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Cardiac surgery-associated acute kidney injury

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Abstract

Acute kidney injury develops in up to 30% of patients who undergo cardiac surgery, with up to 3% of patients requiring dialysis. The requirement for dialysis after cardiac surgery is associated with an increased risk of infection, prolonged stay in critical care units and long-term need for dialysis. The development of acute kidney injury is independently associated with substantial short- and long-term morbidity and mortality. Its pathogenesis involves multiple pathways. Haemodynamic, inflammatory, metabolic and nephrotoxic factors are involved and overlap each other leading to kidney injury. Clinical studies have identified predictors for cardiac surgery-associated acute kidney injury that can be used effectively to determine the risk for acute kidney injury in patients undergoing cardiac surgery. High-risk patients can be targeted for renal protective strategies. Nonetheless, there is little compelling evidence from randomized trials supporting specific interventions to protect or prevent acute kidney injury in cardiac surgery patients. Several strategies have shown some promise, including less invasive procedures in those at greatest risk, natriuretic peptide, fenoldopam, preoperative hydration, preoperative optimization of anaemia and postoperative early use of renal replacement therapy. The efficacy of larger-scale trials remains to be confirmed.

Keywords: Cardiac surgery • Acute kidney injury • Perioperative complications • Prediction • Prevention • Therapy

INTRODUCTION

Cardiac surgery-associated acute kidney injury (CSA-AKI) is characterized by an abrupt deterioration in kidney function following cardiac surgery manifesting as a reduction in glomerular filtration rate (GFR) [1, 2]. Depending on the definition used, the incidence of CSA-AKI is reported to range from 0.3 to 29.7% [3, 4]. AKI requiring dialysis (AKI-D) occurs in 1.2–3.0% of cardiac surgery cohorts [5–7] and is independently associated with mortality. Data suggest that even a small increase (0.3–0.5 mg/dl) in serum creatinine (sCr) after cardiac surgery is associated with a nearly 3-fold increase in 30-day mortality, while a larger increase of >0.5 mg/dl is associated with more than an 18-fold increase in 30-day mortality [4]. Although the overall mortality after open-heart surgery ranges between 1 and 8%, CSA-AKI is associated with a >4-fold increase in the odds of death [8] and significant increases in resource use. Patients requiring renal replacement therapy (RRT) have significantly longer in-hospital stay and notably increased mortality of up to 63% [9]. The development of CSA-AKI is associated with a significant increase in infectious complications [10]. Cardiac surgery on cardiopulmonary bypass (CPB) is the second most common cause of AKI in intensive care unit (ICU) after sepsis [11]. In this review, we will focus on the pathogenesis, risk prediction, early detection using biomarkers and promising protection strategies for CSA-AKI.

DEFINING CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY

AKI has historically suffered from heterogenous definitions. In 2004, the risk-injury-failure-loss-end-stage kidney disease (RIFLE) classification by the Acute Dialysis Quality Initiative Group was introduced as a consensus definition addressing early detection and grading of severity of AKI [12]. The RIFLE criteria have been validated and appear to be a useful tool for diagnosing and monitoring the severity and progression of AKI [13]. The Acute Kidney Injury Network (AKIN) proposed a modification of the RIFLE classification subsequently [14]. Stage 1 of the AKIN classification has been broadened to include patients with an increase in sCr of at least 0.3 mg/dl greater than baseline, based upon accumulating evidence that even minor increments in sCr are associated with adverse outcomes [4]. Conversely, the RIFLE criteria require a 50% increase in sCr from baseline to be included in the risk category (Fig. 1).

The AKIN classification uses a 48 h time window, whereas RIFLE uses a 7-day window. Data suggest that AKIN criteria applied in patients undergoing cardiac surgery without correction of sCr for fluid balance may lead to overdiagnosis of AKI (poor positive predictive value). Balancing limitations of both definition sets of AKI, application of the RIFLE criteria in patients undergoing cardiac surgery

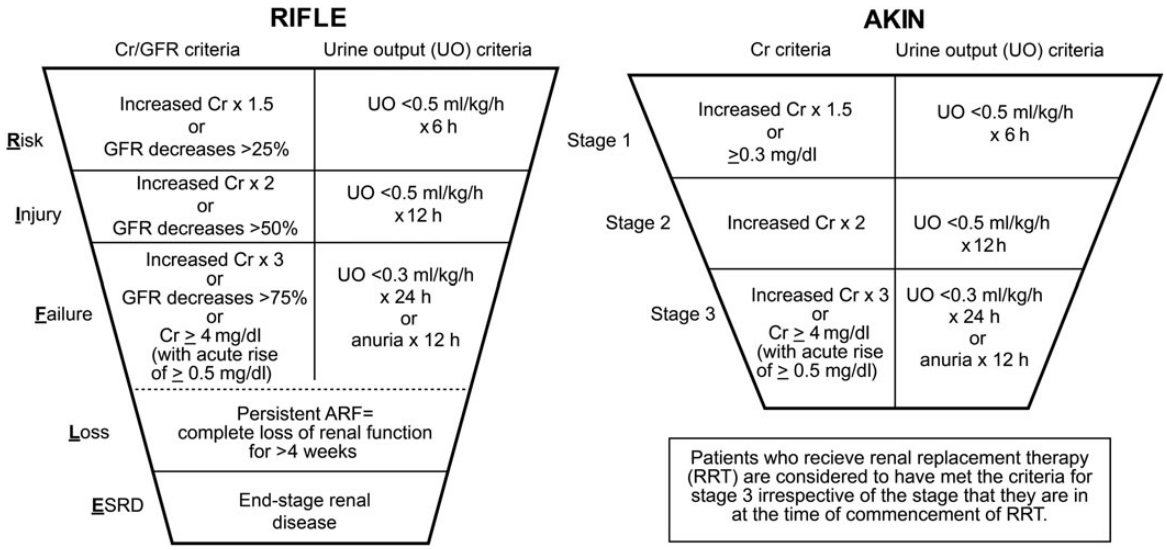

Figure 1: RIFLE and AKIN classifications for acute kidney injury. Cr: serum creatinine; UO: urinary output. With permission from Cruz *et al.* [15].

is suggested [16]. However, both definitions have limitations. Both rely on sCr, which is known to be a less-than-ideal biomarker for AKI. sCr is affected by the level of GFR and by factors independent of GFR, including age, gender, race, body size, diet, certain drugs and laboratory analytical methods [17]. Furthermore, neither indicates the origin of kidney injury (e.g. tubular or glomerular injury). The diagnostic definitions for both classifications are outlined in Fig. 1.

LONG-TERM OUTCOMES AFTER CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY

The available data suggest that CSA-AKI may be a useful predictor of poor long-term prognosis, including chronic renal insufficiency and long-term mortality. According to Hobson *et al.* [18] up to 45% of patients who require dialysis after cardiac surgery may remain dialysis dependant, 33% may have partial renal recovery and only 21% may have complete renal recovery at the time of hospital discharge. Their retrospective study of 2973 patients observed a significant increase in mortality 1 year after the operation in the group with AKI compared with the group with no AKI after cardiac surgery (11 vs 5%). A similar difference was observed 10 years after the operation (56 vs 37%). The survival rate 10 years post-cardiac surgery according to RIFLE criteria was as follows: risk 51%, injury 42% and failure 26%.

Early recovery of renal function after AKI is associated with improved long-term survival in patients undergoing cardiac operations. The percentage decrease in creatinine 24 h after its peak value was the recovery variable that showed the strongest association with long-term mortality [19], with individuals showing the greatest decrease in sCr also having the lowest long-term mortality.

PATHOGENESIS OF CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY

International consensus statements were drawn up regarding the pathophysiology and treatment of AKI in cardiac surgery [2, 20]. The pathophysiological features of CSA-AKI are complex and multifactorial including numerous factors: exogenous toxins, endogenous toxins, metabolic factors, ischaemia–reperfusion injury, microembolization, neurohormonal activation, inflammation, oxidative stress and haemodynamic factors (Table 1). These mechanisms of injury are likely to be active at different times with different intensities, are interrelated and probably synergistic (Fig. 2).

Several nephrotoxic drugs may be associated with CSA-AKI. Intravenous iodinated contrast given in the immediate preoperative period may lead to tubular injury. In a recent study, cardiac catheterization within 5 days of surgery was associated with an almost 2-fold increase in the odds of AKI [22]. Non-steroidal anti-inflammatory drugs given preoperatively might impair the autoregulation of renal blood flow [23]. The impact of the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers on CSA-AKI is still controversial [24].

CPB itself contributes to the pathogenesis by activating a systemic inflammatory response, altering regional blood flow and vasomotor tone in kidneys and generating microemboli. CPB-associated systemic inflammatory response syndrome is triggered primarily by direct contact of blood with the artificial surface of the bypass circuit. Instituting CPB itself decreases the effective renal perfusion pressure up to 30% by altering vasomotor tone and reducing the renal parenchymal oxygen tension, contributing to ischaemia–reperfusion injury [25]. Microemboli are formed during CPB and may be composed of fibrin, platelet aggregates, cellular debris, fat and air. The CPB system filters emboli larger than 40 μm however smaller emboli that are not effectively filtered can damage renal capillaries directly [25]. Haemolysis and release of free haemoglobin during CPB is a well-recognized nephrotoxic mechanism. Increased levels of free red blood cell constituents together with exhaustion of their scavengers, transferrin and haptoglobin, result in a variety of serious clinical sequelae including increased systemic vascular resistance, altered coagulation activity, platelet dysfunction, renal tubular damage and increased mortality [26].

IDENTIFYING AND PREDICTING PATIENTS AT RISK OF CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY

There are several well-recognized independent risk factors for CSA-AKI. They include female sex, preoperative cardiac function (cardiogenic shock, New York Heart Association IV, reduced LV

Table 1: Patophysiological factors in cardiac surgery-associated acute kidney injury.

Preoperative	Intraoperative	Postoperative
Prerenal azotemia	Decreased renal perfusion	SIRS
Impaired LV function	Hypotension	Low CO
Recent over-diuresis	Anaesthetic effect	Volume depletion
Nephrotoxins	Autoregulation impairment	Sepsis
Intravenous contrast	DM	
Other drugs	Vascular disease	
Renovascular disease	Nephrotoxics	
	Free iron and free haemoglobin	
	SIRS	
	Embolic events	
	Haemodilution	

CO: cardiac output; DM: diabetes mellitus; LV: left ventricle; SIRS: systemic inflammatory response syndrome.

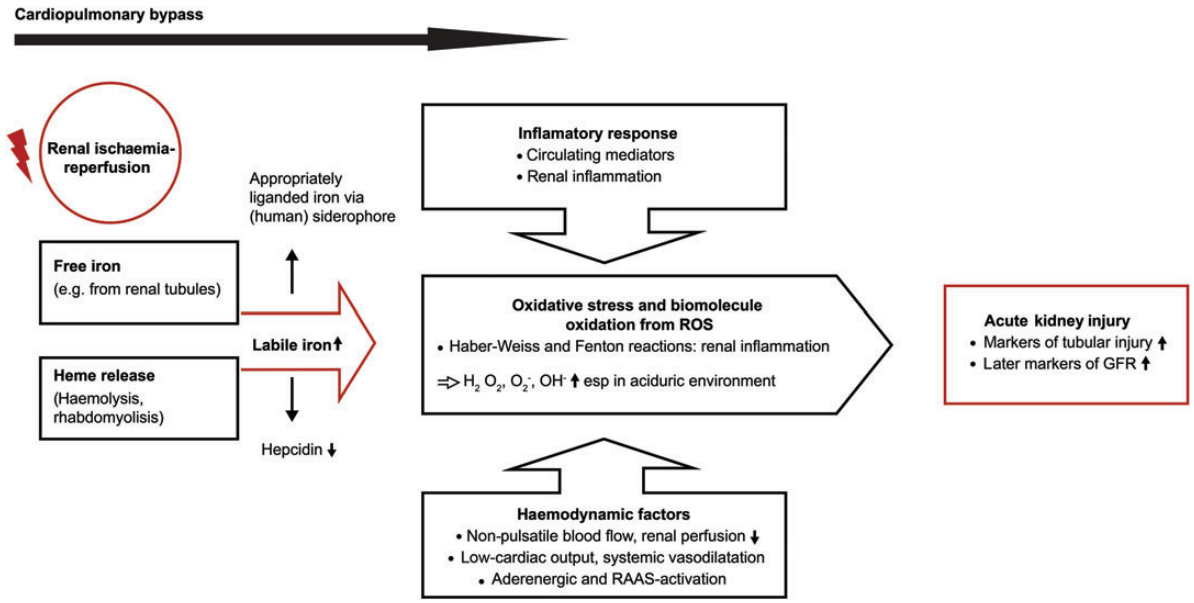

Figure 2: The role of ischaemia–reperfusion injury during CPB and of reactive oxygen species (ROS), poorly ligated iron and iron metabolism regulators in affecting renal injury. GFR: glomerular filtration rate; RAAS: renin–angiotensin–aldosterone system. With permission from Haase *et al.* [21].

ejection fraction, presence of congestive heart failure, preoperative use of an intra-aortic balloon pump), diabetes mellitus, peripheral vascular disease, chronic obstructive pulmonary disease, emergent surgery, reintervention, intraoperative use of aprotinin and preoperative renal impairment [estimated glomerular filtration rate (eGFR) <60 ml/min, creatinine >2.1 mg/dl] [2, 5–8, 27]. This last factor is perhaps the most predictive of CSA-AKI. Other risk factors relate to the operative procedure, such as cross-clamp time [27, 28], the duration of CPB and off-pump coronary artery bypass surgery (CABG). Data from a multicentre observational study suggest preoperative diuretic use as an independent risk factor for AKI-D post-cardiac surgery [27]. Other important intraoperative independent risk factors include transfusion of packed red blood cells (PRBC) and haemodilution on CPB. Based on current evidence, the blood conservation guidelines published by the Society of Thoracic Surgeons and the Society of Cardiovascular Aanesthesiologists suggest maintaining a haematocrit of at least 21% (haemoglobin concentration, 7 g/dl) during CPB [29]. Preoperative anaemia, defined as haemoglobin <12.5 mg/dl, has also been shown to be associated with an increased risk of CSA-AKI, regardless of PRBC transfusion intraoperatively [30]. For all patients undergoing CPB, the risk of AKI increases progressively with the complexity of the planned procedure. Specifically, the risk is lowest in those who undergo coronary artery bypass grafting (CABG) only, while it increases for patients undergoing valve replacement surgery, and is greatest after combined CABG and valve procedures [6].

Several validated risk-predictive models of CSA-AKI requiring RRT have been developed [5–7] to predict AKI risk preoperatively. In recent risk-predictive model comparisons, the Cleveland Clinic score showed promising performance [31, 32]. The models for AKI requiring dialysis are the most robust and externally validated. Among the prediction rules for AKI requiring dialysis after cardiac surgery, the Cleveland Clinic model has been the most widely tested thus far and has shown high discrimination in most of the tested populations. Notably, the Cleveland Clinic Score was validated in a single-centre cohort for predicting not only AKI-D, but

Table 2: Interventions associated with a decreased risk of acute kidney injury after cardiac surgery.

Preoperative	Intraoperative	Postoperative
Adequate hidration and avoid loop diuretics	Avoid anaemia	Start statin when feasible
Surgery after 5 days of coronary angiography	Avoid haemodilution	Avoid nephrotoxic agents
Statin use	Off-pump CABG	Use of early (<3 days) RRT
Anaemia optimization	Use of intra-aortic filtration	
	Use of atrial natriuretic peptide	
	Use of fenoldopam	
	Shorter duration of CPB	
	Optimal glucose control	

RRT: renal replacement therapy.

also milder AKI, defined as RIFLE-injury/AKIN 2, showing acceptable performance for both outcomes [area under the receiver operating characteristic curve (AUROC) of 0.86 and 0.81, respectively].

The Cleveland Clinic score [6] was based on an analysis of a cohort of 33 217 patients. The score was assigned based on 13 preoperative factors, ranging from 0 to 17. In this scoring, patients with the lowest scores (0–2) had a 0.4% risk of developing AKI requiring dialysis, while those with the highest scores (9–13) had a risk of 21.5% of developing the same. Mehta *et al.* [5] used a large study cohort from the Society of Thoracic Surgeons National Cardiac Surgery database composed of almost 450 000 patients who underwent CABG alone, mitral or aortic valve surgery alone or the combination of CABG and aortic or mitral valve surgery between July 2002 and December 2004, to derive a predictive model for postoperative RRT, including a bedside tool to calculate the additive risk score. Wijeysundera *et al.* [7] created a simplified renal index in which only eight factors were used to predict postoperative RRT. New predictive models for CSA-AKI, including intraoperative factors, have been recently published from the Cleveland database. Data suggest that these new models improve performance compared with previous predictive scores [33]. These predictive models may have value for preoperatively informing our patients better, for using potential renal protective strategies in high-risk patients, for better using our resources, for selecting high-risk patients for clinical trials and for making comparisons among institutions.

RENAL PROTECTIVE STRATEGIES

Pharmacological interventions have been inconsistent with their efficacy, and currently there are no known drugs that have conclusively conferred renal protection. This failure might be related to a number of factors.

(i) The pathophysiology of AKI following cardiac surgery is complex, and simple approaches to target single pathways are unlikely to succeed.
(ii) Late pharmacological intervention (measured by a rise in sCr) is likely to meet with failure. By the time sCr is elevated, the person may already have lost 50% of kidney function.
(iii) Patient populations that have been studied are often at low risk of renal dysfunction post-CPB, thus potentially masking small beneficial effects of therapies.
(iv) Most clinical trials enrolled a small number of subjects and are therefore inadequately powered to detect small benefits.

Renal protective strategies are summarized in Table 2.

Preoperative strategies

In the preoperative period, the major goals include optimizing cardiac output, avoiding intravascular volume depletion and continuing congestive heart failure treatment before surgery. Optimizing renal function in elective surgery for patients with reversible AKI should be considered.

Aspirin use has been shown to reduce the risk of cardiovascular events in patients with coronary artery disease. Thus, it is common that patients take aspirin when they present for cardiac surgery. Mangano and the Multicenter Study of Perioperative Ischemia Research Group [34] studied the impact of aspirin use within 48 h of CABG surgery on renal outcomes, including AKI, AKI-D and death caused by renal failure in a multinational prospective cohort study of 5065 patients. Aspirin therapy was associated with a 74% percent reduction in the incidence of renal failure and death from renal failure. These findings were confirmed by a recent observational study evaluating the impact of preoperative aspirin on major outcomes in patients who had cardiac surgery [35]. Among 2868 patients who met the inclusion criteria, 1923 took aspirin (81–325 mg daily) at least once within 5 days preceding their surgery versus 945 not taking aspirin (non-aspirin therapy). Preoperative aspirin therapy was associated with a significant decrease in the risk for 30-day mortality and postoperative renal failure [35].

Preoperative use of diuretic has been associated with increased risk of RRT in a retrospective study [27]. Patients may benefit from avoiding preoperative anaemia, defined as haemoglobin <12.5 mg/dl [30]. A recent pilot study found that the administration of erythropoietin before surgery reduced the risk of AKI and improved postoperative renal function [36]. Yoo *et al.* [37] reported the results of a single-centre randomized controlled trial (RCT) of single-dose erythropoietin plus an iron supplement or placebo given a day before surgery. They found a significant reduction in AKI (24 vs 54%) in the intervention group. As transfusion is an independent risk factor for AKI after cardiac surgery and the transfusion rate was lower in the erythropoietin group, it is unclear whether the preserved postoperative renal function was due to a renoprotective effect of erythropoietin or reduced transfusion. Recent data suggest that transfusing PRBC preoperatively could be associated with a lower perioperative free iron and transferin saturation with a trend towards lower AKI rates after surgery [38]. Further studies are required to affirm the benefit of transfusing PRBC or optimizing haemoglobin preoperatively in anaemic patients. Nephrotoxic agents such as non-steroidal antiinflammatory drugs should be discontinnued. Exposure to radiocontrast agents should be avoided or minimized, along with time to allow renal recovery

whenever posible [22]. Whether angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be discontinued before surgery to reduce CSA-AKI is still controversial [24, 39].

The preoperative prophylactic use of RRT on patients with sCr >2–2.5 mg/dl has been shown to decrease morbidity and mortality in two randomized controlled trials [40, 41]. However, the cost-effectiveness of preoperative prophylactic use of RRT needs to be further studied. Therefore, these results need to be replicated in further trials before prophylactic haemodialysis can be recommended for all patients with pre-existing impairment of renal function.

So far studies optimizing perioperative haemodynamics using fluids and/or inotropes have not been designed to examine renal outcomes. Some data suggested a significant reduction in length of hospital stay and in postoperative complications [42, 43]. Preoperative intravenous hydration may reduce the incidence of AKI in patients with chronic kidney disease (CKD) undergoing cardiac surgery. A small randomized trial using an intravenous infusion of 0.45% normal saline at 1 ml/kg/h for 12 hours before surgery versus no hydration showed that AKI developed in 9 of the 30 (30%) patients in the hydration group versus 8 of 15 (53%) patients in the control group [44]. Four patients in the control group (27%) but none in the hydration group required dialysis after surgery ($P < 0.01$). Even though results need to be validated by larger trials, the data suggest that patients should be euvolemic and off diuretics before surgery to avoid AKI.

Intraoperative management strategies

An association between intraoperative anaemia, blood transfusion and AKI has long been noted. However, there is evidence to suggest that low preoperative and intraoperative haemoglobin levels are associated independently with CSA-AKI [8], but ironically, there is also evidence to suggest that intraoperative transfusion is independently associated with CSA-AKI [8, 27]. Karkouti *et al.* [45] found that it is not the absolute level of haemoglobin that is important, but its change from baseline. They found the risk of AKI was significantly increased when haemoglobin decreased more than 50% below baseline. The impact of glucose control on renal outcomes remains controversial. The benefits of a tight glucose control strategy have not been replicated in multicentre studies, and the lack of benefit and increased potential harm was confirmed again in a recent meta-analysis [46]. The large multicentre Nice Sugar study demonstrated no outcome benefit in tight glucose control compared with a regimen that targeted a blood sugar level of <180 mg/dl and had an unacceptable incidence of hypoglycaemia [47].

With regard to the mean arterial pressure (MAP) required during CPB, a recent prospective observational study on 410 patients showed that a higher magnitude and duration of MAP below the lower limit of cerebral autoregulation was independently associated with AKI [48]. Whether maintaining MAP above the lower limit of cerebral autoregulation is renal protective should be further studied.

A recent meta-analysis on 1185 patients suggests that pulsatile perfusion during CPB is beneficial in renal preservation and should be considered. It was found that the pulsatile perfusion group had significantly higher creatinine clearance ($P = 0.004$) and lower serum lactate levels ($P = 0.012$) in the ICU [49].

Recent data suggest an increase risk of AKI-D associated with the use of hydroxyethyl starch (HES) for fluid resuscitation in ICU [50]. Therefore, we should use caution when using these colloids for resuscitation in cardiac surgery.

Surgical strategies

Off-pump CABG (OPCABG) allows systemic pulsatile flow and no exposure to an extracorporeal circuit, thus reducing the inflammatory cytokine response. Most available data do not support a decreased risk of AKI requiring RRT associated with OPCABG procedures. However, data do support a decrease risk of mild AKI associated with OPCABG. In 2009, Shroyer *et al.* [51] reported data from a multicentre randomized controlled trial, the randomized on/off bypass trial, on 2203 patients undergoing CABG surgery either 'off-pump' or 'on-pump'. Data showed no significant differences in RRT requirements [0.8 vs 0.9%, relative risk (RR) 0.90 (0.37–2.20), $P = 0.82$]. However, the trial has some important limitations. The trial enrolled low-risk male patients in whom avoidance of CPB was unlikely to greatly improve the expected excellent outcomes, though conversely surgeons were remarkably inexperienced in the off-pump procedure. The CABG off or on pump revascularization study (CORONARY) trial was recently published by Lamy *et al.* [52]. It is a multicentre randomized controlled trial with 4752 patients. This data suggest that OPCABG was associated with no significant differences in RRT requirement [hazard ratio (HR), 1.04 (0.61–1.76), $P = 0.59$]. However, a definition for initiation of RRT was lacking. Hence, patients with the same clinical situation might have been managed differently. Furthermore, OPCABG was associated with a significant decrease in mild AKI, defined by RIFLE-risk [HR, 0.87 (0.76–0.98), $P = 0.02$] or AKIN stage 1 [HR, 0.87 (0.80–0.96), $P = 0.01$]. The CORONARY trial at 1 year follow-up showed no difference in RRT requirements and mild AKI were not analysed [53]. Data suggest that the use of intra-aortic filtration may decrease the risk of CSA-AKI in moderate to high-risk patients for postoperative morbidity and mortality (13.7 vs 23.9%, $P = 0.04$) [54].

Miniature CPB systems may be directly and indirectly renoprotective [55]. Minimally invasive parasternotomy might be also renoprotective [56].

Pharmacological renal protection

Several pharmacological and therapeutic strategies have been used in an attempt to decrease the incidence of CSA-AKI. Although some appeared promising in early studies, conclusive evidence to support their widespread use is lacking.

It has been suggested that the use of prophylactic fenoldopam, a selective dopamine receptor-1 agonist, during cardiac surgery has renoprotective effects. Landoni *et al.* [57] in a meta-analysis of 13 randomized and case-matched studies on 1059 patients undergoing cardiac surgery concluded that the use of fenoldopam significantly decreased the requirement for RRT and decreased ICU length of stay and in-hospital mortality. Zangrillo *et al.* [58] in a recent meta-analysis of 440 patients focusing only on randomized placebo-control trials showed that fenoldopam consistently and significantly reduced the risk of CSA-AKI (OR = 0.41; 95% confidence interval [CI], 0.23–0.74; $P = 0.003$) with no difference with regard to RRT requirement and mortality. The authors suggest that the size of this benefit is so large for a single intervention that it is likely implausible. Because the number of enrolled patients was small and there was no effect on RRT or survival, a large, multicentre and appropriately powered trial is needed to confirm these promising results. A large randomized controlled trial on 1000 patients is underway to assess the effectiveness of fenoldopam on CSA-AKI prevention (NCT00621790).

Haase *et al.* [59] in a pilot double-blind, randomized controlled trial with 100 patients found a significant reduction ($P < 0.043$) in postoperative AKI, liberally defined as an increase of 25% from baseline creatinine within the first 5 postoperative days, as well as a significant decrease in urinary neutrophil gelatinase-associated lipocalin (NGAL), associated with the use of sodium bicarbonate infusion. However, no differences were found when consensus definition of AKI (RIFLE or AKIN) was used.

Furthermore, a recent multicentre double-blind RCT on 350 high-risk patients for developing CSA-AKI showed that more patients receiving bicarbonate developed CSA-AKI [defined as an increase in sCr concentration >25% or 0.5 mg/dl (44 μmol/l) from baseline to peak value at any time within the first 5 days after CPB] compared with control patients (47.7 vs 36.4%, odds ratio (OR), 1.60 [95% CI, 1.04–2.45]; unadjusted $P = 0.032$). After multivariable adjustment, a non-significant unfavourable group difference affecting patients receiving sodium bicarbonate was found for the primary endpoint (OR, 1.45 [0.90–2.33], $P = 0.120$). A greater postoperative increase in urinary NGAL in patients receiving bicarbonate infusion was observed compared with control patients ($P = 0.011$). The incidence of postoperative RRT was similar, but hospital mortality was increased in patients receiving sodium bicarbonate compared with control (6.3 vs 1.7%, OR, 3.89 [1.07–14.2], $P = 0.031$) [60]. In this study, a slightly larger dose of bicarbonate was used compared with the Haase *et al.* [59] study (5.1 vs 4 mmol/kg during 24 h). Both studies used the same definition of CSA-AKI. Whether the difference in sodium bicarbonate dose used in both studies might have any impact on renal outcomes might be further studied. The debate is still open, but current data do not actually support routine use of bicarbonate for CSA-AKI prevention.

Statins attenuate inflammation and oxidative stress. However, Liakopoulos *et al.* [61] in a meta-analysis of 30 000 cardiac surgery patients found that preoperative statin use was associated with an absolute risk reduction in mortality, atrial fibrillation and stroke, but not myocardial infarction or AKI. A retrospective analysis of 324 patients, found that the incidence of AKI was lower when statins were restarted early postoperatively and higher in patients in whom statin therapy was withdrawn [62]. A randomized control trial is underway to assess the effectiveness of statins on CSA-AKI prevention (NCT00791648).

A multicentre, randomized, placebo-controlled trial of nesiritide versus placebo in 303 patients with left ventricular dysfunction (LVEF < 40%) undergoing cardiac surgery with CPB found that perioperative renal function was better in the nesiritide group (lower peak rise in sCr, smaller decrease in eGFR and greater 24-h urine output) [63]. These findings were even more pronounced in the subgroup with baseline renal insufficiency (sCr >1.2 mg/dl). Furthermore, length of hospital stay was shorter in the nesiritide group. In a recent Cochrane meta-analysis [64] including 493 patients undergoing cardiovascular surgery from 8 randomized controlled trials there was no difference in mortality between the atrial natriuretic peptide (ANP) and control groups (RR, 0.73, 95% CI, 0.37–1.43). ANP was associated with a significant reduction in the need for RRT (RR, 0.35; 95% CI, 0.18–0.70). Another recent meta-analysis [65], including 934 adult patients from 13 randomized controlled trials showed that natriuretic peptide administration was associated with a reduction in acute renal failure requiring dialysis (OR, 0.32 [0.15–0.66]) and a statistically non-significant trend towards a reduction in 30-day or in-hospital mortality (OR, 0.59 [0.31–1.12]). Recently, there have been three trials showing benefit from using human ANP in on-pump CABG surgery in three different types of patient populations: patients with preoperative normal renal function [66], patients with preoperative ventricular disfunction [67] and patients with preoperative CKD [68]. The benefits of using hANP on the first two studies were only seen in laboratory-based markers (i.e. creatinine and eGFR). Conversely, the RCT involving patients with preoperative CKD showed a benefit regarding not only AKI, but also AKI requiring RRT. However, these same authors' concluded that their observations needed confirmation in a larger, adequately powered, prospective multicentre study.

Postoperative strategies

The early use of RRT after cardiac surgery, compared with late RRT, has repeatedly been associated with improved in-hospital survival in patients with CSA-AKI [69, 70]. A retrospective study of 1264 patients showed an association between increased survival and early RRT (0.78 + 0.2 days) compared with late RRT (2.5 + 2.2 days) after cardiac surgery [69]. RRT duration was similar ($P > 0.05$). However, in-hospital mortality was 22 vs 43% for early and late RRT respectively. Data from a multicentre retrospective study [70] suggest that early RRT (<3 days after cardiac surgery) was associated with significantly decreased ICU length of stay (12.5 + 17.5 vs 7.9 + 10.7 days) and mortality (80.4 vs 53.2%). Interestingly, the group with better outcomes and early RRT had worse baseline (sCr 1.58 + 1.14 mg/dl vs 1.26 + 0.52 mg/dl, $P = 0.014$) and 48 h postoperative renal function (increase from baseline sCr 124.2 + 160.4 vs 68.3 + 87.1%).

The early use of RRT may be an important factor used to increase survival in patients with CSA-AKI.

Since pharmacological interventions have been inconsistent with their efficacy and currently there are no known drugs that have conclusively conferred renal protection, a randomized, multicentre, double-blind, placebo-controlled phase II study of AC607 will assess the safety and efficacy of postoperative intra-arterial administration of allogeneic bone marrow-derived human mesenchymal stem cells into renal arteries to patients who had CSA-AKI within the first 48 h postoperatively (NCT01602328). This study follows the positive results from a phase 1 AC607 trial in cardiac surgery subjects, which showed an excellent safety profile and encouraging data on the incidence of AKI and hospital length of stay.

EARLY DETECTION OF ACUTE KIDNEY INJURY: THE ROLE OF BIOMARKERS

Diagnosis of AKI is mainly based on increases in sCr indicating loss of excretory renal function, defined by RIFLE and AKIN clasifications. Although the use of such AKI definitions is of prognostic value [71], its use delays the diagnosis of significant AKI by 24-72h when compared to diagnosis with new renal biomarkers of tubular injury such as NGAL. sCr requires several hours to days to accumulate, it increases in serum only after 50% or more of renal function is lost, and its concentration is affected by multiple confounding factors [17].

In response to renal injury, increases in NGAL levels predict AKI 24–72 h before diagnostic creatinine increases and are of prognostic value [72]. NGAL has generated the greatest interest as a biomarker for the diagnosis of CSA-AKI. A recent meta-analysis derived an AUC_{ROC} of 0.78 for early diagnosis of AKI after cardiac surgery by plasma and urinary NGAL [72]. In addition, the 12-h

plasma NGAL strongly correlated with length of stay and mortality [73]. It is not known how other comorbidities affect NGAL concentrations. A meta-analysis on 2322 critically ill patients with predominantly cardiorenal syndrome from 10 prospective observational studies suggest that in the absence of diagnostic increases in sCr, NGAL detects patients with likely subclinical AKI who have an increased risk of adverse outcomes [74]. However, a number of key issues, including the wide variability in reported diagnostic performance [75–77], require clarification before adoption of NGAL into clinical practice. The predictive value of NGAL improves with increasing RIFLE class of AKI [78].

Several other potential biomarkers have been identified, including cystatin C, IL-18, L-type fatty acid-binding protein (L-FABP), N-acetyl-B-D-glucosaminidase (NAG) and others. Cystatin C is a potential marker of GFR. It also appears to be independent of age, sex and lean muscle mass. Because of mixed results in early studies, its precise value in the diagnosis and prognosis of CSA-AKI is unclear [73]. Acute tubular injury secondary to a variety of causes, including CSA-AKI, results in a significant increase in urinary concentrations of IL-18. Urinary IL-18 concentrations appear to correlate better with the duration of CPB in adults than CSA-AKI itself, suggesting that IL-18 may be a marker of inflammation rather than a marker of specific kidney injury in those undergoing CPB [73]. Measurements combining different biomarkers may improve the detection of AKI-CPB. A prospective cohort study of 77 patients undergoing cardiac surgery suggested that combined urinary biomarkers can detect AKI with higher accuracy than either biomarker measurement alone (AUC_{ROC} 0.81 vs 0.72 for L-FABP at 4 h alone and AUC_{ROC} 0.75 for NAG alone) [79]. In addition, AKI risk prediction was improved when a combination of the biomarker panel and clinical predictors was used (AUC_{ROC} 0.86 vs AUC_{ROC} 0.79). Koyner *et al.* [80] in an observational study on 380 patients suggested that biomarkers predict progresion of CSA-AKI. Biomarkers measured on the day of AKI diagnosis improve risk stratification and identify patients at higher risk of progression of AKI and worse patient outcomes. Biomarkers included urinary IL-18, urinary albumin to creatinine ratio (ACR) and urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL); the primary end point (progression of AKI defined by worsening AKIN stage) occurred in 45 (11.8%) patients. Each biomarker improved risk classification compared with the clinical model alone, with plasma NGAL performing the best.

Despite the enthusiasm regarding the potential uses of new biomarkers, most are not available for routine use in clinical practice. Many of the early studies have reported wide variations in diagnostic characteristics, and confounders for the various individual biomarkers are not well understood. Early studies for evaluating biomarkers also excluded patients with pre-existing kidney disease, a high-risk group for CSA-AKI and a group in whom early diagnosis and stratification of disease are key.

Early diagnosis is key to early treatment of AKI, when the damage may be reversible, as opposed to too late when creatinine is used to detect AKI.

CONCLUSION

AKI after cardiac surgery is a major perioperative complication that is associated with significant morbidity, mortality and associated costs. Preventive strategies are limited and the evidence for most interventional therapies is as yet not substantive. As our understanding of the pathogenesis of AKI after cardiac surgery grows, we will be able to direct preventive and therapeutic strategies better. Current approaches include deferring elective surgery until there is adequate recovery following pre-existing renal injury, careful preoperative risk stratification of patients and consideration of less invasive procedures in those at greatest risk. Intraoperatively, the aim should be 'haemodynamic optimization' with goal-directed therapy that includes volume enhancement and judicious use of blood transfusion and inotropic support. We should attempt to avoid renal injury associated with prolonged aortic cross-clamping, prolonged CPB, intravascular haemolysis or contrast dye exposure. The most promising prospects for pharmacological renal protection appear to lie with atrial natriuretic peptide and fenoldopam but much more data are needed. Finally, early treatment by RRT of patients early diagnosed by panels of biomarkers may improve outcomes.

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