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Review

ACUTE KIDNEY INJURY AFTER OPEN-HEART SURGERY PROCEDURES

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SUMMARY – Cardiac surgery-associated acute kidney injury (CS-AKI) is a major complication associated with increased morbidity and mortality. There are multiple diagnostic criteria for CS-AKI. Despite many new investigations available for improved AKI diagnostics, creatinine and urea remain the cornerstone of diagnostics in everyday clinical practice. There are three major pathophysiological mechanisms that contribute to kidney injury, i.e. renal hypoperfusion, inflammation with oxidative stress, and use of nephrotoxic agents. Some risk factors have been identified that can be modified during the course of treatment (use of nephrotoxic agents, duration of cardiopulmonary bypass, type of extracorporeal circulation, postoperative low cardiac output or hypotension). The aim of AKI prevention should always be to prevent aggravation of renal failure and, if possible, to avoid progression to renal replacement therapy, which in turn brings worse long-term outcomes.

Key words: *Kidney injuries; Cardiac surgery; Perfusion; Oxidative stress; Dialysis*

Introduction

Acute kidney injury (AKI) is one of the most prevalent major complications following open-heart surgery[1]. Its incidence ranges from 5% to 42%, depending on diagnostic criteria and population studied[2]. It is clinically important because of higher perioperative mortality (up to 3- to 8-fold), prolonged intensive care unit (ICU) stay, and increased costs[3-5]. Even subtle decrease in renal function could potentially be associated with increased mortality, especially after previous percutaneous coronary interventions[6]. In the ICU, AKI after cardiac surgery (CS-AKI) represents the second most common cause of all-cause AKI, just after sepsis[7]. CS-AKI is a type 1 representative of the 'cardiorenal syndrome', a condition in which acute failure of one organ deteriorates the function of another one. Classification of cardiorenal syndrome has been proposed by Ronco *et al*. in 2008 and has five types (Table 1)[8].

Diagnostic Criteria

There are over 30 AKI definitions found in the literature; however, clinically the most widely used classifications are the following:

- Risk, Injury, Failure, Loss of kidney function and End-stage renal failure (RIFLE)[9];
- Acute Kidney Injury Network (AKIN)[10]; and
- Kidney Disease: Improving Global Outcomes (KDIGO)[11] (Table 2).

Although numerous new biomarkers (cystatin C, neutrophil gelatinase-associated lipocalin, interleukins 6 and 18, kidney injury molecule-1, liver-type fatty acid binding protein, N-acetyl-β-D-glucosaminidase, α1 microglobulin, glutathione transferase-π, tissue inhibitor of metalloproteinase 2, insulin-like growth factor-binding protein 7)[13-15] have been investigated

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Table 1. Cardiorenal syndrome[8]

Type	Inciting event	Secondary disturbance	Example
Type 1	Rapid worsening of cardiac function	Acute kidney injury	Acute cardiogenic shock or acute decompensation
Type 2	Chronic abnormalities in cardiac function	Progressive chronic kidney injury	Chronic heart failure
Type 3	Abrupt worsening of kidney function	Acute heart failure or arrhythmia	Acute kidney injury
Type 4	Chronic kidney disease	Decreased cardiac function, ventricular hypertrophy	Chronic glomerular disease
Type 5	Acute or chronic systemic disorder	Combined cardiac and renal dysfunction	Diabetes mellitus, sepsis, vasculitis, sarcoidosis

Table 2. Comparison of acute kidney injury classifications[12]

RIFLE		AKIN		KDIGO	
Criterion	Creatinine definition	Criterion	Creatinine definition	Criterion	Creatinine definition
Risk	≥1.5-fold baseline SCr increase or ≥25% GFR decrease	Stage 1	≥1.5-fold or ≥26.5 μmol/L baseline SCr increase within 48 h	Stage 1	≥1.5-fold baseline SCr increase within 7 d or ≥26.5 μmol/L within 48 h
Injury	≥2-fold baseline SCr increase or ≥50% GFR decrease	Stage 2	≥2-fold baseline SCr increase	Stage 2	≥2-fold baseline SCr increase within 7 d
Failure	≥3-fold baseline SCr increase or ≥75% GFR decrease or SCr ≥353.6 μmol/L	Stage 3	≥3-fold or ≥44.2 μmol/L baseline SCr increase or RRT initiation	Stage 3	≥3-fold baseline SCr increase within 7 d or SCr ≥353.6 μmol/L or RRT initiation
Loss	RRT >4 weeks				
End stage	RRT >3 months				

SCr = serum creatinine; GFR = glomerular filtration rate; RIFLE = Risk, Injury, Failure, Loss of kidney function and End-stage renal failure; AKIN = Acute Kidney Injury Network; KDIGO = Kidney Disease: Improving Global Outcomes; RRT = renal replacement therapy

for more accurate AKI diagnosis, the most frequently used and recommended by the Acute Disease Quality Initiative (ADQI) Group still are creatinine and urea[16].

Creatinine is a metabolic product of creatine phosphate breakdown in the skeletal muscle metabolism. Its usefulness comes from a relatively constant secretion rate through glomerular filtration, whereas on the other hand, none of it is reabsorbed. The main disadvantage is its dependence on muscle mass (more substrate for phosphorylation through creatine kinase), muscular rhabdomyolysis or medication intake (cimetidine, trimethoprim-sulfamethoxazole or probenecid)[17]. Blood tests for creatinine are significantly cheaper compared to other biomarkers listed above.

Urea is one of the nitrogen metabolism products, which is formed mainly from amino acids. Urea transports nitrogen and thus creates osmotic gradient for water reabsorption in the loop of Henle. Its main disadvantage is responding to external kidney unrelated factors such as weight loss (increased proteolysis, more amino acids, more nitrogen) and dehydration (excessive need for water reabsorption)[18].

Pathophysiology

The mechanisms that influence CS-AKI are not yet fully understood. They could be distinguished into three major groups, as follows:

- renal hypoperfusion (prerenal AKI);
- inflammation and oxidative stress (renal AKI); and
- nephrotoxic medications and agents (renal AKI)[19,20].

Renal hypoperfusion

Renal hypoperfusion is the consequence of non-pulsatile low-flow circulation state during surgery maintained by extracorporeal circulation (ECC). In addition, fast temperature changes are observed during surgery, which in turn affect renal flow. The latter could also be compromised by excessive intraoperative bleeding. Open-heart procedures often present a state of unstable cardiac output, and since the kidneys take up to 20% of cardiac output, any decrease in cardiac output (either through increased resistance or decreased pressure gradient) will eventually compromise renal flow. Prolonged kidney ischemia leads to acute tubular necrosis, since the proximal tubule is one of the most metabolically active tissues and consequently sensitive to oxygen deprivation. After ECC termination, ischemia-reperfusion injury (IRI) can decrease cellular energy storage with direct mitochondrial damage and oxidative phosphorylation reduction. On the other hand, IRI causes massive influx of reactive oxygen species (ROS). Intravascular hemolysis occurs after blood contacting artificial surfaces in the ECC circuit, thus liberating hemoglobin, which leads to nitric oxide suppression, afferent arterial vasoconstriction, and increased heme oxygenase 1 expression[21].

Inflammation and oxidative stress

Surgical tissue injury and blood exposure to artificial materials coupled with blood transfusions cause massive inflammatory cell accumulation and complement activation. The main factor in ROS creation is the iron accumulated from hemoglobin release. It affects renal cell proliferation *via* lipid peroxidation and/or protein oxidation[22].

Nephrotoxic medications and agents

Kidney function is also affected by various xenobiotics, frequently used pre-, intra- and postoperatively. The main groups are antibiotics (glycopeptides, aminoglycosides), nonsteroidal anti-inflammatory drugs and antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers). Major impact of contrast dye (used in many diagnostic procedures) on kidney injury has been proven, as it is used for some diagnostic procedures (coronary angiography, computed tomography). A response *via* the sympathetic nervous system is triggered, resulting in renin-angiotensin-aldosterone axis activation and increased vasopressin and endothelin production, all leading to afferent arterial vasoconstriction and diminished renal flow. In patients with infective endocarditis, septic emboli are frequent, which can also lead to tubular necrosis. A similar effect can be observed after cholesterol emboli due to extensive aortic manipulation[23].

Regardless of the mechanism, CS-AKI can also be classified according to the onset timing into early AKI (in the first seven days after surgery) and late AKI (in more than seven days after surgery, most frequently after cardiogenic shock)[20].

Acute Kidney Injury Risk Factors

Wang and Bellomo have divided risk factors by their relevance at different times with respect to the cardiac surgery procedure[20]. Preoperative risk factors include female sex, advanced age, pre-existing comorbidities (chronic kidney disease (CKD), previous cardiac surgery, diabetes mellitus (DM), chronic obstructive pulmonary disease, arterial hypertension, hypercholesterolemia, congestive heart failure, left ventricular ejection fraction <35%, and obesity)[24]. Intraoperative factors include use of nephrotoxic medications, emergency surgery, cardiopulmonary bypass (CPB) time, and complexity of surgery[25]. Postoperative risk factors include postoperative hypotension/cardiogenic shock, low hematocrit (<24%), and need for blood transfusion[26].

However, risk factors could also be classified according to the possible impact they could have in order to prevent CS-AKI. The non-modifiable factors are female sex, advanced age, pre-existing comorbidities, emergency surgery, and complexity of surgery. The factors that could be at least potentially influenced are preoperative obesity in patients undergoing elective procedures, nephrotoxic substance use, CPB time, cross-clamp time, non-pulsatile flow, and intraoperative or postoperative bleeding.

The role of CPB is still controversial. There have been only three randomized controlled trials compar-

ing on-pump *versus* off-pump coronary artery bypass grafting (CABG) surgeries. The CORONARY trial was conducted on 4752 patients in 79 centers worldwide, who were randomly assigned to off-pump or on-pump CABG. At one year after surgery, no reduction in mortality, myocardial infarction, stroke or new renal failure requiring renal replacement therapy (RRT) was observed[27]. The ROOBY trial enrolled 2203 patients in 18 centers, who were randomly chosen for either off-pump or on-pump CABG. Interestingly, some differences proved to be statistically significant in perioperative data, such as residents being the 'primary surgeons' ($p<0.001$), conversion to other treatment ($p<0.001$), duration of surgery ($p=0.05$), number of grafts performed, and ratio between the number of planned and performed grafts ($p<0.001$), all in favor of on-pump CABG. There were no differences regarding renal failure at 30-day follow-up, including renal failure requiring RRT. Unfortunately, no data on renal function after one year are reported[28]. In the HEPCON trial, which included 120 patients, Deininger *et al.* compared three different types of CPB, i.e. conventional CPB, minimally invasive CPB, and off-pump CABG. Temporary superiority of minimally invasive CPB and off-pump surgery was recorded in regard to acute tubular necrosis *via* free hemoglobin measurement ($p<0.001$), but with no significant long-term differences[29].

Prediction

The ADQI Group recommends routine implementation of risk-prediction models for all cardiac surgical procedures, using estimated glomerular filtration rate (eGFR), cystatin C or albuminuria to predict postoperative AKI[16]. The Cleveland Clinic Score, the Mehta Score and the Simplified Renal Index score are all validated scores in predicting AKI, especially severe AKI prone to RRT[30-32]. Of all the predicting scores for severe AKI, the Cleveland Clinic Score is most widely tested and showed high discrimination in the tested cohorts[33]. Birnie *et al.* developed a KDIGO-based score to predict AKI of all stages, not only severe AKI. The following independent risk factors for developing end-stage AKI have been identified: age >75 years, female sex, body mass index (BMI) >35, active smoking status, New York Heart Association (NYHA) class 4, preoperative DM, arterial hypertension, and GFR >90 mL/min[34]. Taking into account the high risk of AKI development, using the Reynolds Risk Score can predict the overall cardiovascular risk[35].

Prevention and Therapy

There are some useful principles for optimal postoperative patient management, as follows:

- low cardiac output avoidance with the use of inotropes and blood volume substitution (hematocrit >24%, role of pulsatile CPB is still controversial);
- hypotension avoidance with optimal volume management and vasopressors (mean arterial pressure (MAP) >60 mm Hg, use of balanced solutions over 0.9% saline to prevent hyperchloremia;
- nephrotoxic agent avoidance; and
- glycemic index optimization (blood glucose <6.1 mmol/L)[12,16,20].

Nevertheless, even with optimal management, 2%-6% of patients develop severe AKI for which RRT must be initiated[23]. RRT initiation criteria are as follows:

- clinical: anuria ≥6 h or urine output ≤200 mL over 12 h or volume overload (pulmonary edema unresponsive to diuretics); and
- laboratory: hyperkalemia >6.5 mmol/L or metabolic acidosis pH <7.2 or urea >30 mmol/L or creatinine >300 μmol/L[36].

Many preventive measures were investigated in recent years. Antonic reports no significant reduction in CS-AKI using perioperative intravenous antioxidant ascorbic acid ($p=0.779$). However, it was a small, single-center study enrolling only 100 elective low-risk on-pump CABG patients[37]. Bailey *et al.* investigated a potential renoprotective effect of urine alkalization using sodium bicarbonate through decreased complement activation and prevention of tubular hemoglobin cast formation. Performing a meta-analysis on 877 patients from three double-blind randomized controlled trials, they demonstrated only reduction in severe AKI development and RRT avoidance ($p<0.001$), but no statistical significance was achieved in overall AKI ($p=0.29$)[38]. Yang *et al.* proved osmotic agent mannitol involvement in renal function decrease in patients with contrast-induced nephropathy, with no beneficial effects regarding CS-AKI in their meta-analysis con-

taining 626 patients from nine randomized controlled trials (p=0.59)[39]. Scrascia *et al*. conducted a meta-analysis on 931 patients in 14 trials in regards to steroid use in cardiac surgery patients in order to modulate inflammatory response, but were unsuccessful in proving its beneficial effect (p=0.79)[40]. The ADQI Group does not recommend levosimendan, statins, and N-acetylcysteine[16].

Minimally Invasive Cardiac Surgery and Renal Function

Although the incidence of minimally invasive approaches for cardiac surgery procedures is increasing, literature covering the topic of AKI after these procedures is scarce. A recent study by Vandewiele *et al*. found no important clinical differences in renal function between minimally invasive cardiac surgery (MICS) and conventional median sternotomy with mitral and/or tricuspid valve surgery despite longer CPB and aortic cross-clamp times in the MICS group[41]. In the aortic valve position, comparison between MICS and transaortic transcatheter aortic valve implantation (TAVI) revealed a higher risk of AKI development in the TAVI group (p=0.017), with higher preoperative EuroSCORE II having no impact on postoperative AKI[42]. Left ventricular assist devices (LVADs) significantly improve kidney function with a trend towards better renal outcomes after MICS but with no statistical significance due to a small group size[43].

Conclusion

Cardiac surgery-associated acute kidney injury remains a serious complication after cardiac surgery with a high incidence and clinically important short- and long-term consequences, especially in patients requiring RRT. Sixty-day mortality of patients requiring RRT after cardiac surgical procedures exceeds 50%[44]. Short-term consequences of CS-AKI are uremia (increased capillary permeability, increased risk of bleeding, altered mental status), electrolyte imbalance (dysrhythmias, muscular weakness, altered mental status), acid-base imbalance (increased proteolysis, hemodynamic instability), and volume overload (interstitial edema, increased intraabdominal pressure, disturbed oxygen diffusion)[20,44-47]. Long-term consequences of CS-AKI are deterioration of pre-existing CKD (with a trend towards a higher risk of developing postpericardiotomy syndrome[48]) with increased hospital readmission rate with the Major Adverse Kidney Events composite adaptation, consisting of >25% eGFR reduction, RRT or death, which could in case of impairment after 90 days meet the criterion for CKD[49]; increased mortality (Ferreiro *et al*. proved a transient association of CS-AKI with long-term mortality that progressively decreases and vanishes five years after surgery[50]); decreased quality of life; and increased risk of further cardiovascular events[20,44-47].

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Sažetak

AKUTNO BUBREŽNO OŠTEĆENJE NAKON OPERACIJA NA OTVORENOM SRCU

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Akutno bubrežno oštećenje povezano s kardiokirurgijom (*cardiac surgery-associated acute kidney injury*, CS-AKI) je značajna komplikacija s visokim pobolom i smrtnošću. Postoji više dijagnostičkih kriterija za dijagnozu CS-AKI. Usprkos mnogim novim istraživanjima, kreatinin i ureja ostaju temelj dijagnostike. Glavni patofiziološki procesi koji doprinose bubrežnom oštećenju su bubrežna hipoperfuzija, upala uzrokovana oksidativnim stresom i bubrežno oštećenje uzrokovano upotrebom nefrotoksičnih sredstava. Tijekom terapije može se utjecati na nekoliko čimbenika rizika (upotreba nefrotoksičnih sredstava, trajanje kardiopulmonarne premosnice, tip izvantjelesne cirkulacije, smanjeni minutni volumen ili poslijeoperacijska hipotenzija). Cilj prevencije AKI je spriječiti progresiju bubrežnog oštećenja koje zahtijeva kompleksniju terapiju i donosi lošije dugoročne ishode.

Ključne riječi: *Bubrežno oštećenje; Kardiokirurgija; Perfuzija; Oksidativni stres; Dijaliza*