Acute Kidney Injury Associated with Cardiac Surgery

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Acute renal failure (ARF) occurs in up to 30% of patients who undergo cardiac surgery, with dialysis being required in approximately 1% of all patients. The development of ARF is associated with substantial morbidity and mortality independent of all other factors. The pathogenesis of ARF involves multiple pathways. Hemodynamic, inflammatory, and nephrotoxic factors are involved and overlap each other in leading to kidney injury. Clinical studies have identified risk factors for ARF that can be used to determine effectively the risk for ARF in patients who undergo bypass surgery. These high-risk patients then can be targeted for renal protective strategies. Thus far, no single strategy has demonstrated conclusively its ability to prevent renal injury after bypass surgery. Several compounds such as atrial natriuretic peptide and N-acetylcysteine have shown promise, but large-scale trials are needed.

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Acute renal failure (ARF), depending on the specific definition, occurs in up to 30% of all patients who undergo cardiac surgery (1–15). ARF that requires dialysis occurs in approximately 1% (1–15). The development of kidney injury is associated with a high mortality, a more complicated hospital course, and a higher risk for infectious complications (1–15). Even minimal changes in serum creatinine that occur in the postoperative period are associated with a substantial decrease in survival (16). Furthermore, the majority of patients who develop ARF that requires dialysis (ARF-D) remain dialysis dependent, leading to significant long-term morbidity and mortality (17). Despite advances in bypass techniques, intensive care, and delivery of hemodialysis, mortality and morbidity associated with ARF have not markedly changed in the last decade (1–15). These data highlight the importance of understanding the pathophysiology of ARF associated with cardiac bypass surgery and implementing specific therapies that are based on this knowledge in well-designed clinical trials.

Incidence and Prognosis of ARF after Bypass Surgery

Depending on the definition of ARF, the incidence of ARF varies across studies, with a range of 1 to 30% (1–15). Conlon *et al.* (1) described a cohort of 2843 patients who underwent cardiopulmonary bypass (CPB) over a 2-yr period. ARF (defined as a rise in serum creatinine >1 mg/dl above baseline) occurred in 7.9% of patients, and ARF-D occurred in 0.7%. Other studies that used a definition of ARF as a 50% or greater rise in serum creatinine from baseline demonstrated a rate as high as 30% (2–15). Chertow *et al.* (15) analyzed 42,773 patients who underwent CPB and found an incidence of ARF-D of 1.1%. The incidence of ARF is dependent on the particular type of CPB surgery. Typical coronary artery bypass grafting has the lowest incidence of ARF (approximately 2.5%) and ARF-D (approximately 1%), followed by valvular surgery with an incidence of ARF of 2.8% and ARF-D of 1.7% (18,19). The highest risk group includes combined coronary artery bypass grafting/valvular surgery with an incidence of ARF of 4.6% and ARF-D of 3.3% (18,19)

Mortality associated with the development of ARF is as high as 60% in some studies but likely averages 15 to 30%, depending on the definition of ARF and the postoperative period studied (hospital discharge or 30-d mortality) (1–15). In patients who require dialysis, the mortality is uniformly high in all studies and averages 60 to 70% (1–15). Chertow *et al.* (15) in a multivariate analysis that adjusted for comorbid factors identified the occurrence of ARF-D as an independent determinant of the risk for death with an odds ratio of 7.9. It is interesting that even small rises in serum creatinine are associated with significant mortality. Lassnigg *et al.* (16) demonstrated that the 30-d mortality of patients who developed a 0- to 0.5-mg/dl and >0.5-mg/dl rise in serum creatinine was 2.77- and 18.64-fold higher, respectively, than patients without a change in serum creatinine. These results are qualitatively similar to studies by Thakar *et al.* (20) in which 31,677 patients who underwent cardiac surgery were analyzed. Mortality was 5.9% ($P < 0.0001$) when GFR declined 30% or more but did not require dialysis and 0.4% ($P < 0.001$) in patient with <30% decline in GFR. The development of post-CPB ARF also influences long-term mortality as identified by Loef *et al.* (21), who found that the hazard ratio for death at 100 mo after hospital discharge was 1.63 in patients who developed a 25% or greater rise in serum creatinine after surgery. This increase in long-term mortality was independent of whether renal function had recovered at discharge from the hospital. Lok *et al.* (22) also found that patients who experienced ARF after CPB had a relative risk for death at 1 yr of 4.6 as compared with patients who did not sustain renal injury.

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Patients who do develop ARF-D often remain dialysis dependent. Leacche *et al.* (17) studied 13,847 patients who underwent CPB procedures. Of patients who developed ARF-D, 64% required permanent dialysis and the 1-yr survival was only 10%.

The link between the development of ARF and mortality likely involves numerous factors, including those directly related to hemodialysis (hemodynamic instability, catheter-related infections, ventricular ectopy, and visceral ischemia); immune dysregulation associated with ARF; platelet dysfunction; and other, less defined associations. Registry data from Liano *et al.* (23) demonstrated that in patients with ARF, infections were the cause of death in 40%. In patients who underwent CPB, Thakar *et al.* (24) also demonstrated a high risk for infections. In patients with ARF-D, the incidence of serious infections, including sepsis, was 58.5% as compared with 3.3% in all patients who underwent CPB (24).

Risk Factors Associated with ARF

Several studies have examined the risk factors associated with the development of ARF after CPB (Table 1). The particular type of surgery is important, with valvular procedures associated with a higher risk. In almost all studies, certain risk factors have been repeatedly associated with an increased risk for ARF (2,4,6–8,14,25–30). These include female gender, reduced left ventricular function or the presence of congestive heart failure, diabetes, peripheral vascular disease, preoperative use of an intra-aortic balloon pump, chronic obstructive pulmonary disease, the need for emergent surgery, and an elevated preoperative serum creatinine. This last factor is perhaps the most predictive, with the risk for ARF-D approaching 10 to 20% in patients with a baseline preoperative creatinine 2.0 to 4.0 mg/dl (25–30). In patients with a preoperative creatinine >4.0 mg/dl, the risk for ARF-D rises to 25 to 28% (25–30). Importantly, almost all of the defined risk factors relate to either impaired renal perfusion or decreased renal reserve.

Several other risk factors have been identified but are more controversial and, thus, individually they do not play as prominent a role in determining the risk for ARF. In aggregate, however, these factors may be important and potentially modifiable. These include factors specifically related to the bypass procedure itself, such as cross-clamp time (31–33), duration of CPB (31–33), pulsatile *versus* nonpulsatile bypass flow (34,35), normothermic *versus* hypothermic bypass (36–38), and on- *versus* off-pump coronary artery bypass (OPCAB) surgery (39–45).

Table 1. Risk factors associated with ARF[a]

Patient-Related	Procedure-Related
Female gender	Length of CPB
Chronic obstructive pulmonary disease	Cross-clamp time
Diabetes	Off-pump *versus* on-pump
Peripheral vascular disease	Nonpulsatile flow
Renal insufficiency	Hemolysis
Congestive heart failure	Hemodilution
LV ejection fraction <35%	
Need for emergent surgery	
Cardiogenic shock (IABP)	
Left main coronary disease	

[a]LV, left ventricular; IABP, intra-aortic balloon pump; CPB, cardiopulmonary bypass.

One of the most controversial risk factors is OPCAB *versus* traditional on-pump CPB. OPCAB obviously removes the bypass circuit but can be associated with greater hemodynamic instability secondary to ventricular compression as the heart is manipulated to access the coronary arteries (42). This comparison allows separation of the risk factors specifically associated with the bypass procedure itself from other peri-, intra-, and postoperative factors. Early nonrandomized studies suggested that renal tubular injury (as assessed by urinary markers) was lessened in the group that received OPCAD (43,44). Subsequent studies have also suffered from the lack of randomization, single-site experience, and differences in patient comorbidities and baseline risk for developing ARF between the OPCAB and CPB groups. Thus, despite several large, retrospective series, the answer is still unclear, but the bulk of the data support a lower risk for ARF in patients who undergo OPCAB, especially patients with pre-existing renal insufficiency (45–48). This is further supported by a significant decrease in inflammatory markers in patients who undergo OPCAB as compared with those who undergo CPB (46,47).

CPB is associated with the generation of free hemoglobin and iron through hemolysis that typically occurs during the procedure (48). Hemolysis may be caused by cardiotomy suction, the duration of perfusion, occlusive roller pumps, turbulent flow in the oxygenator, and blood return through cell savers (48). This may contribute to oxidative stress and renal tubular injury (49). In an early study, a low preoperative serum ferritin level (potentially indicative of a reduced ability to bind free iron) was associated with an increased risk for ARF after CPB (50). However, a larger study could not validate this finding (32).

During CPB, hemodilution is induced to decrease blood viscosity in the hope of improving regional blood flow in the setting of hypoperfusion and hypothermia as well as limiting the need for blood transfusion (51,52). The resulting increase in regional blood flow is thought to offset any risk of decreased oxygen carrying capacity of the blood. However, two recent studies demonstrated that hemodilution (down to hematocrits <25%) is associated with an increased risk for renal injury as measured by changes in serum creatinine (53,54). This may be due to impairment of oxygen delivery to an already hypoxic renal medulla or to alterations in systemic inflammatory mediators caused by regional ischemia.

Predictive Scoring Systems

Several groups have developed clinical scoring systems that help to predict the risk for ARF with CPB (30,55,56). The aim is to select patients who are at high risk and then to adopt strategies that would offer renal protection. The most recent scoring system analyzed 33,217 patients with a large validation sample. A score is given on the basis of 13 preoperative factors and ranges from 0 to 17 (30) (Table 2). In the lowest risk group (score 0 to 2), the risk for ARF-D was 0.4%, whereas in the highest risk group (score 9 to 13), the risk rose to 21.5%. Chertow *et al.* (55) investigated the risk for developing ARF in 43,642 patients who underwent CPB. They were able to determine important preoperative clinical variables, such as patient age, preoperative creatinine clearance, use of an intra-aortic balloon pump, and left ventricular dysfunction, that predicted subsequent ARF. These clinical scoring systems require validation across several medical centers before their routine use can be adopted. Furthermore, given that these scoring systems attempt to identify a small number of high-risk patients, they will have good negative predictive power but necessarily low positive predictive power. However, they provide a very useful framework to identify patients who are at risk and may benefit from peri- or intraoperative renal protective strategies.

Pathogenesis of ARF

No systematic studies of the pathologic changes in the kidney have been undertaken in patients with ARF associated with CPB, and it is largely assumed that the pathologic lesion is acute tubular necrosis. This is usually confirmed by the presence of granular casts in the urine of patients who develop ARF. Physiologic studies by Moran and Myers (57) substantiated this in 10 patients with protracted severe ARF after CPB. It was demonstrated that the transmembrane gradient for glomerular ultrafiltration was significantly diminished, likely from intratubular obstruction and hypertension as a result of sloughing from injured tubular epithelial cells. They also demonstrated that there was significant transtubular back-leak of glomerular ultrafiltrate across the injured epithelium. These pathologic features are likely the downstream result of early events that are depicted in Figure 1 (58–63). In this schema, ARF begins with an early phase of vasomotor nephropathy in which there is associated alterations in vasoreactivity and renal

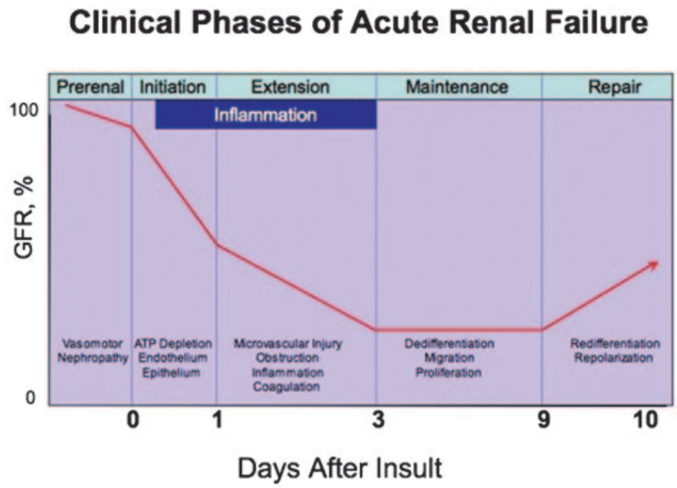

Figure 1. The clinical phases of acute renal failure occur across a continuum of stereotypical pathologic changes. From Sutton *et al.* (61).

perfusion leading to prerenal azotemia and eventually cellular ATP depletion and oxidative injury (initiation phase). These processes lead to activation of bone marrow–derived cells, endothelial cells, and renal epithelial cells and a resulting proinflammatory state. Inflammatory cells adhere to activated endothelium in the peritubular capillaries of the outer medulla, leading to medullary congestion and further hypoxic injury to the S3 segment of the proximal tubule (extension phase). Furthermore, elaboration of inflammatory mediators (as discussed below) leads to additional cellular injury. Tubule cells then begin the process of proliferation (maintenance phase) and re-differentiation. Ultimately, polarity and function are reconstituted (repair phase).

Clinically, the pathogenesis of ARF associated with CPB can be divided into preoperative, intraoperative, and postoperative events (Table 3). The sum of all of these various insults is ultimately reflected in the development of tubular injury that when severe enough is manifested as a rise in serum creatinine often associated with a decreased urine output.

Table 2. Cleveland Clinic Foundation Acute Renal Failure Scoring System[a]

Risk Factor	Points
Female gender	1
Congestive heart failure	2
LV ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG + valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to <2.1 mg/dl (reference to 1.2)	2
Preoperative creatinine >1.2[b]	5

[a]COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass graft. From Thakar *et al.* (30).
[b]Minimum score = 0; maximum score = 17.

Preoperative Events

As mentioned above, patients who enter CPB often have received minor or major renal insults. Patients have had recent myocardial infarctions or severe valvular disease with reduced left ventricular function and reduced renal perfusion. In the extreme, patients may be in cardiogenic shock and require inotropic support or an intra-aortic balloon pump. This preexisting prerenal state may be exacerbated by the use of diuretics, nonsteroidal anti-inflammatory drugs (NSAID), angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), which impair the autoregulation of renal blood flow (63). Furthermore, episodes of preoperative hypotension may lead to sublethal endothelial injury, which may impair the production of vasodilatory substances such as endothelial nitric oxide and promote vasoconstriction as a result of the release of endothelin, catecholamines, and angioten-

Table 3. Pathophysiologic factors in ARF[a]

Preoperative	Intraoperative	Postoperative
Lack of renal reserve	Decreased renal perfusion	Systemic inflammation
Renovascular disease	hypotension	Reduced LV function
Prerenal azotemia	lack of pulsatile flow	Vasoactive agents
recent diuresis	vasoactive agents	Hemodynamic instability
NPO status	anesthetic effects	Nephrotoxins
impaired LV function	Embolic events	Volume depletion
ACEI/ARB	CPB-induced inflammation	Sepsis
Nephrotoxins	Nephrotoxins	
intravenous contrast	free hemoglobin	
other medications		
Endotoxemia		
Inflammation		

[a]ARF, acute renal failure; NPO, nothing by mouth.

sin II, promoting further tubular ischemia and injury (64–66). Compounding these factors may be a lack of renal functional reserve as a result of underlying chronic kidney disease, including small- and large-vessel renovascular disease. These hemodynamic alterations in the preoperative setting may increase the vulnerability of the kidney (particularly the inner stripe of the outer medulla, where metabolic demands are high and the pO_2 is between 10 and 20 mmHg) to any further ischemic or nephrotoxic insult (67,68).

There may be activation of inflammatory mediators in the preoperative period that also serve to prime the kidney for subsequent injury. Endotoxin levels have been noted to be elevated in some patients in the preoperative period, despite no evidence of active infection, and these levels have been correlated to postoperative myocardial dysfunction (69–71). The elevation in preoperative endotoxin levels may reflect the effect of poor cardiac output states' contributing to intestinal ischemia and bacterial translocation or may be related to the preoperative care of patients (*e.g.*, subclinical catheter infections) (72). Levels of TNF-α have also been shown to be elevated in patients with pre-existing congestive heart failure and may also play a role in stimulation of the immune system (73,74).

Nephrotoxic medications or intravenous contrast that is given in the immediate preoperative period may also lead to overt or occult tubular injury that can interact with other factors to lead to ARF. These medications include vasoactive (pressor) drugs, NSAID, ACEI, ARB, and antibiotics.

Thus, the preoperative period is a critical time when events (hemodynamic, nephrotoxic, and inflammatory) can occur and can lead to subtle renal injury that is not necessarily reflected by changes in GFR. This subtle injury is likely substantiated by the fact that the preoperative risk scoring systems all rely on factors that ultimately act to reduce renal perfusion, result in lack of renal functional reserve, or set up a proinflammatory milieu.

Intraoperative Events

The intraoperative period is a critical time when patients are exposed to anesthesia and cardiopulmonary bypass. These events lead to dramatic hemodynamic effects as well as activation of both innate and adaptive immune responses that can initiate or extend renal injury.

Hemodynamic Effects

CPB is associated with significant hemodynamic changes, and the maintenance of cardiovascular stability during CPB requires interplay between the function of the CPB machine and patient factors such as systemic vascular resistance, venous compliance, and autoregulatory capacity of various vascular beds. The ultimate goal is to maintain regional perfusion at a level that supports optimal cellular and organ function. Thus, any decrease in renal perfusion during CPB, depending on its magnitude and duration, can lead to significant cellular injury.

Minute oxygen consumption (VO_2) is the major determinant of blood flow requirements normally and during CPB. Experimentally, CPB flow rates have been determined by calculating VO_2 at different perfusion rates. Perfusion is increased until VO_2 reaches a plateau, after which further increases in CPB flow rates do not lead to increases in oxygen consumption. In general, CPB flow rates of 1.8 to 2.2 L/min per m^2 are recommended on the basis of this analysis (75,76). However, it is not known what the effect of this flow rate is on regional renal blood flow and local oxygen delivery rates.

In addition to CPB flow rates, perfusion pressure during CPB is an important determinant of adequate nutrient delivery to vascular beds. Perfusion pressure is determined by the interaction of blood flow and overall arterial resistance. Resistance, in this case, is related to actual friction resistance because of the steady, nonpulsatile nature of CPB, which negates the elastance, inertial, and reflective components of arterial resistance during normal pulsatile flow (77). Friction resistance is primarily a function of vasomotor tone and blood viscosity (which is further dependent on hematocrit and temperature). Importantly, both variables are changing during CPB (*e.g.*, blood viscosity increases as hypothermia is induced and vasomotor tone is affected by anesthesia) and lead to associated changes in perfusion pressure. In general, a mean perfusion pressure of 50 to 70 mmHg is maintained during CPB (77).

Given hemodynamic goals of a mean perfusion pressure of 50 to 70 mmHg and CPB flow rates of 1.8 to 2.4 L/min per m^2, it is not known what effect these goals have on renal perfusion and oxygen delivery. The majority of studies on autoregulation of regional blood flow during CPB has focused on the cerebral circulation and demonstrates preserved cerebral autoregulation with these parameters (78,79). Small studies have suggested that mean arterial pressures on CPB >70 mmHg lead to higher intraoperative creatinine clearances but without a change in postoperative renal function as compared with pressures between 50 and 60 mmHg (80). Thus, it is likely that renal perfusion and autoregulation are also maintained as long as these hemodynamic goals are met. However, these values are likely near the minimum blood flows that support normal organ function, and any perturbation may lead to ischemia and cellular damage. Furthermore, the effect of these parameters in patients with impaired baseline renal function is not known. In patients with pre-existing hypertension, the relationship between renal blood flow and mean arterial pressure is shifted such that falls in BP that normally would not impair renal perfusion now do so. This means that higher mean pressure may be required to maintain adequate renal perfusion in these patients (81). Furthermore, if there is any degree of pre-existing acute tubular necrosis, then autoregulatory capacity of the kidney may be lost and renal blood flow becomes linearly dependent on pressure (82).

Whether alterations of these CPB flow and pressure goals would lead to improved renal outcomes is not known. However, Gold *et al.* (83) reported that maintenance of higher perfusion pressures in the range of a mean perfusion pressure of 70 mmHg was associated with a reduced incidence of cardiac and neurologic complications when compared with patients whose pressures were maintained at 50 to 60 mmHg. Renal function was not assessed in this study.

Other procedural factors that likely have an impact on renal hemodynamics include hemodilution (oxygen delivery capacity), hypothermia (oxygen consumption), the absence of pulsatile perfusion, and the use of crystalloid *versus* colloidal prime solutions. As discussed above, with the exception of hemodilution, no deleterious effects on renal function have been found associated with alterations in body temperature or in the absence of pulsatile flow.

In total, these hemodynamic changes may lead to regional renal ischemia and cellular injury that could either initiate acute kidney injury (AKI) or extend pre-existing renal injury. Furthermore, these hemodynamic changes are potentially modifiable.

Inflammation

CPB provokes a systemic inflammatory response syndrome (SIRS; Figure 2) (84,85). Contact of blood components with the artificial surface of the bypass circuit, ischemia-reperfusion injury, endotoxemia, operative trauma, nonpulsatile blood flow, and pre-existing left ventricular dysfunction all are possible causes of SIRS in this setting (86–88). In its most severe form, a spectrum of injury that includes one or more of the following clinical manifestations may be observed: Pulmonary, renal, gastrointestinal, central nervous system, and myocardial dysfunction; coagulopathy; vasodilation and increased capillary permeability; hemolysis; pyrexia; and increased susceptibility to infection (89).

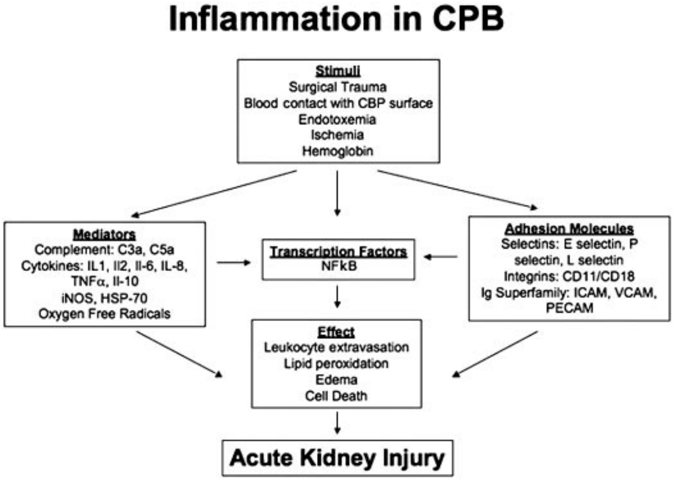

Figure 2. The inflammatory cascade activated by cardiac bypass surgery and its role in the production of acute kidney injury. Stimuli during the surgical procedure activate a host of inflammatory mediators, adhesion molecules, and proinflammatory transcription factors. These effects lead to cellular injury and acute renal failure.

During CPB, both neutrophils and vascular endothelium are activated with upregulation of adhesion molecules such as CD11b and CD41 (89–92). Platelets also undergo activation, degranulation, and adherence to vascular endothelium (91,93). These events led to elaboration of cytotoxic oxygen-derived free radicals (94), proteases (95), cytokines (96), and chemokines (96,97). These inflammatory mediators, such as IL-6, IL-8, and TNF-α, show a considerable rise in serum levels during CPB and generally reach peak levels 2 to 4 h after termination of CPB (84).

CPB is also a potent activator of factor XII (Hageman factor) to factor XIIa (90). This process initiates the intrinsic coagulation system, the kallikrein system, and the fibrinolytic system (97). Furthermore, complement proteins are activated through both the classical and the alternative pathways (97–99). Ultimately, this humoral response amplifies the cellular response that leads to neutrophil, endothelial, and monocyte activation and further elaboration of proinflammatory cytokines (97–101). Finally, diffuse end-organ ischemia likely causes endothelial cells, circulating monocytes, and tissue-fixed macrophages to release cytokines and oxygen-derived free radicals that further drive the inflammatory response (97–101).

The end result of this generalized inflammatory response induced by CPB within the kidney is not known. It is interesting that animal models of renal ischemia-reperfusion injury have clearly demonstrated the pathologic role of interstitial inflammation and the elaboration of proinflammatory cytokines and reactive oxygen species in the production of tubular injury (100–103). This local inflammatory response in experimental models is identical to that seen on a more global scale during CPB. Thus, it is likely a safe assumption that CPB-induced inflammation has significant deleterious effects on the kidney through similar mechanisms. Despite efforts to produce a CPB system that does not produce contact activation of blood components, this goal has not been realized and CPB still remains a potent proinflammatory stimulus (104,105).

Other Events Associated with CPB

Macroscopic and microscopic emboli, both gaseous and particulate, are often generated during CPB. These emboli are temporally related to certain intraoperative events such as aortic cannulation and aortic clamp placement and release (106–109). One study demonstrated a significant correlation between the total number of Doppler-detected emboli and postoperative changes in serum creatinine (109). This suggests that embolic events to the renal circulation may be responsible in part for postoperative changes in GFR.

Aprotinin is a serine protease inhibitor and potent antifibrinolytic agent that is used to attenuate blood loss and transfusion requirements during CPB (110). Aprotinin is eliminated by glomerular filtration and is actively reabsorbed by the proximal tubules, where it is metabolized (111). Aprotinin also inhibits the production of renal kallikreins and kinins involved in vasodilatory responses (112). For these reasons, there has been concern that the use of aprotinin may lead to renal injury. Several studies in patients who underwent CPB, as well as liver transplantation, did not demonstrate any renal toxicity directly attributable to aprotinin use (113–115).

CPB exposes blood to nonphysiologic surfaces and shear forces that lead to lysis of red blood cells with release of free hemoglobin into the circulation (116). In the presence of oxidants such as hydrogen peroxide and superoxide, free low molecular mass iron is released from the heme moiety into the circulation (117). This redox active iron is able to participate in organic and inorganic oxygen radical reactions, such as stimulating lipid peroxidation and catalyzing the formation of damaging hydroxyl radicals with subsequent tissue damage (118). Normally, iron-transporting proteins such as transferrin and lactoferrin sequester this free iron and minimize its potential toxicity (119). However, in some cases, the release of free iron can be so great as to saturate the iron-binding capacity of transferrin. At this point, all iron-binding antioxidant capacity is lost and the serum displays pro-oxidant features (120). How often this occurs during CPB is not fully known, but it may be as high as 25% of cases (120,121). Reperfusion injury during CPB may exacerbate further the oxidant stress in the setting of free circulating iron. However, Tuttle *et al.* (32) could not find an association between low iron-binding capacity and the risk for ARF after CPB. Although deferoxamine has been demonstrated to decrease the occurrence of lipid peroxidation during CPB, no studies have investigated any protective role of iron chelation in human kidney injury (122).

Postoperative Events

The postoperative events that are critical in affecting renal function are similar to traditional causative mechanisms seen in the general intensive care setting. Thus, the use of vasoactive agents, hemodynamic instability, exposure to nephrotoxic medications, volume depletion, and sepsis/SIRS all are critical events that can lead to kidney injury. A critical factor is postoperative cardiac performance and the need for either inotropic or mechanical support. In the presence of postoperative left ventricular dysfunction, the risk for significant renal injury becomes very high as the vulnerable kidney is subjected to marginal perfusion pressures.

General Measures to Prevent AKI after Cardiac Surgery

Identification of High-Risk Patients

In patients who undergo cardiac surgery, identifying patients who are at high risk for ARF is critically important. The important risk factors and scoring systems that can be used for this identification purpose have been discussed above.

Optimization of Renal Perfusion and Avoidance of Nephrotoxins

Factors that alter renal blood flow and lead to prerenal azotemia should be identified and corrected. Treatment of volume depletion and congestive heart failure before cardiac surgery will increase cardiac output and renal perfusion. Perioperative hydration and the use of hemodynamic monitoring and inotropic agents to optimize cardiac output may be necessary. It is unknown whether intraoperative optimization of bypass flow, perfusion pressure, and oxygen delivery would affect the subsequent development of AKI, although conceptually this would seem to be a reasonable goal. Medications such as NSAID and other nephrotoxic agents should be discontinued. Whether ACEI and ARB should be discontinued before surgery is not known and is a source of some debate (123–125). If radiographic contrast is needed, then newer isosmolar contrast agents may be less toxic (126). In stable patients, cardiac surgery should be postponed in patients with contrast-induced ARF.

Pharmacologic Interventions to Prevent AKI after Cardiac Surgery

Pharmacologic interventions have been attempted with inconsistent results, and at this time, there are no known drugs that have demonstrated conclusively renal protection (Table 4). The failure of these measures to prevent ARF after cardiac surgery may be related in part to a number of factors. First, the pathophysiology of ARF after CPB is more complex than originally considered, and simple approaches to target single pathways are unlikely to succeed. Second, late pharmacologic intervention is likely to meet with failure. Third, patient populations that have been studied are often at low risk for renal dysfunction after CPB, thus potentially masking small beneficial effects of therapies. Last, most clinical trials enroll a small number of patients and are powered inadequately to detect small benefits. Most therapeutic trials in ARF after CPB have been prevention studies in which treatment was initiated

Table 4. Pharmacologic interventions for the prevention of kidney injury after CPB

Treatment	RCT	*n*	Protection	Comments
Diuretics				
ref. 140	Y	126	None	Furosemide deleterious
ref. 141	N	50	None	Furosemide deleterious
Dopamine				
ref. 127	Y	50	None	Dopamine showed no benefit
ref. 128	Y	40	None	Dopamine showed no benefit
Fenoldopam				
ref. 131	N	108	Yes	50% decrease in ARF
ref. 132	Y	80	Yes	0.39 mg/dl lower Scr post-op
ref. 133	N	70	Yes	Case-control series, lower ARF
Theophylline				
ref. 134	Y	56	None	Scr and GFR unchanged
ANP				
ref. 138	Y	61	Yes	Less dialysis required at day 21
Mannitol				
ref. 144	Y	40	Yes	Lower Scr in treated children
ref. 145	N	56	Yes	Higher urine output with mannitol
ref. 146	N	15	No	No difference in urinary markers[b]
ref. 147	Y	100	No	No difference in urinary markers[b]
Pentoxifylline				
ref. 150	Y	40	Yes	No change in GFR, less injury by urinary markers[b]
Dexamethasone				
ref. 152	Y	20	No	No change in GFR, urinary markers[b]
Clonidine				
ref. 156	Y	156	Yes	Higher GFR in clonidine group
ref. 157	Y	48	Yes	Higher GFR in clonidine group
Diltiazem				
ref. 160	Y	24	No	Similar GFR to control
ref. 161	Y	60	Yes	Improvement in urinary markers[b]
ref. 162	N	414	No	Increased ARF with diltiazem
ref. 163	Y	330	No	No difference in GFR or ARF

[a]RCT, randomized, controlled trial; Scr, serum creatinine.
[b]Refers to the excretion of tubular proteins that can serve as a sensitive marker of tubular injury (164).

before the insult and in the majority of cases have shown no significant benefits. These strategies are listed in Table 4 and reviewed briefly here.

Drugs that Increase Renal Blood Flow

In low doses (3 μg/kg per min), dopamine stimulates DA-1 and DA-2 dopamine receptors, increasing renal blood flow and inhibiting proximal tubule sodium reabsorption. Although dopamine has been used extensively, studies have failed to show its efficacy in ARF after cardiac surgery (127,128) or associated with other conditions (129). Thus, there is no role for the use of dopamine in the treatment or prevention of ARF.

Fenoldopam is a selective DA-1 agonist that has been used in the prevention of ARF with variable results. In patients who had chronic kidney disease and underwent cardiac angiography, fenoldopam failed to reduce renal dysfunction, 30-d morality, dialysis, or rehospitalization (130). However, small randomized or uncontrolled studies that used fenoldopam demonstrated a reduction of renal dysfunction in patients who underwent cardiac surgery (131–133). A potential complication is the associated systemic hypotension that occurs after administration of fenoldopam. The beneficial effect of renal vasodilation in this situation may be offset by systemic hypotension that results in an overall net reduction of blood flow to the kidney. This systemic hypotensive effect may be abrogated by local infusion of fenoldopam directly into the renal arteries using a novel vascular delivery system (Be*neph*it catheter; FlowMedica Inc., Fremont, CA; www.flowmedica.com).

Theophylline, a nonselective adenosine antagonist, is thought to block vasoconstriction induced by A1-adenosine receptors. In a recent clinical trial, theophylline infusion in CPB was ineffective in reducing the incidence of ARF (134).

Drugs that Induce Natriuresis

Atrial natriuretic peptide (ANP) increases natriuresis by increasing GFR as well as by inhibiting sodium reabsorption by the medullary collecting duct (135). In a multicenter trial, anaritide, a 25–amino acid synthetic form of ANP was administered to critically ill patients to treat acute tubular necrosis (136). Whether patients received anaritide or not, the dialysis-free survival was the same in both groups. Although a subgroup of oliguric patients benefited from anaritide in the original study, this observation was not confirmed in a follow-up study (137). Hypotension was a complicating factor in 46% of patients who received anaritide (136,137). In a recent study, recombinant human ANP (rhANP) was used to treat ARF after cardiac surgery in patients who required inotropic support for heart failure (138). In patients who received rhANP, there was a significant reduction in the incidence of dialysis at day 21 after the start of treatment. In this trial, ANP was infused at a lower rate (50 as opposed to 200 ng/kg per min; thus lowering the incidence of hypotension) and for a more prolonged period than previous studies. These changes may explain the benefit seen in this study as opposed to earlier ones.

Diuretics may reduce the severity of ARF by preventing tubule obstruction and decreasing oxygen consumption (139). In a double-blind, randomized, controlled trial, furosemide treatment was found not to be protective as the incidence of ARF was twice that of the dopamine or placebo group (140). Similar negative results have been seen in other studies (141,142).

Mannitol has a variety of effects, including the production of an osmotic diuresis with a reduction of tubular obstruction, as well as the capability of scavenging free radicals. It is often added to the prime solution during CPB, with the thought that it may help to maintain urine output during the procedure, minimize tissue edema, and serve as a free radical scavenger (143). An early study in children who underwent cardiac surgery demonstrated than prophylactic administration of mannitol (0.5 g/kg body wt) was beneficial in the prevention of ARF (144). Fisher *et al.* (145) demonstrated that mannitol added to the CPB prime solution was effective at maintaining urine output at varying doses. However, several other studies did not confirm these findings, and the potential role of mannitol remains unclear (146,147). In fact, Carcoana *et al.* (147) showed an increased urinary excretion of β-2 microglobulin in patients who received mannitol and dopamine, suggestive of increased tubular injury in this group.

Sirivella *et al.* randomly assigned 100 patients with postoperative oliguric or anuric renal failure to therapy with either intermittent doses of loop diuretics or a continuous infusion of mannitol, furosemide, and dopamine (2 mg/kg per min) (148). Whereas 90% of patients who received the intermittent diuretic required dialysis, only 6.7% of the patients who received the continuous mannitol, furosemide, and dopamine infusion required dialysis. Furthermore, early therapy with this "cocktail" was associated with early restoration of renal function. Future studies are required before this approach can be broadly recommended.

Drugs that Block Inflammation

Inflammation is well documented to occur during CPB and has a prominent role in the pathogenesis of ARF and CPB (63,97). It thus is an attractive therapeutic target. Pentoxifylline, a phosphodiesterase inhibitor, blocks the activation of neutrophils by TNF-α and IL-1 (149) and TNF-α release by inflammatory cells (150). Pentoxifylline has been demonstrated to reduce cardiac dysfunction and TNF-α release in ischemia-reperfusion models (151). However, pentoxifylline did not affect renal function in elderly patients who underwent cardiac surgery (152). Dexamethasone also failed to protect against renal dysfunction after cardiac surgery (153). A recent study examined the effect of blocking complement activation in patients who underwent CPB. A single-chain antibody specific for human C5 (pexelizumab) was found to block complement activation and postoperative myocardial injury. However, renal function was not an outcome measure of this pilot study (154).

N-acetylcysteine (N-AC) has been shown to block inflammation and oxidant stress in cardiac surgery patients and thus may hold promise as a simple, nontoxic protective measure (155,156). However, N-AC has not been used in a prospective clinical trial that examines renal outcomes. N-AC has been studied most extensively in the prevention of radiocontrast-induced nephropathy. In this area, the utility of N-AC has been questioned with the publication of a meta-analysis of 16 controlled studies that demonstrated no protective benefit (157).

Other Strategies

The sympathetic nervous system is activated during and after cardiac surgery and may lead to impairment of renal function through a hemodynamic mechanism. Clonidine (an α-2 agonist) has been used to attenuate these effects, with improvement in hemodynamic stability during CPB (158). In a study of 48 normal-risk patients who underwent cardiac surgery, preoperative treatment with clonidine prevented the deterioration of renal function in this small trial, with creatinine clearances significantly higher in the clonidine-treated group 24 h after CPB (159).

Diltiazem has been used in clinical trials to prevent ARF after cardiothoracic surgery. Diltiazem has been shown to inhibit some of the inflammatory effects of CPB and is often used to prevent vasospasm of radial grafts (160,161). Although diltiazem reduced urinary excretion of markers of tubule injury (α glutathione s-transferase and N-acetyl-β-glucosaminidase) (162), its effectiveness in the prevention of renal dysfunction was inconsistent (163–165).

In patients who were at highest risk for AKI, prophylactic hemodialysis has been attempted (166). In a single study, 44 patients with a baseline serum creatinine >2.5 mg/dl were randomly assigned to either perioperative prophylactic dialysis or dialysis only when postoperative ARF that required the procedure was indicated (control). In the group that received prophylactic dialysis, mortality was 4.8 *versus* 30.4% in the control group. Furthermore, postoperative ARF that required dialysis was reduced from 34.8% in the control group to 4.8% in the intervention arm. These results will have to be repeated in other randomized, controlled studies before this invasive approach can be broadly recommended.

Conclusion

CPB surgery is associated with a high risk for AKI. This injury is associated further with substantial morbidity and mortality. The pathogenesis of kidney injury during CPB is complex and involves hemodynamic, inflammatory, and other mechanisms that interact at a cellular level. At present, no pharmacologic interventions have demonstrated conclusively efficacy in the prevention of renal dysfunction after cardiac surgery. Therapies such as rhANP, fenoldopam, N-AC, and clonidine have shown modestly encouraging results in small trials and need to be confirmed in larger studies that are designed appropriately to assess renal outcomes.

Ultimately, a successful therapy will utilize strategies that target these multiple pathways. This integrated strategy would target hemodynamic, inflammatory, and oxidative pathways and act both at the points of proximal cellular injury and at later downstream events, such as tubular regeneration. CPB offers an attractive model to study these pathways, because the timing of the insult is known and potentially modifiable.

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