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Identification of modifiable risk factors for acute kidney injury after cardiac surgery

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a common problem after cardiac surgery and is associated with an increase in morbidity, mortality and duration of hospital stay. With this study we aimed to identify potential risk factors for cardiac surgery associated AKI (CS-AKI) in a single-centre population with a special focus on modifiable risk factors.

Methods: Retrospective single-centre cohort study of 565 consecutive patients who underwent isolated coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass. AKI was defined by the AKIN classification. Known risk scores were applied when possible.

Results: Of the population, 14.7% were diagnosed with AKI. When considering baseline characteristics we found a significant difference in age, preoperative estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) stage and urgency of surgery between the CS-AKI group and the control population. Regarding the intraoperative characteristics, patients with CS-AKI had a significantly lower haematocrit and were more likely to receive a transfusion of packed cells. Postoperative administration of furosemide and packed cell transfusions were also associated with AKI. We found no differences in other characteristics (history of diabetes mellitus, history of congestive heart failure, sex, body mass index (BMI), history of cardiac surgery, low cardiac output and need for intra-aortic balloon pump (IABP), duration of cardiopulmonary bypass (CPB) and cross clamping).

Conclusion: In our series we could identify intraoperative administration of packed cells and postoperative administration of furosemide or packed cells as potentially modifiable risk factors in the development of AKI.

KEYWORDS

Acute renal injury (AKI), cardiac surgery, haematocrit, modifiable risk factors, transfusion

INTRODUCTION

Acute kidney injury (AKI) is common in hospitalised patients and is associated with an increase in morbidity and mortality as well as an increase in the duration of the hospitalisation.[1] Moreover, AKI is associated with a higher risk for advanced chronic kidney disease (CKD) and end-stage renal disease in the long term.[2] Cardiac surgery associated AKI (CS-AKI) is a well-described problem and recent studies report an incidence of 2-30% depending on the definition.[3] CS-AKI is the result of a complex of different pathophysiological mechanisms leading to a global decrease in renal function causing a rise in serum creatinine (sCr). Many independent risk factors for CS-AKI were defined but in general the cause of AKI is multifactorial as these risk factors reduce functional renal reserve. As such, AKI, and especially worse cases, seldom come alone and are generally part of multiple organ dysfunction syndrome or even multiple organ failure. CS-AKI is seen in patients undergoing different operations varying from isolated revascularisation or valve replacement to extensive, combined procedures, cardiac transplantation and the use of assist devices.

After sepsis, cardiac surgery is the second most important cause of AKI in intensive care patients[4] and AKI is an independent risk factor for mortality.[3,5] When renal replacement therapy (RRT) is needed in this group mortality exceeds 50%.[5] Several algorithms were suggested to predict the risk of CS-AKI, but definitions of AKI as

well as the included risk factors are diverse and difficult to reproduce. Since the introduction of the RIFLE classification by the Acute Dialysis Quality Initiative (ADQI) in 2004,[6] a more uniform definition of AKI gives the opportunity to compare different studies. A modification by the Acute Kidney Injury Network (AKIN) in 2007[7] made the classification more sensitive and included the additional criterion of time (AKI developing within 48 hours). Both classification systems have been validated in different populations of cardiac surgery patients and have shown to correlate with short-term outcome.[8]

With this study we aimed to identify possible risk factors for CS-AKI in a single-centre population of 565 patients who underwent isolated CABG with a special focus on modifiable risk factors. Furthermore, we evaluated the performance of several known risk scores.

MATERIALS AND METHODS

We conducted a retrospective, observational, single-centre cohort study and reviewed the cases of 578 consecutive patients who underwent isolated CABG with the use of cardiopulmonary bypass during an 18-month period between June 2009 and November 2010. All patients were adults. Patients on chronic dialysis (n=2), with a history of renal transplantation (n=2) or with survival <24 hours after surgery (n=6) were excluded. One patient underwent concurrent aortic valve surgery, for one patient insufficient data were available and one patient needed a cardiac assist device and these patients were also excluded. Data were extracted from the cardiac surgery electronic database and the electronic data management system used in the intensive care unit. After exclusion 565 patients were withheld for further analysis. In the perioperative period, the following parameters were examined: demographic characteristics, diabetes mellitus, CKD stage, history of cardiac surgery, history of congestive heart failure, history of low cardiac output, urgency of surgery, intraoperative lowest haematocrit, intraoperative and postoperative packed cell transfusion, sCr (at admission, and every 24 hours for a minimum of 48 hours and a maximum of seven days and after eight weeks), estimated glomerular filtration rate (eGFR), postoperative administration of furosemide, duration of cardiopulmonary bypass (CPB) and cross-clamping, need for intra-aortic balloon placement (IABP), need for RRT, duration of AKI and global physical functioning eight weeks after surgery. During the aforementioned period there were no changes in anaesthesia, CBP technique or fluid protocol.

AKI was defined by the AKIN criteria (*table 1*)[7] and eGFR was estimated with the Cockcroft-Gault formula and the Modification of Diet in Renal Disease (MDRD) formula.

Table 1. *AKIN criteria*[7]

	Serum creatinine criteria	Urine output (UO) criteria
Stage 1	Increased sCr x 1.5 or ≥0.3 mg/dl	UO <0.5 ml/kg/h x 6 hours
Stage 2	Increased sCr x 2	UO <0.5 ml/kg/h x 12 hours
Stage 3	Increased sCr x 3 or sCr ≥4 mg/dl (with acute rise ≥0.5 mg/d)	UO <0.3 ml/kg/h x 24 hours or anuria x 12 hours

Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage they are in at commencement of RRT.

Classification of AKI was based on changes in sCr alone and assessed by two different persons. Discrepancies were solved by consensus. Baseline kidney function as described by CKD stage was classified according to the criteria of the Kidney Disease Outcomes Quality Initiative (K/DOQI, *table 2*)[9] with an exception for CKD stage I, which could not be determined because of lacking data concerning proteinuria or history of kidney injury. History of diabetes mellitus was defined as the need for medication to lower the glycaemia. Congestive heart failure was defined by clinical signs of decompensation or signs of congestion with cardiac ultrasound (decreased variation of vena cava inferior with respiration and/or a dilated vena cava inferior). Low cardiac output was defined as a left ventricle ejection fraction below 40%. Urgency of surgery was classified as urgent (within 24 hours after initial diagnosis) or non-urgent. The EuroSCORE is the preoperative risk stratification model with the highest discriminatory power for both 30-day and one-year mortality after open heart surgery. This model is based on 17 predictors of mortality and uses information regarding the patient, cardiac status and type of surgery.[10] Usefulness of several other risk scores specific for the prediction of the need for RRT or other forms of AKI in our population was also evaluated (Cleveland score,[11] Mehta score[12] and AKICS/ Simplified Renal Index (SRI) score).[13]

Table 2. *Chronic kidney disease stages*[1]

Stage	Criteria
1	GFR >90 ml/min/1.73 m² with persistent albuminuria >30 mg/24 h
2	GFR 60-89 ml/min/1.73 m²
3	GFR 30-59 ml/min/1.73 m²
4	GFR 15-29 ml/min/1.73 m²
5	GFR <15 ml/min/1.73 m² or end-stage renal disease

[1]**Applicable when present for three or more months, irrespective of cause; GFR = glomerular filtration rate.**

STATISTICS

Data were analysed using SPSS 20. Continuous variables are listed as mean ± standard deviation and were analysed by an unpaired T-test. Categorical variables are listed as frequencies and were analysed by χ^2 test. Univariate and multivariate logistic regression was applied to evaluate potential modifiable risk factors associated with AKI. In a first approach all variables that were significantly different between the group with AKI and the group without AKI were included as covariates in a univariate analysis. Age, eGFR, and haematocrit were transformed into binary variables. For this purpose, a cut-off point was determined using ROC analysis. Next, a multivariate model was constructed with significant covariates. A p-value ≤0.05 was considered statistically significant.

RESULTS

Comparison of patient characteristics

Patient characteristics are reported in *table 3*. Our database covers >97% of information except for information considering duration of CPB and cross-clamping, which is only known for 46% of the patients. We performed no correction for missing data but there was no difference in the occurrence of AKI between the two groups when we compared the group with known CPB duration with the group without. The majority of the patients were male with a mean age of 67 ± 9.6 years, and 83 patients (14.7%) were diagnosed with AKI. RRT was necessary in two of them (0.4%) and both patients died during the initial admission. Subgroups of different stages of AKI were too small for further statistical analysis (AKIN stage 2: 4 patients; AKIN stage 3: 3 patients). First an univariate analysis including associated factors was assessed (*table 4*) followed by a multivariate model including potentially modifiable risk factors (*table 5*). Transfusion both intraoperatively and postoperatively and the administration of furosemide remained significant.

Evaluation of different scoring systems

In our population only the SRI score[13] was applicable for specific renal risk scores and was determined for 551 patients (98%). The Mehta score and Cleveland score were not applicable, mainly because of lack of data and differences in the definitions used. For mortality risk scores, the EuroSCORE was determined for all patients but three and was significantly higher in patients suffering from AKI.

Table 3. *Patient characteristics (univariate analysis)*

Characteristics	No AKI (n=482) 85.3%	AKI (n=83) 14.7%	p
Baseline			
• Age (years) (n=565)	66.5 ± 9.4	69.9 ± 10.2	0.05
• Female sex (n=565)	89 (18.5%)	16 (19.3%)	0.86
• BMI (kg/m²) (n=565)	27.3 ± 4.2	28.6 ± 4.7	0.06
• eGFR (ml/min/1.73m²) (n=565)	87.9 ± 30.9	74.8 ± 34.0	< 0.01
• CKD stage (n=565)	1.3 ± 1.2	1.9 ± 1.2	< 0.01
• Diabetes mellitus (n=565)	88 (18.3%)	16 (19.3%)	0.70
• History of cardiac surgery (n=565)	6 (1.2%)	3 (3.6%)	0.11
• Congestive heart failure (n=550)	23 (4.9%)	6 (7.4%)	0.35
• Ejection fraction < 40% (n=553)	16 (3.4%)	6 (7.4%)	0.26
• IABP (n=565)	8 (1.7%)	1 (1.2%)	1
• Urgent surgery (n=563)	24 (5.3%)	11 (13.4%)	0.03
• EuroSCORE (n=562)	3.6 ± 2.6	5.2 ± 3.5	< 0.01
• SRI score (n=551)	0.5 ± 0.7	0.8 ± 1	< 0.01
Perioperative			
• Transfusion of packed cells (n=565)	56 (11.6%)	21 (25.3%)	<0.01
• Lowest haematocrit (%) (n=565)	24.8 ± 2.1	24.1 ± 3.1	<0.01
• Duration of cardiopulmonary bypass (min) (n=266)	90.2 ± 26.9	85.8 ± 26.7	0.56
• Duration of cross clamping (min) (n=266)	35.3 ± 13.5	34.1 ± 14.1	0.56
Postoperative			
• Administration of furosemide (n=563)	289 (60%)	70 (84.3%)	<0.01
• Transfusion of packed cells (n=563)	78 (16.3%)	35 (42.2%)	<0.01

AKI = acute kidney injury; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IABP = intra-aortic balloon pump; SRI = Simplified Renal Index.

DISCUSSION

In our population we found a relatively low incidence of AKI in comparison with other studies. Possible factors are a short duration of cardiopulmonary bypass and low mean EuroSCORE. We found a significant association between the development of CS-AKI with several previously described risk factors such as preoperative eGFR and CKD stage, but not for diabetes mellitus, need for IABP, or duration of CPB and cross-clamping. Possible explanations are the low incidence of the need for IABP and the relatively short CPB and cross-clamping time in both groups. We were only able to test one renal risk score in our population (SRI score) and we only found a difference in univariate analysis. Transfusion both intraoperatively and postoperatively and the administration of furosemide appear to play a significant role in the development of CS-AKI. As preoperative haematocrit is associated with the lowest intraoperative haematocrit,[14] we suggest that this could be a potentially controllable risk factor for AKI

Table 4. *Factors associated with acute kidney injury, univariate analysis*

	Units of increase	Regression coefficient (β_1)	OR (95% confidence interval)	p
eGFR <60 ml/ min/1.73 m²	0 (≥60) 1 (<60)	2.53	1.53-2.16	< 0.01
Age >70 (per year)	0 (≤70) 1 (>70)	2.00	1.25-3.21	< 0.01
Urgent surgery	0 (not urgent) 1 (urgent)	2.95	1.39-6.28	<0.01
Haematocrit <20% during CPB	0 (haemato-crit ≥20%) 1 (haemato-crit <20%)	2.75	1.15-6.55	=0.02
Transfusion of packed cells during surgery	0 (no transfusion) 1 transfusion	2.58	1.46-4.55	<0.01
Diuretics after surgery	0 (no diuretic) 1 diuretic	3.56	1.92-6.61	<0.01
Transfusion of packed cells after surgery	0 (no transfusion) 1 (transfusion)	3.76	2.28-6.19	<0.01
Creatinine > 1 mg/dl	0 (≤1 mg/dl) 1 (>1 mg/dl)	2.94	1.82-4.77	<0.01

CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; OR = odds ratio.

Table 5. *Potentially modifiable risk factors: multivariate analysis*

	Units of increase	Regression coefficient (β_1)	OR (95% CI)	p
Diuretics after surgery	0 (diuretic) 1 (diuretic)	3.44	1.82-6.51	<0.01
Transfusion of packed cells during surgery	0 (no transfusion) 1 (transfusion)	2.20	1.19-4.07	=0.01
Transfusion of packed cells after surgery	0 (no transfusion) 1 (transfusion)	2.98	1.77-5.01	<0.01
Haematocrit	0 (haematocrit ≥ 20%) 1 (haematocrit <20%)			=0.43
Intercept (β_0)	-0.01			

as well. Possible mechanisms are that transfused red blood cells (RBCs), being deficient in 2,3-diphosphoglycerate, have an inability to properly load and unload oxygen. Additionally, stored RBCs are less supple and deformable and may physically obstruct the smaller capillaries, leading to further organ ischaemia. Furthermore, transfused RBCs have an artificially shortened lifespan, and their haemolysis leads to an increase in circulating free iron.[15] One should be careful in transfusing these patients with a possible role for optimising the haematocrit preceding surgery or predonation of packed cells as recently suggested by Karkouti *et al.*[16] A confounding factor, however, is the amount of blood loss during surgery which is not known for our population. Although postoperative transfusion of packed cells is a significant risk factor for CS-AKI this can also be a mere surrogate marker for sicker or older patients with a higher bleeding risk. Use of diuretics in an attempt to prevent CS-AKI has not shown any benefits and Lassnigg *et al.* also report detrimental effects with an increase in the incidence of AKI.[17] Another report stated that the use of diuretics in an attempt to restore urine output can only indicate the severity of AKI and does not improve functional outcome.[18] Our study has several shortcomings, one of them being the lack of power, partly secondary to the large number of confounding factors in CS-AKI. Another important issue is the use of surrogate markers, for example for kidney function. Serum creatinine comes into play as a marker for decreasing kidney function when already more than 50% of kidney function has been lost and is only useful after a steady state is reached. Creatinine clearance is a better marker although again with considerable delay.[19] Repeated four-hour creatinine clearance measurements in critically ill patients allow earlier detection of AKI, as well as progression and recovery compared with plasma creatinine[20] but this information was not available for our population. Although eGFR was estimated both by the Cockroft-Gault and MDRD formulas only the values derived from the first formula were reported as in the majority of earlier studies. Considering earlier recognition of AKI using biomarkers several potentially useful markers are under investigation. An ideal biomarker is specific for AKI, has a high sensitivity in the early stages of disease, correlates with disease severity and has prognostic value.[21] In the field of cardiac surgery, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase associated lipocalin (NGAL) are getting much attention. KIM-1 is a transmembranous protein expressed in dedifferentiated proximal tubule cells after ischaemia or toxicity but not in normal tissue. This makes urinary KIM-1 a possible diagnostic marker differentiating between renal AKI on the one side and prerenal AKI or CKD on the other. In a population of 103 cardiac surgery patients KIM-1 turned out to be superior when compared with other urinary biomarkers (Cystatin C, interleukin 18 and urinary NGAL) in the early detection of AKI.[22] NGAL is a transport molecule expressed in neutrophils and epithelial cells. In AKI transcription of NGAL in the kidney increases and both urinary and serum NGAL are early markers of AKI with a slight superiority for urinary NGAL. Increase in NGAL correlates with the risk of the need for RRT. Since individual sensitivity and specificity of biomarkers is low, a combination of both

markers could be useful as a predictor of AKI.[19,21] A recent meta-analysis concerning prevention of CS-AKI showed that none of the studied pharmacological interventions (dopamine, fenoldopam, calcium channel blockers, natriuretic peptides, diuretics and N-acetylcysteine) can significantly reduce mortality. Only fenoldopam and natriuretic peptides can possibly influence occurrence of AKI and the need for RRT positively. Overall the quality of the included studies was poor with a total of 4605 patients for 49 studies with a wide variation of definitions used.[23] In conclusion, although several patient characteristics and intraoperative measures cannot be influenced, there is a role for modifying risk factors such as preoperative haematocrit, intraoperative transfusion of packed cells and postoperative administration of packed cells and diuretics. Future research is warranted to standardise AKI criteria and further development of risk assessment algorithms could improve outcome prediction for this important clinical problem after major cardiac surgery.

EARLIER PRESENTED DATA (ABSTRACTS)

Annual Congress of the European Society of Intensive Care Medicine (ESICM) October. 2011 Berlin: Short-term morbidity of coronary artery bypass grafting due to acute kidney injury. Intensive Care Medicine 2011; Suppl 1: S60. Annual Congress of the American Society of Nephrology (ASN) November 2011, Philadelphia: Identification of potentially controllable risk factors for acute kidney injury after cardiac surgery. J Am Soc Nephrol 2011; 22: 130A.

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