequate renal blood flow and perfusion pressure involves the defence of both cardiac output and systemic arterial pressure. The initial approach should be intravascular volume expansion to reverse hypovolaemia. Inotropic and vasopressor therapy may then be initiated for the management of low cardiac output and systemic arterial hypotension, respectively. Despite historic concerns, norepinephrine is an excellent first-line vasopressor agent. There is no firm evidence to suggest that the drug compromises renal, hepatic, or gastrointestinal blood flow when used to treat arterial hypotension. Vasopressin and terlipressin may be useful agents in the treatment of post-operative catecholamine-resistant vasodilatory shock. The optimal therapeutic target for systemic arterial pressure for renal protection has not been established. A minimum mean arterial pressure of 65–75 mm Hg is often targeted in clinical practice; however, a higher target may be necessary in patients with pre-existing hypertension.

Avoidance of nephrotoxic drugs

Minimizing perioperative exposure to nephrotoxic drugs is crucial in the prevention of ARF. The use of once-daily aminoglycoside dosing and the use of lipid formulations of amphotericin B have been demonstrated to lower the risk of nephrotoxicity associated with these drugs. There are concerns regarding the risk of renal injury associated with the antifibrinolytic agent aprotinin. Recent controversial evidence suggests that the use of aprotinin during coronary artery bypass graft (CABG) surgery may be associated with an increased risk of ARF requiring dialysis.

Glycaemic control

Strict glycaemic control using intensive insulin therapy improved survival and reduced the incidence of ARF requiring RRT in a landmark trial in mechanically ventilated surgical ICU patients. Perioperative hyperglycaemia during cardiac and vascular surgery is associated with increased renal morbidity and overall mortality. Although the current evidence suggests that strict normoglycaemia is required for optimum benefit, this approach increases the risk of hypoglycaemia, the clinical significance of which is unknown in the ICU setting. It is not yet clear whether rigorous intra-operative glycaemic control reduces morbidity and mortality in patients undergoing cardiac and vascular surgery.

Cardiac surgery

The conduct of CPB during cardiac surgery may affect the incidence of post-operative ARF. Limiting the duration of CPB and maintaining adequate flow and perfusion pressure are of primary importance. Several other strategies related to the management of the CPB circuit may reduce renal injury, including avoidance of excessive haemodilution, avoidance of red cell transfusion, extracorporeal leucodepletion, and haemofiltration during CPB. Many of the postulated mechanisms of ARF after cardiac surgery relate to the use of CPB, hence off-pump surgery may theoretically offer renal protection. However, the evidence that off-pump CABG (OPCABG) surgery reduces renal morbidity is conflicting.[8] New developments in minimally invasive surgical techniques that avoid ascending aortic manipulation may result in a reduction in renal morbidity.

Vascular surgery

Endovascular aneurysm repair (EVAR) is rapidly becoming the technique of choice for repair of abdominal aortic aneurysms, in preference to open surgical repair. Both techniques are associated with worsening renal dysfunction in patients with pre-existing renal insufficiency. At present, it is not clear whether there is a significant difference between open repair and EVAR in terms of the occurrence of acute post-operative renal dysfunction in patients with CRF.[9]

Post-operative complications

A number of post-operative complications are known to be associated with renal dysfunction. Prompt diagnosis and management of acute cardiac dysfunction, haemorrhage, sepsis, rhabdomyolysis, and intra-abdominal hypertension are essential to prevent the development of ARF. Rhabdomyolysis should be initially treated with aggressive intravascular volume expansion; diuretic therapy and urinary alkalinization may be considered. Abdominal compression syndrome caused by intra-abdominal hypertension is associated with diminished renal perfusion and may precipitate ischaemic ATN. Timely recognition of abdominal compression syndrome, by intra-vesical pressure measurement, followed by decompressive laparotomy may provide the optimal management of this condition.

Pharmacological strategies

The postulated pathophysiology of ATN suggests that perioperative interventions that optimize renal oxygen delivery may prevent ARF. However, pharmacological strategies (Table 3) that increase renal blood flow or decrease renal oxygen consumption have not proved successful. Despite extensive investigation, few drug interventions have been demonstrated to provide clinical benefit and some have been clearly shown to be ineffective. A recent systematic review examined 37 randomized, controlled trials comprising 1227 patients and concluded that there is no evidence that

Table 3 Postulated pharmacological perioperative renal protection strategies

Drug	
Vasodilators	Dopamine agonists
	Adenosine antagonists
	Calcium-channel antagonists
	Angiotensin-converting enzyme inhibitors
	Sodium nitroprusside
Diuretics	Loop diuretics
	Osmotic diuretics
Natriuretic peptides	Atrial natriuretic peptide
	Urodilatin
	B-type natriuretic peptide
Antioxidants	*N*-acetylcysteine
	Corticosteroids
Other agents	Volatile anaesthetic agents
	Insulin-like growth factor-1
	Erythropoietin
	Mesenchymal stem cells

pharmacological interventions are effective in protecting renal function during surgery.[10]

Dopamine agonists

Dopamine acts on a number of different types of receptors. Renal blood flow is increased by dopaminergic receptor-mediated renal vasodilatation, beta-adrenoreceptor stimulation increases cardiac output, and alpha-adrenoreceptor increases renal perfusion pressure. A large multi-centre trial has demonstrated that low-dose dopamine does not prevent ARF, avert the need for RRT, or reduce the mortality in critically ill patients with early acute renal dysfunction in ICU. In the perioperative setting, dopamine increases post-operative urine output but does not improve outcome. A number of systematic reviews have concluded that there is no role for low-dose dopamine for clinically significant renal protection.[11]

Dopexamine is a synthetic dopamine analogue with beta-adrenergic and dopaminergic effects. Perioperative use of dopexamine does not provide renal protection for cardiac or vascular surgical patients.[12]

Fenoldopam increases renal blood flow by its selective action on dopamine-1 receptors. At present, there is conflicting evidence regarding its usefulness as a potential renal protective agent. Recent trials suggest that the drug does not prevent radio-contrast-induced nephropathy in patients with pre-existing renal impairment, does not improve outcome in critically ill ICU patients with early acute renal dysfunction, and does not protect perioperative renal function in high-risk cardiac surgical patients. However, a meta-analysis of 16 randomized, controlled trials comprising 1290 patients suggested a beneficial impact of fenoldopam in critically ill patients.[13]

Other renal vasodilator agents

Theophylline, an adenosine antagonist, reverses adenosine-mediated renal arterial vasoconstriction, but it does not appear to prevent perioperative ARF during CABG. Similarly, *calcium-channel antagonists* and *angiotensin-converting enzyme inhibitors* have not been shown to produce renal protection. A recent single centre trial demonstrated that *sodium nitroprusside* administration during the rewarming phase of CPB in patients undergoing CABG decreases the incidence of post-operative ARF.

Diuretics

In the setting of acute renal dysfunction, diuretics increase urine output by decreasing tubular re-absorption through several mechanisms. Increasing tubular flow maintains patency and prevents obstruction and back-leak. Loop diuretics inhibit tubular re-absorption in the loop of Henlé whereas mannitol acts primarily as an osmotic diuretic. The available evidence for the use of diuretics in surgical and critically ill patients is scarce. The perioperative use of neither loop diuretics nor mannitol demonstrates significant renal protection in patients undergoing cardiac surgery. However, a recent meta-analysis of five randomized, controlled trials enrolling 555 patients demonstrated that loop diuretics did not increase mortality in patients with ARF.[14] A randomized trial of loop diuretic treatment for ARF in critical illness has been proposed.

Natriuretic peptides

Natriuretic peptides induce a natriuretic and diuretic effect by increasing glomerular perfusion pressure and filtration. These peptides have shown conflicting results in the prevention of ARF. Large multi-centre trials have demonstrated that atrial natriuretic peptide (ANP) does not prevent death or dialysis in critically ill patients with ARF. However, in a small single centre trial, recombinant human ANP has been shown to reduce the need for dialysis in post-operative cardiac surgical patients with early acute renal dysfunction.

N-acetylcysteine

Substantial evidence supports the prophylactic use of the antioxidant *N*-acetylcysteine (NAC), along with intravascular volume expansion, for the prevention of radio-contrast nephropathy. Disappointingly, recent trials in the perioperative and ICU settings have shown a lack of renal protective benefit of NAC. These trials have been performed in high-risk patients undergoing cardiac surgery,[15] open abdominal aortic aneurysm repair,[16] and abdominal aortic EVAR.

Future strategies

Several experimental strategies are currently undergoing investigation including volatile anaesthetic agents, insulin-like growth factor-1, erythropoietin, and mesenchymal stem cells.

Practical strategies

Practical strategies for perioperative renal protection are set out in Table 4.

Table 4 A practical approach to perioperative renal protection. CPB, cardiopulmonary bypass

Preoperative
Optimize volume status, cardiac output, and systemic arterial pressure
Withhold nephrotoxic drugs
Maintain glycaemic control in diabetic patients
Correct metabolic and electrolyte disturbances
Delay surgery until recovery of acute renal dysfunction if possible
Arrange pre-operative dialysis for dialysis-dependent patients
Administer isotonic i.v. fluids and *N*-acetylcysteine for prevention of radiocontrast-induced nephropathy
Intraoperative
Optimize volume status, cardiac output, and systemic arterial pressure
Avoid nephrotoxic drugs
Consider maintaining tight glycaemic control in all patients
Cardiac surgery
Maintain adequate flow and mean systemic arterial pressure during CPB
Limit the duration of CPB
Avoid excessive haemodilution
Avoid red cell transfusion
Consider extra-corporeal leucodepletion
Consider haemofiltration during CPB
Consider off-pump coronary artery bypass surgery
Vascular surgery
Consider abdominal aortic endovascular aneurysm repair
Post-operative
Avoid nephrotoxic drugs
Maintain strict glycaemic control in all patients
Promptly treat acute cardiac dysfunction
Control haemorrhage
Manage sepsis aggressively
Recognize and treat rhabdomyolysis
Recognize and treat intra-abdominal hypertension
Provide appropriate organ support for multiple organ dysfunction syndrome
Institute renal replacement therapy for RIFLE grade F acute renal dysfunction

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Please see multiple choice questions 23–26