VIA MEDICA

REVIEW ARTICLES

Perioperative management of cardiac surgery patients who are at the risk of acute kidney injury

Łukasz Krzych[1], Maciej Wybraniec[2], Jerzy Chudek[3], Andrzej Bochenek[1]

[1]1st Department of Cardiac Surgery, University Hospital No. 7, Medical University of Silesia, Upper-Silesian Medical Centre in Katowice, Poland
[2]University Hospital No. 7, Medical University of Silesia, Upper-Silesian Medical Centre in Katowice, Poland
[3]Department of Pathomorphology, Medical University of Silesia in Katowice, Poland

Abstract

Acute kidney injury is one on the most frequent and clinically important of all postoperative complications in the cardiac surgery setting. It is estimated that almost half of patients suffer from a deterioration in kidney function after cardio-pulmonary by-pass. Renal insufficiency affects the outcomes in terms of an increase in postoperative morbidity and mortality and a decrease in the quality of life. Recently, a modified and unified classification of cardio--renal syndrome has been established that takes into account the bilateral association between the heart and the kidneys. Because acute decompensation in heart function leads to acute kidney damage, cardiac surgery-associated acute kidney injury may be recognised as a type 1 cardio-renal syndrome from a pathophysiological point of view. This paper aims to review current data on the diagnosis of acute kidney injury and preventive strategies that can be implemented in cardiac surgery perioperative care.

Key words: acute kidney injury; cardio-renal syndrome; biochemical markers, neutrophil gelatinase-associated lipocalin; diuretics; renal replacement therapy, haemofiltration

Anaesthesiology Intensive Therapy 2013, vol. 45, no 3, 155–163

Cardiac surgery-associated acute kidney injury (CSA--AKI) is a common and clinically relevant complication in cardiac surgery. Various degrees of impaired renal function are observed in 19–45% of patients undergoing surgical procedures under extracorporeal circulation [1]. A coherent classification of cardio-renal syndrome (CRS) has been recently proposed; this classification describes interactions between heart and kidney pathology [2]. According to this classification, CSA-AKI is a clinical entity of type 1 CRS, in which acute cardiac decompensation initiates a chain of events leading to acute kidney injury. The aim of the review is to present the current knowledge regarding the prevention and treatment of acute kidney injury that are an integral element of management of cardiac surgery patients.

EPIDEMIOLOGY OF CSA-AKI

According to various estimates, AKI complicates up to 45% of cardiac surgical procedures [1,3,4]. In patients undergoing coronary artery bypass grafting, the duration of AKI has been shown to correlate with postoperative mortality rates. The hazard ratio (HR), which assesses the risk of death, is found to be 1.66 (95% CI: 1.32–2.09), 1.94 (95% CI: 1.51–2.49) and 3.40 (95% CI: 2.73–4.25) for the durations of 1–2 days, 3–6 days and ≥ 7 days, respectively [3,5]. Similar results have been reported by other authors [4].

NOMENCLATURE, CLASSIFICATION AND THE PATHOPHYSIOLOGY OF CSA-AKI

According to the classification system presented (Table 1) [2], CSA-AKI is a type 1 cardio-renal syndrome unless it is caused by other factors (e.g., contract-induced nephropathy, drug nephrotoxicity, generalised infection) [6]. It is characterised by an increase in the plasma creatinine concentration by 50% compared to the baseline value during the 7 postoperative days and a decrease in the glomerular filtration rate by 25% or a urine output less than 0.5 mL kg^{-1} per hour for more than 6 h (according to the criteria of the Risk Injury Failure Loss End-Stage Renal Disease, RIFLE) [7]. The alter-

Table 1. Classification of cardio-renal syndrome. According to [2]

Type	Characteristics
1	Acute cardiac failure leads to acute kidney injury
2	Chronic cardiac failure leads to chronic renal disease
3	Acute kidney injury leads to acute cardiac failure
4	Chronic renal disease leads to chronic cardiac failure
5	An external factor leads to simultaneous injury to the heart and kidneys

native criteria of the Acute Kidney Injury Network (AKIN) allow for the diagnosis of CSA-AKI based on an absolute increase in creatinaemia by at least 0.3 mg dL^{-1} (26.2 μmol L^{-1}) during a 48 h period [8, 9]. The most recent guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) suggest uniform standards for diagnosing AKI based on the two classification systems mentioned above (RIFLE and AKIN) (Table 2) [10].

Although CSA-AKI characteristic of type 1 CRS is the major topic of this review, type 2 CRS may also develop in cardiac surgery [11]. In many cases, patients undergoing surgical procedures under extracorporeal circulation suffer from congestive heart failure because they have had coronary disease for many years. The percentage of patients with preoperatively compromised kidney function is high; their conditions predispose them to the development of AKI after surgery and increase the hospital mortality and incidence of other postoperative complications [12, 13]. This relationship has been used for many years to assess the operative risks in cardiac surgery. The classic Parsonnet risk scale [14] included dialysis therapy in the operative risk stratification. Newer scales take into account such parameters as the baseline creatinine concentration (the Cleveland Clinic Foundation [15]) or the estimated glomerular filtration rate (eGFR) (the European System for Cardiac Operative Risk Evaluation — EuroSCORE) [16].

Type 5 cardio-renal syndrome, a special case of multiple organ failure [17], is important because anaesthesiologists are faced with it most frequently. Generally, the simultaneous deterioration of cardiac and renal functions occurs because of low cardiac output syndrome or septic shock. Its initial endogenous cause is likely gastrointestinal mucosal ischaemia favouring bacterial translocation. The common exogenous cause in cardiac surgery is sternal wound infection or pneumonia; in the ICU setting, this condition can be caused by an infection of a different underlying cause. The presence of bacterial lipopolysaccharides in blood induces a generalised dilation of resistance arteries and leads to reduced arterial pressure and decreased renal perfusion. Additionally, the mediators of the generalised inflammatory response, such as tumour necrosis factor-alpha (TNF-α), exert direct cardiodepressive effects, likely by enhanced expression of inducible nitric oxide synthase in cardiomyocytes [18], thus decreasing the cardiac output and glomerular filtration.

As far as pathogenesis is concerned, CSA-AKI is a much broader term than individual types of CRS. Although acute circulatory failure resulting in renal ischaemia plays a pivotal role in its development, CSA-AKI is the condition complicating pre-existing chronic cardiac dysfunction (including right-, left-ventricular, diastolic/systolic, ischaemic/other than ischaemic), hence pre-existing renal dysfunction. Irrespective of these other dysfunctions, its pathology is superimposed by the action of cytokines and pro-inflammatory substances that are formed in response to perioperative tissue trauma, which can easily lead to the development of peripheral hypoperfusion and shock. The systemic inflammatory response syndrome (SIRS), which is initiated by the activation of immune cells during blood flow through the peristaltic pump and contact with an oxygenator membrane, is important [19]. A different clinical picture is observed when the postoperative course is complicated by the development of severe infection and its systemic consequences.

RISK FACTORS OF CSA-AKI

To date, several potential risk factors of CSA-AKI have been identified, including preoperative (older age, diabetes mellitus, smoking and elevated baseline creatinine concentration) and intraoperative factors (use of inotropic drugs, transfusions of blood preparations, time of aortic cross-clamping, and the necessary re-use of extracorporeal circulation); factors connected with cardio-pulmonary bypass

Table 2. Diagnosis of AKI according to KDIGO 2012 [10]

Stage	Change in creatinine concentration [creat.]	Urinary output
1	≥ 1.5–1.9 × ↑ [creat.] within 7 days* or > 26.2 μmol L^{-1} (0.3 mg dL^{-1}) during 48 h*	↓ < 0.5 mL kg^{-1} h^{-1} for ≥ 6 h
2	≥ 2–2.9 × ↑ [creat.]*	↓ < 0.5 mL kg^{-1} h^{-1} for ≥ 12 h
3	≥ 3 × ↑ [creat.]* or [creat.] ≥ 353.6 μmol L^{-1} (4 mg dL^{-1}) or initiation of renal replacement therapy or ↓ eGFR < 35 mL min^{-1} 1.73 m^{-2} in patients < 18 years of age	↓ < 0.3 mL kg^{-1} h^{-1} for ≥ 24 h or anuria for ≥12 h

*compared to the baseline creatinine concentration, **compared to the baseline GFR level

(CPB) (diuresis and use of furosemide during CPB); and five postoperative parameters (transfusions required and use of diuretics or of vasoconstrictive, inotropic or anti-arrhythmic drugs) [20, 21].

The most recent meta-analysis carried out by Kumar et al. [22], based on 9 independent studies involving patients undergoing surgery under extracorporeal circulation, demonstrated that the time of extracorporeal circulation in patients who developed AKI was significantly longer compared to patients without this complication. In one of the statistical models, the average absolute difference in surgery duration between both groups was approximately 25 min. The risk of AKI was found to be lower by 39% when mini-CPB was used instead of conventional CPB [23]. Based on the above observations, it can be assumed that the extent of surgery affects the risk of development of CSA-AKI.

The risk of AKI was twice as high in patients with baseline anaemia [24] receiving perioperative transfusions of red blood cell concentrate (RBCC) or otherwise. A positive correlation was observed between the number of RBCC units transfused and the incidence of AKI. The same group of researchers widened their analysis and assessed the prophylactic importance of transfusions in patients with preoperative anaemia [25]. They showed that patients with a baseline haemoglobin concentration of 10–12 g dL^{-1} who preoperatively received 2 units of RBCC required significantly fewer post-procedure transfusions. The management described did not limit the risk of CSA-AKI. Unnecessary transfusions should be avoided to limit the development of postoperative AKI; excessive haemodilution during CPB is associated with impaired renal function in the postoperative period [26]. The results of another large randomised trial differ to some extent. According to that trial, the risk of death is comparable, irrespective of the degree of haemodilution, or more precisely of the transfusion threshold assumed — more liberal (to maintain haematocrit ≥ 30%) versus more restrictive strategy (to maintain haematocrit ≥ 24%) [27].

It is difficult to explain the above observations; therefore, it is advisable to refrain from their clinical interpretation. Physicians providing cardiac surgery patients with perioperative care should consider all the elements discussed earlier.

DIAGNOSIS OF CSA-AKI

Early diagnosis of AKI encounters the diagnostic barrier, and commonly determined serum creatine concentrations have numerous limitations and do not fulfil the conditions of an ideal AKI marker [28]. In most cases, the creatinine concentration increases 4–5 days after the exposure to a causative factor, albeit not earlier than after 24–48 h [2, 28]. Despite a decrease in the number of active nephrons, the concentration of creatinine increases only very slightly during the first days, as the process of substance accumu-

lation in blood requires time and the relationship between creatinine concentration and GFR is of an exponential nature. During the first 24 h after surgery, the serum creatinine concentration can even decrease due to haemodilution following extracorporeal circulation [29]. Such a long delay in the diagnosis exposes patients with an unfavourable preoperative history to the adverse consequences of AKI, including a higher risk of death during the postoperative period. Intensive attempts are being undertaken to find an effective method of early (preferably in the preoperative period) identification of patients who will develop acute kidney injury. Such attempts are made in cardiac intensive surveillance units of cardiac surgery departments but are also increasingly common in intensive care units.

The strategies with the most potential as identification methods are linked with determinations of neutrophil gelatinase-associated lipocalin, Lipocalin-2 (NGAL), whose concentration rapidly increases in serum after 1–2 hours and in urine 4–6 hours after damage to the renal tubule epithelium in cases of kidney injuries of various aetiology [28–32]. This finding has been reliably confirmed in many studies that are well summarised by the meta-analysis conducted by the TRIBE-AKI group. The analysis involved 1219 cardiac surgery patients from 10 independent clinical trials who had serial determinations of NGAL in serum as well as NGAL and IL-18 in urine. Elevated NGAL concentration in serum and urine was associated with a fivefold higher risk of CSA-AKI; it was an independent risk factor of early death and correlated with longer hospitalisation and the risk of chronic renal disease [33]. There were no differences in the NGAL determinations in the postoperative period between individuals undergoing cardio-pulmonary bypass under extracorporeal circulation and otherwise [34]. It can be implied that the generalised inflammatory process accompanying CPB most likely does not generate an additional risk of AKI whose development is associated with preoperative risk factors and perioperative complications.

Considering their numerous medical conditions and initially severe clinical states, patients after heart transplant are at a particular risk of complications. In this group of patients, the incidence of clinically significant chronic kidney disease (CKD) diagnosed at eGFR < 60 mL min^{-1} was found to range from 38 to 64%, depending on the method of eGFR calculations [35]. CKD is an adverse sequel of primary CSA-AKI. Przybyłowski and Małyszko demonstrated that determinations of NGAL after heart transplantation not only helped in early identification of patients at risk of acute cardio-renal syndrome but also correlated with the renal function expressed using the serum concentration of creatinine (correlation coefficient r = 0.70; $P < 0.001$), of cystatin C (r = 0.74; $P < 0.001$) and of eGFR (r = 0.56; $P < 0.001$) [36]. NGAL determinations are particularly useful in elderly

patients whose other parameters of kidney function do not indicate any pathology [37].

The observations in a cohort of 136 children who underwent CPB procedures are also optimistic. Elevated urine concentrations of NGAL two hours after the completion of surgery were associated with a severe course of AKI and occasionally with prolonged impairment of renal function, risk of dialysis, total duration of hospitalisation and mortality rates. In the group in question, the incidence of CSA-AKI was 51%, which markedly deviated from the mean percentages [38]. Another study published in mid-2010 dampens the enthusiasm connected with the clinical usefulness of NGAL. Its authors highlight the low sensitivity of determinations, at only 38.7% [39]. Randomised clinical trials are needed to determine whether the initiation of interventions based on increased NGAL concentrations may contribute to lower mortality rates after cardiac surgical procedures.

Recently, the concept of using Doppler examination of renal arteries to predict the risk of CSA-AKI has received interest. This relatively simple and inexpensive method is based on measurements of the resistive index (RI), which is proportional to the intensity of vascular bed contraction or compression [40] according to the equation ,

$$RI = \frac{PSV - MDV}{PSV}$$

where PSV is the peak systolic velocity and MDV indicates the minimum end-diastolic velocity of blood flow. RI is measured once the arcuate and interlobular arteries have been localised using colour Doppler or power Doppler imaging. Based on the study findings, the upper value of the normal RI range was assumed to be 0.7 [40].

RI effectively predicted the development of AKI in septic shock or mechanically ventilated patients; it is hoped that RI can be successfully used in cardiac surgery.

A group of French researchers recently published the results of their study in 65 patients over 60 years of age with risk factors of kidney injury who underwent elective procedures under extracorporeal circulation. The RI measurement was correlated not only with the occurrence of AKI 1-4 days after surgery but also with the severity of its course. The above results are consistent with observations in patients after kidney transplants, demonstrating the usefulness of the RI determinations in the early period following kidney transplantation to predict the early function of transplanted kidneys [41]. Further prospective studies are required to accurately assess the usefulness of RI determinations in cardiac or post-cardiac surgery intensive therapy [42].

MANAGEMENT OF CSA-AKI

The treatment of acute kidney injury complicating the early postoperative period remains challenging and is often the source of clinical dilemmas amongst the therapeutic team, i.e., an anaesthesiologist-intensivist, cardiac surgeon, cardiologist or internist-nephrologist, because the maintenance of kidney function is as important as the support of cardiovascular function. No coherent guidelines for the treatment of cardio-renal syndrome consistent with evidence-based medicine (EBM) principles have been accepted.

PHARMACOLOGICAL METHODS

The issue of diuretics used in CSA-AKI is of particular importance. The attempt to reverse the unfavourable redistribution of fluids by intensive diuretic therapy seems a logical step to prevent and treat cardio-renal syndrome. There are reports regarding potentially nephrotoxic effects of these drugs [43]. The loop diuretics, which are most frequently used in acute circulatory failure, act by blocking the co-transporter $N^+K^+2Cl^-$ in the ascending limb of the loop of Henle. This blockage enhances the delivery of sodium ions to the macula densa and activates tubuloglomerular feedback; subsequently, the secretion of adenosine increases, and the afferent glomerular arteriole contracts, which is likely to result in more severe ischaemia of the renal medulla. A more relevant factor is the reduced renal flow associated with decreased vascular bed filling. If the drugs induce hypovolaemia, diuretics intensify the sympathetic system activation and stimulate the renin-angiotensin-aldosterone system and the secretion of vasopressin. Although these mechanisms counteract the reduction in the effective volume of arterial blood, they simultaneously impair intrarenal circulation and enhance renal hypoxia. Diuretic therapy requires monitoring of its consequences. Ronco and colleagues recently proposed a therapeutic strategy based on monitoring the well-known parameters of hydration, i.e., the balance of fluids, the arterial pressure, and the intravascular volume, and on measurements of novel biomarkers, such as the N-terminal prohormone B-type brain natriuretic peptide (NT-proBNP) or kidney injury molecule (KIM-1) and bioimpedance (the 5B therapy— balance of fluids, blood pressure, blood volume, biomarkers, bioimpedance) [44]. The use of the last two markers should be discussed in detail.

In the only published randomised prospective clinical trial, Damman and co-workers demonstrated that a 3-day withdrawal of diuretics induced increases in concentrations of KIM-1, N-acetyl-glucosamine (NAG) and NT-proBNP. After re-institution of the diuretics, the plasma concentrations of the elevated markers decreased, suggesting beneficial effects of the therapy applied on KIM-1 [45]. In the near future, measurements of biomarkers are likely to become one method to assess the efficacy of diuretic therapy.

A novel and simple method enabling the estimation of total water content in the body is the measurement of bioimpedance [46]. The examination is based on the as-

sumption that the human body behaves as an electric circuit of a defined resistance. Considering this assumption, computer-assisted calculations of bioimpedance are performed and expressed graphically as a vector. The vector's length is inversely proportional to the body water content (a short vector = overhydration). The nutritional state and fat content do not affect the accuracy of examinations. The measurement of bioimpedance detects fluid retention with a sensitivity of 88% and a specificity of 87% [47]. The usefulness of this technique has been positively verified while assessing diuretic therapy, e.g., in the treatment of acute cardiac failure. The lengthening of the bioimpedance vector and the decrease in the NT-proBNP concentration below 250 pg mL^{-1} on discharge were not associated with a better prognosis [47].

The measurements of central venous pressure (CVP) are relevant for the assessment of vascular bed filling and volaemia. If necessary and possible, patients requiring intensive diuretic therapy and an intravenous continuous supply of fluids should be invasively haemodynamically monitored. In most cases of hypervolaemia, the CVP should be approximately 8 cm of H_2O. It is worth re-emphasising that a high CVP (a worse outflow of venous blood from kidneys) is associated with a higher risk of death and the development of renal failure [48].

The use of dopamine and fenoldopam, a selective agonist of dopaminergic receptors, for the prevention and treatment of AKI should be discussed. Based on the largest available meta-analysis of 61 clinical trials, it can be concluded that the use of a "diuretic" dose of dopamine does not significantly affect either survival or renal function [49]. The KDIGO guidelines note that because convincing data on the efficacy of dopamine are lacking, the risk of its adverse effects, e.g., tachyarrhythmias, myocardial ischaemia, impaired intestinal perfusion, hypopituitarism or suppression of T lymphocytes, should be considered [10]. The information regarding the beneficial effects of fenoldopam is slightly more encouraging. The compilation of the available data does not speak in favour of its widespread use [10], mainly because of insufficient data from large-scale randomised clinical trials. A meta-analysis of 13 randomised and non-randomised trials published to date shows that the use of fenoldopam in cardiac surgery patients allows for limiting the requirements for renal replacement therapy by 63% and reduces the risk of early death by 46% [50]. In a randomised study carried out by Morelli and co-workers [51] amongst septic patients, the use of fenoldopam reduced the risk of AKI by 53% and was associated with a ICU stay shortened by approximately 3 days. Slightly conflicting are the results from another meta-analysis summarising only the data from randomised studies [52]. Although fenoldopam significantly reduced the risk of AKI in cardiac surgery

patients (OR = 0.41), its beneficial effects on renal replacement therapy requirements, ICU stay and survival were not observed [52].

A commonly raised issue is related to the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in CRS1. A potential adverse effect of ACEIs results from a decrease in the descending arteriole tension, which reduces intraglomerular hypertension in chronic kidney disease but can also significantly reduce glomerular filtration [6, 53]. It is generally believed that patients with cardio-renal syndrome are too often deprived of routinely used drugs because of ungrounded fears of the further deterioration of renal function. Blockers of the renin-angiotensin-aldosterone system should not be routinely discontinued in AKI in the course of acute decompensation of the circulatory system because their beneficial cardiac effects may outweigh the risk of further impairment of renal function. In such cases, the concentration of creatinine, urine output per hour and concentration of potassium should be frequently monitored [54] (Table 4).

An extremely relevant element of management in acute and chronic cardiac failure is the avoidance of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs inhibit the production of vasodilating prostaglandins, causing the contraction of straight arteries, which results in ischaemia of the renal medulla or necrosis of the renal papilla in extreme cases. This effect can also occur with paracetamol, which is considered to be less harmful. The preferable analgesics in circulatory failure are opioids and metamizole [55–57]. Patients receiving both ACEIs and diuretics and patients with diabetes are at the highest risk [58].

Finally, the influence of statin therapy on the development of CSA-AKI should be outlined. Although preliminary reports (mainly retrospective) documented that the risk of AKI in patients receiving statins was lower [59, 60], the controlled studies did not confirm those promising observations [61, 63].

Novel drugs that are likely to be used in the treatment of coexisting cardiac and renal pathology are worth highlighting. One of these drugs is nesiritide, a human recombinant BNP [64]. This drug should exert natriuretic, vasodilating and anti-inflammatory effects. In practice, its efficacy in the treatment of cardiac and renal failure has not been demonstrated, despite an observed improved tolerance of the symptoms [6].

The drugs from the group of vasopressin receptor V2 antagonists (vaptans) have a different uptake point. The only examined drug from this group, tolvaptan, alleviates the severity of symptoms in acute circulatory failure but does not reduce the mortality rates or improve renal function [65].

The blockage of the type 1 adenosine receptor localised, among other places, in the afferent glomerular arterioles is

Table 3. Methods of CSA-AKI prevention. Based on [6, 10]

CSA-AKI prevention methods
Proper selection of patients for cardiac surgery by a multi-disciplinary medical team (the Heart Team) consisting of a cardiologist, an invasive cardiologist, a preventive cardiologist, an anaesthesiologist, a diabetes specialist, a nephrologist, and a geriatrician; assessment of the surgical risk based on history taking, co-morbidities, results of additional tests
Assessment of the risk of contrast-induced nephropathy before surgery (patients after coronary angiography, patients qualified for TAVI)
Shortening of extracorporeal circulation, particularly keeping the aorta clamping time to a necessary minimum
Avoidance of intraoperative hypotension and arterial blood fluctuations
Strict monitoring of balance of fluids; prevention of dehydration (and overhydration) by monitoring the hydration (and using diuretics)
Continuous haemodynamic monitoring (arterial pressure, CVP, bioimpedance, etc.)
Monitoring of the plasma creatinine concentration, urinary output per hour and determinations of NGAL (for early identification of patients at risk of AKI)
Nephrotoxic drugs should not be used in the perioperative period
Strict control of glycaemia in the perioperative period (preferable glycaemia in the range of 110–149 mg dL^{-1})
Treatment of anaemia by transfusions of blood preparations (usually when the concentration of haemoglobin < 7 g dL^{-1} or haematocrit < 21%)

interesting. The mechanism of action of such an antagonist consists of blocking the tubuloglomerular feedback. In this manner, adenosine receptor antagonists can reduce the resistance to diuretics and exert natriuretic effects without impairing the GFR. Phase III trials regarding the use of rolofylline (a selective type 1 adenosine receptor antagonist) in acute decompensated cardiac failure with hypervolaemia are being performed (PROTECT) [66].

NON-PHARMACOLOGICAL METHODS

An alternative to the pharmacological approach to cardio-renal syndrome treatment is continuous renal replacement therapy (CRRT). According to the current recommendations, CRRT techniques are preferable to intermittent ones, particularly in haemodynamically unstable patients [10] (Table 3).

CRRT is a theoretically safer and more predictable method of intravascular volume reduction and does not disturb the body's electrolyte balance. Unlike diuretics, haemofiltration does not induce neurohumoral reflex activation that impairs the intrarenal circulation. CRRT can sensitise the nephron to the action of diuretics in cases of diuretic resistance [67]. Nevertheless, the use of continuous veno-venous haemofiltration (CVVH) is expensive and has a risk of severe complications, such as haemorrhage or crossed air embolism in cases of a patent foramen ovale (PFO). A theoretical hazard is the dialysis-related decompensation syndrome and the destructive neurological consequences [68]. This syndrome is associated with a sudden drop in the extracellular concentrations of metabolic products (e.g., urea) and an increasing concentration gradient of these substances through the cell membrane, which usually occurs in intermittent haemodialysis procedures; this possibility should be considered when the continuous method is introduced too rapidly with a high accumulation of nitrogen metabolites [68].

Considering the above discussions, a question of which method is superior for the treatment of cardio-renal failure remains, and the opinions are inconsistent. The Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study partially showed that CVVH is more effective in removing excess fluid compared to diuretics and contributes to a reduced 90-day mortality without affecting the incidence of AKI [69]. The relevance of these observations has been repeatedly challenged, mainly because the study was not blinded, the population of patients included was small and the diuretic doses were inappropriately chosen. The multi-centre randomised clinical trial called Cardio-Renal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) has been designed [70], which compared the effects of ultrafiltration or the intensification of pharmacological therapy on the renal function in patients with decompensated heart failure. The intensification of pharmacotherapy was understood as increased doses of diuretics and the use of vasodilators and/or positive inotropic agents. Most importantly, it was documented that ultrafiltration was an intervention that was not as efficacious and was not as safe [70]. Similar controlled studies devoted to cardiac surgery patients with AKI can be expected in the near future.

SUMMARY

The early diagnosis and adequate treatment of acute kidney injury accompanying cardiac failure are challenging for physicians providing care to patients in the immediate perioperative period. Further progress in perioperative care requires the introduction of new markers, such as NGAL, KIM-1, interleukin-18 or liver fatty acid-binding protein (L-FABP)[71]. It will likely be necessary to determine several markers in the form of a specific study panel, which should allow for the early and extremely specific identification of patients at risk of CSA-AKI and allow for the use of new, not yet designed methods of treatment. The development of

Table 4. CSA-AKI treatment methods; based on [6, 10]

Current

1. Simultaneous use of intravenous fluids and catecholamines in patients with low arterial pressure, a negative fluid balance and impaired renal perfusion

   • Balanced crystalloid solutions are recommended; with colloids, mainly balanced hydroxyethyl starch solutions (6% HES 130/0.4), the colloid-crystalloid ratio of 1:3 at the max. dose of 50 mL kg b.w. $^{-1}$ day^{-1}

   • Noradrenaline is recommended based on peripheral vascular resistance; dopamine in "a diuretic dose" is not recommended

2. Use of loop diuretics in cases of overhydration

   • It is recommended to adjust the doses of diuretics to the current volaemia assessed using the arterial pressure (and its curve), bioimpedance and central venous pressure

   • It is not recommended to use diuretics for the "prevention" of CSA-AKI in patients with a high risk of its development

3. Potentially nephrotoxic drugs should be avoided

   • Do not use non-steroidal anti-inflammatory drugs; treatment of choice: opioids, methimazole and paracetamol

   • Do not use aminoglycoside antibiotics, amphotericin B or cytostatics

   • Angiotensin convertase inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and spironolactone should be used only if absolutely necessary and should be avoided because of the risk of hypokalaemia and deterioration of renal perfusion

4. Institution of continuous veno-venous renal replacement techniques (haemofiltration, haemodialysis, haemodiafiltration) in life-threatening cases of acidosis, hyperkalaemia, uraemia, overt clinical overhydration, including pulmonary oedema

   • When selecting patients, their clinical states, especially their haemodynamic efficiency, should be considered

   • Vascular access is recommended: right internal jugular vein → femoral vein → left internal jugular vein → subclavian vein

   • Continuous techniques are recommended (also in patients chronically dialysed before surgery); intermittent dialysis therapy should be used only in exceptional cases

5. Treatment of AKI should be combined with strict glycaemic control (recommended values of 110–149 mg dL^{-1}), enteral nutrition (recommended fulfilment of requirements of 20–30 kcal kg b.w. $^{-1}$ day^{-1} with protein supply 0.8–1.0 g kg b.w.$^{-1}$ day^{-1} in patients without RRT, 1.0–1.5 g kg b.w.$^{-1}$ day^{-1} in patients with intermittent RRT and 1.7 g kg b.w.$^{-1}$ day^{-1} in patients with CRRT); parenteral nutrition is recommended only in patients with clear contraindications for enteral therapy or as an addition

Future

1 The management described above will be instituted once the kidney injury factor exerts its action based on the determinations of early markers of AKI, such as NGAL, KIM-1 or interleukin 18, when clinical AKI symptoms are still absent

2. Prospective clinical trials comparing the efficacy of pharmacological therapy and renal replacement techniques in cardiac surgery patients are required

3. On-going studies assess the efficacy of nesiritide (recombinant human B-type natriuretic peptide), vaptans (type 2 arginine vasopressin-receptor antagonists), and rolofylline (selective adenosine 1 receptor antagonist)

continuous renal replacement methods should facilitate the choice of a correct, effective therapy. We hope to witness advances likely to contribute to an improved efficacy of treatment of acute renal failure, which should shorten the ICU stays and reduce the mortality rates in this group of patients.

References:

1. Hoste EA, Kellum JA, Katz NM, et al.: Epidemiology of acute kidney injury. Contrib Nephrol 2010; 165: 1–8.

2. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R: Cardiorenal syndrome. J Am Coll Cardiol 2008; 52: 1527–1539.

3. Brown JR, Kramer RS, Coca SG et al: Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg 2010; 90: 1142–1149.

4. Swaminathan M, Hudson CCC, Phillips-Bute BG, et al.: Impact of Elary renal recovery on survival after cardiac surgery-associated acute Sidney injury. Ann Thorac Surg 2010; 89: 1098–1105.

5. Wyckoff T, Augoustides JGT: Advances in acute kidney injury associated with cardiac surgery: the unfolding revolution in early detection. J Cardiothorac Vasc Anesth 2012; 26: 340–345.

6. Ismail Y, Kasmikha Z, Green HL, McCollough PA: Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment. Semin Nephrol 2012; 32: 18–25.

7. Bellomo R, Kellum JA, Ronco C: Defi ning and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Intensive Care Med 2007; 33: 409–413.

8. Mehta RL, Kellum JA, Shah SV, et al.; Acute Kidney Injury Network: Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007; 11: R31.

9. Englberger L, Sur RM: Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011; 15: R16.

10. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl 2012; 2: 1–138.

11. Jois P, Mebazaa A: Cardio-renal syndrome type 2: epidemiology, pathophysiology, and treatment. Semin Nephrol 2012; 32: 26–30.

12. Howell J, Keogh BE, Bonser RS, Graham TR: Mild renal dysfunction predicts in-hospital mortality and post-discharge survival following cardiac surgery. Eur J Cardiothorac Surg 2008; 34: 390–395.

13. Lombardi R, Ferreiro A: Risk factors profi le for acute kidney injury after cardiac surgery is diff erent according to the level of baseline renal function. Ren Fail 2008; 30: 155–160.

14. Parsonnet V, Dean D, Bernstein AD: A method of uniform stratifi cation of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989; 79 (supl. I): 3.

15. Sudkamp M, Geissler HJ, Holzl P, de Vivie ER: Risk stratifi cation in heart surgery: do risk scores facilitate the determination of indications? Z Kardiol 2000; 89: 667–673.

16. *Higgins TL, Estafanous FG, Loop FD, et al.:* Stratifi cation of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. JAMA 1992; 267: 2344–2348.

17. *Soni SS, Ronco C, Pophale R, et al.:* Cardio-renal syndrome type 5: epidemiology, pathophysiology and treatment. Semin Nephrol 2012; 32: 49–56.

18. *Muller-Werdan U, Engelmann H, Werdan K:* Cardiodepression by tumor necrosis factor-alpha. Eur Cytokine Netw 1998; 9: 689–689.

19. *Kilger E, Heyn J, Beiras-Fernandez A, Luchting B, Weis F:* Stress doses of hydrocortisone reduce systemic infl ammatory response in patients undergoing cardiac surgery without cardiopulmonary bypass. Minerva Anestesiol 2011; 77: 268–274.

20. *Parolari A, Pesce LL, Pacini D; Monzino Research Group on Cardiac Surgery Outcomes:* Risk factors for perioperative acute kidney injury after adult cardiac surgery: role of perioperative management. Ann Thorac Surg 2012; 93: 584–591.

21. *Brown JR, Kramer RS:* Determinants of acute kidney injury duration after cardiac surgery: an externally validated tool. Ann Thorac Surg 2012; 93: 570–576.

22. *Kumar AB, Suneja M, Bayman EO, Weide GD, Tarasi M:* Association between postoperative acute kidney injury and duration of cardiopulmonary bypass: a meta-analysis. J Cardiothorac Vasc Anesth 2012; 26: 64–69.

23. *Benedetto U, Luciani R, Goracci M, et al.:* Miniaturized cardiopulmonary bypass and acute kidney injury in coronary artery bypass graft surgery. Ann Thorac Surg 2009; 88: 529–535.

24. *Karkouti K, Wijeysundera DN, Yau TM, et al.:* Infl uence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. Anesthesiology 2011; 115: 523–530.

25. *Karkouti K, Wijeysundera DN, Yau TM, et al.:* Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology 2012; 116: 613–621.

26. *Huybregts RA, de Vroege R, Jansen EK, et al.:* The association of hemodilution and transfusion of red blood cells with biochemical markers of splanchnic and renal injury during cardiopulmonary bypass. Anesth Analg 2009; 109: 331–339.

27. *Hajjar LA, Vincent JL, Galas FR, et al.:* Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010; 304: 1559–1567.

28. *Sudnik U, Bachorzewska-Gajewska H, Dobrzycki S, Małyszko J:* Przewlekła choroba nerek u pacjenta kardiologicznego. Możliwości oceny funkcji nerek w codziennej praktyce lekarskiej. Kardiologia Oparta na Faktach 2010; 3: 302–312.

29. *Englberger L, Sur RM:* Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011; 15: R16.

30. *Lyngkaran P, Schneider H, Devrajan P, et al.:* Cardio-renal syndrome: New perspective in diagnostics. Semin Nephrol 2012; 32: 3–17.

31. *Mishra J, Ma Q, Prada A, et al.:* Identifi cation of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14: 2534–2543.

32. *Schmidt-Ott KM, Mori K:* Dual action of neutrophil gelatinase-associated lipocalin. J Am Soc Nephrol 2007; 18: 407–413.

33. *Parikh CR, Devarajan P, Zappittelli M, et al.:* Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol 2011; 22: 1748–1757.

34. *Wagener G, Gubitosa G, Wang S, et al.:* A comparison of urinary neutrophil gelatinase- associated lipocalin in patients undergoing on versus off pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth 2009; 23: 195–199.

35. *Przybylowski P, Malyszko J, Malyszko JS:* Chronic kidney disease In prevalent orthotopic heart transplant recipients using a new CKD-EPI formula. Ann Transplant 2010; 15: 32–35.

36. *Przybylowski P, Malyszko J, Malyszko JS:* Serum neutrophil gelatinase-associated lipocalin correlates with kidney function in heart allograft recipients. Transplant Proc 2010; 42: 1797–1802.

37. *Przybylowski P, Malyszko J, Malyszko J:* Kidney function assessed by eGFR, cystatin C and NGAL (neutrophil gelatinase-associated lipocalin) in relation to age in heart allograft recipients. Med Sci Monit 2010; 16: CR440-4.

38. *Bennett M, Dent CL, Ma Q, et al.:* Urine NGAL predicts severity of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol 2008; 3: 665–673.

39. *Perry TE, Muehlschlegel JD:* Plasma neutrophil gelatinase-associated lipocalin and acute postoperative kidney injury in adult cardiac surgical patients. Anesth Analg 2010; 110: 1541–1547.

40. *Tublin ME, Bude RO, Platt JF:* The resistive index in renal doppler sonography: where do we stand? Am J Radiol 2003; 180: 885–892.

41. *Chudek J, Kolonko A, Krol R, Ziaja J, Cierpka L, Wiecek A:* The intrarenal vascular resistance parameters measured by duplex Doppler ultrasound shortly after kidney transplantation in patients with immediate, slow, and delayed graft function. Transplant Proc 2006; 38: 42–45.

42. *Bossard G, Bourgoin P, Corbeau JJ, Huntzinger J, Beydon L:* Early detection of postoperative acute kidney injury by Doppler renal resistive index in cardiac surgery with cardiopulmonary bypass. Br J Anaesth 2011; 107: 891–898.

43. *Gottlieb SS, Skettino SL, Wolff A, et al.:* Eff ects of BG9719 (CVT-124), an A1-adenosine receptor antagonist, and furosemide on glomerular fi ltration rate and natriuresis in patients with congestive heart failure. J Am Coll Cardiol 2000; 35: 56–59.

44. *Ronco C, Kaushik M, Valle R, et al.:* Diagnosis and management of fl uid overload in heart failure and cardio-renal syndrome: The "5 B" Approach. Semin Nephrol 2012; 32: 129–141.

45. *Damman K, Kam Chuen Ng MJ, MacFadyen RJ, et al.:* Volume status and diuretic therapy in systolic heart failure and the detection of early abnormalities in renal and tubular function. J Am Coll Cardiol 2011; 57: 2233–2241.

46. *Piccoli A:* Bioelectric impedance vector distribution in peritoneal dialysis patients with diff erent hydration status. Kidney Int 2004; 65: 1050–1063.

47. *Valle R, Aspromonte N, Giovinazzo P, et al.:* B-type natriuretic peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. J Card Fail 2008; 14: 219–224.

48. *Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL:* Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol 2009; 53: 582–588.

49. *Friedrich JO, Adhikari N, Herridge MS, Beyene J:* Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. Ann Intern Med 2005; 142: 510–524.

50. *Landoni G, Biondi-Zoccai GG, Marino G, et al.:* Fenoldopam reduces the need for renal replacement therapy and in-hospital death In cardiovascular surgery: a meta-analysis. J Cardiothorac Vasc Anesth 2008; 22: 27–33.

51. *Morelli A, Ricci Z, Bellomo R, et al.:* Prophylactic fenoldopam for renal protection in sepsis: a randomized, double-blind, placebo-controlled pilot trial. Crit Care Med 2005; 33: 2451–2456.

52. *Zangrillo A, Biondi-Zoccai GG, Frati E, et al.:* Fenoldopam and acute renal failure in cardiac surgery: a meta-analysis of randomized placebo-controlled trials. J Cardiothorac Vasc Anesth 2012; 26: 407–413.

53. *Bakris GL, Weir MR:* Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160: 685–693.

54. *Shlipak MG:* Pharmacotherapy for heart failure in patients with renal insufficiency. Ann Intern Med 2003; 138: 917–924.

55. *Fored CM, Ejerblad E, Lindblad P, et al.:* Acetaminophen, aspirin, and chronic renal failure. N Engl J Med 2001; 345: 1801–1808.

56. *Perneger TV, Whelton PK, Klag MJ:* Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinfl ammatory drugs. N Engl J Med 1994; 331: 1675–1679.

57. *Krzych ŁJ:* Kliniczne aspekty stosowania metamizolu w specjalnych populacjach pacjentow. Anestezjol Ratown 2011; 5: 473–481.

58. *Musu M, Finco G:* Acute nephrotoxicity of NSAID from the foetus to the adult. Eur Rev Med Pharmacol Sci 2011; 15: 1461–1472.

59. *Welten GM, Chonchol M, Schouten O, et al.:* Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome. Nephrol Dial Transplant 2008; 23: 3867–3873.

60. *Munoz MA, Maxwell PR, Green K, Hughes DW, Talbert RL:* Pravastatin versus simvastatin for prevention of contrast-induced nephropathy. J Cardiovasc Pharmacol Ther 2011; 16: 376–379.

61. *Prowle JR, Calzavacca P, Licari E, et al.:* Pilot double-blind, randomized controlled trial of short-term atorvastatin for prevention of acute Sidney injury after cardiac surgery. Nephrology (Carlton) 2012; 17: 215–224.

62. *Murugan R, Weissfeld L, Yende S, et al.:* Association of statin use with risk and outcome of acute kidney injury in community-acquired pneumonia. Clin J Am Soc Nephrol 2012; 7: 895–905.

63. *Liakopoulos OJ, Kuhn EW, Slottosch I, et al.:* Preoperative statin therapy for patients undergoing cardiac surgery. Cochrane Database Syst Rev 2012; 4: CD008493.

64. *Hernandez AF, O'Connor CM, Starling RC, et al.:* Rationale and design of the acute study of clinical effectiveness of nesiritide in decompensated heart failure trial (ASCEND-HF). Am Heart J 2009; 157: 271–277.

65. *Konstam MA, Gheorghiade M, Burnett JC Jr, et al.:* Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. JAMA 2007; 297: 1319–1331.

66. *Weatherley BD, Cotter G, Dittrich HC; PROTECT Steering Committee, Investigators, and Coordinators:* Design and rationale of the PROTECT study: a placebo-controlled randomized study of the selective A1 adenosine receptor antagonist rolofylline for patients hospitalized with acute decompensated heart failure and volume overload to assess treatment effect on congestion and renal function. J Card Fail 2010; 16: 25–35.

67. *Jaski BE, Ha J, Denys BG, Lamba S, Trupp RJ, Abraham WT:* Peripherally inserted veno-venous ultrafiltration for rapid treatment of volume overloaded patients. J Card Fail 2003; 9: 227–231.

68. *Zepeda-Orozco D, Quigley R:* Dialysis disequilibrium syndrome. Pediatr Nephrol 2012; 27: 2205–2211.

69. *Costanzo MR, Guglin ME, Saltzberg MT, et al.:* Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. J Am Coll Cardiol 2007; 49: 675.

70. *Bart AB, Goldsmith SR, Lee KL, et al.:* Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012; 367: 2296–2304.

71. *Ronco C, McCullough P, Anker SD, et al.:* Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J 2010; 31: 703–771.

Corresponding author:
Łukasz Krzych, MD, PhD
I Oddział Kardiochirurgii, SP SK nr 7 SUM
Gornośląskie Centrum Medyczne
ul. Ziołowa 47, 40–635 Katowice, Poland
tel.: +48 32 359 86 11, faks: +48 32 252 70 66
e-mail: l.krzych@wp.pl