REVIEW

Serum creatinine role in predicting outcome after cardiac surgery beyond acute kidney injury

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Received: January 11, 2014 Revised: April 7, 2014
Accepted: July 12, 2014
Published online: September 26, 2014

Abstract

Serum creatinine is still the most important determinant in the assessment of perioperative renal function and in the prediction of adverse outcome in cardiac surgery. Many biomarkers have been studied to date; still, there is no surrogate for serum creatinine measurement in clinical practice because it is feasible and inexpensive. High levels of serum creatinine and its equivalents have been the most important preoperative risk factor for postoperative renal injury. Moreover, creatinine is the mainstay in predicting risk models and risk factor reduction has enhanced its importance in outcome prediction. The future perspective is the development of new definitions and novel tools for the early diagnosis of acute kidney injury largely based on serum creatinine and a panel of novel biomarkers.

Key words: Creatinine; Acute kidney injury; Cardiac surgery; Outcome; Biomarker

Core tip: This manuscript aims to review the latest achievements in the diagnosis and treatment of acute kidney injury (AKI). Despite much progress in recent years, especially in the development of novel biomarkers, serum creatinine still plays the major role. Creatinine is not only the mainstay of definition, diagnosis and prediction of AKI, but also the most important predictor of outcome after cardiac surgery, including mortality and morbidity as well as hospital length of stay.

INTRODUCTION

Creatinine is an important determinant in cardiac surgery. Rise in the level of serum creatinine has a significant impact on surgical outcome. Acute kidney injury (AKI) is basically defined by perioperative changes in serum creatinine level. Even minimal changes in serum creatinine not high enough to be defined as AKI worsen the outcome of patients who undergo cardiac surgery. Sensitivity of serum creatinine is low and its response to renal insult is slow and late. However, serum creatinine level still constitutes the main measure for the assessment of renal function thanks to the simplicity and availability of its measurement. Similarly, serum creatinine is the cornerstone of the consensus definitions of AKI. Indeed, an acronym for Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal failure (RIFLE), acute kidney injury network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) all use creatinine for grading the severity of AKI[1,2]. The principal role of creatinine as a main predicting factor in the scoring systems for risk estimation is well known[3]. Creatinine has, therefore, been included in the first three important risk factors for mortality after cardiac surgery by newer prediction scores[4].

With little tolerance, we assume an abrupt rise in serum creatinine as acute kidney injury (AKI). Due to

the unique characteristics and specifications of AKI that occur after cardiac surgery, it has been called cardiac surgery associated AKI (CSA-AKI). In recent years, many investigations have been performed to find answers to key questions on the prevention and treatment of CSA-AKI in the perioperative period. Numerous studies have been performed and are underway with their focus on the CSA-AKI[2,5] and there are promising results, especially in prophylactic management. However, recruitment of patients with minimum risk of AKI for clinical trials on CSA-AKI treatment is the main reason why most of these studies lack the sufficient power to be conclusive[2,5]. Furthermore, inconsistency in the definition of AKI between different studies makes it difficult to analyze the results of these studies in meta-analyses[5,6].

This review covers the following: (1) association of serum creatinine with cardiac surgery-associated mortality and morbidity; (2) serum creatinine role in diagnosis of cardiac surgery-associated acute kidney injury; (3) risk factors for high perioperative serum creatinine; (4) risk models for AKI after cardiac surgery; (5) creatinine and the outcome prediction in cardiac surgery; and (6) prevention and treatment on the horizon.

ASSOCIATION OF SERUM CREATININE WITH CARDIAC SURGERY-ASSOCIATED MORTALITY AND MORBIDITY

The development of postoperative AKI has been recognized as the strongest risk factor for death in patients undergoing cardiac surgery[7]. It has been shown that AKI occurs in up to 40% of patients undergoing cardiac surgery[2]. As much as the incidence is rare (1% to 5%), mortality among patients with AKI who require renal replacement therapy (RRT) or become dialysis dependent is more than 50% and approaches 80% in patients who need dialysis, while the overall mortality rate after cardiac surgery hardly exceeds 8%[7-9].

AKI increases postoperative morbidity, length of stay in the intensive care unit (ICU) and hospital and costs of care[10]. High level of preoperative serum creatinine is associated with higher risk of RRT and need for dialysis after cardiac surgery[11,12]. Even minimal changes in serum creatinine increase postoperative mortality significantly. Indeed, 30 d mortality was reported to be 2.8 and 18.6 fold higher with up to a 0.5 mg/dL and more than 0.5 g/dL creatinine rise, respectively, compared to no change in a group of patients who underwent cardiac surgery[13]. The risk of AKI increases in valvular and combined surgery compared to myocardial revascularization two to four times, respectively[11,14,15].

It has been indicated repeatedly in different studies that serum creatinine rise after cardiac surgery is followed by long-term chronic kidney disease (CKD) and mortality[16-19]. Moreover, higher degrees of preoperative kidney insufficiency are accompanied by a proportionally higher risk of CSA-AKI and need for RRT[20]. Pathophysiologi-

cal studies indicate that cardiac patients with AKI are more likely to have progressive renal changes beyond the acute episode even after reduction of serum creatinine to normal levels[19,21,22].

AKI has been divided into pre-renal, renal and post-renal with regards to etiology. In surgical patients, pre-renal etiology, followed by renal etiology, is the most common cause of AKI[23]. As volume changes are common during cardiac surgery, CSA-AKI can be divided into volume responsive and non-volume responsive which usually matches pre-renal and renal etiologies. Renal etiology of CSA-AKI is caused by various factors, including ischemia and ischemia-reperfusion injury, inflammation and oxidative stress, exogenous and endogenous toxins, metabolic abnormalities and neurohormonal activation[24]. They can briefly be divided into hemodynamic, inflammatory and nephrotoxic factors[25,26].

SERUM CREATININE ROLE IN DIAGNOSIS OF CSA-AKI

In this section, we discuss that new equations have improved the calculation of glomerular filtration rate estimation (eGFR), especially in people with suboptimal kidney function and near normal real GFR. Moreover, new consensus systems are focused on more accurate practical definitions of AKI so that they can be better tools for outcome prediction. Nonetheless, there are obstacles to employing these formulas and definitions in cardiac surgery and creatinine still rules supreme.

Kidney impairment after cardiac surgery is acute in onset and most probably occurs in patients without a previous history of renal insufficiency. However, conventional formulas for eGFR have been released by studies on patients with renal impairment. Similarly, well-known definitions of AKI have been developed by analyzing data from patients with previous CKD. Paradoxically, most of the studies on AKI diagnosis and management after cardiac surgery have been performed in people without CKD, while we know CKD is the most important predictor of postoperative AKI. This shows how challenging it is to study the most important complication of cardiac surgery.

Creatinine clearance and eGFR methods

Serum creatinine has been used to determine GFR for a long time. Even the diagnosis and staging of CKD has been made through serum creatinine measurement. However, the serum concentration of creatinine is affected by factors such as age, gender, ethnicity, diet, muscle mass and medication. Moreover, creatinine will not be higher than the normal range until 50% of renal function is lost[27]. Direct measurement of GFR with inulin or radionuclides is expensive and complex and thus not suitable for routine use. Furthermore, the older method of 24 h urine sampling for the measurement of creatinine clearance is not easy to perform and the results are biased owing to some tubular secretion of creatinine that causes

up to 40% overestimation of GFR compared to inulin clearance[27]. That is why better tools for the assessment of GFR are required.

There are several creatinine-based formulas for the estimation of GFR that are widely used in research and clinical practice. The Cockcroft-Gault formula, named after the two scientists who developed it in 1976, is the most common surrogate for creatinine clearance in the estimation of GFR[28]. This formula employs age and weight as well as gender to calculate eGFR. The formula is useful due to simplicity and ease of calculation and it underscores the importance of age in estimating GFR: for the same level of creatinine, eGFR decreases to half at age 80 compared to age 20. However, the use of this simple equation in obese patients is not possible. Accordingly, ideal body weight, which is calculated taking height into account, is utilized in this group of people. Similarly, using adjusted body weight again while considering the role of height improves the GFR estimation in the elderly[29]. These shortcomings limit its application in the laboratory to report creatinine clearance.

Another common formula was developed by the Modification of Diet in Renal Disease (MDRD) Study Group in 1999[30]. It was simplified in 2002 by omitting albumin and blood urea nitrogen to a 4-variable MDRD which estimates GFR using the variables of age, gender, race and serum creatinine[31]. Laboratories use this formula to report eGFR. This formula estimates GFR more precisely in patients with CKD. Nevertheless, both 6-variable and 4-variable MDRDs underestimate GFR in healthy individuals with creatinine clearance more than 60 mL/min. Furthermore, compared to the Cockcroft-Gault equation, MDRD do not adjust for body mass index and thus underestimates GFR in obese and overestimates GFR in underweight people[32,33].

The most important shortcoming of both Cockcroft-Gault and MDRD equations is their development in patients with CKD. What is more, it has been shown that both formulas have lower precision in people with normal GFR[33-35]. Cockcroft-Gault overestimates and MDRD underestimates GFR in this group of healthy population[36]. Renal insufficiency in cardiac surgery is acute in onset and most probably in patients without any history of CKD. These formulas may, therefore, not be as useful in this group of patients[37]. To overcome this problem, the CKD-epidemiology collaboration (CKD-EPI) developed a new formula in 2009. This equation is superior to MDRD when GFR is more than 60 mL/min. Unlike the other two formulas, CKD-EPI was developed through several studies in populations with suboptimal renal function[38]. Advantageous in the CKD-EPI equation is its probable improved cardiovascular risk prediction compared to MDRD in a middle-age population[39]. Findings in previous studies will probably need revision through a new formula[40].

Development of new equations and making modifications to the available ones reflect the attempts to make eGFR an ideal surrogate for real GFR as much as possible. However, the closer we get to an accurate estimate of GFR, the farther we get from a clinically more practical tool. The most important drawback to employing these formulas in clinical practice is the fact that we cannot find a formula to fit all clinical conditions. Accuracy of eGFR is compromised when the clinical condition is different from the populations from which the equations were derived. Malnutrition or reduction in muscle mass from illness or amputation, extremes of muscle mass and diet (such as vegetarians), different ethnicities from those included in studies used for the development of the equations, or changes in the non-GFR determinants over time are the most probable determinants of large differences between real and estimated GFR[27,34].

A newer concept is to add laboratory parameters that are not dependent on body muscle mass and nutrition so as to obtain a better estimation of GFR. Using cystatin C, an index of glomerular function, is believed to be promising in different investigations in adults and children[34,41,42]. There are even equations based on cystatin C to calculate GFR[42,43]. However, cystatin C needs adjustment for age, gender and race, although adjusted cystatin C is probably superior to adjusted creatinine in developed equations[44]. Moreover, the lack of an international standard to calibrate cystatin C limits the use of these equations. More to the point, we do not know whether the routine use of cystatin C merits its cost as there is no evidence that it improves outcome significantly[45].

Preoperative creatinine and occult renal insufficiency

Discussion on preoperative creatinine revolves around the most important risk factor for CSA-AKI which is previous renal insufficiency[8,46]. Nevertheless, no unique level of serum creatinine as a threshold for renal insufficiency has been defined[47]. Predictor models for AKI are also not consistent: although most of them have reported preoperative renal insufficiency as a risk factor, their definitions for renal insufficiency are largely diverse from baseline creatinine of 1.5 mg/dL and eGFR of 60 mL/min as cut off points for dialysis dependency[48]. This holds true for most of the predictor models of outcome in cardiac surgery that have included preoperative renal insufficiency as a predictor[3,4,49]. Proteinuria, the most prevalent parameter used in the definition of CKD, is also absent in most of them due to a lack of data on urinalysis[5].

There is no debate on patients who are dialysis dependent or need renal replacement therapy. We recognize these problems as kidney disease. The most challenging are the patients whose serum creatinine level is within normal range but their real GFR or eGFR is low. We call this condition occult renal insufficiency and it is usually defined as eGFR < 60 mL/min when creatinine is in normal range. Several studies have shown that the incidence of morbidity and mortality after cardiac surgery is higher in patients with occult renal insufficiency[50-53].

AKI definition systems: RIFLE, AKIN and KDIGO

Despite the recognized importance of AKI, one of the major problems in conducting studies on the subject is

Table 1 Definition and classification for acute kidney injury

	Serum creatinine/GFR criteria	Urine output criteria
RIFLE classification		
Definition	SCr rise ≥ 1.5 times baseline or GFR decrease > 25% within 7 d	
Staging	R (Risk) SCr rise up to 2 times baseline or GFR decrease > 25%	< 0.5 mL/kg per hour for ≥ 6 h
	I (Injury) SCr rise up to 3 times baseline or GFR decrease > 50%	< 0.5 mL/kg per hour for ≥ 12 h
	F (Failure) SCr rise 3 times baseline or more or GFR decrease > 75% or absolute SCr ≥ 4 mg/dL with acute rise ≥ 0.5 mg/dL	< 0.5 mL/kg per hour for ≥ 24 h or anuria ≥ 12 h
	L (Loss) persistent AKI > 4 wk, need for RRT	
	E (ESRD) persistent loss > 3 mo, need for dialysis	
AKIN classification		
Definition	SCr rise ≥ 1.5 times baseline or ≥ 0.3 mg/dL within 48 h	
Staging	1 SCr rise up to 2 times baseline or ≥ 0.3 mg/dL	< 0.5 mL/kg per hour for ≥ 6 h
	2 SCr rise up to 3 times baseline	< 0.5 mL/kg per hour for ≥ 12 h
	3 SCr rise 3 times baseline or more or absolute SCr ≥ 4 mg/dL with acute rise ≥ 0.5 mg/dL or need for RRT	< 0.3 mL/kg per hour for ≥ 24 h or anuria ≥ 12 h
KDIGO classification		
Definition	SCr rise ≥ 1.5 times baseline within seven days or ≥ 0.3 mg/dL within 48 h or oliguria	
Staging	1 SCr rise up to 2 times baseline or ≥ 0.3 mg/dL	
	2 SCr rise up to 3 times baseline	
	3 SCr rise 3 times baseline or more or absolute SCr ≥ 4 mg/dL with acute rise ≥ 0.5 mg/dL or need for RRT	

GFR: Glomerular filtration rate; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; RIFLE: An acronym for Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal failure; SCr: Serum creatinine; AKI: Acute kidney injury; RRT: Renal replacement therapy.

the lack of consensus regarding the diagnosis as there are more than 30 different definitions for AKI[47]. In the past decade, several consensus systems have been introduced to define AKI uniformly in different studies. Perioperative changes in the serum concentration of creatinine are the cornerstone of the definition in these systems. In 2004, the RIFLE criteria were proposed by the Acute Dialysis Quality Initiative group[47].

A revised version of the RIFLE criteria was suggested by the AKIN group in 2007. There are four main changes in AKIN compared to RIFLE (Table 1): GFR changes have been omitted from the definition system; time period of seven days for creatinine changes has been replaced by 48 h; creatinine changes as low as 0.3 mg/dL is the lowest measure to be considered as AKI; and the two outcome determinants in RIFLE (loss and end stage) are deleted to define AKI in three stages[54].

Following the establishment of the AKIN scoring system, the resultant debate over the supremacy of each criterion prompted comparative research[55-60], which disclosed that AKIN was not more efficient than RIFLE and that some authors still preferred to employ RIFLE with some modifications[55]. Modified RIFLE stages anyone who needs RRT in category F (failure) regardless of the level of serum creatinine. A recent study performed with this method reported an incidence of 14% for AKI and showed that CSA-AKI aggravated short and long term outcomes in cardiac patients[19]. Nevertheless, a large survey of 1881 patients by Bastin et al[61] indicated that the incidence of AKI with both AKIN and RIFLE criteria was mostly equal (25.9% and 24.9%, respectively), but hospital mortality was predicted more precisely by AKIN. Another dispute was over the sensitivity of the two definitions insofar as whether or not the designated thresholds sufficiently diagnose all the cases of renal impairment. Studies have shown that there are concerns about the adequacy of the AKIN and RIFLE criteria inasmuch as that by the current standards, some AKI cases may be left undiagnosed. Lassnigg et al[62] described a new scoring system and reported that determining the amount of serum creatinine changes within 48 h was more capable than the RIFLE or AKIN criteria in predicting post-surgical outcomes.

This idea and the results of other studies encouraged researchers to propose a new definition. The KDIGO workgroup has recently reviewed these criteria and published a single definition for use in both clinical practice and research. AKI is defined when any of the following three criteria are met: an increase in serum creatinine by 50% in seven days, an increase in serum creatinine greater than 0.3 mg/dL in 48 h or oliguria[1]. There is a paucity of data to judge KDIGO as few studies have employed this criterion to date[63,64]. However, AKI incidence using KDIGO definition is probably lower than that using AKIN and RIFLE. Reported incidences of AKI in different studies ranged from 26%-49% for AKIN[55,60], 19%-30% for RIFLE[55,60] and 15%-16% for KDIGO[63,64].

Thanks to the development of consensus systems for the definition of AKI, it is possible currently to compare studies around the world and newer definitions have improved their employment in cardiac patients. Nevertheless, we are still far from an ideal practical definition of CSA-AKI. One reason may be the effect of the minimal changes in creatinine on outcome. Although this has been investigated largely in patients undergoing cardiac surgery[13,62], it is not limited to cardiac patients[65]. The AKIN definition sets a lower minimum level of serum creatinine as the diagnosis cut off point for AKI. However, even people who are outside of the minimum level have a worse outcome compared to patients with almost no change in serum creatinine. As employing the current systems for AKI definition in clinical practice is not easy, many of the studies performed to date have utilized these definitions partially. This is probably more pronounced in the RIFLE criteria which require seven days of follow-up

for the diagnosis to be completed[66].

AKI biomarkers, creatinine as a biomarker

Conventional biomarkers: An ideal biomarker for AKI is noninvasive, specific and sensitive for the detection of AKI within 24 h and is detected and measured in a rapid and reproducible way. Moreover, it should stratify risk and identify AKI subtypes[1,27,67,68]. A single biomarker that can fulfill all these criteria has yet to emerge[69]. Serum creatinine as a biomarker is still the only reliable tool for the assessment of AKI. Urine output is readily available and more sensitive to hemodynamic changes compared to creatinine. However, its variations are not specific, especially during cardiac surgery with cardiopulmonary bypass (CPB), and unavoidable hemodynamic changes, due to medications, such as diuretics, mannitol and other fluids, and possible measures such as ultrafiltration. In addition, the well- known term of non-oliguric renal failure denotes that normal urine output does not guarantee normal renal function[70,71]. The other marker, urinalysis, can differentiate pre-renal from renal failure in patients with decreased urine output which is very helpful in guiding treatment. Obviously urinalysis is not suitable for prophylactic measures due to its delayed response to renal insult[71].

With regard to eGFR formulas, we know that there is a lag between the renal event and serum creatinine changes that may be as long as 48 h, while we expect to know the occurrence of renal impairment immediately after surgery. As creatinine is not a sensitive measure, GFR may decrease up to 50% before the creatinine starts to change. Moreover, as creatinine is not specific, its value is influenced by changes in age, gender, race and muscle mass, as discussed before. In cardiac surgery, changes in total body volume, protein intake and medications may extend the list[27,72]. These factors are so important that, for instance, volume overload was reported to be superior to creatinine in predicting outcome after cardiac surgery in a recent study[73].

Novel biomarkers: Using the most sensitive and specific biomarker for AKI is the ideal solution for the optimal estimation of GFR and rapid diagnosis of renal insult. As was noted, such a biomarker should be biologically stable and as a laboratory assay should be quick, reliable and cost effective with a high discriminative power[67]. So important is this issue that finding a suitable biomarker was recommended as the key search area in 2005[74]. Currently, two large studies are underway to assess the role of novel biomarkers in the diagnosis and prognosis of AKI: multicenter National Heart, Lung and Blood Institute-sponsored Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study and the Assessment, Serial Evaluation and Subsequent Sequelae of AKI study. The latter is also aimed at evaluation of long term complications of AKI[75]. The results of these large studies are expected to shed sufficient light on the matter.

In recent years, more than 20 biomarkers have been introduced and most of them have been tested in studies of post-cardiac surgery[68,76]. Four novel biomarkers have been studied most frequently: neutrophil gelatinase-associated lipocalin (NGAL), interlukin-18 (IL-18), kidney injury molecule-1 (KIM-1) as markers of tubular injury and cystatin C as a marker of glomerular function. NGAL, followed by IL-18, is more promising as an early diagnostic tool and may qualify for entry into clinical practice. KIM-1 has delayed response and cystatin C needs adjustment for age, gender and race[2,69,77].

NGAL: NGAL is a protein that normally binds to small iron-carrying molecules. NGAL is significantly upregulated in response to renal tubular injury. Role of NGAL in the diagnosis of AKI has been the most extensively studied in cardiac surgery[78]. First, animal studies in 2003 showed that NGAL was markedly upregulated early after ischemic injury[79]. Then its rapid rise following renal insult drew attention. Level of urinary NGAL one hour post-CPB significantly predicted the risk of AKI after cardiac surgery[80]. Plasma NGAL levels two hours after CPB were strongly correlated with the duration and severity of AKI[81]. Other studies showed that NGAL levels were predictive of CSA-AKI when measured both in urine and plasma[82-85].

It is noteworthy that the predictive power of NGAL in pediatric surgery is striking, whereas its sensitivity and specificity for AKI prediction in adult cardiac surgery is not high enough to employ it as the sole biomarker for CSA-AKI[78,86]. It shows that the nature of CSA-AKI in adults is probably more complex. Degrees of chronic renal impairment before cardiac surgery may explain part of this inconsistency between the response of biomarkers to renal insult in adults and children. It is evident from recent studies that the diagnostic performance of NGAL is significantly influenced by baseline renal function[84,87].

IL-18: IL-18, a pro-inflammatory cytokine, is a biomarker of AKI and is detectable in urine four to six hours after CPB, peaking at 12 h[88]. A multi-center study showed that plasma NGAL and urine IL-18 peaking within 6 h after cardiac surgery not only predicted AKI earlier than serum creatinine, but also predicted important outcomes such as length of stay in the ICU and hospital, dialysis and death[89].

However, there are some challenges regarding the use of the currently available biomarkers. First, biomarkers are being evaluated in comparison with creatinine as a gold standard while the weakness of serum creatinine to be a sensitive and specific marker has been the main cause of directing research into finding novel biomarkers[90]. Second, many of the studies undertaken to date have excluded patients with CKD[70] while CKD is the most important risk factor for postoperative AKI. Discrepancy between clinical practice and the results of research may arise as biomarkers are under the influence of baseline renal function[11,12]. Third, the level of bio-

Table 2 Risk factors for acute kidney injury	
Preoperative	**Intraoperative**
Patient related	Patient related
Renal dysfunction/high SCr[1]	Low venous compliance
Advanced age	Low systemic vascular resistance
Female gender	Autoregulatory systems disturbances
NYHA FC IV	**Low output syndrome**
Reduced LVEF or CHF	**(pressor/IABP need)**
Left main CAD	**Type of surgery**
Diabetes mellitus	Valvular
Poor glycemic control	Re do surgery
Peripheral vascular disease	Emergency
COPD	
Coexisting liver disease	
Preoperative IABP	
Pulmonary rales	
Genetic predisposition	
Modifiable	Procedure related[3]
Extremes of SBP[2]	On-pump cardiac surgery
Sepsis[2]	Nonpulsatile flow on CPB
Medications (NSAID, ARB)	Hypothermic CPB
Contrast dye	Deep hypothermic circulatory arrest
	Duration of CPB (> 100-120 min)
	Perfusion pressure
	Hemodilution during CPB
	Blood transfusion
	Hemolysis
	Embolism

[1]Risk factors with higher level of evidence are in bold; [2]both patient related and modifiable; [3]and also modifiable. NYHA FC IV: New York Heart Association Function class IV; LVEF: Left ventricle ejection fraction; CHF: Congestive heart failure; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; IABP: Intra-aortic balloon pump; SBP: Systolic blood pressure; NSAID: Nonsteroidal anti-inflammatory drug; ARB: Angiotensin receptor blockers; CPB: Cardiopulmonary bypass; SCr: Serum creatinine.

markers increases in response to injury. Although novel biomarkers are superior due to earlier response, the ideal biomarker would be one that predicts AKI preoperatively. Promising results have been reported with ouabain[91]. Fourth, the pathogenesis of AKI is multifactorial. Hemodynamic, inflammatory and nephrotoxic factors are responsible and overlap each other in leading to kidney injury[25]. This complex pathology affects finding a unique biomarker with high accuracy in the diagnosis of AKI. Consequently, no biomarker by itself is an accurate and reliable predictor for the diagnosis and risk estimation in AKI. Combination of biomarkers as a diagnostic panel would probably allow the determination of the risk and severity, as well as the early diagnosis of AKI[76,92].

RISK FACTORS FOR HIGH PERIOPERATIVE SERUM CREATININE

Risk factors for increased level of serum creatinine and the development of AKI have been widely studied[10,71]. There are two main groups of risk factors: preoperative and intraoperative. Most of the preoperative risk factors are patient-related and most of the intraoperative risk factors are procedure-related. Usually, intraoperative risk

factors are more likely to be modifiable[25] (Table 2). Postoperative factors, such as blood drainage and need for excessive transfusion and emergent exploration, as well as myocardial infarction, are of limited interest due to late onset and low chance of their benefit in AKI prediction and prevention[10].

Preoperative risk factors
Preoperative risk factors are not the same in different studies. The most reported risk factors include advanced age, female gender, New York Heart Association Function class IV, reduced left ventricular ejection fraction or congestive heart failure, diabetes mellitus, poor glycemic control, peripheral vascular disease and chronic obstructive pulmonary disease. Other factors such as the need for preoperative intra-aortic balloon pump and pulmonary rales have been noted in studies. However, the most predictive risk factor has consistently been preoperative renal dysfunction[2,71]. Thakar et al[14] developed a risk index for predicting the need for dialysis after cardiac surgery based on preoperative factors. This study showed that the value of preoperative serum creatinine as an equivalent for renal dysfunction is the most important predictor for AKI.

Several studies have suggested that medications such as non-steroidal anti-inflammatory drugs and angiotensin receptor blockers (ARB) be stopped before cardiac surgery in order to decrease the risk of AKI[25]. More recently, genetic predisposition to AKI has been studied. According to many polymorphism studies, apolipoprotein was associated with AKI and its epsilon-4 allele has been the only genotype protective against AKI compared to other forms of allele[93,94].

Intraoperative risk factors
Contrary to many preoperative risk factors that are well known for their role in the development of CSA-AKI, the identification of intraoperative risk factors is challenging. Maintaining stable hemodynamics is probably the most important point in kidney protection during cardiac surgery, especially on the CPB. This is supported by the finding that many intraoperative risk factors are associated with hemodynamic instability: low-output syndrome; intraoperative intra-aortic balloon pump use; pressor need prior to CPB; and the need for deep hypothermic circulatory arrest. However, the management of hemodynamic changes is not easily feasible because patient factors such as venous compliance, systemic vascular resistance and autoregulatory systems are responsible for cardiovascular stability during cardiac surgery and are difficult to control[10].

Rather than surgery type (valvular, re do, emergency), modifiable procedure-related risk factors include on-pump cardiac surgery, CPB nonpulsatile flow and hypothermic CPB. Current data is insufficient to confirm the association between these CPB parameters and the risk of CSA-AKI[2,71]. Other more established CPB-related risk factors are duration of CPB (> 100-120 min), perfu-

sion pressure, hemodilution during CPB, blood transfusion, hemolysis, most commonly due to cardiotomy suction, and embolism[2,95,96]. The role of CPB in inducing systemic inflammatory response syndrome (SIRS) and consequently CSA-AKI has been shown in different cardiac surgery events. The inflammation is related to perfusion pressure, hemodilution, blood transfusion, hypothermia, hemolysis and embolism[97,98]. SIRS and other physiological untoward events explain how much longer CPB time increases the incidence of CSA-AKI. A meta-analysis in 2009 showed that mean CPB time and mean cross clamp time were significantly longer in patients who developed AKI. No safe time limit has been reported, however[99].

Surgical technique

Surgical techniques with minimum CPB usage potentially lessen the adverse complications of the inflammatory response. Minimally invasive cardiac surgery, including transcatheter aortic valve implantation, or minimally invasive mitral valve surgery decreases the incidence of AKI[100]. The other technique is mini CPB or miniaturized extracorporeal circuit with unproven efficacy in CSA-AKI prevention[101]. Off-pump coronary artery bypass (OPCAB) is another technique to ameliorate CPB-related complications and aortic manipulations. However, it is interesting that the effectiveness of OPCAB in preventing CSA-AKI is controversial and still one of the most debated topics in cardiac surgery. Although OPCAB has been shown to be superior in many studies[102-105], the results of recent large trials results have documented that it does not decrease important endpoints, especially the need for RRT[106,107]. This may place an emphasis on the importance of hemodynamic stability in AKI prevention on account of the fact that during OPCAB, episodes of hypotension are inevitable. Overall, we conclude that at least in patients with lower risk for AKI, OPCAB may not decrease the likelihood of kidney impairment after cardiac surgery.

Hemodynamic

Perioperative hypotension during CPB increases the incidence of CSA-AKI. It is more important to preserve end-organ function and cellular oxygen delivery during CPB with its unique pressure and nonpulsatile flow characteristics. Thus, it is not the absolute hypotension but perfusion pressure that plays a pivotal role in protecting susceptible organs such as the kidney against CSA-AKI. The kidney medulla is more vulnerable since its oxygen delivery is already low[108,109]. The difference between preoperative and intraoperative blood pressure may be a more important predictor of CSA-AKI compared to absolute hypotension. A study in 2010 showed that when this difference is more than 25 mmHg the incidence of CSA-AKI increases[110].

Hemodilution

The carrying capacity of oxygen is influenced by hemo-

dilution which is inevitable during CPB. This adds to hemodynamic changes due to nonpulsatile flow and puts the kidney at danger of ischemia[109]. It has been suggested that hematocrit levels less than 24% increase the risk of CSA-AKI[111-113]. However, in all probability, preoperative hematocrit plays an important role[114]. The most important factor is the balance between oxygen delivery and oxygen consumption which is crucial everywhere in the body, not least in the kidney which is more susceptible to ischemia[24]. Even the probable risk of hypothermia during CPB may be explained by reperfusion ischemia due to rapid rewarming[115].

That hemodilution has some adverse effects does not mean that blood transfusion is absolutely beneficial in improving renal function. RBC storage more than 14 d has been associated with increased organ injury[116]. Moreover, the adverse effects of packed cell transfusion when hemoglobin level is not low outweigh its benefits[117,118].

Evidence-based blood conservation techniques include increasing preoperative blood volume by drugs such as erythropoietin and decreasing postoperative blood loss (tranexamic acid and aminocaproic acid), preserving the patient's own blood by autologous techniques, such as predonation and intraoperative hemodilution, and intraoperative cell salvage[119].

CPB flow

Pulsatile flow is believed to improve renal function by decreasing peripheral vascular resistance, optimizing microcirculation and decreasing tissue edema[120,121]. However, the inconsistent results of studies cannot support its routine use for protection against CSA-AKI[122-124].

RISK MODELS FOR AKI AFTER CARDIAC SURGERY

Identification and categorization of high-risk patients allows optimal decision-making for earlier intervention and better management, along with the identification of the patients who do not respond to conventional treatments. Risk prediction models can also be used as research tools to select high risk patients for performing studies on AKI. Several risk stratification models have been developed by research groups in patients undergoing different surgeries[11,125].

As discussed before, CSA-AKI has its own characteristics. Although some risk factors for AKI are common in general and cardiac surgery, the risk scores developed in a general surgery population underestimate the risk of AKI in cardiac surgery[126]. There are several risk prediction models that have been developed in the field of cardiac surgery[11,14,15,127-130].

Chertow et al[11] developed the first risk score using a large population database in 1997. This algorithm stratified preoperative risk for dialysis based on data from 43 medical centers gathered in the Continuous Improvement in Cardiac Surgery Study. Then three other predictive risk models were developed, all of which aimed at predicting

the need for dialysis as outcome[14,127,128]. The most validated model with a high level of precision and the best discriminative power is the Cleveland Clinic Score which was published in 2005 by Thaker et al[14] (Candela-Toha et al[126], Di Bella et al[131], Englberger et al[132] and Heise et al[133]).

In 2006, the Society of Thoracic Surgeons Bedside Risk Tool was developed by Mehta et al[128] through the analysis of a multicenter dataset of more than 600 hospitals. Simplified Renal Index was developed by Wijeysundera et al[127] from a Toronto cohort in 2007. Validation studies by other researchers indicate that recalibration of every risk score is needed for optimal risk prediction in any center[134-136]. Other available models are aimed at predicting AKI not requiring dialysis. They have not been externally validated, however, and due to different definitions of AKI it is difficult to generalize them[16,129,130].

The most important criticism to the available risk models is their lack of prediction for CSA-AKI. There are still different definitions for AKI and there is no guideline to recommend a specific prediction model[2,48]. As discussed before, we need to add novel biomarkers to the current risk models and AKI definitions so as to be able to develop scoring systems for the prediction of the earlier stages of AKI. A study by Parikh et al[89] indicated that adding urine IL-18 and plasma NGAL to the risk models improved risk prediction by 25% and 18% respectively.

CREATININE AND THE OUTCOME PREDICTION IN CARDIAC SURGERY

The critical role of creatinine as a strong predictor has been incorporated in the different mortality risk scores that are currently in use for cardiac surgery patients[3,49,137]. Known risk models have employed a wide range of risk factors from only three to dozens[3,4]. However, high level of serum creatinine or its equivalents (past history of kidney dysfunction, need for renal replacement therapy and/or dialysis) has been the constituent in almost all of them. The first scoring system was developed by Parsonnet et al[138] in 1989, which included serum creatinine in 14 independent variables. Subsequently, Higgins et al[139] proposed the Cleveland Clinic score in 1992. Cleveland Clinic score was basically developed for coronary artery bypass graft (CABG) operations with or without associated valve surgery and included creatinine among 9 independent variables included in this score. Another mortality predictor introduced in 1992 was the Northern New England score which was developed for isolated CABG operations and included preoperative dialysis dependency as a surrogate for high serum level of creatinine[140]. Nilsson et al[3] and Magovern et al[141] developed another risk algorithm to be applied in isolated CABG with promising results compared to a group of 18 risk models.

In the last decade, the additive[142] and the logistic[143] EuroSCORE predicting tools were developed and subsequently widely validated. These scores are prepared to be applied in all cardiac surgeries in adult patients and each of them includes 17 independent variables. Serum creatinine receives a score of two when its absolute value is more than 200 μmol/L (2.25 mg/dL). EuroSCORE overestimates mortality and its performance in high risk patients is not good. EuroSCORE Ⅱ was released in 2012 to improve the accuracy of this measure[144].

The risk score developed by the Society of Thoracic Surgeons is more complex, built on a database with more than five million records and including several hundred variables[145]. The risk calculator is available freely at: http://riskcalc.sts.org/STSWebRiskCalc273/. On the other hand, Ranucci et al[4] recently proposed a simple score with only three variables, including creatinine, and demonstrated that this risk model was superior to or as effective as the other more complex risk scoring systems. Creatinine in this score has an absolute cut off point of 2 mg/dL. In patients with serum level of creatinine higher than 2 mg/dL, one point is added to sum of the patient's risk. The formula is as follows: age (years)/ejection fraction (%) +1 (if serum creatinine > 2 mg/dL).

The main weakness of existing risk models is their inaccuracy in different time periods and patients' conditions and various regional settings which emphasizes the dynamic trends in cardiac surgery[146,147]. Moreover, known risk models are principally prepared to predict mortality. So, we probably are unable to accurately predict morbidity and cost of care by the available risk models. The other major flaw is the lack of a consensus definition of time span for mortality by these models[137].

PREVENTION AND TREATMENT ON THE HORIZON

Briefly, no treatment or prophylactic measure studied thus far has received sufficient evidence-based support to be employed in AKI management[66]. However, avoidance of AKI by preventive measures remains the mainstay of management in high risk patients. Contrast induced AKI is probably an exception in that it is preventable and manageable by hydration, N-acetyl cysteine and bicarbonate[148].

Renoprotective measures include preventive simple maneuvers such as avoidance of nephrotoxic drugs, hydration, glycemic control, maintenance of renal perfusion and goal directed therapy (GDT), as well as more advanced pharmacological interventions[1,2,70,71] (Table 3).

Preventive measures
Renal injury can be mitigated by two approaches: preventing CSA-AKI from being superimposed on CKD by appropriate risk assessment and preventing subclinical or silent AKI from occurring before cardiac surgery. Management of the adverse effects of contrast dye is an example of the second approach. The role of contrast dye in the occurrence of CSA-AKI is well known and as it is not avoidable, the minimum possible dose of preferably newer non-ionic contrast with lower osmolality should be used[149,150]. Timing of surgery following contrast angiography may play a role in CSA-AKI. It has been shown

Table 3 Potential preventive measures and pharmacological interventions in acute kidney injury

Preventive measures
    Avoidance of nephrotoxic drugs
    Angiotensin-converting enzyme inhibitors
    Angiotensin receptor blockers
    Hydration
    Glycemic control
    Maintenance of renal perfusion
    Goal directed therapy
    Ischemic preconditioning
    Prevention of CI-AKI
        Hydration
        N-acetyl cysteine
        Bicarbonate
        Timing of surgery
Pharmacological interventions
    Fenoldopam
    Nesiritide
    Sodium bicarbonate
    Mannitol
    Atrial natriuretic peptide
    Brain-type natriuretic peptide
    Early postoperative renal replacement therapy
    Continuous renal replacement therapy
    Ultrafiltration

CI-AKI: Contrast induced acute kidney injury.

that cardiac surgery within 24 h of angiography is not safe. In the case of large contrast dose administration it is better to postpone surgery for five days[151,152].

Sufficient hydration is protective not only in patients at risk of contrast-induced nephropathy[153], but also in patients with underlying renal insufficiency[154]. Ideal fluids have been thoroughly investigated to be recognized, without consistent results[1,71]. It appears from studies to date that colloids are not superior to crystalloids in improving outcome[155,156]. Moreover, recent studies have shown that contrary to previous belief, clinical application of semisynthetic colloids, especially hydroxyethyl starch solutions, are increasingly difficult to justify in the perioperative period[156]. Of more importance is probably maintaining normal renal perfusion as 80% of patients diagnosed with AKI after surgery have had an episode of perioperative hemodynamic instability[157]. GDT, involving the use of enough fluid and blood along with inotropes to optimize hemodynamic parameters and oxygen delivery, is a recommended strategy[156,158,159]. Fluids are required to be prescribed as a drug[156]. This is possible through the employment of physiological parameters such as the plethysmographic variability index, stroke volume variation and pulse pressure variation in advanced monitoring systems[159]. Further studies are needed to optimize protocols[156,159].

Angiotensin-converting enzyme inhibitors and ARB are potential nephrotoxic medications commonly used in cardiac patients. Avoiding them has not been shown to change the incidence of CSA-AKI and the subject is still controversial[160,161].

Other measures, such as ischemic preconditioning us-

ing three 5 min intervals of ischemia separated by exactly the same times and interval of reperfusion in the thigh, have been shown to reduce the risk of CSA-AKI[162].

Pharmacological interventions

Finding a pharmacological agent for the management of CSA-AKI has been challenging due to the absence of standard definitions and end-points[1,2,26,70,163]. Many drugs have been investigated to date to control the serum level of creatinine and renal protection. Fenoldopam, a selective agonist of dopamine-1 receptor, is the only drug that consistently and significantly has reduced the risk of AKI, followed by nesiritide with initial promising results[1,164,165].

Sodium bicarbonate was found in a known pilot study in 2009 to decrease the risk of AKI by 20%[166]. However, another large study in 2012 questioned its usefulness[167]. This is also true for statins. First reports on its usefulness were not supported by the following studies[168-171].

It has been known since 2001 that low-dose dopamine is not justified for the prevention and treatment of AKI[172,173]. Furosemide infusion, especially in combination with dopamine, is even detrimental and may increase postoperative creatinine[174,175]. Mannitol is an osmotic diuretic that has been used routinely in priming solution for decades. Currently there is debate on its usefulness in cardiac surgery and studies have been inconclusive. However, it is probably reasonable to continue its use as a harmless fluid until strong evidence, guidelines and recommendations are published[176,177].

Atrial natriuretic peptide and brain-type natriuretic peptide (BNP) are endogenous diuretics with promising effects on renal function in cardiac surgery[178-180]. BNP is highly associated with postoperative AKI such that it has been considered as a biomarker for AKI in the recent report of TRIBE-AKI study[181]. Nesiritide, the recombinant human BNP, has been shown to be beneficial according to initial results. Further studies are required before applying nesiritide routinely in daily clinical practice[182,183].

N-Acetylcysteine has protective effects on contrast-induced nephropathy[184]. Be that as it may, its prophylactic administration in cardiac surgery is under question. Recent meta-analyses have concluded that current data do not support its routine use in cardiac surgery and it has obtained least strength evidence among prophylactic measures for renal protection[1,163,185].

Current data is insufficient to support preoperative prophylactic RRT. The best starting time for postoperative RRT is also controversial. Most studies have found lower mortality with the earlier initiation of RRT[163,186,187]. In addition, recent guidelines suggest that using continuous RRT is superior to standard intermittent RRT in hemodynamically unstable patients[148]. It is clinically indicated and applicable, although reviews to date have not found differences in survival between the two modes[188]. Similarly, the benefits of ultrafiltration on CSA-AKI prevalence and severity in adult cardiac surgery warrants further investigation.

CONCLUSION

Recent advances in diagnosis and management of CSA-AKI have opened new perspectives for scientists and medical practitioners. However, creatinine still plays the main role in diagnosis and prediction. New consensus classification for AKI (KDIGO) and new formula for eGFR calculation (CKD-EPI) are promising for better evaluation of patients at risk of postoperative AKI. Incorporating a panel of novel biomarkers in diagnosis and prevention could enhance the quality of the prediction and cause supportive care to be employed earlier. Results of large studies are expected to qualify the capability of these achievements to improve patients' daily care. With respect to the AKI prevention and management, notwithstanding the large number of studies, more attempts are required to reach the optimal prophylactic and therapeutic goals.

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