AKI Associated with Cardiac Surgery

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Abstract

Approximately 18% of patients undergoing cardiac surgery experience AKI (on the basis of modern standardized definitions of AKI), and approximately 2%–6% will require hemodialysis. The development of AKI after cardiac surgery portends poor short- and long-term prognoses, with those developing RIFLE failure or AKI Network stage III having an almost 2-fold increase in the risk of death. AKI is caused by a variety of factors, including nephrotoxins, hypoxia, mechanical trauma, inflammation, cardiopulmonary bypass, and hemodynamic instability, and it may be affected by the clinician’s choice of fluids and vasoactive agents as well as the transfusion strategy used. The risk of AKI may be ameliorated by avoidance of nephrotoxins, achievement of adequate glucose control preoperatively, and use of goal-directed therapy hemodynamic strategies. Remote ischemic preconditioning is an exciting future strategy, but more work is needed before widespread implementation. Unfortunately, there are no pharmacologic agents known to reduce the risk of AKI or treat established AKI.

Introduction

AKI is a relatively common complication of cardiothoracic surgery and has short- and long-term survival implications, even for those who do not progress to renal failure. In a modern series, the incidence of new-onset renal failure requiring dialysis is approximately 2% (1). Currently, there are no active treatments for AKI, and therefore, the focus of clinicians is on prevention and risk factor management. In-depth knowledge of the risk factors and pathogenesis for AKI offers clinicians some guidance for the prevention and management of AKI.

ARF after Cardiothoracic Surgery: Incidence and Implications

Incidence

Before development of the RIFLE criteria for AKI (2,3) and most recently, the AKI Network (AKIN) criteria (4), there was no standardization of the definition of kidney injury. This made comparisons between centers as well as the conduct of clinical trials difficult. On the basis of these standardized definitions of AKI (RIFLE injury or AKIN stage II), it seems that the occurrence rate ranges from 4%–9% after cardiac surgery (5–8), although the risk of any decrease in renal function (RIFLE risk or AKIN stage I) is approximately 17%–49% (2,8–12). The more recently developed Kidney Disease Improving Global Outcomes criteria for AKI attempts to reconcile the differences between the RIFLE and AKIN measures and also seems to be valid in patients undergoing cardiothoracic surgery (13). In a modern series, the need for RRT ranges from 2%–6% (1,7–9,11,12). Patients who require extracorporeal membrane oxygenation after cardiac surgery are at particularly high risk, with a >80% incidence of AKI (14). In patients undergoing pediatric cardiac surgery, the incidences of kidney injury and failure (RIFLE criteria) are 10% and 3%, respectively. Eight percent of pediatric patients undergoing cardiac surgery require dialysis (Table 1) (15).

Biomarker-Assisted Diagnosis

Serum creatinine levels rise 24–72 hours after renal injury, thus limiting the ability of therapeutic maneuvers to be applied at the earliest stages when they may be the most beneficial (16). In response, several plasma and urinary biomarkers have been developed to diagnose AKI as well as better risk-stratify patients. These include neutrophil gelatinase–associated lipocalin (NGAL) (17), IL-18 (18), cystatin C (19), kidney injury molecule-1 (20), and others (21). In the Translational Research Investigating Biomarker Endpoints in AKI study, preoperative cystatin C performed better than serum creatinine in predicting the risk of AKI post-surgery (22), and preoperative albuminuria as well as brain natriuretic peptide were also predictive of postoperative AKI (23,24). Postoperatively, urine IL-18 and plasma NGAL peaked within 6 hours after intensive care unit (ICU) admission, and these rises were strongly associated with AKI (AKIN stages II or III) (25). Furthermore, these biomarker elevations were predictive of worsening AKI and mortality over time (even up to 3 years after surgery) (26). The use of biomarkers for both risk stratification and early diagnosis of AKI in patients undergoing cardiac surgery requires additional integration into care pathways to best assess their use in improving outcomes.

Implications

In adults undergoing cardiac surgery, the development of AKI is associated with prolonged ICU and hospital lengths of stay and an increased risk of death (8,10,12,27). AKI in the perioperative period is associated with a higher risk of subsequently developing
CKD (28). For those who develop a new need for hemo-
dialysis, 64% will require dialysis permanently, and up to
90% will die within 1 year (29,30). In patients requiring
extracorporeal membrane oxygenation, the need for RRT
is associated with a 2.3-fold increase in the risk of death
(14). Although the reasons for this increase in mortality are
not fully understood, it seems that an increased incidence
of infection is a major contributor (27,31). Of note, the pre-
dictive values of the RIFLE and AKIN criteria for mortality
after cardiac surgery seem to be similar (10–12).

The Pathogenesis of AKI

The pathogenesis of AKI is complex, not fully understood
(32–41), and complicated by the difficulties associated with
the acquisition of real-time kidney data in humans. Renal
biopsies are invasive, and there are no convenient and reli-
able means of measuring real-time renal blood flow. His-
topathologic studies are, thus, limited to animal models or
postmortem analyses in humans (41).

Numerous factors likely play a role in the development
of AKI in the perioperative period. These include exposure
to both exogenous (such as medications) and endogenous
(such as iron or heme pigments) toxins, ischemia-reperfusion
injury, embolization, hemodynamic alterations, neurohor-
monal activation, metabolic factors, inflammation, and oxi-
dative stress. These factors likely interact with each other at
different time points along the continuum of cardiac surgery
and recovery, making individual contributions difficult to
elucidate.

Nephrotoxins

Patients undergoing cardiac surgery are exposed to mul-
tiple potential nephrotoxic drugs, including antibiotics, non-
steroidal anti-inflammatory agents (NSAIDs; e.g., aspirin),
angiotensin-converting enzyme inhibitors (although there
are some retrospective data suggesting a protective effect
in a broad population of patients undergoing surgery) (42),
angiotensin receptor blockers, and intravenous radio-
contrast agents. NSAIDS are known to impair the autoregu-
lation of renal blood flow (43), and the use of intravenous
contrast agents before cardiac surgery has been shown to
increase the risk of perioperative AKI (5,44–46). Interest-
ingly, preoperative use of low-dose aspirin (not >325 mg
daily) seems to be associated with a reduction in the inci-
dence of major adverse cardiac events and renal dysfunction
(47). This paradox may be explained by the beneficial effects
of long-lasting platelet inhibition outweighing the harm of
impaired autoregulation. The effect of angiotensin-converting
enzyme inhibitors on renal function in patients undergoing
cardiac surgery is not fully understood and is controversial,
with studies showing both benefit and harm (48).

Regional Hypoxia

Preoperatively, many patients presenting for cardiac surgery
will have experienced one or more episodes of hypotension.
This can lead to endothelial injury, the response to which is
local release of endothelin, angiotensin II, and catechol-
amines, all of which lead to vasoconstriction and may ex-
acerbate ischemia (49–51). Animal models suggest that renal
ischemia leads to NF-κB (a TNF transcription factor) activa-
tion, suggesting an inflammatory component to the hypoxia
response (see below) (52).
Atherosclerotic emboli exacerbate inadequate oxygen delivery and are particularly problematic during aortic cannulation and manipulation of the aortic cross-clamp (53–57). There may be a relationship between the embolic burden detected by transcranial Doppler and postoperative renal dysfunction (54). Atheroembolic disease may be particularly problematic in elderly patients (58).

Additionally, in the immediate intraoperative period, a combination of simultaneous alterations in renal vasoreactivity and perfusion pressure can produce regional hypoxia. In particular, the inner stripe of the renal medulla, which has high metabolic demands and a normal PaO₂ of 10–20 mmHg, is particularly susceptible (59,60). This injurious process is thought to lead to an inflammatory state in which inflammatory cells adhere to the peritubular capillary endothelium, causing medullary congestion and further reduction in the delivery of oxygen.

**Mechanical Blood Trauma**

Because of mechanical trauma caused by blood pumping (centrifugal pumps, which are now almost exclusively used as the primary pump during cardiopulmonary bypass, have been shown to improve some markers of renal function compared with roller pumps) (61), oxygenator turbulence, cardiectomy suction, and cell saver use, cardiopulmonary bypass is associated with hemolysis and the generation of free hemoglobin and iron (62,63), all of which contribute to the production of oxidative stress and renal injury (64). Specifically, hemoglobin subjected to hydrogen peroxide or superoxide may release free iron into the circulation (65), which then participates in biochemical reactions, resulting in hydroxylation formation and tissue damage (66). There may be a relationship between ferritin (which binds free hemoglobin) and the amelioration of AKI in patients undergoing CPB, although this is not clear (67,68).

**Inflammation**

Cardiopulmonary bypass results in the production of a systemic inflammatory response syndrome thought to be triggered by contact between blood and the artificial surfaces of the CPB circuit (69). The activation of neutrophils, platelets, vascular endothelium, and factor XII (Hageman factor) leads to the production of free radicals (70), cytokines (71), chemokines (72,73), proteases (74), and increased platelet adhesion (75) as well as activation of the intrinsic coagulation system, the kallikrein system, and fibrinolysis (72). Kidney injury and the subsequent reduction in glomerular filtration seem to reduce the ability of the body to remove inflammatory markers (e.g., TNF-α, IL-6, and IL-β) (76). The exact contribution of this inflammatory upregulation to kidney injury in humans undergoing cardiopulmonary bypass is not known; however, on the basis of animal data, which clearly show an inflammatory component to kidney injury (34,77–79), it is assumed to be substantial (35).

**Perioperative Variables and AKI**

**Preoperative Risk Factors**

Preoperative demographic risk factors that have been associated with the development of AKI after cardiac surgery include preexisting kidney disease (12,80–82), reduced left ventricular function (81–83), chronic obstructive pulmonary disease (81,82), diabetes (10,81,83), older age (10,12,27,80,83), and women (10,30,81). Additionally, prior cardiac surgery (81–83) and emergency surgery (27,81) have both been associated with an increased risk of AKI in patients undergoing cardiac surgery. Some of these risk factors have been combined to develop scoring systems capable of predicting the likelihood of AKI after cardiac surgery (81,82,84). The use of these systems is predicated on the ability to modify the risk of AKI with cardiac surgery.

**Urine Output**

The role of intraoperative urine output as a predictor for postoperative AKI is controversial, with several studies of patients not undergoing cardiac surgery showing no relationship between intraoperative urine output and postoperative kidney function (85,86). Reduced urine output is widely considered to be a part of the stress response to surgery, and the predictive use of intraoperative urine output in patients undergoing cardiac surgery has not been firmly established.

**Intravenous Contrast Administration**

Patients who present for cardiac surgery have often received intravenous contrast before their operation. The use of intravenous contrast before cardiac surgery does seem to increase the incidence of AKI and has led some to recommend delaying surgery for a period of time after contrast administration (5,44–46).

**Hemodynamic State**

Although inotrope use (15) and postoperative hemodynamic instability (27,80) are both known risk factors for the development of AKI after cardiac surgery, there are no prospective, randomized, controlled trials (RCTs) that suggest either an optimal mean arterial pressure or the use of specific vasoactive pharmacologic agents in this patient population. However, a recent large, prospective RCT of low (65–70 mmHg) versus high (80–85 mmHg) mean arterial pressure in patients with septic shock revealed no difference in mortality but a higher incidence of atrial fibrillation in the high-pressure group (87). Interestingly, secondary analysis of the chronic hypertension group revealed a decrease in the incidence of AKI (defined as a doubling of serum creatinine) and the need for RRT in the high-target group (87). The secondary nature of this analysis, patient population studied, and inexact definition of chronic hypertension cast doubt on the applicability of this finding to the cardiac surgery population.

**Vasopressor Selection**

The clinician has the ability to use several different vasopressor agents to support unstable hemodynamics. However, these agents have variable effects on renal blood flow, GFR, and renal outcomes. Animal studies suggest that α₁-AR agonists (e.g., methoxamine and phenylephrine) reduce urine output and renal blood flow (88–90). Animal studies also suggest that, over the range of 5–20 μg/kg per minute, dopamine increases cardiac output and renal blood flow (91,92). Dopamine administration also leads to a DA₁-mediated natriuresis, although the mechanism is not clear (93). There are three subtypes of vasopressin receptors—V₁, V₂, and V₃ (94). Activation of V₁ₐ (V₁) receptors leads to vascular
smooth muscle contraction in both arterial and venous vasculature (94–96). Activation of V₂ receptors, which are present only in the kidneys, leads to incorporation of aquaporins into the distal tubules and collecting ducts, thereby increasing the retention of free water by the kidneys (94,97,98). Low doses of vasopressin have been shown to produce a diuresis in humans (99–101), likely because of efferent arteriolar vasoconstriction (102). At higher doses, vasopressin can produce renal afferent vasoconstriction (103,104) and eventually vasoconstriction (102). At higher doses, vasopressin can produce renal afferent vasoconstriction (103,104) and eventually decreased urine output, most likely because of a combination of V₁-mediated reductions in renal blood flow and V₂-mediated free water retention (105).

Because of these mechanistic differences, some investigators have postulated that preferential use of a vasopressin agonist (or mixed-β-agonist) over a pure α-agonist might improve renal function. Others have hypothesized that the addition of a dopamine agonist would increase renal blood flow and decrease the incidence of AKI. In patients in septic shock, replacing norepinephrine with phenylephrine lead to decreased creatinine clearance and increased arterial lactate (106). A small trial comparing phenylephrine with norepinephrine as the first-line vasopressor therapy revealed a trend toward higher urine output in the norepinephrine group (107). A comparison between norepinephrine and vasopressin in patients with septic shock showed improved renal function and urine output in the vasopressin groups (108). That said, the Vasopressin versus Norepinephrine Infusion in patients with Septic Shock trial, which randomized patients with sepsis already on high-dose norepinephrine infusions (0.5 μg/kg per minute) to additional norepinephrine or vasopressin, found only a slight trend toward decreased renal dysfunction in the vasopressin group (109). Given these findings, it is reasonable to use either norepinephrine or vasopressin for hemodynamic support in the patient postcardiac surgery.

**Intravenous Fluid Selection**

The choice of intravenous fluids may affect renal outcomes in patients undergoing cardiac surgery. Traditionally, surgeons have been concerned that their perceived ability to remain intravascular in the face of systemic inflammation and endothelial dysfunction. Unfortunately, much of the data on colloids in cardiac surgery has been retracted (110). Thus, the physician caring for patients who undergo cardiac surgery will partially rely on data from other patient populations when making fluid management decisions.

The Saline versus Albumin Fluid Evaluation trial, which compared albumin with normal saline in patients who were critically ill, found no difference in mortality (renal outcomes were not reported) (111). Smaller studies of non-albumin colloids revealed concern associated with the use of hydroxyethyl starch (HES) (112,113) as did the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis trial (114). The Crystalloid Hydroxy-Ethyl Starch Trial trial randomized patients who were critically ill to normal saline and HES and found a higher incidence of kidney injury as well as an increase in the need for RRT in the HES group, although there was no difference in mortality (115). The Scandinavian Starch for Severe Sepsis/Septic Shock Trial trial compared Ringer’s acetate with HES in patients with severe sepsis and found an increased risk for RRT in the HES group (116). The Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill trial randomized patients who were critically ill to either crystalloids (normal saline, hypertonic saline, or lactated Ringer’s) or colloids (gelatin, dextrans, HES, or albumin) and found no difference in 28-day mortality (the primary outcome) or the need for RRT (117). The wide variety of crystalloids and colloids used makes this study difficult to interpret. The Albumin Italian Outcome Sepsis trial randomized patients with severe sepsis to crystalloid or albumin and found no difference in mortality or renal dysfunction between groups (118).

On the basis of multiple large RCTs showing worsened renal outcomes in patients who were critically ill and received HES and the lack of any benefit for the use of any colloid, we cautiously advise against the use of HES in patients undergoing cardiac surgery and recommend crystalloid solutions with the knowledge that this patient population has not been adequately studied.

**Cardiopulmonary Bypass**

There is an association between the use of cardiopulmonary bypass and the development of AKI, with combined surgical procedures (valve replacement and coronary artery bypass) and prolonged cardiopulmonary bypass times increasing the incidence of AKI in adults (8,35,119) and children (15). The optimal perfusion pressure and flow rates in humans undergoing cardiopulmonary bypass are not known, and both higher perfusion pressure (120) and the use of pulsatile flow (121) have failed to improve postoperative renal function. In animals, renal blood flow seems to be decreased during cardiopulmonary bypass (122,123), although there is a stable period of autoregulation (down to flows as low as 1.6 L/min per minute²) (123). Maximal renal blood flow on cardiopulmonary bypass is approximately 55% of prebypass flow (123). On the basis of two small studies, it seems that higher perfusion pressures may improve renal function during cardiopulmonary bypass but do not affect postoperative function (120,124). The existence of CKD as well as chronic hypertension may affect the ideal mean arterial pressure, because renal injury seems to be accompanied by a loss of autoregulation (125,126). Some data suggest that off-pump coronary artery bypass (OPCAB) surgery reduces the incidence of perioperative AKI (127–131); however, this finding is not universal (131,132). Furthermore, the reduction in AKI may not necessarily affect long-term kidney outcomes (125). These relatively small studies must be interpreted in the context of the The Coronary Artery Bypass Grafting Survey Off- or On-pump Revascularisation Study trial, which randomized 4752 patients to on- versus off-pump coronary artery bypass graft and showed no difference in survival or any other meaningful clinical outcome, including new renal failure requiring dialysis (133). It is difficult to explain the failure of OPCAB to reduce AKI rates, especially given the clear effect of cardiopulmonary bypass on inducing in inflammation (134,135). One hypothesis is that the increased hemodynamic instability that occurs with OPCAB (132) negates the benefits of avoiding cardiopulmonary bypass.

**Hematocrit during Cardiopulmonary Bypass**

Because cardiopulmonary bypass machines are primed with crystalloid, colloid, or both, the increase of cardiopulmonary
bypass is associated with hemodilution. There is clearly a relationship between the lowest hemoglobin during cardiopulmonary bypass and both the development of AKI (136,137) and low cardiac output failure (138); however, retrospective analyses suggest that the risk of low cardiac output failure is not ameliorated by the transfusion of packed red blood cells (138). This finding is consistent with the growing body of literature suggesting that transfusion of packed red blood cells in patients who were critically ill is associated with either no improvement or a worsening of meaningful clinical outcomes (139–142). That said, there may be an optimal range of hemoglobin (around 8.5 g/dl) that balances the advantages of hemodilution (and less release of free hemoglobin) with the risks of inadequate oxygen delivery during cardiopulmonary bypass (137). Unfortunately, the effect of transfusion during cardiopulmonary bypass has not been specifically studied.

Perioperative Transfusion of Packed Red Blood Cells

Surgeon et al. (138) performed a retrospective study suggesting that postoperative low-output heart failure, although related to the lowest hematocrit during CPB, was not prevented by the administration of packed red blood cells. Another analysis by the same group reported that the perioperative administration of 1–2 units packed red blood cells to patients undergoing CABG surgery was associated with a 16% increase in mortality (143). Karkouti (144) identified 20 observational studies showing an association between transfusion of packed red blood cells and AKI (and 1 study that found no difference). Since that time, additional studies have added to the growing body of literature suggesting that anemia and the use of packed red blood cells are independent risk factors for AKI after cardiac surgery (145–147). Catalytic iron (i.e., circulating iron not bound to any proteins) can produce hydroxyl radicals, cause oxidative tissue damage, and has been proposed as a nephrotoxin (148). A recent analysis of catalytic iron levels in a population of patients who were critically ill found a strong relationship between the amount of blood products transfused and catalytic iron levels as well as between catalytic iron levels and the probability of developing AKI, suggesting a potential mechanism for the relationship between blood product transfusion and AKI (148).

There is one moderately sized prospective RCT focused on transfusion of packed red blood cells in patients undergoing cardiac surgery (using hematocrits of 24% and 30% as a threshold), and it shows no difference in mortality between groups (139). Unfortunately, this study was not powered to detect changes in the incidence of AKI. A propensity-matched analysis of 322 patients who were Jehovah’s Witnesses and refused blood transfusions during cardiac surgery (compared with 48,986 patients who received transfusions) was notable for an improvement in 1-year survival, a reduction in both complications and length of stay, and no difference in renal failure (as defined by the Society of Thoracic Surgeons database) or the need for dialysis in the Jehovah’s Witness group (149). Also of interest, Koch et al. (150) recently proposed that the age of packed red blood cells may be related to the probability of causing AKI after cardiac surgery. This study, although provocative and important, must be put into context given the large number of smaller, conflicting studies that have not shown a clear association between red blood cell age and the risk of transfusion (151).

Given the relationship between the use of packed red blood cells and the development of AKI in patients undergoing cardiac surgery (which is independent of the risks associated with anemia) as well as the growing body of prospective RCTs showing no benefits associated with transfusion of packed red blood cells in any setting, we recommend that the clinician be extremely cautious with the use of these products. Clinical decisions regarding transfusion risk should be on the basis of a complex assessment of oxygen supply and demand matching (including but not limited to measures of cardiac output, venous oxygen saturation, and lactate).

Prevention of AKI

Nonpharmacologic Strategies

Glucose Management. The landmark study by van de Berghe et al. (152) was conducted in a surgical (including cardiac) ICU setting and showed a significant reduction in mortality and AKI in patients who received strict glucose control. This group’s medical ICU study (153) as well as studies by other authors have been unable to replicate these results, and a recent meta-analysis of all RCTs on the topic suggested the potential for harm with strict glycemic control. This combined with the recent trial by Gandhi et al. (155) comparing strict with conventional glucose during cardiac surgery, which showed an increased risk of mortality in the strict group, make it difficult to advocate for strict glucose control in the cardiac surgery patient population. This is further supported by a recent large, retrospective analysis of patients undergoing cardiac surgery, in which patients maintained with moderate parameters (126–179 mg/dl; mean=152 mg/dl) experienced less morbidity and mortality than those maintained by strict (<127 mg/dl) or liberal (>179 mg/dl) criteria (156).

Neuraxial Blockade. It has been suggested that thoracic epidural analgesia (TEA) reduces the stress response to surgery (157), although this is controversial, because it has not been shown universally (e.g., in patients undergoing cardiac surgery) (158). Still, several investigators have proposed that this analgesic modality may reduce the incidence of complications, including AKI. One small RCT showed a significant decrease in the risk of AKI in patients undergoing CABG surgery who received a thoracic epidural (159). A larger cohort study examining the use of TEA in patients undergoing cardiac surgery found a decreased need for dialysis (160). The results of these studies must be balanced by the failure of a Cochrane Database Review to show a mortality reduction in patients undergoing cardiac surgery who received TEA (161) as well as the potential risk associated with the use of TEA in a patient who may require full heparinization.

Immunomodulation. Several attempts have been made to modulate the inflammatory response to cardiopulmonary bypass, including the use of steroids (14 RCTs including 933 patients), smaller circuits (nine RCTs including 947 patients), and application of leukocyte filters (six RCTs including 374 patients) (162). Of these three strategies, only leukocyte filtration seems to be efficacious, with a 0.18 odds ratio (OR) (95% CI, 0.05 to 0.64) of developing a unified worsening renal function outcome as defined by the authors (because
many studies took place in the pre-AKIN era (162). These results are consistent with animal studies suggesting that leukocyte infiltration can be harmful to renal function (78,79). It is important to point out that the individual immunomodulation RCTs are relatively small, making it difficult to detect a difference in higher-stage AKI or the need for hemodialysis. Larger and more definitive studies are required before global changes in practice can be recommended. The Steroids in Cardiac Surgery trial, which has, thus far, randomized over 7000 patients undergoing cardiopulmonary bypass to methylprednisolone versus placebo, will soon offer additional insight into the potentially protective effect of anti-inflammatories during cardiac surgery (163).

**Goal-Directed Therapy.** In an effort to reduce the time required to recover from surgery, anesthesiologists and surgeons have developed hemodynamic protocols on the basis of the concept of goal-directed therapy (GDT). GDT protocols shift the perioperative physician’s focus away from traditional hemodynamic end points (e.g., mean arterial pressure and central venous pressure, the latter of which is not at all predictive of the hemodynamic response to volume loading [164,165]) and has been associated with impaired renal function in a variety of clinical environments (166) and toward more modern end points: either cardiac output, stroke volume, and fluid responsiveness (the expected increase in cardiac index after a volume challenge) (164,165) or an index of oxygen supply to demand matching (e.g., SvO2) (167).

Three meta-analyses have attempted to assess the use of GDT and/or fluid optimization protocols for the management of patients in the perioperative period. Gurgel and do Nascimento (168) examined 32 RCTs encompassing 5056 patients and found a significant reduction in mortality (OR, 0.67) in the high-risk (expected mortality >20%) group. Hamilton et al. (169) examined 29 RCTs encompassing 4085 patients and found a significant reduction in mortality (OR, 0.48) and surgical complications (OR, 0.43) for all patients. A meta-analysis including 1910 patients from nine studies specifically examining colorectal surgery showed reductions in hospital stay and complications (170). None of these meta-analyses focused on patients undergoing cardiac surgery specifically.

Although many GDT trials are not powered sufficiently to detect changes in renal outcomes, at least two studies have shown a decrease in perioperative AKI after the use of structured hemodynamic management protocols. Donati et al. (171) randomized 135 high-risk patients undergoing abdominal surgery to usual care (on the basis of BP and central venous pressure) or goal-directed intraoperative hemodynamic management (designed to keep oxygen extraction ratio at <27%) and found a reduction in organ failure (from 40% to 13%; P<0.001), including a reduction in kidney injury (from 10% to 3.0%). Pölönen et al. (172) compared standard of care postoperative hemodynamic management with a GDT strategy designed to keep SvO2>70% and lactate <2 mEq/L and realized a 1-day reduction in length of stay as well as a reduction in total organ failures (6.6% to 1%; P<0.01) as well as kidney failure (1.5% to 0.5%) in the GDT group.

A more recent GDT trial in patients undergoing cardiac surgery showed a reduction in length of stay and complications in the group with fluids management that was guided by stroke volume variation (173). Although this study was not powered to detect changes in the incidence of AKI, there was a trend toward reduced AKI in the protocol group (three versus eight; P=0.20). Application of these protocols to postbypass care holds promise.

**Preemptive Hemodialysis.** There are at least three small RCTs assessing the concept of early or preemptive hemodialysis in patients who are critically ill (174–176). Bouman et al. (176) randomized 106 critically ill patients to early high-volume hemodialysis, early low-volume hemofiltration, or late low-volume hemofiltration and found no difference in survival or renal outcomes. Durmaz et al. (175) randomized 42 patients undergoing cardiac surgery with a creatinine of 2.5 mg/dl or higher to either prophylactic dialysis or dialysis only in the case of renal failure and reported a reduction in mortality (4.8% versus 30%) in the preemptive group. Sugahara and Suzuki (174) randomized 28 patients undergoing cardiac surgery to dialysis as soon as urine output fell to <30 ml/hour or dialysis as soon as urine output fell to <20 ml/hour and reported improved survival in the earlier hemodialysis group. Routine ultrafiltration during cardiac surgery does not seem to be efficacious (177). The small sizes of these studies as well as the lack of evidence in other patient populations (178) make these data difficult to interpret.

**Atheroma Filtration Devices.** Because it is believed that dislodgement of atheromatous material during cross-clamping may lead to development of embolic ischemic events in the brain and elsewhere, filtration devices have been developed in an attempt to capture potentially embolic material (179). The ability of these devices to prevent renal injury during or after cardiac surgery has not been documented; however, it is worth noting that no technology (e.g., intra-aortic filter and dynamic bubble trap) has been shown to reduce the incidence of neurologic injury, which may occur through this mechanism (180).

**Remote Ischemic Preconditioning.** Remote ischemic preconditioning (RIPC) describes the technique of applying mild nonlethal ischemia (such as through limb compression with a BP cuff) followed by reperfusion with the goal of protecting other organs from a subsequent episode of ischemia-reperfusion (181). Although the mechanism of distant organ protection is not known, it is postulated that humoral, neurogenic, and modulation of inflammatory mediators are involved (182). A recent meta-analysis of clinical trials of RIPC in patients undergoing cardiac and vascular interventions (11 trials and 1216 patients) showed that RIPC decreased the risk of AKI with marginal significance (OR, 0.70; P=0.06) (183). Currently, there are several large-scale RCTs examining whether RIPC might be of benefit in decreasing the incidence of AKI after cardiac and vascular procedures (registration nos. NCT01071265, NCT01247545, NCT01067703, and NCT01328912).

**Stem Cells.** In animal models, allogeneic mesenchymal stem cells (MSCs) have shown promise in ameliorating AKI from ischemia-reperfusion injury, cisplatinum, and glycerol (184). The primary modes of action for MSCs are paracrine and endocrine, because engraftment after differentiation into target cells is absent or rare and fusion of MSCs with renal cells is not observed. These observations served as the basis for the design and conduct of a phase 1 clinical trial, in which allogeneic MSCs were administered to study participants at
high risk of AKI after undergoing on-pump cardiac surgery (CABG and/or valve surgery). Allogeneic MSCs are administered to patients through a femoral catheter into the distal thoracic aorta. In this first trial, 16 participants were enrolled with a primary focus on safety. Initial observations show that therapy with allogeneic MSCs was safe and that the therapy was associated with protection of kidney function and reduction of both length of hospital stay and need for readmission. Additional larger-scale RCTs are now active (registration nos. NCT00733876 and NCT01602328).

Current and Future Pharmacologic Strategies

At this time, there are no known effective pharmacologic strategies for either prevention or treatment of AKI in the setting of cardiac surgery. In our prior review, we highlighted the state of clinical trials in 2006 (185). Since then, no large well designed RCTs have shown benefit of any strategies in the amelioration of AKI. It remains that most clinical trials are relatively small and underpowered to detect any benefit in reducing the incidence of AKI, hampering the ability to find effective therapies.

Avoidance of Nephrotoxins. The simplest strategy for the prevention of AKI is the avoidance of nephrotoxins. Several classes of nephrotoxins are commonly used in the preoperative management of patients undergoing cardiac surgery, and these include antibiotics (cephalosporins [186], vancomycin [187], and aminoglycosides [188] have all been shown to have nephrotoxic potential), NSAIDs (including aspirin [189,190]), and intravenous contrast agents (191). Patients who receive a heart or lung transplant are subjected to additional nephrotoxic exposure, including calcineurin inhibitors (192). Lastly, HEVs (see above) should be avoided in the setting of cardiac surgery, because there are alternative colloids (e.g., albumin) for which there is no known potential for increased risk of AKI. The use of renin angiotensin system blockers in the preoperative period and their role in postoperative AKI are controversial, with conflicting results on their effects on postoperative kidney function. A recent meta-analyses revealed that preoperative RAS use was associated with an increased odds for both postoperative AKI (OR, 1.17; 95% CI, 1.02–1.35; P = 0.01) (193). However, more recent analysis implies that AKI in this setting is functional in nature and not associated with structural injury as detected by biomarkers (194). Importantly, an RCT (registration no. NCT02096406) will be investigating this issue.

Dopamine Agonists. Despite the known ability of dopamine to increase renal blood flow at low doses, multiple studies of dopamine in cardiac and noncardiac surgical populations have failed to show a benefit in terms of either mortality or renal function (195–198). Fenoldopam, a selective D1 agonist, has showed some promise in small studies (not all of them randomized) (199–202), although this has not been universal (203). The available meta-analytic data suggest a renoprotective effect in patients undergoing cardiac surgery, but larger well designed trials are needed (204).

Diuretics. Diuretics have been suggested as potentially nephroprotective agents (205), but this is controversial. A retrospective analysis of furosemide given after cardiac surgery suggested that it may lead to hypercreatinemia (206), and a prospective, randomized, double-blinded comparison of furosemide and dopamine with placebo in patients undergoing cardiac surgery found that furosemide was associated with worse renal function (on the basis of 48-hour creatinine changes) (207). Whether these changes are because of kidney injury per se or rapid changes in intravascular volume depends on the speed at which changes in intravascular volume and renal function affect serum levels of creatinine. Kinetic models suggest that creatinine levels do not achieve a steady state for several days after a change in renal function (208). Interestingly, a small comparison of furosemide versus placebo during and after cardiac surgery showed a statistically insignificant trend toward increased postoperative creatinine in the furosemide group but a highly significant difference in the excretion of retinol-binding protein, suggesting that the furosemide group maintained significantly better proximal tubular function (209). Thus, in the immediate postoperative period, furosemide (and likely, any forced diuresis) should only be initiated for specific medical indications, keeping in mind the potential to cause or exacerbate kidney injury.

Mannitol, which functions as an osmotic diuretic, also behaves as a free radical scavenger. Despite this, the renal outcomes associated with the use of mannitol in cardiac surgery are mixed (210–213). There are some data suggesting that atrial natriuretic peptide (214) and B-type natriuretic peptide (215) may be of benefit in patients undergoing cardiac surgery. Notably, two RCTs have suggested that atrial natriuretic peptide can improve kidney function in patients undergoing cardiac surgery with a low ejection fraction (216) and CKD (217). In combination, these data suggest that natriuretic peptides have great potential.

α2AR Agonists. Although there were some pilot data to support the use of the α2AR agonist clonidine for the amelioration of AKI in patients undergoing cardiac surgery (218,219), a recent large RCT of perioperative clonidine in patients undergoing noncardiac surgery showed no benefit of clonidine on the primary composite outcome, no effect of clonidine on renal dysfunction postoperatively, and an increased incidence of hypotension in the clonidine group (220). Dexmedetomidine, a centrally acting α2 agonist, was shown to increase urine output in a small trial of patients undergoing cardiac surgery (221).

Anti-Inflammatory Agents. N-acetylcysteine, which has anti-inflammatory effects and has been shown to block oxidant stress, has been used to modify the inflammatory response to cardiopulmonary bypass in patients undergoing cardiac surgery (222,223) as well as combat contrast-induced nephropathy (224). However, a meta-analysis including 1407 patients from 15 RCTs showed no difference in kidney injury defined as a creatinine increase of 25% above baseline (225). Dexamethasone is a known anti-inflammatory agent, and its effect on markers of kidney injury after cardiac surgery has been tested in at least two RCTs, both of which were negative (226,227).

Hepatic Hydroxymethyl Glutaryl-CoA Reductase Inhibitors. Some retrospective data have suggested that the perioperative use of hepatic hydroxymethyl glutaryl-CoA reductase inhibitors (statins) reduce the risk of AKI after cardiac surgery (228,229); however, this may be caused by a healthy user bias (230), because a more rigorous, propensity matched analysis (231) failed to reveal a benefit for this class of drugs. A recent large, prospective RCT of rosuvastatin in sepsis-associated acute respiratory distress syndrome revealed a significant increase in the incidence of kidney failure (232).
Other Strategies. Other pharmacologic agents that have been used in an effort to ameliorate AKI associated with cardiopulmonary bypass include theophylline (which inhibits adenosine-mediated vasoconstriction) (233), pentoxyfylline (which blocks neutrophil activation) (234), and diltiazem (235–237), all of which showed no benefit. Sodium bicarbonate has been advocated as a potentially renal protective agent; however, a recent RCT of 350 patients undergoing cardiac surgery found an increase in kidney injury (on the basis of both creatinine and NGAL changes) and mortality, the combination of which led the Data Safety and Monitoring Committee to terminate the trial after an interim analysis suggested a lack of efficacy and possible harm (238). Several other strategies are in clinical trials: THR-184 (registration no. NCT01830920), erythropoietin (numerous trials), and curcumin (registration no. NCT01225094) to name a few.

Conclusion
AKI occurs in approximately 4%–9% of patients undergoing cardiac surgery, with 2%–6% of patients ultimately developing the need for RRT. Patients who develop AKI
after surgery have reduced long-term survival, regardless of their need for RRT. There are no active treatments for AKI, and therefore, the focus of clinicians is on prevention. Table 2 presents a summary of evidence-based recommendations for the reduction of AKI risk. Of available risk modification strategies, several seem particularly promising—minimizing the use of intravenous contrast agents before cardiac surgery, reducing the use of α-adrenergic agents by adding vasopressin (which has no renal afferent effects) to patients who require vasoactive support, eliminating the use of colloids, which contain HES, restricting the use of exogenous blood products to patients who have symptomatic anemia or present with a compelling physiologic indication (as opposed to passing an arbitrary threshold), and avoiding the use of diuretics, except for specified medical indications. It is hoped that application of these preventative strategies as well as improvement in the care pathways of patients postoperatively will result in reduction in AKI rates.

Disclosures

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