ORIGINAL ARTICLE **CARDIAC SURGERY**

PREDICTORS OF ACUTE KIDNEY INJURY ASSOCIATED WITH CARDIOPULMONARY BYPASS

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Abstract

Objectives: To study the incidence of acute kidney injury (AKI) in the postoperative period of cardiac surgery in patients without preoperative renal insufficiency who underwent cardiac surgery with cardiopulmonary bypass (CPB), and to explore the association between the incidence of AKI and predictors related to CPB.

Methods: Observational, cross-sectional study. Participants were divided in two groups, those who developed AKI in the postoperative period and those who did not develop AKI. Kidney Disease: Improving Global Outcomes - Clinical Practice Guideline for Acute Kidney Injury (KDIGO) classification was used to characterize AKI. The analysis included preoperative variables (anthropometric data, cardiovascular risk factors and blood parameters), as well as the type of surgery, intraoperative variables related to CPB, and postoperative creatinine variation. Association between variables was studied with binary logistic regression.

Results: We have included 329 patients, of which 62 (19%), developed AKI. There were statistically significant differences between the groups in age (p<0.001; OR (95%)-1.075 (1.037-1.114)), duration of CPB (p=0.011; 1.008 (1.002-1.014)), urine output during CPB (p=0.038; 0.998 (0.996-0.999)), mannitol and furosemide administration during CPB, (respectively, p=0.032; 2.293 (1.075-4.890) and p=0.013; 2.535 (1.214-5.296)).

Conclusions: A significant number of patients developed AKI in the postoperative period of cardiac surgery and this incidence was influenced by factors related to CPB, namely: age, duration of CPB, urine output during CPB, mannitol and furosemide administration during CPB.

INTRODUCTION

The incidence of acute kidney injury (AKI) in postoperative period of cardiac surgery varies from 1% up to 30% of the patients.[1-3]

One of the main causes for AKI after cardiac surgery is ischemia secondary to renal hypoperfusion.[4,5] Renal perfusion is autonomously regulated for the maintenance of glomerular filtration rate (GFR) until the mean arterial pressure falls below 80 mmHg. In cardiopulmonary bypass (CPB), whenever mean pressure is below this limit, the risk of developing AKI increases.[5,6] This incidence can also be affected by the type of surgery. Coronary artery bypass grafting (CABG) is associated with a lower occurrence of AKI, followed by valvular replacement surgeries (VRS), and finally the combination of both.[7,8]

The most commonly classifications used to characterize AKI are: RIFLE (Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease), AKIN (Acute Kidney Injury Network), and KDIGO (Kidney Disease: Improving Global Outcomes - Clinical Practice Guideline for Acute Kidney Injury).[2,9] These classifications have different diagnostic criteria for AKI, which may contribute to the variability of results between previous studies. The KDIGO classification has a higher prognostic power when compared to others, since it maintains its prognostic power when hemodynamic variables (e.g.: CPB time) are taken into account.[2]

There are non-modifiable risk factors associated with an increased risk of developing AKI, such as advanced age, female gender, diabetes mellitus, hypertension or pre-operative chronic kidney disease, as well as factors related to CPB such as duration of CPB, aortic cross-clamp time, hypothermia, hemodilution, and reduced urinary output during CPB.[8,10,11]

CPB duration influences the development of AKI.[6,10] The visceral hypoperfusion that it causes reduces oxygen supply and compromises renal function, contributing to ischemia-reperfusion injury.[8] It is a multifactorial aggression to the body, particularly to renal function, and the

longer it is, the bigger the risk of postoperative complications in various organs and systems.

Blood transfusion, due to the transformations that erythrocytes undergo during storage (release of free iron and haemoglobin), may lead to compromise of oxygen transport, increased oxidative stress and leukocytes and coagulation cascade activation, triggering an inflammatory response.[3,5,12]

Hemodilution during CPB is a risk factor for AKI, because although it makes blood more fluid and theoretically improve visceral perfusion[8,11], the risk of AKI may double when the haematocrit during CPB is less than 23% and transfusions are required.[13] According to The Society of Thoracic Surgeons and The Society of Cardiovascular Anaesthesiologists Guidelines, during CPB, haemoglobin should be maintained at least at 7 g/dL.[14]

We aim to evaluate the incidence of AKI in postoperative period of cardiac surgery in patients without preoperative renal insufficiency and who underwent cardiac surgery with CPB, and to determine the association between the incidence of AKI in the postoperative period of cardiac surgery and factors related to CPB.

METHODS

Study Design

Observational, retrospective and cross-sectional study.

For data collection, *SClinic*® database, as well as surgical, CPB and daily records of hospitalization were consulted.

Data was collected between January 2016 and January 2017.

In patients who returned to the operating room during the postoperative period, only records from the second intervention were considered.

Analytical data was collected according to service's blood tests plan, i.e., 1st and 4th postoperative days, and hospital discharge (which may coincide with the 4th day). Blood tests that were not collected on the 4th postoperative day (3rd or 5th day) were considered as the second harvests to be performed at the hospital. In those patients who developed AKI, all blood tests during hospitalization were scrutinized to obtain maximum serum creatinine (SCr) value.

To characterize AKI, the first two criteria of the three of the KDIGO Clinical Practice Guideline for Acute Kidney Injury classification were used[9]:
- Increase in SCr by $\geq$ 0.3 mg/dl within 48 hours;
- Urine volume < 0.5 ml/kg/h for 6 hours;
- Increase in SCr to $\geq$ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.

The third criterion was not used in this study because it applies to a period of analysis superior to patients' standard time of hospitalization in this service (5 days).

This classification also allows characterizing the degree of severity of AKI, according to the criteria described in Table 1.

Participants selection

Sampling method was non-random.
Inclusion criteria were:
- Patients with age $\geq$ 18 years undergoing cardiac surgery with CPB at Cardiothoracic Surgery Department of Centro Hospitalar de Vila Nova de Gaia/Espinho (CHVNG/E) from January 1st to December 31th 2015.
- Although KDIGO 2012 G2 stage translates a slight decrease in GFR, it may or may not be associated with renal injury and was considered for inclusion.[15]

Exclusion criteria were:
- Patients with preoperative renal insufficiency identified by KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, (Table 2);
- Patients who according to KDIGO 2012 classification were in G3 to G5 stages;

Table 1	Staging of acute kidney injury according to KDIGO classification	
Stage	**Serum creatinine**	**Urine output**
1	1.5 – 1.9 times baseline or $\geq$ 0.3 mg/dl ($\geq$ 26.5 μmol/l) increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0 – 2.9 times baseline	< 0.5 ml/kg/h for $\geq$ 12 hours
3	3.0 times baseline or Increase in serum creatinine to $\geq$ 4.0 mg/dl ($\geq$ 353.6 μmol/l) OR Initiation of renal replacement therapy or, in patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2	< 0.3 ml/kg/h for $\geq$ 24 hours or Anuria for $\geq$ 12 hours

Source: Kellum & Lameire, (2012) (9)

Table 2	Chronic kidney disease stages according to KDIGO 2012 classification.	
GFR category	**GFR (mL/min/1.73m²)**	**Terms**
G1	≥ 90	Normal or high
G2	60 - 89	Mildly decreased
G3a	45 - 59	Mildly to moderately decreased
G3b	30 - 44	Moderately to severely decreased
G4	15 - 29	Severely decreased
G5	< 15	Kidney failure

Source: Eknoyan & Lameire, (2013) (15)

- Patients who died at the time of data collection, who underwent re-operation during the study period, who had no blood tests on the first day after surgery, and those submitted to circulatory arrest during CPB.

Preoperative GFR was calculated using Cockcroft-Gault formula (((140- Age) x weight (kg)) / (serum creatinine (mg/dL) x 72)) x 0, 85 (if female).[16]

Participants were divided into two groups, the group that underwent CPB and developed AKI (dAKI) in postoperative period of cardiac surgery and the group that underwent CPB but did not develop AKI (nAKI) in postoperative period.

Ethical issues

Anonymity and confidentiality of the data identifying the participants were guaranteed, respecting Helsinki Declaration (revised in Fortaleza in 2013).

A number was assigned to each case/patient, and a specific database was created for this study, stored on the principal investigator's personal computer, with encrypted access.

Patient's informed consent did not apply as it was an observational and retrospective study based on the collection of data and information routinely recorded in databases/clinical records.

Study protocol was submitted and approved by CHVNG/E Ethics Committee in December 2015.

Statistical analysis

Frequencies and proportions for categorical variables, as well as measures of central tendency and dispersion for quantitative variables were used to characterize the sample.

To study the relationship between independent and dependent variables, Binary Logistic Regression was performed. Results were adjusted for some confounders, namely: gender, age, weight, height, body mass index and CPB duration, since these were considered to be variables that could influence the results of the other variables analysed. A significance level of 5% ($p=0.05$) was considered. To analyse the data collected, IBM® SPSS® Statistics (Statistical Package for the Social Sciences) Version 24.0 software was used.

RESULTS

We included patients undergoing cardiac surgery with CPB between January 1st and December 31st 2015 at the CHVNG/E's Cardiothoracic Surgery Department. The final sample consisted of 329 patients of which 62 (18.8%) developed AKI and 267 (81.2%) did not develop (Figure 1).
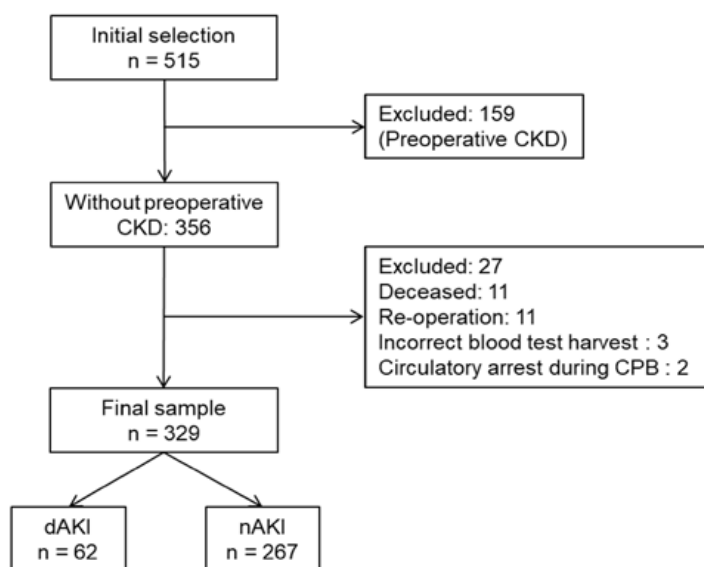
Footnotes: AKI – acute kidney injury; CPB – cardiopulmonary bypass; dAKI – group that developed AKI; nAKI – group that did not develop AKI.

Figure 1 *Sample selection.*

Table 3 **Sample characterization**

Variables	dAKI (n=62)	nAKI (n=267)	p
Age (years)	70.4 (7.7)	64.7 (10.0)	< 0.001
Weight (kg)	79.5 (12.3)	73.8 (12.5)	0.776
Height (m)	1.7 (0.1)	1.6 (0.1)	0.957
BMI (kg/m2)	28.9 (3.8)	27.6 (4.1)	0.950

Sex
  Female
  Male
	21 (33.9)
	41 (66.1)
		123 (46.1)
		144 (53.9)
			0.906

Arterial hypertension	43 (69.4)	153 (57.3)	0.592
Dyslipidemia	36 (58.1)	123 (46.1)	0.676
Diabetes	23 (37.1)	64 (24.0)	0.166
Overweight	54 (87.1)	192 (72.0)	0.410
Hb pre-CPB (g/dL)	12.6 (1.8)	14.1 (13.1)	0.527
Ht pre-CPB (%)	38.7 (5.7)	38.9 (5.0)	0.824
Cr pre-CPB (mg/dL)	0.9 (0.2)	0.8 (0.2)	0.275
GFR pre-CPB (ml/min)	84.2 (22.7)	88.8 (22.4)	0.398

Footnotes (1): Categorical variables are described in n (%) and quantitative variables in mean (SD).
Footnotes (2): CPB – cardiopulmonary bypass; Cr – creatinine; dAKI – group that developed AKI; GFR – glomerular filtration rate; Hb – haemoglobin; Ht – haematocrit; nAKI – group that did not develop AKI; SD – standard deviation.

Characteristics of the group that developed AKI (dAKI) and the one that did not develop AKI (nAKI) are described in Table 3. There are statistically significant differences in age between dAKI and nAKI groups, OR (95% CI) = 1.08 (1.03 – 1.11).

Table 4 shows the different types of surgery performed and the proportion of patients who underwent each type of surgery in each group. There were no statistically significant differences between the groups regarding the type of surgery and the subsequent development of AKI.

Table 5 shows the intraoperative variables, and their behaviour in the two groups analysed. There are statistically significant differences in CPB time, urine output during CPB, mannitol and furosemide administration during CPB. CPB time, mannitol and furosemide administration during CPB results translate into a positive association between a longer CPB and the development of AKI, as well as between the administration of these drugs and the development of this pathology. In urine output during CPB, results suggest a negative influence of this variable on the development of AKI. In the remaining variables there were no significant associations between their occurrence and AKI development.

According to the two criteria selected, the patients who developed AKI were categorized in severity stages, 47 patients were classified in stage 1, (36 according to creatinine criterion, 10 by urine output and 1 by both criteria). In stage 2 we have 10 patients, and in stage 3, 5 patients, all by creatinine criterion. Five patients were classified in different stages with the two criteria, but the creatinine value stages them in a higher stage, so this criterion was validated.

Table 6 shows dAKI's creatinine variation during postoperative period. The maximum value recorded shows a 36.8% (in female) and 53.8% (in male) increase in relation to normality's upper limit. In postoperative period, 2 subjects (3.2% of dAKI group) required a dialysis technique (venovenous hemofiltration), being included in stage 3.

DISCUSSION

In this study, the incidence of AKI in the postoperative period was 19%, using KDIGO classification. Age, CPB

Table 4 **Type of surgery and acute kidney injury development**

Type of surgery	n	dAKI (n=62)	nAKI (n=267)	p	Odds Ratio (95% CI)
CABG – n (%)	19 (5.8)	3 (4.8)	16 (6.0)	0.599	1.436 (0.372 – 5.544)
VRS – n (%)	224 (68.1)	41 (66.1)	183 (68.5)	0.501	0.799 (0.415 – 1.537)
CABG + VRS – n (%)	45 (13.7)	12 (19.4)	33 (12.4)	0.654	1.197 (0.545 – 2.629)
Others – n (%)	41 (12.5)	6 (9.7)	35 (13.1)	0.916	1.058 (0.372 – 3.011)

Footnotes: CABG - coronary artery bypass grafting; CI – confidence interval; dAKI – group that developed AKI; nAKI – group that did not develop AKI; VRS - valvular replacement surgeries.

Table 5	Intraoperative variables and acute kidney injury development

Variables	dAKI (n=62)	nAKI (n=267)	p	Odds Ratio (95% CI)
Addition of blood in the priming	2 (3.2)	11 (4.1)	0.529	0.586 (0.111 – 3.088)
CPB time (minutes)	118.8 (92.6)	94.3 (38.2)	0.011	1.008 (1.002 – 1.014)
Aortic cross-clamp time (minutes)	80.1 (44.7)	71.7 (35.0)	0.177	0.991 (0.979 – 1.004)
Urine output during CPB (ml)	255.3 (208.9)	308.5 (284.3)	0.038	0.998 (0.996 – 0.999)
Mean pressure during CPB (mmHg)	68.7 (8.9)	66.2 (7.7)	0.052	1.039 (1.00 – 1.079)
Min BP during CPB (mmHg)	53.4 (9.7)	52.3 (8.4)	0.272	1.020 (0.985 – 1.057)
Min T during CPB (ºC)	37.3 (38.1)	36.1 (30.9)	0.737	1.001 (0.993 – 1.010)
Min Hb during CPB (g/dL)	8.5 (1.5)	8.5 (1.4)	0.520	0.919 (0.711 – 1.188)
Min Htc during CPB (%)	26.0 (4.6)	26.1 (4.1)	0.554	0.975 (0.896 – 1.061)
Blood transfusion during CPB	10 (16.1)	30 (11.2)	0.489	1.357 (0.572 – 3.220)
Cell-saver used	6 (9.7)	10 (3.7)	0.273	2.049 (0.567 – 7.401)
Mannitol administration during CPB	15 (24.2)	28 (10.5)	0.032	2.293 (1.075 – 4.890)
Furosemide administration during CPB	17 (27.4)	36 (13.5)	0.013	2.535 (1.214 – 5.296)

Footnotes (1): Categorical variables are described in n (%) and quantitative variables in mean (SD).
Footnotes (2): BP – blood pressure; CI – confidence interval; CPB – cardiopulmonary bypass; dAKI – group that developed AKI; Hb – haemoglobin; Ht – haematocrit; Min – minimum; nAKI – group that did not develop AKI; SD – standard deviation; T- temperature.

Table 6	dAKI's creatinine variation during postoperative period.

Creatinine value (mg/dL)	dAKI			
	Female	Normal range	Male	Normal range
1st postoperative day - *Mean (SD)*	1.2 (0.4)		1.6 (0.5)	
4th post-operative day - *Mean (SD)*	0.8 (0.3)	0.51 – 0.95	1.2 (0.6)	0.67 – 1.17
Maximum during stay - *Mean (SD)*	1.3 (0.7)		1.8 (0.8)	
At the day of discharge - *Mean (SD)*	0.7 (0.2)		1.1 (0.4)	

Footnotes (1): Categorical variables are described in n (%) and quantitative variables in mean (SD).
Footnotes (2): BP – blood pressure; CI – confidence interval; CPB – cardiopulmonary bypass; dAKI – group that developed AKI; Hb – haemoglobin; Ht – haematocrit; Min – minimum; nAKI – group that did not develop AKI; SD – standard deviation; T- temperature.

time, urine output during CPB, mannitol and furosemide administration during CPB were risk factors for AKI development. We also find that CPB had an influence on renal function's evolution in postoperative period of cardiac surgery, and that it may lead to the development of AKI.

The incidence of AKI after CPB is similar to the values described in literature, 26.6% by Schopka et al. (2014) (AKIN classification), 19% by Sampaio et al. (2013) (KDIGO classification) and 24.3% by Pontes et al. (2007) (classification not specified).[1,2,17]

With regard to preoperative characteristics, there were statistically significant differences in age. Age is often referred in literature as an AKI risk factor.[2,6,8] For Sampaio et al. (2013) and Rodrigues et al. (2009), age was associated with the development of AKI, and, as in this study, the older the subjects were, the bigger the risk of AKI.[2,6] Age is also reported in the literature as an integral part of the pathophysiological process of AKI because elderly patients are more likely to develop variations in their analytical parameters related to renal function, such as creatinine (due to hypovolemia,

atherosclerotic disease of the renal arteries, and changes in the renal autoregulation mechanisms), and so may be more prone to develop some degree of renal compromise.[4,5] According to Schopka et al., (2014), Pontes et al., (2007) and Brito et al., (2009), age was not associated with AKI development, which, in Pontes et al. (2007) and Brito et al. (2009) studies, may be due to the fact that the mean ages of the groups that developed and didn't develop AKI were lower than those of this study so that creatinine values could also be lower, reflecting a more preserved renal function. The study by Schopka et al. (2014) had different methods from this study.[1,17,18]

Regarding the type of surgery to which patients were submitted, literature indicates that CABG is associated with a lower occurrence of AKI, followed by VRS and finally the combination of both[7,8], and that was not observed in this study. In Rodrigues et al. (2009) study only valvular surgery was associated with AKI, but its sample was considerably higher than ours.[6]

Regarding CPB related variables, there were statistically significant differences in CPB time, urine output during

CPB, mannitol and furosemide administration during CPB. Several studies have evaluated the influence of CPB time on AKI development, showing that the longer it is, the bigger the risk[6,10,11,18], as found by this study. The longer the CPB the longer the time the organism is exposed to non-pulsatile flow, microembolic aggressions that affect renal capillaries circulation, and to inflammatory response caused by free hemoglobin or by the contact of blood with an artificial surface.[4,5,7,8] These results are in contrast to those of Schopka *et al.*, (2014) and Pontes *et al.*, (2007), who did not find any relationship between the variables in CABG, which may be due to the fact that the study by Schopka *et al.* (2014) had a significantly different methodology from this study, and the mean CPB time in both groups (with and without AKI) in the study by Pontes *et al.* (2007) was significantly lower than that in this study.[1,17]

Concerning urine output during CPB, the results obtained revealed that there are statistically significant differences between the two groups analysed, showing a negative association between this variable and AKI development. That is, the greater the volume of diuresis obtained during CPB the more protected the individual is against AKI development. Literature reports that a low urinary output during CPB is a risk factor for AKI, supporting the results obtained in this study.[10] According to Pontes *et al.*, (2007), diuresis volume in CPB did not influence AKI development, however the study of the association between these variables was made using different statistical tests from those used in this study, (t-Test).[17]

Results obtained for mannitol and furosemide administration during CPB demonstrate a positive association of these variables with AKI development. According to Goren and Matot (2015), the use of mannitol or loop diuretics (e.g.: furosemide) during surgery may be detrimental to renal function because of its potential nephrotoxicity and should only be used to treat hypervolemia.[3,9] According to Karajala *et al.* (2009), the danger of loop diuretics is that they decrease the circulating volume, leading to renal blood flow and GFR reduction. The reduction of effective arterial volume stimulates adrenergic and renin-angiotensin systems, causing vasoconstriction in renal cortex, which redistributes kidney circulation, and affects oxygen consumption's self-regulation, worsening renal injury.[19]

Aortic cross-clamp time was not associated with AKI development, although the mean was higher in dAKI group than in nAKI group. This is referred as a risk factor for deterioration of renal function[18], and this was not observed in this study, as it was not observed in the study by Schopka *et al.*, (2014), and that may be due to the application of different AKI definition criteria.[1]

In the present study, there were no statistically significant differences between the two groups regarding preoperative values of haemoglobin and haematocrit, nor with respect to minimum haemoglobin values during CPB, and haematocrit, or as to addition of blood in the priming, blood transfusion during CPB or administration of blood collected in cell-saver. In the study by Keyvan Karkouti *et al.* (2009)[5], sample size was significantly higher than that

of this study, and patients who underwent reoperations during the period under analysis were analysed according to the first surgery, which may coincide with a period of hemodynamic instability and compromise intra-operative blood parameters. All these factors may positively influence the association with AKI development, justifying their results.

With regard to AKI staging, 75.8% of the patients who developed AKI were included in the less severe stage. In the study by Schopka *et al.*, (2014) the majority of patients undergoing CABG with CPB were enrolled in stage 2 (unspecified classification).[1]

Regarding postoperative creatinine variation in dAKI group, it is similar between both sexes during hospitalization, being normalized at the day of discharge. According to Pontes *et al.*, (2007), postoperative creatinine in dAKI group presented a mean (SD) of 1.8 (0.3) in the average of the first 5 days, being this value different from those recorded in this study because it results from an average.[17]

Regarding the need for renal replacement therapy, in this study 2 subjects (3.2% of dAKI group) required venovenous hemofiltration. According to Schopka *et al.*, (2014), 2.9% (n=21) of the group who underwent CABG with CPB required renal replacement therapy. In the study by Sampaio et al. (2013), 7% (n=4) of patients who developed AKI (KDIGO classification) required hemodialysis, in the study of Rodrigues *et al.* (2009), 23% (n=18), and in the study by Pontes *et al.*, (2007), 5.6% (n=1) of the patients with AKI required dialysis.[1,2,6,17]

During the study, some limitations were observed: sample size; the nature of the study, not allowing to standardise the way data was collected; not having access to data on physical files of deceased patients; the KDIGO classification for the definition of AKI was not used in most of the studies consulted, making it difficult to adequately compare the results.

CONCLUSION

In conclusion, these results fit in the results spectrum described in literature, however it should be analysed cautiously once AKI incidence after CPB after cardiac surgery may also be influenced by other variables that were not considered in this study.

A prospective study that analyses the variables collected in this study and others that might influence the development of AKI may be carried out, with the application of new AKI biomarkers discussed in literature (e.g.: NGAL - neutrophil gelatinase-associated lipocalin), allowing an earlier detection of this pathology and thus probably a more rapid intervention.

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