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Management of Acute Kidney Injury after Cardiovascular surgery

Even nowadays Acute Kidney Injury (AKI) remains an important concern after cardiovascular surgery (CVS) because of poor outcomes in terms of morbidity and lethality. Postoperative course of a renal failure can vary in several clinical settings, lasting few days from onset or showing subclinical forms up to chronicization and need for renal replacement therapy with subsequent prognostic implications. Understanding and resolving pathophysiological issues of AKI represent the keystone in the attempt to improve final outcome.
Currently, biomarkers may be a challenging and promising way to reveal a renal damage after CVS even before of clear changes in serum creatinine or urine output, thus allowing both a preoperative risk stratification and an earlier detection of postoperative AKI. Indeed, early and aggressive strategies, sometimes synergistic, could help to recover renal function avoiding the progression of the complication up to an irreversible phase.
In case of unresponsiveness to medical therapy, dialysis will become necessary in order to treat critical fluids overload and severe impairments of acid-base and electrolytic status, but nevertheless it is still characterized by important adverse effects until death.
Hereby, this perspective article will provide an overview of resources and a guide of treatment options with the aim of enhancing AKI management after cardiac and vascular surgery.

KEY WORDS: Acute kidney injury, Acute renal failure, Cardiac surgery, Vascular surgery

Introduction

Even nowadays Acute Kidney Injury (AKI) continues to be an important complication after cardiovascular surgery (CVS) associated to poor outcomes in terms of morbidity and mortality. AKI definition is usually expressed by an acute reduction of glomerular filtration rate (GFR) *de novo* or worsening of GFR on pre-existing chronic kidney disease (CKD), with a temporal pattern within hours to days after surgery. Interestingly, renal failure after CVS presents variable clinical expressions, lasting few days from occurrence or showing subclinical forms in which renal function is just impaired before real changes in serum creatinine (sCr) and urine output (UO) up to chronicization and need for renal replacement therapy with obvious prognostic implications. Hereby, this manuscript aims at providing an overview of resources and a guide of treatment options so as to improve final outcome of AKI after CVS.

Discussion

Over last decades a paradigm shift in the classification and conceptual understanding of AKI syndrome has seen the introduction of RIFLE and then AKIN (a RIFLE modified version) criteria in the clinical practice, in the attempt to define AKI syndrome and give a prognostic stratification in several settings of critical patients [1].
Moreover, KDIGO classification borned as combination of RIFLE and AKIN definition systems, has shown higher sensitivity in AKI detection and stronger predictive power of in-hospital mortality [2], currently representing daily the reference classification because of clarity and reproducibility widely recognised.

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In accordance with KDIGO classification, the flow chart usually used to define and stratify AKI syndrome was:
– increase in sCr ≥ 0.3 mg/dL (≥ 26.5 μmol/L) within 48 hours;
– increase in sCr ≥ 1.5 times baseline (known or presumed value);
– UO < 400-500 mL/kg/h for 6 hours;
– staging patients into three functional classes according to low UO and sCr increase from baseline values.
Very often, dealing with unknown baseline sCr values, the Modification of diet in renal disease equation suggests a baseline GFR of 75 mL/min/1.73 m², not applicable anyway in CKD patients with acute failure [3].
Planing a successful strategy, the goal should be an early postoperative recognition of AKI and the prevention of complication progression from stage AKI KDIGO 1 to stage 2 or 3 (Fig. 1); how long a renal failure lasts will be the most important predictor in terms of prognosis.
Nevertheless, these traditional classification systems present significant limitations, because don't consider nature/level (tubular or glomerular) of renal injury and the requirement for dialysis, neither are able to identify earlier renal damages [3]. In this view, these limitations may be offset by the compelling use of novel biomarkers, supplementing traditional definition systems, in order to detect stress of renal function, even before clear variations in sCr or UO [4]. Elevation of sCr is influenced by extrarenal factors too and can require up to 24-72 hours because of the compensation of residual functioning nephrons; oliguria isn't a renal marker since generated also from volemia perturbations or various types of shock, nevertheless use/abuse of diuretics in the daily clinical practice can influence UO. Nowadays several biomarkers, both plasma and urinary, identify injured tubular level and their use, especially in combined modality, have shown beneficial effects for the prevention and prognosis of AKI [4,5], highlighting new improvements in quality of patients care.
Therefore, preoperative risk stratification will express a major risk of AKI by:

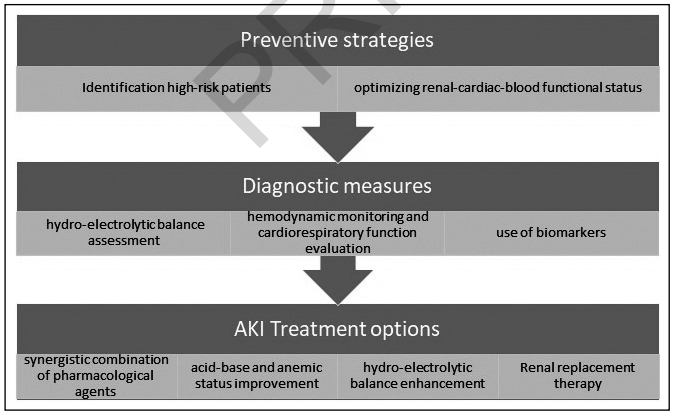

Fig. 1

– Cystatin C, *'a marker of GFR'*, absorbed mostly from proximal tubule and then catabolized;
– proteinuria, underlining how microalbuminuria can be expression of renal impairment linked to an hypertensive or diabetic disease.
In order to detect earlier postoperative AKI, main biomarkers are represented by:
– both serum and urine NGAL, a lipocalin protein produced by neutrophils activated, suggesting an intrinsic cause of AKI;
– urinary L-FABP, prognostic marker of renal ischemia, as expression of oxidative stress linked to ischemia;
– KIM-1, that reflects a proximal tubular damage, predicting need for dialysis and death;
– TIMP2*IGFBP7, an association strongly predictive of very early tubular damage for values ≥ 0.3 (ng/ml) ^{2}/1000, therefore allowing to reduce worsening of renal complication and stay hospital lenght, in particular in ICU [6-7].

AKI Post-CVS Pathogenesis

Several well-known risk factors are involved in the genesis of a renal failure after CVS, mostly linked to a multifactorial etiology (Table I); in the daily practice, however, most often we refer to elderly patients suffering from multiple comorbidities and with a baseline atheroembolic burden. On the other hand, advanced age identifies a subtype of patients especially vulnerable to renal complication development. Despite AKI after CVS recognizes multifactorial etiology and pathophysiology, anyway the impact of hemodinamic factors plays a key role about an adequate renal perfusion. A renal hypoperfusion generates a mismatch in the susceptible medullary region and the impairment of oxygen supply-demand balance may lead to a clinically significant renal damage after a prolonged ischemic status.
In terms of mechanisms promoting AKI, cardiac and vascular surgery outline two different cathegories of patients, mainly in relation to the type of surgery and the whole perioperative management (*in primis*, use of

TABLE I - *Main risk factors for AKI development after cardiovascular surgery.*

Advanced age at surgery
Reduced creatinine clearance (GFR< 60 mL/min)
Type of performed surgery
Sepsis
COPD
Preoperative left ventricle dysfunction
Longer CPB duration (>140 min) and Cross-clamp times
Perioperative bleeding and use of blood transfusions
Preoperative administration of NSAID, contrast agents, antibiotics and other drugs
Preoperative anemic status
Female sex
Emergency

TABLE II - *This diagram describes different steps to treat AKI post CVS*

Correcting hypovolemia through 'noble mass' or hydration
Adjusting acid-base balance and electrolytes disturbances
Assessing need for inotropic support and optimizing VAM
Loop diuretics repeated boli immediately after albumin infusion
Loop diuretics plus methylxanthines infusion
Loop diuretics and 'renal range' dopamine administration
Low-dosage Mannitol therapy
Dialysis if patient unrefractory to all previous therapies

cardiopulmonary bypass (CPB), aortic cross-clamping and drugs) [6]. Indeed, in cardiac surgery the relationship between heart dysfunction and renal hypoperfusion is a relevant topic, because pump failure of left heart or a *'back pressure'* from a right cardiac dysfunction can mine renal perfusion (central cause of AKI), thereby pharmacological support often improves ventricles function and various inotropic drugs intend to optimize the fragile balance between preload and afterload, before surgery too.

On the other side, in vascular surgery the effects of exotoxins (as contrast agents used in percutaneous or hybrid procedures) and endotoxins (as myoglobin release in case of rhabdomyolysis) together to ischemia-reperfusion damages represent the main predictors of renal failure after surgery. In addition, close to hemodynamic disturbances or athero-emboligen mechanical factors, a perioperative immuno-phlogistic response, mediated from release of cytokines and chemokines beyond an increased oxidative stress, can provide further contribute to development and maintainance of AKI after CVS, frequently in the context of a systemic inflammatory response syndrome. Regardless of some renal specific factors, also we should learn to look at acute renal failure as a part of a systemic failure.

How to Face AKI Post-CVS: Therapeutic Management

Some interesting risk models for AKI have been described, as Cleveland score for cardiac surgery patients [8] or the risk prediction model illustrated recently by *Safley et al* for patients undergoing peripheral vascular interventions [9].

According to a preventive strategy, preoperative identification of *'high-risk'* AKI patients may be considered a good starting point, through a simple evaluation of baseline renal function (sCr and urine analysis) that can rule out a CKD, the most predictable risk factor for AKI, or proteinuria, as well as B-type natriuretic peptide dosages will give a general idea about heart compensation status.

Preoperative improvement of cardiac, renal and hemoglobinic functional status is a crucial issue, in particular in fragile patients. In low to moderate EF patients, levosimendan infusion together to compensation therapy impacts significantly cardiac status preventing a central cause of AKI. Indeed, hemoglobin test reflects blood supply capacity and, even more so thinking to CPB linked-hemodilution, the likelihood of perioperative transfusional support, that represents another independent AKI risk factor (due to catalytic iron levels circulating); EPO plus iron administration some weeks before surgery in case of Hb<12.5 in elective patients affected by CKD proves to be an helpful option.

Simultaneously, renal functional status should be optimized in accordance with:

– a correct hydration (also periprocedural);

– NSAID avoidance about pain management, ACE-inhibitors/ARB and Metformin discontinuation before surgery;

– delayed interventions from 24 to 72 hours after iodinated contrast administration for preoperative procedures if possible, using N-Acetylcysteine intravenous infusion plus hydration with the aim of reducing contrast-induced nephrotoxicity. In case of patients at high-risk for AKI contrast volume reduction, use of carbon dioxide angiography or IVUS up to echo-assisted peripheral procedures might represent suitable nephroprotective strategies.

Detecting and differentiating cause types of AKI (pre-renal, renal, post-renal) will highlight the therapeutic management and an early recognition of renal complication should suggest an earlier and aggressive treatment in the attempt to enhance final outcome [10]. A proper evaluation of volemia is an essential step, maintaining adequate intravascular volume in the perioperative period, because hypovolemia leads to a sympathic-mediated arteriolar vasoconstriction into the glomerular system with worsening of GFR. Furthermore, the administration of '*noble mass'* (packed red blood cells–albumin-fresh frozen plasma) is better than crystalloid or saline solutions, since postoperative anemic status or disprotidemia/hypoalbuminemia are very common findings. Certainly, decrease hemoglobin >50% from baseline values and the perioperative duration of anemia represent the best predictors of adverse outcomes, thereby perioperative cut-off threshold of hb >8 is strongly recommended. Electrolytes disturbances, frequently associated to renal failure, must be monitored and managed, remembering that kidneys' function is influenced by the neuro-hormonal stimulation; in case of hypotonic hyponatremia linked to cardiac dysfunction, sodium intravenous administration can decrease the postoperative risk of AKI in a patient with pre-existing hyponatremia. Moreover, AKI prevention should come through

a proper hemodynamic monitoring and cardiorespiratory function evaluation. Perioperative MAPs values > 70 mmhg as well as a sinus rythm maintainance preserve patients from dangerous cardiovascular collapses, even temporary, that may esitate in low cardiac outputs leading to renal hypoperfusion; moreover, mechanical ventilation with lower tidal volume (< 10 ml/kg) and without PEEP as well as an early discontinuation from ventilatory support are characterized from better clinical outcomes.

Benefits and limits of a primary renal therapy

Even though often relied on limited data, up to now several reports have shown no absolute evidence of effectiveness of various drugs in order to prevent postoperative AKI, probably mainly in relation to a so much multifactorial etiology and pathophysiology. Interestingly, new drugs as dexmedetomidine and vasopressin (this last one especially in case of vasoplegic syndrome) have shown promising outcomes in terms of nephroprotection [2]. Nevertheless, once enhanced hydroelectrolytic balance and evaluated need for inotropic support in case of central cause of AKI, an active pharmacological therapy is suggested in case of persistent low or absent urine output for managing volume status (Table II). The goal of a primary renal therapy should aim at unlocking and substaining diuresis, surely not at preventing postoperative AKI.

On the basis of a personal multicentric clinical experience gained on the field, aggressive management with multiple, simultaneous and synergistic pharmacological strategies represents a successfull rationale to achieve better outcomes. In this view, loop diuretics role is particularly important in the attempt to avoid harmful volume overloads (*in primis* life-threatening pulmonary edema) and improve dangerous electrolytes imbalances, such as iperkaliemia. Diuretics administration should be performed through repeated boli immediately after albumin infusion in order to call fluids from *'third-space'* and may be associated to slow infusion of methylxanthines (theophyllin/aminophyllin), non-selective adenosine antagonists able to increase GFR by smooth muscle relaxation in the afferent arteriolar glomerular bed, taking advantage of an action synergism among the two drugs.

Hence, in case of unresponsiveness of diuresis, another synergistic infusion of dopamine plus furosemide can show better clinical outcomes than non-responders.

Use of dopamine at lower doses (so-called *'renal range'* up to 3 μg/kg body weight) has been a much debated topic; many studies have presented no beneficial results in the management of AKI post-CVS, even focusing on harmful effects in opposition to the supposed renal vasodilator effect.

Indeed, dopamine agonists as Fenoldopam (selective D1) might have theoretically more renoprotective features in terms of postoperative AKI reduction, anyway without favourable impact on need for dyalisis and in-hospital mortality, as founded in the clinical trial by *Bove et al* [11]. On the other hand, despite dopamine isn't a renoprotective drug, it remains a natriuretic hormone that can contribute to unblock diuresis, especially on the first day of treatment improving urine output and renal physiology, likely in relation to minor or transient tubular damages. Role of dopamine should be reconsidered in special scenarios, as the cardiorenal syndrome or in the post-pump AKI, enhancing effect of diuretics in case of resistant edema and underlining the importance of renal dopaminergic system [12].

Then, in case of persistent oligo-anuria, low-dosage Mannitol (100-150 cc) can represent the last pharmacological attempt; beyond free radical scavenging features, this osmotic diuretic prevents renal epithelial vascular congestion and tubular obstruction, inducing a concomitant intra-renal prostaglandine synthesis and, thereby, increasing renal blood and urine flow.

Eventually, renal replacement therapy should be considered as the last step after failure of all conservative strategies because of related-adverse effects and higher lethality rates (40-70%). Although starting time is controversial topic, continuous veno-venous hemofiltration is usually recommended in case of hemodynamic instability in order to treat significant fluid overloads in critical patients and in case of severe hyperkaliemia/dysnatremia or acidosis.

Riassunto

Ancora oggi l'insorgenza di un'insufficienza renale acuta dopo interventi di chirurgia cardiovascolare assume un ruolo prognostico determinante in termini di mortalità e di morbilità. Un danno renale postoperatorio può variare da forme subcliniche o a rapida regressione fino a quadri severi che possono culminare nella necessità di ricorrere ad emodialisi, l'intraprendere della quale è contraddistinta da rilevanti effetti clinici avversi con aumento significativo della letalità. Comprendere l'eziologia e guidare una condotta clinica interpretando correttamente la fisiopatologia di un'insufficienza renale rappresenta un requisito fondamentale nell'intento di migliorare l'*outcome* finale. Attualmente molti *biomarkers* si stanno rivelando promettenti opzioni per riconoscere precocemente un incipiente danno renale, ancora prima del riscontro di rialzi laboratoristici degli indici di funzionalità renale e della comparsa clinica di oligo-anuria, permettendo talora anche una buona stratificazione di rischio preoperatoria.

Una volta ottimizzato il bilancio idro-elettrolitico del paziente e valutata la necessità per un eventuale supporto inotropo in caso di causa centrale di IRA, strategie farmacologiche sincrone, multiple e sinergistiche sono suggerite al fine di sbloccare e sostenere la ripresa della

diuresi evitando pericolosi sovraccarichi di liquidi a livello sistemico. Quanto a lungo dura un'insufficienza renale rappresenterà il più importante determinante prognostico.

Quest'articolo si propone lo scopo di fornire una panoramica delle risorse e delle opzioni di trattamento attualmente disponibili per migliorare la gestione dei pazienti che sviluppano una disfunzione renale acuta dopo interventi di chirurgia cardiaca e vascolare.

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