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Renal failure and heart surgery

Abstract

CSA-AKI is common after cardiac surgery, and even small increases in serum creatinine are associated with significant increases morbidity and mortality. A variety of risk factors have been identified for the development of CSA-AKI, but a precise precipitating event or events which lead to this complication have yet to be identified. Moreover, current diagnostic methods for detecting AKI lag behind the point of injury by 24-48 hours. Current technologies to close this gap include biomarkers and cerebral autoregulation monitoring data, but clear methodologies for their use have yet to be perfected. There have similarly been many failed interventions aimed at ameliorating AKI, though goal-directed perfusion strategies on CPB may hold promise.

Keywords: kidney, renal function failure, acute kidney injury, cardiac surgery

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Abbreviations: CSA-AKI, cardiac surgery associated acute kidney injury; ADQI, acute dialysis quality initiative; RIFLE, risk-injury-failure-loss-end stage renal disease; AKIN, acute kidney injury network; CPB, cardiopulmonary bypass; CHF, congestive heart failure; IGFBP7, insulin-like growth-factor binding protein 7; TIMP-2, tissue inhibitor metallo proteinases; RRT, renal replacement therapy

Scope of the problem

Cardiac surgery associated acute kidney injury (CSA-AKI) develops in 5% to 40% of patients.[1-5] The precise etiology of CSA-AKI is unclear, but can result from a variety of factors including ischemia resulting from hypotension, hemorrhage, or circulatory arrest, nephrotoxic agents, and the development of postoperative complications including sepsis. Unfortunately, mortality rates for new patients requiring dialysisremain staggeringly high, at around 1/3 in mixed patient populations.[6,7] Patients who double their serum creatinine or need acute dialysis have a 2 to 5-fold higher risk of death.[8] Even mild or subclinical deteriorations in renal function profoundly increase the risk for major adverse outcomes after cardiac surgery.[3,4,9,10]

Definition of renal failure in cardiac surgery

In 2004 the American Society of Nephrology Renal Research Group introduced the term "acute kidney injury" (AKI) in an effort to systematize terminology and risk stratification for patients. This terminology was adopted to reflect the entire spectrum of the disease: from minimal elevations in serum creatinine to anuric renal failure; from functional deviations to structural changes; and from pre-renal azotemia to acute tubular necrosis. A consensus definition of AKI was proposed by the Acute Dialysis Quality Initiative (ADQI), which introduced the RIFLE (Risk-Injury-Failure-Loss-End Stage Renal Disease) criteria.[11] These criteria have since been modified by the Acute Kidney Injury Network (AKIN), which specifies a timeframe of 48 hours within which AKI occurs,along withthree classifications describing increases in serum creatinine relative to baseline(Table 1).[12] In most patients after cardiac surgery, serum creatinine will increase only by 0.1-0.2mg/dL. If creatinine increases more than 0.3mg/dL, AKI is diagnosed.

Risk factors

In general, clinical AKI is thought to be multifactorial, and seemingly minor insults may result in renal failure in high-risk patients. In humans,the exact cause of CSA-AKI is unknown but thought to be precipitated by an ischemic event. Many authors have attempted to identify risk factors for AKI after cardiac surgery. These have been reported to include age,[13,14] preoperative renal impairment,[14,15] diabetes,[16] cerebrovascular disease,[16] prolonged cardiopulmonary bypass (CPB) time,[13-15,17] valve procedures,[13-15,17,18] postoperative hypotension,[14] or hemolysis and ensuing pigment nephropathy.[19]

The kidneys are similar to the brain in that they have highly efficient intrinsic auto regulation mechanisms that maintain an RBF over a wide range (MAP 60 to 120mm Hg) of renal arterial perfusion pressures.[20].Disruption of this mechanism causes pre-renal azotemia, a term which has been replaced with concept of volume-responsive AKI by the ADQI and AKIN groups, since pre-renal azotemia and acute tubular necrosis develop in parallel in AKI. The main mechanism is a reduction in renal perfusion with a modest reduction of GFR, an increase in creatinine and BUN, which are often accompanied by oliguria. Non-volume-responsive AKI is thought to be caused by renal ischemia with subsequent rapidly progressive and profound reduction in GFR.[21]

The issue: when exactly CSA-AKI happens and why?

Currently, there are no evidence-based guidelines to support any specific fluid use or vasoactive medication to improve renal function. Similarly, there are no devices or biomarkers which can identify either optimal renal perfusion or ischemia in real time to prevent CSA-AKI. What we do have is a general consensus that volume depletion and congestive heart failure (CHF) symptoms should be addressed and corrected as part of the management of AKI.[22]

The major issue with CSA-AKI management, however, is the delay indiagnosis caused by using standard clinical diagnostic criteria (serum creatinine and calculated GFR). These detect AKI when it is already well established, 24-48 hours after the injury. Moreover, serum creatinine has limited sensitivity and specificity because its serum levels depend significantly on non-renal factors such as age,

sex and muscle mass. To prevent CSA-AKI, detection of AKI must happen within a "window of opportunity" for interventions, just as now exists for stroke and MI treatment. As such, there is a need to develop a clinically viable, real-time, continuous, and non-invasive monitor to assess renal function or at least renal perfusion.

Novel strategies at detection

The AKI research network evaluated several novel biomarkers in clinical trials with the goal of diagnosing CSA-AKI within the first 24hours after the injury. These biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule 1 and interleukin-18.[23,24] Their levels increase within 2 hours of injury and denote a 5-6-fold increased risk of AKI.

As of September 5, 2014, Nephro Check, a test by Astute Medical, was approved by the FDA to detect the presence of an insulin-like growth-factor binding protein 7 (IGFBP7) and the tissue inhibitor metallo proteinases (TIMP-2) in the urine, which are associated with acute kidney injury.[25] Within 20minutes, the test provides a score based on the amount of the proteins present which correlates to the patient's risk of developing AKI within 12hours of the test being performed. However, a recent paper called into question whether these markers can adequately detect patients who will develop AKI on the day of surgery, as opposed to the first postoperative day.[26]

During hypoperfusion, renovascular autoregulation is compromised earlier and more severely than cerebrovascular autoregulation.[27] Innovative technology to determine the lower limit of the cerebral autoregulation threshold has been developed and validated at Hopkins. Excursions of MAP below the lower limit of cerebral autoregulation were independently associated with AKI.[28] Because of this, observations of cerebral perfusion may be used as a surrogate for renal perfusion.

Table 1 RIFLE and AKIN classifications for AKI[12,40]

RIFLE			AKIN		
Stage	**Cr/GFR criteria**	**Urine output criteria**	**Stage**	**Cr criteria**	**Urine output criteria**
Risk	Increased Cr x 1.5-2.0 or GFR decreased > 25%	UO < 0.5mL/kg/hr x 6hr	1	Increased Cr x 1.5-2.0 or ≥ 0.3mg/dL	UO<0.5mL/kg/hr x 6hr
Injury	Increased Cr x 2.0-3.0 or GFR decreased > 50%	UO < 0.5mL/kg/hr x 12hr	2	Increased Cr x 2.0-3.0	UO < 0.5mL/kg/hr x 12hr
Failure	Increased Cr x 3.0 or GFR decreased > 75% or Cr ≥4 mg/dL (with acute rise of ≥ 0.5 mg/dL	UO < 0.3mL/kg/hrx 24 hr or anuria x 12hr	3	Increased Cr x 3.0 or Cr ≥4 mg/dL (with acute rise of ≥ 0.5mg/dL)	UO<0.3mL/kg/hr x24hr or anuria x 12hr
Loss	Persistent ARF =complete loss of renal function for >4weeks		Patients who receive renal replacement therapy (RRT) are considered to have met AKINcritera for stage 3 regardless of the stage they are in prior to RRT initiation.		
ESRD	End Stage Renal Disease				

Increases specified are defined as increases from baseline serum creatinine (i.e.: a patient with AKIN stage 1 AKI will have a serum creatinine 1.5-2.0 times baseline: or 50-100% higher than baseline).

AKI, acute kidney injury; RIFLE, risk-injury-failure-loss guidlines; AKIN, acute kidney injury network guidelines; CR, serum creatinine; UO, urine output; GFR, glomerular filtration rate; ARF, acute renal failure; ESRD, end-stage renal disease; RRT, renal replacement therapy

Table 2 Accepted Indications for Renal Replacement Therapy in Patients with AKI

1	Refractory fluid overload
2	Hyperkalemia (plasma potassium concentration >6.5mEg/L) or rapidly rising potassium levels
3	Signs of uremia: such as pericarditis: neuropathy: or an otherwise unexplained decline in mental status
4	Metabolic acidosis (pH<7.1)
5	Certain alcohol and drug intoxications

Novel strategies on prevention and treatment

A list of attempted and failed strategies to prevent CSA-AKI includes:diuretics (furosemide, mannitol);[29] renal vasodilators (dopamine, fenoldopan, Ca channel blockers); atrial natriuretic peptides (nesiritide); anti-oxidants (N-acetylcysteine); ACE-inhibitors;[30] anti-inflammatory drugs (steroids); ultrafiltration; anti-apoptotic agents; urinary alkalinization by sodium bicarbonate;[31] statins;[32] human recombinant erythropoietin;[33] and remote ischemic pre conditioning.[34] Trials conducted on renotropic progenitor cells administration were prematurely terminated by the company (AlloCure).

Currently, the most promising strategy to reduce CSA-AKI is goal-directed perfusion management using oxygen delivery (DO_2 level>270ml/min/m^2) and its ratio to CO_2 production (DO_2/VCO_2>5.3).[35] Maintaining cardiopulmonary bypass (CPB) flows above 54mL/kg/min, mean arterial pressureless than 26mmHg from baseline and avoiding hyperthermia (core temperature >37 degrees Celsius) have been proposed as protective strategies during bypass.[19,36,37]

Finally, prolonged loss of kidney function requires renal replacement therapy (RRT). Accepted indications for RRT are presented in Table 2. Whether initiation of earlier or prophylactic dialysis prior to the development of symptoms and signs of renal failure offers any clinical or survival benefit is unproven. Several trials have shown that the modality of RRT-either intermittent or continuous-hasno impact on outcomes in patients with AKI.[38] Treatment with higher intensity continuous RRT or with early RRT also did not provide any additional benefit.[39]

Conclusion

In summary, knowledge of CSA-AKI is critical to the provider caring for cardiac surgery patients. To the extent that etiologies such as hypotension and low oxygen delivery have been identified as risk

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factors for CSA-AKI, clinicians should apply this knowledge to their routine clinical practice.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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